Assessing the Safety of Cholinesterase Inhibitor Discontinuation in Patients with Moderate to Severe Alzheimer’s Disease in a Long Term Care Setting

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science (MSc.)

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Abstract

Cholinesterase inhibitors (ChEIs) are the first line pharmacotherapy for the symptoms of Alzheimer’s disease (AD). Though ChEIs offer modest cognitive benefits in early AD, literature addressing their continued use in severe AD is scarce. This study assessed the safety of discontinuing ChEIs in institutionalized moderate-severe AD patients. Twenty-six patients were randomized, double-blind to ChEI continuation or placebo for 8-weeks. Vitals, weight (kg) and adverse events (AEs) were monitored biweekly. Chi-square test revealed no significant association between semi-blinded treatment allocation and AE occurrence ($\chi^2=(1,26)=0.99$, $p=0.32$). Groups showed no differences on clinically significant weight loss ($\chi^2=(1,26)=1.9$, $p=0.17$), mean weight loss ($F=531$, $p=.473$), pulse rate ($F=.624$, $p=.437$), or side effects ($F=.224$, $p=.640$).

Preliminary results suggest that either ChEIs are well tolerated or that these drugs are no longer providing therapeutic benefit. Study completion (recruitment of 60 patients and unblinding) will generate more comprehensive data for determination of safe ChEI discontinuation guidelines.
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List of Abbreviations

Aβ – amyloid β-peptide
ACB – anticholinergic cognitive burden scale
Ach – acetylcholine
ACHe – acetylcholinesterase
AD – Alzheimer’s Disease
AE – adverse event
APOE – apolipoprotein E
BADL – basic activities of daily living
BID – bis in die ("twice daily")
BP – blood pressure
BuChE – butyrylcholinesterase
CGI – clinician’s global impression
CGI-C – clinician’s global impression of change
ChAT – choline acetyltransferase
ChEI – cholinesterase inhibitor
CNS – central nervous system
CPG – clinical practice guideline
CSF – cerebral spinal fluid
CT – computed tomography
CYP – cytochrome
DPZ – donepezil
DSM-IV - Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
GAL – galantamine
iADL – instrumental activities of daily living
ITT – intention-to-treat
LOCF – last-observation-carried-forward
MAR – medical administration record
MMSE – mini mental status exam
MRI – magnetic resonance imaging
NINCDS-ADRDA - National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NNH – number needed to harm
NNT – number needed to treat
PET – positron emission tomography
PLB – placebo
PNS – parasympathetic nervous system
POA – power of attorney
PRN – pro re nata ("as needed")
RCT – randomized control trial
RIV – rivastigmine
SAE – serious adverse event
SIB – severe impairment battery test
UKU – Udvalg for Kliniske Undersøgelser
18F-FDG – fluorine-18 fluorodeoxyglucose
1 INTRODUCTION

1.1 Statement of Problem

Cholinesterase inhibitors (ChEIs) donepezil, galantamine and rivastigmine are the first line pharmacological treatment for the symptoms of Alzheimer’s disease (AD). Currently, ChEIs are marketed for use in mild to moderate stages of the disease, with donepezil and, more recently, the rivastigmine patch receiving approval for use in severe AD. However, it has been recommended by multiple Clinical Practice Guidelines (CPGs) that these drugs be used for symptomatic management of all stages of the disease (Canadian Study on Health and Aging, 1994; Herrmann and Lanctôt, 2011; Herrmann et al., 2013; Jansen-Ortho, 2008; Novartis, 2008; Pfizer, 2007). Despite these guidelines, there is much controversy surrounding the long-term use of ChEIs as well as their use in a moderate to severe AD population.

While randomized control trials (RCTs) of ChEIs in mild to moderate AD have shown significant improvements in areas of cognition, behavior and global function (Birks, 2006; Corey-Bloom J, 1998; Lanctot et al., 2003b; Rogers et al., 1998a; Rogers et al., 1998b), these studies are relatively short in duration, lasting on average only 3 to 6 months (Herrmann and Lanctôt, 2011; Schneider, 2012). However, a recent population based study of 29 000 AD patients concluded that patients are remaining on these drugs for much longer periods of time, finding community dwelling patients using ChEIs for 2.4 years on average and those in primary care facilities taking ChEIs for up to 2.8 years (Herrmann et al., 2007a; Herrmann et al., 2007b). Considering this, literature with respect to ChEI use in institutionalized patients with more severe stages of the disease is limited. This is especially concerning because these patients have more comorbid illnesses (Kuo
et al., 2008; Volicer and Hurley, 1997), are taking more medications (Hansdottir and Gudmannsson, 2013; Vetrano et al., 2013) and are estimated to one day represent 90% of total patients residing in long-term care (Canadian Study on Health and Aging, 1994; Herrmann and Gauthier, 2008; Herrmann et al., 2007a). Furthermore, it has been theorized that as AD progresses, cholinergic neuronal loss is more profound and continued ChEI therapy may no longer confer any clinical benefit (Brangman, 2003; Herrmann and Lanctôt, 2011; Schneider, 2012). In addition, although ChEI therapy is generally well tolerated, their use is commonly associated with adverse events (AEs) often as a direct result of cholinergic system stimulation (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006). The most commonly reported AEs include nausea, diarrhea, insomnia, vomiting, muscle cramping, fatigue, and weight loss (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006). Altogether, given the lack of data surrounding long-term use in a more severe, institutionalized population coupled with the potential for ChEI associated side effects, investigation of ChEI discontinuation in this population is warranted. Better understanding of the safety and consequences of ChEI discontinuation will help to define future CPGs and improve patient management in AD.

1.2 Purpose of Study and Objective

Specifically, the primary objective of this study is to examine whether discontinuation of ChEIs will be safer than continued ChEI treatment through collection of adverse event reports and monitoring of common ChEI associated side effects. The secondary objective of this study was to examine the relationship between treatment allocation and changes in physiological measures such as weight loss, pulse rate and blood pressure as well as a side effect rating scales between groups. This study also
explored the effects of anticholinergic burden on ChEI tolerability. Taken together, this study aimed to assess the safety and tolerability of discontinuing ChEIs in institutionalized patients with moderate to severe AD.

1.3 Statement Of Research Hypotheses And Rationale For Hypotheses

1.3.1 Primary Hypothesis

The proportion of patients experiencing any adverse event will be smaller in the placebo group when compared to the continuation group, as measured by adverse event reports.

Rationale: This is the first study to look at the effects of discontinuation of all three ChEIs in a severe, institutionalized AD population. While studies of ChEIs over 3 to 6 months have shown that AEs are experienced more frequently in the ChEI group (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006), studies assessing the safety of ChEI cessation after long-term use are limited and even more so in a moderate to severe, institutionalized population. One recently conducted discontinuation study of community dwelling moderate to severe AD patient found no difference between groups on occurrence of AEs between the continuation group and placebo group (Howard et al., 2012). However, institutionalized patients generally have more comorbid illnesses, are taking more concomitant medications and are more functionally impaired than community dwelling counterparts (Kuo et al., 2008; Vetrano et al., 2013; Volicer and Hurley, 1997; Wattmo et al., 2011). Thus, cessation of ChEIs in institutionalized advanced AD patients may result in less AEs occurring in the placebo group due to the alleviation of ChEI related side effects in comparison to the ChEI continuation group.
1.3.2 Secondary Hypotheses

1) The proportion of patients experiencing weight loss (loss of 1.66% of total weight from baseline to 8 weeks) will be smaller in the placebo group in comparison to the continuation group.

2) The mean weight loss (kg) in the placebo group will be lower than the continuation group.

3) The mean increase in heart rate in the placebo group will be higher when compared to the continuation group.

4) The mean side effect scores, as measured by the UKU, will be lower in the placebo group in comparison to the continuation group.

5) The mean decrease in systolic blood pressure (mmHg) in the placebo group will be lower when compared to the continuation group.

6) The mean decrease in diastolic blood pressure (mmHg) in the placebo group will be lower when compared to the continuation group.

Rationale: Given the risk of AEs in AD patients and the fact that patients are remaining on these drugs for long periods of time, it is necessary to establish the effects of ChEI discontinuation on measures of weight loss, pulse rate and blood pressure. It is also important to examine the adverse event burden associated with continuing. The specific rationale for each hypothesis is shown below.

1 and 2) Up to 40% of patients with AD experience weight loss (Berlinger and Potter, 1991; Burns et al., 1989; Morgan et al., 1986; Singh et al., 1988; Tavares and Rabins,
1987). Although the mechanism of weight loss in AD is believed to be multifaceted, it has been linked to ChEI therapy due to the risk of gastrointestinal adverse events with usage (Gillette-Guyonnet et al., 2000). These adverse events include nausea, vomiting, abdominal cramping and anorexia (Birks, 2006; Lanctot et al., 2003b). ChEI use has also been associated with weight loss exclusively (Birks, 2006; Lanctot et al., 2003b). Therefore, it is likely that patients discontinued from ChEIs will experience less clinically significant or average weight loss (kg) than those assigned to continue.

3) ChEI use has been associated with a number of adverse cardiovascular effects. A number of studies have reported an increased incidence of bradycardia and syncope in association with ChEI use (Bordier et al., 2006; Gauthier, 2001; Gill et al., 2009; Hernandez et al., 2009; McLaren et al., 2003; Park-Wyllie et al., 2009). Thus, discontinuation of ChEIs in this population is hypothesized to alleviate bradycardia and elevate heart rate.

4) The most commonly reported ChEI related AEs include nausea, diarrhea, insomnia, vomiting, muscle cramping, fatigue, and weight loss (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006). Considering studies of ChEIs have shown that AEs are experienced more frequently in the ChEI group (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006), ChEI discontinuation is theorized to result in decreased side effect scores as measured by the Udvalg for Kliniske Undersøgelse (UKU) side effect rating scale. The UKU has been validated in a number of studies that have assessed the side effects of psychotropic medications (Jordan et al., 2004; Kim et al., 2008; Lambert et al., 2003; Lindstrom et al., 2001).
5 and 6) Published data have revealed that ChEI treatment in AD patients can be associated with elevations in blood pressure (Claassen et al., 2009; McLaren et al., 2003) as cholinergic stimulation of the sympathetic nervous system can increase peripheral arterial resistance (Masuda, 2004). Therefore, it is hypothesized that cessation of ChEIs will lower blood pressure in those allocated to discontinue versus those remaining on ChEI therapy.

1.3.3 Exploratory Hypothesis

Anticholinergic cognitive burden (ACB) scores will be associated with increased frequency of anticholinergic adverse events and reduced ChEI discontinuation tolerability.

**Rationale:** Studies have reported that 30-70% of AD patients are using an anticholinergic drug concurrently with their ChEI (Chatterjee et al., 2010; Herrmann et al., 2007b; Schubert et al., 2006). The concurrent use of medications with high anticholinergic activity and ChEIs can lead to pharmacologic antagonism, reducing the therapeutic efficacy of both drugs (Boudreau et al., 2011; Carnahan et al., 2004). Moreover, anticholinergic drugs have been found to increase the risk of AEs and delirium in AD as well as exacerbate cognitive impairment in patients (Boudreau et al., 2011; Boustani et al., 2008; Cai et al., 2013; Meyer et al., 2010; Tune, 2001). Anticholinergic medications are therefore considered inappropriate to use in this population. Thus, it is hypothesized that patients with higher anticholinergic burden as measured by the anticholinergic cognitive burden (ACB) scale will experience a higher frequency of anticholinergic
related AEs and reduced ChEI discontinuation tolerability due to the risk of experiencing unopposed anticholinergic effects.

The primary results of this study will help to provide more information regarding the safety of ChEI use and discontinuation in the moderate to severe institutionalized AD population, thereby allowing clinicians to make more informed ChEI treatment decisions. The secondary analyses will help elucidate the effect of ChEI therapy and discontinuation on common adverse events such as weight loss and bradycardia.
1.4  Review of the Literature

1.4.1  Alzheimer’s Disease

In 1906, at a psychiatry conference in Tübingen, Germany, Dr. Alois Alzheimer was the first to describe abnormalities in the brain of a patient who had passed away of an unusual mental illness (Moller and Graeber, 1998). The patient, a 51-year-old woman, clinically presented with severe memory loss, psychosocial impairment and was disoriented to time and place (Alzheimer et al., 1995; Cipriani et al., 2011). Alzheimer also described neuronal loss and the presence of dense fibrils and miliary bodies in the brain of his patient (Alzheimer et al., 1995; Cipriani et al., 2011), which are now known as prominent pathological features of the disease better known today as Alzheimer’s disease (AD).

1.4.2  Prevalence and Impact

Characterized by cognitive and functional decline, AD is an irreversible and progressive degenerative disorder of the brain and is the most prevalent form of dementia, accounting for 60%-70% of all dementias (Thompson et al., 2004; World Health Organization, 2012). AD currently impacts 35.6 million people globally (Alzheimer's Disease International, 2009) and this number is expected to increase with an estimated 7.7 million new cases being reported each year (World Health Organization, 2012). A recent meta-analysis estimated that by the year 2030, 65.7 million people will have AD and that number would roughly double every 20 years, reaching 115.4 million by 2050 (Prince et al., 2013; World Health Organization, 2012). In 2010, it was revealed that the global cost of dementia was US$604 billion per year and that 85% of the expenses were due to care associated with the disease while only 16% were due to direct
medical costs (Wimo et al., 2013; World Health Organization, 2012).

In Canada, AD has an estimated prevalence of 0.95% (303 878) and by 2038; this number is projected to increase to 1.9% (770 811) (Alzheimer Society of Canada, 2010). Factoring in opportunity costs of caregivers, the total economic burden of AD in Canada in 2008 was estimated to be CAD$15 billion (Alzheimer Society of Canada, 2010). With Canada’s aging population it has been forecasted that by 2038, AD related expenses will be upwards of CAD$153 billion (Alzheimer Society of Canada, 2010).

1.4.3 Non-Modifiable Risk Factors

AD is considered a multifactorial disease for which the causes are not yet fully understood. Nonetheless, a couple of non-modifiable risk factors have been identified which are thought to be associated with disease onset and these will be discussed in the following sections.

1.4.3.1 Age

AD is characteristically considered a disease of the elderly although it is not considered a normal part of the aging process. Age is thought to be the most important risk factor for developing AD, as often the disease does not set in until a minimum adult age is reached (Gleichmann et al., 2011; Herrup, 2010). For people aged 60-64, AD prevalence is less than 1% (Ferri et al., 2005). In comparison, for those 85 and older, AD prevalence has been estimated to range from 24% to 33% (Ferri et al., 2005). Furthermore, a nationwide sample of the Canadian population aged 65 years or older found that people with advanced age (≥80 years) were 7 times more likely to develop AD (Lindsay et al., 2002). As age increases, it has been found that two enzymes that degrade
beta-amyloid (Aβ), insulin-degrading enzyme and neprilysin, diminish in number and this reduction leads to the accumulation of Aβ in the brain (Caccamo et al., 2005).

1.4.3.2 Genetics

Genetics is the second strongest risk factor for AD succeeding advancing age. It has been estimated that 25% of people over the age of 55 have a first degree relative with AD (Slooter et al., 1998). AD can either be familial or sporadic in nature. In the rare familial form, disease onset is typically before the age of 65, with some patients developing the disease as young as 30. Also known as early-onset AD, there have been three autosomal dominant genes identified that appear to be associated with this form of the disease. A mutation was identified on the amyloid precursor protein (APP) found on chromosome 21 (Goate et al., 1991; Goldgaber et al., 1987; Kang et al., 1987; Tanzi et al., 1987) as well as mutations in both the presenilin 1 and 2 genes, on chromosomes 14 and 1 respectively (Blennew et al., 2006; Levy-Lahad et al., 1995; Sherrington et al., 1995). Generally, presenilin mutations are responsible for most cases of the early onset AD (Mayeux, 2003). These mutations cause overproduction of beta-amyloid (Aβ) peptides, which in turn result in neuronal dysfunction. Due to the high penetrance of these genes, patients with these mutations have a 95% chance of developing AD (Loy et al., 2013).

The sporadic form, also known as late-onset AD, is considered genetically complex, as both genetic and environmental factors contribute to the manifestation of the disease. However, a large twin study observed heritability of sporadic AD to be 79%, suggesting a major genetic component (Gatz et al., 2006b). Although the interactions between genes and the environment remain unclear, an association was reported between
allelic variants of the apolipoprotein E (APOE) allele and sporadic AD onset (Corder et al., 1993; Loy et al., 2013; Poirier et al., 1993). It was found that those with the ApoE E3/E4, or E4/E4 genotypes, when compared to those with the common E3/E3 genotype, were at higher risk of developing AD (Loy et al., 2013) with the heterozygous E4 genotype tripling AD risk and the homozygous E4 variant increasing risk 15-fold (Farrer et al., 1997; Loy et al., 2013). Typically, APOE functions in the brain as a lipoprotein transporter and catalyzes the breakdown and clearance of Aβ peptides (Poirier, 1994). Although the exact mechanism of disease promotion is still yet to be elucidated, the APOE4 variant was found to be less functionally efficient at Aβ clearance, causing the build up of these peptides (Jiang et al., 2008). The E4 variant was also found to contribute to the formation of tangles and impair mitochondrial function in the brain, leading to neuronal damage (Iurescia et al., 2010). As a result, the E4 allele is thought to be responsible for most of the genetic risk associated with sporadic AD (Ng et al., 1990; Raber et al., 2004), though development of AD is not necessarily due to the presence of the E4 allele. In fact, 75% of E4 heterozygotes never actually get the disease and up to half of AD patients do not carry the homozygous E4 variant (American Society of Human Genetics, 1995).

Other novel candidate genes have been recently identified with genome wide association studies, such as complement receptor 1, clusterin, and phosphatidylinositolbindingclathrin assembly protein, though association is weak and only minor risk may be associated due to the heterogenous nature of sporadic AD (Zetzsche et al., 2010).
1.4.4 Modifiable Risk Factors

Over 30 different modifiable risk factors have been proposed to be contributing factors to the development of AD (Alzheimer Society of Canada, 2011). Many of the common risk factors associated with AD are connected with vascular disease (Breteler, 2000; Kivipelto et al., 2001; Mangialasche et al., 2012). They include cardiovascular disease (Newman et al., 2005; Soneira and Scott, 1996; Stampfer, 2006), stroke (Werring et al., 2010; Wiesmann et al., 2013), type II diabetes (Cheng et al., 2011; Luchsinger, 2010; Matsuzaki et al., 2010), hypertension (Glynn et al., 1999; Kivipelto et al., 2001; Skoog et al., 1996), hypercholesterolemia (Bhatnagar et al., 2008; Kivipelto et al., 2001; Renner et al., 2009), obesity (Petanceska, 2007) and smoking history (Rusanen et al., 2011; van Duijn and Hofman, 1991). It is unclear whether vascular risk factors directly contribute to the pathogenesis of AD or whether they exacerbate the underlying disease.

Other risk factors of AD include history of traumatic brain injury (Breunig et al., 2013; Mayeux et al., 1995; Roberts et al., 1994), Down syndrome (Granic et al., 2010; Lott and Dierssen, 2010), post-menopausal state (Vina and Lloret, 2010), history of depression (Green et al., 2003; Ownby et al., 2006), chronic inflammatory conditions (Perry, 2010), chronic stress (Yaffe et al., 2010), lack of mental or physical exercise (Andel et al., 2005; Bherer et al., 2013; Gatz et al., 2006a), low education levels (Mortimer et al., 2003), loneliness (Wilson et al., 2007), spouse with dementia (Norton et al., 2010), low vitamin D levels (Soni et al., 2012), high homocysteine levels (Zhuo and Pratico, 2010), saturated dietary fats (Takechi et al., 2010), drug abuse and excessive drinking (Tyas, 1996). However, it is of note that the literature on proposed AD risk factors was recently reviewed and aside from age and genetic factors, a panel found
insufficient scientific evidence to support many of the above-mentioned associations due to flaws in research design (Daviglus et al., 2010).

1.4.5 Pathogenesis

The exact pathogenic processes underlying AD onset and progression remain largely unknown. Though many mechanisms are believed to be behind the cause of AD, at present time the dominant hypothesis is considered to be the amyloid cascade hypothesis. The amyloid cascade hypothesis suggests that AD related neuronal degeneration and resultant dementia is caused by an imbalance in Aβ production and clearance in the brain (Hardy and Selkoe, 2002). The increase in the Aβ peptide is thought to be the initiating event, eventually leading to degeneration of the neurons and AD (Hardy and Selkoe, 2002).

Aβ peptides were first extracted and sequenced in the mid 1980’s from the meningeal blood vessels of patients with AD and Down’s Syndrome (Glenner and Wong, 1984a; b; Hardy and Selkoe, 2002). Furthermore, microscopic examination of the cortical and medial temporal areas of the AD brain revealed lesions comprised of neuritic plaques and neurofibrillary tangles. When the plaques were examined more closely, it was discovered that they were primarily composed of Aβ peptides (Masters et al., 1985). Following these findings, the APP gene on chromosome 21 was cloned (Goldgaber et al., 1987; Kang et al., 1987; Robakis et al., 1987; Tanzi et al., 1987) and mutations in this gene were observed to lead to amyloidosis (Hardy and Selkoe, 2002; Levy et al., 1990; Van Broeckhoven et al., 1990) in addition to AD pathologies (Goate et al., 1991; Haass et al., 1994; Hardy, 1992; Mullan et al., 1992). Initially thought to be an abnormal protein specific to AD, it was found that Aβ was produced under normal physiological conditions.
through APP metabolism (Haass et al., 1992). In a healthy individual, APP metabolism could either be amyloidogenic, leading to the formation of Aβ via the action of proteases β- and γ-secretases (Haass et al., 1992; Seubert et al., 1992; Shoji et al., 1992), or non-amyloidogenic via α-secretase (Claeysen et al., 2012; Kojro and Fahrenholz, 2005; Selkoe, 1996). In the amyloidogenic pathway, cleavage of APP produces hydrophobic Aβ fragments (Haass et al., 1992), which are broken down enzymatically (Carson and Turner, 2002) and removed from the brain as mediated by the low-density lipoprotein receptor-related protein (Tanzi et al., 2004). In the non-amyloidogenic pathway, APP is cleaved by α-secretase to form a soluble protein (APPsα) that has neuroprotective properties (Kojro and Fahrenholz, 2005). In familial AD, studies have shown that mutations in the APP gene favoring the amyloidogenic pathway (Cai et al., 1993; Citron et al., 1992; Suzuki et al., 1994) or mutations in the γ-secretase catalytic component presenilin (Alzheimer's Disease Collaborative Group, 1995; De Strooper et al., 2012; Sherrington et al., 1995), cause the overproduction of Aβ42 peptides, which eventually leads to the development of AD.

In the sporadic form of AD, there is limited evidence to support a specific dysregulation of Aβ metabolism that causes disease onset. However, in both familial and sporadic AD, it is theorized that soluble Aβ undergoes conformational changes into two specific species of soluble Aβ fragments (Aβ42 and Aβ40) (Glenner and Wong, 1984a). These Aβ42 and Aβ40 fragments are more prone to aggregate into Aβ oligomers and initiate the misfolding of other Aβ fragments (Jarrett et al., 1993). Eventually these oligomers accumulate to form the larger insoluble fibrils that are characteristic component of amyloid plaques (Cappai and Barnham, 2008; Hardy and Higgins, 1992;
Selkoe, 1991). These events ultimately lead to synaptic dysfunction, neuronal death and deficits in neurotransmitters, all of which are hallmarks of AD. Though it was originally thought that fibrils and plaques were the cause of the neurotoxic changes observed, studies have shown that higher levels of soluble Aβ are what actually correlate with disease severity and progression (McLean et al., 1999; Pimplikar, 2009; Suzuki et al., 1994; Younkin, 1995).

Another pathogenic mechanism is the hyperphosphorylation of the tau protein, which make up the neurofibrillary tangles also observed in AD (Grundke-Iqbal et al., 1986; Nukina and Ihara, 1986). In a physiological normal state, the tau protein acts to promote microtubule assembly and stabilization (Grundke-Iqbal et al., 1986; Nukina and Ihara, 1986). In AD, tau becomes hyperphosphorylated causing destruction of microtubules and interruption of axonal transport, which leads to neuronal and synaptic impairment (Goedert et al., 2006; Iqbal et al., 2005; Schneider and Mandelkow, 2008). Hyperphosphorylated tau, similar to Aβ, is also susceptible to aggregation into fibrils and tangles, which further impact neuronal and synaptic function (Thal et al., 2000). It remains unknown whether tau is directly responsible for AD or if it is a downstream event.

Numerous other processes have also been implicated in AD pathogenesis. Studies have found that in addition to the characteristic plaques and tangles, there are a number of inflammatory markers present in the neurodegenerative process (Akiyama et al., 2000; Lue et al., 1996; Rogers and Shen, 2000). These include the activation of microglia, astrocytes and proinflammatory mediators, which cause the release of cytotoxic molecules such as chemokines, complement proteins, proteinases and reactive oxygen
species (Floyd, 1999; Pratico et al., 2000; Pratico et al., 2001; Swardfager et al., 2010). Additionally, cell cycle deregulation and mitochondrial dysfunction have also been postulated to be involved in the disease process (Castellani et al., 2002; Lin and Beal, 2006) but it remains unclear to what extent these and the above-mentioned mechanisms contribute to AD pathology.

1.4.6 Clinical Features of Alzheimer’s Disease

AD takes a characteristic clinical course that is reflective of the underlying neuropathologic processes taking place. The progression of AD from mild to severe stage of dementia is outlined in the following sections.

1.4.6.1 Mild Alzheimer’s Disease

Patients presenting with mild AD will typically display difficulties with short-term memory and often require assistance with instrumental activities of daily living (iADLS), such as managing finances, driving or completing household chores (Forstl and Kurz, 1999; Trobe et al., 1996). Patients will also exhibit difficulties planning, organizing and may have impaired judgment (Forstl and Kurz, 1999). In addition, patients may start to show signs of vocabulary and verbal fluency deficits (Chobor and Brown, 1990; Locascio et al., 1995). Generally, a patient will score 21–26 out of 30 on the Mini Mental State Exam (MMSE), indicating cognitive impairment is present (Feldman et al., 2008). Some patients with mild AD may also experience behavioural disturbances, which commonly include symptoms such as depression and apathy at this stage (Cummings and Cole, 2002; Geda et al., 2013; Kawas, 2003; Mack et al., 1999; McKeith and Cummings, 2005). Patients may be able to live independently but assistance with iADLs will be
required as mentioned previously and, therefore, a support system is strongly recommended.

1.4.6.2 Moderate Alzheimer’s Disease

As AD progresses to the moderate stage, patients will demonstrate further deterioration of memory and have more profound language deficits as increased paraphasia and circumstantial speech may be evident (Forstl and Kurz, 1999). Patients at this stage may no longer be capable of comprehending written materials, reading or writing descriptive paragraphs (Cummings et al., 1986; Neils et al., 1989). They may also become more disoriented to time and place and begin wandering (Devanand et al., 1997; Fedor, 2005). At this stage patients may require assistance with some basic activities of daily living (BALDs) such as eating and bathing. Some patients may also experience more profound behavioural disturbances, such as irritability and agitation at this stage of the disease (Cummings and Cole, 2002; Fedor, 2005; Geda et al., 2013; Kawas, 2003; Mack et al., 1999; McKeith and Cummings, 2005).

1.4.6.3 Severe Alzheimer’s Disease

Severe AD, estimated by the Canadian Study of Health and aging to account for 50% of all cases (Canadian Study on Health and Aging, 1994; Herrmann et al., 2007a), is characterized by further deterioration of episodic and semantic memory, worsening aphasia, as well as the inability to independently carry out BADLs (Feldman and Woodward, 2005; Herrmann and Gauthier, 2008; Schwam and Xu, 2010). Patients who progress from the moderate to severe stage will often score 10 or less on the MMSE (Herrmann and Gauthier, 2008) and may experience exacerbated neuropsychiatric
symptoms such as agitation, apathy, depression, aberrant motor behavior, hallucinations, delusions and disinhibition (Boller et al., 2002). In addition, due to communicative difficulties, patients with severe AD are often unable to participate in meaningful conversation or describe discomfort effectively, which may increase the risk of developing other medical conditions such as malnutrition, urinary tract infection or pneumonia (Forchetti, 2005; Volcer, 2001).

As the disease progresses, severe AD patients require total care, including assistance with BADLS such as dressing, grooming, toileting and eating. Caregivers of these patients frequently have difficulty managing the demands of caring for their loved one and may find emergent or worsened neuropsychiatric symptoms challenging. Studies have shown that caregivers, especially of severe patients with behavioural disturbances, experience increased burden (Mohamed et al., 2010) and are at increased risk of experiencing anxiety and depressive symptoms (Baumgarten et al., 1994; Ferrara et al., 2008). As a result of the increased care need associated with disease severity, it is often necessary for both the caregiver and the patient, to place the patient into a long-term care facility. It has been estimated that those with moderate to severe AD will represent 90% of total patients residing in long-term care (Canadian Study on Health and Aging, 1994; Herrmann and Gauthier, 2008; Herrmann et al., 2007a).

1.4.7 Diagnosis

At present time, a definitive diagnosis of AD can only be made through post-mortem neuropathological examination of the brain (McKhann et al., 1984; Mirra et al., 1993). Therefore, the diagnosis of AD in a patient is clinically integrative, often involving several important components. Medical history, physical and psychiatric
assessment, family interview and laboratory testing are all required to diagnose AD (Feldman et al., 2008). Physicians can often diagnose AD using diagnostic criteria developed by the National Institute of Neurological and Communicative Disease and Stroke and the Alzheimer’s Disease and Related Disorders Association (NINCDS- ADRDA) and the Diagnostic and Statistical Manual of Mental Health Disorders Fifth Edition (DSM-V) (American Psychiatric Association, 2013; McKhann et al., 1984; McKhann et al., 2011). Laboratory testing is often used to rule out other causes of memory loss such as low vitamin B12 or thyroid disorders and to examine AD associated biomarkers, which will be discussed in the following section.

1.4.8 Biomarkers

Updated diagnostic criteria have increasingly included recommendations for the use of biomarkers in the diagnostic workup of a patient. To date there have been many different candidate biomarkers of AD proposed in the literature such as those found in the blood, the cerebral spinal fluid (CSF) and the brain via neuroimaging techniques (McKhann et al., 2011). For example, candidate blood based biomarkers such as plasma Aβ, plasma protein clusterin (Hardy et al., 2011; Schrijvers et al., 2011; Thambisetty et al., 2010) and signaling proteins (Blennow et al., 2010; Ray et al., 2007) have been associated with elevated risk of AD development and increased disease progression (Mayeux et al., 2003; Mehta et al., 2000). However, other studies have reported conflicting evidence (Blennow et al., 2010; Fukumoto et al., 2003; Irizarry, 2004; Mehta et al., 2000; Mehta et al., 2001) and, therefore, efforts to find the perfect blood based biomarkers are ongoing.
The CSF is a far more established and validated source for biomarkers that are associated with AD. The most notable biomarkers include total tau (T-tau), phosphorylated tau (P-tau) and Aβ42 (Blennow et al., 2010). Studies have shown that T-tau levels and P-tau levels are increased in AD in comparison to controls and have been shown to be associated with the amount of neurofibrillary tangles in the brain (Blennow and Hampel, 2003; Buerger et al., 2006; Fagan and Holtzman, 2010; Tapiola et al., 2009). With regard to CSF Aβ42, patients with AD will have reductions in Aβ42 levels by approximately 50% and this is thought to be due to increased amounts of Aβ42 being deposited into the amyloid plaques instead of migrating to the CSF (Blennow et al., 2006; Rosen and Zetterberg, 2013; Strozyk et al., 2003; Tapiola et al., 2009). All three of these CSF biomarkers measured together offers the best diagnostic accuracy and studies have shown that this combination can differentiate controls and patients with MCI from those with early AD with 75-95% accuracy (Blennow et al., 2010; Johansson et al., 2011; Mattsson et al., 2009).

Structural (e.g., computed tomography (CT) and magnetic resonance imaging (MRI)) and functional neuroimaging techniques (e.g., single-photon emission computed tomography (SPECT) and positron emission tomography (PET)) have also been considered for their potential as diagnostic tools (Blennow et al., 2006; Feldman et al., 2008). The use of MRI and CT allow for structural assessment of cerebral atrophy and are useful for exclusion of other causes of dementia such as brain tumor, subdural hematoma or hydrocephalus (Feldman et al., 2008; Nestor et al., 2004). Specifically, MRI measurement of atrophy in the hippocampus has been able to stage an AD brain and can distinguish between those with AD from healthy controls with high diagnostic
accuracy (>85%) (Jagust, 2006; Kloppel et al., 2008; Sabuncu et al., 2011). However, it should be noted that atrophy in the medial temporal lobe is not exclusive to AD pathology and can be seen in normal aging, depression and other forms of dementia (Frisoni et al., 1999; Laakso et al., 1996). As a result, structural MRI is not able to easily differentiate between AD and other causes of hippocampal atrophy. In addition to MRI measures, functional neuroimaging techniques such as PET or SPECT also provide useful diagnostic information. Specifically, fluorine-18 fluorodeoxyglucose (18F-FDG) PET and SPECT are used to measure brain metabolism and perfusion in patients with AD (Ewers et al., 2011; Noble and Scarmeas, 2009; Nordberg et al., 2010). Another form of PET is amyloid PET, which uses an amyloid tracer to measure amyloid plaque load in the brains of patients. As such, amyloid PET may be a useful technique in early diagnosis, disease staging and evaluation of treatment response in AD.

Taken together, biomarkers such as blood and CSF, as well as neuroimaging techniques, such as MRI, PET and SPECT, provide supportive information and should be considered collectively with clinical, neuropsychological, and laboratory measures in order to establish a more accurate diagnosis of AD.

1.4.9 Pharmacological Management of AD

Pharmacologic treatment for AD remains only symptomatic, as there is no therapeutic agent with the ability to correct or modify the underlying neurodegenerative loss. Current treatment focuses primarily on targeting the neurotransmitter systems impacted by disease progression in order to better regulate AD symptomology. Other pharmacological interventions have attempted to modify the course of the disease but
none have been successful to date (Castellani and Perry, 2012; Extance, 2010; Tayeb et al., 2013; Vellas et al., 2013).

1.4.9.1 Symptomatic Treatment

Symptomatic treatment of AD is achieved through use of the ChEIs and the NMDA-receptor antagonist memantine. The following sections will focus primarily on the ChEIs and outline their role in treatment.

1.4.9.1.1 The Cholinergic Hypothesis

In 1974, Drachman and Leavitt suggested that memory loss and impaired cognition was associated with deficits in central cholinergic neurotransmission after noticing similarities between cognitive performance of healthy individuals with scopolamine-induced impairment and the elderly (Drachman and Leavitt, 1974). Shortly after this discovery, three independent studies reported that post-mortem examination of AD brains displayed drastic reductions in choline acetyltransferase (ChAT), the enzyme responsible for acetylcholine synthesis (Bowen et al., 1976; Davies and Maloney, 1976; Perry et al., 1977; Pinto et al., 2011; Wilkinson et al., 2004). Further evidence of presynaptic cholinergic deficits of the AD brain included selective degeneration of cholinergic neurons in the nucleus basalis of Meynert (Whitehouse et al., 1982) and reductions in both choline uptake (Rylett et al., 1983) and ACh release (Nilsson et al., 1986). Finally, strong associations between severity of cognitive impairment and reductions in cholinergic activity were noted in AD patients (Francis et al., 1993; Perry et al., 1978; Sims et al., 1983; Wilcock et al., 1982). Taken together, these findings all led to the establishment of the ‘cholinergic hypothesis’, which suggests that cholinergic
neuronal degeneration in the septal nuclei and basal forebrain, in addition to the loss of cholinergic neurotransmission, contributes to the cognitive deficits characteristic of AD (Bartus et al., 1982; Francis et al., 1999). The ‘cholinergic hypothesis’ has provided the framework for the development of pharmacological therapies that enhance central cholinergic transmission.

1.5 The Cholinesterase Inhibitors

To date, the most successful pharmacological approach to treating the symptoms of AD has been through the use of the ChEIs. The cholinesterase inhibitors enhance cholinergic neurotransmission through the inhibition of acetylcholinesterase, thereby preventing the hydrolysis of acetylcholine into acetate and choline (see figure I and II). The FDA approved the first ChEI, tacrine-huperzine A, in 1993 for use in the symptomatic treatment of mild to moderate AD. Meta-analysis of tacrine trials showed that it slowed cognitive deterioration and improved global function within the first three months of use (Qizilbash et al., 1998) though it was associated with a high incidence of adverse events, including gastrointestinal AEs and hepatotoxicity (Ames et al., 1990; Qizilbash et al., 2000; Watkins et al., 1994). Due to the poor tolerability profile of tacrine and lack of approval in Canada, the second-generation ChEIs donepezil, galantamine and rivastigmine are used more routinely in clinical practice. The pharmacological properties of each drug are outlined in table 1. Donepezil, a reversible and specific inhibitor of acetylcholinesterases, was the second cholinesterase inhibitor to receive regulatory approval and is the only ChEI approved for use in all stages of AD. Galantamine and rivastigmine were approved shortly after for use in mild to moderate AD. Both donepezil and galantamine act selectively on AChE and are hepatically metabolized by the
CYP2D6 and CYP3A4 enzymes (Wilkinson et al., 2004). In addition, galantamine also acts as an allosteric modulator of presynaptic nicotinic receptors. Rivastigmine has a slightly different profile in that it reversibly targets both AChE and butyrylcholinesterase (BuChE) and is not hepatically metabolized (Wilkinson et al., 2004). Studies have found that although the properties of each ChEI are slightly different, they all have similar efficacy in treatment of AD (Birks, 2006; Lanctot et al., 2003b).

These drugs have been the focus of many studies, with upwards of 30 RCTs examining their utility as a symptomatic AD therapy (Blennow et al., 2006). Various studies of the cholinesterase inhibitors have found that when compared to placebo, ChEIs are efficacious in areas of cognition, behavior and function, with improvement or stabilization maintained for 3 to 6 months (Birks, 2006; Burns et al., 1999; Corey-Bloom and Veach, 1998; Lanctot et al., 2003b; Raskind et al., 2000; Rogers et al., 1998b; Rosler et al., 1999; Wilcock et al., 2000). Additional meta-analyses have shown that ChEIs can provide stabilization in areas of cognition and global functioning into the severe stages of AD (Schmitt and Wichems, 2006; Winblad et al., 2009). It has therefore been recommended that if ChEIs are well tolerated by the patient, therapy should be continued into the later stages of the disease (Cheewakriengkrai and Gauthier, 2013).
<table>
<thead>
<tr>
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<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
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<tbody>
<tr>
<td><strong>Target Enzyme</strong></td>
<td>Selective AChE</td>
<td>Selective AChE</td>
<td>Reversible AChE and BuChE</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>70 hrs</td>
<td>7-8hrs</td>
<td>1 hr</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>100%</td>
<td>80-100%</td>
<td>96%</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>Hepatic (CYP2D6 and CYP3A4)</td>
<td>Hepatic (CYP2D6 and CYP3A4)</td>
<td>Esterase hydrolysis</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>75% Renal</td>
<td>95% Renal</td>
<td>97% Renal</td>
</tr>
<tr>
<td><strong>Recommended Dosage</strong></td>
<td>10 mg/day</td>
<td>16-24mg/day</td>
<td>6-12mg/day</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>All stages of AD</td>
<td>Mild – moderate AD</td>
<td>Mild – moderate AD</td>
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AChE acetylcholinesterase; BuChE butyrylcholinesterase; CYP Cytochrome
Figure I: Acetylcholinesterases hydrolyze acetylcholine (Ach) to choline and acetate.

Figure II: ChEIs inhibit acetylcholinesterase enzymes to allow increased levels of Ach in the synaptic cleft for a longer duration.
1.5.1 Tolerability

The tolerability of medication has significant influence on its clinical efficacy. ChEI tolerability profiles are especially important, as the AD population they are being used to treat is elderly and patients often have multiple comorbid illnesses, frequently necessitating polypharmacy (Hansdottir and Gudmannsson, 2013; Kuo et al., 2008; Vetrano et al., 2013; Volicer and Hurley, 1997). Moreover, cholinergic innervation is found throughout the body and, as a result, ChEIs can affect other systems outside of the CNS. In light of the AEs associated with tacrine use, the safety and tolerability of the second generation ChEIs were important factors to consider in their development. A Cochrane review of the second generation ChEIs concluded that the ChEIs were generally well tolerated though their use was associated with greater instance of AEs and withdrawal due to AEs compared to placebo (Birks, 2006). It should be noted that ChEI related AEs are more frequently reported during the titration phase of therapy (Pratt et al., 2002; Rogers et al., 1998b; Rosler et al., 1999; Tariot et al., 2000).

Due to cholinergic innervation in the parasympathetic nervous system, the gastrointestinal system (GI) system is most commonly affected by the ChEIs. Overstimulation of the cholinergic system has been shown to increase both gastric acid secretion (Lewin, 1999) and intestinal propulsion (Galligan and Burks, 1986; Jackson et al., 2004). Nausea and vomiting are caused by increases in central acetylcholine levels leading to increased dopamine release in the hypothalamus (Thompson et al., 2004). As a result of this, GI related AEs such as nausea, vomiting, diarrhea and abdominal pain are often the most frequently reported AEs in ChEI trials (Birks, 2006; Lanctot et al., 2003b; Takeda et al., 2006). For instance, the Cochrane review found that 32% of ChEI users
experienced nausea in comparison to 9% of users on placebo. Similar differences were also observed in vomiting (21% ChEI vs. 5% placebo), diarrhea (14% ChEI vs. 8% placebo) and abdominal pain (11% ChEI vs. 6% placebo). This is in support of numerous other meta-analyses, which have assessed the tolerability of ChEIs and reported similar GI AE results (Birks et al., 2009; Hansen et al., 2008; Lanctot et al., 2003b; Masterman, 2004; Ritchie et al., 2004). In addition, various studies have demonstrated a clear dose-response effect, with higher dosages of ChEIs being associated with increased risk of GI related adverse events (Birks, 2006; Cummings et al., 2012; Cummings et al., 2013; Imbimbo, 2001).

Numerous studies have found negative associations between weight loss and AD suggesting anorexia and weight loss may be significant ChEI-related adverse events. Patients who experience weight loss are more likely to have a decreased quality of life (Crogan and Pasvogel, 2003), increased disease progression (Albanese et al., 2013; Berlinger and Potter, 1991; White et al., 1997) as well as increased risk of morbidity (Mazzali et al., 2002) and mortality (Guerin et al., 2009; White et al., 1998). It is thought that the GI related adverse effects of cholinesterase inhibitors might cause decreased appetite in patients and subsequent weight loss. Some studies have shown a relationship between ChEI use and weight loss (Birks, 2006; Raskind et al., 2000; Tariot et al., 2000), with ChEI users losing more weight than those on placebo. The Cochrane review reported that patients on ChEIs were three times more likely to experience weight loss than those on placebo (Birks, 2006). Other studies have reported that up to 17% of ChEI users experience anorexia and weight loss (Cummings, 2003; Imbimbo, 2001). However, several long-term studies have reported a similar amount of weight loss between groups
(Gillette-Guyonnet et al., 2006; Gillette-Guyonnet et al., 2005; Guerin et al., 2009; Guerin et al., 2005) and these results may reflect an improvement in tolerability over time or a greater number of sensitive patients withdrawing prematurely.

Although not as widely reported as gastrointestinal AEs or weight loss, ChEI use has also been associated with adverse cardiovascular effects. For instance, numerous studies have reported an increased incidence of bradycardia among ChEI users (Bordier et al., 2006; Gauthier, 2001; Gill et al., 2009; Hernandez et al., 2009; McLaren et al., 2003; Park-Wyllie et al., 2009). The reduced heart rate caused by ChEI administration is thought to be a result of autonomic stimulation of muscarinic receptors belonging to the pacemaker cells of the heart (Dhein et al., 2001). However, there is question as to whether consistent patterns of clinically significant cardiovascular treatment effects exist, as many trials have reported no serious changes in heart rate (Burns et al., 1999; Feldman et al., 2001; Mohs et al., 2001; Pratt et al., 2002; Rogers et al., 1998a). Specifically, one study of nursing home patients reported a similar incidence of bradycardia between groups (5% placebo vs. 6% donepezil) (Tariot et al., 2001). Other cardiovascular related events reported in association with ChEI include orthostatic hypotension, dizziness and syncope (Birks, 2006; Gill et al., 2009; Hartikainen and Bell, 2011; Kim et al., 2011). One large population based study reported patients receiving ChEIs were more likely to visit the hospital for syncope than in controls, 31.5 vs. 18.6 per 1000 people respectively (Gill et al., 2009). Furthermore, some studies have reported ChEI treatment to be associated with elevations in blood pressure (Claassen et al., 2009; McLaren et al., 2003) while others have not (Bordier et al., 2006; Isik et al., 2010; Isik et al., 2012a; Isik et al., 2012b; Masuda, 2004). Disagreement within the literature regarding
ChEI associated adverse events highlights the variation in ChEI response in different study populations and the need for further investigation.

1.5.1.1 Drug-drug Interactions

Due to the high prevalence of comorbid illness and the pervasive polypharmacy in the AD population, the potential for drug-drug interactions between ChEIs and concomitant medications must be considered (Andersen et al., 2011). For example, a large community based study found that 93% of patients were taking at least one other concomitant medication in addition to a ChEI (Relkin et al., 2003). Similarly, a healthcare database study of 28 961 community dwelling and institutionalized patients found patients were taking an average of 8-9 medications concomitantly with their ChEI (Herrmann et al., 2007b). This study also reported that 37% of patients were using either an anticholinergic drug or a benzodiazepine with their ChEI (Herrmann et al., 2007b).

Generally, physicians will use anticholinergic medications to treat what is originally thought as symptoms of old age (i.e. urinary incontinence) when in fact it is side effects from ChEI use (Gill et al., 2005). The concurrent use of medications with high anticholinergic activity and ChEIs can lead to pharmacologic antagonism, reducing the therapeutic efficacy of both drugs (Boudreau et al., 2011; Carnahan et al., 2004).

Moreover, anticholinergic drugs have been found to increase the risk of AEs and delirium in AD and are therefore considered inappropriate to use in this population as well as exacerbate cognitive impairment in patients with dementia (Boudreau et al., 2011; Boustani et al., 2008; Cai et al., 2013; Meyer et al., 2010; Tune, 2001). In addition to anticholinergic medications, physicians should practice caution when prescribing beta-blockers concomitantly due to the increased risk of bradycardia. However, the large
community based study mentioned previously found that the incidence of bradycardia was not significantly increased with concurrent use of ChEIs and beta-blocker or calcium channel blocker medication (Relkin et al., 2003).

1.5.2 Cholinesterase Inhibitors Use in Severe AD

Studies have also demonstrated that ChEIs can provide stabilization in areas of cognition and global functioning into the severe stages of AD (Schmitt and Wichems, 2006; Winblad et al., 2009). These studies are outlined in table 2. For instance, one study conducted a pooled analysis of 3 RCT trials of donepezil use in severe AD and reported significant differences between groups on measures of cognition, ADLs and global function in favour of donepezil (Winblad et al., 2009). However, no difference was seen between groups on behavioural measures. This is in contrast to other trials of ChEI use in moderate to severe AD, which have reported decreases in neuropsychiatric symptoms (Aupperle et al., 2004; Gauthier et al., 2002). In terms of tolerability, while most of these studies have reported greater frequency of AEs in the ChEI treatment group, they are often described as being mild and transient in nature. Therefore, it has been recommended that if ChEIs are well tolerated by the patient, therapy should be continued into the later stages of the disease (Cheewakriengkrai and Gauthier, 2013; Herrmann et al., 2013).
<table>
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<th>Study</th>
<th>Population and Design</th>
<th>Outcomes</th>
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<tr>
<td><strong>Howard et al., 2012</strong>&lt;br&gt;n=295 community dwelling moderate to severe AD&lt;br&gt;PLB-controlled, 52 week discontinuation study of chronic ChEI users (2.5 years).&lt;br&gt;Patients were randomized to one of four groups: DPZ continuation, DPZ + memantine continuation, placebo, placebo + memantine</td>
<td>Safety:&lt;br&gt;• # of AEs&lt;br&gt;Primary DPZ group:&lt;br&gt;↑MMSE (+1.9pts)&lt;br&gt;↓BADLS (-3pts)&lt;br&gt;Greater cognitive stabilization and less functional impairment.</td>
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<td><strong>Winblad et al., 2009</strong>&lt;br&gt;Meta analyses from three multicenter, randomized, double-blind, PLB-controlled trials of donepezil in severe AD&lt;br&gt;Studies:&lt;br&gt;Homma et al., 2008&lt;br&gt;n=325 severe AD. A 24-week, randomized, parallel-group, double-blind PLB-controlled trial&lt;br&gt;Black et al., 2007&lt;br&gt;n=343 severe AD. A 24-week, randomized, parallel-group, double-blind PLB-controlled trial&lt;br&gt;Winblad et al., 2006&lt;br&gt;n=248 severe, institutionalized AD. 6-month, double-blind, parallel-group, PLB-controlled trial</td>
<td>Safety:&lt;br&gt;• AEs in 80.6% DPZ vs. 73.0% PLB&lt;br&gt;• SAEs in 11.6% DPZ &amp; 11.5% PLB&lt;br&gt;• Withdrawal due to AE (12% DPZ vs 6.9% PLB)&lt;br&gt;• AEs that led to discontinuation in the DPZ group were anorexia, UTI, nausea, and diarrhea vs in the PLB group were pneumonia, anxiety, and agitation&lt;br&gt;Pooled analysis:&lt;br&gt;↑ 2.6 pts from baseline to endpoint on total SIB score for patients on DPZ vs. −3.7 for patients on PLB (total difference=6.4pts)&lt;br&gt;↑proportion of patients treated with DPZ showed more stabilization on SIB&lt;br&gt;↓functional decline in favor of DPZ on ADL&lt;br&gt;-Significance in favor of DPZ on CIBIC+&lt;br&gt;↔ NPI similar between groups</td>
<td></td>
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<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Study Design</td>
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| Burns et al., 2009            | N=207       | moderate to severe AD patients in a nursing home setting | 6-month, double-blind, randomized, PLB-controlled trial | ● 88% had AE in GAL group vs. 89% in PLB  
   ● common AEs were UTI, vomiting, diarrhea, nausea and falls.  
   ● SAEs (18% GAL vs. 21% PLB)  
   ● 15% of GAL patients vs. 16% PLB discontinued treatment due AEs  
   Primary:  
   ↑ 1.9 pts from baseline to endpoint on total SIB score for patients on GAL vs. −3.0 for patients on PLB (total difference=4.36pts)  
   ↓MDS-ADL by 1.2 pts in GAL group vs. 1.6 pts in PLB group |
| Bullock et al., 2005          | n=998       | moderately severe AD patients in a community setting | Patients were randomly allocated to RIV 3-12 mg/day or DPZ 5-10 mg/day | ● GI related AEs were most common cause for discontinuation in either group.  
   ● AEs (82% RIV vs. 64.7% DPZ)  
   ● SAEs (31.7% RIV vs. 32.5% DPZ)  
   Primary:  
   ↔ on measures of cognition and behaviour  
   ↑ ADLs and global function for patient on RIV vs. DPZ |
| Cummings et al., 2005         | n=173       | nursing home residents with moderate to severe AD | 26-week, open-label study across 13 centers in the United States | ● 19% (n=33) patients discontinued due to AEs  
   ● 97% of patients experienced at least 1 AE  
   Primary:  
   3.2-point mean improvement in NPI-NH total score |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Safety</th>
<th>Primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aupperle et al., 2004</td>
<td>n= 95</td>
<td>n= 95</td>
<td>Intervention: RIV 1.5 mg BID for 1-2 weeks, increased by increments of 1.5mg BID based on tolerability, until maximum tolerated dose met (6 mg BID).</td>
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</tr>
</tbody>
</table>
|                                             | institutionalized with moderate to severe AD | 52 weeks total | • 94.7% experienced an AE  
• accidental trauma, vomiting, respiratory infection among the most common AEs.  
• Withdrawal due to AE (4.2%) |         |
|                                             |              |              | Primary: improvements in NPI-NH from baseline were observed for 10 of the 12 individual NPI-NH domains (reduction of at least ≥ 30%) |         |
| Burns et al., 2004                          | n=117        | n=117        | Intervention: RIV 6-12 mg/day or placebo |         |
|                                             | moderate to severe AD | Retrospective analysis of pooled data from three randomised, placebo-controlled, double-blind, 6-month trials | • GI events were most common RIV associated AEs (nausea, vomiting and anorexia)  
• drop out was lower in patients with less severe AD |         |
|                                             |              |              | Primary: mean ADAS-Cog score ↓ by 6.3 points in the placebo group vs. ↑ by 0.2 points in the rivastigmine group |         |
| Gauthier et al., 2002                       | n=290        | n=290        | Intervention: DPZ started 5mg/day for 28 days then 10mg/day thereafter or placebo |         |
|                                             | moderate to severe AD | Randomized to DPZ or PLB in 24-week, double-blind, placebo-controlled trial | • Not reported in this study.  
• ↓ NPI scores (improvement) for patients on DPZ in subcategories of anxiety, apathy and irritability. |         |
| Feldman et al., 2001                        | n=299        | n=299        | Intervention: DPZ started (5 mg/day for the first 28 days and 10 mg/day thereafter or placebo |         |
|                                             | moderate to severe AD | Randomized to DPZ or PLB in 24-week, double-blind, placebo-controlled trial. | • AEs (83% DPZ vs. 80% PLB)  
• Withdrawal due to AEs (8% DPZ vs. 6% PLB) |         |
|                                             |              |              | Primary: donepezil showed benefits on the CIBIC+ |         |
1.5.3 Cholinesterase Inhibitors and Long-term Use

As previously discussed, a number of RCTs that led to the marketing of ChEIs showed that treatment could provide modest therapeutic benefit for up to 6 months duration (Birks, 2006; Burns et al., 1999; Corey-Bloom and Veach, 1998; Lanctot et al., 2003b; Raskind et al., 2000; Rogers et al., 1998b; Rosler et al., 1999; Wilcock et al., 2000). Despite this, studies have revealed that ChEIs are being used for much longer than 6 months. One population based study of 29 000 AD patients found that community dwelling patients remained on ChEIs for an average of 2.4 years and those in primary care facilities were on ChEIs for up to 2.8 years (Herrmann et al., 2007a; Herrmann et al., 2007b). Additionally, over half (54%) of the observed population remained on ChEIs up
until death (Herrmann et al., 2007a; Herrmann et al., 2007b; Mansour et al., 2011). At this time, it is still unclear how long ChEI treatments are effective and whether patients with more advanced AD derive any benefit from continued therapy (Herrmann et al., 2011). Many studies have attempted to address the questions surrounding the long-term use of ChEIs and table 3 provides a summary of these studies.

Since being introduced to the market, there have been a limited number of double blind RCTS that evaluate the long-term use of ChEIs in AD. In 2001, two 12 month RCTs in mild to moderately severe populations both reported that 12 months of donepezil therapy resulted in less deterioration of global function and reduced cognition decline when compared with the placebo group (Mohs et al., 2001; Winblad et al., 2001). Similarly, the widely criticized AD2000 trial found that donepezil use over two years was associated with better mini mental state exam (MMSE) and ADL scores though it did not delay institutionalization or functional decline (Black and Szalai, 2004; Courtney et al., 2004; Holmes et al., 2004a; Kaiser et al., 2005). More recently, a 52-week study conducted by Howard et al (2012), also referred to as the DOMINO trial, evaluated 295 moderate to severe community dwelling AD patients who were treated with donepezil between 2 to 3 years prior to enrollment. Participants were randomized to either continue on donepezil or be placed on placebo substitution with or without the concurrent use of memantine (Howard et al., 2012). The study found that patients allocated to continue had less cognitive and functional decline when compared to those on placebo (Howard et al., 2012). The group concluded that donepezil continuation in comparison to discontinuation conferred a 32% cognitive and 23% functional benefit over the 52-week trial period.
Interestingly, AE occurrence between both the ChEI group and placebo group was the same (Howard et al., 2012).

<table>
<thead>
<tr>
<th>Study</th>
<th>Population and Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard et al., 2012</td>
<td>n=295 community dwelling moderate to severe AD</td>
<td>Safety: # of AEs</td>
</tr>
<tr>
<td></td>
<td>PLB-controlled, 52-week discontinuation study of chronic ChEI users (2.5 years).</td>
<td>Primary DPZ group: MMSE (+1.9pts)</td>
</tr>
<tr>
<td></td>
<td>Patients were randomized to one of four groups: DPZ continuation, DPZ + memantine</td>
<td>↓BADLS (-3pts) Greater cognitive stabilization and less functional impairment.</td>
</tr>
<tr>
<td></td>
<td>continuation, placebo, placebo + memantine</td>
<td></td>
</tr>
<tr>
<td>Aupperle et al., 2004</td>
<td>n= 95 institutionalized with moderate to severe AD</td>
<td>Safety: 94.7% experienced an AE accidental trauma, vomiting, respiratory infection among the most common AEs.</td>
</tr>
<tr>
<td></td>
<td>26-week open-label extension to a 26-week open-label study, 52 weeks total</td>
<td>Withdrawal due to AE (4.2%)</td>
</tr>
<tr>
<td></td>
<td>Intervention: RIV 1.5 mg BID for 1-2 weeks, increased by increments of 1.5mg BID based</td>
<td>Primary: improvements in NPI-NH from baseline were observed for 10 of the 12 individual NPI-NH domains (reduction of at least ≥ 30%)</td>
</tr>
<tr>
<td></td>
<td>on tolerability, until maximum tolerated dose met (6 mg BID).</td>
<td></td>
</tr>
<tr>
<td>Lyketsos et al., 2004</td>
<td>n=288 mild to moderate AD</td>
<td>Safety: mild to moderate AEs agitation, nausea, depression and anorexia among most commonly reported AEs no increase in AEs over extended exposure</td>
</tr>
<tr>
<td></td>
<td>Open-label extension study of 5-month, randomized, double-blind, parallel-group,</td>
<td>Primary: sustained cognitive benefits on ADAS-Cog/11 scores at 18.5 months</td>
</tr>
<tr>
<td></td>
<td>placebo-controlled study of galantamine. Total duration was 18 months.</td>
<td></td>
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<tr>
<td></td>
<td>Intervention: GAL titrated to 12mg BID</td>
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</tr>
<tr>
<td>Mohs et al., 2001</td>
<td>n=431 mild to moderate AD</td>
<td>Safety: AE in DPZ (GI, headaches) SAE: 12.1% DPZ vs. 8.1% PLB Withdrawal due to AE (9.3%DPZ vs. 5.5%PLB)</td>
</tr>
<tr>
<td></td>
<td>PLB-controlled, 54 week study</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intervention: DPZ started (5mg/day)</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Participants</td>
<td>Design</td>
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<tr>
<td>Winblad et al., 2001</td>
<td>n=255 mild to moderate AD PLB- controlled, 52 week study</td>
<td>Intervention: DPZ started (5mg/day for 28 days then 10mg/day thereafter) or placebo</td>
</tr>
<tr>
<td>Farlow et al., 2000</td>
<td>n=532 mild to moderately severe AD Open-label extension of 26 week PLB-controlled study, 26 week study</td>
<td>Intervention: RIV (2-12mg/day)</td>
</tr>
<tr>
<td>Raskind et al., 2000</td>
<td>n=353 mild to moderate AD Open-label extension of 26 week placebo-controlled study, 26 week study</td>
<td>Intervention: GAL (24-32mg/day)</td>
</tr>
<tr>
<td>Minthon et al., 2009</td>
<td>n=217 mild to moderate AD Open-label, multicenter observational study over 24 months. Patients included were taking RIV.</td>
<td></td>
</tr>
</tbody>
</table>

### 2 Year Data

- Minthon et al., 2009
  - n=217 mild to moderate AD
  - Open-label, multicenter observational study over 24 months. Patients included were taking RIV.
  - Safety: ● 25.6% of withdrawals to adverse events
  - Primary: 67% of completers exhibited cognitive decline as assessed by the MMSE and ADAS-cog. 47% showed an unchanged/improved CIBIC rating.
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients Description</th>
<th>Intervention</th>
<th>Safety</th>
<th>Primary</th>
</tr>
</thead>
</table>
| Bullock et al., 2005          | n=998 moderately severe AD patients in a community setting | Patients were randomly allocated to RIV 3-12 mg/day or DPZ 5-10 mg/day | ● GI related AEs were most common cause for discontinuation in either group.  
  ● AEs (82% RIV vs. 64.7% DPZ)  
  ● SAEs (31.7% RIV vs. 32.5% DPZ) | Primary:  
  ➔ on measures of cognition and behaviour  
  ↑ ADLs and global function for patient on RIV vs. DPZ |
| Grossberg et al., 2004        | n=2010 mild to moderate AD | Meta-analysis of two open-label extension studies of four RCTs, 104 week study in total | Safety:  
  ●↑AE in lower doses  
  ● GI symptoms 3-4X more likely in 1st year vs. second year | Primary: ADAS-Cog scores of treated group decreased 4-5 points less than hypothetical control group |
| Doody et al., 2001b           | n=763 mild to moderate AD | Open-label extension of 2 placebo-controlled studies, 144 week study in total | Safety:  
  ● 92% experienced an AE  
  (diarrhea, nausea and headache were most common treatment related AEs)  
  ● Mild and transient AEs | Primary: DPZ ADAS-Cog scores decreased 10-12 points below baseline. Concluded long-term DPZ use may have confer some advantages. |
| Courtney et al., 2004         | n=565 community-resident patients with mild to moderate AD | 12-week run in where patients randomly allocated DPZ (5 mg/day) or PLB then rerandomised to either DPZ (5 or 10 mg/day) or PLB, with treatment continuing as long as deemed appropriate | Safety:  
  ● ➔ AEs  
  ● ➔ death  
  ● ➔ behaviour | Primary: No significant difference on rates of institutionization and progression of disability (↑BADLs) between groups |
<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Design</th>
<th>Treatment</th>
<th>Safety</th>
<th>Primary Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scarpini et al., 2011</td>
<td>n= 139 community dwelling with mild to moderate AD</td>
<td>Open label phase: 12 months on GAL</td>
<td>RCT withdrawal phase: continuation or placebo for 24 months. Total of 36 months.</td>
<td><strong>Safety:</strong>  ● AE in GAL (34% vs. 27%) ○ Withdrawal due to AE (10.5%GAL vs. 6.3%PLB)</td>
<td>Primary: Placebo subjects were more likely to discontinue prematurely for any reason. ↔ ADAS-Cog between groups</td>
</tr>
<tr>
<td>Wallin et al., 2011</td>
<td>n=280 mild AD</td>
<td>Open-label study, 36 months in total.</td>
<td>GAL (8mg-24mg/day)</td>
<td><strong>Safety:</strong>  ● 9.3% of withdrawals due to adverse events</td>
<td>Primary: MMSE decline of 2-4 points seen in treatment was comparable with historical cohort data. ADAS-Cog scores of treated group decreased 5-6 points less than historical cohort data</td>
</tr>
<tr>
<td>Burns et al., 2007</td>
<td>n=579 mild to moderate AD</td>
<td>Open-label extension study of a 24-week RCT, 162-weeks in total</td>
<td>Intervention: DPZ (5-10mg/day)</td>
<td><strong>Safety:</strong>  ● 85% experienced an AE (diarrhea (12%), nausea (11%) were most common) ○ 15% discontinued due to AEs</td>
<td>Primary: 50% less change ADAS-Cog (mean Δ =15.6pts) compared to non-treated, historical cohort</td>
</tr>
<tr>
<td>Raskind et al., 2004</td>
<td>n=194 mild to moderate AD</td>
<td>Open-label extension of 2 placebo-controlled studies, 36 months in total</td>
<td>Intervention: GAL (24mg/day)</td>
<td><strong>Safety:</strong>  ● GI AEs in long-term users ○ most common AE was psychiatric disorder (65.7%) ● Mild and transient AEs</td>
<td>Primary: 50% less change in ADAS-Cog (mean Δ = 10.2pts) compared to projected placebo group</td>
</tr>
<tr>
<td>Pirttila et al., 2004</td>
<td>n= 491 mild to moderate AD</td>
<td>Open label continuation trial following enrollment 12-month trial, patients received GAL 24 mg/day for a total of 24 months</td>
<td></td>
<td><strong>Safety:</strong>  ● 93% experienced an AE ○ most common AEs were agitation (16%), insomnia (12%), fall (11%), and urinary tract infection (10%)</td>
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</tr>
<tr>
<td>Study</td>
<td>Patients (Table 36 months)</td>
<td>AEs</td>
<td>Safety</td>
<td>Notes</td>
<td></td>
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<tr>
<td>Gordon et al., 2003</td>
<td>n=130 mild to moderate AD</td>
<td>•Mild and transient AEs</td>
<td>•Not assessed.</td>
<td>Less change in MMSE (2.8 points) in treatment group compared to naturalistic, untreated group</td>
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<tr>
<td></td>
<td>Retrospective study over 3 years</td>
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<td></td>
<td>DPZ (5mg-10mg/day) and vitamin E (1000 U/day)</td>
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<tr>
<td>Schwalen and Hammond, 2003</td>
<td>n=240 mild to moderate AD</td>
<td>Safety: •Not assessed.</td>
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<tr>
<td></td>
<td>Open-label extension of 2 placebo-controlled studies, 48 months in total</td>
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<td></td>
<td>GAL (24mg/day)</td>
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<td>4 Year Data</td>
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<tr>
<td>Small et al., 2005</td>
<td>n=83 (for 5 year data)</td>
<td>Safety: •22.4% discontinued due to AEs</td>
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<tr>
<td></td>
<td>Pooled RIV data from two pooled open-label extensions of four 6-month, randomized, placebo-controlled trials</td>
<td>•AEs in long-term users</td>
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<tr>
<td></td>
<td></td>
<td>•Mild and transient AEs</td>
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<tr>
<td></td>
<td></td>
<td>•Most common AEs: nausea (40.3%), vomiting (27.9%), agitation (25.1%), accidental trauma (21.0%), dizziness (20.7%) and diarrhea (18.9%)</td>
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<td>Primary: MMSE score in patients continuing to receive RIV was 7.3 points higher than vs projected group at endpoint</td>
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<tr>
<td>5 Year Data</td>
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<tr>
<td>Rogers et al., 2000</td>
<td>n=133 mild to moderately severe AD</td>
<td>Safety: •19% discontinued due to AEs</td>
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<tr>
<td></td>
<td>240 week long open-label study of DPZ use following 14 week PLB controlled double blind RCT</td>
<td>•93% experienced an AE</td>
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<tr>
<td></td>
<td></td>
<td>•Mild and transient AEs</td>
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<td></td>
<td>Primary: ADAS-cog and CDR-SB decline after first 6-9 months. ADAS-cog: 6.07 in DPZ vs. 9–11 points in untreated at endpoint.</td>
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</table>
Due to the ethical limitations of conducting long-term RCTS, a number of open-label trials have also attempted to examine the outcomes of chronic ChEI use. Most of these studies were extended from 26-week pharmaceutical sponsored RCTs and use data from the placebo groups in the RCTs or naturalistic studies to model disease progression for comparison to open-label treatment groups. Many of the open-label studies have suggested that the cognitive benefits of donepezil (Doody et al., 2001a; Doody et al., 2001b), rivastigmine (Doraiswamy et al., 2002; Farlow et al., 2000) and galantamine (Blesa et al., 2003; Marcusson et al., 2003) therapy can be sustained for as long as two years. These studies have all described associations between ChEI use and delays in cognitive deterioration in comparison to projected placebo groups or historical untreated cohort data (Blesa et al., 2003; Burns et al., 2007; Grossberg et al., 2004; Klatte et al., 2003; Wallin et al., 2011). Longer trials, lasting 4 or 5 years in duration, have been completed though the sample sizes are low and combine data from several cohorts (Small et al., 2005). One long-term study of donepezil showed that after 5 years, decline in ADAS-cog/11= 11-item AD Assessment Scale cognitive subscale; AE adverse event; CIBIC-Plus Clinician's Interview-Based Impression of Change Plus Caregiver Input; DPZ donepezil; GAL galantamine; GI gastrointestinal; GPS Gottfries-Bråne-Steen scale; MMSE mini mental state exam; PLB placebo; RIV rivastigmine
Mendiondo et al., 2000; Small et al., 2005). Despite these positive results, long-term open-label studies must be interpreted with caution as they are non-blinded and introduce biases (Birks, 2006; Bullock and Dengiz, 2005; Wattmo, 2013). For example, many of these studies report decreased rates of AEs after longer periods of usage (Grossberg et al., 2004; Raskind et al., 2004; Small et al., 2005). However, it should be noted that withdrawal rates for these studies are typically high as time passes due to adverse events and AD progression. Some studies have reported 45% withdrawal after two years and as high as 80% withdrawal after 3 years (Doody et al., 2001b; Johannsen, 2004). Therefore, those who remain in these studies are typically healthier and introduce survivorship bias, which can lead to the false conclusion that the pharmacotherapy is superior to no treatment (Johannsen, 2004). In addition, comparison to naturalistic studies often raises issues of demographic and clinical differences between cohorts and often overestimates the rate of decline in the untreated group, causing the active treatment to appear more efficacious (Birks, 2006; Johannsen, 2004).

1.5.4 Cholinesterase Inhibitor Discontinuation

Patients are remaining on ChEIs for long periods of time and often until death although the literature on long-term ChEI use is limited. It has been suggested that patients are remaining on these drugs due to lack of definitive ChEI discontinuation protocols. For instance, it has been recommended by multiple CPGs that ChEIs be used for symptomatic management of all stages of the disease, including severe AD (Canadian Study on Health and Aging, 1994; Herrmann and Lanctôt, 2011; Jansen-Ortho, 2008; Novartis, 2008; Pfizer, 2007) and treatment should be continued until there is no longer a
demonstrated therapeutic benefit (Herrmann et al., 2007a; Herrmann et al., 2013; National Institute for Health and Clinical Excellence (NICE) Guidelines, 2011; Vellas et al., 2005). Although correlates of enhanced treatment response have been determined (Lanctot et al., 2003a), literature addressing clinically relevant treatment response is relatively sparse and questions surrounding the definition of therapeutic benefit and safe discontinuation protocols remain largely unanswered (Herrmann et al., 2007a; Richard and van Gool, 2006).

To date, only three double blind RCTs have directly evaluated the effects of ChEI cessation (summarized in table 4). The previously discussed DOMINO trial found that patients in the discontinuation arm had significantly lower MMSE scores and BADL scores 6 weeks into the study when compared to the continuation group (Howard et al., 2012). However, it should be noted that the original recruitment goal of 430 participants was not met and this weakened the power of the study. Moreover, only half of the patients assigned to continue on donepezil participated for the full duration of the trial, which may suggest that those who did not complete the study found that the medication was not efficacious (Howard et al., 2012). The results of the DOMINO trial reflect those previously found by Holmes et al (2004) who studied donepezil discontinuation in patients with mild to moderate AD with neuropsychiatric symptoms. Though the trial randomized patients who were treated with donepezil for only 3 months, the authors found that the donepezil discontinuation group also had lower MMSE scores and experienced more neuropsychiatric symptoms than those who continued active medication (Holmes et al., 2004b). With both trials it is difficult to ascertain whether deterioration of the placebo group was caused by a loss of therapeutic effect or the
appearance of withdrawal symptoms. Another RCT looked specifically at galantamine cessation in mild to moderate AD for 24 months following a 12-month open label phase and found that patients were more likely to drop out prematurely if in the placebo arm for any reason or due to lack of efficacy but did experience fewer adverse events than those in the continuation group (Scarpini et al., 2011). These RCTs, however, all focused on ChEI withdrawal in community dwelling populations and only one has examined it in the context of moderate to severe AD. With numbers of moderate to severe AD patients living in primary care facilities increasing, more RCTs are needed to determine the effects of ChEI discontinuation in this population.

Table 4: RCTs assessing ChEI discontinuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population and Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Howard et al., 2012</td>
<td>n=295 community dwelling moderate to severe AD Patients on DPZ ≥3 months were randomized to one of four groups: DPZ continuation, DPZ +memantine continuation, placebo &amp; placebo + memantine</td>
<td>Safety: ●↔#AEs ●↑Falls in PLB (12% vs 7%) ●↑deterioration of AD in PLB (6.4% vs 3%) ●↑GI AEs in DPZ (6.4% vs 2.3%)  Primary: Placebo group vs. DPZ continuation: ↓MMSE (-1.9pts) ↑BADLS (+3pts)</td>
</tr>
<tr>
<td></td>
<td>Duration: 52 weeks</td>
<td></td>
</tr>
<tr>
<td>Scarpini et al., 2011</td>
<td>n= 139 community dwelling with mild to moderate AD Open label phase: 12 months on GAL</td>
<td>Safety: ●↑AE in GAL (34% vs. 27%) ●Withdrawal due to AE (10.5% GAL vs. 6.3% PLB)  Primary: Placebo subjects were more likely to discontinue prematurely for any reason. ↔ ADAS-Cog between groups</td>
</tr>
<tr>
<td></td>
<td>RCT withdrawal phase: continuation or placebo for 24 months. Total duration was 36 months.</td>
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</table>
Recently, an open label study by Suzuki and colleagues was conducted, examining ChEI discontinuation in 44 institutionalized patients with AD and behavioural symptoms (Suzuki et al., 2013). Patients in the discontinuation group had to be taking ChEIs for a minimum of 3 years prior to study entry in contrast to the control group, which was never treated with ChEIs previously (Suzuki et al., 2013). In contrast to the findings of DOMINO, Suzuki et al. reported significant decreases in neuropsychiatric symptoms, such as agitation and irritability, in those discontinued off of donepezil compared to control, although differences between the groups were not significant (Howard et al., 2012; Suzuki et al., 2013). In addition, no changes were observed between groups on the MMSE (Suzuki et al., 2013).

ChEI discontinuation has also been examined by a number of retrospective cohort studies, and some have been outlined in more detail in table 5. Some studies assessing determinants of ChEI discontinuation have found that a main reason for discontinuing therapy in many patients was due to lack of ChEI tolerability (Caroe and Moe, 2009; Frankfort et al., 2005). These studies both found that patients who were experiencing
treatment related AEs stopped therapy within the first 3-6 months (Caroe and Moe, 2009; Frankfort et al., 2005). Moreover, other studies have suggested that more severe cognitive impairment and low ChEI dosage can predict discontinuation due to insufficient benefit or perceived lack of efficacy (Kroger et al., 2010; Lee et al., 2007; Umegaki et al., 2008). Interestingly, Diaello and colleagues found that patients who were discontinued were more behaviorally aggressive and spent less time engaging in leisurely activities (Daiello et al., 2009).

Table 5: Retrospective Cohort Studies assessing ChEI discontinuation

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kroger et al., 2010</td>
<td>n=3369 participants (≥50 years old) enrolled in the Dutch PHARMO Record Linkage System between July 1998 and January 2008</td>
<td>Patients on RIV or GAL in the PHARMO RLS followed. Considered discontinued if in PHARMO RLS for 90 days after ChEI treatment end. Group looked at determinants of discontinuation and the CDS.</td>
<td>-60% of patients were discontinued within 3 years -females, patients with higher CDS and those on lower than therapeutic dose were more likely to discontinue</td>
</tr>
<tr>
<td>Daiello et al., 2009</td>
<td>n=178 nursing home residents with AD or other dementias enrolled in Rhode Island Medicaid program between January 2004 and December 2005</td>
<td>Patients selected for the discontinuation group had to be on continuous ChEI therapy for 3 - 9 months. The continuation group received ChEIs for &gt;9months..</td>
<td>Discontinuation Group (n=62): Primary: ↑ABS ↔ DRS Secondary: ↔ ADL ↔ CPS ↔ continence ↓Leisure time</td>
</tr>
<tr>
<td>Lee et al., 2007</td>
<td>n= 52 severe AD/dementia patients in LTC</td>
<td>Review committee recommended tapered discontinuation of ChEI in 13 patients based on decline in cognition, behavior and function.</td>
<td>During 4 month follow up - 4 patients were restarted on ChEI (due to ↓ in ADL or family request) -9 remained off ChEI</td>
</tr>
</tbody>
</table>
Several case studies have described the effects of ChEI discontinuation. Singh and Dudley (2003) described two cases of patients who experienced withdrawal symptoms 5 to 6 days after abrupt donepezil cessation. It was postulated that withdrawal symptoms were caused by lack of CNS compensation following ChEI cessation (Singh and Dudley, 2003). Other case studies have also described episodes of delirium, cognitive decline, increased anxiety and paralytic ileus following ChEI discontinuation (Bidzan and Bidzan, 2012; Fisher and Davis, 2008; Okazaki et al., 2006). Conversely, some reports have reported on the alleviation of cardiac related adverse events and anxiety following ChEI cessation (Corbo et al., 2013; Tanaka et al., 2009). Table 6 provides a summary of case studies that have observed the effects ChEI discontinuation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Case</th>
<th>Clinical Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corbo et al.,</td>
<td>n=1</td>
<td>Galantamine</td>
<td>↓ anxiety and ↓ nightmares after cessation</td>
</tr>
<tr>
<td>2013</td>
<td>moderate AD</td>
<td>(8mg/day for 4 months)</td>
<td>discontinued</td>
</tr>
<tr>
<td>Bidzan and</td>
<td>n=1</td>
<td>Donepezil</td>
<td>↑ dementia symptoms &amp; delirium</td>
</tr>
<tr>
<td>Bidzan, 2012</td>
<td>mild AD</td>
<td>(10mg/day for 10 months)</td>
<td>↑ anxiety, ↓ attention, sleep 3 days after cessation</td>
</tr>
</tbody>
</table>
1.5.5 Long-term Use, Safety and Discontinuation in Institutionalized Patients

As mentioned in the previous section, three double blind RCTs have directly evaluated the effects of ChEI cessation in a community dwelling AD population.

However at the present time, there have been no double blind RCT studies that address ChEI discontinuation in the setting of a moderate to severe institutionalized AD population. Given the fact that patients residing in long-term care have more severe AD (Leon-Salas et al., 2013), present with more comorbid illnesses (Kuo et al., 2008; Volicer and Hurley, 1997), are taking more medications (Hansdottir and Gudmannsson, 2013; Vetrano et al., 2013) and have been taking ChEIs for extended periods of time, more

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample Size</th>
<th>Treatment</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tanaka et al., 2009</td>
<td>n=2 AD</td>
<td>Donepezil (5mg-10mg/day for ‘many years’) discontinued</td>
<td>↓ arrhythmia, ↓ QT prolongation and ↓ bradycardia after cessation</td>
</tr>
<tr>
<td>Fisher and Davis, 2008</td>
<td>n=1 mild mixed dementia</td>
<td>Galantamine (8mg/day for 1.5 years) discontinued, restarted and then discontinued a second time.</td>
<td>Upon 1st discontinuation: ↓ in cognition, behavior and functional status 2 weeks following cessation. Upon 2nd discontinuation: ↓ QT prolongation, ↓ syncope and ↓ delirium upon cessation.</td>
</tr>
<tr>
<td>Okazaki et al., 2006</td>
<td>n=1 moderate dementia</td>
<td>Donepezil (5mg/day for 3 years) discontinued</td>
<td>Clinical observation of paralytic ileus. Upon restart symptoms improved immediately.</td>
</tr>
<tr>
<td>Singh and Dudley, 2003</td>
<td>n=2 Lewy body dementia and mixed dementia</td>
<td>Donepezil (5mg/day for 2 years and 10mg/day for 13 months) discontinued</td>
<td>↓ in mood, ↑ agitation, ↓ sleep and ↓ concentration 5-6 days after cessation</td>
</tr>
</tbody>
</table>
research is needed to determine the effects and safety of discontinuing ChEI therapy in this population.
2 MATERIALS AND METHODS

2.1 Study Design

The safety of ChEI discontinuation in patients with moderate-severe AD was assessed in an 8-week, randomized, double blind, placebo-controlled trial involving patients residing in the long term care facilities of Sunnybrook Veterans’ Centre and North York Seniors’ Health Centre. The primary nurses also participated in this study, as information regarding patient behavior and any adverse events experienced by the patient was required. The Research Ethics Boards in both hospitals approved this study.

2.2 Participant Selection

Thirty participants residing in long-term care facilities at Sunnybrook Hospital and North York General Hospital in Toronto, Ontario, Canada were screened according to the eligibility criteria described below. Written, informed consent was obtained from the legal representatives of the patient, by the study coordinator and investigator prior to the commencement of study procedures. Verbal consent was also obtained from the patient’s attending physician to ensure the patient was in a medically stable condition and able to participate.

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

To be included, patients must be:

- Aged >55 years
- Meet Diagnostic Statistical Manual of Mental Disorder-IV (DSM-IV) criteria for primary degenerative dementia
• Meet National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for probable AD of at least one year’s duration
• Score \(\leq 15\) on the MMSE (moderate to severe)
• Receiving donepezil, galantamine (8mg, 16mg, 24mg) or rivastigmine (oral) for at least 2 years, with a stable dose for at least 3 months prior to study entry
• Patients with a current order for any regularly administered psychotropic (e.g. SSRIs, SNRIs, trazodone, atypical or typical antipsychotics) must have been on a stable dose for at least 1 month prior to study entry

2.3.2 Exclusion Criteria

Patients with the following conditions will be excluded:
• Dementia due to any etiology other than AD
• Significant difficulty ingesting oral medications
• Current evidence of any uncontrolled medical illness that would interfere with the subject's participation in the study

2.4 Study Drugs

This study required a maintenance dose of donepezil (Aricept®) 5 and 10mg, galantamine (Reminyl®) 8 and 16mg, or rivastigmine (Exelon®) 1.5, 3, 4.5 and 6mg. For those in the discontinuation arm, a placebo substitution was required. The active ingredients for the test articles were purchased through the Sunnybrook Health Sciences Centre Pharmacy.

Donepezil reaches peak plasma concentration after approximately 3-4 hours after
dosage administration and has a pharmacokinetic half-life (t<sub>1/2</sub>) of 70 hours (Pfizer, 2007). For patients originally taking donepezil, if randomized to maintenance arm, daily doses for days 1 through 14 contained one donepezil tablet of the patient’s specified dosage if or, if in discontinuation arm, a 5mg donepezil tapering dose if previously stabilized on donepezil 5mg or 10mg. For those discontinued, at the end of week 2, the tapering dose of donepezil was discontinued and patients were placed on a placebo substitution for the remainder of the study (see figure III).

![Administration procedure for donepezil](image)

**Figure III: Administration procedure for donepezil.** *Patients stabilized on 10 mg donepezil at baseline will be titrated down to donepezil 5 mg for 2 weeks, while patients stabilized on donepezil 5mg at baseline will remain on donepezil 5 mg for 2 weeks prior to placebo substitution.*
Galantamine reaches peak plasma concentration after 1.2 hours and has a $t_{1/2}$ of 7-8 hours (Jansen-Ortho, 2008). For patients originally taking galantamine, daily doses for days 1 through 14 contained one galantamine tablet of patient’s specified dosage if in the maintenance arm or an 8mg galantamine tapering dose if previously stabilized on 24mg, 16mg or 8mg and in the discontinuation arm. At the end of week 2, the tapering dose of galantamine was discontinued and patients were placed on a placebo treatment for the remainder of the study (see figure IV).

Rivastigmine reaches peak plasma concentration after approximately 1 hour and has a relatively short plasma $t_{1/2}$ of 1-2 hours (Novartis, 2008). For patients originally taking rivastigmine, daily BID doses for days 1 through 14 contained one rivastigmine tablet of the patient’s stabilized dosage if continuing or a 3mg rivastigmine tapering dose if previously stabilized on rivastigmine 6mg, 4.5 mg or 3mg. At week 2, discontinuing patients were administered placebo. Patients in the discontinuation arm who were stabilized on rivastigmine 1.5mg remained on 1.5mg until day 14, at which time they were placed on to placebo (see figure V).

Placebo substitution was achieved using the process of overencapsulation which involves the use of an inert placebo tablet (ODAN Pharmaceuticals) placed in an empty DB capsule, identical in appearance to the test article, and back filled with the identical inert filler (see figure VI). Both maintenance and placebo dosage were identical in appearance to ensure proper blinding.

Study personnel provided usage instruction to nursing staff after randomization and were responsible for replacing medication vials. Patient compliance was measured using the medical administration record (MAR) in addition to biweekly pill counts.
conducted by study personnel.
Randomization

Continuation Group

Placebo Group

Baseline
- Stabilized on GAL 24mg
- Stabilized on GAL 16mg
- Stabilized on GAL 8mg

Weeks 1-2
- GAL 24mg
- GAL 16mg
- GAL 8mg

Weeks 3-9
- GAL 24mg
- GAL 16mg
- GAL 8mg
- Placebo
Figure V: Administration procedure for rivastigmine. BID = bis in die ("twice daily"), RIV = rivastigmine.
2.5 Demographics

During the screening process, trained study personnel collected demographic information regarding age, sex, medical history, duration and severity of dementia as well as comorbid illnesses via chart review and/or POA interview. Concomitant medication and PRN medications used 3 months prior to screening were also recorded using the MAR. Physiologic measures of weight (kg), blood pressure (mmhg) and heart rate (bpm) were conducted and recorded at screening and each study visit thereafter.

2.6 Procedures

Assessments were conducted at screening, baseline, 2, 4 and 8-weeks, according to the schedule in Table 7. Patients were screened within one-week +/- 3 days of a
baseline visit. At screening, patients underwent a complete physical evaluation by the study physician and physiological measures were recorded. Cognition at screening was assessed with the patient using the MMSE. Pending a successful screening visit, eligible patients were randomized in blocks using a computer-generated code determined by the pharmacy to 8 weeks of double-blind treatment with either continuation of their regular maintenance dose of cholinesterase inhibitor or a placebo substitution with a 2 week taper.

At the baseline visit, the physical evaluation was repeated and concomitant and PRN medication use since the screening visit were recorded. Cognition was assessed using the MMSE and severe impairment battery (SIB). Disease severity was determined using the Clinician’s Global Impression (CGI), a 7 point global rating performed by an experienced clinician. Safety was assessed with the primary nurse using both adverse event reports and the Udvalg for Kliniske Undersøgelser (UKU) side effect rating scale, a 48 item standardized symptom checklist, which was also completed with the primary nurse. These repeated for the 4 week and 8 week visits. The nurse was also instructed to inform study personnel of any adverse events experienced by the patient at any time during the patient’s enrollment in the study. All AEs were noted in an AE report and followed-up until resolution. All SAEs were reported to and reviewed by the research ethics board. The cholinesterase inhibitor discontinuation study also looked at cognitive and behavioural outcomes that were not directly evaluated in this study.
### Table 7: Study Assessment Schedule

<table>
<thead>
<tr>
<th>Assessments</th>
<th>Screening -7 ± 3 days</th>
<th>Baseline 0 days</th>
<th>2 week 14 ± 3 days</th>
<th>4 week 28 ± 3 days</th>
<th>6 week 42 ± 3 days</th>
<th>8 week 56 ± 3 days</th>
<th>Retrieved Drop-Out</th>
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<tr>
<td><strong>Screening</strong></td>
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<tr>
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<tr>
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<td><strong>Outcomes</strong></td>
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<td>MMSE</td>
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<tr>
<td>CGI &amp; CGI-C</td>
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<td>Pill Count</td>
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</tbody>
</table>

Abbreviations: NPI-NH=neuropsychiatric inventory-nursing home edition, MMSE= mini-mental status examination, SIB=severe impairment battery, CGI=clinician’s global impression, CGIC=clinician’s global impression of change, UKU= Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale
2.7 Study Assessments

2.7.1 Adverse Event Reports

The nursing staff at both Sunnybrook Veterans’ Centre and North York Seniors’ Health Centre were instructed to inform study personnel of any adverse events experienced by the patient at anytime during the patient’s enrollment in the study. Study staff also monitored patients’ charts and progress notes to ensure all AEs were reported. Any AEs were noted in an AE report in both the case report file and the protocol binder and followed-up until resolution. In the instance where a patient unintentionally lost weight, clinically significant weight loss was considered to be a decrease in total body weight by 1.66%. This number was derived from studies which defined clinically significant involuntary weight loss as a 5% decrease in body weight over a 6-months period (Bouras et al., 2001; Gillette Guyonnet et al., 2007; Leff, 2003). On average, this is a loss of 0.83% per month, which converts to 1.66% loss over the 8-week trial period. Therefore, any weight loss of 1.66% or greater was recorded as an AE. In addition, behavioural AEs were monitored using the NPI-NH and were noted when a patient experienced an NPI-NH total increase by ≥50% (Iverson et al., 2002; Kaufer et al., 1996). In order to ensure complete reporting of AEs, the UKU, a safety checklist, was also used at assessments biweekly with the primary nurse. SAEs were considered any event that resulted in hospitalization or death. All SAEs were noted in a similar fashion to AEs and reported to the research ethics board.

2.7.2 Vitals and Weight

Patient weight (kg) was measured on the first of every month by nursing staff and recorded in the online charting system. Furthermore, blood pressure (mmHg) and pulse
rate (bpm) measurements were taken by trained study personnel at baseline, 2-week, 4-week and 8-week visits using an electronic vitals machine for each patient.

2.7.3 The Udvalg for Kliniske Undersøgelser (UKU) scale

The Udvalg for Kliniske Undersøgelser (UKU) scale (Lingjaerde et al., 1987) is a comprehensive 48-item side effect rating scale used to assess the side effects of psychopharmacological medications. The side effect list is organized into ‘psychic’, ‘neurological’, ‘autonomic’ and ‘other’ domains (Lingjaerde et al., 1987). The assessment is to be completed with the patient, however due to the population in this study the UKU was assessed with the primary nurse of the patient. The primary nurse was asked to rate whether a side effect was seen since the last visit and asked to score how severe the side effect observed was (0=not present, 1=mild, 2=moderate or 3=severe). The nurse was then asked to rate whether he/she thought the side effect was causally related to treatment (impossible, possible or probable). Side effect scores are then added together for a total side effect score. The UKU has been validated in a number of studies that have assessed the side effects of psychotropic medications (Jordan et al., 2004; Kim et al., 2008; Lambert et al., 2003; Lindstrom et al., 2001).

2.7.4 The Anticholinergic Cognitive Burden (ACB) scale

The Anticholinergic Cognitive Burden (ACB) scale (Boustani et al., 2008) is a scale that lists medications with known anticholinergic effects based on their severity of anticholinergic exposure (possible, probable or definite). It is a tool designed to help clinicians quickly determine if anticholinergic medications are associated with central side effects. According to the ACB, medications with ‘possible’ anticholinergic effects
are given a score of 1, while ‘probable’ and ‘definite’ medications are assigned a score of 2 and 3, respectively. For each patient in the study, a list of current concomitant medications were collected and scored by study staff at baseline. Each medication score was added together to provide a cumulative ACB score. A higher total ACB score indicates the patient has a higher anticholinergic burden and is at an increased risk of experiencing central side effects. The ACB has been validated as a useful tool of central side effect measure in elderly AD populations (Fox et al., 2011a; Fox et al., 2011b; Pasina et al., 2013) and in other non-AD populations (Lanctot et al., 2013).

2.8 Statistical Analysis

Statistical analyses were performed using SPSS Statistics version 20.0 Copyright © 2011 by IBM Corporation, Armonk, NY, USA. Analyses were performed according to intention-to-treat (ITT) procedures, using the last-observation-carried-forward (LOCF). Baseline demographics and clinical characteristics were compared between treatment groups using ANOVAs for continuous variables and chi-square of Fisher’s exact test for categorical variables. When the hypothesis of normality was not met, nonparametric Kruskal-Wallis tests were used. Continuous variables were summarized using mean ± standard deviation and all analyses were 2-tailed with a significance level of p<0.05.

2.8.1 Primary Hypothesis

The proportion of patients experiencing any adverse event will be smaller in the placebo group when compared to the continuation group, as measured by adverse event reports.
To test the hypothesis that patients on placebo will experience fewer adverse events than those in the continuation group, the proportion of patients experiencing an AE in each group were compared using a $\chi^2$ of Fisher’s exact test.

2.8.2 Secondary Hypothesis

1) The proportion of patients experiencing weight loss (loss of 1.66% of total weight from baseline to 8 weeks) will be smaller in the placebo group in comparison to the continuation group.

2) The mean weight loss (kg) in the placebo group will be lower than the continuation group.

3) The mean increase in pulse rate (bpm) in the placebo group will be higher when compared to the continuation group.

4) The mean side effect scores, as measured by the UKU, will be lower in the placebo group in comparison to the continuation group.

1) To test the hypothesis that patients on placebo will experience less clinically significant weight loss than those in the continuation group, the proportion of patients experiencing clinically significant weight loss in each group were compared using $\chi^2$ of Fisher’s exact test.

2) For this hypothesis, differences in mean weight loss (kg) between treatment groups were determined using a mixed model ANOVA.

3) For this hypothesis, differences in mean pulse rate (bpm) between treatment groups were determined using a mixed model ANOVA.
For this hypothesis, differences in mean systolic blood pressure (mmHg) between treatment groups were determined using a mixed model ANOVA.

For this hypothesis, differences in mean diastolic blood pressure (mmHg) between treatment groups were determined using a mixed model ANOVA.

For this hypothesis, differences in mean UKU score between treatment groups were determined using a mixed model ANOVA.

2.8.3 Exploratory Hypothesis

Anticholinergic cognitive burden (ACB) scores will be associated with increased frequency of anticholinergic adverse events and reduced ChEI discontinuation.

To test this hypothesis, ACB score was included as covariate in ANCOVA examining the relationship between treatment allocation and frequency of adverse events. It was also added in as a covariate in mixed models ANOVA looking at weight loss, pulse rate and blood pressure change between groups.

2.9 Sample Size Consideration

A sample size calculation was performed for the primary hypothesis described previously. The proportion of patients experiencing AEs while taking ChEIs (P₁) was 0.66 as reported in a previous meta-analysis by our group. For a chi square test of independence, in order to detect a large effect size of 0.48 with an α =0.05 and power of 0.80, a sample size of 30 patients in each group was required.
3 RESULTS

3.1 Participant Recruitment

A total of 236 ChEI users residing in long-term care at Sunnybrook Veterans’ Centre and North York Senior’s Health Centre were screened via chart review by study staff for long-term ChEI use (≥2 years) and the presence of probable AD. Of those patients, 193 patients were excluded mainly due to being on a ChEI for less than 2 years (72 patients) or poor health status/death while in consent process (39 patients). Consent was obtained for 43 patients from the POA, however 13 were excluded thereafter (7 due to high MMSE scores, 3 passed away before screening and 1 POA withdrew consent). The remaining 30 were screened but 4 were excluded following screening (3 due to high MMSE and 1 was transferred to critical care). Therefore, 26 patients were randomized to either ChEI continuation or discontinuation. Although sample size calculations suggested that 30 in each group would be required to achieve adequate power and detect significant associations, the results reported within this study represent a preliminary safety analysis and recruitment for the main study is still ongoing. As data collection also remains ongoing, all analyses were completed with semi-blinded treatment allocation list and, therefore, patients were either grouped into “treatment group A” or “treatment group B” and actual treatment allocation was not revealed. Eleven patients were randomized to treatment group A and 15 to treatment group B. In group A, 2 patients discontinued before study endpoint due to AEs and in group B, 1 patient discontinued due to an AE and 1 was lost to follow up. Following intent to treat procedures, data for non-completers was included using the LOCF. Patient recruitment is illustrated in figure VII.
Figure VII: Participant flow diagram
3.2 Demographics and Clinical Characteristics

The baseline and clinical characteristics of all 26 patients included in the ChEI discontinuation safety study are outlined in Table 8. The patients in each treatment group, 11 in group A and 15 in group B respectively, were not significantly different in any baseline parameter.

Table 8: Baseline Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total (n=26) Mean±SD</th>
<th>Treatment Group A (n=11) Mean±SD</th>
<th>Treatment Group B (n=15) Mean±SD</th>
<th>Statistic (F or χ²)</th>
<th>p-value (significance at p≤0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>87.9 ± 3.0</td>
<td>87.6 ± 2.9</td>
<td>88.1 ± 3.0</td>
<td>.001</td>
<td>0.98</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>73.1</td>
<td>54.5</td>
<td>86.7</td>
<td>3.33</td>
<td>.095</td>
</tr>
<tr>
<td>Cholinesterase Inhibitor, (%)</td>
<td>50.0</td>
<td>45.5</td>
<td>53.3</td>
<td>.158</td>
<td>1.00</td>
</tr>
<tr>
<td>Donepezil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>30.8</td>
<td>36.4</td>
<td>26.7</td>
<td>.280</td>
<td>.683</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>19.2</td>
<td>18.2</td>
<td>20.0</td>
<td>.014</td>
<td>1.00</td>
</tr>
<tr>
<td>Number of Medical Comorbidities</td>
<td>6.5 ± 2.4</td>
<td>6.8 ± 2.7</td>
<td>6.3 ± 2.2</td>
<td>.278</td>
<td>.598</td>
</tr>
<tr>
<td>Number of Concomitant Medications</td>
<td>10.2 ± 3.8</td>
<td>9.2 ± 3.6</td>
<td>10.9 ± 3.9</td>
<td>.078</td>
<td>.270</td>
</tr>
</tbody>
</table>

Common Medical Comorbidities (%)

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Treatment Group A</th>
<th>Treatment Group B</th>
<th>Statistic (F or χ²)</th>
<th>p-value (significance at p≤0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardio-cerebrovascular Disease</td>
<td>84.6</td>
<td>90.9</td>
<td>80.0</td>
<td>.580</td>
<td>.614</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.2</td>
<td>18.2</td>
<td>20.0</td>
<td>.014</td>
<td>1.00</td>
</tr>
<tr>
<td>Condition</td>
<td>Memantine</td>
<td>Antidepressants</td>
<td>Antipsychotics</td>
<td>Beta-blocker</td>
<td>Alpha-blocker</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------</td>
<td>----------------</td>
<td>----------------</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Cancer</td>
<td>30.8</td>
<td>36.4</td>
<td>26.7</td>
<td>.280</td>
<td>.683</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.4</td>
<td>27.3</td>
<td>6.7</td>
<td>2.07</td>
<td>.279</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>15.4</td>
<td>27.3</td>
<td>6.7</td>
<td>2.01</td>
<td>.279</td>
</tr>
<tr>
<td>Bone Disease</td>
<td>57.7</td>
<td>54.5</td>
<td>33.3</td>
<td>1.17</td>
<td>.426</td>
</tr>
<tr>
<td>Mood Disorder</td>
<td>26.9</td>
<td>18.2</td>
<td>33.3</td>
<td>.740</td>
<td>.658</td>
</tr>
</tbody>
</table>

**Common Concomitant Medications (%)**

**Psychotropics**

- Memantine: 46.2, 45.5, 46.7, .004, .951
- Antidepressants: 42.3, 27.3, 33.3, 1.77, .246
- Antipsychotics: 26.9, 18.2, 33.3, .740, .658

**Antihypertensives**

- Beta-blocker: 15.4, 9.1, 20.0, .580, .614
- Alpha-blocker: 15.4, 9.1, 20.0, .580, .614
- Calcium Channel Blocker: 19.2, 18.2, 20.0, .014, 1.00
- Diuretics: 23.1, 18.2, 26.7, .257, 1.00
- Other Antihypertensives: 30.8, 36.4, 26.7, .280, .683

**Other**

- Insulin Preparations: 11.5, 9.1, 13.3, .112, 1.00
- NSAIDs: 53.8, 54.5, 53.3, .004, .951
- Analgesics: 34.6, 27.3, 40.0, .454, .683
<table>
<thead>
<tr>
<th>Category</th>
<th>11.5</th>
<th>18.2</th>
<th>6.7</th>
<th>.824</th>
<th>.556</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>42.3</td>
<td>54.5</td>
<td>33.3</td>
<td>1.17</td>
<td>.426</td>
</tr>
<tr>
<td>Gastric Acid Inhibitors</td>
<td>30.8</td>
<td>18.2</td>
<td>40.0</td>
<td>1.42</td>
<td>.395</td>
</tr>
<tr>
<td>Thyroid Medication</td>
<td>15.4</td>
<td>27.3</td>
<td>33.3</td>
<td>2.07</td>
<td>.279</td>
</tr>
<tr>
<td>Vitamins and Minerals</td>
<td>92.3</td>
<td>90.9</td>
<td>93.3</td>
<td>.053</td>
<td>1.00</td>
</tr>
<tr>
<td>Laxatives</td>
<td>34.6</td>
<td>18.2</td>
<td>46.7</td>
<td>2.28</td>
<td>.217</td>
</tr>
</tbody>
</table>

**Baseline Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>Mean ± SD</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>68.4 ± 14.0</td>
<td>64.2 ± 14.5</td>
<td>71.5 ± 13.2</td>
<td>.527</td>
<td>.196</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mm Hg)</td>
<td>126.5 ± 21.0</td>
<td>133.3 ± 21.0</td>
<td>121.5 ± 20.1</td>
<td>.008</td>
<td>.160</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mm Hg)</td>
<td>70.1 ± 10.6</td>
<td>70.6 ± 10.2</td>
<td>69.8 ± 11.3</td>
<td>.045</td>
<td>.864</td>
</tr>
<tr>
<td>Pulse Rate (bpm)</td>
<td>65.4 ± 11.9</td>
<td>68.2 ± 10.4</td>
<td>63.3 ± 12.8</td>
<td>.334</td>
<td>.307</td>
</tr>
<tr>
<td>ACB</td>
<td>1.2 ± 1.1</td>
<td>0.91 ± 1.2</td>
<td>1.5 ± 1.1</td>
<td>1.90</td>
<td>.169</td>
</tr>
<tr>
<td>CGI</td>
<td>3.9 ± 0.66</td>
<td>3.7 ± 0.79</td>
<td>3.9 ± 0.59</td>
<td>.746</td>
<td>.388</td>
</tr>
<tr>
<td>MMSE</td>
<td>6.8 ± 5.1</td>
<td>8.6 ± 6.0</td>
<td>5.5 ± 4.2</td>
<td>3.48</td>
<td>.154</td>
</tr>
<tr>
<td>SIB</td>
<td>54.9 ± 28.6</td>
<td>57.0 ± 28.7</td>
<td>53.4 ± 29.5</td>
<td>.295</td>
<td>.758</td>
</tr>
<tr>
<td>NPI-NH Disruption</td>
<td>17.4 ± 13.4</td>
<td>11.7 ± 7.2</td>
<td>21.6 ± 15.4</td>
<td>2.40</td>
<td>.125</td>
</tr>
<tr>
<td>NPI-NH Disruption</td>
<td>7.2 ± 6.1</td>
<td>5.6 ± 5.6</td>
<td>8.4 ± 6.3</td>
<td>1.70</td>
<td>.193</td>
</tr>
<tr>
<td>UKU (n=25)</td>
<td>12.7 ± 10.6</td>
<td>12.0 ± 11.9</td>
<td>13.3 ± 9.8</td>
<td>.776</td>
<td>.378</td>
</tr>
</tbody>
</table>

ACB anticholinergic cognitive burden score; CGI Clinician’s Global Impression; MMSE Mini-mental status examination; NPI-NH Neuropsychiatric Inventory-Nursing Home Version; NPI-NH Neuropsychiatric Inventory-Nursing Home Version; NPI-NH Disruption Neuropsychiatric Inventory-Nursing Home Version Disruption Score; NSAID non-steroidal anti-inflammatory drug; SD standard deviation; SIB severe impairment battery test; UKU The Udvalg for Kliniske Undersøgelser
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment Group A (n=11)</th>
<th>Treatment Group B (n=15)</th>
<th>F</th>
<th>p-value (significance at p≤0.05)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>64.2±14.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>63.2±14.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>-1.0±2.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>71.5±13.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>71.2±11.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>-0.25±3.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>2.9</td>
<td>.091</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>133.3±21.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>125.6±20.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>-7.6±13.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>121.5±20.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>125.1±22.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>4.5±20.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>1.9</td>
<td>.094</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>70.6±10.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>67.6±6.2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Change Mean±SD</td>
<td>-2.9±9.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline Mean±SD</td>
<td>69.8±11.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Mean±SD</td>
<td>70.4±9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change Mean±SD</td>
<td>-0.33±14.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td></td>
<td></td>
<td>1.1</td>
<td>.618</td>
</tr>
<tr>
<td>Pulse Rate (bpm)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CGI / CGI-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>8.6±6.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIB</td>
<td>57.0±28.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| CGI-C Clinician’s Global Impression of Change; MMSE Mini-mental status examination; NPI-NH Neuropsychiatric Inventory-Nursing Home Version; SIB severe impairment battery test; UKU Udvalg for Kliniske Undersogelser
3.3 Adverse Events

A total of 28 AEs and 1 SAE were reported for 17 patients, of which 3 were thought to be possibly related to study drug. The SAE was considered unrelated to the study medication. There was no evidence that the frequency of adverse events differed according to treatment group (F(1,24) = 0.13, p=0.71). The most commonly reported AEs in the total group were unintentional weight loss (20.7%) and falls (20.7%). Further detail regarding AEs in both treatment group A and B are provided in Table 10 and Figure VIII.

![Graph showing Frequency of Adverse Events Across Treatment Groups]

Figure VIII: Frequency of Adverse Events Across Treatment Groups.
A total of 28 AEs and 1 SAE were reported by nursing staff for 17 patients at study follow up.
N= number of patients

Table 10: Adverse Events by Treatment Group

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Treatment Group A N (% of AE)</th>
<th>Treatment Group B N (% of AE)</th>
<th>Total N (% of total AEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unintentional Weight loss (kg)</td>
<td>4 (66.6)</td>
<td>2 (33.3)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Fall</td>
<td>3 (50)</td>
<td>3 (50)</td>
<td>6 (20.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0 (0)</td>
<td>3 (100)</td>
<td>3 (10.4)</td>
</tr>
<tr>
<td>Respiratory Tract Infection</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Deterioration of behavior</td>
<td>1 (50)</td>
<td>1 (50)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Deterioration of AD</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Syncope</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Put on Intravenous therapy</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Cough, unproductive</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Perineum Wound</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Oral Thrush</td>
<td>1 (100)</td>
<td>0 (0)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Seizure (ER)</td>
<td>0 (0)</td>
<td>1 (100)</td>
<td>1 (3.4)</td>
</tr>
<tr>
<td>Total (AE and SAEs)</td>
<td>11 (37.9)</td>
<td>18 (62.1)</td>
<td>29 (100)</td>
</tr>
</tbody>
</table>
3.4 Planned Analyses

3.4.1 Primary Hypothesis

The proportion of patients experiencing any adverse event will be smaller in the placebo group when compared to the continuation group, as measured by adverse event reports.

There was no statistically significant difference between treatment allocation and the occurrence of an adverse event as measured by adverse event reports in a chi-square test of independence $\chi^2=(1, 26) =0.99, p = 0.32, (p= 0.42, Fisher's exact test)$ (see Table 11 and Figure IX).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>AE +</th>
<th>AE -</th>
<th>Total</th>
<th>$\chi^2$</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N)</td>
<td>(%)</td>
<td>n (N)</td>
<td>(%)</td>
<td>n (N)</td>
</tr>
<tr>
<td>A</td>
<td>6 (11)</td>
<td>54.5</td>
<td>5 (11)</td>
<td>45.5</td>
<td>11 (26)</td>
</tr>
<tr>
<td>B</td>
<td>11 (15)</td>
<td>73.3</td>
<td>4 (15)</td>
<td>26.7</td>
<td>15 (26)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17 (26)</td>
<td>65.4</td>
<td>9 (26)</td>
<td>34.6</td>
<td>26 (26)</td>
</tr>
</tbody>
</table>

AE: adverse event, n: number of patients with or without adverse events, N: number of patients in treatment group A and/or B
p-value derived from Fisher’s Exact Test
* significance at p≤0.05
3.4.2 Secondary Hypotheses

1) The proportion of patients experiencing weight loss (loss of 1.66% of total weight from baseline to 8 weeks) will be smaller in the placebo group in comparison to the continuation group.

There was no statistically significant association between treatment allocation and the occurrence of clinically significant weight loss (kg) as measured by adverse event reports in a chi-square test of independence $\chi^2=(1, 26) = 1.9$, $p = 0.17$, ($p = 0.35$, Fisher's exact test) (see table 12 and figure X).
Table 12: Treatment group and prevalence of clinically significant weight loss (kg).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N)</td>
<td>(%)</td>
<td>n (N)</td>
</tr>
<tr>
<td>A</td>
<td>4 (11)</td>
<td>36.4</td>
<td>7 (11)</td>
</tr>
<tr>
<td>B</td>
<td>2 (15)</td>
<td>13.3</td>
<td>13 (15)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>6 (26)</td>
<td>23.1</td>
<td>20 (26)</td>
</tr>
</tbody>
</table>

n: number of patients with or without clinically significant weight loss, N: number of patients in treatment group A and/or B
p-value derived from Fisher’s Exact Test
*significance at $p \leq 0.05$

Figure X: Frequency of clinically significant weight loss (kg) according to treatment group.
A mixed model ANOVA was conducted to determine whether there were statistically significant differences in weight loss (kg) between treatment group A and treatment group B over the course of the trial. Mauchly’s test of sphericity was met (p>0.05) and Levene’s test indicates that all variances are homogenous for all levels of repeated measures. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean weight loss, \(F(1,24) = .531, p = .473\). The main effect of treatment group showed no significant difference in weight measurements between treatment groups A and B, \(F(1,24) = 2.115, p = .159\). Additionally, the main effect of pre and post treatment was not significantly different in weight measurements (kg), \(F(1, 24) = 1.427, p = .244\). The results of the mixed model ANOVA are represented in table 13 and figure XI.

<p>| Table 13: Mixed model ANOVA showing no difference in weight change between treatment group A and B |</p>
<table>
<thead>
<tr>
<th>Treatment Group A Mean±SD</th>
<th>Treatment Group B Mean±SD</th>
<th>F</th>
<th>df</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Weight (kg)</td>
<td>64.2±14.5</td>
<td>71.5±13.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End point Weight (kg)</td>
<td>63.2±14.4</td>
<td>71.2±11.7</td>
<td>0.531</td>
<td>1.24</td>
</tr>
<tr>
<td>Weight Change (kg)</td>
<td>-1.0±2.0</td>
<td>-0.25±3.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*significance at p≤0.05
Figure XI: Weight change (kg) between treatment groups A and B from baseline to endpoint. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean weight loss.

3) The mean increase in pulse rate (bpm) in the placebo group will be higher when compared to the continuation group.

A mixed model ANOVA was conducted to determine whether there were statistically significant differences in pulse rate between treatment group A and treatment group B over the course of the trial. Mauchly’s test of Sphericity was met (p>0.05) and Levene’s test indicates that all variances are homogenous for all levels of repeated measures. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean pulse rate (bpm), $F(1, 24) = .624, p = .437$. The
main effect of treatment group trended toward statistical significance difference in pulse rate measurements between treatment group A and B, \( F(1,24) = 3.408, p = .077. \)

The main effect of time was not significantly different in pulse rate measurements (bpm) between baseline and endpoint, \( F(1, 24) = 1.832, p = .189. \) The results of the mixed model ANOVA are represented in table 14 and figure XII.

**Table 14: Mixed model ANOVA showing no difference in pulse rate change between treatment group A and B**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group A Mean±SD</th>
<th>Treatment Group B Mean±SD</th>
<th>( F )</th>
<th>df</th>
<th>( p )-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Pulse rate (bpm)</td>
<td>68.2±10.4</td>
<td>63.3±12.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End point pulse rate (bpm)</td>
<td>73.0±8.7</td>
<td>64.5±10.0</td>
<td>0.624</td>
<td>1,24</td>
<td>.437</td>
</tr>
<tr>
<td>Pulse rate change (bpm)</td>
<td>4.8 ± 9.1</td>
<td>1.3 ± 12.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

bpm beats per minute
*significance at \( p \leq 0.05 \)

Figure XII: Pulse rate change (bpm) between treatment groups A and B from baseline to endpoint. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean pulse rate change.
A mixed model ANOVA was conducted to determine whether there were statistically significant differences in UKU score between treatment group A and treatment group B over the course of the trial. Mauchly’s test of Sphericity was met (p>0.05) and Levene’s test did not indicate that all variances were homogenous for all levels of repeated measures, though the mixed model ANOVA is robust to deviations from normality. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean UKU score $F(1, 23) = .224, p = .640$. The main effect of treatment group trended toward statistical significance difference in UKU score between treatment group A and B, $F(1,23) = .005, p = .944$. The main effect of time was not significantly different in UKU score between baseline and endpoint, $F(1, 23) = .072, p = .791$. The results of the mixed model ANOVA are represented in table 15 and figure XIII.

**Table 15: Mixed model ANOVA showing no difference in UKU change between treatment group A and B**

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group A Mean±SD</th>
<th>Treatment Group B Mean±SD</th>
<th>$F$</th>
<th>df</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline UKU score</td>
<td>12.0±11.9</td>
<td>13.3±9.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End point UKU score</td>
<td>12.5±9.9</td>
<td>11.6±8.1</td>
<td>0.224</td>
<td>1,23</td>
<td>.640</td>
</tr>
<tr>
<td>UKU Change</td>
<td>0.45±9.0</td>
<td>0.45±9.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

UKU Udvalg for Kliniske Undersøgelser Side Effect Rating Scale

*significance at p≤0.05
Figure XIII: UKU change between treatment groups A and B from baseline to endpoint. NOTE: lower scores indicate less side effect burden. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean UKU change.

5) The mean decrease in systolic blood pressure (mmHg) in the placebo group will be lower when compared to the continuation group.

A mixed model ANOVA was conducted to determine whether there were statistically significant differences in systolic blood pressure (mmHg) between treatment group A and treatment group B over the course of the trial. Mauchly’s test of Sphericity was met (p>0.05) and Levene’s test indicates that all variances are homogenous for all levels of repeated measures. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean systolic blood pressure (mmHg), $F(1, 24) = 2.312, p = .141$. The main effect of intervention showed no
significant difference in systolic blood pressure (mmHg) measurements between treatment group A and B, $F(1,24) = .670, p = .421$ and the main effect of time was not significantly different in systolic blood pressure measurements (mmHg) between baseline and endpoint, $F(1, 24) = .298, p = .590$. The results of the mixed model ANOVA are represented in table 16 and figure XIV.

Table 16: Mixed model ANOVA showing no difference in systolic blood pressure between treatment group A and B from baseline to endpoint

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group A Mean±SD</th>
<th>Treatment Group B Mean±SD</th>
<th>$F$</th>
<th>df</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Systolic BP (mmHg)</td>
<td>133.3±21.0</td>
<td>121.5±20.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endpoint Systolic BP (mmHg)</td>
<td>125.6±20.7</td>
<td>125.1±22.7</td>
<td>2.31</td>
<td>1,24</td>
<td>.141</td>
</tr>
<tr>
<td>Systolic BP Change (mmHg)</td>
<td>-7.6±13.5</td>
<td>-0.33±14.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*significance at $p \leq 0.05$

Figure XIV: Systolic blood pressure change (mm Hg) between treatment groups A and B from baseline to endpoint. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean systolic blood pressure.
A mixed model ANOVA was conducted to determine whether there were statistically significant differences in diastolic blood pressure (mmHg) between treatment group A and treatment group B over the course of the trial. Mauchly’s test of Sphericity was met (p>0.05) and Levene’s test indicates that all variances are homogenous for all levels of repeated measures. There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean diastolic blood pressure (mmHg), $F(1, 24) = .591, p = .449$. The main effect of intervention showed no significant difference in diastolic blood pressure (mmHg) measurements between treatment group A and B, $F(1,24) = .110, p = .743$ and the main effect of time was not significantly different in diastolic blood pressure measurements (mmHg) between baseline and endpoint, $F(1,24) = .256, p = .618$. The results of the mixed model ANOVA are represented in table 17 and figure XV.

Table 17: Mixed model ANOVA showing no difference in diastolic blood pressure between treatment group A and B from baseline to endpoint.

<table>
<thead>
<tr>
<th></th>
<th>Treatment Group A Mean±SD</th>
<th>Treatment Group B Mean±SD</th>
<th>F</th>
<th>df</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Diastolic BP (mmHg)</td>
<td>70.6±10.2</td>
<td>69.8±11.3</td>
<td>.591</td>
<td>1,24</td>
<td>.449</td>
</tr>
<tr>
<td>End point Diastolic BP (mmHg)</td>
<td>67.6±6.2</td>
<td>70.4±9.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic BP Change (mmHg)</td>
<td>-2.9±9.6</td>
<td>-0.3±14.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*significance at p≤0.05
There was no statistically significant interaction between the treatment intervention and time (pre and post treatment) on mean diastolic blood pressure.

3.4.3 Exploratory Hypothesis

Anticholinergic cognitive burden (ACB) scores will be associated with increased frequency of anticholinergic adverse events and reduced ChEI discontinuation.

To explore the effects of concomitant anticholinergic exposure in both treatment groups, an analysis of covariance (ANCOVA) was conducted. After adjustment for ACB score, there was no statistically significant difference in adverse event frequency between the interventions, F(1,23) = .110, p = .743. The ACB itself was not significantly associated with frequency of AEs, F(1,23)=.006, p=.938). ACB score was added as a covariate into the mixed models ANOVAs to investigate whether it was having an
influence on ChEI tolerability. In the weight loss mixed model ANOVA, when controlling for ACB score, the model remained non significant (F(1,24)=.211, p=.650) and ACB as a covariate was not associated (F(1,24)=1.00, p=.326). In the pulse rate mixed model ANOVA, when controlling for ACB score, the model was not significant (F(1,24)=.733, p=.401) and ACB as a covariate was also not significant (F(1,24)=.178, p=.677). In the systolic blood pressure mixed model ANOVA, when controlling for ACB score, the model was not significant (F(1,24)=2.33, p=.141) and ACB as a covariate was also not significant (F(1,24)=.104, p=.750). In the diastolic blood pressure mixed model ANOVA, when controlling for ACB score, the model was not significant (F(1,24)=.522, p=.477) and ACB as a covariate was also not significant (F(1,24)=.001, p=.977). In the UKU mixed model ANOVA, when controlling for ACB score, the model was not significant (F(1,23)=.649, p=.429) and ACB as a covariate was also not significant (F(1,24)=2.13, p=.158).

3.5 Post-Hoc Analyses

3.5.1 Primary Hypothesis

Since treatment allocation was not significantly associated with occurrence of an AE, we wanted to investigate whether or not treatment allocation was associated with worsening on the CGI scale. There was no statistically significant association between treatment allocation and worsening of CGI status as measured by the CGI in a chi-square test of independence $\chi^2=1, 26 =0.99, p = 0.32, (p= 0.42, Fisher's exact test). (see table 18).
Table 18: Treatment group and CGI Change Scale

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Yes</th>
<th>No</th>
<th>Total</th>
<th>( \chi^2 )</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (N) (%)</td>
<td>n (N) (%)</td>
<td>n (N) (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>5 (11) 45.5</td>
<td>6 (11) 54.5</td>
<td>11 (26) 42.3</td>
<td>.99</td>
<td>0.42</td>
</tr>
<tr>
<td>B</td>
<td>4 (15) 26.7</td>
<td>11 (15) 73.3</td>
<td>15 (26) 57.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9 (26) 34.6</td>
<td>17 (26) 65.4</td>
<td>26 (26) 100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CGI-C Clinician’s Global Impression of Change; n number of patients with or without CGI worsening; N number of patients in treatment group A and/or B

p-value derived from Fisher’s Exact Test

*significance at p ≤ 0.05

Logistic regression analysis was performed to ascertain the effect of treatment allocation on the likelihood of CGI worsening. The logistic regression model was not statistically significant (\( \chi^2(1) = .986, R^2=.050, p=.321 \)), indicating that treating allocation was not associated with CGI worsening.

A Spearman's rank-order correlation was then run to assess the relationship between change in CGI status and changes in behavioural, cognitive and physiological measures. Change scores were calculated by subtracting baseline values from endpoint values. The results are illustrated in table 19. There was negative associations between changes in CGI status and change in cognition (MMSE \( r=-.498, p=.010 \) and SIB \( r=-.600, p=.001 \)) and a positive association was seen with behaviour (NPI-NH \( r=.429, p=.029 \)).

Physiological changes measured during the course of the trial were not associated with CGI change (weight \( r=.173, p=.397 \), pulse rate \( r=.230, p=.258 \), UKU score \( r=.383, p=.059 \), AE frequency \( r=-.009, p=.996 \)).
To further examine which specific NPI behaviours were associated with change in CGI, Spearman's rank-order correlation was run against each of the 12 behaviours included in the NPI. Of the 12, CGI change was significantly associated with apathy ($r = .404$, $p = .010^*$).
p=.040), disinhibition (r=.446, p=.023) and irritability (r=.430, p=.028). It was not significantly associated with any other behavioural measure on the NPI.

3.5.2 Secondary Hypotheses

3.5.2.1 Clinically Significant Weight loss

Logistic regression analysis was performed to ascertain the effect of treatment allocation on the likelihood of losing clinically significant weight when controlling for baseline weight. The logistic regression model was not statistically significant ($\chi^2(2) = 2.56$, $R^2=.126$, p=.278), indicating that treatment allocation when controlling for baseline weight was not associated with clinically significant weight loss.

3.5.2.2 Mean Weight loss

In order to see whether controlling for clinical covariates had an effect on the main mixed model, we controlled for age and gender separately. When controlling for age the model was still not significant (F(1,24)=.420, p=.523) and age as a covariate was not associated (F(1,24)=.772, p=.389). When controlling for gender, the model was not significant (F(1,24)=.232, p=.635) and gender as a covariate was also not associated (F(1,24)=.278, p=.603).

3.5.2.3 Pulse Rate

In order to see whether controlling for clinical covariates had an effect on the main mixed model, we controlled for age and gender separately. When controlling for age the model was still not significant (F(1,24)=1.05, p=.315) and age as a covariate was associated with pulse rate change (F(1,24)=4.62, p=.042). When controlling for gender, the model was not significant (F(1,24)=.832, p=.371) and gender as a covariate was also
not associated (F(1,24)=.270, p=.608). Controlling for beta-blocker use (F(1,24)=.578, p=.455) and antihypertensive use (F(1,24)=.578, p=.455) in separate models was also not significantly associated and they were not associated as covariates

We wanted to look at the proportion of patients who saw increases in pulse rate versus those who did not. There was no statistically significant association between treatment allocation and increase in pulse rate in a chi-square test of independence, $\chi^2=(1, 26) =1.76$, $p = 0.177$. We then looked at the proportion of patients who had bradycardia (pulse rate <60 bpm) present at study endpoint. There was a trend toward statistically significant association between treatment allocation and presence of bradycardia at endpoint in a chi-square test of independence, $\chi^2=(1, 26) =3.47$, $p = .063$ (Fisher's Exact Test: $p=.113$) (see table 20).

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Did patient have bradycardia at endpoint?</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>(%)</td>
<td>No</td>
<td>(%)</td>
<td>Yes</td>
<td>(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n (N)</td>
<td>n (N)</td>
<td>n (N)</td>
<td>n (N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>11 (26)</td>
<td>100</td>
<td>11 (11)</td>
<td>0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>4 (15)</td>
<td>11 (15)</td>
<td>73.3</td>
<td>15 (26)</td>
<td>57.7</td>
<td>3.47</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>15 (26)</td>
<td>84.6</td>
<td></td>
<td>26 (26)</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20: Treatment group and Bradycardia

n number of patients with or without bradycardia; N number of patients in treatment group A and/or B
p-value derived from Fisher’s Exact Test
*significance at $p\leq0.05$

Of those with bradycardia at baseline, 100% of cases were alleviated in group A and 60% of cases were alleviated in group B but there was no statistically significant
association between groups and disappearance of bradycardia, \( \chi^2=(1, 26) =1.60, p = 0.206 \) (FET=0.46).

3.5.2.4 UKU

In order to see whether controlling for clinical covariates had an effect on the main mixed model, we controlled for age and gender separately. When controlling for age the model was still not significant (F(1,23)=.247, p=.624) and age as a covariate was not associated (F(1,23)=.374, p=.547). When controlling for gender, the model was not significant (F(1,23)=.322, p=.576) and gender as a covariate was also not associated (F(1,24)=.145, p=.707).

3.5.2.5 Blood Pressure

In order to see whether controlling for clinical covariates had an effect on the main mixed model looking at systolic blood pressure, we controlled for age and gender separately. When controlling for age the model was still not significant (F(1,24)=2.40, p=.135) and age as a covariate was not associated (F(1,24)=.383, p=.542). When controlling for gender, the model trended towards significance (F(1,24)=3.70, p=.067) and gender as a covariate was not associated (F(1,24)=1.81, p=.192).

In order to see whether controlling for clinical covariates had an effect on the main mixed model looking at diastolic blood pressure, we controlled for age and gender separately. When controlling for age the model was still not significant (F(1,24)=.505, p=.484) and age as a covariate was not associated (F(1,24)=.264, p=.613). When controlling for gender, the model was not significant (F(1,24)=.681, p=.418) and gender as a covariate was not associated (F(1,24)=.114, p=.739).
3.5.3 Exploratory Hypothesis

We then wanted to assess whether ACB scores were associated with changes on the MMSE and SIB between groups. When controlling for ACB score in a mixed model looking at MMSE change between groups, analysis revealed the model was not significant (F(1,24)=2.908, p=.108) and ACB as a covariate was also not associated (F(1,24)=.199, p=.660). When controlling for ACB score in a mixed model looking at SIB change between groups, analysis revealed the model was not significant (F(1,24)=.792, p=.383) and ACB as a covariate was also not associated (F(1,24)=1.75, p=.199).

3.5.3.1 Cholinergic Side Effects

We also wanted to look at whether or not cholinergic side effect burden was present and significantly different between groups. AEs and UKU side effects that were considered to be possibly ChEI treatment related (weight loss, nausea, vomiting and diarrhea) were summed up in the study population. Patients who experienced no ChEI related side effects were given a score of 0. While patients who experienced one, two or three ChEI related side effects were given a score of 1, 2 or 3 respectively. A score of 1 indicated mild burden whereas 2 or 3 indicated moderate or severe side effect burden. Treatment group A (Median±Interquartile range 1.0±2.0) and treatment group B (1.0±3.0) had similar ChEI burden scores and a Kruskal-Wallis test indicated there was no significant difference between the groups ($\chi^2(1)=.119$, p=.730).
### 3.5.4 Post-hoc Power Calculation

A post-hoc power calculation was conducted to determine whether the primary analysis was adequately powered to detect a true significant difference between groups. Total sample size of the group was 26 and consisted of 11 patients in treatment group A and 15 patients in treatment group B. Prevalence of AEs at endpoint was 54.5% in group A and 73.3% in group B. Using a two-tailed significance ($\alpha$) of 0.05, association between treatment group and incidence of AE was detected with 16.7% power. In order to accurately accept or reject our primary hypothesis, a sample size of 100 patients in each treatment group would be required to detect an association and provide 80% power.

### 3.5.5 Number Needed to Treat

The Number Needed to Treat (NNT) was calculated for each group using the equation $NNT = 1/$Absolute Relative Risk (ARR) (Cook and Sackett, 1995). Assuming that treatment group A was the discontinuation group, NNT was calculated to be 5.3 (95% CI 1.8–5.5). Therefore, 6 patients needed to be treated with treatment A to prevent one additional adverse event. Conversely, if we assume treatment B was the discontinuation group, the NNT is calculated to be a negative reciprocal and instead indicates the Number Needed to Harm (NNH). As such, NNH was 5.3 and as a result 6 patients need to be treated with treatment B to cause one additional AE.
4 GENERAL DISCUSSION AND CONCLUSIONS

This study explored the safety surrounding ChEI discontinuation after long-term use in moderate to severe institutionalized AD patients. The results suggested that treatment allocation between groups was not associated with incidence of AEs ($\chi^2=(1, 26) =0.99, p = 0.32, (p= 0.42, Fisher's exact test)$). Similarly, groups showed no differences on measures of clinically significant weight loss (independence $\chi^2=(1, 26) =1.9, p = 0.17, (p= 0.35, Fisher's exact test)$), general weight loss ($F(1,24) = .531, p = .473$), pulse rate ($F(1, 24) = .624, p = .437$), systolic blood pressure ($F(1, 24) = 2.312, p = .141$), diastolic blood pressure ($F(1, 24) = .591, p = .449$) or side effects as measured by the UKU ($F(1, 23) = .224, p = .640$).

4.1 Treatment Allocation and Adverse Events

The present study hypothesized that the discontinuation group would experience fewer AEs than those patients who remained on the ChEIs. However, the data revealed no significant difference between the groups and the occurrence of AEs. These results could be interpreted to support the view that the ChEIs are a well-tolerated drug class when used in a moderate to severe population. Our results confirm the findings of other studies that have described similar safety outcomes (Black et al., 2007; Blesa et al., 2003; Burns et al., 2004; Feldman et al., 2001; Homma et al., 2008; Tariot et al., 2001; Winblad et al., 2009). For instance, a 24-week long double-blind RCT of community dwelling patients with moderate to severe AD by Feldman and colleagues reported a similar incidence of AEs between those taking donepezil and those who were treated with placebo (83% vs. 80%) (Feldman et al., 2001). Another study by Tariot et al. that examined a subgroup of severe institutionalized patients also reported a comparable
incidence of AEs between both groups and concluded that disease severity had no impact on the ChEI tolerability (Tariot et al., 2001). Though, it is of note that those studies were different in design from the present study in that they were reporting on AE occurrence after short-term use of ChEIs. In terms of similar trial design examining ChEI discontinuation, the DOMINO study reported that both the donepezil continuation group and placebo group experienced the same number of AEs (Howard et al., 2012). Similar results were also found in a trial of galantamine discontinuation, with 34% of patients being maintained experiencing an AE compared to 27% of the placebo group (Scarpini et al., 2011). Generally, AEs and more specifically ChEI related AEs are more frequently reported during the titration phase of therapy (Pratt et al., 2002; Rogers et al., 1998b; Rosler et al., 1999; Tariot et al., 2000). Considering this, the population examined in this study had been on ChEIs for 2 years or longer. Therefore, it could be suggested that patients in this trial were on a well-tolerated dose of ChEI and consequently, would not experience significantly more AEs when compared to the placebo group. This would support the findings of other long-term trials that have reported decreased rates of AEs after extended periods of usage (Grossberg et al., 2004; Raskind et al., 2004; Small et al., 2005). However, it could also be argued that the lack of difference observed between this study’s treatment groups may be caused by loss of ChEIs efficacy. It has been reported that as AD progresses to a more advanced stage, the therapeutic effects of ChEIs may be lost over time and that continued use offers no increased survival benefit (Geldmacher et al., 2006; Lopez et al., 2002; Winblad et al., 2006). Furthermore, it has been documented histologically that as AD progresses to more severe stages, there is major decline in cholinergic markers such as cholinergic neurons, acetyl cholinesterase, choline
acetyltransferase and acetylcholine (Court and Perry, 1991; Giacobini, 2003; Giacobini et al., 1989; Perry et al., 1978; Richter et al., 1980; Schliebs and Arendt, 2011). These histological findings have been confirmed through more modern imaging techniques such as PET and MRI, which have also found reductions in these markers (Bohnen et al., 2005a; Herholz et al., 2007; Iyo et al., 1997). Such cholinergic deficits have been shown to correlate with increased cognitive deterioration and disease severity (Davis et al., 1999). Furthermore, numerous studies of chronic ChEI use have shown that patients will often return to baseline levels of cognition and global function approximately one to two years following initiation of ChEI treatment (Doody et al., 2001b; Doraiswamy et al., 2002; Lyketsos et al., 2004; Pirttila et al., 2004; Rogers et al., 2000). Taken together, these changes may indicate that once a patient passes a certain threshold of cholinergic loss and AD severity over time, there is no longer enough acetylcholine or functional cholinergic neurons in the brain for cholinesterase inhibition to have a therapeutic effect. Moreover, studies of the CSF of AD patients have shown that the reversible ChEIs (donepezil and galantamine), may induce upregulation of acetylcholinesterase, which can lead to acquired tolerance after prolonged administration of these medications (Darreh-Shori and Soininen, 2010; Giacobini, 2000; Imbimbo, 2001; Lane et al., 2006; Poirier, 2002). Consequently, patients may experience diminished response to the ChEIs and this may offer explanation as to why no difference was seen between groups in the present study. It should be noted that the literature addressing ChEI tolerance after chronic use in AD patients is very limited and more research in this area is needed.

In addition to acquired tolerance, it has also been suggested that peripheral red blood cell (RBC) assay measurements of central cholinesterase inhibition may be
overestimating the ability of the ChEIs to inhibit central cholinesterase. Studies have reported that after administration of the highest approved doses of ChEIs, RBC assays reported between 50% and 80% central cholinesterase inhibition (Jann et al., 2002; Rogers and Friedhoff, 1996; Sabbagh and Cummings, 2011). However, this is in contrast to PET imaging studies that have examined central cholinesterase inhibition in patients with mild to moderate AD and found that the ChEIs inhibit acetylcholinesterases by only 20-40% (Canadian Study on Health and Aging, 1994; Bohnen et al., 2005b; Herholz, 2005; Kaasinen et al., 2002; Kuhl et al., 2000; Sabbagh and Cummings, 2011). The results of the PET imaging studies have subsequently led to the study and marketing of higher doses of ChEI, particularly the 23mg dosage of donepezil, with the intention of enabling greater central cholinesterase inhibition and improved drug efficacy for more severe patients (Cummings et al., 2013; Sabbagh and Cummings, 2011; Sabbagh et al., 2013). It is conceivable that examining central cholinesterase inhibition in a severe population would reveal even lower inhibition rates due to the ongoing loss of cholinergic markers seen with disease progression. These findings may also justify why the groups had similar AE rates with regards to centrally related AEs. Overall, the lack of significance difference observed between groups on AE incidence can be interpreted in two different ways. Firstly, that ChEI treatment is well tolerated in this population as some studies have previously suggested or secondly, that the ChEIs are simply no longer working due to chronic tolerance and are thus comparable to placebo.

4.2 Treatment Allocation, Physiological Measures and Side Effects

This study was unable to demonstrate a significant difference between groups on measures of clinically significant weight loss or on measures of physiological change.
with respect to mean weight loss, pulse rate and blood pressure in mixed model ANOVAs. Additional analyses also showed no difference between groups on the UKU side effect rating scale scores over time.

4.2.1 Weight loss

In the present study, 58% of patients lost weight over the 8-week study period and of those 40% lost a clinically significant amount of weight. While short term studies reported ChEI use to be associated with weight loss (Birks, 2006; Lanctot et al., 2003b; Raskind et al., 2000; Tariot et al., 2000), this study found no association between treatment groups and weight loss. However, the results of our study support several other long-term studies that reported similar findings previously (Gillette-Guyonnet et al., 2005; Gillette-Guyonnet et al., 2006; Guerin et al., 2009; Guerin et al., 2005). For example, an observational study that followed 486 community dwelling patients with mild to moderate AD over 1 year found that ChEI use was not associated with clinically significant weight loss (defined as ≥ 4% of initial weight lost) and was, in fact, found to be a protective factor (Gillette-Guyonnet et al., 2005; Gillette-Guyonnet et al., 2006).

More recently, Droogsma et al. also concluded that weight loss in AD was not attributed to long-term ChEI therapy in a retrospective study of galantamine use over 37 months in 303 community dwelling AD patients (Droogsma et al., 2013). Instead this group found weight loss to be associated with lack of informal caregiver and theorized that long-term ChEI use (> 3 months) allowed patients to adapt to the ChEI following the titration phase, therefore reducing the risk of treatment related weight loss (Droogsma et al., 2013; Gillette-Guyonnet et al., 2005). Considering our study was looking at patients who had been using these medications for 2 years or more, it is possible that patients in the
continuation group had adapted to their respective ChEI. Moreover, it should be noted that lack of association in the present study may be due to the fact patients were institutionalized and nursing staff carefully monitored daily nutritional intake, though no associations were found in studies of community dwelling patients without nutritional interventions.

Additionally, numerous studies have found that weight loss is frequently associated with AD (Berlinger and Potter, 1991; Burns et al., 1989; Morgan et al., 1986; Singh et al., 1988; Tavares and Rabins, 1987), with up to 40% of patients experiencing weight loss at some point in the disease (Gillette-Guyonnet et al., 2000). Although weight loss in AD has been linked to the peripheral effects of ChEI therapy, there are many other factors that could be contributing to its etiology. The weight loss seen in our population could be caused by factors such as hyper metabolic state (Aziz et al., 2008), increased behavioural symptoms (White et al., 2004) and changes in appetite regulatory mechanisms (Grundman et al., 1996; Morley, 2001; Tataranni et al., 1999). Thus, with all things considered, weight loss observed in AD may not be associated with long-term ChEI therapy and, therefore, continued use may be safe and well tolerated in late stage dementia.

4.2.2 Cardiovascular Effects

Although not as widely reported as gastrointestinal AEs, ChEI use is also associated with cardiovascular effects such as bradycardia. While we had anticipated a significant increase in heart rate for one of the groups, analyses revealed that there was no significant difference between treatment allocation groups and change in pulse rate. Though our findings support one group that examined the cardiovascular effects of all
three ChEIs and concluded that ChEI use had no effect on pulse rate, blood pressure or electrocardiogram readings (Isik et al., 2010; Isik et al., 2012a; Isik et al., 2012b), they appear to conflict with results of numerous studies that have reported a relationship between decreased heart rate or bradycardia and ChEI use (Bordier et al., 2006; Gauthier, 2001; Gill et al., 2009; Hernandez et al., 2009; McLaren et al., 2003; Park-Wyllie et al., 2009). Most notably, large, population-based cohort studies have found that new ChEI users have an increased risk of hospitalization for bradycardia in comparison to AD patients not receiving ChEIs (Gill et al., 2009; Hernandez et al., 2009). However, those studies were looking at the incidence of bradycardia in patients who had just initiated ChEIs whereas in this study patients were taking these medications for 2 years or more. As previously discussed, ChEI related AEs are more frequently reported during the titration phase of therapy (Pratt et al., 2002; Rogers et al., 1998b; Rosler et al., 1999; Tariot et al., 2000) so perhaps pulse rate changes are more apparent upon therapy initiation. As such, patients who may have experienced cardiovascular related AEs such as bradycardia may have been discontinued from ChEI therapy earlier on and were therefore not included in this study. Another explanation for similarity between groups is that episodes of bradycardia can be transient in nature (Gill et al., 2009) and although it might have been present, it is possible that it was not detected during clinical assessments. Similarity may also be explained by general neurocardiovascular instability associated with AD, which can result in bradycardia and blood pressure changes regardless of ChEI treatment (Kenny et al., 2002).

Interestingly, in post-hoc analyses examining treatment allocation and presence of bradycardia at end point, we found a trending association between groups. Analyses
showed that a greater proportion of patients in treatment group B had bradycardia at study endpoint in contrast to treatment group A, which had no patients. Although, we are unable to accurately comment, as treatment allocation in the present study remains unknown, unblinding of treatment groups upon study completion may reveal a treatment effect.

With respect to blood pressure, while we would have expected the discontinuation group to have significantly lower blood pressure, our study found no significant difference between treatment groups on systolic and diastolic blood pressure change measures. These results conflict with previous studies that have reported ChEI treatment in AD patients is associated with elevations in blood pressure (Claassen et al., 2009; McLaren et al., 2003). However, as previously discussed, other studies have also reported similar findings to our own (Bordier et al., 2006; Isik et al., 2010; Isik et al., 2012a; Isik et al., 2012b). Our results may be explained by the variability of ChEI activity in the autonomic nervous system as ChEIs can stimulate both the parasympathetic and sympathetic nervous system. Parasympathetic stimulation can slow pulse rate, which can cause lowered blood pressure while sympathetic stimulation can increase peripheral arterial resistance and blood pressure (Masuda, 2004). The cardiovascular effects of ChEI use are complex and remain unclear in published literature (Gill et al., 2009). Moreover, many studies focus primarily on orthostatic hypotension and not on general blood pressure measures so comparison to other studies was limited. However, from this study, it can be concluded that systolic and diastolic blood pressure were not significantly affected by cholinesterase inhibitor use and are safe to use in this respect.
4.2.3 UKU

Similar to the occurrence of AEs, this study found no differences found between groups in terms of side effect change as measured by the UKU side effect rating scale. Patients in either group remained relatively stable in terms of side effects score, with little change reported. As discussed previously, these results could be interpreted to support the view that the ChEIs are well-tolerated and side effects after prolonged use are minimal (Black et al., 2007; Blesa et al., 2003; Burns et al., 2004; Feldman et al., 2001; Homma et al., 2008; Tariot et al., 2001; Winblad et al., 2009). Alternatively, they could also be explained by acquired tolerance of the continuation group after prolonged ChEI use, leading to upregulation of acetylcholinesterase enzyme and therefore, diminished ChEI effect (Darreh-Shori and Soininen, 2010; Imbimbo, 2001; Lane et al., 2006; Poirier, 2002). In addition, side effects seen in the discontinuation group may be caused by withdrawal symptoms, which may explain why both groups appear to be similar. Moreover, the presence of many comorbid illnesses and polypharmacy in this frail population may also be the cause of similarity between groups, as side effects thought to be attributed to study drug use in the discontinuation group may have been from sickness or other medications.

4.3 Anticholinergic Medication

In total, 65.4% of the study population was receiving at least one medication with known anticholinergic properties. However, this study found no association between the effects of concomitant anticholinergic exposure on both treatment groups and frequency of adverse events. This study also reported no association between the effects of concomitant anticholinergic burden in both treatment groups and tolerability in terms of
weight loss, vitals or UKU side effect scores. In addition, in post hoc analyses looking at ACB scores and cognition between groups, it was found that ACB was not associated with cognitive performance on the MMSE or the SIB. These finding contradict other published data that has found increased anticholinergic burden can cause more adverse events and further cognitive deterioration (Jewart et al., 2005; Konishi et al., 2010; Shah et al., 2013). However, our results support the findings of Fox and colleagues who examined the relationship between changes in cognition and anticholinergic cognitive burden in patients with AD who were concomitantly using ChEIs. That group found that anticholinergic medication burden as measured by the ACB was not associated with increased deterioration in cognition (Fox et al., 2011a). Similarly, Bottiggi et al. found that concomitant use of ChEIs and anticholinergic medications did not negatively impact functional and cognitive status (Bottiggi et al., 2007). Considering the results of those studies in addition to ours, it may be concluded that anticholinergic medications may not be not be as damaging to cognition as originally speculated. Furthermore, they may also not impact the tolerability of discontinuing ChEIs in a moderate to severe population.

4.4 Post-hoc Analyses

Since treatment allocation was not significantly associated with occurrence of an AE, we wanted to examine whether the proportion of CGI-C worsening was related to treatment allocation in post-hoc analyses. In addition, we investigated whether CGI-C was associated with changes in behavioural, cognitive and physiological measures. Analyses indicated that there was no association between treatment group and worsening as measured by the CGI. However, regardless of treatment group, we did see that CGI worsening was associated with worsening cognitive scores and behavioural symptoms,
specifically apathy, disinhibition and irritability. Moreover, similar to the results of the main analyses, CGI worsening was not associated with side effect occurrence or changes in physiological measures. It is possible that while no differences were found between our groups on measures of AE occurrence or physiological parameters, there are subtle changes in behaviour and cognition being detected by the study clinicians. Worsening on the CGI-C may also be reflective of general disease progression over time across groups and this could explain why the primary and secondary analyses yielded no difference between groups.

4.5 Limitations

The main limitation of this study was the small sample size. Recruitment for this study was challenging as the patient population was frail, at an advanced age and had multiple comorbid illnesses. Aside from not being on a ChEI for more than 2 years, patients were mainly excluded because they were not medically stable enough to participate or in palliative care. The original sample size calculation estimated 30 patients per group would be required to achieve an adequate power of 80%. However, due to the small numbers in this study, post-hoc analysis revealed that analytical power was only 16.7%. As a result, we acknowledge that the analyses were susceptible to type II error and differences that existed between the groups may have not been detected. Continued patient recruitment and a larger sample size should improve the power for these analyses in the future. A larger sample size may also change the results of this study and differences between groups may be seen. Secondly, due to small numbers, we did not compare AEs between the individual ChEIs, nor did we examine dosage effects. However, the second generation ChEIs we studied have similar efficacy and are thought
to possess similar tolerability profiles (Birks, 2006; Gill et al., 2009; Hogan et al., 2004).

Thirdly, the study design used a fixed tapering regimen in the discontinuation arm and we therefore acknowledge that a slower tapering schedule might have influenced our results. However, in order to maintain consistency across the different ChEIs, a 2-week taper was assessed to be appropriate. Finally, as previously mentioned, the main study is still actively recruiting and consequently, to protect the integrity of the main study, treatment allocation for this study was semi-blinded. Therefore, we are unable to comment on which group was discontinued or maintained on ChEI treatment. With that being said, no significant differences were seen between groups on AE occurrences or on physiological measurements.

Furthermore, clinically significant weight loss was calculated in this study based on studies which defined clinically significant involuntary weight loss as a 5% decrease in body weight over a 6-months period (Bouras et al., 2001; Gillette Guyonnet et al., 2007; Leff, 2003). We applied these findings to our own study time line and calculated that clinically significant weight loss would be 1.66% of total body weight lost over the 8-week study period. This percentage of weight loss over a shorter time span has not been validated in any other study and as a result, may not be clinically relevant. However, assuming a progressive weight loss without nutritional interventions, these patients were on course to lose clinically significant weight by definition of the above-mentioned studies. Additionally, the weight loss observed in this very frail population may have been due to poor health status, sickness during the trial and/or disease progression, which may not be truly reflective of treatment adverse events.
This study was unable to evaluate the effects of ChEI discontinuation on orthostatic blood pressure, as the majority of patients included in this study were wheelchair bound or bed bound. While we recognize this may have been a better correlate of discontinuation response (Lanctot et al., 2003a), we were unable to accurately measure it in this population. In addition, when quantifying anticholinergic exposure, the ACB scale did not account for dose or frequency of medication when scoring and this may have influenced our results.

Finally, this study took place at Sunnybrook Veterans’ Centre where residents are predominantly male and, therefore, this may have introduced sampling bias due to the overrepresentation at this site.

4.6 Future Directions and Recommendations for Future Studies

The second generation ChEIs have been well studied in patients with AD, with many clinical trials reporting on their modest effects on cognition and good tolerability profiles. However, as mentioned, the literature discussing ChEI discontinuation in more severe populations remains sparse. To date, only the DOMINO trial and this RCT have examined ChEI cessation in severe AD patients who have used these drugs for upwards of 2 years. This safety study in particular, did not find significant association between treatment allocation and the occurrence of AEs, nor did it find any difference in groups on physiological measures. However, at the present time, the main ChEI discontinuation study is actively recruiting and data collection is ongoing. Recruitment in the present study was challenging due to the nature of a moderately severe AD population discussed previously. Therefore, it would be highly advantageous to add additional centres to recruit from for the main study and for future studies addressing this topic. Once the
recruitment goal of the main study is met, treatment allocation will be revealed and placebo and ChEI continuation groups will be compared. Upon study completion, a larger sample size will improve power for statistical analyses and will offer more conclusive evidence with respect to the safety of ChEI discontinuation. With treatment allocation fully unblinded, it will be possible to more accurately determine whether or not discontinuation of ChEIs is safer than continued use. Closer examination of patients who were able to discontinue safely will help to determine when, and in which type of patients, it is safe and appropriate to discontinue therapy. It would also be interesting to perform a subgroup analysis examining whether disease severity has an impact on ChEI discontinuation tolerability. Additionally, looking for any predictive factors of safe discontinuation in our study population would help provide more information to clinicians when considering cessation of therapy for patients. The variability in treatment response highlights the need to identify those who respond positively to continued ChEI therapy versus those who do not, in an effort to improve drug efficacy, patient management and its cost benefit in the treatment of AD (Van Der Putt et al., 2006). Creating a predetermined measurement, such as cognitive test score cut-off, as a marker of treatment cessation is not clinically sound. Ultimately, it would be ideal to find biomarkers of ChEI treatment response, making selection of patients who would not benefit from therapy initiation or continued therapy easier. For instance, Davidsson and colleagues found that ChEI activity can be measured in the cerebral spinal fluid and that patients who are non-responders to therapy will have significantly decreased levels of acetylcholinesterase in the CSF (Davidsson et al., 2001). In addition, that group found that a subgroup of patients with higher levels of CSF biomarkers ‘total tau’ (T-tau) and
‘phosphorylated tau’ (P-tau) and low levels of Aβ42 were more likely to have poor ChEI treatment outcomes and experience more rapid cognitive deterioration over time (Wallin et al., 2010). Those findings coupled with the research of Maruyama and colleagues, who have proposed novel neuroimaging techniques to measure tau in the brains of patients with AD (Maruyama et al., 2013), may enable a non-invasive approach to evaluating ChEI efficacy after long-term use. Future studies that explore this subgroup of patients and evaluate whether these biomarkers are predictive of safe discontinuation would be interesting. These techniques may also be useful to examine the relationships between ChEI use and tolerance in this population after prolonged use, as the literature addressing this issue remains limited. Taken together, it would be highly advantageous to conduct larger, multi-centre discontinuation studies to allow for more evidence on this controversial topic and to help clarify future CPGs.

4.7 Implications for Future Research

Until more effective therapies are available, ChEIs remain the first line therapy for treatment of the symptoms associated with AD. While some evidence suggests ChEIs provide some benefit into the advanced stages of AD, there is still uncertainty as to whether these modest benefits outweigh the risks. Since treatment allocation and risk of AEs were not associated, there is evidence to support the notion that ChEIs are well tolerated when used in a moderate to severe institutionalized population. These findings may also suggest that patients develop tolerance to ChEI therapy over time, increasing the risk for withdrawal phenomena upon discontinuation (Singh and Dudley, 2003). Altogether, this study has the potential to add to the limited knowledge regarding the safety of ChEI discontinuation after long-term use in a moderately-severe
institutionalized population. However, considering the heterogeneous response to ChEI treatment, clinicians should be cognizant of the risks associated with ChEI use in patients with moderate to severe AD including increased chance of falls, gastrointestinal adverse events, syncope, bradycardia, pace maker insertion and hip replacement (Birks, 2006; Gill et al., 2009). Further study is required to fully understand the role of ChEI therapy in late stage dementia and to determine the consequences of discontinuation in this frail population. Such studies will add to literature and help clinicians to safely use ChEI in patients with AD.

4.8 Conclusion

This study, which examined the safety of ChEI discontinuation in 26 moderate to severe AD patients, found no association between treatment group and AE occurrence. While prolonged use of cholinesterase inhibitors into later stages of the disease appears to be generally well tolerated and not associated with weight loss or cardiovascular effects, neither group worsened suggesting that discontinuation was not associated with negative outcomes. However, further study is needed to determine the relationship between long-term ChEI use and acquired drug tolerance in this population. Clinicians should remain mindful of the risk of ChEI related adverse events associated with continued use as well as the risk for withdrawal symptoms upon discontinuation. Although this study was limited by small sample size, the main study is still actively recruiting and unblinding of treatment groups in the future may reveal a treatment effect. Continued investigation of ChEI discontinuation safety will help to determine which patients may benefit from discontinuation and clarify discontinuation protocols in the future.
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LIST OF PUBLICATIONS, ABSTRACTS AND PRESENTATIONS

Refereed Journal


Abstracts


Presentations


APPENDICES

Appendix A – REB Approval
To: Dr. Krista Lanctôt  
Neuropsychopharmacology  
Room FG05

From: Dr. Philip Hébert

Date: May 28, 2013

Subject: A Discontinuation Study of Cholinesterase Inhibitors for the Treatment of Severe Alzheimer's Disease in a Long Term Care Setting

Project Identification Number: 107-2010

The Research Ethics Board is in receipt of your amendment submission form dated May 13, 2013 and has reviewed and approved the following documents pertaining to the above referenced study.

- Summary of changes, Protocol Version 1.6 dated May 9, 2013
- Protocol Version 1.6 dated May 9, 2013

This study may continue at Sunnybrook Health Sciences Centre.

During the course of the research, any significant deviations from the approved protocol and/or any unanticipated developments must be brought to the attention of the Research Ethics Board.

Thank you for keeping the Board informed.

Philip C. Hébert, MD FPCP  
Chair, Research Ethics Board

OR

Brian Murray, MD FRCP(C) D,ABSM  
Vice-Chair, Research Ethics Board

The Research Ethics Board of Sunnybrook Health Sciences Centre Operates in Compliance with the Tri-Council Policy Statement 2nd edition, ICH GCP Guidelines, Part C Division 5 of the Food and Drug Regulations, Part 4 of the Natural Health Products Regulations, and Part 5 of the Medical Devices Regulations. All Health Canada regulated trials at Sunnybrook are conducted by a Qualified Investigator.

Fully affiliated with the University of Toronto
November 20, 2012

Dr. Goran Eryavec
North York General Hospital
4001 Leslie Street
Toronto, Ontario

Dear Dr. Eryavec:

Re: NYGH REB 12-0207
A discontinuation study of cholinesterase inhibitors for the treatment of severe Alzheimer’s disease in a long term care setting.

The above-named protocol was reviewed at a meeting of the North York General Hospital Research Ethics Board on October 23, 2012. This submission was reviewed at a meeting of the Board where a quorum was maintained.

The proposal is approved for the next 12 months. If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If the study is expected to continue beyond the expiry date, you are responsible for ensuring the study receives annual re-approval. The REB must also be notified of the completion or termination of this study and a final report provided.

If, during the course of the research, there are any serious adverse events, changes in the approved protocol or consent form, or any new information that must be considered with respect to the study, these should be brought to the immediate attention of the Board. As the Principal Investigator, you are responsible for the ethical conduct of this study.

The REB of NYGH functions under the guidance of the Tri-Council Policy Statement and the ICH/GCP Guidelines.

Sincerely,

[Signature]

David Kaplan, MSc (Health Policy & Bioethics), MD, CCFP
Associate Chief of Family & Community Medicine
Chair, Research Ethics Board, North York General Hospital
Assistant Professor, Department of Family & Community Medicine
Faculty of Medicine, University of Toronto

October 23, 2012
Date of Approval

October 23, 2013
Expiry Date
APPENDICES

Appendix B – Study Consent Form
INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Study Title: A discontinuation study of cholinesterase inhibitors for the treatment of severe Alzheimer’s disease in a long term care setting

Investigators: K.L. Lanctôt, PhD Sunnybrook Health Sciences Centre
N. Herrmann, MD Sunnybrook Health Sciences Centre
S.E. Black, MD Sunnybrook Health Sciences Centre
E. Williams, MD Sunnybrook Health Sciences Centre

This is an investigator-initiated study supported by the Alzheimer Society of Canada

INFORMED CONSENT

You are being asked to consent on behalf of your loved one to participate in a research study. A research study is a way of gathering information on a treatment, procedure or medical device or to answer a question about something that is not well understood.

This form explains the purpose of this research study, the tests and procedures involved, possible risks and benefits, and the rights of participants.

Please read this form carefully and ask any questions you may have. Please ask the study staff or the investigator to clarify anything you do not understand or would like to know more about. Make sure all your questions are answered to your satisfaction before deciding whether to participate in this research study.

INTRODUCTION

You are being asked to consider providing consent on behalf of your loved one to participate in this study. Your loved one has Alzheimer’s disease and is currently on a medication, either Aricept, Exelon or Reminyl, which are all part a class of medications called cholinesterase inhibitors. Patients on cholinesterase inhibitors often take them for at least 2 years. While cholinesterase inhibitors have been shown to have a small positive effect on cognitive, emotional and behavioural problems that occur with Alzheimer’s, they are not always effective, and can cause side effects such as nausea, diarrhea, insomnia, vomiting, muscle cramping, fatigue and anorexia. In such cases, it may be more beneficial to stop the cholinesterase inhibitor to reduce the risk of these side effects and minimize interactions with other medications. The goal of this study is to determine whether the benefits of discontinuing cholinesterase inhibitors outweigh the risk, and who might benefit most.

WHAT IS THE USUAL TREATMENT?
Currently, patients with Alzheimer’s would be prescribed Aricept, Exelon, Reminyl or Ebixa, which have been approved by Health Canada for the treatment of Alzheimer’s. In Canada, only Aricept and Ebixa are approved for patients with severe Alzheimer’s disease.

**WHY IS THIS STUDY BEING DONE?**
The purpose of this study is to determine what effects discontinuing cholinesterase inhibitors may have on patients who may not be experiencing any benefits.

**WHAT WILL HAPPEN DURING THE STUDY?**
If you decide to consent your loved one to participate in this study, they will be asked to undergo an initial assessment which will involve a medical evaluation (including a physical exam and an assessment of blood pressure, heart rate and weight) and a brief test of memory. We will be collecting their demographic information, medical history and current medications.

Once it has been determined that your loved one is eligible to participate in the study, they will then be randomly assigned into one of two groups. One group will receive their regular dose of cholinesterase inhibitor, while the other group will receive placebos. The placebos look the same as their cholinesterase inhibitor. Neither you, your loved one, their nurse, nor the investigators will know which your loved one will be receiving.

During the study, your loved one will be monitored and assessed by trained study personnel. There will be 4 assessment dates (at the screening, when they begin taking the medication, 4 weeks into taking the medication and at 8 weeks), each of which will take approximately 30 minutes to complete. Assessments will include a physical examination, an adverse event review and a questionnaire about their memory. We will also be speaking with their primary nurse regarding their mood, behaviours and activities of daily living. There will also be a short assessment at 2 weeks, to determine any adverse events.

**HOW MANY PEOPLE WILL BE IN THIS STUDY?**
It is anticipated that 60 people will participate in this study, all from Sunnybrook Health Sciences Centre’s long-term care unit.

**WHAT ARE THE RISKS AND HARMs OF PARTICIPATING IN THIS STUDY?**
Your loved one may experience side effects from participating in this study. Some side effects are known and listed below, but there may be side effects that are not expected. If you decide to consent your loved one to participate in this study, you should contact Jordana O’Regan, study coordinator, at 416-480-6100 x3185 about any side effects or study-related injuries that they experience.
If they are in the group that receives their current cholinesterase inhibitor medication, there should be no change in the side effects they experience. These include nausea, diarrhea, insomnia, vomiting, muscle cramping, fatigue and anorexia.

If they are in the group that receives placebo and are removed from their cholinesterase inhibitor, you or their primary nurse may notice a worsening of memory or behaviours, such as increased aggression.

**WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?**
It is unknown whether the participant will benefit from this study.

**CAN PARTICIPATION IN THIS STUDY END EARLY?**
The investigators may decide to remove your loved one from this study without your consent for any of the following reasons:

- The investigators decide that continuing in this study may be harmful to your loved one
- They are unable or unwilling to follow the study procedures

If your loved one is removed from the study, the investigators will discuss the reason with you. They will be asked to complete the assessments that would have been conducted at week 8 as soon as possible.

You can also choose to end your loved one’s participation at any time. If you withdraw voluntarily from the study, you are encouraged to contact Jordana O’Regan at (416) 480-6100 x3185 immediately. The information about your loved one that was collected before they left the study will still be used. No new information will be collected without your permission.

**WHAT ARE THE COSTS OF PARTICIPATING IN THIS STUDY?**
Neither you nor your loved one will incur costs as a result of participation in this study.

**ARE STUDY PARTICIPANTS PAID TO PARTICIPATE IN THIS STUDY?**
No financial compensation or reimbursement for participation in this study will be given.

**WHAT OTHER CHOICES ARE THERE?**
Your loved one does not have to participate in this research study to receive treatment for their condition. Other medications and treatments are available and can be discussed with their doctor.

**COMMUNICATION WITH YOUR FAMILY DOCTOR**
For the purposes of this research study we are required to inform your loved one’s family doctor of their participation in this study.

**DO THE INVESTIGATORS HAVE ANY CONFLICTS OF INTEREST?**
The investigators do not have any conflicts of interest in this study.

**WHAT ARE THE RIGHTS OF PARTICIPANTS IN A RESEARCH STUDY?**

All participants in a research study have the following rights:

1. You have the right to have this form and all information concerning this study explained to you and if you wish translated into your preferred language.

2. Participating in this study is your choice (voluntary). You have the right to refuse to participate, or to stop participating in this study at any time without having to provide a reason. If you choose to withdraw, it will not have any effect on your future medical treatment or health care. Should you choose to withdraw from the study you are encouraged to contact Jordana O'Regan, Department of Psychiatry at 416-480-6100 ext. 3185 immediately.

3. You have the right to receive all significant information that could help you make a decision about participating in this study. You also have the right to ask questions about this study and your rights as a research participant, and to have them answered to your satisfaction, before you make any decision. You also have the right to ask questions and to receive answers throughout this study. If you have any questions about this study you may contact the person in charge of this study (Principal Investigator) Dr. Krista Lanctôt at 416-480-6100 x2241. If you have questions about your rights as a research participant or any ethical issues related to this study that you wish to discuss with someone not directly involved with the study, you may call Dr. Philip C. Hébert, Chair of the Sunnybrook Research Ethics Board at (416) 480-4276.

4. By signing this consent form, you do not give up any of your legal rights.

5. You have the right to receive a copy of this signed and dated informed consent package before participating in this study.

6. You have the right to be told about any new information that might reasonably affect your willingness to continue to participate in this study as soon as the information becomes available to the study staff. This may include new information about the risks and benefits of being a participant in this study.

7. If you become sick or injured as a direct result of your participation in this study, your medical care will be provided.

8. Any of your personal information (information about you and your health that identifies you as an individual) collected or obtained, whether you choose to participate or not, will be kept confidential and protected to the fullest extent of the law. All personal information collected will be kept in a secure location. The study staff, the Sunnybrook Research Ethics Board, and the regulatory authority(ies) (Health Canada and/or FDA) will have access to your personal information for purposes associated with the study, but will only be allowed to access your records under the supervision of the Principal Investigator and will be obligated to protect your privacy and not disclose your personal information. None of your personal information will be given to anyone without your permission unless required by law. When the results of this study are published, your identity will not be disclosed. The data for this study will be retained for 25 years.

9. If, as a result of your participation in this study, any new clinically important medical information about your health is obtained, you will be given the opportunity to decide whether you wish to be made aware of that information.

10. You have the right to access, review and request changes to your personal information (i.e. address, date of birth).

11. You have the right to be informed of the results of this study once the entire study is complete.
DOCUMENTATION OF INFORMED CONSENT

Full Study Title: A Discontinuation Study of Cholinesterase Inhibitors for the Treatment of Severe Alzheimer’s Disease in a Long Term Care Setting

Name of Participant: __________________________________________________________

Participant/Substitute decision-maker
By signing this form, I confirm that:
• This research study has been fully explained to me and all of my questions answered to my satisfaction
• I understand the requirements of participating in this research study
• I have been informed of the risks and benefits, if any, of participating in this research study
• I have been informed of any alternatives to participating in this research study
• I have been informed of the rights of research participants
• I have read each page of this form
• I authorize access to my personal health information, medical record and research study data as explained in this form
• I have agreed to participate in this study or agree to allow the person I am responsible for to participate in this study
• I understand that my family doctor will be informed of my participation in this research study

_________________________________________  ___________________________  __________
Name of participant/Substitute decision-maker (print)  Signature  Date

Person obtaining consent
By signing this form, I confirm that:
• This study and its purpose has been explained to the participant named above
• All questions asked by the participant have been answered
• I will give a copy of this signed and dated document to the participant

_________________________________________  ___________________________  __________
Name of Person obtaining consent (print)  Signature  Date

Statement of Investigator
I acknowledge my responsibility for the care and well being of the above participant, to respect the rights and wishes of the participant as described in this informed consent document, and to conduct this study according to all applicable laws, regulations and guidelines relating to the ethical and legal conduct of research.

Dr. Krista Lanctôt_________  ___________________________  __________
Name of Investigator (print)  Signature  Date