THE EFFECT OF CHOLINESTERASE INHIBITORS ON THE RISK OF FALLS AND INJURIES IN PATIENTS WITH ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

By

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT

OF THE REQUIREMENTS FOR THE DEGREE OF

MASTERS OF HEALTH RESEARCH METHODOLOGY
in the Department of Clinical Epidemiology and Biostatistics

MCMASTER UNIVERSITY

December 2009

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Acknowledgements

It is a pleasure to thank the many people who made this thesis possible.

First and foremost, I would like to extend gratitude to my Masters supervisor, Dr Parminder Raina. Throughout my thesis-writing period, he provided encouragement, sound advice and valuable feedback that was instrumental in my learning and progress at each step.

This systematic review would not have been possible without Dr Lina Santaguida. She has been a sincere mentor, guide and friend throughout. With her enthusiasm, her inspiration, and her great efforts to explain things clearly and simply, she helped me through the HRM program. I sincerely thank her for her continued support and precious insight in guiding my research.

I would like to thank Dr. George Heckman and Dr. Mohit Bhandari for helping me through the thesis data collection and writing process and for being a source of impeccable guidance and information. I would also like to thank my external reviewer and defense committee member, Dr. Jennie Wells, for her time and invaluable feedback.

I also take this opportunity to thank all members of the EPC Staff: Ms Lynda Booker, Ms Roxanne Cheeseman, Dr.Lauren Griffith, Ms. Mary Gauld, Dr. Mark Oremus, Ms. Rashmi Dmello, Ms. Maureen Rice, and Ms. Cecile Royer for their help and support during this project, for their kind assistance with writing letters, giving wise advice and helping with various applications. It was an honour and a privilege to have known and worked with such wonderful people. I thank you all for making this a memorable experience.

I will also like to acknowledge Ontario Premier's Research Excellence Award provided by Ontario Ministry of Innovation for supporting this project.

I wish to thank my father, my wife and my children for helping me get through the difficult times, and for all the emotional support, camaraderie, love and care they provided.

Lastly, and most importantly, I wish to thank my late mother for being in my thoughts always to help, guide and motivate me through all these times. Thank you for your blessing and for smiling upon me from skies above. I dedicate this to you.

1. INTRODUCTION

1.1 The Aging Population

With old age now spanning a period of 20 years or more, the characteristics and experiences of seniors are varied. Currently, low fertility rates, longer life expectancy, and the effects of the baby boom generation are among the factors contributing to the aging of Canada's population. Between 1981 and 2005, the number of older people over the age of 65 in Canada increased from 2.4 million to 4.2 million and their share of the total population jumped from 9.6% to 13.1%[1]. The demographic trends will continue to vary considerably across age groups in the years ahead. According to the most recent population projections, the proportion of seniors in the Canadian population could nearly double in the next 25 years[2].
Between 2006 and 2026, the number of seniors is projected to increase from 4.3 million (13.2%) to 8.0 (21.2%) million. The number of Canadians aged 85 or greater will nearly double as well, rising from about 500,000 in 2006 to about 900,000 in 2026[3].

1.2 Mild cognitive impairment (MCI) and cognitive impairment no dementia (CIND)

For many patients MCI and CIND may represent a pre-dementia state, where normal aging, MCI and dementia characterize a continuum of cognitive states. As per the Third Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, 2006 there is currently insufficient evidence to recommend the use of Cholinesterase inhibitors (ChEIs) in MCI (Grade C, Level 1)[4]. In a systematic review of randomized controlled trials (RCTs) examining the role of ChEIs in MCI, Raschetti et al[5] concluded that ChEIs did not significantly delay the onset of Alzheimer's disease (AD) or dementia. Moreover, this study also concluded

that the risks associated with ChEIs are not negligible in AD. Raina et al[6] observed that as far as cognition and global assessment function were concerned, no benefit occurred with the use of donepezil in patients with MCI; however donepezil reduced rates of conversion to Alzheimer disease in the short term, but differences relative to placebo disappeared by 36 months.

1.3 Dementia

Based on the findings from the Canadian Study of Health and Aging (CSHA), the prevalence of dementia, in the population older than age 65 years, is 8% and the best estimates of lifetime risk of Alzheimer's disease range from 14.5% to 26.2% of the population[7]. In Canada, there are 60,150 new cases of dementia each year, and there are currently about 450 000 people with all forms of dementia. This figure is expected to double over the next 30 years in Canada[8].

There are numerous criteria that are used for clinical or research purposes to diagnose dementia. The essential symptoms of dementia are acquired impairment in short and long-term memory, associated with impairment in abstract thinking, impaired judgement, and other disturbances of higher cortical function, or personality changes. Dementia is a clinical syndrome characterized by acquired losses of cognitive and emotional abilities severe enough to interfere with daily functioning and the quality of life. The disturbance is severe enough to interfere with work or usual social activities or relationship with others. The diagnosis of dementia is not made if these symptoms occur in the presence of delirium[9]. This is the most widely used definition of dementia and is based on the Diagnostic and Statistical Manual of Mental Disorders, Third Edition, (DSM-III), Revised (DSM-IIIR), DSM-IV, DSM-IV-TR and National Institute of Neurological and Communicable Disorders and Stroke-Alzheimer's Related Disorders association (NINCDS-ADRDA)[10,11,12]. This DSM III-R definition of dementia has good

reliability, particularly with respect to Alzheimer's disease. The DSM-IV version, although identical to DSM-III, has not been validated[9]. The systems based on the various editions of the DSM and NINCDS-ADRDA are commonly used in the United States and Canada; those based on the International Classification of Diseases (ICD) in continental Europe; and the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX) in the United Kingdom[13]. The diagnosis of dementia is clinical and there is good evidence to retain the diagnostic criteria currently in use [9].

According to the Canadian Collaborative Cohort of Related Dementias, within the dementia group, AD constitutes 47.2% of the subjects. The rest of the dementias are comprised of mixed dementias 33.7%, vascular dementia 8.7%, frontotemporal degenerations 5.4%, dementia with Lewy bodies 2.5%, and unclassifiable 1.8%[14]. AD is 1% among people aged 65–74 years, 6.9% among those 75–84 years and 26% among those aged 85 years and older[15].There are currently about 18 million people worldwide with AD and this figure is projected to reach 34 million mark by 2025. Much of this increase will be in the developing countries, and will be due to the ageing population. Currently, more than 50% of people with AD live in developing countries and by 2025, this will be over 70 %[16].

1.4 Alzheimer's disease

AD is the most common form of dementia. First identified in 1906, AD is a slowly advancing brain disease that results in death for the patient. AD can occur at any age, even as young as 40 years, but its occurrence is much more common in older adults. In fact, the rate of occurrence of the disease increases exponentially with age, which means that it occurs very rarely among those 40-50 years old, increases between 60 and 65 years, and is very common over 80 years. With increasing life expectancy, both incidence and prevalence of all dementias

increases with age as the number of patients with the disorder to be found in any community depend on the proportion of older people in the community. Traditionally, the developed countries had large proportions of elderly people, and so they had many cases of AD in the community at one time. However, the developing countries are now undergoing a demographic transition so that more persons are surviving to an old age[76].

In 1984, NINCDS-ADRDA task force defined three categories of AD: possible, probable and definite AD. In possible AD, the major clinical signs include unusual losses of memory, deterioration of language and perception, judgement problems that compromise the person's ability to carry out activities of daily living, and behavioural problems such as agitation and paranoia. In probable AD, dementia is established clinically and confirmed by neuropsychological tests (cognitive loss accompanied by memory loss). In definite AD, the clinical picture of probable AD is confirmed at autopsy by histopathological findings of neurofibrillatory plaques and tangles.[17]

The classic gross neuro-anatomical observation of a brain from a patient with AD is diffuse atrophy with flattened cortical sulci and enlarged cerebral ventricles[18]. The pathognomic microscopic findings are senile plaques, neurofibrillatory tangles, and neuronal loss with granulovascular degeneration of the neurons. As the disease progresses, brain cells lose the ability to function properly as they are damaged and destroyed[8].

Although the cause of the dementia of Alzheimer's type remains unknown, progress has been made in understanding the molecular basis of the amyloid deposits that are a hallmark of the disorder's neuropathology. Some studies have indicated that as many as 40 percent of patients have a family history of dementia of Alzheimer's type; thus genetic factors are presumed to play a part in the development of the disorder. AD presents itself in two main forms: early-

onset and late-onset. Early-onset AD is rare, occurs in about 5 percent of all people who have AD and is found in the age group of 30 to 60 years. Some cases of early-onset AD are inherited, called familial AD (FAD), and are caused by a number of different gene mutations on chromosomes 21, 14, and 1. The inheritance pattern is autosomal dominant and these mutations cause an increased amount of the beta-amyloid protein to be formed which is a major component of AD plaques. No specific gene has been identified as the cause for the late-onset AD; however, one predisposing genetic risk factor does appear to increase a person's risk of developing the disease. This increased risk is related to the apolipoprotein E (APOE) gene found on chromosome 19. Many studies have confirmed that the APOE e4, an allele of the apolipoprotein E gene, increases the risk of developing AD; however the underlying mechanism is not well understood. These studies also have helped explain some of the variation in the age at which AD develops, as people who inherit one or two APOE e4 alleles tend to develop AD at an earlier age than those who do not have any[85].

People with one copy of this allele have AD three times more frequently than those with no apo-e4 allele, and people with two copies of this allele have the disease eight times more frequently than those with no apo-e4 allele[18].

1.5 Alzheimer's disease and applicable pharmacology

The major neurotransmitters that are contributors to dementia are acetylcholine, nor-epinephrine, dopamine, glutamate, serotonin, and gamma-amino butyric acid (GABA), although other neurotransmitters have been elucidated as well. Deficits in these neurotransmitters are associated with the neuronal death; alterations in the gross structural zones of the brain, and change in behaviour, learning, and memory. It is difficult to identify a single neurotransmitter primarily associated with these behavioural changes, due to the complex nature of brain neuronal

circuitry, the interaction of transmitters, and the different effects that these transmitters have at different synapses[19].

Evidence exists for both glutamatergic and cholinergic involvement in the aetiology of AD. The glutamatergic hypothesis suggests over activation of N-methyl-D-aspartate (NMDA) receptors, which are pivotal in learning and memory, by glutamate leading to neuronal damage causing cognitive decline in patients with AD[19]. The neurotransmitters that are most often hypothesized to be hypoactive in AD are acetylcholine and norepinephrine. Decreased norepinephrine activity in AD is suggested by the decrease in norepinephrine containing neurons in the locus ceruleus found in pathological examinations of the brains with AD.

Several studies have suggested specific degeneration of cholinergic neurons in the nucleus basalis of Meynert in persons with AD[21]. Patients with AD have reduced cerebral production of cholineacetyltransferase which is the key enzyme for the synthesis of acetylcholine. Acetylcholine is essential for memory and learning and is decreased in both concentration and function in patients with AD leading to impaired cortical cholinergic function[20]. The rationale for ChEIs therapy is that increasing acetylcholine levels reduces symptoms in patients with Alzheimer's disease.

1.6 Pharmacotherapy in Alzheimer's disease

Pharmacotherapy is the primary therapeutic intervention aimed to improve symptoms or delay the progression of AD. These may be divided into two major groups: those enhancing cholinergic function and those which either directly or indirectly reduce free radical/inflammatory processes in the brain. Currently, Cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) are the primary drug treatment options for patients with

mild to moderate AD approved in the United States of America whereas tacrine is no longer available for use in Canada[22]. Cholinergic neurotransmission occurs when Acetylcholine (ACh) released from the presynaptic neuron binds to nicotinic or muscarinic postsynaptic ACh receptors and ChEIs increase cholinergic transmission by inhibiting cholinesterase at the synaptic cleft and thereby increasing acetylcholine levels[23, 24]

A number of studies have used these three cholinesterase inhibitors as intervention and it has been suggested that these three cholinesterase inhibitors are efficacious for mild to moderate Alzheimer's disease.[25]. Perras et al[26], in a systematic review of RCTs of ChEIs for AD showed that ChEIs can lead to modest short-term decreases in functional disability and global impressions of disability. The clinical significance of these changes is difficult to predict. Birks et al [27] observed that cognitive function of about 10% of AD patients treated with ChEIs increase by 2.7 points on a 70 point Alzheimer Disease Assessment Scale-Cognitive (ADAS-Cog) scale over six months when compared to placebo. Raina et al[6] observed that the treatment of dementia with ChEIs can result in statistically significant but clinically marginal improvement in measures of cognition and global assessment of dementia. Burns et al[28], described ChEIs as safe and effective and can be prescribed for people in the moderate stages of AD. These three ChEIs are all approved and viable treatment option for most patients with mild to moderate AD in Canada[29].

Of the most widely used ChEIs (donepezil, rivastigmine, galantamine) for the treatment of mild to moderate AD, it is suggested that ChEIs results in a modest but significant therapeutic effect and modestly but significantly higher rates of adverse events and discontinuation of treatment[30]. A study by Feldman et[31, 32] al showed that patients with AD, treated with donepezil, show less decline in measures of functional impairment over a 6 month period. Only few double-blind, randomized, placebo-controlled trials have investigated ChEI drug treatment beyond 6

months. Studies by Winblad et al[33,34], Mohs et al[35] and Karaman et al[36] show decreased overall functional decline in drug-treated AD patients over a 1 year period, but overall there is a general lack of RCTs examining the long-term efficacy of ChEI treatment. Given that AD symptoms evolve over 5 to 8 years of disease progression, longer-term studies of ChEI treatment of AD would be invaluable to assess the functional benefit on the overall progression of the disease.

1.7 Falls and Injuries in the elderly

Dementia and associated falls are major co-morbidities in elderly populations. Dementia is an independent risk factor for falls; it can increase the risk of falling by impairing judgement, gait, perception (both visual and spatial) and the ability to recognise and avoid hazards. Approximately 30% of people above 65 years of age and living in the community fall every year and a fifth of all fallers require medical attention[37]. Older people with cognitive impairment and dementia are at increased risk of falls with an annual incidence of around 60% (twice that of cognitively normal older people) [37]. Older people with dementia are at increased risk of sustaining any fracture, with further additional risk of sustaining a fractured neck of femur; this type of fracture is associated with particularly poor outcomes[38]. Moreover, after treatment of fractures, fallers have worse outcomes, a higher risk for institutionalization, and a higher mortality compared with cognitive healthy seniors. Fallers with dementia are approximately five times more likely to be admitted to institutional care than older people with dementia who do not fall[38].

Falls have severe consequences on the physical, psychological health and social well being of the elderly; for example falls are associated with increased mortality, hospitalization, and institutionalization among seniors. Fall-induced injuries include fractures, soft tissue bruises and contusions, head injuries and lacerations, which represent one of the most common causes of

longstanding pain, functional impairment, disability, and death in the elderly. Identification of falls prevention strategies can be the keys to reducing the burden of injuries among individuals with AD, but further research needs to be done to ascertain as to how best falls can be prevented in these patients and what strategies have a significant impact in preventing falls[39].

In general, a fall is regarded as a complex, multifactorial phenomenon caused by several risk factors. A fall is defined as 'an unintentionally coming to rest on the ground, floor, or other lower level and not due to a seizure or an acute stroke'[40]. Falls and injuries are common amongst elderly people with AD and these increase with age. Injuries affect more than 50% of the community–dwelling elderly persons with AD yearly, and over 40% of these injuries are related to falls[40]. The odds of a fall related injury are between 1.5 and 4.5 times greater for those with mental health (MH) conditions, such as AD, among both elderly men and women [41]. When compared with elderly fallers in general, older people with dementia who fall have different demographic characteristics. They are older, more likely to be female and more likely to be living in institutional care[42, 43].

1.8 Risk Factors for Falls

Older people with dementia have a higher prevalence and greater severity of risk factors for falls compared with cognitively normal older people. They also have more marked impairments of gait and balance relative to cognitively normal older people [38]. Normal gait requires attention as a necessary cognitive resource. It has been postulated that restricted attention resource allocation while walking and impairment of executive function are important factors associated with greater risk of falls in elderly population with dementia[44]. Various risk factors for falls include postural instability; impairments of gait and balance; poor vision; history

of previous falls; medication use (for example, antidepressants, beta-blockers and diuretics); neurological conditions (for example, dementia, depression, Parkinson disease, and stroke); cardiovascular diagnosis (for example orthostatic hypotension); and the environment (for example, loose rugs, or uneven ground)[45,46]. Most falls in elderly people are associated with multiple risk factors[47].

Kallin et al[48] undertook a population based study to elicit the risk factors associated with falls among older, cognitively impaired people in geriatric care setting. The residents were assessed by means of the Multi-Dimensional Dementia Assessment Scale, supplemented with questions concerning the use of physical restraints, pain, previous falls during the stay, and falls and injuries during the preceding week. They found that almost 10% of the participants had fallen in the previous week. They concluded that history of falls, the ability to get up from a chair, the need for a walking aid (such as cane or walker), pain, cognitive impairment, and use of neuroleptics or antidepressant- selective serotonin reuptake inhibitors (SSRIs), were associated with falls[48].

Leipzig et al[49] observed weak association between digoxin, type IA anti-arrhythmic, diuretics and falls in older adults. However no association was found for the other classes of cardiac or analgesic drugs examined. They considered this evidence as based solely on observational data, with minimal adjustment for confounders, dosage, or duration of therapy. They concluded that older adults taking more than three or four medications were at increased risk of recurrent falls. Tinneti et al[46] observed that cognitive impairment is a risk factor for falls among elderly persons living in the community.

It is hypothesized that impairments of gait and balance are partially attributable to central neurodegenerative processes in AD[38]. Evidence showing decreased motor performance by

people with cognitive impairment and dementia when performing an additional cognitive task (dual task conditions) supports this hypothesis, and suggests impairment of attentional control as a possible mechanism contributing to the increased fall risk observed in dementia[44]. In addition, there are behavioural risk factors for falls, such as wandering and agitation, which manifests predominantly in people with cognitive impairment or dementia[46].

1.9 Fall Prevention Strategies

There is an extensive body of research evidence on the causes of falls and how to prevent them in older people in general and this research-based knowledge about fall risk factors and effective fall prevention programmes has grown in the last two decades[50]. Some of the interventions, aimed at preventing falls, include targeting gait and balance impairments, eliminating or changing medications known for contributing to falls in the elderly, minimizing environmental risk factors, and decreasing orthostatic hypotension, exercise alone, and modification of the environment, either alone or in combination with exercise[38].

Although there is evidence to suggest that demented patients can comply with interventions known to reduce risk of falls in cognitively normal populations, and also that these interventions can modify targeted risk factors for falls, there is no convincing evidence that falls can be prevented in older people with dementia[38] .Shaw et al[38] in their systematic review and meta-analysis found no generalizable benefit from multifactorial or individual intervention strategies in older people with dementia. Oliver et al[69], in a review of studies targeting falls prevention strategies, concluded that these strategies have not significantly prevented falls in patients with dementia.

1.10 Cholinesterase inhibitors (ChEIs) and Falls

ChEIs have been used in the treatment of AD over the last 20 years but there are limited studies evaluating their association with falls and injuries. Furthermore, the literature, in general, is deficient in comparing the post treatment morbidity including adverse events and cost of treatment relative to the natural progression of the disease and associated morbidity. The ChEIs may alter the risk of falls and injuries in elderly AD patients in a complex manner. There are competing mechanisms linking ChEIs with falls in patients with AD.

One of the mechanisms suggests that as individual cognition improves, fall and injury risk may be reduced by improvements in insight, memory, judgment and visual spatial ability in the short term. A study by Montero-Odasso et al[44] provides evidence that ChEIs may reduce falls risk in patients with mild AD. In particular, donepezil improved gait significantly in this patient population resulting in a more stable walk as compared to the control group. Additionally, these improvements were elicited as early as one month into the treatment and sustained for 4 month at which point the study terminated. Interestingly, it has also been suggested that symptomatic therapy drugs, such as ChEIs, (particularly donepezil) may also be effective as a disease-modifying drugs[70]. Bullock et al[71] observed a possible trend towards a lower risk of falling in galantamine treated patients with mild-to-moderate AD. Moreover, it has been postulated that ChEI may reduce the risk of falls in people with AD by a few mechanisms including reducing gait variability, increasing gait velocity and improving gait performance[44].

The other mechanism however argues for the opposite effect of ChEIs in AD. There is evidence that patients with Alzheimer's disease exhibit an unusually high prevalence of orthostatic hypotension and carotid sinus hypersensitivity[72, 73]. McLaren et al[74] studied the cardiovascular effects of donepezil and observed that heart rate variability, which is used to

assess autonomic function, is impaired by donepezil in people with neurodegenerative dementia. It also revealed a tendency for hypotensive disorders to be exaggerated[74]. Gill et al [75] reported that ChEIs can provoke symptomatic bradycardia and syncope and drug-induced syncope may also precipitate fall-related injuries, including hip fractures. Thus, there is potential for cholinesterase inhibitors to cause adverse cardiovascular effects and consequently falls and other serious morbidity in older people[74].

Elderly population with dementia may have number of co-morbidities and these may interact with pharmacological effects of ChEIs. Clinical trials usually have strict exclusion criteria and exclude patients with co-existing illnesses and concurrent pharmacotherapy. Clinical practice, however, presents a wide spectrum of older population with one or more co-morbidities and more prone to pharmacological side effects and interactions than represented in the clinical trials. The study groups in clinical trials are usually healthier than typically seen in clinical practice. The clinical trials potentially underestimate and underreport falls and related injuries.

Because of the competing mechanisms of action, and conflicting findings about the association of ChEIs and falls, we are proposing to conduct a systematic review of the available evidence about impact of these drugs on the risk of falls and injuries in patients with AD.

1.11 Summary and objectives

As the world's population ages, we can expect to see increasing numbers of people with dementia, and they now account for a constantly increasing proportion of older people living in the community and residential care facilities. AD is the commonest type of dementia and the prevalence increases exponentially with age. Falls and related injuries are important risk factors for fractures with worse outcomes, institutionalisation, increased morbidity and mortality in all older people. In addition, dementia is also recognized as a major risk factor for progression of

disability in this physically fragile population. In patients with dementia, falls and related injuries can further accelerate disability and increased burden on caregivers. Hence, preventing falls in persons with dementia will affect the rate of progression of disability.

The burden of falls and their consequences, such as injuries that include fractures and functional limitations are well-known health problems in older populations. ChEIs have been used in the treatment of AD over the last 20 years, and there are limited studies evaluating their association with falls and injuries. Furthermore, the literature is in general deficient in comparing the post treatment morbidity including adverse events and cost of treatment relative to the natural progression of the disease and associated morbidity.

ChEIs enhance cholinergic neurotransmission and there is evidence that this is beneficial for people with AD. Treatment with ChEIs has been associated with small improvements in the rate of decline of cognitive function and activities of daily living. As individual cognition improves, fall and injury risk may be reduced by improvements in insight, memory, judgment and visual spatial ability in the short term. Although the potential benefits of ChEI have been evaluated, their association with the risk of falls and injuries remains unclear. The effect of such drugs may alter the risk of falls and injuries in elderly AD patients in a complex manner.

The primary objective of this review is to assess the impact of ChEIs on the risk of falls and injuries in patients with AD. The outcomes of interest include all accidental injuries or falls, fractures, and syncope; these outcomes may be considered to be outcomes of harm. The primary outcome of this systematic review will be determined for ChEIs currently used and approved within Canada, which include donepezil, rivastigmine, and galantamine. In addition, this review aims to investigate the potential impact on the risk of falls and injuries as the duration of ChEIs therapy increases.

2. METHODOLOGY

Studies having patient population with diagnosis of Alzheimer's dementia (AD) were considered for systematic review. The diagnosis of dementia was based on National Institute of Neurological and Communicable Disorders and Stroke-Alzheimer's Related Disorders association (NINCDS-ADRDA), Diagnostic and Statistical Manual (DSM-III), DSM-III R (Revised), or DSM-IV criteria. Trials including patients with AD of any severity were eligible.

2.1 Types of intervention

Studies of interest were those in which participants received a cholinesterase inhibitor (ChEI), namely donepezil, galantamine or rivastigmine. Only randomized, controlled trials (RCT) that compared a ChEI with placebo or another ChEI were considered for this review. Trials of combination therapy were excluded to avoid synergistic effects of the combination therapy.

2.2 Types of outcome measures

The primary outcomes of interest were:

1. Injury: damage inflicted on the body as the direct or indirect result of an external force, with or without disruption of structural continuity[77].

2. Fall: an incident in which a patient suddenly and involuntary comes to rest upon the ground or surface lower than the original position, not due to stroke, syncope, or an overwhelming blow or trauma[40].

3. Fracture: diagnosis based upon radiological evaluation showing disruption of bony structure.

4. Syncope: Transient loss of consciousness that is accompanied by loss of postural tone due to inadequate cerebral blood flow and not due to stroke, seizure, or transient ischemic attack[78].

As these outcomes were not the primary end-points of ChEI trials, they were not readily reported in published articles. In such cases, the corresponding authors were contacted via email requesting more detailed or missing information related to the outcomes of interest in this systematic review.

2.3 Search strategy for identification of studies

The Cochrane Dementia and Cognitive Improvement Group (CDCIG) specialized register was searched using the following terms in various combinations:

1. Cholinesterase inhibitor or donepezil or aricept or rivastigmine or exelon or ENA713 or galantamine or reminyl.
2. Alzheimer's disease, Acute Confusional Senile Dementia, Alzheimer Type Senile Dementia, Dementia, Alzheimer Type, Dementia Primary Senile Degenerative, Dementia Senile.
3. Randomized controlled trials (RCT)

In addition, a comprehensive search of the literature was conducted to capture all relevant, published studies on the topic of AD and ChEI. Following electronic databases were searched:

1. MEDLINE (January 1986-December2007).
2. EMBASE (January 1986-December2007).
3. The Cochrane Central Database of Controlled Trials (January 1986- December 2007).

The manufacturers of the ChEIs were contacted for additional information. Abstracts of symposia from the following organizations were hand-searched up to December 2007: American Geriatrics Society, American Academy of Neurology, and International Symposium on Advances in Alzheimer's disease Therapy, British Geriatrics Society, and European Society of Neurology. Reference lists from eligible studies for this review were hand-searched for any relevant additional studies. The principal authors of the eligible studies, which did not provide

adequate information about the adverse events of interest for this systematic review, were contacted and requested for any additional data.

2.4 Methods of the review

Standardized forms were developed for screening, as well as for data extraction. The forms were stored online using Systematic Review Software (SRS; Trial Stat Corp., Ottawa, Ontario). For title and abstract screening, two independent raters evaluated the citations that were obtained from the literature search. Articles that met the inclusion criteria and others, with insufficient information to determine if they met the criteria, were retrieved for further assessment. Once retrieved, the full text of the article was screened to determine if the inclusion criteria were satisfied. At this stage, an article could be excluded from further review only if both raters agreed that it did not satisfy the inclusion criteria. Disagreements were resolved by consensus. Articles that successfully passed the full text-screening phase were included for complete data extraction.

2.5 Inclusion/exclusion criteria

A list of inclusion/exclusion criteria was developed to screen studies for this systematic review. The criteria were as follows:

Language: Studies published in English language only were eligible.

Study Design: All randomized, blinded, and placebo-controlled trials of patients with AD who received a ChEIs were candidates for inclusion. Crossover trials were included if data was available from the initial phase prior to crossover. Studies with an open –label phases were included if outcome data were available from the closed-label phase. Case series, case reports,

editorials, letters, comments, opinions, abstracts, and conference proceedings were excluded from the systematic review. Population: Any age with any severity of AD was included. Outcomes: Studies with any of the following outcomes were included: injury, falls, fractures and syncope.

2.6 Quality Assessment

The quality assessment of each primary study was undertaken using the Jadad scale which has been shown to be reliable and valid for randomized trials[79]. Numerous tools for assessing quality have been developed, though none has been shown to be clearly superior[80]. The Jadad method was selected for its simplicity and ease of scoring. This method judges study quality based on three domains: randomization, blinding and accounting for withdrawals and drop outs. It is a five questions scale where each question has to be answered with either a yes or a no. Each yes would score a single point and each no zero point. It is composed of the following questions[79].

1) Is the study randomized?

2) Is the study double blinded?

3) Is there a description of withdrawals and drop outs?

4) Is the randomization adequately described?

5) Is the blindness adequately described?

The McMaster Quality Assessment Scale of Harms (McHarm) scale was used to evaluate the reporting of the adverse events. McHarm scale[81] is a quality assessment checklist specific to harms in primary studies. There are 15 items in total and each is evaluated with an answer of "yes", "no", or "unsure". A classification of "yes" on the McHarm is indicative of meeting the criteria for the quality item and given a score of 1. Conversely, a classification of "no" or

"unsure" is given a score of 0. It has been recommended that each item within the scale be considered individually rather than having one composite score[81]. Two raters conducted the quality of reporting of adverse events for each article. Differences were resolved by consensus.

McMaster Quality Assessment Scale for Harms (McHarm)	Rating
1. Were the harms PRE-DEFINED using standardized or precise definitions?	Yes No Unsure
2. Were SERIOUS events precisely defined?	Yes No Unsure
3. Were SEVERE events precisely defined?	Yes No Unsure
4. Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?	Yes No Unsure
5. Was the mode of harms collection specified as ACTIVE?	Yes No Unsure
6. Was the mode of harms collection specified as PASSIVE?	Yes No Unsure
7. Did the study specify WHO collected the harms?	Yes No Unsure
8. Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?	Yes No Unsure
9. Did the study specify the TIMING and FREQUENCY of collection of the harms?	Yes No Unsure
10. Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes No Unsure
11. Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Yes No Unsure
12. Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Yes No Unsure
13. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Yes No Unsure
14. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes No Unsure
15. Did the author(s) specify the type of analyses undertaken for harms data?	Yes No Unsure

2.7 Data extraction

Data extraction forms were designed to gather information on baseline characteristics including the subjects' age and gender, dose and duration of drug therapy and any harmful effects of the ChEIs (specifically for incidence of injury, falls, fractures and syncope). Every attempt was made to extract information as to how harms were assessed and reported. Two reviewers independently extracted data from individual articles and supplementary information provided by authors and assessed the quality of all studies that met the eligibility criteria. Data extracted were then compared and discrepancies resolved by consensus and discussion with a third reviewer.

2.8 Data analysis

The adverse events were reported as total number of events and as a percentage of subjects. Summary estimate for a specific outcome was calculated when two or more studies provided sufficient information for the adverse event. Statistical software (Revman, 5.0, Cochrane Collaboration), was used to compute the standard meta-analysis.The typical statistical method for combining results of multiple studies is to weight individual studies and this was done using Revman 5.0 software. The weighting of the individual studies represents the amount of information they contribute and more specifically, by the inverse variances of their effect estimates. This gives studies with more precise results (having narrower confidence intervals) more weight.

Statistical tests for heterogeneity were carried out using Chi-square and I^2 statistic. The Chi^2 test (χ^2) assesses whether observed differences in results are compatible with chance alone. A low P value or a large Chi-squared statistic relative to its degree of freedom provides evidence of heterogeneity of intervention effects. The Chi-squared test has low power to detect

heterogeneity when studies have small sample sizes or there are few studies within the meta-analysis. The I^2 statistic is used for quantifying inconsistency across studies. I^2 is calculated as (Q-df) / Q X 100% where Q is the chi-squared statistic and df is its degree of freedom . This describes the percentage of the variability in effect estimates that is due to heterogeneity. A rough guide to interpretation of I^2 is as follows: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity[82].

The results of individual trials were pooled under the random-effects assumption to obtain a Mantel-Hansel Relative Risk for each outcome. The fixed-effect assumption implies that the true effect of intervention, in both magnitude and direction, is the fixed (same) across studies. This assumption implies that the observed differences among study results are due solely to the play of chance and that there is no statistical heterogeneity. A random-effects meta-analysis model, on the other hand, involves an assumption that the effects being estimated in the different studies are not identical, but follow some distribution.

The risk ratio (or relative risk) is the ratio of the risk of an event within the two groups relative to each other.The relative risk was selected over using the effect measure of absolute risk reduction because of its familiarity to clinicians and also because most adverse events were reported as proportions or frequency counts. In addition, the absolute risk reduction, which may be defined as the difference between the control group's event rates and the experimental group's event rates, may be unreliable given the fact that that there is potential under-reporting of some of the outcomes of interest; most of the studies having reported only those adverse events that occurred in 5% or more of the patient population.

3. RESULTS

3.1 Literature Review and Screening

The literature search yielded 14740 citations that were eligible for inclusion as per the eligibility criteria. Figure 1 shows the final number of eligible studies for evaluation, and the inclusion/ exclusion criteria are detailed in Chapter 2. A search of the reference lists of abstracted articles yielded no additional citations of interest. In total, 14146 citations were excluded from further review after the initial levels of title and abstract screening; 594 citations proceeded to full text screening. Of these 594 articles, 568 were excluded for various reasons outlined in Figure 1 and a total of 26 studies advanced to the data extraction phase. Several trials were identified as "companion papers", indicating that the results for these related studies were based on the same study subjects. The main publication was selected for data extraction (usually the first chronological publication), and the remaining related studies were searched for any additional data .The "companion papers", however, were not considered as unique studies. Only English-language reports were included in this review. Although this is acknowledged as a possible source of bias, the overall proportion of potentially eligible non-English studies for review in title and abstract was small (7%)[6].

In total there were 17 unique studies[51-53, 55-68] from 26 different reports evaluating donepezil, galantamine and rivastigmine .There were 11 studies[51-53, 55-62] (Table 1) comparing donepezil versus placebo, three studies[63-65] (Table 4) evaluating galantamine versus placebo, two studies[66-67] (Table 5) did comparative evaluation of donepezil with galantamine and one study[68] (Table 6) compared donepezil with rivastigmine .

Figure1. Flow diagram showing the final number of studies meeting the eligibility criteria.

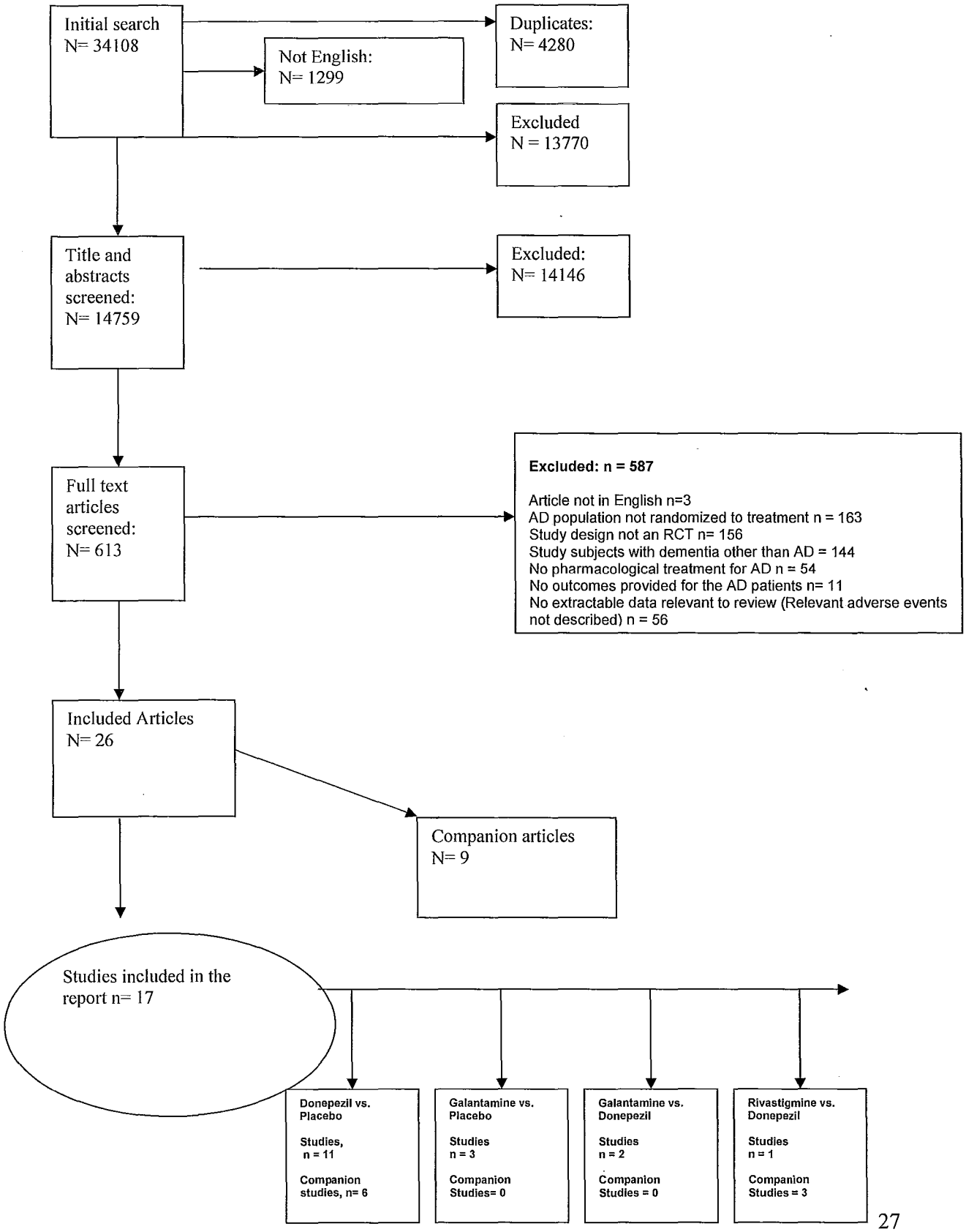


Figure 1 shows the process of selection of the studies for this systematic review. There were 56 studies where no extractable data relevant to this systematic review was reported (Appendix Table 18). 35 studies were excluded as the adverse events of interest for this review namely falls; accidental injuries; fractures; and syncope were not reported. These studies comprised of 9 studies on donepezil, 16 studies on rivastigmine, 6 studies on galantamine, and there were 2 comparative studies between donepezil and galantamine and 2 comparative studies between donepezil and rivastigmine. 20 studies were excluded as no details about any adverse events were provided and this comprised of 10 studies on donepezil, 5 studies on galantamine and 5 studies on rivastigmine. One cross-over study[54] mentioned no adverse events of interest before the crossover stage.

3.2 Donepezil versus Placebo

There were 11 unique studies from 17 different publications evaluating donepezil versus placebo that were eligible for this systematic review. Table 1 describes the characteristics of these studies at baseline. All the eligible studies were published during last 13 years (n = 1, 1996), (n = 2, 1998), (n = 1, 2000), (n = 4, 2001), (n = 1, 2004) (n = 1, 2006) (n = 1, 2007). Three studies[51-53] were undertaken by the same research group at different time periods but had unrelated cohorts of patients. In addition two more studies[56, 61] were undertaken by another research group at different time periods and had unrelated cohorts of patients.

Three studies[51-53] used DSM III criteria; five studies[55,57,59-61] used DSM IV criteria and six studies[52,56,58,59,61,62] used DSM IV and/or NINCDS-ADRDA criteria to diagnose dementia. In most of the studies, patients were recruited from the community and were ambulatory outpatients[51-53, 55, 57, 59, 60]. In two trials[58, 61] patients were recruited from assisted care/ nursing care facilities and in two trials[56, 62] patients were recruited from either community or residential

care facility/ assisted living settings. A total of 3260 participants (sample size 153 to 473 participants) were randomly assigned in these 11 placebo controlled trials. Mean ages of the study subjects ranged from 48 to 102 years with most studies representing ages in the mid to upper 70s. The patients included in one trial[58] were on average older than in the other studies, and were more likely to have co-morbid illness.

The severity of the disease was measured by the Mini Mental State Examination (MMSE) scale in all studies. Patients were recruited with mild to moderate dementia, (MMSE 10-26) in most of the studies[51-53, 55, 58, 59]. Other studies had variable MMSE score at baseline; 1-10[61], 5-17[56], 12-20[57], 2-14[62], 21-26[60]. Four studies[51-53, 57] required a Clinical Dementia Rating (CDR) of 1 (mild) or 2 (moderate) at screening and baseline.

Dementia was described as "probable" in 3 studies[52, 57, 60] and "probable or possible" in 5 studies[56, 58, 59, 61, 62]. Severity of dementia was described as mild to moderate in 3 studies[55, 57, 59], mild to moderately severe in 3 studies[51-53] moderate to severe in 1 study[56], and severe in 1 study[61]. Other studies [58, 60, 62] used the term probable or possible AD only and did not describe severity of AD.

The list of study exclusions was quite extensive and consistent across the different studies. Patients were excluded if they had insulin-dependent diabetes mellitus or other endocrine disorder, asthma, obstructive pulmonary disease or clinically significant uncontrolled gastrointestinal, hepatic or cardiovascular diseases. Patients known to be hypersensitive to cholinesterase inhibitors or who had taken tacrine or other investigational medicines within one month of baseline were excluded. Concomitant medications such as anticholinergics, anticonvulsants, antidepressants and antipsychotic were not allowed. Drugs with central nervous system activity were prohibited or partially restricted.

The studies had many features in common. They were all multi-centre, randomized and double blind. There were 8 parallel group studies[51, 52, 55, 56, 58, 59, 61, 62]. Six studies[51-53, 57, 58, 60] were based in USA, and one each in Japan[55], Europe[59], Sweden[61], England[62] and one in Canada, Australia and France[56].

Most studies[56, 57, 59, 61] evaluated daily doses of 5 mg of donepezil for 28-30 days and 10mg thereafter, and one study evaluated daily doses of 5 mg for 6 weeks and 10mg thereafter[60]. One study evaluated 5 mg daily[55] and one study[62] evaluated 10mg daily for the duration of the study. One study[52] compared 5-mg and 10-mg doses, and another study[51] compared 1, 3 and 5mg doses. All trials compared donepezil with placebo. The duration of the drug intervention (including titration) was 12 weeks[51, 52, 62], 24 weeks[56, 58, 60, 61], 52 to 54 weeks[57, 59], or 98 weeks[58].

All studies that compared donepezil with placebo evaluated some outcomes of benefit such as the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog), Mini-Mental State Examination (MMSE), clinician-based impression of change with caregiver input (CIBIC-plus), Severe Impairment Battery (SIB), Clinical Dementia Rating Sum of the Boxes (CDR-SB) or Neuro- psychiatric Inventory (NPI) and also reported one or more outcomes of harm (i.e. fractures, falls, injury or syncope).

Table 1. The characteristics of the included studies at baseline (Donepezil v Placebo).

Author Year of Publication Country	Study Duration in weeks	No. Of patients Randomized	Mean MMSE	Mean age	% age Females	Dose mg/day with titration	Study Quality (Jadad)
1.Rogers 1996[51] USA	12	161	18.6	71.8	60	1,3,5 mg/d X 12 wks	Rand=1/2 Blind=1/2 With=1/1
2.Rogers 1998a[52] USA	12	468	19.5	73	63	5mg/d X 1 wk; 10mg/d X 11Wks	Rand=1/2 Blind=1/2 With=1/1
3.Rogers 1998b[53] USA	24	473	19.0	73.4	62	a.5 mg/d X 24 wks; b.5 mg/d X 1 wk;10mg/d X 23 Wks	Rand=1/2 Blind=1/2 With=1/1
4. Homma 2000[55] Japan	24	268	17.2	69.8	67	5mg/d X 24 wks;	Rand=1/2 Blind=1/2 With=1/1
5. Feldman 2001[56] Canada Australia, France	24	290	11.8	73	61.0	5mg/d X 4 wks; 10mg/d X 20Wks	Rand=1/2 Blind=1/2 With=1/1
6.Mohs	54	431	17.1	75.3	62.9	5mg/d X 4	Rand=1/2

2001[57]						wks; 10mg/d	Blind=1/2
USA						X 50Wks	With=1/1
7.Tariot	24	208	14.4	85.7	82	5mg/d X 4	Rand=2/2
2001[58]						wks; 10mg/d	Blind=2/2
USA						X 20Wks	With=1/1
8.Winblad	52	286	19.3	72.5	64	5mg/d X 4	Rand=2/2
2001[59]						wks; 10mg/d	Blind=1/2
Europe						X 48Wks	With=1/1
9.Seltzer						5mg/d X 6	Rand=1/2
2004[60]	24	153	24.1	74.0	53.6	wks; 10mg/d	Blind=1/2
USA						X 18Wks	With=1/1
10.Winblad	26	248	6.1	84.9	76.6	5mg/d X 1	Rand=2/2
2006[61]						month;	Blind=1/2
Sweden						10mg/d X	With=1/1
						5months	
11. Howard	12	272	8.2	84.7	85	10 mg/d X	Rand=2/2
2007[62]						12Wks	Blind=2/2
England							With=1/1

***Rand=Randomization; Blind= Blinding; With= Withdrawals**

3.3 Adverse events

Reporting of adverse events was quite variable. Some of the studies mentioned that details of adverse events were ascertained by questioning of each patient at each assessment

through scheduled questioning and spontaneous reporting[52, 57, 58, 60]. Some of the studies[51, 55] mentioned that all events reported by the patients, or noticed by the caregivers or physicians, were recorded together with the date of onset and cessation, severity and relationship to the medication. Other studies[52, 56, 61] mentioned that monitoring of adverse events was carried out throughout the study but no further details were provided. Most of the studies[52-53, 56-61] reported only those adverse events that occurred in 5% or more of the patients. One study[51] reported most frequently occurring adverse events, where as another study[55] reported those adverse events that occurred in more than 3 patients and there were no details provided in one study[62] . Many adverse events were mild and transient lasting only few days and resolved with continued donepezil treatment without the need for any dose modification[59]. The majority of the adverse events reported were mild[52, 56], mild and transient[53, 60], mild or moderate and transient[61], mild to moderate[58, 59] either with no apparent relationship to the dose of Donepezil[51]; and unrelated or possibly related to Donepezil[57] . Of the 45 different adverse effects examined in patients with Alzheimer dementia and treated with donepezil, diarrhea and nausea were reported most frequently.

Three studies[60-62] reported falls but the exact number or percentage of patients having falls in either group were not reported by one of these[60] . Four studies[55, 59, 61, 62] reported fractures, two studies [57, 59] reported syncope and eight studies reported accidental injuries[51, 52, 56-61]. Four studies reported different combination of adverse events : two studies[60, 61] reported falls and accidental injuries, two studies[57, 59] reported accidental injuries and syncope, two studies[59, 61] reported fractures and accidental injuries and one study[62] reported falls and fractures.

Falls: There was no difference in incidence of falls in the treatment group and placebo as reported in one study [61] and only marginal difference, 1.6% in donepezil and 1.5% in placebo groups, as reported in another study[62].

Fractures: Three studies[59, 61, 62] reported more incidence of fractures in donepezil group (ranging between 1.6% and 6%) as compared to placebo group (ranging between 0% to 3.5%). However, one study[55] reported more incidences of fractures in placebo group (2%) as compared to the treatment group (1%).

Syncope: Two studies[57, 59] reported more incidence of syncope in donepezil group (ranging between 1.4% and 6.3%) as compared to placebo group (ranging between 0% to 2.8%). In one study[60] syncope was mentioned as one of the adverse events observed but the exact number/ percentage of patients having syncope in both groups was not mentioned. In one study[52] one patient of syncope was observed in donepezil group and was considered to be possibly treatment related.

Accidental injury: This was the most common of the four outcomes of harm, observed and reported by 8 studies[51, 52, 56-61]. Six studies[51, 57-61] reported more incidence of accidental injuries in the patients treated with donepezil than in the placebo group ranging between 6% and 65% in donepezil group and ranging between 0% to 55% in placebo group. Two studies[59, 52] reported higher incidence of accidental injuries in the placebo group than in the donepezil group (10% and 8%[59] and 7% and 6% [52] respectively).

3.4 Serious events

Serious/severe adverse events varied from 1% to 25 % in the treatment group and 0 to 26% in placebo group across all 11 studies. While describing all the adverse events, five trials[51,

[52, 56, 58, 59] specified an operational definition of serious adverse event where as six studies[53, 55, 57; 60-62] did not put forth any such definition.

Table 2: Eligible studies evaluating Donepezil and reporting the percent of subjects experiencing harms.

Study Year	No. of patients	With serious events	Fractures	Syncope	Accidental Injuries	Falls	Remarks
Rogers 1998a[52]	D=158 P=153	D=2(1%) P=1(1%)	D=NR P=NR	D=NR P=NR	D=NR P=NR	D=NR P=NR	
Rogers 1998b[53]	D=157 (10 mg/d) P=162	D=15(10%) P=9(6%)	D=NR P=NR	D=NR P=NR	D=NR P=NR	D=NR P=NR	
Feldman 2001[56]	D=144 P=146	D=18(12.5%) P=17(11.6%)	D=NR P=NR	D=NR P=NR	D=11(7.6%) P=14(9.6%)	D=NR P=NR	O
Mohs 2001[57]	D=214 P=217	D=26(12.1%) P=19(8.8%)	D=NR P=NR	D=2(1%) {2R} P=0	D=1(0.5%) P=2(1%){1R}	D=NR P=NR	X
Tariot 2001[58]	D=103 P=105	D=10(10%) P=17(16%)	D=NR P=NR	D=NR P=NR	D=67(65%) P=58(55%)	D=NR P=NR	O
Winblad 2001[59]	D=142 P=144	D=35(24.6%) P=20(3.9%)	D=6(4.2%) P=3(2.1%)	D=3(2.1%) P=1(0.7%)	D=2(1.4%) P=0	D=NR P=NR	X
Winblad 2006[61]	D=128 P=120	D=31(24%) P=31(26%)	D=7(6%) P=4(3%)	D=NR P=NR	D=7(6%) P=6(5%)	D=17(13%) P=15(13%)	O

D=Donepezil
P=Placebo
X=Fracture/Accidental injury/Fall/Syncope-Defined as serious adverse event
O= Fracture/Accidental injury/Fall/Syncope -Not defined as serious adverse event
NR= Not reported
R=Judged by the investigator to be either possibly or definitely related to Donepezil
DB=Double blind phase
EP= (2 Year) extension period

Four studies[53, 56, 57, 59] reported more occurrence of serious/severe adverse events in patients treated with donepezil than in the placebo group; in contrast, three studies[52, 58, 61] reported more serious/severe in the placebo group .Three studies[51, 55, 62] did not report any serious/severe adverse events. One study[60] reported same percentage (5%) of serious/severe adverse events in both the groups. Few studies[52, 59, 60] reported some of the adverse events as

possibly related to the study drug: One study [60] reported one incidence of fall and cerebral haemorrhage; another[59] had one incidence of moderate nausea, and another[52] had one incidence of syncope.

3.5 Withdrawal Rates due to adverse events:

Rates of withdrawal due to adverse events ranged from 5% to 18% in treatment groups and 1% to 11% in placebo groups. Eight studies[51-53, 56, 57, 59, 61, 62] reported more withdrawals due to any adverse events in patients treated with donepezil as compared to placebo group. One study [55] reported same percentage of withdrawals (6%) in both groups. Only one study [58] reported less withdrawals in donepezil group (11%) as compared to (18%) in placebo group; with marginal difference in patients under 85 years of age (13% and 14% in donepezil and placebo groups respectively) and more than double incidence in patients 85 years or more (9% and 20% in donepezil and placebo groups).

3.6 Deaths

There was variable reporting of incidence of death in patients treated with donepezil and placebo in various studies. Three studies[51, 55, 60] did not report any deaths. One study[59] reported more cases of death in patients treated with donepezil (2.8%) as compared with placebo (2.1%). A single case of death was reported in donepezil treated group in one study[56]. There were more deaths observed and reported, in the placebo group as compared with donepezil group, in rest of the studies[52-53, 57-58, 61-62] (ranging between 1% and 16% in placebo group and between 0% and 14% in donepezil groups respectively).

3.7 Methodological Quality of Studies

Most of the studies were funded by industry sponsors[51-53, 56-62]. One trial[55] did not specify the source of support. The quality of studies was variable. Two studies[58, 62] scored 5 out of 5 on Jadad scale describing randomization, blinding and withdrawals with adequate description of randomization and blinding. Two studies[59, 61] scored 4 out of 5; with adequate description of randomization but blinding was not adequately described. Remaining seven studies[51-53, 55-57, 60] scored 3 out of five; having inadequate description of randomization and blinding. All studies, however, had taken into consideration the number of withdrawals from the trials.

McMaster Quality Assessment Scale of Harms (McHarm) was used for assessing the quality of reporting adverse events. In general, the quality of reporting harms was low to moderate in all trials. The harms were pre-defined in 7 studies[51-53, 55, 57-58, 61] where as rest of the studies did not put forth any standard definition of the reported harms. Furthermore, serious events were precisely defined in only 3 studies[56-58] and a single study[57] precisely defined severe events. Nine studies specified the number of deaths in each group[51-53, 56-59, 61-62].The methods of collecting harm was described as active in 10 studies[51-53, 55-56, 58-62] while one study[57] described the mode of collecting harms as passive. Four studies also mentioned personnel collecting the data; their training and background for collecting the information on harms[55, 57, 60, 61]. Eight studies[51-53, 55, 58- 61] described the timing and frequency of collection of harms. None of the trials described use of any standard scale or checklist for collection of harms. Only four studies[55, 57, 59, 60] described the type of statistical analyses undertaken for harms data.

3.8 Data Analysis

Relative risk for each harms outcome was calculated for all studies. It is defined as the probability of an outcome in the treatment group divided by the probability of the outcome in the

placebo group. The figures that follow show the meta-analyses of the harms in the eligible studies

3.9 Meta-analysis

Figure 2: Meta-analysis of accidental Injuries [Donepezil (DPZ) vs. Placebo (PLB)]

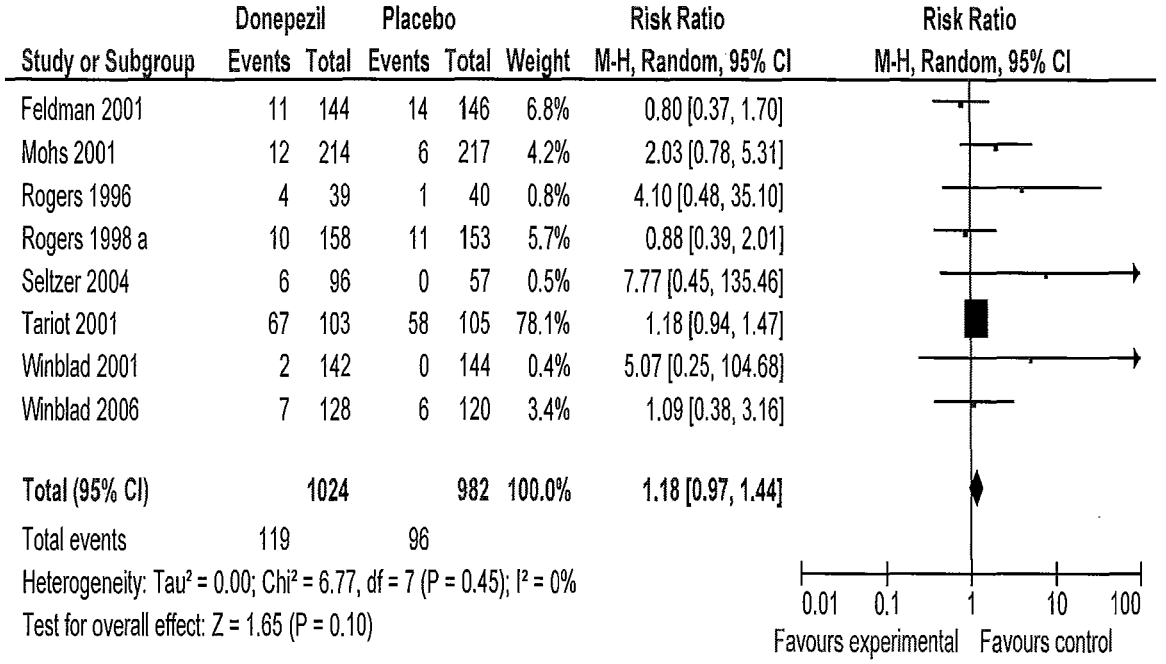
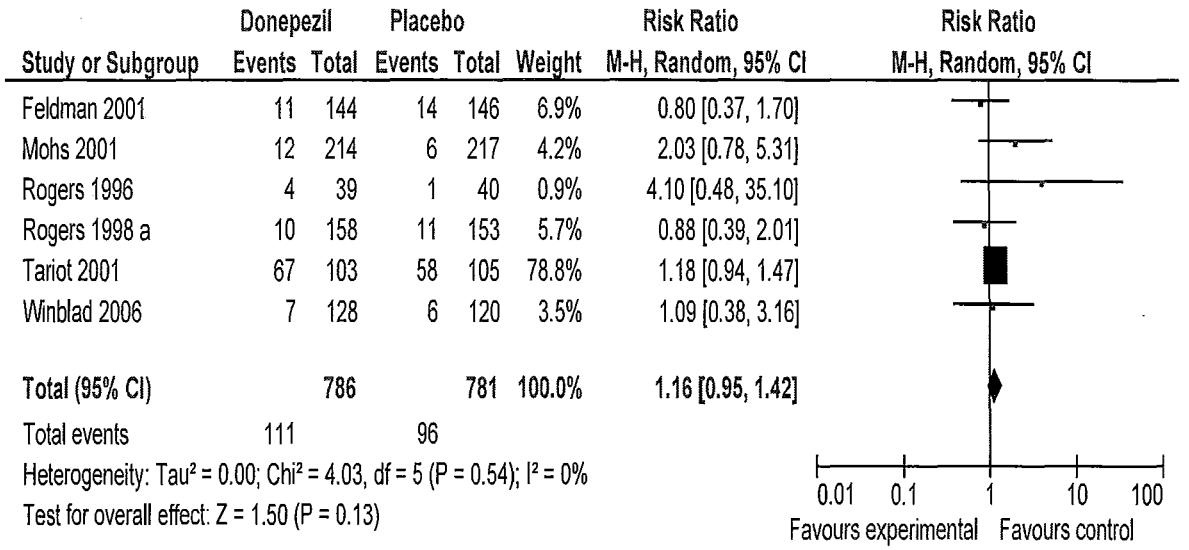


Figure 2 shows that four studies[51, 57, 58, 61] had relative risk ranging from 1.09 to 4.10 indicating that subjects receiving donepezil were at higher risk of getting accidental injuries compared to patients receiving placebo. However, the relative risk in all studies did not reach statistical significance as the confidence interval included 1. Two studies[52, 56] showed a relative risk of less than 1 (0.80 and 0.88) which suggests that there is decreased risk of having accidental injuries in the treatment group compared with the placebo group however these results were not statistically significant.

Figure 3: Meta-analysis of accidental injuries with two studies[59, 60] excluded



Two studies[59, 60] reported no accidental injuries in placebo group resulting in very high relative risk (5.07 and 7.77). But again these were not found to be statistically significant. Removal of these two studies[59, 60] did not significantly change the summary estimate of the relative risk in the meta-analysis; the pooled relative risk with all eight studies included was 1.18 (95% C.I 0.97, 1.44) (figure 2) and with two studies[59, 60] excluded was 1.16 (95% C.I 0.95, 1.42) (figure 3).

Figure 4: Meta-analysis of fractures

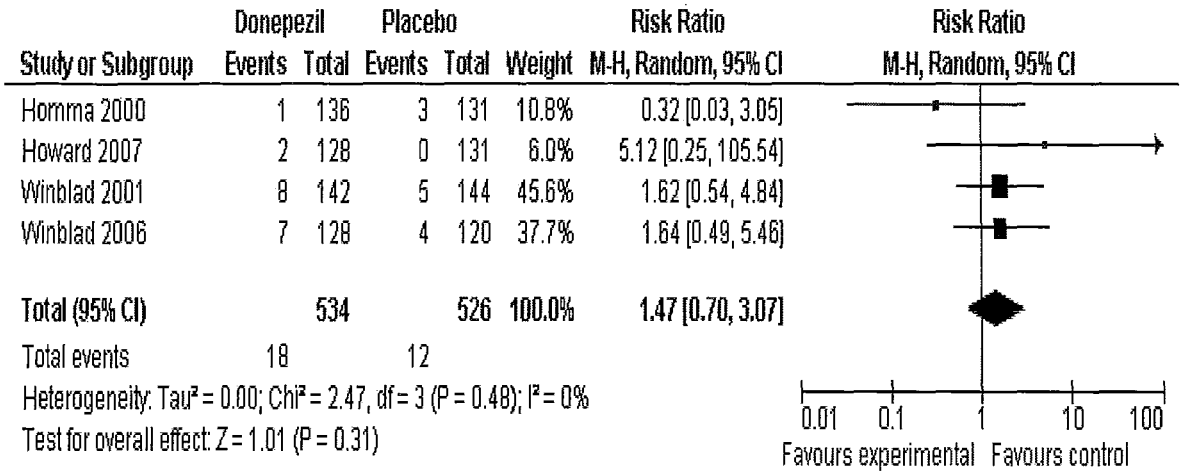


Figure 4 shows that two studies [59, 61] observed relative risks as 1.62 and 1.64 indicating that subjects receiving donepezil were at higher risk of getting fractures compared to patients receiving placebo. However, the relative risk in all studies did not reach statistical significance. One study [55] showed a relative risk of 0.32 suggesting decreased risk of having fractures in the treatment group compared with the placebo group. However like previous studies, these results were not statistically significant. One study [62] reported no fractures in placebo group resulting in very high relative risk 5.12 but these results did not reach statistical significance.

Figure 5: Meta-analysis of falls

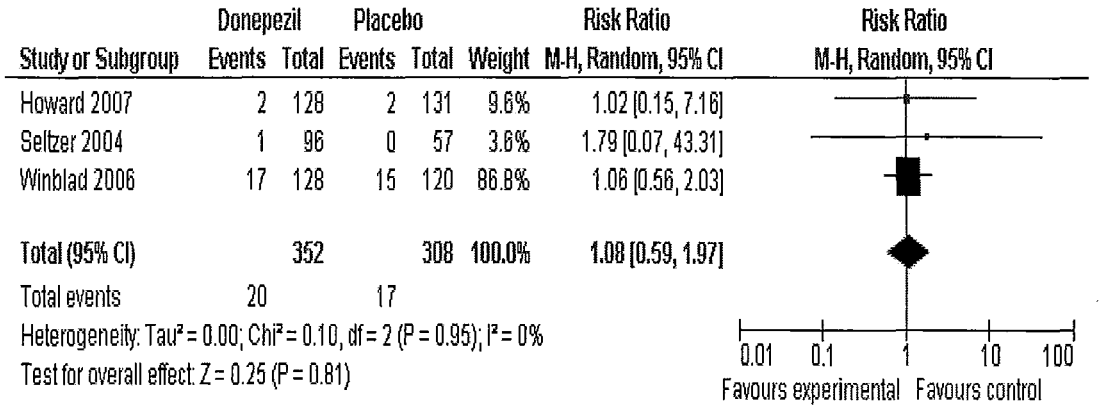


Figure 5 shows that two studies [62, 61] observed relative risks as 1.02 to 1.06 indicating that subjects receiving donepezil were at higher risk of getting falls compared to patients receiving placebo. However, the relative risk in all studies did not reach statistical significance. One study[60] reported no falls in placebo group resulting in a relative risk of 1.79, however not statistically significant.

Figure 6: Meta-analysis of syncope

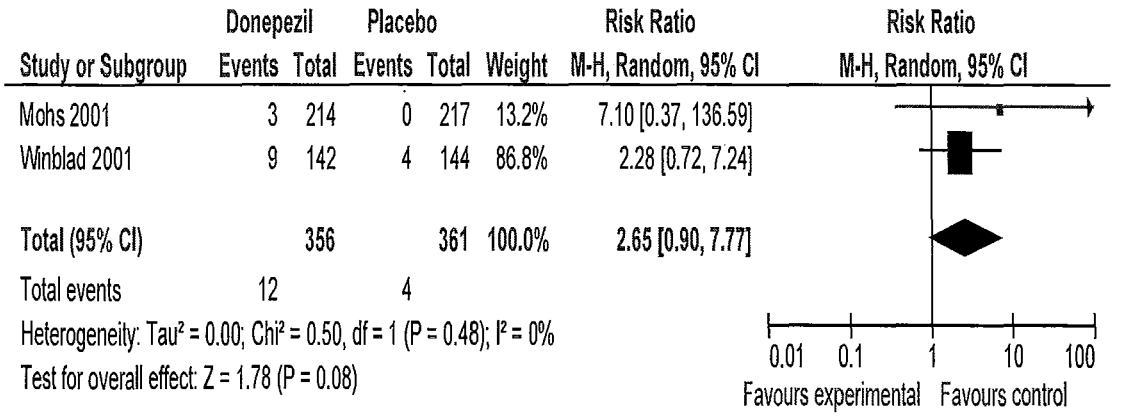


Figure 6 shows that one study[59] observed relative risk of 2.28 indicating that subjects receiving donepezil were at higher risk of getting syncope compared to patients receiving placebo. However, the relative risk did not reach statistical significance. Other study[57] reported no syncope in placebo group resulting in a very high relative risk of 7.10 but again this was not found to be statistically significant.

Table 3: Meta-analysis of all adverse events in studies comparing Donepezil v Placebo

Number of Studies (Reference) Total Sample size	Adverse Event	Number of Adverse Events (%) Drug [Min, Max, %]	Placebo [Min, Max, %]	Magnitude of Summary effect (95% CI)
8	Accidental	119(11.6%)	96(9.8%)	RR: 1.18
2243	injuries	[5.5, 65.0]	[0.0, 55.2]	(0.97, 1.44)
4	Fractures	18(3.4%)	12 (2.3%)	RR: 1.47
1060		[1.0, 6.0]	[0.0, 3.5]	(0.70, 3.07)
3	Falls	20 (5.7%)	17 (5.5%)	RR: 1.08
660		[1.04, 13.0]	[0.0, 13.0]	(0.59, 1.97)
3	Syncope	12 (3.4%)	4(1.0%)	RR: 2.65
356		[1.4, 6.3]	[0.0, 2.8]	(0.90, 7.77)

3.10 Accidental injuries

For Donepezil 10mg/day versus placebo for all severity levels of AD, the summary estimate for accidental injuries showed pooled relative risk of 1.18 indicating that patients in the donepezil group were 1.18 times more likely to have accidental injury as an outcome of harm as compared to patients on placebo. However, this did not reach statistical significance. (Pooled relative risks 1.18, 95% CI = 0.97, 1.44). It was found that for Chi^2 distribution the p-value was 0.45 meaning thereby that there is no statistical difference in the proportion of individuals with accidental injuries in Donepezil and placebo groups. The tests for heterogeneity were not significant ($Tau^2 = 0.00$ and $I^2 = 0\%$). (Figure 2)

3.11 Fractures

For Donepezil 10mg/day versus placebo for all severity levels of AD, the summary estimate for fractures showed pooled relative risks of 1.47 indicating that patients in the donepezil group were 1.47 times more likely to have fractures as an outcome of harm as compared to patients on placebo. However, this did not reach statistical significance. (Pooled relative risks 1.47, 95% CI = 0.70, 3.07).For Chi-square distribution the p-value was 0.48 showing no statistical difference in the proportion of individuals with fractures in Donepezil and placebo groups. The tests for heterogeneity were not significant ($Tau^2 = 0.00$ and $I^2 = 0\%$). (Figure 4)

3.12 Falls

For donepezil 10mg/day versus placebo for all severity levels of AD, the summary estimate for falls showed pooled relative risks of 1.08 indicating that patients in the donepezil group were 1.08 times more likely to have falls as an outcome of harm as compared to patients on placebo. However, this did not reach statistical significance. (Pooled relative risks 1.08, 95% CI = 0.59, 1.97). For Chi-square distribution the p-value was 0.95 showing no statistical difference in the proportion of individuals with falls in Donepezil and placebo groups. The tests for heterogeneity were not significant ($Tau^2 = 0.00$ and $I^2 = 0\%$). (Figure 5)

3.13 Syncope

For donepezil 10mg/day versus placebo for all severity levels of AD, the summary estimate for syncope showed pooled relative risks of 2.65 indicating that patients in the donepezil group were 2.65 times more likely to have syncope as an outcome of harm as compared to patients on placebo. However, this did not reach statistical significance. (Pooled

relative risks 2.65, 95% CI = 0.90, 7.77). For Chi-square distribution the p-value was 0.48 meaning no statistical difference in the proportion of individuals with syncope in donepezil and placebo groups. The tests for heterogeneity were not significant ($Tau^2 = 0.00$ and $I^2 = 0\%$). (Figure 6)

3.14 Galantamine versus placebo

There were 3 unique studies[63-65], evaluating galantamine versus placebo, that were eligible for this systematic review. All studies were published from 2004 onward (n = 1, 2004) (n = 1, 2005) (n = 1, 2006). The studies had many features in common. They were all multi-centre, randomized and double blind. One study [63] comprised of three phases: (1) a 4 week single blind placebo run-in-phase (2) a 6 month randomized double blind, placebo controlled, parallel group phase and (3) a 6 month open-label phase using the active test drug only. No separate data for adverse events for the double blind phase was provided in this study [63]. Another study [64] was a parallel group study, where as the third study [65] had the first 3 months of the study as double-blinded placebo-controlled and after 3 months, the placebo group started taking galantamine for 9 months while the galantamine group continued on galantamine. One study [64] was conducted in USA, Australia, Canada, South Africa, and New Zealand. Another study[63] was based in Sweden and one trial [65] was carried out in Canada, Denmark, Finland, France, Germany, Israel, The Netherlands, Poland, and United Kingdom.

A total of 1274 participants (sample size 18 to 971 participants) were randomly assigned in these placebo controlled trials. One study [63] enrolled patients with Alzheimer disease plus cerebrovascular disease, another study [64] had patient population with mild to moderate Alzheimer's disease and third study [65] had patients with mild Alzheimer's disease. All three studies used NINCDS-ADRDA criteria to diagnose Alzheimer's disease. In one study[64] patients

were recruited from the community and were ambulatory outpatients; in the other trial[63] the source of the patients could not be ascertained from the report and in the remaining trial[65] patients were admitted in inpatient geriatric clinics. Mean ages of the study subjects ranged from 70.9 to 76.6 years in the galantamine group and 65.8 to 76.3 in the placebo group. The severity of the disease was measured by the MMSE scale. Patients were recruited with mild to moderate dementia (MMSE 10-25) in two studies[63, 64] and with mild dementia in the remaining study[65]. Dementia was described as "possible" in one study[63] and "probable" in the other[64].

Patients were excluded from study entry[63, 64] if they had other neurodegenerative disorders or cognitive impairment due to acute cerebral trauma, vascular dementia, hypoxic cerebral damage, vitamin deficiency states, infection, primary or metastatic cerebral neoplasia, significant endocrine or metabolic disease, mental retardation, history of epilepsy or convulsions, active peptic ulcer; clinically significant hepatic, renal, pulmonary, metabolic, or endocrine disturbances; urinary outflow obstruction; cardiovascular disease that would impede subject's ability to complete the trial, or cardiac disease potentially resulting in syncope or other alterations of mental status. Exclusion criteria also included the use of any other agent for the treatment of dementia.

One study [63] evaluated galantamine daily dose of 4mg/d for the first week and titrated up 4mg/d every week over a six-week period until 24mg/d, which was continued for additional 4.5 months in the double blind phase. The other study [64] evaluated galantamine daily dose of 8mg/day x 4 weeks, titrated to a maximum of 16-24mg in increments of 8mg/day every 4 weeks and after week 12, the patient's dose remained fixed for the remainder of the study (end of week 26). This trial compared extended-release galantamine with the usual formulation. The third study [65] evaluated galantamine 16-24mg/day. The duration of the drug intervention varied from 3

months[65] to 6 months[64]. One study [63] had 6 months of double blind and then 6 months of open-label extension including period of titration..

All studies, that compared galantamine with placebo, evaluated outcomes of benefit that included ADAS-cog, CIBIC-plus, NPI, ADL- DAD scale, MMSE, and also outcomes of harm (i.e. fractures, falls, injury or syncope).

Table 4. The characteristics of the included studies at baseline.

Author Year Country of Publication	Duration weeks	No. Of patients	Mean MMSE	Mean age	% age Females	Dose mg/day	Study Quality
1.Bullock 2004[63] 62 Countries	26(Double blind)+26(Open label)	285	20.4	76.5	51.3	4mg/d X 1wk titrated by 4mg/wk to 24mg/d	Rand=1/2 Blind=2/2 With=1/1
2.Brodaty 2005[64] USA, Canada, Australia, S.Africa, New-Z	26	971	17.95	76.5	64	8mg/d X 4 wks titrated by 8mg/d every 4 wks to16-24	Rand=2/2 Blind=2/2 With=1/1
3.Shori 2006[65] Sweden	12	18	26.2	69.2	44.4	16-24mg/d	Rand=2/2 Blind=1/2 With=1/1

***Rand=Randomization; Blind= Blinding; With= Withdrawals**

3.15 Adverse events

Adverse events were monitored throughout each study period [63] but the details regarding their reporting and collection were not provided. The common harms reported in galantamine studies were gastrointestinal symptoms (nausea, vomiting, and diarrhea), eating disorders or weight loss, and dizziness. Serious/severe adverse events were reported by one study[63] and were similar (1%) in both galantamine as well as in the placebo group. Two studies[63, 64] reported falls, no study reported fractures, one study[65] reported syncope and two studies[63, 64] reported accidental injuries.

Falls: One study [64] reported no difference in incidence of falls in the treatment group and placebo (6% in both groups). The other study[63] observed 16% incidence of falls in placebo/galantamine as well as galantamine/galantamine groups but no separate data for adverse events for the double blind phase was provided.

Syncope: One study[65] reported one patient, out of 17 patients that continued with open label phase following 3 months of double –blind phase, was withdrawn from the study because of syncope and this was considered to be possibly related to galantamine.

Accidental injury: One study [63], reported overall higher incidence of accidental injuries in the placebo/ galantamine group than in the galantamine/ galantamine group (13% and 8%) however no separate data for adverse events for the double blind phase was provided. The other study [64] reported 6% incidence of accidental injuries in placebo group and 4% and 8% in galantamine and galantamine prolonged release groups respectively.

3.16 Rates of withdrawal due to adverse events

Rates of withdrawal due to adverse events ranged from 7% to 26% in treatment groups and 5 to 17% in placebo groups. Two studies [64], [65] reported more withdrawals due to any adverse

events in patients treated with galantamine as compared to placebo group. No separate data for adverse events for the double blind phase was provided by the third study [63].

There was variable reporting of incidence of death in patients treated with galantamine and placebo in various studies. One study [64] reported more cases of death in patients treated with prolonged release capsule (PRC) galantamine (1%) as compared with placebo or galantamine (<1%). The other study [63] reported 1.6% incidence of death as a reason for withdrawal but did not specify the cause of the death or the group in which it was observed. The third study[65] did not report any deaths in either group.

3.17 Quality Assessment

Two studies[64-65] were funded by the industry whereas the funding source was not reported for the other study[63]. All studies had good score on Jadad scale. Two studies[63, 65] scored 4 out of 5. Where as one study [63] had adequate description of blinding but not the randomization; the other study[65] had adequate description of randomization but not the blinding. The third study [64] had adequate description for both randomization and blinding, hence scored 5 out of five. All three studies had taken into consideration the number of withdrawals from the study.

McHarm was used for assessing the quality of reporting adverse events. In general, the quality of reporting harms was low to moderate in all trials. The harms were pre-defined in 2 studies[63-64] where as the remaining study[65] did not put forth any standard definition of harm. Further serious and severe events were precisely defined in only 1 study[64]. Two studies[63, 64] specified the number of deaths in each group but no separate data for adverse events for the double blind phase was provided by one of these studies [63]. The method of collecting harm was described as active by one study [64] while other two studies[63, 65] did not mention whether it was active or passive method. None of the studies described the person who collected the harms data

or their training and background. Only one study[64] described the timing and frequency of collection of harms. None of the trials described use of any standard scale or checklist for collection of harms and only one study[64] described the type of statistical analyses undertaken for harms data.

One study[64] compared 319 patients on galantamine prolonged release capsules (PRC) with 326 patients on galantamine and 320 patients on placebo. The relative risk was observed to be 1.34 when patients on galantamine PRC were compared with placebo suggesting that patients on treatment were 1.34 times more likely to have accidental injuries as compared to patients on placebo. However, the relative risk did not reach statistical significance. In contrast, the relative risk was observed to be 0.65 when patients on galantamine were compared with placebo suggesting that patients on treatment were 0.65 times less likely to have accidental injuries as compared to patients on placebo. The relative risk, however did not reach statistical significance.

3.18 Studies of Comparative Effectiveness: Donepezil versus Galantamine

There were two studies [66, 67] that compared donepezil with galantamine. One study [66] compared donepezil (10 mg/d) with galantamine (24mg/d) in 182 patients. This trial was sponsored by industry and carried out in UK. It used NINCDS-ADRDA criteria to diagnose dementia. The patients were recruited from the community and were ambulatory outpatients. Mean ages of the study subjects was 74.1 years in the galantamine group and 72.8 in the donepezil group. Dementia was described as "probable" and MMSE score was 9-18 at baseline and the duration of the drug intervention was 52 weeks. The list of exclusions included use of an ChEIs within 30 days prior to study entry; neurodegenerative disorders other than AD; multi-infarct dementia or clinically active cerebrovascular disease; post-traumatic brain injury, hypoxic cerebral damage, or neoplasia; and coexisting medical conditions that would compromise the

patient's ability to safely complete the trial. It evaluated some outcomes of benefit like ADAS-cog; Bristol ADL, NPI, MMSE, and Screen for Caregiver Burden and also reported one or more outcomes of harm viz. fractures, falls, injury or syncope.

The other study[67] a pilot study in 63 patients to evaluate the potential of galantamine and donepezil to affect sleep in patients with mild to moderate Alzheimer disease and lasted only 8 weeks. This trial was sponsored by industry and carried out in USA. The patients were recruited from the community. Mean ages of the study subjects was 76.5 years in the galantamine group and 77.8 in the donepezil group. Patients had a score of 10-24 on MMSE at baseline. It evaluated CIBIC-Plus, Actigraphy, Pittsburgh Sleep Quality Index and adverse events.

Table 5. The characteristics of the included studies at baseline.

Author Year of Publication	Duration weeks	No. Of patients	Mean MMSE	Mean Age	% age Females	Dose mg/day	Study Quality
1.Wilcock 2003[66] UK	52	188	14.9	73.5	62.1	G 8mg/d X4wks, 16mg/d X 8wks,24mg/d 40wks D=5mg/d X 4 wks,10mg/d X48 wks	Rand=1/2 Blind=1/2 With=1/1
2.Ancoli-Israel 2005[67] USA	8	63	19.4	77.5	62	G 8mg/d X4wks, 16mg/d X 4wks D=5mg/d X 4 wks,10mg/d X4 wks	Rand=1/2 Blind=1/2 With=1/1

***Rand=Randomization; Blind= Blinding; with= withdrawals**

3.19 Adverse events

In one trial[66] the adverse events were monitored throughout the study and the site investigators oversaw management of adverse events and in the other study [67] data regarding spontaneously reported adverse events were collected at every visit. In one study [66] adverse

events were reported as transient and of mild-to-moderate intensity. The most frequently reported adverse events were nausea, agitation, vomiting, headache, and falls. In the other trial [67] the adverse events were described as mostly mild to moderate in severity. The most common adverse events occurring in the trial were diarrhoea, constipation, injury, pain, headache, nausea, and bronchitis.

One study [66] reported falls where as the other study [67] reported accidental injuries as the adverse events observed in the trials. Fractures and syncope were not reported by either trial. There were more serious/severe adverse events observed among the patients treated with donepezil as compared to galantamine (20% and 19% in one study[66], and 13% and 10% in the other study[67]), however these differences were not statistically evaluated for significance.

Falls: The incidence of falls was 16.5% and 8.8 % in patients treated by galantamine and donepezil respectively as reported in one study [66].

Accidental injury: One study[67] reported marginally higher incidence of accidental injuries in the galantamine group (7%) as compared to donepezil group (6%).

3.20 Withdrawal rates due to adverse events

Rates of withdrawal due to adverse events ranged from 10% to 13% in treatment groups. One study [66] reported similar percentage of withdrawals in either group (13%) where as the other study[67] reported higher incidence of withdrawals in donepezil (13%) as compared to galantamine group (10%).

There was variable reporting of incidence of death in patients treated with galantamine and placebo in various studies. One study [66] reported more cases of death in patients treated with donepezil (3.3%) as compared with patients treated with galantamine (2.1%). The other study[67] did not report any deaths in either group.

3.21 Quality Assessment

Both studies[66, 67] were funded by the industry and had 3 out of 5 on the Jadad scale having inadequate description for both randomization and blinding. However both studies had taken into consideration the number of withdrawals from the study. McHarm was used for assessing the quality of reporting adverse events. In general, the quality of reporting harms was low to moderate in all trials. The harms were not pre-defined in both studies. Further serious and severe events were not precisely defined too. Both studies specified the number of deaths in each group. The method of collecting harm was described as active in 1 study[66] while the other study[67] described it as passive method. None of the studies reported the person and their training and background for collecting the information on harms. Both studies described the timing and frequency of collection of harms. None of the trials described use of any standard scale or checklist for collection of harms. Both studies described the type of statistical analyses undertaken for harms data.

3.22 Studies of Comparative Effectiveness: Donepezil versus Rivastigmine

One large trial [68] compared donepezil (up to 10 mg/d) with rivastigmine (up to 12 mg/d) in 998 patients with moderately severe Alzheimer disease over 2 years. This was a prospective, randomized, double blind, parallel- group, multicentre study from 94 centers in Australia, Canada, France, Germany, Italy, Spain and the UK. Dementia was described as "probable". The severity was described as moderate to moderately-severe. Patients had a score of 10-20 on MMSE at baseline. This trial was sponsored by industry. It used DSMIV and NINCDS-ADRDA criteria to diagnose dementia. The patients were recruited from the community and were

ambulatory outpatients. Mean ages of the study subjects was 75.8 in the donepezil group and 75.9 in the rivastigmine group.

The list of exclusions included a current diagnosis of any primary neurodegenerative disorder other than Alzheimer's disease (including Parkinson's disease); and advanced, severe, progressive or unstable disease or disability; a major depressive episode; active, uncontrolled seizure disorder or peptic ulceration; acute ,severe or unstable asthmatic conditions, severe or unstable cardiovascular disease, a history of diagnosis of cerebrovascular disease, a known hypersensitivity to drugs similar to rivastigmine or donepezil; the use of any cholinesterase inhibitor or other approved treatment for AD during the 6 weeks prior to randomization, the use of any investigational drug or treatment known to cause major organ system toxicity or any new psychotropic medication, during the 4 weeks prior to randomization; and finally any anti cholinergic drugs at randomization.

This trial[68] evaluated some outcomes of benefit like Severe Impairment Battery (SIB) Alzheimer's Disease Cooperative Study- Activities of Daily Living scale (ADCS-ADL), Neuro-psychiatric Inventory(NPI), MMSE, also reported one or more outcomes of harm i.e. fractures, falls, injury or syncope.

Table 6. The characteristics of the included study at baseline.

Author, Year, Country of publication	Duration weeks	No. of patients	Mean MMSE	Mean age	% age Females	Dose mg/day	Study Quality
1.Bullock 2005[68] Aus, Can, UK, Fran., Spain, Ger, Italy	104	998	<15(43.4%) >15(56.6%)	75.9	68.7	R=3mg/d X 4 wks titrated by 3mg/d (4wk intervals) to max. of 12mg/d then maintained D= 5mg/d 8wks, 10mg/d 8wks then maintained	Rand=2/2 Blind=2/2 With=1/1

***Rand=Randomization; Blind= Blinding; with= withdrawals**

3.23 Adverse events

Assessments were undertaken at regular intervals to ensure adequate monitoring and recording of adverse events. Information about all adverse events was recorded at each follow up visit, whether volunteered by the subject or carer, or discovered through investigator questioning or examination.

In this trial [68] the most frequently reported adverse events were nausea, agitation, vomiting, anorexia, diarrhea, weight decrease, headache and falls. The incidence of falls was 5% and 2 % in patients treated by rivastigmine and donepezil respectively. Accidental injuries, fractures and syncope were not reported by this trial. There were marginally more serious/severe adverse events observed among the patients treated with donepezil as compared to rivastigmine (33% and 32%). Rates of withdrawal due to adverse events ranged from 14% (rivastigmine) to 7% (donepezil).More cases of death were reported in patients treated with donepezil (1%) as compared with patients treated with rivastigmine (0%).

3.24 Quality Assessment

This study was funded by the industry. This study had a score of 5 out of 5 on Jadad scale having adequate description for both randomization and blinding and had taken into consideration the number of withdrawals from the study as well. McHarm was used for assessing the quality of reporting adverse events. The collection of harms was well reported (maximum quality score).The harms were pre-defined and serious events were precisely defined too. The study specified the number of deaths in each group .The method of collecting harm was described as active as well as passive. It also mentioned the person and his training and background for collecting the information on harms. It also described the timing and frequency of collection of harms. However the trials did not describe use of any standard scale or checklist

for collection of harms. The studies also described the type of statistical analyses undertaken for harms data.

4. DISCUSSION

The patient population (AD), pharmacotherapy (ChEIs), and the outcomes (adverse events) were the important issues in evaluating evidence for this review. This review systematically evaluated the evidence for the effect of ChEIs (donepezil, galantamine and rivastigmine) on the risk of falls and injuries in patients with AD.

4.1 Synopsis of key findings

There were eleven trials[51-53, 55-62] yielding consistent results for the outcomes of interest for donepezil and three[63-65] for galantamine but no such studies were available for the rivastigmine. For comparative effectiveness there were two trials[66, 67] comparing donepezil with galantamine and another trial[68] comparing donepezil with rivastigmine.

4.2 Donepezil trials

A total of 3260 patients with mean age ranging between 48 and 102 years were analysed. Most of the studies[52-53, 56-61] reported only those adverse events occurring in 5% or more of the patients; or most frequently occurring adverse events[51]; or occurring in more than 3 patients[55]. Of the 45 different adverse events, diarrhoea and nausea were reported most frequently.

Three studies[59, 61, 62] reported more incidence of fractures in donepezil group (ranging between 1.6% and 6%) as compared to placebo group (ranging between 0% to 3.5%). However, one study[55] reported more incidences of fractures in placebo group (2%) as compared to the treatment group (1%). There was no difference in incidence of falls in the treatment group and placebo as reported in one study [61] and only marginal difference, 1.6% in donepezil and 1.5% in placebo groups, as reported in another study[62]. Two studies [57, 59] reported more incidence of syncope in donepezil group (ranging between 1.4% and 6.3%) as compared to placebo group

(ranging between 0% to 2.8%). Six studies[51, 57-61] reported more incidences of accidental injuries in the patients treated with donepezil than in the placebo group ranging between 6% and 65% in donepezil group and ranging between 0% to 55% in placebo group. Two studies[59, 52] reported higher incidence of accidental injuries in the placebo group than in the donepezil group (10% and 8%[59] and 7% and 6% [52] respectively).

The quality of all the trials included in this review was variable. Most of the studies[51-53, 55-57, 60] scored 3 out of five on Jadad scale providing inadequate description of randomization and blinding. Two studies[59, 61] scored 4 out of 5; with adequate description of randomization but blinding was not adequately described. Remaining two studies[58, 62] scored 5 out of 5. All studies had taken into consideration the number of withdrawals from the trials. McHarm was used for assessing the quality of reporting adverse events and overall quality of reporting harms was low to moderate in all trials.

4.3 Galantamine trials

Three studies[63-65] evaluated galantamine versus placebo. A total of 1274 participants were analysed. Mean ages of the study subjects ranged from 70.9 to 76.6 years in the galantamine group and 65.8 to 76.3 in the placebo group. One study [64] reported no difference in incidence of falls in the treatment group and placebo (6% in both groups). The same study reported 6% incidence of accidental injuries in placebo group and 4% and 8% in galantamine and galantamine prolonged release (PRC) groups respectively. The relative risk was observed to be 1.34 when patients on galantamine PRC were compared with placebo suggesting that patients on treatment were 1.34 times more likely to have accidental injuries as compared to patients on placebo. In contrast, the relative risk was observed to bc 0.65 when patients on galantamine were compared with placebo suggesting that patients on treatment were 0.65 times less likely to have accidental

injuries as compared to patients on placebo. The relative risks, however did not reach statistical significance.

The other study[63] observed 16% incidence of falls in placebo/galantamine as well as galantamine/galantamine groups. Same study reported overall higher incidence of accidental injuries in the placebo/ galantamine group than in the galantamine/ galantamine group (13% and 8%) however no separate data for adverse events for the double blind phase was provided. One study[65] reported one patient, out of 17 patients that continued with open label phase following 3 months of double –blind phase, was withdrawn from the study because of syncope and considered this to be possibly related to galantamine. All studies had good score on Jadad scale. One study [64] scored 5 out of 5. Other studies[63, 65] scored 4 out of five with one study [63] having adequate description of blinding but not the randomization and the other study[65] having adequate description of randomization but not the blinding. All three studies had taken into consideration the number of withdrawals from the study. McHarm was used for assessing the quality of reporting adverse events and overall quality of reporting harms was low to moderate in all trials.

4.4 Trials of Comparative Effectiveness

There were two studies [66, 67] that compared donepezil with galantamine. One study [66] compared 182 patients with mean ages of the study subjects being 74.1 years in the galantamine group and 72.8 in the donepezil group. The other study[67] was a pilot study in 63 patients with mean ages of the study subjects as 76.5 years in the galantamine group and 77.8 in the donepezil group. The incidence of falls was 16.5% and 8.8 % in patients treated by galantamine and donepezil respectively as reported in one study [66]. The other study[67] reported marginally higher incidence of accidental injuries in the galantamine group (7%) as compared to donepezil group (6%). One large trial [68] compared donepezil (up to 10 mg/d) with rivastigmine (up to 12 mg/d) in

998 patients with mean ages of the study subjects as 75.8 in the donepezil group and 75.9 in the rivastigmine group. The incidence of falls was 5% and 2 % in patients treated by rivastigmine and donepezil respectively. Both studies[66, 67] scored 3 out of 5 on the Jadad scale having inadequate description for both randomization and blinding, however, both studies had taken into consideration the number of withdrawals from the study. McHarm was used for assessing the quality of reporting adverse events and overall quality of reporting harms was low to moderate in all trials.

4.5 Meta-analysis

For Donepezil 10mg/day versus placebo for all severity levels of AD, the summary estimate for accidental injuries showed a pooled relative risk of 1.18; this indicates that patients in the donepezil group were 1.18 times more likely to have accidental injury as compared to patients on placebo (pooled relative risks 1.18, 95% CI = 0.97, 1.44). The summary estimate for fractures showed pooled relative risks of 1.47 indicating that patients in the donepezil group were 1.47 times more likely to have fractures as compared to patients on placebo (pooled relative risks 1.47, 95% CI = 0.70, 3.07). The summary estimate for falls showed pooled relative risks of 1.08 indicating that patients in the donepezil group were 1.08 times more likely to have falls as compared to patients on placebo (pooled relative risks 1.08, 95% CI = 0.59, 1.97). The summary estimate for syncope showed pooled relative risks of 2.65 indicating that patients in the donepezil group were 2.65 times more likely to have syncope as compared to patients on placebo (pooled relative risks 2.65, 95% CI = 0.90, 7.77). However all pooled relative risks did not reach statistical significance.

4.6 Possible mechanisms and explanations for the findings

This meta-analysis has shown a trend towards increased incidence, (although not statistically significant) of falls and related injuries in patients with AD on ChEIs. There are various mechanisms that provide a biological rationale for these findings. ChEIs can cause adverse cardiovascular effects and consequently falls and therefore serious morbidity in older people. Evidence suggests that patients with AD have high prevalence of orthostatic hypotension and carotid sinus hypersensitivity[77]. Donepezil impairs heart rate variability and there is a tendency for hypotensive disorders to be exaggerated in these patients of AD on Donepezil[79]. In addition, ChEIs can provoke symptomatic bradycardia and syncope, which may precipitate fall-related injuries, including hip fracture[80]. With ChEIs individual cognition improves and is also associated with improvements in insight, memory, judgment, and visual spatial ability in the short term. This might actually make patients on ChEIs more mobile and physically active but may increase the risk of falls and associated injuries in this physically fragile population.

There were no studies that reported falls and related injuries in patients treated with Rivastigmine. All ChEIs can cause centrally-mediated gastrointestinal events (mostly nausea and vomiting) and these adverse events and are mostly observed during the dose-escalation phase of therapy. These events have been associated more with the dual acetylcholinesterase/butyrylcholinesterase (AChE/BuChE) inhibitor rivastigmine than with the AChE-selective inhibitors donepezil and galantamine, probably due to rivastigmine's higher potency. Other side effects associated with ChEIs include cardiorespiratory events associated with peripheral cholinergic activity. These symptoms are mostly reported during the maintenance phase of therapy and are more frequently reported with donepezil, but are rarely reported with rivastigmine. These differences are due to the drugs' respective pharmacology[86]. Rivastigmine

preferentially inhibits the G1 isoform of cholinesterase, predominantly located in the cortex, hippocampus and in neuritic plaques and has a longer duration of action. It prevents the breakdown of acetylcholine and butyrylcholine by inhibition of AChE in the central nervous system compartment more than in the periphery. Rivastigmine has more gastrointestinal adverse events and less impact on cardiac receptors[86]. Given the specificity of rivastigmine for cholinesterase isoforms, it is least likely to cause cardiac rhythm effects. This lack of cardiac effect can partially explain possible reason for less occurrence of fall and related injuries in rivastigmine treated patients.

4.7 Limitations of the included studies

There were important limitations with the studies considered for this review and they included variation in doses, short duration of the study period, lack of clear definitions of the outcomes and their severity, poor reporting of adverse events and limited direct comparison of different treatments.

Most of the studies evaluated daily doses of 5mg of donepezil titrated to 10mg after 4-6 weeks for remaining duration of the studies. However these studies did not provide much information about dose-response effect and these might be correlated to adverse events such as falls and related injuries. One study[55] used 5mg/day and another study[62] used 10mg/day for the entire duration. One study[52] compared 5-mg and 10-mg doses, and another study[51] compared 1, 3 and 5mg doses. This variation in the doses limited comparability across studies

Except for the studies by Winblad et al [59] and Mohs et al [57] in which patients were treated for 52 and 54 weeks respectively, the available trials are limited to 12 and 24 weeks of treatment. AD is a slowly progressive disease and usually runs a clinical course of 5 to 10 years. Studies of 6-12 months duration may be long enough to adequately capture significance on the trials'

primary outcome measures and possibly some secondary outcome measures, but represents an inadequate time frame to access safety and risk of harm from falls and related injuries Randomized trial evidence of longer term effects is not currently available and given the wide spectrum of rate of progression of AD in different individuals, extrapolation can be misleading.

Trials were inconsistent in classifying serious events or the severity of adverse events. The reporting of the harms was mostly poor. There has been under-reporting of the adverse events as most of the studies reported harms only when observed in 5% or more of the patient population. Published rates of adverse events in controlled trials may underestimate the rates seen in clinical practice. Further most of the trials did not use any standardized tool or checklist for collection of harms. In addition, most of the studies have also not reported about any training background of the personnel involved in the process of collecting the information about adverse events, and capturing information on the basis of self-report from individuals with cognitive decline can be unreliable.

4.8 Bias

The potential biases associated with systematic reviews are poor quality of included studies, funding of the studies by pharmaceutical industry and the presence of publication and outcome reporting bias. All trials, irrespective of their quality, were included in this systematic review and most of them had good scores on the Jadad scale. However methods of randomization and/or blinding were not adequately described in most of the studies. Most of the studies were funded by industry sponsors and only English language reports were included in this systematic review, and these are acknowledged as possible sources of bias.

4.9 Comparison of results with those from other published studies.

Gill et al [75], in a longitudinal study evaluating administrative data for the long term impact of the use of ChEIs, observed that ChEIs in elderly demented patients are associated with increased rates of syncope and hip fractures. They concluded that, patients on ChEIs had more frequent hospital visits for syncope (31.5 vs. 18.6 events per 1000 person-years; adjusted hazard ratio, 1.76; 95% confidence interval, 1.57 - 1.98). They also had a higher frequency of other syncope-related events vs. control subjects and these included hospital visits for hip fracture (22.4 vs. 19.8 events per 1000 person-years; HR, 1.18; 95% CI, 1.04 - 1.34). A retrospective study by Pakrasi et al [81]of 160 consecutive patients with dementia treated with ChEIs found that 1 patient (0.8%) experienced syncope in those treated with donepezil (n=125); and 1 (3.8%) treated with rivastigmine (n=26) experienced syncope. Birks et al [25]showed the incidence of syncope to be significantly higher in patients on ChEI compared with those given a placebo [41/1194 (3.43%) compared with 19/1012(1.87%)] [(OR 1.90, 95% CI 1.09 - 3.33, p=0.02)]. Raina et al [6] reported pooled relative risk of 1.19 (0.98, 1.44) for accidental injuries in patients with AD treated with donepezil. The findings from these studies are consistent with those in this systematic review in showing that these specific under recognized harms are a problem and should be weighed carefully against the modest benefits, by the prescribing clinicians.

4.10 Future research directions.

These findings suggest that there is a need for placebo controlled, randomized trials of ChEIs, in patients with AD, over longer periods of time and describing the adverse events in greater details. There is also a need for better collection of harms, and appropriate reporting techniques. Other important issues for future research are the cost-effectiveness of the ChEIs

and the duration of treatment in patients with AD. It would be important to have randomized trials with longer duration of treatments that examine economic outcomes such as cost of care and the need for institutionalization and this will also help in establishing the maximum duration of treatment.

These new trials will be extremely useful but are likely to have practical or ethical dilemma. These RCTs will have lot of challenges to overcome. They are bound to be very expensive and the patient population will be extremely challenging with inherent behaviour and cognitive problems and caregiver issues. There will also be a lot of confounders in the form of significant medical, psycho-social, and environmental co-morbidities that may have significant bearing on number of important clinical issues. Better trial designs with development of more sensitive tools would help capture both benefits and hazards. Well designed open- label extension trials may be one way to address these important clinical questions.

4.11 Clinical implications

The population in the eligible studies within this review consisted of carefully diagnosed patients with mild, moderate or severe AD, but this definition of severity raises some concern. The MMSE was used most often across studies but this may not accurately depict true disease severity levels. The MMSE may not represent the cognitive and functional differences between various categories (mild, moderate, and severe) in a clinically meaningful manner and this contributes to heterogeneity and limits the inferences that can be drawn across studies[25]. The severity of disease, using the MMSE, was defined as mild with subjects scoring above 17 and those scoring in the 17 to 10 range as moderate, and below 10 as severe but these limits have changed over time[27]. Most of the trials excluded patients with co-existing illnesses and

concurrent pharmacotherapy; hence the study groups may have been healthier than typically seen in clinical practice. Patients with AD, seen in clinical practice, often have other medical illnesses and are more prone to pharmacological side effects and interactions[27]. Therefore, the published adverse events may underestimate the rates seen in actual clinical practice.

In clinical practice, many clinicians may be unaware of potential harmful cardiovascular effects of ChEIs. These drugs act by enhancing vagal influences on the heart promoting bradycardia which can result in neurocardiogenic syncope. This can lead to fall related injuries including hip fractures[75]. Patients with AD frequently have neurocardiovascular instability and ChEIs may worsen these deficits. Theoretically, ChEIs can induce sinus bradycardia, sino-atrial block, and aggravate pre-existing sinus node disease and atrioventricular block. Major contraindications of ChEIs include, but are not limited to, the sick sinus syndrome, and left bundle-branch block. Based on existing evidence, intensive cardiovascular screening is not justified; however vigilance is required for potential cardiovascular adverse effects of ChEIs[84]. Disease modifying agents, perhaps in the MCI and CIND stages with better biomarkers, may have an important role to play in future in the management of these elderly patient with AD.

5. CONCLUSIONS

This systematic review has shown that patients with AD treated with donepezil are at increased risk of having falls and related injuries; however the pooled relative risks were not statistically significant as shown by the meta-analysis. There was insufficient data for galantamine treated patients and no data was available for rivastigmine treated patients. The comparisons between the ChEI could not be made because of the paucity of head-to-head trials. The risk of the serious adverse events including falls and related injuries must be weighed carefully against the modest benefits of these ChEIs in patients with AD.

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7. APPENDIX

7.1 Description of tests and rating scales used in the included studies: Global Assessment

1. A Clinician's Interview-Based Impression of Change scale (CIBIC-Plus) provides a global rating of patient function in four areas, general, cognitive, behaviour and activities of daily living. All patients are scored on global severity at baseline and subsequent assessments on a scale of 1-7 are relative to baseline, with 1 showing marked improvement, 7 marked worsening with 4 representing no change. Information is obtained from the caregiver and patient and the clinician is blind to all other measures.

2. One study[59] used the Gottfries, Brane and Steen scale (GBS) for the global assessment. The GBS is a comprehensive scale for rating dementia syndromes, based on a semi-structured interview with the caregiver. A seven-point scoring system, from 0 (normal function) to 6 (maximum disturbance or presence of symptoms) measures orientation, memory and concentration (12 items), activities of daily living (6 items), emotional function (3 items) and pathological aspects of behaviour (6 items).

3. Clinical Dementia Rating Scale (CDR) is usually reported as a score 0.5, 1, 2, and 3. However, these scores are derived from ratings in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care), each scored from 0 (normal) to 3 (severe dementia) and the sum of the ratings (0-18) provides the CDR-sum of boxes (CDRSB).

4. MENFIS, which is a modification of the GBS, evaluates cognitive function (7 items), motivational function (3 items) and emotional function (3 items).

7.2 Cognitive Function

1. Alzheimer's disease Assessment Scale (ADAS-Cog) (Rosen 1984) comprises 11 individual tests, spoken language ability (0-5), comprehension of spoken language (0-5), recall of test instructions (0-5), word finding difficulty (0-5), following commands (0-5), naming object (0-5), construction drawing (0-5), ideational praxis (0-5), orientation (0-8), word recall (0- 10) and word recognition (0-12). The total score ranges from 0-70, the high score indicating greater impairment.

2. Mini Mental State Examination (MMSE) evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. The score ranges from 0 (severe impairment) to 30 (normal).

3. The Quality of Life (QoL) is a self-rated seven item scale, based on a 'social indicators' approach, examining relationships, eating and sleeping, and social and leisure activity. The items are scored on an analogue scale between 0 (worst quality) and 50 (best). The Blau scale originally contained 10 items but only 7 are used now.

4. The Severe Impairment Battery (SIB) is a 40- item questionnaire designed to assess the severity of cognitive dysfunction in advanced AD and is divided into 9 domains: memory, language, orientation, attention, praxis, visuospatial, construction, orientation to name, and social interaction. The score ranges from 0 (greatest impairment) to 100 (no impairment).

7.3 Activities of daily living (ADL):

1. One study[59] used the Progressive Deterioration Scale (PDS), which is a disease specific measure of changes in 29 items of the activities of daily living.

2. Caregiver-rated modified Crichton geriatric rating scale (CMCS) is a nine-point scoring system, from 0(normal function) to 8 (maximum disturbance or presence of symptoms) measures orientation, communication, cooperation, restlessness, ability to dress, work and social activities and leisure. The range of scores is 0-56.

3. Disability Assessment for Dementia (DAD) is a 10 domain, 40 items instrument that measures instrumental and basic activities of daily living. A higher score indicates less behavioural symptomatology.

4. IADL (Lawton 1969), is a scale modified to assess people with moderate to severe dementia. The IADL scale assesses the ability to perform eight complex daily tasks: ability to use the telephone, shopping, food preparation, household tasks, laundry, transportation, responsibility for medications and ability to manage finances. The modified version omits the laundry item and includes items from the Alzheimer's Disease Functional Assessment Change Scale (ADFACS) relating to managing household appliances, mail, hobbies and the ability to get around inland outside home.

5. The modified Physical self-maintenance scale (PSMS) (Lawton 1969), is a 6 item scale that rates self care ability (toileting, feeding, dressing, personal hygiene, locomotion and bathing). The modified version used includes three extra items believed to be important for the provision of basic ADL in moderate to severe Alzheimer's disease (loss of recognition of carer, impaired ambulation and wandering).

6. Modified Alzheimer's disease Cooperative Study activities of daily living inventory for severe Alzheimer's disease (ADCS-ADL-severe) is a 19 item scale for basic and complex abilities validated in patients with moderate to severe dementia. Total score ranges from 0 to 54 (no impairment). Items include basic activities of daily living (eating, bathing) and complex (operating taps, switching lights).

7.4 Behavioural Disturbance

The Neuropsychiatry Instrument (NPI), is a 12 item, carer rated instrument, used to evaluate behavioural and neuropsychiatry symptoms, including delusions, hallucinations, agitation/ aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behaviour, night time behaviour, and appetite/eating disorder. Frequency is rated from 1 (occasional, less than once a week) to 4 (very frequent) and severity from 1 (mild) to 3 (severe). The product of frequency and severity ranges from 1 to 12, with a total score ranging from 12 to 120 for the 10 domains summed. A lower score indicates improvement.

7.5 Stress on carers

The NPI-D, the Neuropsychiatric Inventory Distress scale assesses the degree of distress caused to the carer by the 10 individual items (each scores 0-5) of the NPI.

7.6 Health Resource Utilization

This outcome is assessed in the Feldman 2001[59] study. At a time within 2 days of a clinic visit, carers kept records of the time per day they spent assisting with instrumental and basic ADL using a version of the IADL+ and the PSMS scale.

Table 6: Primary research goals identified in each eligible study comparing donepezil with placebo.

1.Rogers1996[51]	To evaluate the efficacy and safety of donepezil in patients with mild to moderately severe Alzheimer's disease and to examine the relationships between plasma donepezil concentration, red blood cell acetyl cholinesterase activity and clinical response.
2.Rogers 1998a[52]	To evaluate the efficacy and safety of donepezil in patients with mild to moderately severe Alzheimer's disease and to examine the relationships between plasma donepezil concentration, red blood cell acetyl cholinesterase activity and clinical response.
3.Rogers 1998b[53]	To evaluate the efficacy and safety of donepezil in patients with mild to moderate Alzheimer's disease.
4. Homma 2000[55]	To evaluate the safety and efficacy of donepezil hydrochloride at 5mg/day in patients with mild to moderately severe AD.
5. Feldman 2001[56]	To investigate the efficacy and safety of donepezil in patients with moderate to severe AD
6.Mohs 2001[57]	To examine the effects of donepezil compared with placebo on the preservation of function in patients with AD over a 1-year period.
7.Tariot 2001[58]	To evaluate the safety and efficacy of donepezil in the management of patients with AD patients residing in nursing home facilities.
8.Winblad 2001[59]	To evaluate the long-term clinical efficacy and safety of donepezil, versus placebo, over 1 year in patients with mild to moderate AD.
9.Seltzer 2004[60]	To evaluate the efficacy of donepezil in patients with early-stage AD

10.Winblad 2006[61]	To assess the effect of donepezil on cognition and activities of daily living in patients with severe Alzheimer's disease living in nursing homes ran by trained staff.
11. Howard 2007[62]	To assess the effect of 12 weeks of treatment with donepezil on clinically significant agitation in patients with AD.

Table 7: Outcome measures in studies comparing donepezil with placebo

Study	MMSE	ADAS -Cog	CDR-SOB	CIBIC-Plus	QoL	Other
1.Rogers 1996[51]	X	X	X	X	X	ADL
2.Rogers 1998a[52]	X	X	X	X	X	
3.Rogers 1998b[53]	X	X	X	X	X	
4. Homma 2000[55]	X	X				MENFIS J-CGIC, CRICHTON
5. Feldman 2001[56]	X			X		SIB,CIBIS,DADNPI,FRSCSS, CAUST,SF-36
6.Mohs 2001[57]	X		X			ADFACS
7.Tariot 2001[58]	X		X			NPI-NH
8.Winblad 2001[59]	X					GBS, PDS, NPI ,GDS
9.Seltzer 2004[60]	X	X	X			CMBT, Apathy Scale.
10.Winblad 2006[61]	X					ADAS-ADL SIB, CGI-C NPI
11. Howard 2007[62]	X					CMAI,CGIC,NPI,SIB

Table .8: McHarm results for donepezil v placebo studies.

Study Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
1.Seltzer2004	0	0	0	0	1	0	1	1	1	0	1	1	1	1	1
2.Winblad2001	0	0	0	1	1	0	0	0	1	0	1	1	1	1	1
3.Winblad2006	1	0	0	1	1	0	1	1	1	0	1	1	1	1	0
4.Feldman2001	0	1	0	1	1	0	0	0	0	0	1	1	1	1	0
5.Mohs 2001	1	1	1	1	1	1	1	1	0	0	1	1	1	1	1
6.Rogers1996	1	0	0	1	1	0	0	0	1	0	1	1	1	1	0
7.Rogers1990a	1	0	0	1	1	0	0	0	1	0	1	1	1	1	0
8.Rogers1998b	1	0	0	1	1	0	0	0	1	0	1	1	1	1	0
9. Tariot2001	1	1	0	1	1	0	0	0	1	0	1	1	1	1	0
10. Homma 2000	1	0	0	0	1	0	1	1	1	0	1	1	1	1	1
11. Howard 2007	0	0	0	1	0	0	0	0	0	0	1	1	1	1	0

Table.9: Primary research goals identified in each eligible study comparing galantamine with placebo.

Study	Objectives
2.Bullock 2004[63]	To evaluate the long term cognitive effects and safety of galantamine 24mg/day in patients with AD plus cerebrovascular disease or mixed dementia.
1. Brodaty 2005[64]	To evaluate the efficacy and tolerability of a flexible dosing regimen (16 or 24 mg/day) of galantamine prolonged-release capsule (PRC) compared with placebo in subjects with mild to moderate Alzheimer's disease (AD).
3. Shori 2006[65]	To evaluate sub chronic and chronic changes of AChE activity in CSF of AD patients treated with galantamine or placebo for up to 1 year, by determining the activity and protein levels of AChE variants in Cerebrospinal fluid (CSF).

Table 10: Outcome measures in the individual trials comparing galantamine with placebo.

Study	MMSE	ADAS-Cog	CDR-SB	CIBIC-Plus	QoL	Other
1. Bullock 2004[63]		X		X		NPI, ADL-DAD Scale, ADL
2. Brodaty 2005[64]		X		X		
3.Shori 2006[65]		X		X		

Table 11: McHarm results for galantamine v placebo studies.

Study Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
13.Bullock 2004[63]	1	0	0	0	1	0	0	0	1	0	1	1	1	1	1
14.Brodaty 2005[64]	1	0	0	1	0	0	0	0	0	0	1	1	1	1	0
15.Shori 2006[65]	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

Table 12: Primary research goals identified in each eligible study comparing donepezil with galantamine

Study	Objective
1.Wilcock 2003[66]	To compare the long-term efficacy and safety of galantamine 24 mg/ day and donepezil 10 mg/day in patients with Alzheimer's disease.
2.Ancoli-Israel2005[67]	To examine the effects of galantamine and donepezil on patient and caregiver sleep.

Table 13: Outcome measures in studies comparing donepezil with galantamine.

Study	MMSE	ADAS-Cog	CDR-SOB	CIBIC-Plus	QoL	Other
1.Wilcock 2003 [66]	X	X		X		BrADL, NPI, SCB
2. Ancoli-Israel 2005[67]				X		Actigraphy, PSQI

Tab.14: McHarm results for donepezil v galantamine studies.

Study Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
16.Wilcock 2003[66]	0	0	0	1	0	1	0	0	1	0	1	1	1	1	1
17.Ancoli-Israel2005[67]	0	0	0	1	1	0	0	0	1	0	1	1	1	1	1

Tab.15: Primary research goals identified in each eligible study comparing donepezil with rivastigmine.

Study	Objective
1.Bullock 2005[68]	To evaluate the efficacy and tolerability of cholinesterase inhibitor treatment in patients with moderate to moderately-severe AD over a two year period.

Table 16: Outcome measures in studies comparing donepezil with rivastigmine.

Study	MMSE	ADAS-Cog	CDR-SB	CIBIC-Plus	QoL	Other
1.Bullock 2005[68]	X					SIB,ADCS-ADL,GDS,NPI

Table 17: McHarm results for donepezil v rivastigmine studies.

Study Author, Year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15
1.Bullock 2005[68]	1	1	0	1	1	1	1	0	1	0	1	1	1	1	0

Table 18: Reason for Exclusion of Studies

S.No.	Drug	Author	Year	Falls, fractures, injuries and syncope not mentioned	No details of Adverse Events reported
1	Donepezil	Holmes	2004	√	
2.	Donepezil	AD2000 CG	2004		√
3.	Galantamine	Cummings	2004		√
4.	Donepezil	Kemp	2003		√
5.	Donepezil	Krishnan	2003		√
6.	Galantamine	Markowitz	2003		√
7.	Donepezil	Feldman	2003		√
8.	Donepezil	Wimo	2003		√
9.	Donepezil	Gauthier	2002		√
10.	Galantamine	Galasko	2004		√
11.	Galantamine	Hancock	2004		√
12.	Donepezil/ Galantamine	Warner	2004	√	
13.	Donepezil	Holroyd-Leduc	2005	√	
14.	Rivastigmine	Karamen	2005	√	
15.	Galantamine	Orgogozo	2004	√	
16.	Donepezil	Summerton	2004		√
17.	Donepezil/ Ginkgo Biloba	Mazza	2006	√	
18.	Galantamine	Dunbar	2006	√	
19.	Donepezil	Johansen	2006	√	
20.	Rivastigmine	Wesnes	2005		√
21.	Donepezil	Feldman	2005	√	
22.	Rivastigmine / Quetiapine	Ballard	2005		√
23.	Donepezil	Moraes	2006	√	

24.	Donepezil	Dantau	2005	√	
25.	Galantamine /Donepezil	Wilkinson	2004	√	
26.	Rivastigmine	Tekin	2006	√	
27.	Rivastigmine /Fluoxetine	Mowla	2007	√	
28.	Rivastigmine	Winblad	2007	√	
29.	Rivastigmine	Feldman	2007	√	
30.	Donepezil	Black	2007	√	
31.	Rivastigmine	Winblad	2007	√	
32.	Rivastigmine	Mahlberg	2007		√
33.	Galantamine	Rockwood	2007		√
34.	Donepezil	Decarli	2008		√
35.	Donepezil	Moraes	2006	√	
36.	Donepezil	Burns	1999	√	
37.	Donepezil	Newman	1999		√
38.	Donepezil	Winstein	2007		√
39.	Donepezil	Tune	2003		√
40.	Galantamine	Wilcock	2000	√	
41.	Galantamine	Rockwood	2001	√	
42.	Galantamine	Tariot	2008	√	
43.	Galantamine	Raskind	2000	√	
44.	Rivastigmine	Rosler	1999	√	
45.	Rivastigmine	Potkin	2001		√
46.	Rivastigmine	Agid	1998	√	
47.	Rivastigmine	Thomas	2001	√	
48.	Rivastigmine	Wilkinson	2000	√	
49.	Rivastigmine	Forette	1999	√	
50.	Rivastigmine	Kumar	2000	√	
51.	Rivastigmine	Sramek	1996	√	
52.	Rivastigmine	Farlow	2000	√	
53.	Rivastigmine	Corey-Bloom	1998	√	
54.	Donepezil/ Rivastigmine	Fuschillo	2001	√	
55.	Donepezil/ Rivastigmine	Wilkinson	2001	√	
56.	Donepezil	Erikjunti	2002	AEs not separately described for VaD,& AD with CVD	