THE EFFICACY OF A COMBINATION THERAPY OF MEMANTINE AND AN ACETYLCHOLINESTERASE INHIBITOR IN ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background: To date, clinical trials have reported inconsistent results on the efficacy of the combination therapy of Memantine plus an acetylcholinesterase inhibitor (AChEI) over a single-drug therapy in the treatment of Alzheimer's disease. This meta-analysis aim is to assess the efficacy of the combination therapy of Memantine plus an AChEI in the treatment of Alzheimer's disease compared with a single-drug therapy using an AChEI.

Methods: PubMed, Embase, and Cochrane library databases were searched through December 2013. Seven randomized controlled trials were included in the meta-analysis. A random-effects meta-analysis was used. Heterogeneity and publication bias were assessed.

Results: A combination therapy of an AChEI with memantine was associated with modestly better effects in terms of cognition and global function compared to a monotherapy with an AChEI. The effects of the combination therapy were no better than a monotherapy for daily living activity. However, the combination therapy showed benefits over a monotherapy for the behavioral outcome and the effect was independent of the stage of the disease. Moreover, the rate of adverse effects did not differ between a combination therapy and a single therapy.

Conclusions: The findings of this meta-analysis suggest that the combination therapy is more appropriate and should be administered for patients in more advanced stages. However, not all patients may benefit from the combination treatment. Identification of subgroups of patients with Alzheimer's disease who will benefit more from the combination treatment is needed.

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Abbreviations

ACh	acetylcholine
AChE	acetylcholinesterase
AChEI	acetylcholinesterase inhibitor
AChR	acetylcholine receptor
AD	Alzheimer's disease
APOE ε4 allele	apolipoprotein E ε4 allele
APP	amyloid precursor protein
BuChE	butyrylcholinesterase
BMI	body mass index
ChEIs	cholinesterase inhibitors
CI	confidence interval
ELF-EMF	extremely low - frequency electromagnetic fields
FDA	Food and Drug Administration
HSV-1	Herpes simplex virus – type1
NICE	National Institute for Health and Clinical Excellence
NMDA	N-Methyl-D-aspartate
PBAC	Pharmaceutical Benefits Advisory Committee
PS1	presenilin 1
PS2	presenilin 2
RCT	randomized controlled trial
WHO	World Health Organization

Abbreviations for the clinical assessment tools

ADCS-ADL	Alzheimer's Disease Cooperative Study - Activities of Daily Living
BADLS	Bristol Activities of Daily Living Scale
CDR	Clinical Dementia Rating
CGA-NPI	Caregiver-Administered Neuropsychiatric Inventory
CIBIC-Plus	Clinicians Global Impression of Change
K-MMSE	Korean Mini-Mental State Examination
MMSE	Mini-Mental State Examination

NPI   Neuropsychiatric Inventory

SIB   Severe Impairment Battery

SMMSE   Standardized Mini-mental State Examination

1 Introduction

The population ageing is a global phenomenon. Estimates show that in 2050 the world population over the age of 60 will be 2 billion and the proportion of old people will be increasing constantly (United Nations [UN], 2009). The occurrence of dementia is strongly related to population ageing (Qiu, Kivipelto, & von Strauss, 2009). The developing countries are facing a greater challenge as their huge increase in population entails a rise in the number of aged people and as a consequence a rise in the number of people affected by dementia (UN, 2009).

The term 'dementia' describes the clinical syndrome characterized by cluster of symptoms and their progressive worsening which is manifested by difficulties in remembering and gradual loss of memory, mood and behavioural changes, speech impediment and other cognitive functions, such as communication problems, thinking and reasoning problems, and reduction in capability and ultimately inability to perform daily activities (World Health Organization [WHO], 2012).

According to the World Health Organization and Alzheimer's Disease International report, the total number of people with dementia worldwide in 2010 was estimated to be 35.6 million and that figure is expected to double nearly every 20 years to 65.7 million by 2030 and 115.4 million by 2050. The cost of dementia globally in 2010 was $604bn (£381bn; €462bn) (Alzheimer's Disease International, 2010). The report informs that dementia is a global problem and suggests that all governments should take action towards dementia in their national health policies, focused on the key message: "Dementia is not a normal part of ageing" (Alzheimer's Disease International, 2010).

Alzheimer's disease is the most common type of dementia accounting for 50-70% of all dementia cases and maintaining the same proportions in all populations of the globe. The disease was described a century ago by the German psychiatrist Alois Alzheimer and was named after him, in his honor (Ferri et al., 2005; Qiu et al., 2009; Reitz, Brayne, & Mayeux, 2011) .

2 Rationale of this review

The economic impact of Alzheimer's disease and the lack of new more effective drugs, has turned the focus of the investigation on a better treatment with the current available and widely prescribed drugs aiming at reducing the deterioration caused by the disease and hindering its development.

Thus, the current research is focussing on the investigation of the combination of an acetylcholinesterase inhibitor (AChEI) and memantine, which are drugs that have complementary action and are the most commonly used for the treatment of Alzheimer's patients. The combination therapy may be more beneficial than a monotherapy with either one of these drugs.

To date, clinical trials and reviews have reported inconsistent results on the efficacy of the combination therapy over the monotherapy. Some clinical trials among moderate-to-severe patients found some benefits in the combination therapy (Grossberg et al., 2013; Howard et al., 2012; Tariot et al., 2004) ,but no benefits for mild-to-moderate patients (Choi et al., 2011; Farlow, Alva, Meng, & Olin, 2010; Porsteinsson, Grossberg, Mintzer, Olin, & Memantine MEM-MD-12 Study Group, 2008). In addition, a review (Farlow & Cummings, 2007) of published trials found no evidence of the effectiveness of the combination therapy over the monotherapy for the earlier stages of Alzheimer's disease. Other reviews found some evidence in support of using the combination therapy over the monotherapy for moderate stage (Farlow & Cummings, 2007) and moderate-to-severe stage (Tampi & van Dyck, 2007). Moreover, some other reviews suggested that the combination therapy is the most effective for the treatment of all stages of Alzheimer's disease (Grossberg, Edwards, & Zhao, 2006; Standridge, 2004) .

A thorough investigation in the contents of the reviews showed that the variability of their outcomes is dependent on the period they were conducted, on the studies they included, on the approach they used (narrative or systematic) and on the outcome measures (i.e. different measurement scales). As the outcomes of the reviews are shaping opinions of the decision makers for the approval of a drug to be prescribed by

the national health systems, the issue of cost-effectiveness is involved with the efficacy of a drug. The research findings showed that although a combination therapy increases the treatment costs, it decreases total lifetime Alzheimer's disease-related care costs (Weycker et al., 2007).

Hence, there is a need for further examination on the efficacy of the combination therapy of an AChEI together with memantine for Alzheimer's patients, through an updated review which may provide a better insight in the matter.

3 Objectives

Overall objective

The aim of this systematic review and meta-analysis was to assess the efficacy of a combination therapy of Memantine plus an AChEI in the treatment of Alzheimer's disease compared to a single-drug therapy using an AChEI.

Specific objectives

- To assess the effects of the combination therapy of memantine plus an AChEI on the declination of Alzheimer's patients in terms of cognitive function, activities of daily living and global function compared to treatment of with only an AChEI.

- To assess the safety and tolerability of the combination therapy of memantine plus an AChEI compared to an AChEI monotherapy.

4 Review of literature

4.1 Dementia and Alzheimer's disease

Dementia is a uniform term, which comprises many different types of that syndrome. The most common types are: Alzheimer's disease, vascular dementia, dementia with Lewy bodies, fronto-temporal dementia, mild cognitive impairment, Creutzfeldt-Jakob disease, Korsakoff's syndrome. Diseases which affect the neuronal system such as multiple sclerosis, motor neurone disease, Parkinson's disease and Huntington's disease incorporate increased risk of dementia without constituting dementia type themselves (Lakey, Chandaria, Quince, Kane, & Saunders, 2012). Interestingly, some types of dementia are far more common than others and especially Alzheimer's disease is keeping dominant position among all (Lakey et al., 2012).

The Alzheimer's type dementia is a progressive neurodegenerative disorder characterized by the presence of excess neuritic extracellular amyloid plaques – which are usually surrounded by dystrophic neurites – and intracellular neurofibrillary tangles in the cerebral cortex (Cummings & Cole, 2002; Reitz et al., 2011) .

There is increasing evidence that the pathology of Alzheimer's starts decades before the onset of the clinical symptoms and many biomarkers are associated with it. Furthermore, it is supported that once the symptoms of dementia appear, significant neuronal loss has already occurred and the disease progression is inevitable (Sperling et al., 2011).

Currently there is no cure for Alzheimer's at any stage of the disease. Recent research suggests that treatments should intervene during the symptomatic period of the neurologic damage rather than later at the onset of symptomatic dementia (Sperling et al., 2011).

Estimations show that there were over 35 million people with dementia worldwide in 2010. This number is anticipated to nearly double every 20 years, to reach to 65.7

million in 2030, and 115.4 million in 2050 (Alzheimer's Disease International, 2011). Currently 58% of people with dementia live in developing countries, but by 2050 this number is expected to rise up to 71%. The numbers in developed countries are expected to increase by 100% between 2001 and 2040. Particularly, the fastest growth is taking place in India, China, and their south Asian and western Pacific neighbours where the increase in number of cases is anticipated to exceed 300% (Ferri et al., 2005). In USA one in eight older Americans has Alzheimer's, putting the disease in the position of the sixth leading cause of death in USA. The healthcare payments for the disease in USA alone in 2012 were over 200$ billion (Alzheimer's Association, 2012).

The international literature shows increasing incidence of the disease and its confrontation is putting it in the forefront of research globally. The international research focuses its aims either on treatment and improvement of cognition and quality of life of patients, or on the discovery of the disease's aetiology and therefore its prevention. As regards the first, the research efforts are focusing on the development a new generation of more effective treatments using the most updated findings of medicine and biology. As for the second, the efforts are focusing on all the biological, social, economic and environmental factors that may support a healthy ageing.

4.2 The pathophysiology of Alzheimer's disease

Alzheimer's disease is a progressive brain disorder that damages and eventually destroys brain cells, leading to loss of memory, thinking and other brain functions. Alzheimer's disease is not a part of normal aging, but results from a complex pattern of abnormal changes. It usually develops slowly and gradually gets worse as more brain cells wither and die. Ultimately, Alzheimer's disease is fatal, and currently, there is no cure (Cummings & Cole, 2002).

The pathophysiology lying behind the Alzheimer's disease symptoms is characterized by two microscopic neuropathological hallmarks: the extracellular amyloid plaques and intracellular neurofibrillary tangles (Waldemar & Burns, 2009). The amyloid

plaques' compound is mainly the neurotoxic peptide amyloid (Aβ, Abeta) which is cleaved sequentially from a larger amyloid precursor protein (APP) by two enzymes: β-secretase and γ-secretase (comprising four proteins, one of which is presenilin). Hence, Aβ will not be formed if APP will be cleaved at first by the enzyme α-secretase and not β-secretase (Waldemar & Burns, 2009). Neurofibrillary tangles' compound is mainly the protein tau which binds microtubules and thus facilitates the neuronal transport system. The uncoupling of tau from microtubules and furthermore their aggregation into tangles inhibits transport and has as a consequence the microtubule's disassembly. The phosphorylation of tau may play an important role in this process too (Waldemar & Burns, 2009).

Interestingly, some aspects of Alzheimer's disease pathology are found also in normal ageing, but the increasing density of the neuritic plaques and neurofibrillary tangles that are consequent of the Alzheimer's disease progress can be distinguished from those of normal aged people (Cummings & Cole, 2002; Parsons, Danysz, Dekundy, & Pulte, 2013).

Alzheimer's disease was initially thought to be solely a result of a cholinergic deficit. Although the primary focus has been on the cholinergic system, other neurotransmitters, including dopamine, noradrenalin, serotonin, and glutamate, have been shown to reduce or dysregulate when the disease occurs (Geerts & Grossberg, 2006). The involvement of these neurotransmitters (dopamine, noradrenaline, serotonine and glutamate) during the development of the disease and the interactive regulation of these transmitter actions led to conclusions that the neurotransmitter systems that mostly need to be studied for the pathogenesis of Alzheimer's disease are both the cholinergic and glutamatergic systems (Hynd, Scott, & Dodd, 2004; Terry & Buccafusco, 2003). Thus, the evidence for the rationale of the pharmacological treatment of Alzheimer's disease with AChEIs and memantine is based on the concept of the selective vulnerability of neuronal systems such as the cholinergic, serotonergic, noradrenergic and glutamatergic (Geerts & Grossberg, 2006).

4.3 Prevalence

In 2003, Wimo et al., stated that the population affected by dementia around the world in 2000 was 25 million people and estimated that the future trend of dementia increasing to 63 million cases by 2030 and 114 million by 2050 (Wimo, Winblad, AgueroTorres, & von Strauss, 2003). Two years later a group of experts assigned by the Alzheimer's Disease International, reviewed the available epidemiological data and reported similar estimations: a current number of 24.3 million of dementia cases in ages above 60+ years old, which increases with 4.6 million new cases every year, will double every 20 years, rising finally to 81.1 million by 2040 (Ferri et al., 2005).

Moreover, it was stated that most people with dementia 60+ years old, live in developing countries. Indeed, China and developing western Pacific countries have the highest number of people with dementia (6 million), but not the highest prevalence (4.0%). The European Union follows with 5.0 million people with dementia, but remarkably higher prevalence (5.4%) and then USA with 2.9 million people with dementia and the highest prevalence among the world regions (6.4%).

Interestingly, there were 1.5 million of dementia cases in India and the prevalence was 1.9%. There is a variation in the rates of dementia cases across the world; the numbers in developed countries are going to increase by 100% between 2001 and 2040, whereas in India, China, and other south Asian and western Pacific countries the increase will be more than 300% (Ferri et al., 2005).

Four population-based studies with different inclusion criteria, reported age-specific prevalence of dementia and Alzheimer's disease across four regions (Table 1): Europe, USA, China and Brazil. The European study among people over 65 years of age showed prevalence of 6.4 % for dementia and 4.4 % for Alzheimer's disease (Lobo et al., 2000). The US national representative sample study of individuals over 70 years old yielded prevalence of 9.7 % for Alzheimer's disease (Plassman et al., 2007) while the prevalence for all types of dementia was 13.9%. In China, two different meta-analyses stated that the pooled prevalence of Alzheimer's disease for the population over 60 years old was between 1.6% and 1.9% and the prevalence of

dementia was between 3.0 and 3.2%, rising the current prevalence rate of dementia in China closer to that of the developed countries (Dong et al., 2007; Zhang et al., 2012). The Brazilian study of a community of individuals with low socioeconomic status stated that the prevalence of dementia among individuals over 65 years old was 5.1% and the Alzheimer's prevalence in this population was 1.6% (Scazufca et al., 2008).

Table 1. Prevalence (%) of dementia and Alzheimer's disease by country

Country	Age range	Dementia	Alzheimer's disease	Reference
E.U.	65+	6.4	4.4	(Lobo et al., 2000)
U.S.A	70+	13.9	9.7	(Plassman et al., 2007)
China	60+	3.0-3.2	1.6-1.9	(Dong et al., 2007; Zhang et al., 2012)
Brazil	65+	5.1	1.6	(Scazufca et al., 2008)
Cuba	65+	6.4	Not reported	(Llibre Rodriguez et al., 2008)
Egypt	65+	4.5	2.2	(Farrag, Farwiz, Khedr, Mahfouz, & Omran, 1998)
Israel (Arabs-S. Haifa)	60+	Not reported	20.5	(Bowirrat, Treves, Friedland, & Korczyn, 2001)

Similarly, a survey of urban populations in the cities Havana and Matanzas of Cuba has reported the prevalence of 6.4% for dementia, according to DSM-IV criteria (American Psychiatric Association, 2000), for persons over 65 years old (Llibre Rodriguez et al., 2008) and a study of the Upper Assiut region population in Egypt reported the dementia prevalence of 4.5% and Alzheimer's prevalence 2.2% in persons over 65 years old (Farrag et al., 1998). Beyond the similar rates of various epidemiological studies from different parts of the world, the study of the Arab population of south of Haifa in Israel, yielded crude prevalence estimate for Alzheimer's disease at 20.5% among the individuals over 60 years old (Bowirrat et al., 2001). This exceptional outcome was explained by the authors as a result of the consanguinity among families of this community (Farrer et al., 2003) (Table 1).

However, even though the rates of prevalence seem to converge roughly all around the world, favouring the developing countries, the numbers of dementia and Alzheimer's cases seem to increase tremendously in the developing countries due to their populations sizes.

In addition, over viewing in the pattern of dementia subtypes across the world the proportion of Alzheimer's disease cases among the demented populations remain constant and accounting for 50-70% of all dementia cases, placing Alzheimer's in the position most common form of dementia (Ferri et al., 2005; Qiu et al., 2009).

4.4 Incidence

The global annual incidence of dementia is around 7.5 per 1,000 persons (Ferri et al., 2005). The incidence rate of dementia increases exponentially with age, from approximately one per 1,000 person-years in people aged 60-64 to more than 70 per 1,000 person-years in the ages above 90 year old. The incidence rates of dementia across several regions are similar among the younger ages (under 75 years), but greater variations are seen in individuals aged above 70 years old (Qiu, De Ronchi, & Fratiglioni, 2007).

The pooled data from eight European population studies from seven different countries (Finland, Sweden, Netherlands, Denmark, United Kingdom, France, Spain) showed that the incidence rate of Alzheimer's disease among people over 65 years old in Europe was 19.4 per 1000 person-years. In addition, there has been some geographic variations in the incidence; being higher among the very old people of north-western countries compared with those of southern countries.

The incidence of dementia and Alzheimer's also differed according to age group and gender, rising in the very old ages (over 85 years old), but only among women and not among men (Fratiglioni et al., 2000). However, the Cache County Study found that the incidence of Alzheimer's disease increased with age, peaked, and then started to decline at extreme old ages (over 85 years) for both men and women (Miech et al., 2002).

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Two US large-scale community based studies of persons aged over 65 years old reported an Alzheimer's disease incidence of 15.0 per 1,000 person-years with the sex-specific incidence rates for males and females being 13.0 and 16.9 per 1,000 person-years, respectively (Kawas, Gray, Brookmeyer, Fozard, & Zonderman, 2000; Kukull et al., 2002).

A 3-year follow-up Swedish study involving 987 persons aged 75 years or older found the incidence rate of dementia in the age group of 75-79 years to be 19.6 and 12.4 per 1,000 person-years for women and men, respectively; whereas for the age group above 90 the rates were 86.7 and 15.0 per 1,000 person-years respectively (Fratiglioni et al., 1997).

A 3-year follow-up British study of persons aged 65 or older showed the incidence of all types of dementia 9.2 per 1,000 person-years, of which the Alzheimer's disease incidence was 6.3 per 1,000 person-years (Copeland et al., 1992). Another British population multisite study which aimed to measure the variation of incidence of dementia and Alzheimer's disease across five regions within England and Wales found neither evidence of variation in dementia incidence among these regions, nor slowing of the incidence in the oldest age groups (Matthews, Brayne, & Medical Research Council Cognitive Function and Ageing Study Investigators, 2005).

A recent recent epidemiological study on Alzheimer's disease incidence reported that the incidence increases exponentially with increasing age (Xu, Ferrari & Wang, 2013). Moreover, the incidence of Alzheimer's disease at age 80 was higher in North America (20.6 / 1 000 person years) and Europe (15.1) than in the other countries (8.3). It is noteworthy that this systematic review outcome emerged from 20 studies coming from North America and Europe and only 7 studies that came from other countries (3 from Japan, 1 from China (province of Taiwan), 1 from India, 1 from Nigeria and 1 from Brazil (Ziegler-Graham, Brookmeyer, Johnson, & Arrighi, 2008).

Studies of populations from other than North America and EU countries also demonstrate lower Alzheimer's disease incidence. As an example, the incidence rate in a rural Indian population was estimated at 3.2 per 1000 person-years (Chandra et

al., 2001); in a Brazilian population aged above 65 was estimated at 7.7 per 1000 person-years (Nitrini et al., 2004); and in a Japanese community it was 5.1 and 10.9 per 1000 person-years for men and women respectively (Yoshitake et al., 1995).

In conclusion, an exponential increase in Alzheimer's disease's incidence rate may be related to the age increase in many of the above mentioned populations. This might be an indication that Alzheimer's disease is a consequence of ageing, but interestingly a configuration of a restrain of this upward trend for persons aged above 85 years old may indicate a reduction of the vulnerability in very old people due to genetic or environmental factors or might be simply affected by the survival effect in this old age groups (Miech et al., 2002). However, the distribution by age and gender which may be observed in the rates of Alzheimer's disease, shows that females have increased risk in developing the disease and it is consistent with the findings coming up from the incidence data of the Kungsholmen Project which show that women have approximately 3-fold higher risk of developing the disease (Fratiglioni et al., 1997).

4.5 The burden of the disease

Dementia and Alzheimer's disease have a complex impact on individual and socioeconomic level. Dementia is the major determinant of developing dependence and functional decline. A follow-up study showed that about half of the persons who developed functional dependence had a type of dementia (Aguero-Torres et al., 1998). Reports from WHO (World Health Organization) and Alzheimer's Association underline that Alzheimer's disease is one of the major causes of disability in later life globally, without discrimination between the developed and developing countries (Alzheimer's Disease International, 2010; WHO 2008).

The average survival period after the diagnosis of the Alzheimer's disease is approximately 4-8 years for people over 65 years old, while some patients may live till 20 years after the first diagnosis (Alzheimer's Association, 2013; Arrighi, Neumann, Lieberburg, & Townsend, 2010). Of all these years, on an average, an Alzheimer's patient will spend more years in the most severe stage. Especially, for the patients in the ages between 70 and 80 years, the typical development of the disease

according the Clinical Dementia Rating (CDR) of Hughes, Berg, Danziger, Coben, & Martin (1982), is 3 years in stage 1 (mild), 3 years in stage 2 (moderate) and 4 years in stage 3 (severe) (Arrighi et al., 2010).

Similarly, estimates from a US population show that 40% of the total number of years with the disease is spent in a nursing home (Alzheimer's Association, 2013), and while the deaths from all causes are 30% by the age of 80 years, the percentage for the Alzheimer's disease patients increases to 61% (Arrighi et al., 2010). Also, when the admission to nursing home for the general population of 80 years old is only 4%, for the Alzheimer's disease patients surviving in this age is 75% (Arrighi et al., 2010). Thus, the long duration of the disease before death increases significantly the economic impact of the disease.

The demands for healthcare and social service for the huge and rapidly growing numbers of dementia patients have a major economic impact on the societal level (Alzheimer's Association, 2013; WHO 2008). Surprisingly, the direct medical care costs contribute to 16% of the total costs of the disease, and particularly in the low-income countries, most costs derive from unpaid care provided by family members and others (Alzheimer's Disease International, 2010). Nonetheless, the developing countries are expected to carry the bigger burden of the disease in the future, as the last decade's (2010) estimate shows that 58% of the total people with dementia live in these countries and anticipate that this number in 2050 will rise to 71% (Kinsella & Velkoff, 2002). Dementia costs in developing countries are estimated to be US$73 billion yearly, but the health care needs of the disease require social protection, which seems scarce in these regions (Lakey et al., 2012).

In the World Alzheimer Report 2010 it is commented: "The total estimated worldwide costs of dementia in 2010 were US$604 billion. These costs account for around 1% of the world's gross domestic product, varying from 0.24% in low income countries, to 0.35% in low-middle income countries, 0.50% in high-middle income countries, and 1.24% in high income countries. If dementia care were a country, it would be the world's 18th largest economy, ranking between Turkey and Indonesia. If it were a company, it would be the world's largest by annual revenue exceeding Wal-Mart

(US$414 billion) and Exxon Mobil (US$311 billion)" (Alzheimer's Disease International, 2010).

In the above mentioned total costs are also included - except from the direct costs related to medical, hospital and social care - the family care costs (informal costs) which are not negligible, given that they count approximately 41% of the total costs. As, usually a person with Alzheimer's disease occupies family caregivers with unpaid care status and the burden for these caregivers is high in terms of man-hours occupied into activities related directly or indirectly to the patient. In addition, the caregivers undergo an important psychological burden related to the continuous care and dealing with a person with dementia, as a "full time job" with no breaks for week-ends and holidays (WHO, Alzheimer's Disease International, 2012). As a result, caregivers of Alzheimer's patients show all the features of a chronic stress experience with all the consequent health effects (Schulz & Sherwood, 2008).

In conclusion, while the numbers of persons with Alzheimer's disease are increasing exponentially, the burden of the disease is becoming devastating too. Simultaneously, the disease has an indirect socioeconomic impact, not only on those who have the disorder (i.e. stigmatism, ethical issues), but also on their caregivers and their families which cannot be disregarded (WHO, 2012). Hence, the confrontation or postponement of the onset of the disease and the application of the most effective treatment when the disease occurs is manifested as a global challenge.

4.6 Determinants of Alzheimer's disease

An overview of epidemiological studies, genetic studies, neuroimaging methods and neuropathology research, used to explain the development of Alzheimer's disease. The conclusions converge that it is a multi-aetiology degenerative, incurable and fatal disorder. Its basic etiological risk factors could be resumed in four major categories: biological, genetic, vascular and psychosocial (Povova et al., 2012). Furthermore, other factors such as nutrition, exposure to various substances and inflammation are suspended to play a role for the occurrence of the disease, but with insufficient level of evidence (Povova et al., 2012).

4.6.1 Biological risk factors

4.6.1.1 Ageing

Alzheimer's disease is characterized as an ageing phenomenon. Indeed, increasing age is the most well-established risk factor for Alzheimer's disease, as the incidence of the disease almost doubles with every 5 years of age (Fratiglioni & Rocca, 2001). The strong association of Alzheimer's disease with the increasing age may also be explained as the cumulative effect of different risk and protective factors and their complex interactions over the lifespan (Xu et al., 2013). Indeed, most cases of Alzheimer's disease are developed after the age of 60 years. That type of disease is called late-onset Alzheimer's. However, less than 5% of the cases occur in people in ages between 30 and 60. That is called early-onset Alzheimer's and is known also as familial type Alzheimer's. Estimates show that Alzheimer's disease is the most common dementia diagnosis among the cases with early-onset dementia. The prevalence of early onset of dementia among the general population increases as the age increases (Vieira et al., 2013).

4.6.1.2 Sex susceptibility

Alzheimer's disease is gender related disease, as its prevalence is higher among women than among men. Two follow-up studies found that women are at higher risk of dementia and Alzheimer's disease after the age of 80 than men, whereas men have higher risk in ages younger than 80 years (Fratiglioni et al., 1997; Letenneur et al., 1999). The findings of a recent study also support the hypothesis that sex is associated with Alzheimer's morbidity, as women appear to be at higher risk of disease, especially in the older age (Qiu et al., 2007).

Almost two-thirds of Americans with Alzheimer's disease are women (Qiu et al., 2007). The explanation may be due to the fact that women live longer than men. Women, therefore, are more likely to develop the disease, which is age-related

condition (National Institute of Health [NIH], 2012). Moreover, women suffer from more severe symptoms and experience faster declination than men do (NIH, 2012; Roberts et al., 2012). They have higher prevalence of depression and anxiety, which increase the risk of Alzheimer's disease. Exercise protects against the disease and women exercise less than men (NIH, 2012). Finally, when spouses are caregivers for diseased husbands with Alzheimer's disease, they are experiencing high level of chronic stress and depression, which is increasing the risk for Alzheimer's disease. It is clear that these health effects may be influenced by other cultural and socioeconomic factors. Therefore, spouses with lower socioeconomic status may have lower health performance, or they may have the same life-style and habits like their husbands, thus they are exposed to the same risk factors for Alzheimer's disease (Schulz & Sherwood, 2008).

Last but not least, women health status is influenced by the changes that take place during the menopausal transition which are closely linked to an increased risk of cognitive decline and subsequent occurrence of dementia (Hathaway, 2012).

4.6.1.3 Racial Disparities

There are racial and ethnic differences in the causes, expression, and prevalence of various diseases (Burchard et al., 2003). Burchard et al. support that "the relative importance of bias, culture, socioeconomic status, access to care, and environmental and genetic influences on the development of disease is an empirical question that, in most cases, remains unanswered" (Burchard et al., 2003).

Indeed, the apolipoprotein (APOE) ε4 allele which is a genetic factor with strong association with Alzheimer's disease occurrence has different frequency among patients according to ethnicity and region (Farrer et al., 1997; Gerdes, Klausen, Sihm, & Faergeman, 1992) . Although it exists in all racial and ethnic groups, it is met at different frequencies, ranging from 9% in Japanese populations to 14% in white populations to 19% in black American populations (Burchard et al., 2003); with the highest frequencies met in Sudanese (29%) (Hallman et al., 1991), Dutch (30%) (Smit et al., 1988), and in Finnish (23 - 24%) populations (Hallman et al., 1991).

Interestingly, the expression of APOE ε4 allele varies according to the race and that may conceal genetic or environmental modifiers of this gene (Burchard et al., 2003; Farrer et al., 1997). Lindsay *et al.*, in a systematic review, reported that the APOE ε4 allele frequency in Caucasians and African Americans with Alzheimer's disease in the USA reached 36.7% and 33.2%, respectively. These levels are higher than those of Asiatic Mongoloids (Farrer et al., 1997). However, the findings of a recent study which compared two Chinese populations of different race argued that the lack of significant difference in APOE ε4 allele frequency may be due to the interactions of protective environmental, nutritional and life lifestyle factors or due to a gradual assimilation of these two populations (Del Parigi, Panza, Capurso, & Solfrizzi, 2006).

4.6.2 Genetic susceptibility and familial aggregation

Among the various etiological hypotheses for Alzheimer's disease, the genetic susceptibility hypothesis, which is related to APOE ε4 allele and the familial aggregation, has the strongest level of supporting evidence. Therefore, the genetic factors have the strongest causal relationship with the occurrence of Alzheimer's disease (Qiu et al., 2009). The APOE ε4 allele is the only susceptibility gene correlated to both early- and late-onset Alzheimer's disease. Increasing number of the APOE ε4 alleles, increases the risk of the disease, although this gene is neither necessary nor sufficient for the development of the disease. What is also interesting is that the risk of the disease decreases as the age increases. This gene contributes to the disease in 15% to 20% of cases only (Qiu, Kivipelto, AgueroTorres, Winblad, & Fratiglioni, 2004).

The genetic susceptibility hypothesis is related to the phenomenon of familial aggregation too, which manifests that the first-degree relatives of Alzheimer's patients have a higher lifetime risk of developing the disease than the general population or the relatives of non-demented subjects (Qiu et al., 2009). The familial aggregation causal relationship is not involving only the presence of the APOE ε4 allele, but also other genes susceptibility too (Huang, Qiu, von Strauss, Winblad, & Fratiglioni, 2004). Especially, the early-onset Alzheimer's disease is considered as the result of a mutation in one of the three genes: APP (Amyloid Precursor protein), PS1 (presenilin

1) or PS2 (presenilin 2) (Waldemar & Burns, 2009). Additionally, the phenomenon of familial aggregation may be attributed not only to genetic factors, but also to common environmental or life-style factors, or both (Green et al., 2002).

4.6.3 Risk factors related to vascular hypothesis

The studies on incident cases of Alzheimer's disease show that the disease is associated with cigarette smoking, especially in APOE ε4 allele non-carriers. Besides, research has found an interaction between smoking and the presence of the APOE ε4 allele (Aggarwal et al., 2006; Launer et al., 1999; van Duijn, Havekes, Van Broeckhoven, de Knijff, & Hofman, 1995) .

Alcohol use causes alcohol dementia. Furthermore, middle-aged heavy drinkers who are APOE ε4 allele carriers are 3-fold more likely to develop dementia and Alzheimer's disease. Heavy consumption of alcohol is associated with damages in the brain, whereas moderate alcohol consumption is related to brain atrophy and volume loss (Anttila et al., 2004).

Blood pressure and dementia are associated in a causal relationship more likely age-dependent (Qiu et al., 2007). The midlife hypertension is linked to increased risk of dementia and Alzheimer's disease, as hypertension is related either directly to the neurodegenerative process itself or indirectly causing brain atrophy. Surprisingly, for aged people low blood pressure is found to be predictive of dementia and Alzheimer's disease too (Qiu, von Strauss, Fastbom, Winblad, & Fratiglioni, 2003).

The ischemic heart disease and peripheral arterial disease are associated with increased risk of developing Alzheimer's disease (Newman et al., 2005). Other cardiovascular diseases such as heart failure, atrial fibrillation, and severe atherosclerosis are independently related to increased risk of Alzheimer's disease (Qiu et al., 2006). In addition, patients who have suffered from a stroke or clinically silent cerebral infarction are at increased risk of Alzheimer's disease (Honig et al., 2003; Vermeer et al., 2003). Neuropathological studies suggest that cerebrovascular lesions, atherosclerosis and neurodegenerative changes often coexist in the brain of

Alzheimer's patients (Esiri, Nagy, Smith, Barnetson, & Smith, 1999; Snowdon et al., 1997) .

Persons with diabetes mellitus are facing an increased risk of developing Alzheimer's disease as their cognitive systems may be affected by the disease in various ways (Arvanitakis, Wilson, Li, Aggarwal, & Bennett, 2006). Midlife diabetes or long duration diabetes are considered to be a determinant of Alzheimer's disease. The risk is higher when diabetes occurs in mid-life than in late life (Xu et al., 2009). Moreover, in very old people borderline or prediabetes or impaired glucose tolerance, are related to higher risk of the disease (Xu, Qiu, Winblad, & Fratiglioni, 2007).

The elevated cholesterol in mid-life is associated with an increased risk of Alzheimer's disease in late-life. Decreasing cholesterol after midlife is also considered as a biomarker of poorer cognitive status in late-life (Solomon et al., 2009; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005). In addition, the statins, which are cholesterol lowering drugs, may play a protective role on reducing β-amyloid production, and therefore sustaining the central nervous system against the risk of Alzheimer's disease (Qiu et al., 2009).

The association between body mass index (BMI) and dementia is lifespan-dependent. For middle-aged people a higher BMI is related to an increased risk of dementia in late life (Gustafson et al., 2012; Xu et al., 2011). However, there is also an association between an accelerated decline in BMI and the detection of Alzheimer's disease, approximately in the last 10 years before the onset of the disease (Johnson, Wilkins, & Morris, 2006).

A number of studies support the association of various nutritional elements with an increased risk of Alzheimer's disease such as: (i) Low levels of B12 and folate (Wang et al., 2001) (ii) Moderate intake of saturated fats (Morris et al., 2003), even more for APOE ε4 allele carriers (Kivipelto et al., 2008); (iii) fatty acids intake through various mechanisms such as atherosclerosis and inflammation (Scarmeas, Stern, Mayeux, & Luchsinger, 2006).

4.6.4 Psychosocial and psychological factors

The epidemiological research provides evidence that these factors may play a role in the onset andin the postponement of the disease and thereby affirms the opinion that Alzheimer's disease reflects the cumulative effect of different risk and protective factors over the lifespan (Xu et al., 2013).

Social isolation, poor social network or social disengagement and unsatisfactory contacts with relatives and friends in middle or late life are associated with an increased risk of dementia and Alzheimer's disease in older age (Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Fratiglioni, Wang, Ericsson, Maytan, & Winblad, 2000; Wang et al., 2009). In addition, history of major depression in a person's life span may be a risk factor for later development of Alzheimer's disease and the depressive symptoms may facilitate the conversion of mild cognitive impairment to Alzheimer's disease. Research findings showed that the neuronal plaques and neurofibrillary tangles which are the major hallmarks of Alzheimer's patients' brain are more pronounced in the brains of those with comorbid depression than in those without depression (Caraci, Copani, Nicoletti, & Drago, 2010).

4.6.5 Other factors

Lower education is linked to increased risk of dementia and Alzheimer's disease. The association between low education and dementia is probably not explained solely by the unhealthy lifestyles of the less educated people (Karp et al., 2004), but also by the fact that higher educated persons may have a greater cognitive reserve that can postpone the clinical manifestation of the disease. The unhealthy lifestyles may independently contribute to the depletion of this reserve or directly influence the underlying pathologic processes (Ngandu et al., 2007). Interestingly, although both education and socioeconomic status are strongly interconnected, well-educated

subjects with low socioeconomic status were not found at high risk. Early life factors may play a role in later health and cognitive status (Karp et al., 2004).

Recent studies have demonstrated a strong link between neurodegeneration and chronic inflammation. Inflammations are involved in the atherosclerotic process and thereby in dementia too (DeLegge & Smoke, 2008). Conversely, long-term use of non-steroidal anti-inflammatory drugs was associated with a reduced risk of Alzheimer's disease (Qiu et al., 2007). Herpes simplex virus – type1 (HSV-1) infection contributes to increased proteolysis of APP (Wozniak, Itzhaki, Shipley, & Dobson, 2007). A number of studies suggest that the presence of HSV-1 in the brain is considered to be a risk factor for Alzheimer's disease in elderly APOE ε4 allele carriers (Itzhaki & Wozniak, 2006).

When oestrogens are administrated in late life may increase the risk of dementia, but when they are used in midlife, they may have protective effect (Whitmer, Quesenberry, Zhou, & Yaffe, 2011). Head trauma has been suggested as a possible risk factor for Alzheimer's disease, but this association still remains controversial. Findings show a relevance to the severity of the injury and the disease i.e. there is a 4.5 fold increased risk for severe injuries (Plassman et al., 2000). Contrary, other findings show that a head injury may increase the risk of Alzheimer's disease only in APOE ε4 allele carriers (Mayeux et al., 1995).

Exposures to heavy metals, such as aluminium, have been found to be a risk factor for Alzheimer's disease. Thus, consumption of aluminium from drinking water may be another risk factor for the disease, whereas silica intake from drinking water may be a protective factor (Rondeau, Jacqmin-Gadda, Commenges, Helmer, & Dartigues, 2009). Also, occupational exposures to extremely low - frequency electromagnetic fields (ELF-EMF) has been related to an increased risk of dementia and Alzheimer's disease in a numerous studies (Garcia, Sisternas, & Hoyos, 2008).

Sleep-disordered breathing, characterized by recurrent arousals from sleep and intermittent hypoxemia, and disruption in sleep patterns are linked to poor cognition and dementia when they occur among older adults, especially in those at greater risk

such as patients with mild cognitive impairment or other neurodegenerative diseases (Bombois, Derambure, Pasquier, & Monaca, 2010; Yaffe et al., 2011).

4.6.6 Protective factors

There is scientific evidence that a number of factors may postpone the onset or prevent the occurrence of Alzheimer's disease. An active lifestyle operates as a protective factor for dementia by delaying the clinical onset of the disease, even if the disease almost exists (Paillard-Borg, Fratiglioni, Xu, Winblad, & Wang, 2012). Antihypertensive treatments influence positively the atherosclerotic process and improve the cerebral perfusion, thus provide neuroprotective effects (Qiu, Winblad, & Fratiglioni, 2005). The initiation of treatment in earlier ages (under 75) and longer duration of the treatment may have beneficial effect too (Haag, Hofman, Koudstaal, Breteler, & Stricker, 2009).

Strong adherence to any diet with high intake of fish, fruits and vegetables, and hence, sufficient quantities of anti-oxidants and polyunsaturated fatty acids may decrease the risk of Alzheimer's disease (Kalmijn et al., 1997; Scarmeas et al., 2006) . Similarly, sufficient intake of vitamins C, E, B6, B12, and folate may reduce the risk of the disease (Luchsinger & Mayeux, 2004; Morris et al., 2002). Physical exercise may be either a retarding or even a protective factor for the occurrence of Alzheimer's disease (de Bruijn et al., 2013), as it is promoting brain plasticity and affecting positively cognitive functions maintenance (Qiu et al., 2009). Especially for persons with genetic susceptibility, physical exercise in the middle age may reduce the risk of the disease (Rovio et al., 2005).

Moreover, the participation in cognitively stimulating activities and various types of mentally demanding leisure, social and cultural activities - such as reading, knitting, gardening, dancing, playing board games and musical instruments, may have protective effect especially in women (Crowe, Andel, Pedersen, Johansson, & Gatz, 2003; Wilson et al., 2002). Likewise, greater mental activity and work complexity with people and data during the working life is linked to better memory maintenance (Valenzuela, Sachdev, Wen, Chen, & Brodaty, 2008).

4.7 Pharmacologic management of Alzheimer's disease

The large number of the patients globally and the continuous increasing number of new cases in both developed and developing countries which is strictly connected to the rise of longevity, has made the management of Alzheimer's disease an issue of high priority for the national governments all around the world and urges for the development of more effective treatments (Reitz et al., 2011).

The current pharmacological research is focused on the development of medicines that may halt or reverse the progression with the efforts directed to exploration of new therapeutic approaches based on the role of the several biomarkers related to Alzheimer's disease such as the abnormal deposits of amyloid and tau proteins and the molecular and biological pathways of the disease (Crews & Masliah, 2010).

The drugs that are approved and widely prescribed by physicians during the last decades are the cholinesterase inhibitors (AChEIs) and the NMDA (N-Methyl-D-aspartate) receptor antagonists (memantine). Both drug categories increase the amount of chemicals called neurotransmitters, in the brain, which are important to memory function and provide symptomatic relief and a temporary deceleration of the symptoms of cognitive decline for a period, but they don't show the same positive effects in all patients (Vernon, Goldberg, Dash, & Muralimohan, 2007).

Even the presence of numerous of adverse events and the inability to have a reversible effect on the symptoms of the disease, AChEIs and memantine are the most commonly prescribed drugs for the confrontation of Alzheimer's disease. Therefore the current medical practice focused on the optimization of their use, while expecting for updates from the global research, given that the discovery of a new drug is a long-term process taking approximately 10-15 years from the moment of discovery until its approval and launch in the markets.

The idea of combining the two categories of the aforementioned drugs is based on their complementary action targeted to two different systems that are involved in the occurrence of Alzheimer's disease: the cholinergic and glutamatergic systems.

The cholinergic hypothesis

The cholinergic hypothesis for Alzheimer's disease supports that the cognitive deterioration, which occurs gradually with the disease's development, is partly associated with progressive loss of cholinergic neurons and decreasing acetylcholine (ACh) levels in the brain (Farlow & Cummings, 2007; Francis et al., 1999).

The cholinergic hypothesis of Alzheimer's disease was based on the presynaptic deficits found in the brains of patients with Alzheimer's disease and tried to explain the role of ACh in human behaviour deterioration when the disease had occurred. The cholinergic dysfunction was not associated directly with the cognitive impairment, but rather indirectly, by inferring with attentional processing (Francis, Palmer, Snape & Wilcock, 1999).

Although initially the cholinergic research was focused on inhibition of acetylcholinesterase (AChE), later was reported that butyrylcholinesterase (BuChE) also plays an important role in the degradation of ACh in normal and Alzheimer's patients brains, constituting both AChE and BuChE inhibition an important rational therapeutic goal in the treatment of the disease (Mesulam, Guillozet, Shaw, & Quinn, 2002).

The glutamatergic hypothesis

Glutamate is the most widely distributed excitatory amino acid neurotransmitter in the brain under normal conditions. Among other functions, it plays an important role in the regulation of the NMDA receptor function (Danysz & Parsons, 2003).

There is increasing evidence of the involvement of glutamate-mediated neurotoxicity in the pathogenesis of Alzheimer's disease. The glutamatergic hypothesis for Alzheimer's disease states that pathogenesis of the disease is related to an overactivation of NMDA receptors, which is causing excitotoxicity and neurodegeneration and finally cells death. These are the underlying causes for the Alzheimer's patients' learning and memory deficits that occur during the development

of the disease (Danysz & Parsons, 2003). Thus, achieving the optimal balance of glutamate stimulation without excitotoxicity seems to be an important goal for achieving the optimal treatment of patients with Alzheimer's disease (Geerts & Grossberg, 2006). Memantine was developed to response to this need, as it is an uncompetitive NMDA receptor antagonists that may improve the learning and memory of patients with Alzheimer's disease (Danysz & Parsons, 2003; Geerts & Grossberg, 2006) .

4.7.1 Memantine

Memantine was found in 1968 and it is the first in a novel class of Alzheimer's drugs which act on the glutamatergic system by blocking NMDA glutamate receptors. It is marketed under the brands Axura and Akatinol by Merz, Namenda by Forest, Ebixa and Abixa by Lundbeck (Alzheimer's Disease Management Council [ADMC], 2004). The starting dose for memantine is recommended to be 5 mg once daily increasing by 5 mg increments up to 20 mg/day (10 mg twice daily) (ADMC, 2004).

Memantine has recently received a limited recommendation by the UK's National Institute for Health and Clinical Excellence (NICE), as it is advised to be used as an option for managing Alzheimer's disease for patients in moderate stage who are intolerant or have a contraindication to AChEI's, or for patients in severe stage (National Institute for Health and Clinical Excellence [NICE], 2011). In Australia, the Pharmaceutical Benefits Advisory Committee (PBAC) has not approved the drug as non-cost-effective. Thus, Namenda is not available in Australia (Vernon et al., 2007).

Three clinical studies (Reisberg et al., 2003; Tariot et al., 2004; Winblad & Poritis, 1999), on the efficacy of memantine showed that the drug is effective over a range of outcome measures in patients with moderate-to-severe Alzheimer's disease. A 4-months observational study in moderate-to-severe patients states that memantine had beneficial effects on cognition, activities of daily living and global function in comparison to pre-treatment state of the patients and independently from their pre-treatment status (Rainer et al., 2011).

In the Cochrane systematic review for memantine, which included double-blind, parallel group, placebo-controlled, randomized trials of the drug in a dose of 20 mg/day compared to placebo, in patients with moderate-to-severe Alzheimer's, showed small beneficial effect in two out of three 28 weeks clinical trials .The same data when pooled, showed a beneficial effect in six months on cognition, daily life activities and behaviour – especially less agitation symptoms, which are common in late Alzheimer's disease stage (McShane, Areosa Sastre, & Minakaran, 2006).

In the same review the pooled data from three unpublished studies for mild-to-moderate Alzheimer's disease patients showed marginal beneficial effect at 28 weeks on cognition which was rather intangible clinically and no effect on behaviour, and activities of daily living. The drug was found to be well tolerated and the incidence of adverse effects was low. The authors concluded that the data justified the prescription of memantine to patients with moderate-to-severe Alzheimer's and they opposed the NICE's committee opinion that the evidence for the clinical effectiveness of memantine is currently insufficient (McShane et al., 2006).

In contrast, Hermann et al. 2011, stated that memantine has modest benefits in cognition, function, global and behavioral measures and has presented little potential for drug-to-drug interactions, thus the authors suggested its use as a therapeutic option for the treatment of moderate-to-severe Alzheimer's as a monotherapy or in combination therapy with an AChEI (Herrmann, Li, & Lanctot, 2011).

4.7.2 AChEIs

There is evidence that the AChEIs (donepezil, rivastigmine and galantamine) have shown consistent efficacy on cognitive function, functional impairment, and cognitive stimulation across the spectrum of mild-to-moderate Alzheimer's disease, and showed improvement in non-cognitive features of the disease such as neuropsychiatric symptoms, and caregiver burden (Alzheimer's Disease International, 2011).

The first step toward the best possible long-term management of Alzheimer's disease is the early diagnosis. Furthermore, the early initiation of a treatment with AChEIs

may stabilize or even reduce the rate of symptomatic cognitive and functional decline (Farlow & Cummings, 2007; Rountree et al., 2009). The way each AChEI acts is slightly differentiated. When using donepezil, selective inhibition of AChE occurs, whereas rivastigmine inhibits both AChE and BuChE, and galantamine inhibits selectively AChE and simultaneously modulates nicotinic AChR (ACh receptors) (Farlow & Cummings, 2007).

The best choice among the three AChEIs for an Alzheimer's patient is highly individual and mostly depended on adverse events derived from their use (Alzheimer's Association, 2012). The applicable dosages of the AChEI's vary. Patients are suggested to start with a lower dose increasing gradually, in order to reach maximum effectiveness. However, a number of patients cannot take the highest dose due to the adverse events of the drug (Lakey et al., 2012).

NICE recommends using donepezil, rivastigmine and galantamine in people with mild-to-moderate Alzheimer's disease (NICE, 2011). Similarly, the US Food and Drug Administration (FDA) has approved the use of each of the three AChEIs for the different stage of Alzheimer's disease. Donepezil may be prescribed for patients in mild-to-severe stage, whereas galantamine and rivastigmine may be prescribed only for patients in mild-to-moderate stage (Lakey et al., 2012). Recent studies conducted with the support of Alzheimer's Society showed that patients in the more severe stage of Alzheimer's disease benefit more from AChEIs in motivation, daily function, cognition, but not in agitation or aggression, and additionally in some cases those benefits lasted only 6-12 months (Alzheimer's Association, 2012). Lastly, in a clinical trial when donepezil was compared to rivastigmine in patients with moderate-to-severe Alzheimer's disease, it showed no significant difference between the two treatments, but donepezil was considered more favourable because the patients on the donepezil treatment arm suffered less adverse events than the patients on the rivastigmine treatment arm (Bullock et al., 2005). Similarly, in a pilot study which compared the sleep of patients with mild-to-moderate Alzheimer's disease who were on galantamine and donepezil therapy, the findings were slightly in favour of galantamine, although both drugs did not affect negatively the sleep of patients (Ancoli-Israel, Amatniek, Ascher, Sadik, & Ramaswamy, 2005).

4.7.2.1. Donepezil

Donepezil is a reversible, specific, AChE inhibitor (NICE, 2006 [amended 2009]). It is marketed under the brands Aricept and Aricept ODT (MedicineNet.com, 2013). The oral therapy with donepezil should initiate with a dose of 5 mg/day once daily, and after 4-6 weeks, a dose of 10 mg/day (maximum dose) can be continued if it is tolerated. In general, the minimum therapeutic dose for donepezil is 5 mg/day (ADMC, 2004).

A 2 years clinical study showed that donepezil provided small improvements in cognition and activities of daily living in patients with mild-to-moderate Alzheimer's disease and was well tolerated (Courtney et al., 2004). Another clinical study supported that donepezil demonstrated not only a significant improvement in the symptoms of patients with moderate-to-severe Alzheimer's disease, but also these beneficial effects were associated with less caregiving time and lower levels of caregiver stress (Feldman et al., 2003). Furthermore, in a post-hoc analysis of a double-blind randomized clinical trial of 24 weeks for moderate-to-severe Alzheimer's disease patients, donepezil demonstrated significant efficacy, especially in the subgroup of patients in the more severe stage of the disease and it was found to be safe and well-tolerated (Feldman et al., 2005). Further, in an open label study donepezil showed significant reduction in delusions, irritability and disinhibition in hospitalized patients for a period of 24 weeks (Barak, Bodner, Zemishlani, Mirecki, & Aizenberg, 2001).

In a Cochrane review on donepezil, the meta-analysis showed that donepezil improved cognition significantly regardless of dosage and disease stage. Many adverse events were recorded, but very few patients left a trial as a direct result of the intervention. There was also some dose dependent improvement in global clinical state. Benefits of treatment were also seen in measures of activities of daily living and behaviour, but no effect on the quality of life. The results were similar for all stages of Alzheimer's disease. (Birks & Richard, 2006; (Birks & Richard, 2006; Birks, Grimley Evans, Iakovidou, Tsolaki, & Holt, 2009).

4.7.2.2 Rivastigmine

Rivastigmine is an AChE and BuChE inhibitor, which works by increasing the concentration of acetylcholine at sites of neurotransmission (NICE, 2006 [amended 2009]). It is marketed under the brand Exelon (Alzheimer's Association, 2012).

The recommended oral therapy starts twice daily at 3 mg/day, with increasing gradually up to 6 mg/day, 9 mg/day, and 12 mg/day at maximum, with each dose increase starting after 4 weeks of well-tolerated therapy at each previous stage (ADMC, 2004). The rivastigmine transdermal patch (9.5 mg/24 h) has shown similar efficacy to the rivastigmine capsule (12 mg/day), but with one-third of the incidence of gastrointestinal side effects (Winblad et al., 2007).

With regard to rivastigmine formulation, in a post hoc analysis of three trials, it was found that the rivastigmine transdermal patch was better tolerated than rivastigmine capsules in patients that switched from donepezil tablets and had less gastrointestinal adverse events (Sadowsky, Farlow, Meng, & Olin, 2010). The results of the a cohort study, which investigated the prevalence of attention deficits, anxiety, apathy and agitation symptoms in both community-dwelling and institutionalized Alzheimer's patients, showed that the rivastigmine treated patients experienced improvement in these symptoms together with improvements in caregiver's burden, with the best efficacy marked among the patients in mild-to moderate stage. The authors argue that the effectiveness of rivastigmine may be attributed to its action mechanism, which is different from the other AChEIs, due to BuChE inhibition which may be more important as the disease progresses (Gauthier, Juby, Rehel, & Schecter, 2007).

Another analysis of three large clinical trials on premature discontinuation in rivastigmine-treated patients showed that rivastigmine treated patients had less deterioration in cognitive function than the patients in the placebo therapy after the withdrawal (Farlow, Potkin, Koumaras, Veach, & Mirski, 2003). This explains that the deceleration of cognition worsening in those patients might suggest an effect on disease progression (Farlow et al., 2003).

In a Cochrane review on rivastigmine, the meta-analysis showed that high-dose rivastigmine (6 to 12 mg daily) had statistically significant effect in patients with mild-to-moderate Alzheimer's disease in terms of cognition. Significant benefits were also found in the activities of daily living.

At lower doses (4 mg daily or lower) rivastigmine treatments showed differences in the same direction, but those differences were statistically significant only for cognition. The adverse effects which may be attributed to the pharmacokinetics of the oral drug, were found decreasing either with smaller and more frequent daily doses of capsules or with the use of the lower dose smaller transdermal patch (J. Birks et al., 2009).

4.7.2.3 Galantamine

Galantamine is a selective, competitive and reversible inhibitor of AChE and it is marketed under the brands Razadyne, Razadyne ER, Reminyl (Alzheimer's Association, 2012). The oral therapy is recommended to initiate twice daily at 8 mg/day increasing with gradual increments to 16 mg/day and 24 mg/day at maximum after 4 weeks of well-tolerated therapy in each previous dose regimen. The minimum therapeutic dose of the drug is 16 mg/day. Especially for the drug Razadyne ER the administration is different and it is taken once daily in the morning (ADMC, 2004).

Several lines of preclinical evidence indicated that galantamine has cognitive-enhancing effects (Coyle & Kershaw, 2001). Also in a clinical study which conducted by means of positron emission tomography (PET scan), the effect of galantamine treatment versus placebo on cortical AChE activity and nicotinic receptor binding in 18 Alzheimer's patients in mild stage were investigated, and the authors argue that the patients in galantamine treatment showed better improvement or stabilization of the disease symptoms compared to those in placebo (Kadir et al., 2008).

Similarly, the results of a 12 weeks clinical trial, investigating the effects of a flexible dose of galantamine versus placebo in mild-to-moderate Alzheimer's patients, showed statistically significant benefits for the galantamine-treated group. The tolerability of

the drug was good and the adverse effects raised when the dose regimen increased (Rockwood, Mintzer, Truyen, Wessel, & Wilkinson, 2001).

A secondary analysis of data from a 21-weeks randomized clinical trial (Tariot et al., 2000) showed that the effect of high-dose galantamine (16-24 mg/day) treatment was associated with the reduction in behavioural disturbances and the improvement in existing behavioural problems as well as with significant reduction in caregiver distress (Cummings, Schneider, Tariot, Kershaw, & Yuan, 2004).

In a Cochrane review on galantamine, the meta-analysis showed that the galantamine treatment is efficacious and its adverse effects are similar to the other AChEIs (Loy & Schneider, 2006). Withdrawals due to adverse events increase with increasing in galantamine dose. The greater proportion of patients had significant improvement or stabilization in cognitive and global function for at least 6 months and for doses of 16 to 36 mg/day. However, the findings concern mostly the patients in earlier stages of Alzheimer's disease (Loy & Schneider, 2006).

5 Methods

5.1 Search strategy

This study is a systematic review and meta-analysis. We searched PubMed, Embase and Cochrane library up to September 2012. Articles concerning the efficacy, safety and tolerability of the combination treatment for Alzheimer's disease with memantine and AChEIs were identified up to September 2012. During the process of the first screening all irrelevant articles and duplications were discarded by each author separately. We updated our search later until December 2013.

The databases were searched for the terms "cholinesterase inhibitor" OR "donepezil" OR "rivastigmine" OR "galantamine" AND "Alzheimer" AND "memantine". Our search was limited to clinical trials. The references of selected articles were also hand-searched and selected. Additionally, we searched the clinical trials registries of Lundbeck, Forest and Merz.

Inclusion criteria were: (i) randomized controlled trials; (ii) results reported in English; (iii) trials performed on humans; (iv) probable Alzheimer's disease; (v) comparing the effects of treatment with a combination of an AChEI with memantine (experimental group) with a AChEI (control group). Studies that included other dementia patients together with Alzheimer's patients were excluded from the review.

5.2 Outcomes

The outcomes were (1) changes in measures of cognitive function, (2) activities of daily living function, (3) clinical global function, and (4) behavioural changes. Moreover, the incidence of adverse events for the intervention and control group was studied. We defined adverse effects as all unwanted, troublesome or harmful effects resulted by the therapy.

5.3 Quality assessment

The quality of the included studies was assessed using the Jadad scale (Higgins & Green, 2009 [updated March 2011]). We assessed three domains; randomization, blinding, and patients attrition (the number of patients excluded or lost to follow-up).

5.4 Data extraction

The extracted data were demographic characteristics, the stage of the disease at baseline, and the treatments used for the intervention and control group. The efficacy was assessed on the basis of the changes in patients' outcome measures from their baseline performance and the safety and tolerability were assessed on the basis of the quantitative information related to the occurrence of adverse events. For dichotomous variables, for example the adverse effects, the number of patients experiencing a particular outcome was determined.

5.5 Meta-analysis

Quality of included trials was assessed using the Jadad Scale (Higgins & Green, 2009 [updated March 2011]). Statistical analysis was performed using a random-effects meta-analysis (Borenstein, Hedges, Higgins & Rothstein, 2009). Heterogeneity across studies was assessed by I^2 statistic (Higgins & Thompson, 2002). The I-squared statistic shows the total variation across studies, which is not due to chance. I-squared statistic less than 25% indicates small inconsistency and more than 50% indicates large inconsistency (Higgins & Thompson, 2002). Subgroup analyses were performed for double-blinded and open label trials. Publication bias was assessed by funnel plot and Egger's test (Higgins & Green, 2009 [updated March 2011]). Statistical significance for publication bias was based on a *P* value <0.10 (Borenstein et al., 2009).

6 Results

6.1 Search strategy and selection of studies

Initially, 199 articles were identified in August 2012 and their titles and abstracts were scrutinized. The research strategy yielded 22 relevant studies (Figure 1). Four open-label clinical trials (Dantoine et al., 2006; Olin et al., 2010; Riepe et al., 2007; Shua-Haim et al., 2008) which had only one treatment arm were excluded from meta-analysis. Moreover, three studies published in local languages and eight duplicates were excluded from the review.

Figure 1: Flow chart of the search strategy and selection of studies

6.2 Characteristics of included studies

Finally, five double-blinded randomized controlled trials (RCTs) and two open-label RCTs were included in the meta-analysis (Table 2). Of seven included trials, five were double-blinded RCTs: (Grossberg et al., 2013; Howard et al., 2012; Lundbeck, 2010; Porsteinsson et al., 2008; Tariot et al., 2004) and two were open-label RCTs: (Choi et al., 2011; Farlow et al., 2010),

Of the five double-blinded RTCs, three trials studied patients with moderate-to-severe Alzheimer's disease, one trial studied patients with moderate and one studied patients with mild-to-moderate disease (Table 2). Moreover, two open-label RCTs included patients in mild-to-moderate stage of Alzheimer's disease.

The quality of the included studies was assessed using Jadad scale (Table 2). All five double-blinded RTCs were good quality trials and two open-label RCTs were low quality trials.

Specific characteristics of the seven studies included in the meta-analysis were presented in Table 3. Two double-blinded RCTs (Grossberg et al., 2013; Porsteinsson et al., 2008), have administered treatments with any of the three AChEIs, whereas two other double-blinded RCTs (Howard et al., 2012; Tariot et al., 2004) administered only donepezil in oral formula. Lastly, one double-blinded RCT (Lundbeck, 2010) made no reference to the AChEIs treatment. Furthermore, the two open-label RCTs performed treatments only rivastigmine in transdermal patch formula.

Table 2: Quality assessment of included studies using the Jadad scale

First author & year of publication	Disease severity	Main results	Bias assessment using Jadad scale			
			Randomization	Blinding	Attrition	Total score
Double-blinded RTCs						
Tariot., 2004	Moderate-to-severe	Statistically significant difference in favour of combination therapy for cognition and function	Appropriate/2	Appropriate/2	Reported/1	5
Posteinsson, 2008	Mild-to-moderate	No statistically significant difference between groups	Appropriate/2	Appropriate/2	Reported/1	5
Lundbeck, 2010	Moderate	The primary analysis showed no statistically significant differences between the memantine and placebo groups in total brain atrophy rates (as assessed using BBSI).	Method of randomization not reported/1	Blinding of patients or caregiver not reported/1	Reported/1	3
Howard, 2012	Moderate-to-severe	No statistically significant difference in favour of the combined therapy than single drug therapy either with donepezil or memantine.	Appropriate/2	Appropriate/2	Reported/1	5
Grossberg, 2013	Moderate-to-severe	Statistically significant difference in favour of combination therapy patients than the single drug therapy with an AChEI	Appropriate/2	Appropriate/2	Reported/1	5
Open-label RCTs						
Farlow, 2010	Mild-to-moderate	No significant difference in tolerability, cognition, global function in favour of the combination therapy.	Method of randomization not reported/1	No blinding/0	Reported/1	2
Choi, 2011	Mild-to-moderate	The combination therapy was safe and well-tolerated. No significant difference in cognition, global function and behaviour in favour of the combination therapy.	Method of randomization not reported/1	No blinding/0	Reported/1	2

Table 3: Characteristics of included studies

Authors & year of publication	Treatment arm	Sample size n	Age, mean (SD), years	Females, %	Race white, %	Duration of intervention (in weeks)	Completion rate, %	Stable dosing regimen of AChEI mg (SD)	Dose of memantine during the intervention mg (SD) - dosing scheme
Double-blinded RCTs									
Tariot 2004	Placebo	201	75.5 (8.7)	67	92.5		74.6	Donepezil 9.49 (1.88)	5mg/day up-titrated weekly to 20mg - twice/day
	Memantine	203	75.5 (8.4)	63	90	24	85.1	Donepezil 9.25 (1.79)	
Porsteinsson 2008	Placebo	216	76.0 (8.4)	50.5	95		88.4	Donepezil 8.9 (2.1), Rivastgmine 10.0 (2.6), Galantamine 19.4 (5.2)	5mg/day up-titrated weekly to 20mg - twice/day
	Memantine	217	74.9 (7.6)	53.9	92	24	89.4	Donepezil 9.5 (1.5), Rivastgmine 9.2 (2.8), Galantamine 19.7 (4.6)	
Lundbeck 2010	Placebo	144		52			77.4	NR	20mg - twice/day (weekly titration not mentioned)
	Memantine	134	74	62	100	52	79.2	NR	
Howard 2012	Continue donepezil & Placebo memantine	76	77.2 (7.5)	70	95		74	Donepezil 10 mg/day	5mg/day up-titrated weekly to 20mg - twice/day
	Continue donepezil & active memantine	73	77.5 (9.0)	67	92	52	79.5	Donepezil 10 mg/day	
Grossberg 2013	Placebo	335	76.8 (7.8)	72.5	93		81.2	Donepezil 7.8 (2.6), Rivastgmine 6.8 (2.9), Galantamine 13.5 (5.4)	7mg/day, up-titrated weekly to 28mg/day - once/day - mean 17.00
	Memantine ER*	342	76.2 (8.4)	71.6	95	24	79.8	Donepezil 8.0 (2.8), Rivastgmine 6.8 (2.6), Galantamine 13.5 (5.7)	
Open-label RCTs									
Farlow 2010 FF*	Rivastigmine patch	126	77.3 (7.92)	58.7	84.1	25	75.4	Rivastigmine transdermal patch 4.6mg/day	Not reported
	Rivastigmine* plus memantine	135	77.2 (8.18)	57	91.1	25	75	Rivastigmine transdermal patch 4.6mg/day	
Choi 2011	Rivastigmine patch	84	74.7 (7.7)	83.3	0	16	83.3	Rivastigmine 10cm3 patch/day	20mg/day
	Rivastigmine* plus memantine	88	75.0 (7.3)	75	0	16	87.5	Rivastigmine 10cm3 patch/day	

6.3 Outcome assessment tools

The performed efficacy measure scales were different among the trials. Certain measure scales were primary efficacy tools for some trials, whereas they were secondary efficacy tools for some other trials. Especially, in the included open-label RCTs the efficacy assessment was a secondary outcome measure, while primary aim of these trials were safety and tolerability control.

The outcomes of the studies were assessed using the following assessment tools; the Mini Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975), the Clinician's Interview-Based Impression of Change plus caregiver's input (CIBIC-plus) (Schneider et al., 1997), the Severe Impairment Battery (SIB) (Panisset, Roudier, Saxton, & Boller, 1994), the Alzheimer's Disease Cooperative Study Activities of Daily Living (ADCS-ADL) scale (19- and 23-item) (Galasko et al., 1997), the Bristol Activities of daily Living Scale (BADLS) (Bucks, Ashworth, Wilcock & Siegfried, 1996) and the Neuropsychiatric Inventory (NPI) (Cummings et al., 1994). Especially, when patients in more severe stage were included in the trial, the 19 items version of the ADCS-ADL scale (Galasko et al., 1997) was used, while for patients in milder stage the 23 items version was used (Table 4).

Table 4: Common assessment tools used in the evaluation of pharmacotherapy for
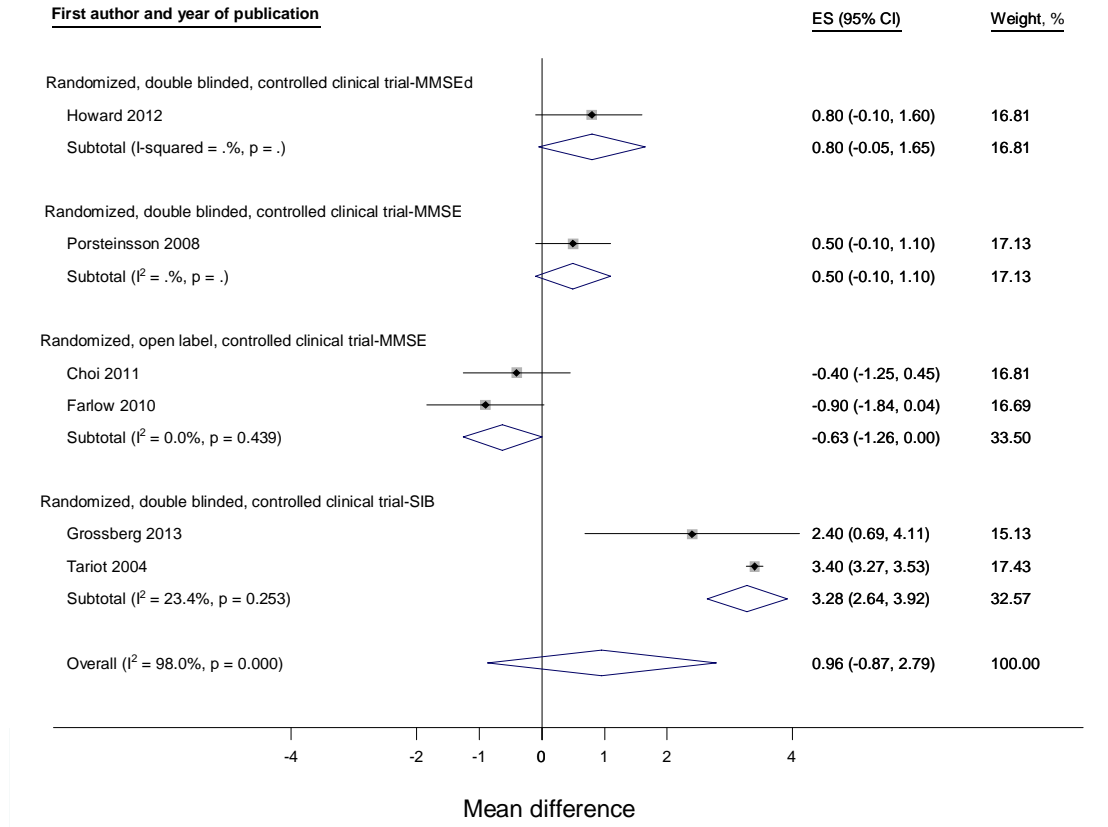
Alzheimer's disease

Scale	Domain	Score Range		Indication of the	Interviewee
		Low	High	higher score	
Mini-Mental State Exam (MMSE) (Folstein et al., 1975)	Cognition	0	30	Better cognition	Patient
Severe Impairment Battery (SIB) (Panisset et al., 1994)	Cognition	0	100	Better cognition	Patient
Alzheimer's Disease Cooperative Study—Activities of Daily Living (ADCS-ADL) (Galasko et al., 1997)	Function/activities of daily living	0	78	Better ADL performance	Caregiver
Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) (Schneider et al., 1997)	Global change	1	7	Global worsening	Patient, Caregiver
Neuropsychiatric Inventory (NPI) (Cummings et al., 1994)	Neuropsychiatric symptoms – behavioral change	0	144	Greater disturbance	Caregiver
Bristol Activities of Daily Living Scale (BADLS) (Bucks et al., 1996)	Function	0	60	Poorer functioning	Patient

6.4 Cognitive function outcome

Six studies were included in the meta-analysis of cognitive function: four double-blinded RCTs and two open-label RCTs (Figure 2). The heterogeneity across the studies was high (I^2 = 98%). Among the double-blinded RCTs one study assessed the cognitive function using MMSE (Folstein et al., 1975), another using the standardized MMSE (Molloy & Standish, 1997) and two other studies using SIB (Panisset et al., 1994). In the two open-label RCTs the cognitive function was assessed using MMSE (Folstein et al., 1975), but the study conducted on Korean population (Choi et al., 2011) used the Korean version of the scale (Kim et al., 2010). The pooled estimate of six trials showed modest beneficial effect for the combination therapy over the monotherapy (Raw mean difference 0.96, 95% CI -0.87 to 2.79). The estimate was not, however, statistically significant.

Interestingly, the two double-blinded RCTs which included moderate-to-severe patients and used the SIB scale (Panisset et al., 1994) (the most appropriate for the cognitive assessment of moderate-to-severe patients) showed significant effects for the combination therapy compared to the monotherapy (Raw mean difference 3.28, 95% CI 2.64-3.92), whereas the studies that included mild-to moderate patients showed no benefit for the combination therapy group over the monotherapy group.

Figure 2. A meta-analysis of six trials on cognitive outcome (mean difference) in the intervention group compared with the control group.

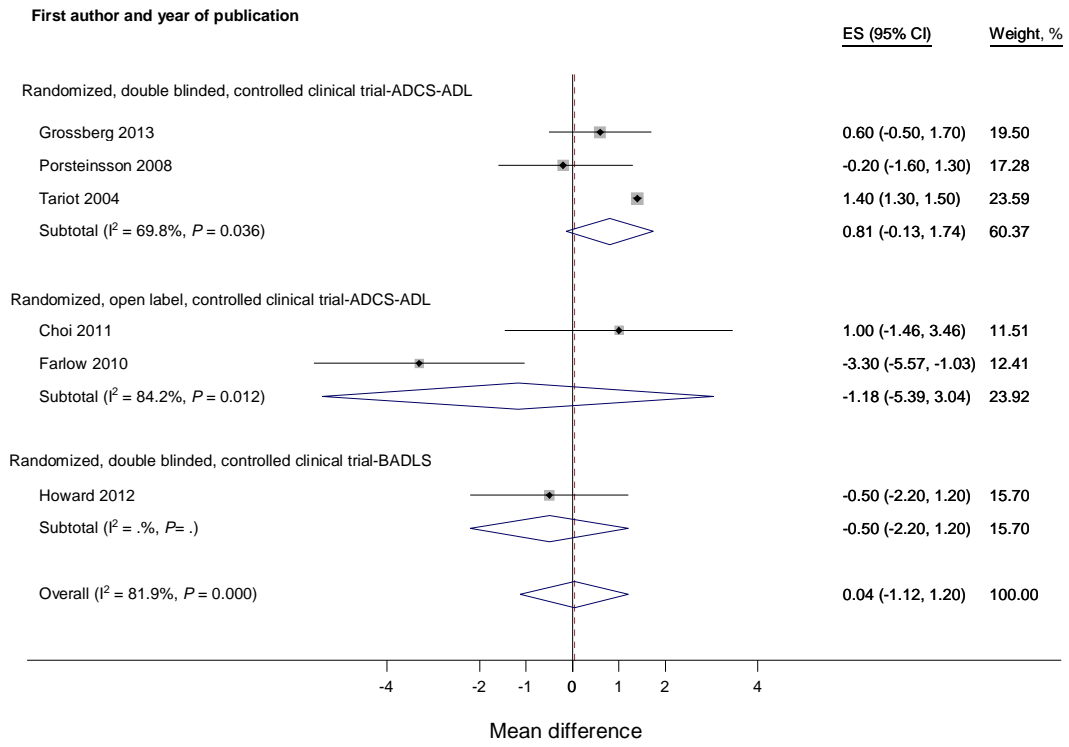| First author and year of publication	ES (95% CI)	Weight, %
Randomized, double blinded, controlled clinical trial-MMSEd		
Howard 2012	0.80 (-0.10, 1.60)	16.81
Subtotal (I-squared = .%, p = .)	0.80 (-0.05, 1.65)	16.81
Randomized, double blinded, controlled clinical trial-MMSE		
Porsteinsson 2008	0.50 (-0.10, 1.10)	17.13
Subtotal (I^2 = .%, p = .)	0.50 (-0.10, 1.10)	17.13
Randomized, open label, controlled clinical trial-MMSE		
Choi 2011	-0.40 (-1.25, 0.45)	16.81
Farlow 2010	-0.90 (-1.84, 0.04)	16.69
Subtotal (I^2 = 0.0%, p = 0.439)	-0.63 (-1.26, 0.00)	33.50
Randomized, double blinded, controlled clinical trial-SIB		
Grossberg 2013	2.40 (0.69, 4.11)	15.13
Tariot 2004	3.40 (3.27, 3.53)	17.43
Subtotal (I^2 = 23.4%, p = 0.253)	3.28 (2.64, 3.92)	32.57
Overall (I^2 = 98.0%, p = 0.000)	0.96 (-0.87, 2.79)	100.00

Mean difference

6.5 Activities of daily living outcome

Six studies were included in the meta-analysis of cognitive function: four double-blinded RCTs and two open-label RCTs (Figure 3). The heterogeneity across the studies was found to be high ($I^2 = 81.9\%$). Five of the studies assessed the activities of daily living outcome using ADCS-ADL measure scale (Galasko et al., 1997), while one double-blinded RCT with moderate-to-severe patients used BADLS (Bucks et al., 1996). The ADCS-ADL (Galasko et al., 1997) scale of 19 items was used in two studies with moderate-to-severe patients. The double-blinded RCT with mild-to-moderate patients used the version of 23 items and the two open-label RCTs did not clarify the version of the measurement scale.

The pooled estimate of six trials showed no difference between the combination therapy and the monotherapy (Raw mean difference 0.04, 95% CI -1.12 to 1.20). A meta-analysis of three double-blinded RCTs with a range of mild-to-severe patients showed modest non-significant beneficial effect for the combination therapy compared with the monotherapy (Raw mean difference 0.81, 95% CI -0.13 to 1.74).
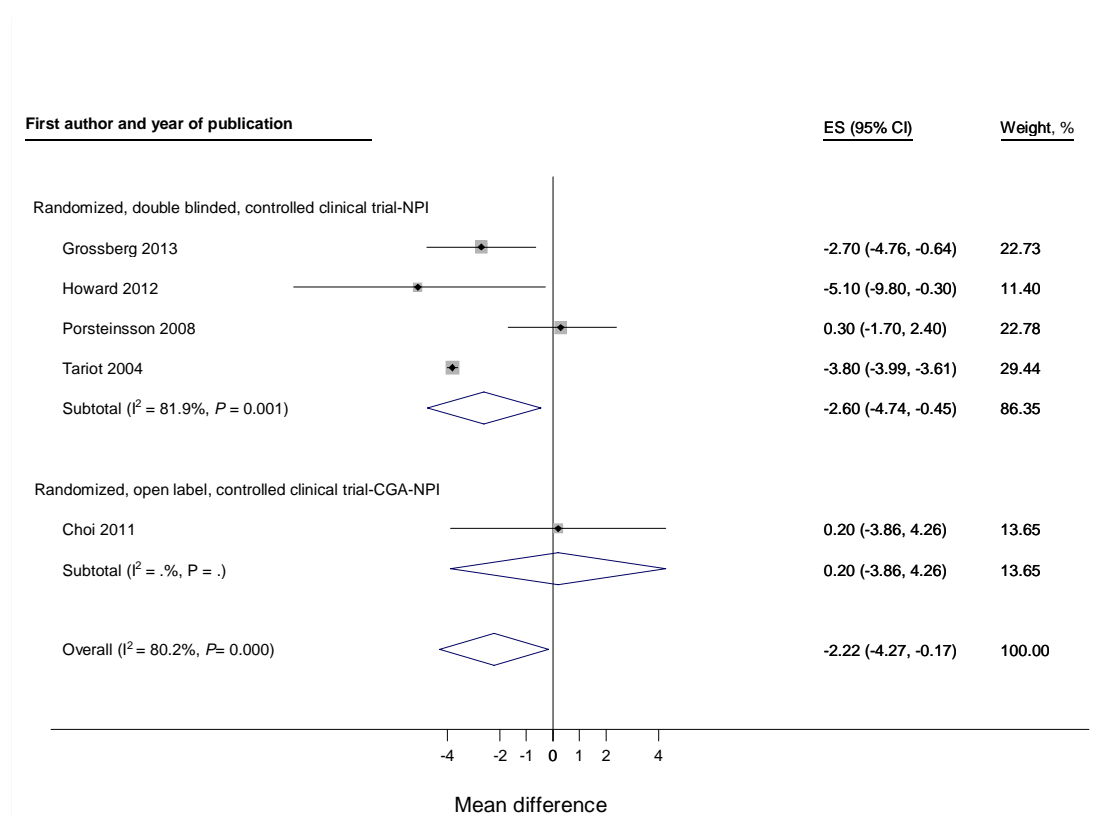
Figure 3. A meta-analysis of six trials on the activities of daily living outcome in the intervention group compared with the control group.

6.6 Behavioural outcome

Five studies were included in the meta-analysis of behavioural change: four double-blinded RCTs and one open-label RCT (Figure 4). The studies were heterogeneous (I^2 = 80.2%). All the double-blinded RCTs estimated the behavioural outcome using NPI (Cummings et al., 1994), whereas the open-label RCT used the caregivers assessed scale CGA-NPI (Kang et al., 2004). The pooled estimate of five trials showed significant superiority of the combination therapy over the monotherapy (Raw mean difference -2.22, 95% CI -4.27 to -0.17). Only patients with moderate-to-severe stage benefited from the combination therapy, but not those with mild-to-moderate stage.

Figure 4. A meta-analysis of five trials on the activities of behavioural outcome in the intervention group compared with the control group
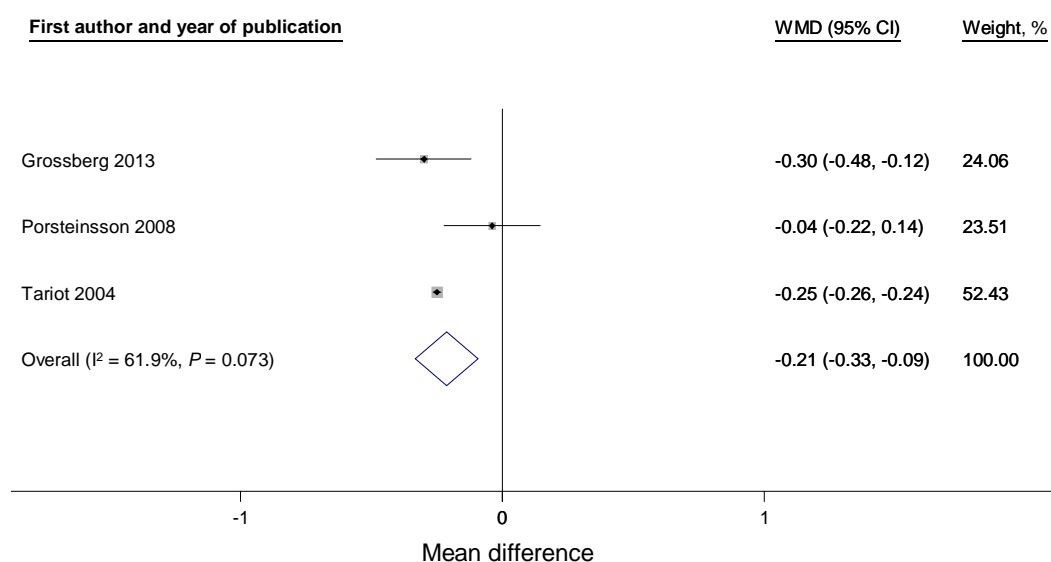
6.7 Global function outcome

Three double-blinded randomized control studies on global function were included in the meta-analysis (Figure 5). All three studies assessed the global function using CIBIC-Plus measure scale (Schneider et al., 1997), which is an end-point assessment tool applied by caregivers. The pooled estimate of three trials showed small benefit in the global function for the combination therapy compared with the monotherapy (Raw mean difference -0.21, 95% CI -0.33 to -0.09).

The three double-blinded RCTs covered a range of mild-to-severe patients. Interestingly, the two trials that included moderate-to-severe patients showed significant small improvement in the global function for patients on the combination therapy, while the study conducted in patients with mild-to-moderate stage showed no significant benefit.

Figure 5. A meta-analysis of three trials on global function

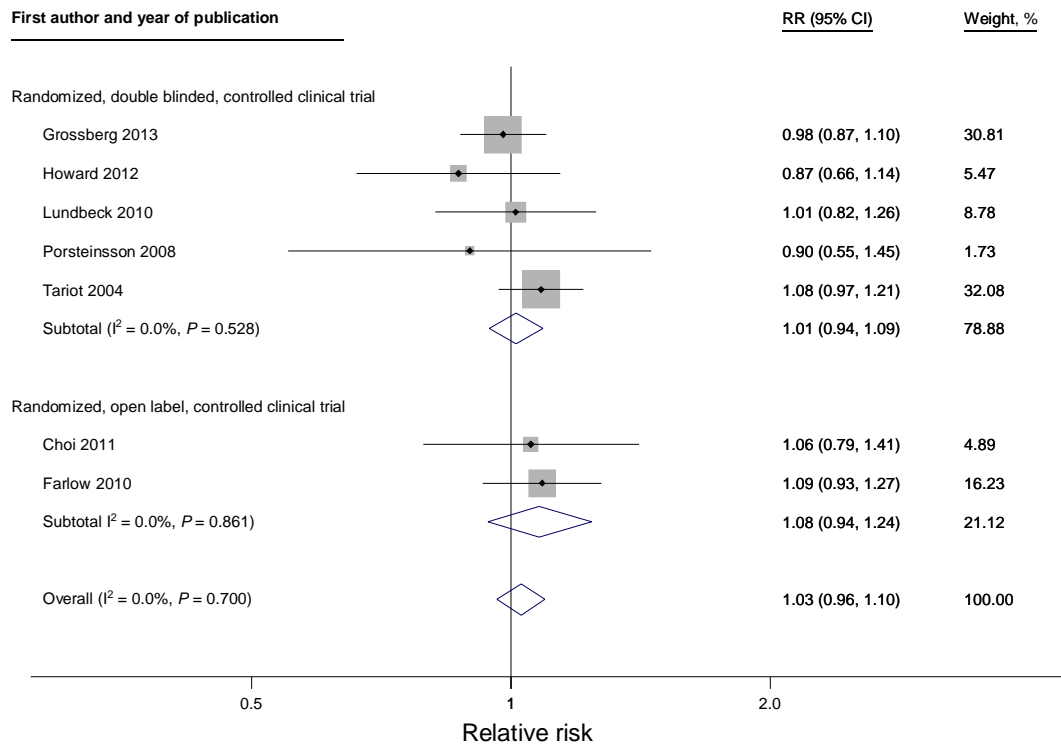| First author and year of publication	WMD (95% CI)	Weight, %
Grossberg 2013	-0.30 (-0.48, -0.12)	24.06
Porsteinsson 2008	-0.04 (-0.22, 0.14)	23.51
Tariot 2004	-0.25 (-0.26, -0.24)	52.43
Overall (I^2 = 61.9%, P = 0.073)	-0.21 (-0.33, -0.09)	100.00

Mean difference: -1, 0, 1

6.8 Adverts events outcome

All five double-blinded RCTs and two open-label RCTs reported adverse effects for the intervention and control group. The pooled estimate of seven trials showed no difference between the two groups (Relative risk 1.03, 95% CI 0.96-1.10, $I^2 = 0.0\%$) (Figure 6). The double-blinded RCTs and open-label RCTs showed similar results.

There are common adverse events which are typical for the AChEIs treatments such as nausea, vomiting, diarrhea, anorexia, insomnia, and fatigue. Memantine has also common adverse events such as confusion, somnolence, falls, and headache (M. R. Farlow & Cummings, 2007). The adverse events were the primary reason for discontinuation of the treatment in the studies.
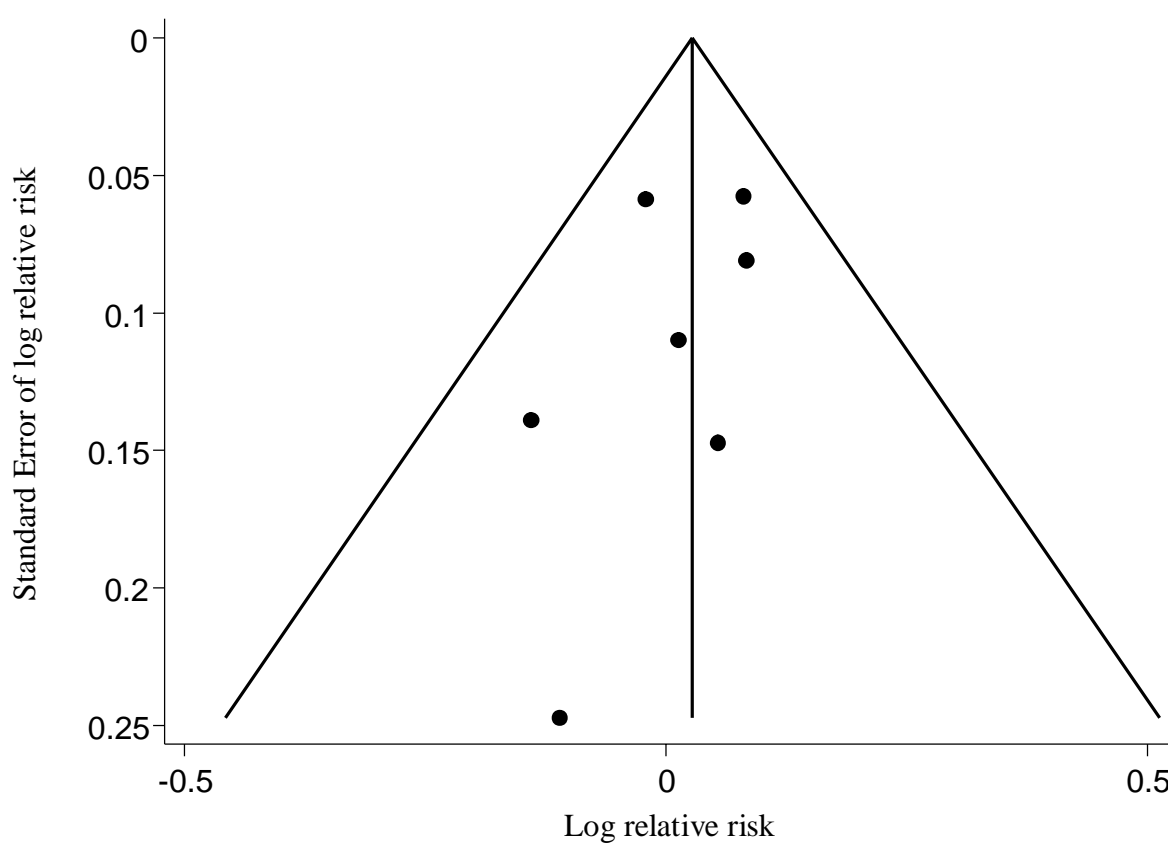
Figure 6. A meta-analysis of seven trials on any side effect in the intervention group compared to the control group.

First author and year of publication	RR (95% CI)	Weight, %
Randomized, double blinded, controlled clinical trial		
Grossberg 2013	0.98 (0.87, 1.10)	30.81
Howard 2012	0.87 (0.66, 1.14)	5.47
Lundbeck 2010	1.01 (0.82, 1.26)	8.78
Porsteinsson 2008	0.90 (0.55, 1.45)	1.73
Tariot 2004	1.08 (0.97, 1.21)	32.08
Subtotal ($I^2 = 0.0\%$, $P = 0.528$)	1.01 (0.94, 1.09)	78.88
Randomized, open label, controlled clinical trial		
Choi 2011	1.06 (0.79, 1.41)	4.89
Farlow 2010	1.09 (0.93, 1.27)	16.23
Subtotal $I^2 = 0.0\%$, $P = 0.861$)	1.08 (0.94, 1.24)	21.12
Overall ($I^2 = 0.0\%$, $P = 0.700$)	1.03 (0.96, 1.10)	100.00

Relative risk (0.5, 1, 2.0)

6.9 Publication bias

There was no evidence of publication bias for all outcomes. All seven studies reported data on adverse effects. The Figure 7 shows a funnel plot for this outcome.

Figure 7: Funnel plot of seven trials on adverse effects

7 Discussion

7.1 Main findings

This meta-analysis of seven clinical trials showed that a combination therapy of an AChEI with memantine is associated with modestly better effects in terms of cognition and global function than a monotherapy with an AChEI. The effects of the combination therapy were no better than a monotherapy for daily living activity. However, the combination therapy showed benefits over a monotherapy for the behavioural outcome and the effect was independent of the stage of the disease.

Although the meta-analysis of double-blinded RCTs and open-label controlled trials on the effects of the combination therapy on cognition were not statistically significant. The two double-blinded RCTs which included patients with moderate-to-severe Alzheimer's disease and used the SIB scale (Panisset et al., 1994), which is the most appropriate for the cognitive assessment of this category of patients, showed significant effects for the combination therapy.

Our subgroup analysis according to the stage of the disease, mild-to-moderate versus moderate-to-severe, may indicate that the combination therapy is more appropriate and should be administered to patients in more advanced stages.

Moreover, this meta-analysis showed a similar rate of adverse effects for a combination therapy and a single therapy.

7.2 Combination therapy in regard to the stage of Alzheimer's disease

The findings of this study do not support the use of combination therapy for the early stage of Alzheimer's disease, but show a beneficial effect over a single therapy for moderate-to-severe stage of the disease.

A number of narrative reviews found that the combination therapy is safe and well tolerated and they supported the superiority of the combination therapy (Parsons et al., 2013; Patel & Grossberg, 2011; Tampi & van Dyck, 2007; Xiong & Doraiswamy, 2005). They have recommended the combination therapy as the best current treatment strategy especially for patients in moderate-to-severe stage of Alzheimer's disease. A Cochrane systematic review on the efficacy of memantine supported memantine as a monotherapy or in combination with an AChEI for patients with moderate to severe Alzheimer's disease (McShane et al., 2006).

For the earlier stages of Alzheimer's disease, the results on the beneficial effects of the combination therapy are inconsistent. Some studies found no evidence that the combination therapy may provide some benefits in that stage of the disease (Xiong & Doraiswamy, 2005). Some other studies demonstrated modest benefits (Tampi & van Dyck, 2007) or similar beneficial effect for the early stage of the disease (Patel & Grossberg, 2011). Moreover, two reviews found that the combination therapy with memantine showed better functional and neuroprotective benefits for patients in the moderate stage of Alzheimer's disease (Farlow & Cummings, 2007; Standridge, 2004) .

However, the opinions expressed by narrative reviews may have been affected by selection and interpretation bias. The selection of studies depends on the preference and the criteria of the authors which may be more arbitrary than those set for systematic reviews.

A number of cohort studies also support the combination therapy for advanced stage of Alzheimer's disease. A study (Schneider, Insel, Weiner, & Alzheimer's Disease Neuroimaging Initiative, 2011) found no benefits for the combination therapy in patients with mild Alzheimer's disease. Moreover, several studies (Atri, Shaughnessy, Locascio, & Growdon, 2008; Lopez et al., 2009; Seinela, Virtanen, & Ripsaluoma, 2012) showed beneficial effects for the combination therapy in patients in more advanced stage. Particularly, the study by Lopez et al. (Lopez et al., 2009) suggested that the combination therapy may delay nursing admission and showed beneficial effects on communication skills and physical health of treated patients.

7.3 Medication adherence

The adherence to medication is discussed in a number of the cohort studies. There is scientific evidence on medication adherence on the impact of the therapy. The longer patients persist with treatment, the better they perform on cognitive, functional and global outcomes (Rountree et al., 2009). The importance of adherence to the treatment in the long-term was supported also by two cohort studies (Atri et al., 2008; Lopez et al., 2009).

7.4 Dose regimen and drug formulation

The dose regimen may play a role in the effect of a therapy either demonstrating better efficacy or affecting the side effects. In a combination therapy, a higher daily dose or an extended release formula of memantine may have better effect (Grossberg et al., 2013).

Similarly, the drug formulas may play a role in the effects of a treatment for Alzheimer's disease. However, rivastigmine patches of different dosage had similar efficacy for groups of Alzheimer's patients in the same stage (Choi et al., 2011; Farlow et al., 2010). With regard to drug formulation, the authors of a study, which reported the beneficial effects for the combination therapy, argued that this effect may be associated with relatively higher concentrations of rivastigmine in capsule formula (Farlow et al., 2010).

7.5 Efficacy assessment tools and their effects on the results

The tools for the assessing the treatment efficacy for Alzheimer's disease have varied in the clinical trials. The efficacy assessment tools can have an impact on the results of the clinical trials.

For example, when trying to determine the disease severity using MMSE (Folstein et al., 1975), any physical, sensory or learning disabilities, communication difficulties, or sufficient fluency of the observed patients should be taken into account. They may affect and bias the results (NICE, 2011). The MMSE (Folstein et al., 1975) scale may evaluate adequately the mild-to-moderate Alzheimer's patients' cognitive status, but for more severe stages of the disease the SIB scale (Panisset et al., 1994) is more appropriate tool (NICE, 2011).

In the study by Howard et al. (2012), the SMMSE scale (Molloy & Standish, 1997) was used to measure the effects of the combination therapy on cognition in moderate-to-severe Alzheimer's patients and showed no significant improvement. These reported values may have been affected by a floor effect which may conceal an overestimation of the patients' deterioration and biased efficacy outcome (Schmitt & Wichems, 2006). In contrast, the effect of the combination treatment on cognition in moderate-to-severe Alzheimer's patients, when was assessed by the SIB scale (Panisset et al., 1994) in the studies by Tariot et al. (Tariot et al., 2004) and Grossberg et al. (Grossberg et al., 2013) showed significant improvement. Similarly, in the Korean population study (Choi et al., 2011) the Korean specified MMSE scale (Kim et al., 2010) was applied for the assessment of mild-to-moderate Alzheimer's patients with low educational status. This scale has been found relatively insensitive in detecting the early stage of dementia, leading to a higher false negative rate (Kim et al., 2010). In this case the insensitivity of the scale and the low educational status may both have biased the results.

The CIBIC-Plus (Schneider et al., 1997) has various formats with different terms of depths and structure which may influence the outcome's validity, especially when estimating outcomes across different studies. Thus it may be an insensitive assessment tool in detecting patients' global function (Quinn et al., 2002).

7.6 Adverse effects of Alzheimer's drugs

The efficacy of a drug depends on its safety and tolerability. Some adverse effects can lead to lack of compliance in a therapy. In Alzheimer's disease the patients' compliance is also affected by a number of comorbidities and concomitant medication use.

This meta-analysis showed a similar rate of the adverse effects for a combination and a single therapy. However, the dropouts differed between the studied groups in the included trials. In two studies (Farlow et al., 2010; Grossberg et al., 2013; Howard et al., 2012) the dropouts were 1.5-fold more in the combination therapy group than the monotherapy group. Contrary, in two other studies (Porsteinsson et al., 2008; Tariot et al., 2004) there were more withdrawals in the monotherapy group than in the combination therapy group. Moreover, the two open-label studies included in this review had more drop-outs in the combination therapy group. The differences in the dropout rates between intervention and control group suggest that a combination therapy may have more adverse effects than a monotherapy.

7.7 The rate of dropouts and imputation methods for missing data

Although the meta-analysis showed similar rate of adverse effects between the two therapies, the occurrence of dropouts differed between the studied groups in different trials. The rate of dropouts and the choice of imputation method for handling missing data may also affect the difference between a combination therapy and a single therapy.

Intention-to-treat (ITT) approach was the most commonly used method for analysing data with missing information in the included RCTs. This method may help to avoid bias associated with the effects of crossover and dropouts. Intention-to-treat method presupposes that the participants should be analysed in the groups to which they were randomized, regardless of whether they received or they adhered to the allocated

intervention. Hence, this principle may lead to consequent concealment of missing data or adherence to protocol guidelines, biasing the efficacy and safety outcomes at any direction (Hollis & Campbell, 1999).

The last observation carried forward (LOCF) imputation method was commonly used for handling missing data in RCTs. In this approach, missing data are replaced with the last available observation values. This method can produce biased estimates of the treatment effects (Little et al., 2012). Especially for Alzheimer's patients, the use of the last value before dropout as end point measure may conceal the degenerative progression of the disease, because it may be more optimistic than if the value was yielded upon the completion of the treatment. Thus, last observation carried forward approach of missing data management, may favour the therapy arms with most dropouts underestimating the decline of patients.

The included trials in this meta-analysis did not provide adequate information for assessing possible bias introduced by use of the last observation carried forward method. However, two trials (Grossberg et al., 2013; Howard et al., 2012) performed a sensitivity analysis to assess the effects of missing data on the results. The results of these trials remained robust after a sensitivity analysis.

8 Future suggestions

The clinical trials included in this meta-analysis were conducted for a relatively short period, of one year maximum. This meta-analysis showed that a combination therapy of memantine with an AChEI may provide some benefits in cognitive function, global function and behavioral symptoms in Alzheimer's patients in advanced stages compared to a monotherapy. In addition, three observational studies (not included in this meta-analysis) reported similar results, supporting the efficiency of a combination therapy especially for this category of patients.

Further studies with a longer follow-up time are needed. Moreover, future studies investigating the efficacy of a treatment should account for the degenerative character of Alzheimer's disease, the speed of the disease's progression, a dose-response relationship, individual characteristics of patients, such as comorbidities (i.e. diabetes, hypertension), biomarkers (i.e. genes associated to Alzheimer's disease, cerebrospinal fluid tau and amyloid protein), other medications and drug interactions, and environmental factors which may affect the disease's progress. Moreover, personal coexisting characteristics of the patients, such as low educational status, learning problems and communication difficulties should be considered to avoid misinterpretation when assessing the efficacy of a treatment. Finally, not all patients may benefit from the combination treatment. Identification of subgroups of patients with Alzheimer's disease who will benefit more from the combination treatment is needed.

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