USE OF MEDICATIONS IN THE ALZHEIMER'S DISEASE POPULATION:

PHYSICIAN AND CAREGIVER PERSPECTIVES

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LIST OF ABBREVIATIONS

ACTS	=	Allocation of Caregiver Time Survey
AD	=	Alzheimer's disease
ADAS-cog	=	Alzheimer Disease Assessment Scale-cognitive subscale
ADAS-noncog	=	Alzheimer's Disease Assessment Scale-noncognitive subscale
AGI	=	Alzheimer Groupe Incorporated
aRSS	=	Abridged Relatives Stress Scale
ASM	=	Alzheimer Society of Montréal
CATS	=	Caregiver Activity Time Survey
CBS	=	Caregiver Burden Scale
CCECS	=	Centre for Clinical Epidemiology and Community Studies
CDR	=	Clinical Dementia Rating
CDR-SB	=	Clinical Dementia Rating – Sum of Boxes
CGIC	=	Clinician Global Impression of Change
ChEI	=	Cholinesterase inhibitor
CI	=	Confidence interval
CIBIC	=	Clinician Interview-based Impression of Change
CIBIC-plus	=	Clinician Interview-based Impression of Change with caregiver input

CLSC	=	*Centre local de services communautaires* (local community services centre)
CSHA	=	Canadian Study of Health and Aging
DPC	=	Double-blind/placebo-controlled/crossover
DPP	=	Double-blind/placebo-controlled/parallel group
GAS	=	Goal Attainment Scaling
GDS	=	Global Deterioration Scale
GI	=	Gastrointestinal
GLM	=	Generalized linear model
ITT	=	Intent-to-treat
κ_w	=	Weighted kappa
LD	=	Listwise deletion
MCI	=	Mild cognitive impairment
MCSD	=	Minimum clinically significant difference
MI	=	Multiple imputation
MMSE	=	Mini-Mental State Examination
N/A	=	Not applicable
NINCDS-ADRDA	=	National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Associations
NS	=	Not statistically significant
NSAID	=	Non-steroidal anti-inflammatory drug
OR	=	Odds ratio

PD	=	Cognitive Subscale of Poulshock and Deimling
Q	=	Question on the caregiver questionnaire
RCQ	=	Respondent to the caregiver questionnaire
Riv	=	Rivastigmine
RTS	=	Respondent to the telephone survey
SCB-obj	=	Screen for Caregiver Burden-objective subscale
SCB-subj	=	Screen for Caregiver Burden-subjective subscale
SD	=	Standard deviation
SIB	=	Severe Impairment Battery
SS	=	Statistically significant

ABSTRACT

Introduction: Research into medications for Alzheimer's disease (AD) is primarily conducted in drug trials, were efficacy is assessed by changes in score on established outcome measurement scales. However, physicians' and caregivers' perspectives on efficacy, along with their perspectives on other factors that may influence prescribing (e.g., adverse effects), remain largely unexplored. The objective of this thesis is to examine these perspectives to gain a broader understanding of the factors that can influence the use of medications in AD.

Methods: Two studies were conducted. The first involved all of the Province of Québec's geriatricians, neurologists, and psychogeriatricians, as well as a random sample of Québec's 8,115 general practitioners. The second study involved 375 caregivers who attended AD-related support groups. Questionnaires were used to collect data on the proportion of patients prescribed cholinesterase inhibitors (ChEIs), efficacy requirements for prescribing new medications, acceptance of adverse effects, physician-caregivers discussions about medications, and caregiver pressure on physicians to prescribe medications.

Results: Response rates were 35.4% (physicians) and 64.4% (caregivers). More stringent efficacy requirements on the part of physicians were negatively associated with prescribing ChEIs, although effect sizes were small and associations were not always statistically significant. More stringent efficacy requirements on the part of caregivers were negatively associated with prescribing in some instances (e.g., required improvements to patients' ability to eat, OR=0.74, 95% CI=0.61 to 0.89), but not in others (e.g., required improvements to patients' speech, OR=1.02, 95% CI=0.81 to 1.19).

Caregivers' willingness to accept adverse effects was positively associated with prescribing ChEIs (odds ratios for 11 adverse effects ranged from 1.83 to 8.30); however, prescribing was not associated with physicians being the first to discuss the use of medications to treat AD (OR=2.37; 95% CI=0.90 to 6.24), nor was it associated with caregiver pressure on physicians to prescribe (OR=1.33; 95% CI=0.49 to 3.58).

Conclusion: This research is the first to show how physician and caregiver perspectives on issues such as efficacy and safety can affect the use of medications in AD.

RÉSUMÉ

Introduction: La recherche sur les médicaments pour la maladie d'Alzheimer (MA) s'effectue principalement lors d'essais cliniques. L'efficacité d'un médicament est déterminé par des variations de scores sur des échelles d'évaluation pré-établies. Cependant, l'avis et les opinions des médecins et celle des personnes aidantes sur l'efficacité-autant que sur d'autres facteurs tels que les effets secondaires-pouvant exercer une influence dans la prescription de medicaments demeurent en grande partie inexplorés. Cette thèse propose d'examiner ces avis et opinions afin d'obtenir une compréhension plus vaste des facteurs pouvant influencer les prescriptions de médicaments pour la MA.

Méthode: Deux études ont été examinés. La première impliquait tous les médecins gériatres, neurologues et psychogériatres du Québec, ainsi qu'un échantillon aléatoire d'omnipraticiens parmi le 8115 médécins de la province. La deuxième étude regroupait 375 personnes aidantes ayant participé à des groupes de soutien concernant la MA. Des questionnaires furent utilisés afin de recueillir des données sur la proportion de patients à qui on a prescrit des inhibiteurs de cholinestérase (ChEIs); les exigences requises pour l'efficacité lors de la prescription de nouveaux médicaments; l'acceptation d'effets secondaires; les échanges entre personnes aidante et médecins sur les médicaments, ainsi que les pressions qu'exercent les personnes soignantes sur les médecins afin que ces derniers prescrivent des médicaments.

Résultats: Les taux de réponse sont de 34.5% pour les médecins et de 64.4% pour les personnes aidantes. Des exigences plus rigoureuses requises des médecins concernant l'efficacité furent associé négativement à la prescription de ChEIs, bien que l'effet «taille

échantillon» soit petit et que les associations n'était pas toujours statistiquement significatives. Des exigences plus rigoureuses des personnes aidantes concernant l'efficacité on été, dans quelques cas, associés négativement à la prescription (i.e., des ameliorations exigées sur la capacité des patients de se nourrir, OR=0.74, 95% CI=0.61 à 0.89), mais pas dans d'autres (i.e., des améliorations exigées concernant l'élocution des patients, OR=1.02, 95% CI=0.81 à 1.19). L'acceptation de la part des personnes aidantes à faire face aux effets secondaires à été positivement associé à la prescription de ChEI (odds ratio pour 11 effets secondaires s'étalant de 1.83 à 8.30). Par contre, la prescription n'a pas été associé aux médecins en tant que premiers à discuter l'utilisation de médicaments pour traiter la MA (OR=2.37; 95% CI=0.90 à 6.24), ni n'a été associée aux pressions exercées par les personnes aidantes envers les médecins afin que ceux-ci prescrivent des médicaments (OR=1.33; 95% CI=0.49 à 3.58).

Conclusion: Cette étude est la première à démontrer comment l'avis et opinions des médecins et personnes aidantes sur des questions telles que l'efficacité et la sécurité des médicaments peut influencer la prescription de certains médicaments dans le traitement de la MA.

STATEMENT OF ORIGINALITY

This thesis is comprised of original work. It is the first study wherein physicians' efficacy requirements for prescribing a medication to treat Alzheimer's disease (AD) were elicited for clinical outcomes in the domains of cognition, behaviour and mood, and the ability to perform basic activities of daily living. It is also the first study wherein physicians' efficacy requirements were elicited for increases in the length of time that patients would be expected to remain in the mild or moderate state of disease. Only one earlier study was conducted in the area of physicians' efficacy requirements. However, requirements were not defined as clinical outcomes, but as changes in scale score on the Mini-Mental State Examination.

In this thesis, caregivers were asked to give their opinions about what AD medications should do for patients in each 15 different domains that are affected by AD (e.g., memory, speech, recognition of surroundings). This marks the first study in which caregivers were asked for such opinions in a formal research setting. These opinions are, in effect, caregivers' efficacy requirements. Caregivers were also asked about their willingness to allow patients to continue taking AD medications in the event of adverse effects. Two earlier studies from a single research centre examined a similar question, although only for one adverse effect (i.e., gastrointestinal bleeding). In this thesis, data were collected for 10 other adverse effects in addition to gastrointestinal bleeding.

New information was also collected in several other areas as part of the thesis research. Physicians were asked about the influence of 16 possible factors (e.g., patient health, degree of familiarity with patient) on the decision to prescribe an AD medication. Caregivers were asked about who first raised the possibility of using medications to treat

AD (i.e., caregiver, physician, someone else), as well as whether they had to put pressure on physicians to prescribe AD medications.

This thesis is the first study wherein associations were examined between the actual prescribing of cholinesterase inhibitors in AD and the following independent variables: physicians' and caregivers' efficacy requirements, caregivers' willingness to accept adverse effects, the type of person who first raised the possibility of using medications to treat AD, and caregiver pressure on physicians to prescribe medications to treat AD.

The questionnaires used to collect data were specifically designed for this thesis research, and the idea for the thesis topic originated with the student.

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1. INTRODUCTION

1.1. Thesis Objectives

For more than 20 years, research into treating Alzheimer's disease (AD) has focused on drug therapy. Since this focus is likely to continue in the future, it is important to examine physician and caregiver perspectives on the use of medications in AD. Most researchers have concentrated on the safety and efficacy of AD drugs in clinical trials, so the literature is largely bereft of information on these perspectives. As will be explained in the following sections, it is hoped that studying the physician and caregiver perspectives will help define clinically important outcomes in AD, provide benchmark efficacy data to facilitate drug development and assessment, and promote a better understanding among physicians and caregivers of each others' attitudes to treating AD.

Specifically, postal questionnaires will be used to obtain information on physicians' and caregivers' efficacy requirements for using a hypothetical, new medication in AD. Additional data will be obtained on the willingness of caregivers to continue their loved ones on drug treatment in the event of adverse effects, whether caregivers or physicians are the first to suggest the use of drug treatment in AD, and whether caregivers have put pressure on a physician to prescribe an AD drug.

The hypotheses to be investigated are that more stringent physicians' and caregivers' efficacy requirements are negatively associated with the current use of

cholinesterase inhibitors (ChEIs), while caregivers' willingness to continue drug treatment in the event of adverse effects, physicians as the first to suggest drug treatment, and caregiver pressure to prescribe an AD drug are all positively associated with the use of ChEIs.

1.2. Alzheimer's Disease

AD is a neurodegenerative disorder that is characterized by a progressive decline in cognitive and functional abilities. Early symptoms include loss of short-term memory, immediate event recall, and attention. Patients may also experience disorientation or depression. Over time, patients lose the ability to perform instrumental activities of daily living, including preparing meals, managing money, shopping, performing housework, and using a telephone. In the later stages of the disease, patients go on to lose the ability to perform basic activities of daily living, which include bathing or showering, dressing, getting in and out of bed or a chair, using the toilet, and eating.[1]

Based on a national study of dementia, the prevalence of AD in the Canadian population aged 65 and over was estimated to be 5% in 1991 (161,000 cases; 95% confidence interval [CI]=148,100 to 173,900). The prevalence was 1% for seniors between 65 and 74 years of age, 7% for seniors between 75 and 84 years, and 26% for seniors aged 85 and over.[2] Approximately 40,000 Canadians develop the disease annually.[3] If the incidence remains constant, then the number of people with AD could reach as many as 509,000 by 2031. This would be an almost five-fold increase from 1991. Over the 1991 to 2031 time period, the total Canadian population is expected to

increase by a factor of only 1.4.[2] In 1991, the annual cost of AD in Canada was estimated to exceed $3.9 billion.[4]

1.3. Drug Treatments for Alzheimer's Disease

There is no cure for AD. Until the early 1980s, the disease was regarded as a normal part of aging and patients received only palliative care. At the time, physicians managed acute or chronic illnesses for which therapies were available and caregivers, typically unpaid relatives, provided day-to-day care. As the disease progressed and patients lost the ability to function independently, many caregivers found they could no longer cope with the burden of caring. To reduce the burden, families often resorted to institutionalization.

In the last two decades, the therapeutic approach to AD changed. The disease came to be regarded as distinct from normal aging and the scientific community initiated research into drug treatments.[5] While caregivers continued to play a paramount role in the daily care of AD patients, and institutionalization remained an option, drug treatments became an important part of managing the disease. Anti-depressant and anti-psychotic medications started being used to address behaviour and mood problems that occur during the course of AD. In addition, research efforts were targeted towards the development of medications that arrest cognitive deterioration, which is the hallmark of the disease.

One class of medications, namely the ChEIs,[6;7] has become the primary means of symptomatically treating cognitive deterioration in AD.[8] ChEIs increase the

availability of acetylcholine to the central synapses of the brain and are believed to counter the cholinergic deficits seen in AD patients.[9] To date, Health Canada has approved three ChEIs for use in mild to moderate AD: donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). These medications have not been approved for treating patients with severe AD.

The ChEIs have been shown to lessen the impact of cognitive decline in mildly to moderately affected patients. However, benefits are modest and have not been observed to last beyond six months to one year of follow-up in clinical trials.[1;7;10] There is some evidence[11;12] to suggest a beneficial effect for donepezil in severely affected patients.

Commonly seen adverse effects, depending on the medication, include gastro-intestinal disturbances, muscle cramps, and insomnia. In clinical trials, the incidence of most reported adverse effects has ranged from 5 to 15%. Some adverse effects such as nausea and insomnia are more frequent and have occurred in 20 to 30% of patients.[10]

In December 2004, Health Canada approved a fourth drug for use in AD. This particular medication, memantine (Ebixa®),[13] is an uncompetitive *N*-methyl-*D*-aspartate, not a ChEI, and has been approved for use in moderately to severely affected AD patients. Like the ChEIs, memantine can lessen the impact of cognitive decline, although the longest follow-up period for which it has been evaluated in clinical trials is 28 weeks.[14]

At the time of data collection for this thesis, memantine had not yet been approved in Canada. Therefore, it was not included on the questionnaires, which were

focused exclusively on medications that had been approved (i.e., the three ChEIs).

1.4. The Use of Drug Treatments in the Alzheimer's Disease Population: Physician and Caregiver Perspectives

The term 'use' refers to the prescribing of drug treatments. It can be the actual prescribing of a drug or the intent to prescribe. Prescribing intent can best be explained by example. If physicians believe a new drug will be efficacious for their patients, then they might express an intention to 'use' the drug. In other words, they are expressing an intention to prescribe the drug.

There are a multitude of factors that explain the intent to use and the actual use of medications in AD. Two important factors are safety and efficacy, and both have been well addressed in the published literature. Several factors that have remained largely unaddressed include concomitant medication use, comorbidity, socio-economic status, and prescribing guidelines. What have also not been explored in depth are 'stakeholder-centred' factors such as the physician and caregiver perspectives on the use of AD medications. These perspectives are important because physicians and caregivers are primarily responsible for selecting treatments for AD patients, given the latter's deteriorating cognitive status.[15-19]

1.4.1. Physician Perspective

The physician perspective is derived from the 'drug choice model,' where physicians' views regarding the potential efficacy of a drug are seen as the motivation to

prescribe.[20;21] One means of understanding the drug choice model is to measure the 'minimum clinically significant difference,' which is the minimum level of drug performance that physicians would require to prescribe a medication to their patients.[22-24]

In AD, the minimum clinically significant difference has been elicited for a ChEI called tacrine (Cognex®).[24] However, the information is of limited use because tacrine was never approved in Canada and it is no longer widely used in the United States. Furthermore, the difference was defined as a quantitative change in score on a cognitive impairment scale.[24] Changes in scale score are not appropriate measures of the difference because the changes do not always capture the clinical impact of a drug on patient symptoms.[25] Examples of more appropriate measures in AD would be physicians' minimum required increases in length of stabilization before cognitive deterioration resumes, or the minimum required numbers of activities of daily living that patients could resume. These requirements would provide a clearer picture of what physicians believe to be relevant clinical outcomes from drug treatment.[26]

1.4.2. Caregiver Perspective

People who provide informal and often unpaid care for AD patients have one overriding demand from any medication: patient benefit. Consequently, the caregiver perspective also involves minimum efficacy requirements for treatment.

Efficacy requirements have been investigated in the caregiver population, although research has been limited to three specific outcomes: a one-year delay to nursing home placement; a one-year increase in patient survival; and a one-year

slowdown in memory loss and AD progression.[27;28] Given the many domains that are affected by AD, further research into caregiver requirements is necessary to provide a more comprehensive understanding of what carers expect from drug therapy.

The caregiver perspective is not limited to efficacy requirements. Since caregivers are usually close relatives who provide regular and often daily hands-on care for AD patients, understanding AD medication use from the caregiver perspective necessitates examining issues such as adverse effects and institutionalization. Caregivers, in an effort to avoid increases in the burden of caring, may be loath to try a medication if certain adverse effects might occur. What adverse effects would caregivers be more or less willing to accept? Except for the case of gastrointestinal (GI) bleeding,[27] this question has not been addressed in the literature. Institutionalization, meanwhile, is an undesirable yet sometimes unavoidable way of relieving caregiver burden. Medications that lessen the burden, perhaps by slowing cognitive decline, may help postpone institutionalization.[29] Just how much of a postponement do caregivers think is important? This question has not been addressed in the literature.

Caregivers, as patient advocates and proxy decision makers, interact with physicians regarding the treatment of AD. This leads to two questions: is the prescribing of AD drugs associated with whether a caregiver or physician first raises the possibility of employing drug therapy, and is prescribing associated with whether a caregiver pressures a physician to prescribe an AD drug? These questions will be addressed within the caregiver perspective to understand some of the dynamics that may influence the prescribing of AD medications.

1.4.3. Practical Applications of Examining the Physician and Caregiver Perspectives on Drug Treatments for Alzheimer's Disease

The physician and caregiver perspectives should be examined to improve the understanding of clinically important outcomes in the treatment of AD.[25;26;28;30;31] To take a case in point, stabilization of cognitive decline, where patients remain in their current disease state for some period of time before decline recommences, is unarguably a key outcome. However, no data exist to suggest what length of stabilization would be minimally acceptable to persons involved in treatment decisions. For example, is any extended stabilization over what is possible with existing treatments acceptable? Or, would a specific minimum improvement be required? What about patient function? What do physicians and caregivers think would be an acceptable improvement in patients' ability to perform activities of daily living? For adverse effects, which ones would have more influence on caregivers' willingness to continue with drug therapy? Answers to these questions are not found in the literature.

Research into outcomes will benefit the treatment of AD by providing benchmark data to guide drug development and assessment. Such benchmarks can act as therapeutic targets for medications under development. For example, if physicians require a six-month increase in length of stabilization before they would prescribe a new AD drug, then medications could be developed with this yardstick in mind. Similarly, medications that are already on the market could be evaluated against this benchmark. The evaluative process can also be used to explain prescribing behaviour.[26] For instance, a new drug may not be widely prescribed, despite favourable findings in clinical trials, because it fails to meet physicians' efficacy requirements. Physicians may also not

prescribe the drug because the trial population is different from the relevant target population that would ordinarily be prescribed the drug. The same issues apply to caregivers because of their often primary role in treatment selection.[19]

Examination of the physician and caregiver perspectives will allow physicians and caregivers to better understand each other's attitudes to treatment. While patient benefit is an overriding concern for all involved, being able to understand the specifics of what each group hopes to accomplish with drug therapy will encourage the formation of a "therapeutic alliance."[32] This alliance involves physicians and caregivers working in tandem to meet a set of shared treatment goals and is therefore an important part of promoting the well being of AD patients.

1.5. Upcoming Chapters

In the next chapter, a literature review will accompany an expanded discussion of the points raised in this introduction. The literature review will include background information on AD and the use of medications to treat the disease. As well, the review will contain a summary of what is known about the physician and caregiver perspectives in AD. The review will present an opportunity to highlight gaps in the literature and establish the relevance of the thesis research. Chapter 3 includes a description of the methods that were undertaken to implement the thesis research, and chapter 4 contains the results. The results will be discussed in chapter 5.

2. LITERATURE REVIEW

2.1. Alzheimer's Disease and Drug Treatment

2.1.1. Alzheimer's Disease

2.1.1.1. Natural History

AD is a neurodegenerative disorder whose primary clinical feature is a progressive decline in cognitive and functional abilities. The first symptoms of the disease often include loss of short-term memory, immediate event recall, and attention. Long-term memory, while initially maintained, also declines over time. Patients in the early stages of AD may also experience disorientation or depression. As the disease progresses, executive functions decline and patients lose the ability to perform instrumental activities of daily living. Instrumental activities include preparing meals, managing money, shopping, performing housework, and using a telephone. Eventually, patients also lose the ability to perform basic activities of daily living, including bathing or showering, dressing, getting in and out of bed or a chair, using the toilet, and eating. In the later stages of AD, behavioural problems such as aggression or apathy are common. Death usually occurs from concurrent illnesses like pneumonia.[1;33]

The estimated mean survival for persons with AD is approximately eight to 12 years from diagnosis. Survival times are variable and will often fall outside of this range. On average, patients progress from the mild to moderate stage of AD in two years, and from the moderate to severe stage in 1.5 to four years.[34] A recent study estimated the

median survival time from onset of AD symptoms to be shorter than previously thought. Median survival, adjusted for length bias, was 3.1 years (95% CI=1.5 to 4.8 years) for persons with probable AD and 3.5 years (95% CI=2.4 to 4.6 years) for persons with possible AD.[35]

2.1.1.1.1. Mild Cognitive Impairment

AD is sometimes preceded by mild cognitive impairment (MCI). MCI is characterized by subjective and objective memory loss that is less intense or debilitating than what is seen in AD patients. The degree of memory loss typically found in MCI patients does not affect daily function, nor does it meet the criteria for a diagnosis of dementia. At presentation, the memory loss may have recently occurred or been present for several years. Every year, approximately 15% of persons with MCI develop dementia, primarily AD.[33]

2.1.1.2. Neurological Features

AD is characterized by cholinergic deficits, amyloid plaques, neurofibrillary tangles, gliosis, and both neuronal and synaptic loss. Research on the causes of AD has focused on factors such as amyloid precursor protein, tau, and apolipoprotein E. More general neurodegenerative processes such as inflammation, oxidation, excitotoxicity, and apoptosis have also been studied.[9] Many researchers believe that AD results from an increase in the production of, or accumulation of, beta-amyloid protein. This production or accumulation leads to nerve cell death via oxidative damage and inflammation.[32] Clinical deficits in AD are believed to be a consequence of changes in brain

pathology. The changes are thought to be associated with neurotransmitter metabolism deficits and the structural loss of brain tissue.[36]

2.1.1.3. Clinical Diagnosis

AD is a syndrome that can only be definitively diagnosed at autopsy by identifying amyloid plaques and neurofibrillary tangles. The disease is diagnosed clinically using the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations (NINCDS-ADRDA) diagnostic criteria,[37] which are summarized in Box 2.1. There are two diagnostic options: 'probable' AD may be diagnosed when clinical symptoms are observed in the absence of another disease that could cause a cognitive deficit; 'possible' AD may be diagnosed when a progressive, severe, cognitive deficit co-exists with a disease that can cause dementia, but which is not thought to be the cause of the cognitive deficit.

In conjunction with the application of the NINCDS-ADRDA criteria, three other elements play a role in the clinical diagnosis of AD: patient history, physical examination, and clinical investigation. Patient history includes taking a family medical history and eliciting information about prior heart disease, psychiatric problems, head injury, medication use, and alcohol or substance abuse. Family members are also asked about the patient's ability to perform instrumental activities of daily living. The physical examination is conducted to identify the presence of concomitant diseases, including diseases that could affect cognition. The neurological component of the physical

Box 2.1: NINCDS-ADRDA Diagnostic Criteria for Alzheimer's Disease

Criteria for clinical diagnosis of **Probable AD** include:

- Dementia established by clinical exam and documented by MMSE or Blessed Dementia scale, confirmed by further neuropsychological tests.
- Deficits in two or more areas of cognition.
- Progressive worsening of memory and other cognitive functions.
- No disturbance of consciousness.
- Onset between the ages of 40 and 90.
- Absence of systemic diseases or other brain diseases that could explain the cognitive changes.

The diagnosis of Probable AD is supported by:

- Progressive deterioration of specific cognitive functions such as language, motor skills, and perception (aphasia, apraxia, agnosia, respectively).
- Impaired activities of daily living.
- Positive family history, particularly if documented neuropathologically.
- Lab results: Normal lumbar puncture, EEG, and evidence of cerebral atrophy on CT or MRI.

Other clinical features consistent with a diagnosis of Probable AD, after exclusion of other causes of dementia:

- Plateaus in clinical course.
- Associated symptoms: depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss.
- Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased motor tone, myoclonus, or gait disorder.
- Seizures in advanced disease.
- CT normal for age.

Features that make the diagnosis of Probable AD **unlikely or uncertain:**

- Sudden apoplectic onset.
- Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness.
- Seizures or gait disturbances at the onset or very early in the course of the illness.

Clinical diagnosis of **Possible AD**

- May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course.
- May be made in the presence of a second systematic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia.
- Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

Source: McKhann G, Drachman D, Folstein M et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984; 34:939-944.

examination seeks to rule out other dementias such as Lewy body or vascular dementia. A mental status examination, often conducted with a basic measurement instrument such as the Mini-Mental State Examination (MMSE),[38] is performed to help stage the severity of disease. After an initial diagnosis is made, clinical investigations are ordered to confirm the diagnosis and to detect concomitant diseases that affect cognition. The primary clinical investigations are laboratory tests (e.g., complete blood count, serum calcium) and computer tomography.[33]

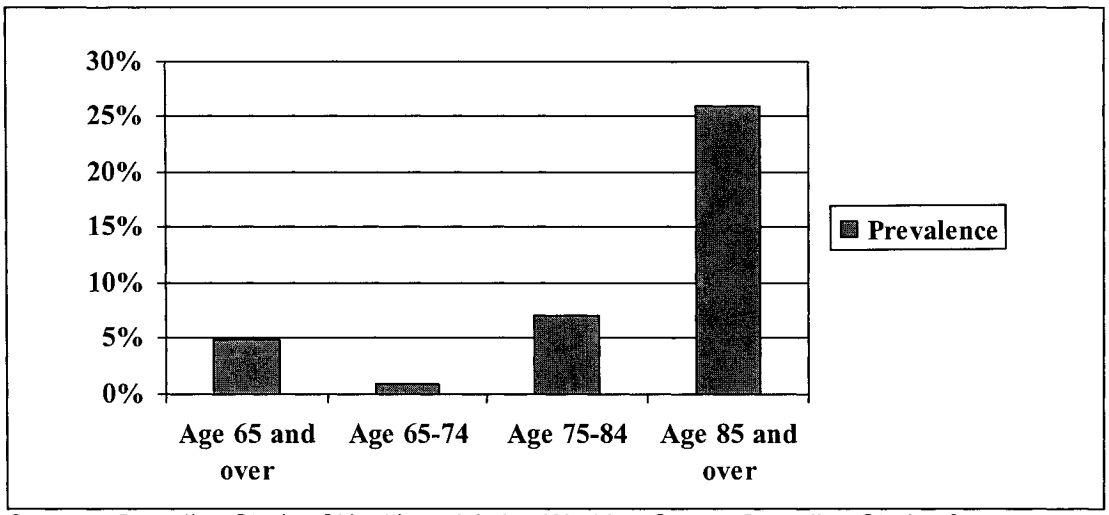
2.1.1.4. Epidemiology

Based on a national study of dementia, the prevalence of AD in the Canadian population aged 65 and over was approximately 5% in 1991 (161,000 cases; 95% CI=148,100 to 173,900). The prevalence was 1% for seniors between 65 and 74 years of age, 7% for seniors between 75 and 84 years, and 26% for seniors aged 85 and over (Figure 2.1).[2] It was estimated that approximately 40,000 new cases of AD occur annually in Canada.[3] In 1991, the annual cost of AD was estimated to exceed $3.9 billion in Canadian dollars.[4]

Since the Canadian population is aging, it has been estimated that there will be a five-fold increase in the number of AD cases between 1991 and 2031,[2] provided the incidence of disease remains constant. If the five-fold increase does occur, then the total number of persons with AD would be 509,000 in 2031. Comparatively, the total population of Canada is expected to rise by a factor of only 1.4 between 1991 and 2031.[2] The situation in the United States is of equal concern because predictions suggest the

number of AD cases will more than triple between now and 2050.[39] If no therapeutic breakthroughs occur in AD, then approximately 10.2 million Americans will have the disease by 2050. This would represent an increase of 8 million cases over today. If a treatment to delay the onset of AD by a median of 6.7 years is introduced in 2010, then the estimated number of cases by 2050 would drop to 6.3 million.[39]

Figure 2.1: The Prevalence of Alzheimer's Disease in Canada (Age ≥65)



Source: Canadian Study of Health and Aging Working Group. Canadian Study of Health and Aging: Study methods and prevalence of dementia. Can Med Assoc J 1994;150:899-913.

Epidemiologic studies have consistently identified three factors as being positively associated with the risk of AD: age, the presence of one or two apoϵ4 alleles, and a family history of AD. Other factors that some, but not all, studies have shown to be associated with an increased risk of AD include head injury, diabetes, and cardiovascular problems (e.g., atrial fibrillation, hypertension, hyperlipidemia). Possible protective factors include higher education, regular physical and social activity, good nutrition, and the use of non-steroidal anti-inflammatory drugs, statins, or estrogen.[33;40]

2.1.1.5. Other Forms of Dementia

There are several forms of dementia, with AD being the most common type. AD affects approximately 55 to 65% of persons with dementia.[33] Other dementias include Lewy body, frontotemporal, vascular, and mixed. There are also miscellaneous degenerative dementias, including Huntington's disease, progressive supranuclear palsy, and dementia due to Parkinson's disease.

Lewy body dementia is named after the neuronal cytoplasmic inclusions (i.e., Lewy bodies) that are the pathologic sign of the disease. The clinical hallmark of the disease is a fluctuating, yet ultimately progressive, decline in cognition. Fluctuations may occur over hours, days, or weeks. During the fluctuations, patients' cognitive abilities can be close to normal or severely impaired. Psychiatric problems such as visual hallucinations are often present in patients with Lewy body dementia. As well, Parkinsonian symptoms such as rigidity and bradykinesia can be present early in the course of disease.[33;34]

Frontotemporal dementia is highlighted by initial presentation with behaviour changes or language disorders. Over time, patients suffer progressive losses of behaviour control and expressive language. Memory impairment may not occur in the early stages of the disease; however, memory testing can identify the underlying cognitive deficits caused by the disease. Patients may initially appear to be suffering from a depressive episode. There are several variants of this dementia, including Pick's disease, frontotemporal dementia with motor neuron disease, primary progressive aphasia,

semantic dementia, and corticobasal degeneration. All of these diseases are characterized by behaviour and language changes.[34]

Vascular dementia is associated with cerebrovascular conditions such as stroke or heart disease. Relative to AD, recognition memory is preserved and there is less forgetfulness. Declines in many areas of cognition (e.g., planning, organizing), even without memory impairment, may be sufficient to diagnose vascular dementia. Vascular dementia can lead to behavioural or psychological problems such as personality changes or depression.[34]

Mixed dementia is generally a combination of AD and vascular dementia. Sometimes it is a combination of AD and Lewy body dementia. The miscellaneous degenerative dementias are large enough disease entities to require more than cursory examination, and this is beyond the scope of the thesis. Therefore, these disease entities are excluded from review.

2.1.2. Drug Treatment

For the past two decades, the medical community has actively sought drug treatments for AD.[5] Several compounds have been evaluated in clinical trials, including donepezil,[9;41-48] rivastigmine,[49-51] galantamine,[52-56] memantine,[13;14;57;58] selegiline,[59-64] metrifonate,[65-69] vitamin E,[62] tacrine,[70-75] propentofylline,[76-78] and ginkgo biloba.[79-85]

Cholinesterase inhibitors[6;7;86] have become the primary pharmaceutical means of treating AD.[8] ChEIs increase the availability of acetylcholine to the central synapses of

the brain and are believed to counter the cholinergic deficits seen in AD patients.[9] To date, three ChEIs have been approved by Health Canada for use in mild to moderate AD: donepezil, rivastigmine, and galantamine. These medications have also been approved in the United States. Tacrine, the first ChEI for AD to be approved in the United States (1993), was not approved in Canada because of its modest efficacy and severe adverse effects profile.[87]

Until recently, donepezil, rivastigmine, and galantamine were the only medications that had been approved for treating AD in Canada. In December 2004, memantine was approved for the symptomatic treatment of patients with moderate to severe AD. Unlike the ChEIs, memantine is an uncompetitive *N*-methyl-D-aspartate antagonist that acts on a brain chemical called glutamate. Memantine had not been approved until after the data for this study were collected and analyzed, so it will not be considered beyond the literature review.

Returning to the ChEIs, as a class these medications have been shown to symptomatically treat cognitive decline, behaviour and mood problems (e.g., neuropsychiatric symptoms), and functional decline in mildly to moderately affected patients. However, benefits are modest and have not been observed to last beyond six months to one year of follow-up in clinical trials. There is little evidence that the ChEIs can modify the course of disease.[1;7;10;86;88] Common adverse effects, depending on the medication, include gastro-intestinal disturbances, muscle cramps, and insomnia. Most of these problems can be avoided, or at least mitigated, by slow titration. Insomnia can be avoided by advising patients to take the medication early in the morning.[89]

In randomized controlled trials, most reported adverse effects have been shown to occur in approximately 5 to 15% of patients. Some adverse effects, including nausea and insomnia, have been shown to occur in as many as 20 to 30% of patients.[10] The impact of adverse effects should not be underestimated since patient management can be made more difficult. This often leads to increased caregiver burden and a shortened time between diagnosis and patient institutionalization.[29]

Much research is still needed to optimize the use of ChEIs. This is especially so in the domains of adequate durations of use, appropriate measures of response, ways of reducing adverse effects, improvements to the understanding of response differences between ChEIs, more effective means of switching from one ChEI to another, and the association between higher dose and efficacy.[88]

The initial yet limited success of first generation ChEIs has provided the impetus for further research into drug therapies.[87] Cholinergic agonists and enhancers are being developed, as are serotoninergic and noradrenergic substances, neuropeptides, calcium channel blockers, gamma-secretase inhibitors, and NMDA antagonists. The use of atypical neuroleptics is a new strategy aimed at treating behavioural symptoms. Additionally, estrogens, non-steriodal anti-inflammatory drugs (NSAIDs), vitamin E, and vaccination with amyloid-beta peptides have been or are being studied for potential benefits in the AD population. Statins are being investigated for a possible prophylactic effect.[90-93]

2.1.2.1. Measuring Drug Efficacy in Clinical Trials: Outcome Measurement Instruments

In clinical trials, the efficacy of ChEIs and other AD medications has been evaluated using a variety of outcome measurement instruments. The Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog),[94] Clinician Interview-Based Impression of Change (CIBIC [or CIBIC-plus when the clinician bases part of the rating on caregiver input]),[95] Global Deterioration Scale (GDS),[96] and Clinical Dementia Rating (CDR)[97] are some of the most frequently used measurement instruments. The ADAS-cog was used in 20 of the 26 clinical trials included in a recent systematic review of AD medications.[1;98] The CIBIC was used in 10 of the trials, the GDS in 4, and the CDR in 7.

Another instrument, the MMSE,[38] was employed in 18 of the trials. The MMSE was initially designed to assess cognition in patients undergoing psychiatric evaluations and to differentiate dementia from depression. Among clinicians, the MMSE is one of the most widely known instruments, and it is often used in both clinical and research settings to establish the stage of AD.

Table 2.1 below lists the major features of the outcome measurement instruments discussed above.

Table 2.1: The Features of Outcome Measurement Instruments that Are Commonly Used in Alzheimer's Disease Drug Trials

Instrument	Constructs Measured	Scoring
Alzheimer's Disease Assessment Scale-cognitive (ADAS-Cog)[94]	Orientation Memory (i.e., immediate event recall, recognition) Language Praxis (e.g., copying, drawing)	Score range from 0 to 70. Higher scores indicate greater dysfunction.
Clinician Interview-Based Impression of Change (CIBIC)[95]	The extent to which drug treatment is responsible for overall improvements in patient health status.	Seven-point scale: 1=very much improved, 2=much improved, 3=minimally improved, 4=no change, 5=minimally worse, 6=much worse, 7=very much worse
Global Deterioration Scale (GDS)[96]	Severity of cognitive impairment	Seven stages: 1=no cognitive decline, 2=very mild cognitive decline, 3=mild cognitive decline, 4=moderate cognitive decline, 5=moderately severe cognitive decline, 6=severe cognitive decline, 7=very severe cognitive decline
Clinical Dementia Rating (CDR)[97]	Cognitive performance in 6 areas: Memory Orientation Problem solving Community affairs Home/hobbies Personal care	Each area is given a score on a five-point scale of impairment (0 = none, 0.5 = questionable, 1 = mild, 2 = moderate and 3 = severe) and an algorithm is used to derive an overall score (stage) of dementia. Sum-of-Boxes: A modified scoring mechanism whereby the ratings in all six performance categories are added to obtain a global dementia ranking of ≤ 18 points (referred to as CDR-SB). Extended CDR: Addition of two stages (4 = profound impairment, 5 = terminal impairment).

Table 2.1: The Features of Outcome Measurement Instruments that Are Commonly Used in Alzheimer's Disease Drug Trials (continued)

Instrument	Constructs Measured	Scoring
Mini-Mental State Examination[38]	Orientation	Score range from 0 to 30.
	Memory (i.e., immediate event recall, recognition)	Higher scores indicate less impairment.
	Language	
	Praxis (e.g., copying, drawing)	

Source: Wolfson C, Moride Y, Perrault A, Momoli F, Demers L, Oremus M. Drug Treatments for Alzheimer's Disease. II. A Review of Outcome Measures in Clinical Trials. Ottawa: Canadian Coordinating Office for Health Technology Assessment, 2000.

In the 26 drug trials, 50 different measurement instruments were used to quantify changes in disease status over time.[98] The large number of instruments was necessary because AD does not have definite biological or physiological markers before death. Also, each instrument measures outcomes in only one of the four domains of interest, which are global health, cognition, behaviour and mood, and function.

2.1.2.2. Psychometric Properties of Outcome Measurement Instruments

Scales must be valid and reliable to communicate something useful about a patient. Validity is the extent to which the scale measures the underlying construct of interest. If a scale is not valid, then it is not measuring what it purports to measure. For example, the GDS is designed to measure the construct 'severity of cognitive impairment,' and higher scale scores are supposed to indicate greater levels of severity. If the GDS were not valid, then conclusions based on the score would be erroneous because the scale and its score are not actually measuring severity.

Test-retest reliability is the extent to which a scale yields the same score across different test administrations, provided the underlying construct has not changed. The score on a scale that 'reliably' measures disease severity would not change over time if the patient's disease status remains stable. Inter-rater reliability is analogous, although the focus is on whether two or more independent raters provide comparable scores for the same person at a single test administration.

Despite the importance of psychometric properties, many outcome measurement instruments have not been assessed for validity or reliability in the AD patient population.[99-102] Where assessments were conducted, samples of 50 or fewer persons were studied. Also, inappropriate statistical measures of agreement, namely the Spearman and Pearson correlation coefficients, were used instead of the more appropriate Kappa statistic or intraclass correlation coefficients. Typically, investigators did not examine responsiveness to change, which is an instrument's ability to detect clinically meaningful within- or between-patient changes in the underlying construct that is being measured. These methodological issues raise the concern that inadequate instruments have been used to measure outcomes in AD drug trials.

2.1.2.3. The Efficacy of Alzheimer's Disease Drugs

Efficacy in AD drug trials is quantified by the change in an instrument's score over the course of follow-up. For each treatment arm, the change can be reported as the mean difference in score between baseline and the end of follow-up. Alternatively, the mean difference for the placebo group can be subtracted from the mean difference for

each active treatment group to obtain a set of summary scores. Sometimes, both types of score are reported. In addition, European regulatory authorities require trial investigators to report the number or proportion of responders. The responders are people for whom changes in score between baseline and the end of follow-up have equalled or exceeded some pre-established threshold. An example of such a threshold is a minimum 4-point improvement on the ADAS-cog.[103]

In the published trials of donepezil, rivastigmine, and galantamine, ADAS-cog scores demonstrated patients who received the active treatment either improved between baseline and the end of follow-up or deteriorated at a slower rate than placebo patients.

Tables 2.2-2.4 below show the treatment effects observed in a series of placebo-controlled, ChEI clinical trials.[10] All of the trials involved patients with mild to moderate AD. Diagnoses were made using the NINCDS-ADRDA criteria and baseline MMSE scores that fell within the range of approximately 11 to 24.

Table 2.2: Donepezil - Efficacy in Placebo-Controlled Clinical Trials

Clinical Trial	Cognitive Outcome	Global Outcome
Rogers et al., 1996[104] *Design*: DPP	ADAS-cog – adjusted mean change in score from baseline at 12 weeks (p-value refers to a comparison with placebo): Placebo = 0.7 1mg/day = -0.9 (p=0.105) 3mg/day = -1.4 (p=0.036) 5mg/day = -2.5 (p=0.002)	Clinical Global Impression of Change[105] clinical improvement subscale – percentage of patients whose global health status did not change, or was minimally, moderately, or much improved at 12 weeks relative to baseline: Placebo = 81% 5mg/day = 89% No results reported for 1mg/day or 3mg/day groups

Table 2.2: Donepezil - Efficacy in Placebo-Controlled Clinical Trials (continued)

Clinical Trial	Cognitive Outcome	Global Outcome
Rogers et al., 1998[47] *Design*: DPP	ADAS-cog – mean difference between groups at 24 weeks (donepezil minus placebo): 5mg/day minus placebo = -2.49 (p<0.0001) 10mg/day minus placebo = -2.88 (p<0.0001)	CIBIC-plus – mean difference between groups at 24 weeks: 5mg/day minus placebo = -0.36 (p=0.0047) 10mg/day minus placebo = -0.44 (p<0.0001)
Rogers et al., 1998[48] *Design*: DPP	ADAS-cog – least squares change in score from baseline at 12 weeks: Placebo = 0.4 5mg/day = -2.1 (p<0.001) 10mg/day = -2.7 (p<0.001)	CIBIC-plus - percentage of patients whose global health status was minimally, moderately, or much improved at 12 weeks relative to baseline: Placebo = 18% 5mg/day = 32% 10mg/day = 38%
Burns et al., 1999[44] *Design*: DPP	ADAS-cog – least squares mean difference between groups at 24 weeks (donepezil minus placebo): 5mg/day minus placebo = -1.5 (p=0.0021) 10mg/day minus placebo = -2.9 (p<0.0001)	CIBIC-plus - percentage of patients whose global health status was minimally, moderately, or much improved at 24 weeks relative to baseline: Placebo = 14% 5mg/day = 21% 10mg/day = 25%
Greenberg et al., 2000[45] *Design*: DPC	ADAS-cog – percentage of patients improved after first receiving placebo for 6 weeks; percentage improved after first receiving 5mg/day donepezil for 6 weeks: Placebo = 19% 5mg/day = 44% (p=0.03 inter-group difference)	Not assessed

Notes: DPP = double-blind/placebo-controlled/parallel group, DPC = double-blind/placebo-controlled/crossover, ADAS-cog = Alzheimer's disease Assessment Scale-cognitive, CIBIC-plus = Clinician Interview-Based Impression of Change with caregiver input.

Source: Clegg A, Bryant J, Nicholson T, et al. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: A rapid and systematic review. Health Technol Assess 2001;5:1-137.

Table 2.3: Rivastigmine - Efficacy in Placebo-Controlled Clinical Trials

Clinical Trial	Cognitive Outcome	Global Outcome
Agid et al., 1998[106] *Design*: DPP	MMSE: No statistically significant differences reported	Clinical Global Impression of Change[105] clinical improvement subscale – percentage of patients whose global health status was moderately or much improved at 13 weeks relative to baseline: Placebo = 30% 4mg/day = 32% 6mg/day = 43%
Corey-Bloom et al., 1998[50] *Design*: DPP	ADAS-cog - mean difference: high-dose rivastigmine group (mean dose 9.7mg/day) minus placebo group at 26 weeks: -3.78 (95% CI: -4.87 to -2.69) (Mean difference between low dose [mean dose 3.5mg/day] and placebo groups not statistically significant.)	CIBIC-plus – mean difference between high dose and placebo groups at 26 weeks: -0.29 (95% CI: -0.51 to -0.07) (Mean difference between low dose and placebo groups not statistically significant.)
Forette et al., 1999[107] *Design*: DPP	ADAS-cog: Mean difference not statistically significant for 10mg/day rivastigmine (twice-daily dosing) and placebo.	CIBIC-plus - percentage of patients whose global health status was minimally, moderately, or much improved at 18 weeks relative to baseline: Placebo = 16% 10mg/day (twice-daily) = 57%
Rösler et al., 1999[51] *Design*: DPP	ADAS-cog – mean change in score from baseline at 26 weeks: Placebo = -1.34 (95% CI: -2.19 to -0.41) 3.7mg/day (average low dose) = -1.37 (95% CI: -2.27 to -0.53) 10.4mg/day (average high dose) = 0.26 (95% CI: -0.66 to 1.06)	CIBIC-plus - percentage of patients whose global health status was minimally, moderately, or much improved at 26 weeks relative to baseline: Placebo = 20% 3.7mg/day = 30% 10.4mg/day = 37%

Notes: DPP = double-blind/placebo-controlled/parallel group, MMSE = Mini-Mental State Examination, ADAS-cog = Alzheimer's disease Assessment Scale-cognitive, CIBIC-plus = Clinician Interview-Based Impression of Change with caregiver input, CI = confidence interval.

Source: Clegg A, Bryant J, Nicholson T, et al. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: A rapid and systematic review. Health Technol Assess 2001;5:1-137.

Table 2.4: Galantamine - Efficacy in Placebo-Controlled Clinical Trials

Clinical Trial	Cognitive Outcome	Global Outcome
Wilcock et al., 2000[55] *Design*: DPP (Note: Clegg et al.[10] reviewed the interim results[108] of this trial. The interim data have since been supplanted by the final results, which are presented here.)	ADAS-cog – mean (standard error) change in score from baseline at 24 weeks (ITT analysis): Placebo = 2.4 (0.41) 24mg/day = -0.5 (0.38) 32mg/day = -0.8 (0.43)	CIBIC-plus - percentage of patients whose global health status was unchanged, or minimally, moderately, or much improved at 24 weeks relative to baseline: Placebo = 49.5% 24mg/day = 61% 32mg/day = 66%
Tariot et al., 2000[54] *Design*: DPP	ADAS-cog – mean (standard error) change in score from baseline (ITT analysis) at 20 weeks: Placebo = 1.7 (0.39) 8mg/day = 0.4 (0.52); not statistically significant vs. placebo 16mg/day = -1.4 (0.35); p<0.001 vs. placebo 24mg/day = -1.4 (0.39); p<0.001 vs. placebo	CIBIC-plus - percentage of patients whose global health status was unchanged, or minimally, moderately, or much improved at 20 weeks relative to baseline: Placebo = 49% 8mg/day = 53% 16mg/day = 66% 24mg/day = 64%
Raskind et al., 2000[53] *Design*: DPP	ADAS-cog – mean (standard error) change in score from baseline (ITT analysis) at 24 weeks: Placebo = 2.0 (0.45) 24mg/day = -1.9 (0.36) 32mg/day = -1.4 (0.44)	CIBIC-plus - percentage of patients whose global health status was unchanged, or minimally, moderately, or much improved at 24 weeks relative to baseline: Placebo = 57% 24mg/day = 73% 32mg/day = 69%

Notes: DPP = double-blind/placebo-controlled/parallel group, ADAS-cog = Alzheimer's disease Assessment Scale-cognitive, ITT = intent-to-treat, CIBIC-plus = Clinician Interview-Based Impression of Change with caregiver input.

Source: Clegg A, Bryant J, Nicholson T, et al. Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: A rapid and systematic review. Health Technol Assess 2001;5:1-137.

Several other placebo-controlled trials[109-116] have been published subsequently. The results of these more recent trials were consistent with the findings shown in Tables 2.2-2.4, namely that there is some benefit for the ChEIs versus placebo.

One exception to the aforementioned group of trials is a long-term study of 486 community-dwelling AD patients who were randomized to donepezil or placebo after completing a 12-week run-in period.[31] Patients could continue in the trial for as long as four years after the run-in period, although in practice only four patients went that far. The majority of patients left the trial by week 54 post-run-in. Reasons for leaving the trial included reaching an endpoint, death, stoppage of treatment after consultation with physician and caregiver, or being withdrawn at the behest of a study centre to continue treatment in an open-label manner. Endpoints included entry to institutionalized care or progression of disability, which was defined as losing two of four basic or six of eleven instrumental activities of daily living. After three years of follow-up, the relative risk of institutionalization in the donepezil versus placebo group was 0.97 (95% CI=0.72 to 1.30), and the relative risk of progression of disability or institutionalization was 0.96 (95% CI=0.74 to 1.24).

2.1.2.3.1. Head-to-Head Comparisons of Cholinesterase Inhibitors

To date, there have been only three head-to-head comparisons of ChEIs in AD[117-119] (see Hogan et al.[120] for a critical appraisal). All three studies were randomized, parallel-group, open-label trials involving mild to moderate AD patients. One of the trials was restricted to patients who were diagnosed with probable AD.[117] In the other two trials, patients could be enrolled if they had a diagnosis of probable or

possible AD.[119;121] Double-blind designs were not feasible for these trials because the ChEIs have different appearances, as well as different dosing and titration schedules.

Two of the trials[117;121] compared donepezil against galantamine. In the first trial,[117] 52 weeks of follow-up data were available for 87 donepezil-treated and 93 galantamine-treated patients. At week 52, the mean difference in ADAS-cog score (donepezil minus galantamine) was 1.21. The difference was not statistically significant at the 5% level of significance (no confidence interval provided in the published report). However, in the sub-group of patients who had baseline MMSE scores of 12 to 18, galantamine was found to be significantly more efficacious. The mean difference on the ADAS-cog in the sub-group analysis was 2.47 ($p<0.05$; no confidence interval in the published report). In both patient groups, there was an almost identical improvement in cognition over the first 13 weeks of the trial. Afterward, patients in both groups experienced cognitive decline. During the second half of the trial, the decline was greater in the donepezil group.

In the second trial[121] of donepezil versus galantamine, the results favoured donepezil. After 12 weeks of follow-up, donepezil-treated patients (n=60) had an average 2-point or better improvement on the ADAS-cog in comparison to galantamine-treated patients (n=52). The p-value for the comparison was <0.01. No confidence interval was provided in the published report. The proportion of patients who had gastrointestinal adverse effects was lower in the donepezil group, with 16% reporting nausea and 9% reporting diarrhea. For galantamine, 23% reported nausea and 14%

reported diarrhea. Vomiting was not reported in donepezil-treated patients, but was reported in 13% of galantamine-treated patients.

The third head-to-head comparison of ChEIs in AD investigated donepezil and rivastigmine.[119] After 12 weeks of following 111 patients (age ≥50), the difference in mean score (donepezil minus rivastigmine) was not statistically significant on the ADAS-cog (difference=-0.15 [95% CI=-1.85 to 1.55]). However, 31% (17/55) of the rivastigmine-treated patients withdrew from the study, whereas only 11% (5/56) of the donepezil-treated patients withdrew. Twelve of the rivastigmine withdrawals and six of the donepezil withdrawals were due to adverse effects. Physicians and caregivers were asked about their satisfaction with the medications. Significantly better ease of use and overall satisfaction were reported for donepezil.

2.1.2.4. The Efficacy of Alzheimer's Disease Drugs in Severely Affected Patients

Some researchers as far back as 1983 have examined the use of drugs in patients with severe AD. Martin et al.[122] conducted a double-blind, crossover trial to evaluate a synthetic peptide, Org 2766, against placebo in patients with 'severe senile dementia.' Patients received the active substance and placebo for separate 4-week periods, with a 2-week placebo washout interspersed between each period. Efficacy measures included global clinical status, cognition, behaviour, and biomedical markers. Data were available for 34 female patients. A difference between Org 2766 and placebo was found for only one patient, and on only one efficacy measure (depression).

Four randomized, placebo-controlled trials have been conducted to examine the efficacy of memantine in patients with severe senile AD-type dementia,[57] severe AD or severe vascular dementia,[58] or moderate to severe (probable) AD.[14;123] In the first trial,[57] which had a 35-day follow-up period, 10 patients received 20 to 30mg memantine intravenously and 10 other patients received a placebo solution intravenously. The researchers did not find any statistically significant differences between the treatment arms.

In the other three trials, the results favoured memantine. The researchers in one trial[58] measured efficacy using the Clinical Global Impression of Change (CGIC).[105] On the CGIC, clinicians are asked to rate changes in patients' global health status using a seven-point scale. The scale ranges from 'very much improved' to 'very much worsened' from baseline. After 12 weeks of follow-up, 60 of 82 memantine patients were 'much improved' or 'minimally improved.' Eighteen memantine patients were 'unchanged' and four were 'very much worsened.' In the placebo group, 38 of 84 patients were 'much improved' or 'minimally improved,' 38 were unchanged,' 3 were 'minimally worsened,' 1 was 'much worsened,' and 4 were 'very much worsened.' The differences between groups were all statistically significant ($p<0.001$).

Another memantine research group used the CIBIC-plus to measure efficacy in their trial.[14] Differences (memantine minus placebo) in mean CIBIC-plus score after 28 weeks of follow-up indicated memantine-treated patients completed the study with less global health decline than placebo-treated patients (mean difference=-0.3, 95% CI=-0.51 to 0.02 [last observation carried forward]; mean difference=-0.3, 95% CI=-0.69

to -0.03 [observed cases]). Overall, a greater proportion of memantine patients completed the study (77% [97/126] of memantine patients versus 67% [84/126] of placebo patients). Thirteen memantine-treated patients and 22 placebo-treated patients withdrew because of adverse effects.

In the fourth memantine-placebo trial,[123] the Severe Impairment Battery (SIB) was used to assess cognitive change in a group of 404 patients. The SIB contains 40 items to measure six components of cognition, namely memory, orientation, language, attention, visuo-spacial ability, and construction. Scores range from 0 to 100. Higher scores represent better levels of cognitive functioning. The trial differed from the other three memantine studies in that all patients were required to be on donepezil for at least six months prior to enrolment. After 24 weeks of follow-up, the mean changes in SIB score from baseline favoured memantine-treated patients. For the last observation carried forward analysis, the mean change in score was 0.9 (standard error=0.67) for the memantine group and -2.5 (standard error=0.69) for the placebo group. Similar changes were reported for the observed case analysis: memantine group (mean change=1.0; standard error=0.70); placebo group (mean change=-2.4; standard error=0.74). In both analyses, the difference between groups was statistically significant ($p<0.001$). Eighty-five percent of the memantine patients (172/203) completed the study versus 75% (150/201) of the placebo patients. Fewer memantine patients (n=15) withdrew because of adverse effects (n=25 placebo patient withdrawals).

To date, only Feldman et al.[11] have evaluated an approved ChEI in severe (probable or possible) AD patients. The researchers undertook a 24-week,

double-blind, placebo-controlled trial of donepezil in 290 moderate to severe AD patients. Using the CIBIC-plus as the primary outcome measure, donepezil-treated patients on average demonstrated comparatively better global health than placebo-treated patients at every measurement point during the follow-up period. The difference (donepezil minus placebo) in mean score between the groups at week 24 was -0.54 ($p<0.0001$).

2.2. The Use of Drug Treatments in the Alzheimer's Disease Population: Physician and Caregiver Perspectives

Many factors, including safety and efficacy, help explain medication use. In the AD literature, safety and efficacy have received most of the attention. However, researchers need to consider other factors to gain a more complete understanding of the use of medications in AD. Two such factors, the physician and caregiver perspectives on the use of AD medications, are the subject of the research for this thesis. These factors are important to study because physicians and caregivers are primarily responsible for making treatment choices on behalf of AD patients. This responsibility is particularly heavy in AD because patients lose the ability to participate in treatment decisions as cognitive decline progresses.[15-18] Cummings, in recognizing the importance of physicians and caregivers, has called for a "therapeutic alliance"[32] to promote the well-being of AD patients. In the alliance, physicians and caregivers would work together to pursue a set of common treatment goals. A first step in forming such an alliance would be to study the physician and caregiver perspectives so that each group's requirements and beliefs regarding drug treatments in AD are quantified and made explicit.

2.2.1. Physician Perspective

2.2.1.1. Definition

For the purpose of the thesis, the physician perspective concerns the minimum level of efficacy that physicians would require from an AD drug in order to prescribe the drug to patients. Presently, the AD literature contains virtually no information about the physician perspective as so defined.

Before expanding upon the physician perspective, some general background theories of prescribing will be reviewed.

2.2.1.2. Prescribing

There are numerous motivating factors that may explain why a physician might choose to prescribe a medication.[21;124-131] Many of these factors have little to do with efficacy. For example, Lexchin[127] believes prescribing has a psychosocial dimension. This is evident when physicians prescribe a medication to satisfy patient demands for drug treatment, rather than to address specific clinical concerns.

Raisch[128] summarizes three theories of physician prescribing: psychosocial, external, and cognitive. In the psychosocial theory, prescribing is viewed as a manifestation of the physician-patient relationship. Physicians may prescribe to exercise power or authority over patients, or to avoid lengthy discussions with patients. In the external theory, prescribing is considered to be influenced by practice type, regulatory requirements, marketing from pharmaceutical companies, colleagues' influence, and

working conditions. In cognitive prescribing theory, prescribing decisions are seen to be influenced by normative values. For example, personal experiences may cause physicians to strongly believe a favourable outcome will result from either prescribing or not prescribing a medication. These beliefs influence whether prescriptions are actually written.

Another view, summarized by Bradley,[21] regards prescribing as behavioural, or habitual, rather than as the product of normative values. Behaviouralist theory applies to situations where prescriptions are written mechanically when a patient presents with a particular set of symptoms, even if a complete examination is not undertaken to explore all the possible causes of the symptoms.

The aforementioned theories should not be viewed as mutually exclusive explanations of physician prescribing. Rather, the theories are complementary. No single theory can entirely explain all prescribing decisions. Physicians have different motivations for writing prescriptions, depending on the situation at hand.

2.2.1.3. Prescribing and the Elderly

Theories of physician prescribing have not been used to explain prescribing in the elderly population. Rather, explanations have been sought empirically by studying the association between physician characteristics and prescribing practice. For example, researchers in New Brunswick found high prescribers were more often male, more likely to have received their training in Canada, and more likely to have received qualification from the Canadian College of Family Physicians. In contrast, physician age,

number of years in practice, mean practice size, and average patient age were not statistically significantly different when high prescribers were compared with low prescribers.[132]

Others interested in prescribing and the elderly have reported numerous physician-based factors that can influence prescribing. These factors include the extent of a physician's medical knowledge, the degree to which a medical problem has been analyzed, and the weighing and acceptance of risk.[15;133;134] Decisions on specific treatment modalities for patients may be affected by relationships between the physician and the patient, or between the physician and the patient's family. Other factors that could affect treatment decisions are a patient's wishes, age, prognosis, and quality of life, as well as healthcare policy and the availability of healthcare resources.[15;133]

The literature search did not yield any publications that linked the topic of prescribing and the elderly to the topic of AD or drug treatments for AD.

2.2.2. Physician Perspective - Prescribing and Alzheimer's Disease: The Role of Efficacy Requirements

2.2.2.1. The Drug Choice Model

According to the drug choice model, physicians choose to prescribe a drug based on their views of the drug's efficacy. Also, the choice of drug is believed to be influenced by the weight that physicians attach to the range of possible outcomes that could result from the prescribing decision.[21] To test the drug choice model, Segal and Hepler[20] presented a hypothetical case of hypertension to physicians. The

physicians were asked about the desirability of several possible treatment outcomes from drug therapy, as well as for the probabilities that the outcomes would occur. The physicians were also asked to explain their individual approaches to treating the hypothetical case of hypertension. By considering both the desirability and the probabilities, Segal and Helper were able to accurately predict 72% of physicians' individual approaches to treatment.

Bradley[21] criticized Segal and Hepler's study[20] because it was based on a purely hypothetical scenario, the sample was restricted to family practice residents from one site only, and the dependent variable was 'prescribing intent' rather than actual prescribing behaviour. Furthermore, Bradley felt the design of Segal and Hepler's data collection questionnaire would steer physicians toward responses that differed from how hypertension was treated in actual practice settings.

In a second study of 40 physicians, Segal and Hepler[135] modified their approach to include actual cases along with the hypothetical cases, although the actual cases were presented as hypothetical. In addition to hypertension, physicians were asked about the treatment of adult-onset diabetes mellitus. For hypothetical cases, Segal and Hepler accurately predicted physicians' approaches to treatment in 81% of the hypertension cases and in 87% of the diabetes cases. The accuracy was somewhat lower for the real cases: 76% for the hypertension cases and 70% for the diabetes cases. All results were statistically significant ($p<0.01$).

2.2.2.2. Efficacy Requirements in Prescribing for Alzheimer's Disease

The drug choice model suggests an approach for studying the use of medications in AD. The approach involves the elicitation of physicians' efficacy requirements for prescribing. Essentially, an 'efficacy requirement' is the minimum level of drug performance that physicians would require before prescribing a medication to their patients. In the case of AD, the minimum level has been quantified in the literature as a numerical change in score of at least a certain magnitude on the MMSE.[24] The minimum level could also be conceived as something more clinically relevant, e.g., the resumption of a patient's ability to perform one or more activities of daily living.

Requirements defined as a minimum level of drug performance have been presented in the literature.[22;23] Parmer et al.[22] elicited such requirements for the treatment of head/neck and lung cancer, and Oremus et al.[23] elicited such requirements for the treatment of female stress urinary incontinence. In both studies, physicians were also asked to provide a 'level of belief' in whether the treatments could meet their requirements. These beliefs were expressed as probabilities, with values closer to 1.0 indicating that physicians had stronger levels of belief.

In the aforementioned requirements and beliefs studies,[22;23] the authors described how physician efficacy requirements can be used to estimate clinically significant treatment differences and calculate sample sizes in clinical trials. However, neither group examined an issue that this thesis explores, namely, whether physician efficacy requirements can help explain medication use. For example, a drug might demonstrate what is thought to be an acceptable degree of efficacy in clinical trials, yet few

physicians prescribe it. If requirements are associated with prescribing, then perhaps the drug is not being used as much as one would expect because it does not meet the average minimum efficacy requirements of most physicians who treat AD patients.

The elicitation of requirements can do more than explain medication use. The requirements can help to guide drug development by suggesting minimum 'performance' levels that medications in the developmental stage of research should be designed to achieve.

'Requirements' as discussed above have only been elicited in one AD-related study. Burback et al.[24] surveyed all geriatricians (n=111) and all neurologists (n=476) who were certified by the Royal College of Physicians and Surgeons of Canada. The survey included a question about the smallest change in MMSE score that would indicate a "noticeable change" in a dementia patient's overall health status. Answers to this question provided data to calculate a minimum clinically significant difference (MCSD) in MMSE score. The authors defined the MCSD as "the smallest difference that patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management."[24] In total, 155 physicians (26%) responded, and the mean MCSD was calculated to be 3.72 points (95% CI=3.50 to 3.95). The authors' next step was to examine 13 clinical trials of tacrine in AD to see if any results met or exceeded the MCSD. For the 12 trials wherein the MMSE was employed, all of the mean changes in scale score were less than the MCSD.

Through this work, Burback et al.[24] made an important contribution to the identification of clinical significance in AD. However, they did not address

whether the lack of clinical significance in the tacrine trials may have affected physicians' prescribing of the drug in standard practice settings. Also, the question to elicit the MCSD was not asked in direct reference to drug treatment. Therefore, the answers may not have reflected the minimum change in score that was clinically significant with respect to medication use. Indeed, the question was embedded in a survey about vascular dementia, so physicians might not have answered specifically for the treatment of AD. The MCSD itself was defined as a change in scale score on a cognition-based instrument. This definition ignores more clinically relevant outcomes in AD, including increases in length of patient stabilization or improvements to behaviour and mood and the ability to perform activities of daily living.[26;31]

2.3. Caregiver Perspective

A top priority of caregivers is clearly the health and well being of AD patients. If an AD medication has a positive impact on patient health, then caregivers would likely want the drug available as a treatment option. However, there has been little research into what caregivers would consider to be a 'positive impact on health.' Defining this would provide caregivers, physicians, and researchers with a benchmark from which to evaluate the therapeutic potential of AD medications.[26]

2.3.1. The Literature on Caregivers and Alzheimer's Disease

The caregiver literature contains a great deal of research into the causes and effects of caregiver burden,[136-158] caregiver opinions on dementia diagnosis,[159-161]

caregiver demographics,[162-164] and patterns of caring for people who have dementia.[165-176]

To date, 18 studies[12;14;27;28;30;114;177-188] have been published on the topic of caregivers and AD medications. In 12 of these studies,[12;14;114;177-185] researchers compared the burden of caregivers of treated patients to that of caregivers of untreated patients. Three other studies were conducted to examine the emotional stress and treatment opinions of caregivers of treated patients.[30;186;187] One study[27] was undertaken to elicit caregivers' opinions on the importance of two potential outcomes from drug treatment, namely a gain of one additional year of life for the patient and a delay of one year before the patient would have to be placed in a nursing home. Another study[28] was carried out to investigate caregivers' willingness to use an AD-slowing medication. The last study[188] in the group was an economic evaluation wherein the costs of caregiving were calculated for a 24-week period. The results of each study will be summarized below.

Reisberg et al.[14] examined caregiver time in a trial of memantine versus placebo in moderate to severe (probable) AD patients (Section 2.1.2.4). They reported that caregivers of memantine-treated patients spent less time providing care than caregivers of placebo-treated patients. Using a last observation carried forward analysis, the mean difference in time between the two groups of caregivers was 45.8 hours per month (95% CI=10.37 to 81.27). The authors did not report the number of caregivers in each group.

Feldman et al. reported[12] on the caregiver outcomes from their study[11] of donepezil in moderate to severe (probable or possible) AD patients (Section 2.1.2.4). At each of four clinic visits, the authors measured caregiver stress on 11 items:

cognitive status, overload, relational deprivation, job-caregiving conflict, economic strains, role captivity, loss of self, caregiving competence, personal gain, management of distress, and expressive support. For caregivers of donepezil-treated patients, the mean score for all 11 items either improved or remained essentially unchanged at week 24 relative to baseline. For caregivers of placebo-treated patients, the mean score declined. However, the between-group difference in mean scores was not statistically significant. Only one of the 11 individual items, caregiver assessment of patient cognitive status, was statistically significantly different between the groups (mean difference in score at week 24 was approximately 4.2; $p<0.001$). The time spent caring for a person with AD was also measured at each clinic visit. Throughout the trial, caregivers in the donepezil group spent less time caring for patients than did their counterparts in the placebo group (mean difference at week 24 - last observation carried forward=52.4 minutes/day for assistance with all activities of daily living; $p=0.004$). Also, 72% of caregivers in the donepezil group indicated caregiving time had either decreased or remained stable at week 24 relative to baseline. The figure for caregivers in the placebo group was 52% ($p=0.002$; last observation carried forward for assistance with all activities of daily living).

The authors of a 12-month clinical trial comparing donepezil and placebo[109] asked the caregivers of participating patients about the amount of time they spent helping with basic and instrumental activities of daily living.[177] Data were recorded via structured interview at weeks 0, 12, 24, 36, and 52. A total of 190 caregivers responded at baseline; 137 caregivers responded at week 52. Throughout the follow-up period, the time burden was lower for caregivers of donepezil-treated patients relative to caregivers of placebo-

treated patients. However, the difference between groups was statistically significant only at week 52, where caregivers in the donepezil group spent an average of 64 less minutes per day caring than caregivers in the placebo group (95% CI=8 to 121 less minutes per day; p=0.03). Average caregiver time decreased in both groups from weeks 0 to 12, but afterwards increased steadily until the end of the trial.

Caregiver time was assessed in a rivastigmine study[178] that was based partially on prospective, observational data and partially on modelling. The observational portion involved 43 patients and caregivers who were followed for an unspecified amount of time. MMSE scores were used to categorize patients as having mild, moderate, or severe AD. Caregivers were asked to specify the amount of time in a 'typical' day that was spent supervising and communicating with patients, and helping patients dress, eat, and keep up a good appearance. Responses were aggregated by disease severity. The savings in caregiver time were estimated using a model of disease state transition.[189] According to the model, patients who received rivastigmine for two years and who began therapy in the mild disease state would remain in the mild state for an additional eight weeks relative to placebo-treated patients. Patients who were in the moderate state when they first received rivastigmine would remain in that state for an additional seven weeks relative to placebo-treated patients. Using the prospective data and the model, the authors estimated that delayed progression for rivastigmine-treated patients would save caregivers an average of 690 hours when patients began therapy in the mild state. The savings would be 204 hours when patients began therapy in the moderate state. The savings would be realized over a two-year period.

Sano et al.[179] used data from two six-month trials[53;55] to investigate the effects of galantamine on caregiver time. During the course of the trials, the caregivers of 411 galantamine-treated AD patients and 414 placebo-treated AD patients were asked to complete the Allocation of Caregiver Time Survey (ACTS)[180] at monthly intervals. The caregivers were required to specify the amount of time they devoted to helping patients bathe, dress, eat, use the toilet, take medications, and clean house. Open-ended questions gave caregivers an opportunity to provide time estimates for activities that were not covered by the ACTS. Caregivers were also asked about the amount of time that they were able to leave patients unsupervised on a daily basis. At the end of follow-up, caregivers of galantamine-treated patients spent an average of 32 minutes less per day involved in caring than caregivers of placebo-treated patients ($p=0.011$). Caregivers of galantamine-treated patients could also leave patients unsupervised for an average of 27 minutes more per day than the caregivers of placebo-treated patients, although the difference was not statistically significant.

Blesa,[180] using data from one of the six-month galantamine trials,[55] found the time caregivers spent supervising placebo-treated patients ($n=186$) had increased by an average of 120 minutes per day over the course of follow-up. The p-value for the increase was <0.001 relative to baseline. In the 24 mg/day ($n=176$) and 32 mg/day ($n=163$) galantamine groups, the respective average times fell by 82 and 98 minutes per day over six months. However, the two reductions were not statistically significantly different from baseline. The average amount of time caregivers spent helping placebo-treated patients with activities of daily living was 23 minutes more per day at six months

relative to baseline (p=0.027). Caregivers spent 61 minutes less at six months helping patients with activities of daily living in the 24 mg/day galantamine group, and 38 minutes less helping patients with activities of daily living in the 32 mg/day group. The latter two reductions were not statistically significantly different from baseline.

Cummings et al.,[181] utilizing data from another galantamine trial,[54] rated the levels of distress for 214 caregivers of patients treated with placebo, 116 caregivers of patients treated with 8mg/day galantamine, 215 caregivers of patients treated with 16mg/day galantamine, and 206 caregivers of patients treated with 24mg/day galantamine. Distress was rated using the Neuropsychiatric Inventory,[190] which measures the behaviour of AD patients in 10 areas (e.g., delusions, hallucinations, anxiety). For each area, caregivers were asked to rate their level of distress on a scale of 0 to 5, with lower scores indicating less distress. After 21 weeks of galantamine treatment, caregiver distress was statistically significantly reduced from baseline in the 24mg/day group (observed case analysis: mean score change=-0.2, p=0.04; last observation carried forward analysis: mean score change=-0.2, p=0.054). The difference in least-square mean score between the caregivers of placebo-treated patients and the caregivers of 24mg/day galantamine-treated patients was –1.5 (95% CI=-2.9 to -0.1). Changes in score for the other groups of caregivers were not statistically significant.

Shikiar et al.[182] studied the 'reduction in caregiver burden' for 546 caregivers who provided care for patients enrolled in a 26-week, placebo-controlled trial of metrifonate.[191] Burden was assessed using measurement scales, including the Screen for Caregiver Burden (objective and subjective subscales) (SCB-obj, SCB-subj),[192]

the Cognitive Subscale of Poulshock and Deimling (PD),[193] the Abridged Relatives Stress Scale (aRSS),[194;195] and the Caregiver Activity Time Survey (CATS).[183] Caregivers were also asked for estimates of the time spent providing care at baseline, 12 weeks, and 26 weeks. At the trial's conclusion, caregivers were asked about overall changes in caregiving time since the beginning of the study. Changes in score between caregivers of metrifonate-treated patients and caregivers of placebo-treated patients were statistically significant at the trial's conclusion on the SCB-subj ($p=0.045$), the PD ($p<0.001$), and the aRSS ($p=0.036$). All changes in score suggested decreased burden for the caregivers of metrifonate-treated patients relative to the caregivers of placebo-treated patients. Differences in score on the SCB-obj and CATS were not statistically significant. The time spent devoted to caregiving was statistically significantly different ($p=.044$) between the metrifonate and placebo groups. On average, caregivers of patients on metrifonate were able to devote half an hour less per day to caring than their placebo counterparts.

Clipp and Moore[183] examined caregiver time in a 24-week, double-blind, placebo-controlled trial of velnacrine maleate, a ChEI that has not been approved for use in AD. The results of the trial, which was conducted by Hoechst-Roussel Pharmaceuticals Inc., have not been published, but the authors had access to the data. Caregivers for the 449 trial patients were asked to complete the CATS at baseline, week 10, and week 24. The caregivers were also asked to identify any paid caregiver services that patients received, as well as the average time in hours and minutes consumed by the paid services. Multiple regression was used to examine the association between patients' cognitive function and caregiver time. Cognition was measured using the cognitive and non-

cognitive portions of the ADAS. Covariates included caregiver sex, caregiver-patient relationship, and type of caregiver (primary or secondary). Statistically significant positive associations were found at baseline between total unpaid caregiver time and cognitive function on the ADAS-cog (memory component only: p=0.008; not significant on the behaviour component) and the ADAS-noncog (p=0.009). There were no statistically significant baseline associations found between paid caregiver time and cognitive function on any segments of the ADAS. For drug-placebo differences in unpaid caregiver time between baseline and the end of follow-up, there were no statistically significant differences in the 150mg/day velnacrine maleate group versus placebo. In fact, unpaid caregiver time increased for both groups over the course of the trial. For the 225mg/day velnacrine maleate group, unpaid caregiver time decreased between baseline and week 24, although the difference versus the placebo group was not statistically significant (p=0.06).

Fillit et al.[184] compared burden in caregivers of patients receiving donepezil to burden in caregivers of patients not receiving donepezil. Two hundred seventy-four unpaid caregivers of patients who used donepezil for at least nine months were individually matched to caregivers of patients who had not used donepezil. The matching variables were the age and physical health status of caregivers. Caregivers were sent a self-administered questionnaire that included the Caregiver Burden Scale (CBS)[196;197] as the primary outcome measure. The CBS measures the level of demand and the degree of distress associated with undertaking 15 typical caregiver activities over a seven day period. Examples of typical activities include managing behavioural problems, providing

personal care, and performing household tasks. Lower CBS scores indicate less burden. For level of demand, Fillit et al. found no statistically significant differences in CBS score between donepezil and non-donepezil caregivers. For distress, the caregivers of donepezil-treated patients had significantly lower CBS scores than the caregivers of patients who were not receiving donepezil (mean difference=0.23, p=0.004).

Caregiver distress was measured using the Neuropsychiatric Inventory[190] in a placebo-controlled trial of donepezil.[114] Randomization was conducted after a 12-week open-label phase during which all patients received donepezil. Between weeks 12 and 18, the Neuropsychiatric Inventory score for caregivers of donepezil-treated patients fell by a median of 1 point (range=-16 to 15), while there was no change for caregivers of placebo-treated patients (change=0; range=-19 to 28). The difference between groups was statistically significant (p=0.03). Between weeks 12 and 24, the score for caregivers in the donepezil group decreased by 2 points (range=-9 to 10), while the score for caregivers in the placebo group increased by 1 point (range=-20 to 23). Again, the difference between groups was statistically significant (p=0.01). Decreases in score indicate less caregiver burden.

The Neuropsychiatric Inventory[190] was also used to measure caregiver distress in a case series of 124 patients with mild or moderate probable AD.[185] All patients were given galantamine for 12 weeks. Sixty-four caregivers contributed data at baseline and the end of follow-up, and their levels of distress decreased over time. The mean score on the Neuropsychiatric Inventory was 8.4 (95% CI=6.8 to 10.0) at baseline and 6.5 (95%

CI=5.1 to 7.9) at week 12. The difference in score was statistically significant ($p<0.05$).

The emotional stress of caregivers was assessed by Harkins et al.,[186] who treated 12 probable AD patients with tacrine for a period of 29 weeks. The authors employed five visual analogue scales specifically designed to measure depression, anxiety, frustration, fear, and anger in caregivers. The score range on each scale was 30 to 120, with higher scores indicating more emotional stress. Data were reported for 11 caregivers. Caregivers of patients who had increased cerebral blood flow after tacrine treatment (group A; n = 6) demonstrated less emotional stress on each of the five scales than did caregivers of patients who had no increased cerebral blood flow (group B; n = 5). For the depression, anxiety, and frustration scales, the combined mean difference in score (group B – group A) was approximately 36 points. For the fear and anger scales, the difference was smaller at approximately 10 points. Harkins et al. did not report standard errors or confidence intervals. The authors were concerned with cerebral blood flow because they hypothesized that changes in flow after drug treatment could help identify long-term responders to the medication.

Moving away from studies of caregiver burden, Shua-Haim et al.[187] sought to investigate caregivers' and families' impressions of the impact of donepezil on patients. The caregivers and families of 57 probable or possible AD outpatients were asked to complete a questionnaire after their relatives had been treated with donepezil for 16 weeks. Caregivers and family members were required to indicate any observed cognitive or behavioural differences since the start of treatment on a five-point scale ('continue to deteriorate' to 'impressive improvement'). If there was improvement, then

examples of the improvement were to be provided. For both basic and instrumental activities of daily living, the questionnaire contained examples of specific activities. Caregivers and family members indicated whether the ability to perform each activity improved or deteriorated. Open-ended questions asked about the reasons for being satisfied or dissatisfied with donepezil, the primary benefit expected from the medication, and the adverse effects experienced by patients. After 16 weeks of treatment, caregivers and family members reported twenty-seven patients (47%) had some cognitive improvement relative to baseline, primarily in language skills and attention. On the other hand, no behavioural improvements were reported. Functional improvement was reported in 21 patients (37%), with most of the improvement being in the area of verbal skills. Caregivers and family members were satisfied with donepezil in the case of 27 patients (47%). The authors did not report data on caregivers' and family members' expectations from the medication.

The idea of expectations was touched upon by Rockwood et al.,[30] who employed Goal Attainment Scaling (GAS) to obtain the treatment goals of caregivers, patients, and physicians in advance of a 52-week, open-label donepezil trial. GAS is a formal process whereby treatment goals are defined in advance, followed-up regularly, and summarized into a score that indicates the extent to which the goals have been attained. A total of 108 mild to moderate AD patients (the authors did not specify a diagnosis of probable or possible AD) were enrolled in the open-label study, and 88 (81%) completed all 52 weeks of follow-up. Caregivers and patients set more goals (total goals=855; mean=9 goals per caregiver-patient dyad) than physicians (total goals=342; mean=3 goals per

physician). This was especially so in the cases of leisure and social interaction. For leisure, 76% of the caregiver-patient dyads set goals, while only 20% of physicians set goals. For social interaction, the percentages were 49% of the dyads and 24% of the physicians. Global caregiver-patient GAS scores had good correlations with the CIBIC-plus (week 12: r=-0.51; week 52: r=-0.56). Physician GAS scores had even better correlations with the CIBIC-plus (week 12: r=-0.82; week 52: r=-0.80). Correlations were negative because higher GAS scores indicate improvement, while lower CIBIC-plus scores indicate improvement. The authors did not report confidence intervals or standard errors for any of the comparisons.

Karlawish et al.[27] examined treatment expectations in a group of 43 caregivers of community-dwelling (probable or possible) AD patients. Data were collected via a structured interview, and 40 caregivers were included in the final analysis. On a six-point scale ranging from 'not at all important' (score=0) to 'extremely important' (score=5), caregivers were asked to indicate the importance of two outcomes for a hypothetical disease-slowing AD medication. The first outcome was a gain of one additional year of life for the patient, and the second was a delay of one year before the patient would require placement in a nursing home. Caregivers were also told to assume that the medication carried a risk of GI bleeding. For this adverse effect, caregivers were asked to specify, in terms of percentages, their risk tolerance for each of three levels of severity: minimal bleeding that stops when the drug is no longer taken; bleeding resulting in hospitalization and possible transfusion or surgery; and bleeding resulting in death. For example, a caregiver who answered 75% for 'GI bleeding resolving after treatment

cessation' would support the use of the medication if this type of bleeding had no more than a 75% chance of occurring. The median rating for the outcome of one additional year of life was 'very important' (score=4); the median rating for one additional year of delay before nursing home placement was 'extremely important' (score=5). Caregiver burden, measured using the Screen for Caregiver Burden,[192] was inversely related to the importance of one additional year of life (r_s=-0.47, p=0.002). Basically, as burden increased, caregivers would attach less importance to the one additional year of patient survival. No statistically significant association was found between burden and the delay to nursing home placement. However, the authors found caregivers tended to view the 'delay' outcome as a proxy for patient quality-of-life. For the question about adverse effects, mean percentage responses were: GI bleeding that resolves after treatment cessation (62%); GI bleeding requiring hospitalization and possible transfusion or surgery (25%); GI bleeding resulting in death (8%). The authors presented summary statistics for these percentages, but no confidence intervals.

In another study by Karlawish et al.,[28] 102 caregivers of patients with mild to severe (probable or possible) AD were asked about their willingness to use two hypothetical AD medications. Both medications were described as requiring once daily administration, with the beneficial effects being a slowdown of memory loss and AD progression for one year. The first drug was risk-free, while the second drug carried a three percent annual risk of GI bleeding that could lead to hospitalization, transfusion, or surgery. Seventeen (17%) of the caregivers would refuse to use the risk-free version of the drug. Half of the caregivers would refuse to use the risky version. In multiple

logistic regression analysis, two variables were found to be negatively associated with refusal: global patient quality-of-life (OR=0.6; 95% CI=0.37 to 0.94) and item-specific patient quality-of-life (OR=0.56; 95% CI=0.36 to 0.88). Specific quality-of-life items included physical health, energy, mood, living situation, memory, family, marriage, friends, view of self as a whole, ability to do chores around the house, ability to do things for fun, money, and view of life as a whole. Two variables were positively associated with refusal: non-white race (OR=6.6; 95% CI=1.7 to 25.1) and caring for a male patient (OR=3.47; 95% CI=1.2 to 10.0).

The cost of caregiving in AD was calculated[188] using data collected as part of a placebo-controlled donepezil trial.[11] Caregivers were asked to estimate the total number of minutes per day spent helping patients with basic and instrumental activities of daily living. Estimates were elicited at weeks 0, 4, 12, and 24. At the same time, the Canadian Utilization of Services Tracking questionnaire,[4] adjusted to incorporate the trial's data collection time points and the frequency of health resources utilization, was employed to obtain information on caregivers' own physician visits, use of medications and counselling, and hospitalizations. The 'cost' of unpaid caregiver time was estimated using the 1998 Ontario minimum hourly wage of $6.85. The costs of health resources were obtained from Ontario fee schedules. Over the 24-week trial, caregivers' own physician and counselling visits, and medication use, cost an average of $32 more per caregiver in the donepezil-treated group relative to the placebo-treated group. Conversely, the cost of unpaid caregiver time was $233 lower per caregiver in the donepezil-treated group relative to the placebo-treated group. None of the differences

were statistically significant.

2.3.2. The Need for Further Examination of the Caregiver Perspective

In 12 of the 18 studies in the previous section, the authors examined the impact of drug treatment on caregiver burden. Only Karlawish et al.[27;28] elicited caregiver preferences for AD medications. Given the importance of caregivers in managing AD, plus ongoing research into improved drug therapies, there is clearly a need for more information about the caregiver perspective on AD medications. At the very least, Karlawish et al.'s work[27;28] should be expanded beyond the three outcomes investigated therein. Other items to explore include the minimum improvements caregivers would require with respect to patient-based factors such as memory, mood swings, and walking. These required improvements are essentially the caregiver equivalents to physician efficacy requirements. As well, given the impact of institutionalization on caregivers, patients, and healthcare costs, more focus should be placed on the importance that caregivers attach to delaying institutionalization. While such delays were addressed by Karlawish et al.,[27] several different lengths of delay, rather than just a one-year delay, should be considered.

Adverse effects may increase the difficulty of patient management and affect caregiver attitudes toward the initiation or continuation of drug therapy. Therefore, Karlawish et al.'s[27;28] examination of caregiver tolerance for the adverse effects of AD medications should be extended to include other adverse effects.

Caregivers, as patient advocates and proxy decision makers, must interact with physicians to manage the treatment of AD patients. However, there has been no examination of the caregiver-physician relationship in the AD literature. Are AD patients more likely to be prescribed medications if physicians rather than caregivers raise the possibility of employing drug therapy? Is prescribing associated with whether a caregiver pressures a physician to prescribe an AD drug? These questions should be addressed to further understand the role of caregivers in AD.

The actual prescribing of AD medications has not been examined in published studies of caregivers and AD. For example, were the patients of caregivers who rated a one-year delay in nursing home placement as 'very important'[27] more likely to be prescribed an AD medication than the patients of caregivers who had a less enthusiastic preference for the outcome? To broaden the question, can the elicitation of treatment outcome preferences provide information to help explain medication use in the AD population? Also, can this information help to guide drug development and assessment? These questions will be addressed by studying the associations between prescribing and caregivers' required minimum improvements to domains that affect people with AD, prescribing and delays to nursing home placement, and prescribing and caregivers' willingness to accept adverse effects.

2.4. Alzheimer's Disease Patients and Drug Therapy

Despite the fact that cognitive impairment is a major facet of the disease, AD patients do play a role in treatment decisions. At least some patients in the mild stage of

disease, and even some in the moderate stage, will have input into their treatment. Some patients may even have the final say on the treatment modality that will be used. However, physicians and caregivers have input into treatment decisions at all stages of the disease, and as the level of cognitive impairment increases, they gradually take on primary responsibility for patient management. Given the 'continual' role of physicians and caregivers, this thesis is focused on these two groups of people. Proper consideration of patient-specific issues, including patient preferences for AD medications, warrants an entirely separate research project.

2.5. Conclusion

In this chapter, the physician and caregiver perspectives on the use of medications in the AD patient population were defined and explained. Given the aging population and ongoing research into new and improved AD medications, the study of these perspectives is timely and will provide data to help guide future drug development and assessment.[6;19;28] In the next chapter, the methods that were used to study the physician and caregiver perspectives will be presented.

3. METHODS

3.1. Overview of Methods

In this chapter, the methods used to study the physician and caregiver perspectives on drug treatments for AD are presented. Self-administered, postal questionnaires were used to collect data. Postal questionnaires have the advantage over face-to-face interviews of being able to reach more subjects in a shorter period of time.[198] In addition, postal questionnaires are cheaper to administer and require fewer personnel resources than face-to-face interviews.[199]

The use of postal questionnaires has been criticized[200-202] because of low response rates and the possibility of non-response bias. In the current research, various strategies were implemented to enhance response rates and, after data collection, to identify possible non-response bias. For the physician questionnaire, a set of standardized guidelines[198] was used to govern questionnaire design and administration. Telephone reminders were also used to prompt non-respondents to answer and return the questionnaire.[203;204] Non-response bias was assessed by comparing the baseline characteristics of respondents to non-respondents and the baseline characteristics of early respondents to late respondents.[205-207] In addition, at the end of the survey period, a random sample of non-respondents was asked to answer some of the more substantive portions of the questionnaire.[198;208] Multiple imputation[209;210] was used to examine the impact of item non-response.

For the caregiver questionnaire, methods to encourage response and to assess bias were similar to the procedures that were used for the physician questionnaire: the standardized guidelines[198] governed the design and administration of the caregiver questionnaire (Section 3.3.1.3); the responses of early respondents were compared to the responses of late respondents (Section 3.3.1.4.2); a random sample of non-respondents was contacted by telephone to answer some of the more salient questions (Section 3.3.1.4.2); and multiple imputation was used to address the problem of missing data (Section 3.3.2.2.3). However, in contrast to the physician study, the characteristics of caregivers who did not respond to the questionnaire could not be compared to the characteristics of caregivers who did respond. This was due to the strict anonymity requirements imposed by the organizations that assisted in the recruitment of caregivers for the study (Section 3.3.1.3).

3.2. Physician Perspective

3.2.1. Physician Questionnaire - From Sample Selection and Design to Bias Assessment

3.2.1.1. Sample

The postal questionnaire was sent to all of the Province of Québec's 49 geriatricians, 215 neurologists, and 53 psychogeriatricians. These specialists were chosen because they were more likely than other specialists to treat AD and to prescribe ChEIs. The questionnaire was also sent to a sample of 486 Québec GPs (6% of the province's 8,115 GPs). GPs are the next most likely group involved in the treatment of

AD. This is especially so outside Montréal, Québec City, and Sherbrooke, where most specialists practice.

The study was restricted to physicians practicing in Québec to avoid possible effect modification or confounding by inter-provincial differences in practice patterns and drug reimbursement policies. Lists of geriatricians, neurologists, and GPs were purchased from the *Collège des médecins du Québec*, which is the professional body governing physicians in Québec. Lists of psychogeriatricians were provided free of charge by the *Société de psychogériatrie du Québec* and the *Association des médecins-psychiatres du Québec*.

To target GPs who were most likely to treat AD patients, the *Fédération de médecins omnipraticiens du Québec* provided without charge a list of GPs (n=191) who had taken continuing medical education courses on geriatrics and the elderly in 2001 and 2002. Questionnaires were mailed to these GPs. Out of the remaining 7,924 GPs, R v1.8.1 software (The R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org) was used to randomly select 295 GPs, all of whom were also sent questionnaires.

The target sample size was 385. This number resulted from the desire to have a sample large enough to detect at least some small to medium effects, but not too large so as to exceed the available number of useful respondents. 'Useful respondents' were defined as physicians who either treated or were likely to treat AD. The sample frame was tailored to contain the most useful respondents through intentional inclusion of physicians who had a specific interest in the elderly, either through their

speciality or because they took continuing medical education courses related to geriatrics.

For the purpose of examining the association between the proportion of AD patients who are currently prescribed ChEIs (i.e., the dependent variable) and physicians' efficacy requirements for prescribing a hypothetical, new AD medication (i.e., the independent variable), an odds ratio of 1.30 was chosen to balance detection of effects with the available number of useful respondents. To achieve a power of 0.80 at a significance level of 0.05, 385 respondents would be needed to detect an odds ratio as small as 1.30, assuming the probability of prescribing a ChEI was 50% at the mean value of the continuous main effect variable. These calculations (PASS 2002 – Power Analysis and Sample Size, NCSS Statistical Software, Kaysville, UT) were done under the assumption that a maximum of 12 covariates would be included in the model along with the main effect variable. Since response rates to postal questionnaires for physicians have been shown to be approximately 48%,[23;48] it was estimated that 803 questionnaires would have to be mailed to garner 385 responses.

3.2.1.2. Development and Content

The first step in developing the physician questionnaire was to use the information from the literature to identify potential topics for questions. Two specialists in AD research, a neuroepidemiologist and a geriatrician, were consulted to supplement the information from the literature review. Once topics were selected, question wording was guided by the principles of questionnaire design.[211;212] Questionnaires from other studies[213;214] were obtained from the authors to help with wording and overall

appearance.

Following the development of a draft questionnaire, one-on-one pre-tests were conducted with three geriatricians, one neurologist, and one GP. Feedback was elicited on questionnaire appearance, appropriateness of questions, and question wording.

The final version of the questionnaire (Appendix A) began with a section wherein physicians were asked to specify how much influence each of 16 factors might have on their decision to prescribe an AD medication. Physicians could choose from five possible responses: would influence, probably would influence, don't know, probably would not influence, or would not influence.

The second section of the questionnaire contained questions on physician requirements, as well as questions on the extent to which physicians believed in their requirements. The third section had a set of questions to quantify the amount and extent to which physicians prescribed medications to treat AD. The third section also contained questions related to ChEIs, namely adverse effects, level of knowledge, sources of information, and caregiver pressure on physicians to prescribe ChEIs. The last section of the questionnaire included questions on respondent characteristics such as age, sex, and the year in which a license was obtained to practice medicine in Québec. To provide details concerning the level to which physicians were involved in the treatment of AD, the last section also contained questions on practice size, estimated numbers of patients in a practice with different types of dementia, and patient distribution across the three severity stages of AD (i.e., mild, moderate, severe).

The final version of the questionnaire was produced in English. Since the majority of respondents were likely to be French speaking, professional translators with experience in health care were employed to translate the questionnaire into French and then to back translate the questionnaire into English. A bilingual geriatrician reconciled discrepancies in question meaning between the final English and French versions of the questionnaire. The same translation process was followed for the cover letters that accompanied the questionnaires.

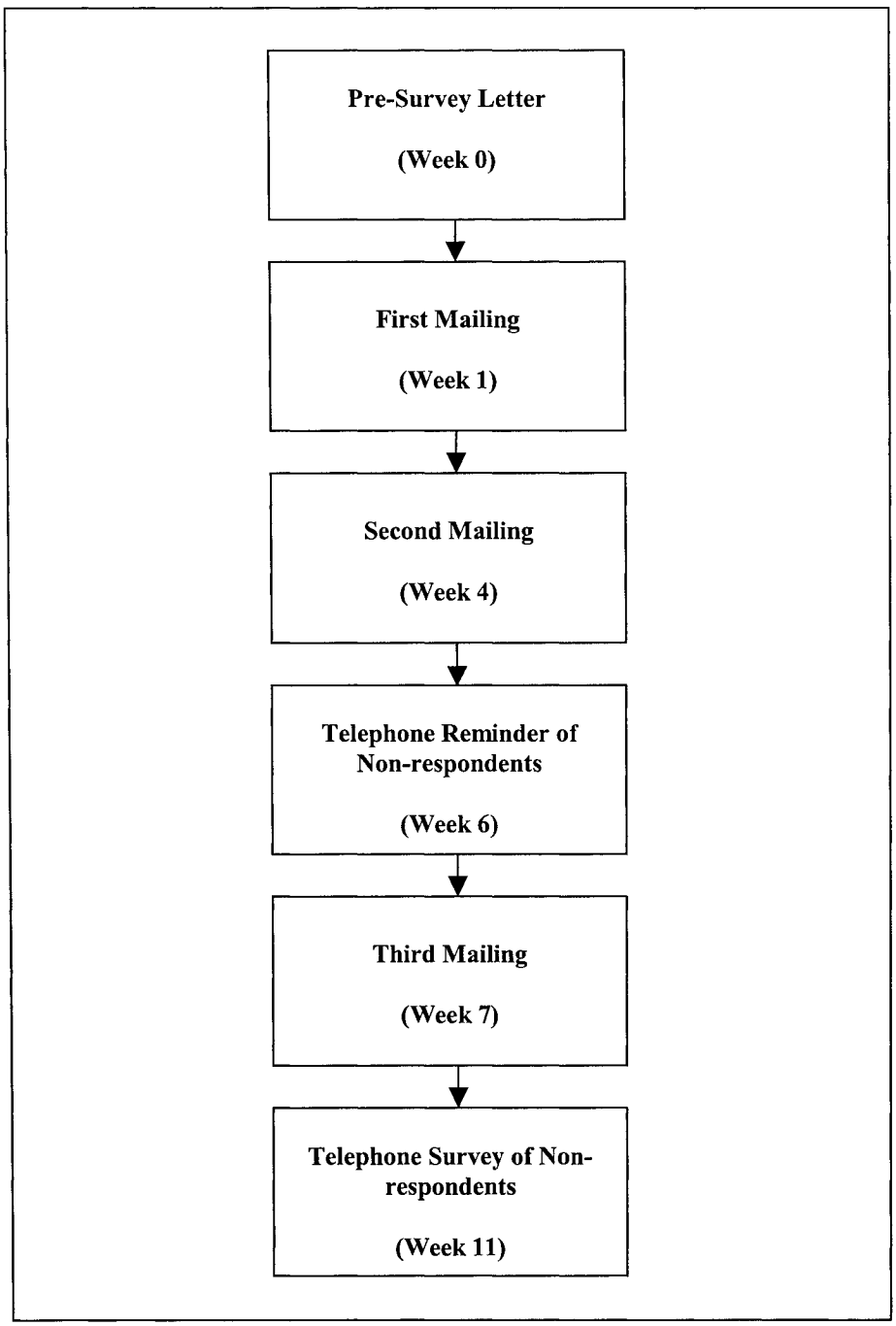
3.2.1.3. Implementation

The questionnaire was administered over the course of six contacts between August and October of 2002 (Figure 3.1). Dillman's 'Tailored Design Method'[198] and Edwards et al.'s recommendations[203] were used to design the mailings and encourage a high response rate. Accordingly, cover letters (Appendix B) were printed on high quality, white bond paper, while the questionnaires were printed on high quality, cream bond paper. The names and logos of McGill University and the Jewish General Hospital were prominently displayed on the cover letters and on the front page of the questionnaire.[215] Each questionnaire package that was sent out contained a cover letter, a questionnaire, and a pre-addressed, pre-stamped envelope. First class, thematic stamps were used rather than metered postage.

A pre-survey letter was mailed one week in advance of the questionnaire to introduce recipients to the study and encourage them to respond. A telephone reminder of non-respondents was conducted between the second and third mailings to further

encourage response.[204] Four weeks after the final questionnaire package was sent, a random sample of non-respondents was contacted to provide data to help assess the potential for non-response bias.

Figure 3.1: Steps in the Administration of the Physician Questionnaire



To prevent respondents from receiving follow-up material in error at later mailings, and to maintain confidentiality, each physician was assigned a unique study identification number. These identification numbers were written on the questionnaires. When a questionnaire was returned, the number was used to remove the respondent's name from the mailing list. To ensure confidentiality, mailing list management and data entry were performed separately.

Recipients who did not wish to participate, or who did not treat AD patients, were instructed in the cover letters to indicate which of the situations applied to them. This was done by ticking off a box on the last page of the questionnaire. Recipients were then asked to return the blank questionnaire.

3.2.1.4. Non-response Bias

Non-response bias was assessed by comparing the characteristics and actual questionnaire responses of respondents versus non-respondents and early versus late respondents. Similarity between groups would suggest less bias.[198;205-208]

Non-respondents were defined as physicians who did not return a questionnaire at all or who indicated that they did not wish to participate. Respondents who returned a questionnaire after the first mailing were considered to be early respondents, while respondents who returned a questionnaire after the second or third mailing were considered to be late respondents.

Comparisons of early versus late respondents have been used to assess non-response bias.[206;207] These comparisons were conducted under the assumption

that late respondents would have been non-respondents had the survey in question consisted of a single mailing. As in the current research, late respondents in the earlier studies were defined as subjects who returned a completed questionnaire after the second or a subsequent mailing.

3.2.1.4.1. Characteristics of Physicians

The following information was available on all physicians who were sent a questionnaire: practice specialty, rural/urban practice location, language - English or French, sex, and the year in which a license was granted to practice medicine in Québec. The specialty of each physician was obtained from providers of the mailing lists. Urban/rural practice location was identified by postal code. Numeral 0 in the second position of a postal code indicates a rural address. Language of physician was judged to be French for physicians with mailing addresses off the Island of Montréal. For physicians with mailing addresses on the Island of Montréal, francophone names were assumed to be indicative of a French speaker and anglophone names were assumed to be indicative of an English speaker. In cases of uncertainty, such as a non-francophone or a non-anglophone name, physicians were assumed to be French speaking unless their mailing addresses were for predominantly English language hospitals. To allow for a comparison of respondents versus non-respondents on language, and to determine the language of the questionnaire that each physician would receive, it was necessary to ascertain language in the aforementioned manner rather than to simply add a query to the questionnaire. Sex of respondents was asked in the questionnaire. For non-respondents, sex was determined by name. The year of licensing to practice medicine in

Québec was obtained from the first two digits of the physicians' provincial medicare billing numbers.

The method of judging the language of physicians was open to misclassification. Some French speaking physicians could have been misclassified as English speaking, and vice versa. However, any potential misclassification would be at worst non-differential because language was judged without regard to whether physicians were respondents or non-respondents. In respondent versus non-respondent comparisons, the presence of non-differential misclassification would be troublesome if the consequent null bias is strong enough to obscure differences between the groups. Although it is not possible to assess whether non-differential misclassification obscured inter-group language differences in the current research, the comparison of respondents and non-respondents should be considered with this possibility in mind. The same caution is extended to the comparison of early and late respondents.

3.2.1.4.2. Actual Questionnaire Responses

For the respondent versus non-respondent comparisons, the names of physicians who did not return the questionnaire were arranged alphabetically and numbered sequentially starting at 1. One hundred of these physicians were randomly selected to be surveyed by telephone. The random selection was conducted using R v1.8.1. The telephone survey was read from a prepared script (Appendix C). Physicians who returned a blank questionnaire and declined participation were excluded from the telephone survey out of respect for their wishes.

Calls to the 100 non-respondents were placed during daytime hours. The non-respondents were asked to answer some of the more substantive questions from the original postal questionnaire (e.g., the questions about physicians' efficacy requirements [Appendix C]). Non-respondents' answers to these substantive questions were compared to respondents' answers to the same questions. Answers based on multiple response categories were compared using Fisher's exact test. Answers that were continuous were compared using the Wilcoxon rank sum test. All tests were two-tailed because the objective was to assess the presence of non-response bias by examining whether the answers provided by respondents and non-respondents were similar or dissimilar to one another. The level of significance was set at 0.05.

Non-response bias was also assessed by comparing early respondents' answers to the postal questionnaire with late respondents' answers to the postal questionnaire. These comparisons, as well as the comparisons of physician characteristics in Section 3.2.1.4.1, were conducted using the same statistical approach employed above.

3.2.1.5. Social Desirability Bias

Social desirability bias occurs when people's responses to questions are influenced by their desire to conform to actual or perceived social or cultural values.[216] One of the most common means of reducing social desirability bias is to collect data using non-personal interview methods such as postal questionnaires.[217-219] Information elicited in private, even sensitive information such as a respondent's health status, are less influenced by the impact of social or cultural norms than information elicited by

telephone or face-to-face interviews.[219;220] In this thesis, the use of a postal questionnaire allowed physicians to respond confidentially and in private.

Another means of reducing social desirability bias is to emphasize the importance of the information being collected.[221] This was done in the cover letters that accompanied the questionnaire (Appendix B). The incidence of AD was stressed in the letters, along with the fact that research is ongoing to develop new and improved AD medications. Phrases in the letters encouraged physicians to respond because their answers would provide timely input to help guide drug development and assessment.

3.2.1.6. Reliability

The test-retest reliability of the physician questionnaire was assessed by sending a shorter version of the questionnaire (Appendix D) to a random sample of 100 respondents. To encourage the respondents to complete this second survey, the short questionnaire contained only a limited number of the most important questions from the original postal questionnaire (e.g., the questions about physicians' efficacy requirements). A list of respondents was arranged alphabetically and numbered sequentially starting at 1. R v1.8.1 was used to select a random sub-sample of 100 respondents from the list. Each of the selected respondents was sent the short questionnaire, along with a cover letter (Appendix E) to explain the reason for the second survey.

The short questionnaire was mailed five weeks after the final mailing of the original postal questionnaire. Three weeks after this short questionnaire was mailed, a

reminder letter and another copy of the short questionnaire were sent to physicians who had not yet returned it.

Weighted Kappa (κ_w)[222] was used to assess test-retest reliability. Weights came from Cicchetti's formula.[223] Individual κ_w statistics were computed for all of the questions contained in both the original postal questionnaire and the short questionnaire. More than one κ_w was calculated for the following questions:

- Section 2 - κ_ws were calculated for each sub-division of:
    - Questions 1a and 1b – sub-divisions: cognition, behaviour and mood, and functional ability; and
    - Questions 2a and 2b – sub-divisions: mild and moderate.
- Section 3 - κ_ws were calculated for each part of questions 3b and 3c:
    - The first part of each question asked respondents if they prescribed ChEIs for patients with MCI (3b) or other forms of dementia (3c). Response options were dichotomous (yes/no).
    - The second part of each question asked respondents who answered 'yes' to the first part to specify the percentage of patients to whom they initiated prescriptions for ChEIs.

Since κ_w is appropriate for categorical and ordinal responses, the responses to questions with continuous response options were categorized. Quartiles were used as

categories if the response values at each cut-off point were the same for both the original postal questionnaire and the short questionnaire. If not, then histograms of response values were compared between questionnaires to see where the data clustered, and either three or four response categories were created based on visual determination of the position and extent of the clustering. The intraclass correlation coefficient[224] could have been used to calculate test-retest reliability for questions with continuous response options. Instead, κ_w was used to have a consistent and comparable measure for all questions.

3.2.2. Physician Questionnaire - Statistical Analyses

3.2.2.1. Descriptive Analysis

Frequency distributions were used to describe the data derived from questions with categorical response options. Means, ranges, and standard deviations were calculated for questions with continuous response options. To clearly present the data that were collected, missing values were not imputed at the descriptive stage.

3.2.2.2. Regression Analysis

A quantitative method (i.e., regression analysis) was chosen as the optimal means of conducting the first investigation into the associations between physicians' and caregivers' efficacy requirements and the current use of ChEIs. A qualitative research method (e.g., consensus panel or focus group) would be an appropriate next step to help explain, in physicians' and caregivers' own words, the reasoning behind the direction of

the associations.[225]

3.2.2.2.1. Explanation of Variables

A total of 28 variables were considered for inclusion in the regression analyses. In some cases, variables were transformed prior to analysis. Each variable is briefly described below.

Proportion prescribed (dependent variable): The proportion of AD patients in a physician's practice for whom prescriptions for ChEIs have ever been initiated. The variable was created by dividing the percentage of AD patients for whom prescriptions were initiated (section 3, question 3a) by 100. Values can range from 0.0 to 1.0.

Index of favourable physician efficacy requirements for prescribing (main effect variable): This variable was defined based on an aggregation of responses to section 2, question 1a. Question 1a asks: "Assume Drug A has been shown to have a positive impact on any or all of the following areas: cognitive status, behaviour and mood, and/or the ability to perform basic activities of daily living. Taking each area separately, what is the minimum effect that you would require the drug to have on the average patient before you would consider prescribing the medication to your own patients? Please circle one choice per area." Choices (i.e., response options) identified by the letter 'a' in the question were given a value of 1, choices identified by the letter 'b' were given a value of 2, and choices identified by the letter 'c' were given a value of 3. For example, choice 'a' for cognitive status is 'To permanently stabilize the level of cognition.' This choice would be assigned a value of 1.

For each respondent, the values of the responses to all three sub-questions (i.e., cognitive status, behaviour and mood, and the ability to perform basic activities of daily living) were summed to obtain an index score that ranged from 3 to 9. Index scores were mean centred to enhance the numerical stability of the variable's estimated regression coefficient. Mean centring was performed by subtracting the mean value of the variable from each observed value of the variable. Higher scores on the mean centred index indicate more stringent efficacy requirements for prescribing a hypothetical new AD medication.

The requirements are defined as 'favourable' because the response options for each sub-question imply beneficial modifications to the course of disease (e.g., a permanent halt to further deterioration or a reversal of deterioration). The sub-questions are based on clinically relevant examples of treatment success.[103]

Index of physician efficacy requirements for prescribing - increased length of stabilization (main effect variable): This variable was defined based on an aggregation of responses to section 2, question 2a. Question 2a asks: "Assume Drug A does not halt or reverse the impact of Alzheimer's disease. Instead, the drug stabilizes the patient for a lengthened period of time, after which decline recommences. What is the minimum increase in length of stabilization that you would require in order to consider prescribing the medication to your patients? Please express your answers in months." The variable is considered as an index because the requirements for mild and moderate patients were elicited separately and then added together to obtain a single value. Higher values of the index indicate more stringent requirements for prescribing the hypothetical

medication. Requirements were not elicited for patients in the severe stage of AD because, at the time of data collection, no medication was approved for use in this group.

Sex (covariate): The sex of the respondent (section 4, question 1).

Age (covariate): The age of the respondent (section 4, question 2).

Total number of patients in a practice (covariate): The total number of patients in a physician's practice (section 4, question 5).

Total number of AD patients in a practice (covariate): The total number of AD patients in a physician's practice (section 4, question 6a).

Percentages of AD patients in a practice with mild, moderate, or severe disease (covariates): A separate variable for each disease state was created to reflect the distribution of AD patients by severity (section 4, question 7).

Level of knowledge regarding the efficacy of ChEIs (covariate): An aggregate of responses to section 3, question 7. The question asks: "How knowledgeable are you with respect to the efficacy of donepezil, rivastigmine, and galantamine?" Physicians were asked to provide separate responses for each medication. 'a' responses were given a value of 0, 'b' responses a value of 1, and 'c' responses a value of 2. For each physician, the values of all three responses were summed to obtain an index score that ranged from 0 to 6. Higher scores indicate more knowledge about the efficacy of ChEIs.

Prescribing indices - use of ChEIs to treat MCI or other dementias (covariates): The variables represent the extent to which physicians use ChEIs to treat MCI or

other forms of dementia. Initially, the variables (one for MCI and one for other forms of dementia) were continuous. A value of 0 indicated a physician did not prescribe ChEIs for the condition in question (section 3, response 'a' to questions 3b or 3c). In cases where ChEIs were prescribed, values between 1 and 100 represented the percentage of patients for whom prescriptions were initiated (section 3, response 'b' to questions 3b or 3c).

Preliminary analyses suggested the presence of a positive error correlation between these variables and the dependent variable. To avoid the possibility of introducing a bias away from the null, these variables were categorized as follows: 0=no patients are prescribed a ChEI; 1=between 1% and 99% of patients are prescribed a ChEI; 2=all patients are prescribed a ChEI.

Prescribing indices - other medications (covariates): Two variables are in this group, the first of which represents the percentage of prescriptions initiated for other medications that were used to treat AD (section 3, question 5). The second variable represents the percentage of patients to whom physicians suggested taking over-the-counter medications for AD-related problems (section 3, question 6). The variables were structured as indices in the same way as the covariates for prescribing ChEIs in MCI and other forms of dementia.

Adverse effects (covariates): For each ChEI, two adverse effects variables were created. The first variable was the percentage of patients who had an adverse effect that was related to the ChEI (section 3, question 4a). The second variable was the percentage of patients whose adverse effects were severe enough to lead to discontinuation of

treatment (section 3, question 4b). Values of 0% were entered when there were no adverse effects or discontinuations. Values of 0 were also entered when a medication was not prescribed.

To distinguish between the two different types of zero values, three dichotomous prescribing indicators were created. Each indicator pertained to a specific ChEI and was assigned a value of 0 when the drug was prescribed and a value of 1 when the drug was not prescribed. An indicator variable was included in regression models when one or both of the corresponding ChEI's adverse effects variables were also in the models.

Level of belief in the ability of ChEIs to meet the favourable efficacy requirements for prescribing (covariate): An aggregate of responses to the three parts of section 2, question 1b. The question asks: "Given your responses to question 1a above, how strongly do you believe existing Alzheimer's medications (i.e., donepezil, rivastigmine, galantamine) can meet your requirements? For each of the three areas below [cognitive status, behaviour and mood, ability to perform basic activities of daily living], please circle the number that best reflects your opinion." The responses to the three areas were summed to obtain a variable that ranged in score from 3 to 30. Scores were mean centred. Higher scores indicate physicians have stronger beliefs in the ability of ChEIs to meet their favourable efficacy requirements for a hypothetical new AD medication.

Level of belief in the ability of ChEIs to meet efficacy requirements for prescribing - increased length of stabilization (covariate): An aggregate of responses to the two parts of section 2, question 2b. The question asks: "Given your responses to question 2a above, how strongly do you believe existing Alzheimer's medications (i.e.,

donepezil, rivastigmine, galantamine) can meet your requirements? For each of the disease states below [mild AD, moderate AD], please circle the number that best reflects your opinion." The responses to each disease state were summed to obtain a variable that ranged in score from 2 to 20. Scores were mean centred. Higher scores indicate physicians have stronger beliefs in the ability of ChEIs to meet their minimum efficacy requirements for increased length of stabilization.

Physician's primary source of information on ChEIs (covariate): Physicians were given nine response options and asked to choose the one that best reflected their primary source of information on ChEIs. Response options were coded 1 through 9 (section 3, question 8).

Specialty (covariate): Physician specialty was obtained from the mailing lists and coded as follows: 0=GP, 1=geriatrician, 2=psychogeriatrician, 3=neurologist.

3.2.2.2.2. Model-building Procedure

Regression analysis was used to examine the hypothesis that more stringent efficacy requirements for prescribing a hypothetical new AD medication were associated with less current prescribing of ChEIs. Given the modest benefits of ChEIs, physicians who had strong treatment expectations were anticipated to be less likely to prescribe ChEIs.

The dependent variable was the proportion of AD patients for whom a physician initiated prescriptions for ChEIs (the 'proportion prescribed'). The dependent variable was assigned a weight of 1 in all regression analyses. This arrangement, called

a quasi-binomial model, was the best available model to fit to the data from the physician questionnaire. The quasi-binomial model is a generalized linear model (GLM) with a scaled Bernoulli variance function and a logit link. In SAS v8.2 statistical software, the quasi-binomial model was operationalized using the PROC LOGISTIC procedure and the 'events/trials syntax'. The 'events' portion was the proportion prescribed, and the 'trials' portion was always assigned the number 1.

Usually, a dependent variable such as the proportion of patients prescribed AD medications would be fitted using weights corresponding to practice size or to the number of AD patients in a practice. Such a model was investigated, but it was found to have a poorer fit than the model that was ultimately chosen. The poorer fit occurred because the proportions of patients prescribed AD medications were based on physician reports, rather than on an actual count of the numbers of patients through some mechanism such as a chart review. Therefore, the proportions did not display binomial behaviour. Other GLMs were fitted to the data, including an unweighted binomial regression with complementary log-log link and a GLM with a negative binomial error structure. However, these alternatives all demonstrated poorer fit to the data than the chosen GLM.

A set of regression models was built for each of the two main effect variables. The following steps were undertaken to construct the model sets. For each set, the objective was to build the best explanatory model of the association between physician efficacy requirements and the proportion prescribed.

- A simple regression analysis was performed for each main effect or covariate and the dependent variable.

- Covariates that had statistically significant associations with the dependent variable in the simple regression analyses were first assessed as potential effect modifiers of the association between physician requirements and the proportion prescribed. To be an effect modifier, the interaction term (covariate x main effect) had to be statistically significant at the 5% level in a model that also included the covariate, main effect, and dependent variable.

- All covariates that were found not to be effect modifiers were then assessed as potential confounders. Each potential confounder was added to a crude model containing only the main effect and the dependent variable. The covariate was considered a confounder if its addition to the crude model changed the odds ratio of the main effect by at least 10%.[226]

- An initial full model (i.e., model 1) was specified to include the main effect and all effect modifiers, confounders, and interaction terms.

- Since the interplay of different mixes of variables can have an impact on the main effect under study, a second full model (i.e., model 2) containing all of the independent variables was compared to model 1. A reduced model (i.e., model 3), composed of the variables that were retained in model 2, was compared to models 1 and 2.

- A stepwise regression analysis (i.e., model 4) was run, using the variables identified in model 2, to further account for the interplay between mixes of variables. Variables were selected for entry into the stepwise model if their estimated regression coefficients had p-values of ≤ 0.25. The p-value for retention in the stepwise model was also ≤ 0.25.[227] The main effect variable was forced into every model because the objective was to explain the association between the main effect and the dependent variable.

- The best explanatory model was selected using a two-step process. First, models 1 through 4 were checked to see which one provided the most precise estimate of the regression coefficient for the main effect variable (i.e., the estimate with the smallest standard error). Second, in cases where the decision was not clear cut because all of the standard errors were large, a new model was created that contained the main effect variable and any other covariate that demonstrated some importance in at least one of the four models. An important covariate could have been an effect modifier, a confounder, or a covariate that had a statistically significant association with the dependent variable. The model with the most precise estimate of the regression coefficient for the main effect variable was chosen as the best explanatory (i.e., final) model.

- Once the final model was chosen, outliers were identified using deviance residuals and influential observations were identified using differences in parameter estimates between the final model and a leave-one-observation-out model (delta-beta method).[227] Outliers and influential observations

were deleted and the final model was re-run to see if the estimated regression coefficient of the main effect variable would become more precise. If the standard error of the estimated coefficient decreased by at least 10%, then the outliers and influential observations would be excluded from the final model. Otherwise, all of the observations would be included in the model.

- The linearity of all continuous variables in the final model was assessed by grouping each such variable into quartiles and plotting the dependent variable logits for the quartile means against the quartile midpoints. The plots were examined for evidence of linearity. If a continuous variable was not linear, then squared, cubed, and categorical transformations were performed to improve model fit. Transformed versions of the variables were selected for inclusion in the model using the chi-square statistic at the 5% level of significance.

3.2.2.2.3. Missing Data and Multiple Imputation

The primary source of missing data in the questionnaire was item non-response. To address item non-response, the model-building procedure was carried out twice, once using listwise deletion and once using multiple imputation. Listwise deletion excludes observations that have missing data, even if the missing data are confined to a few variables. Most statistical software programs implement listwise deletion, despite the concomitant loss of power and the increased potential for biased regression coefficients.[228]

Conversely, multiple imputation[209] uses the available data to create a set of

plausible values that are substituted for the missing data. Relative to other methods of handling missing data, including listwise deletion, mean imputation, or hot deck imputation, multiple imputation preserves the entire data set and allows for the estimation of unbiased regression coefficients.[229;230] Multiple imputation also produces more precise approximations of the standard errors of estimated regression coefficients.[228;230]

In this thesis, multiple imputation was used as a diagnostic tool to examine if missing values had an undue influence on the regression analysis. Following the procedure outlined by Schimert et al.,[231] a conditional Gaussian model and a non-informative prior distribution were employed to create five imputed datasets, with 250 iterations between each dataset. The five datasets were analyzed separately and then combined to produce single summary results, which included average estimates of regression coefficients and standard errors for the independent variables. Analysis of the imputed datasets followed the steps outlined in Section 3.2.2.2.2 above. To assess the impact of the missing data, the results of the analysis with multiple imputation were compared to the results of the analysis with listwise deletion.

The missing data were assumed to be missing at random, which means the probability of a missing value does not depend on the value itself. An example would be missing values on age that occurred because respondents accidentally skipped the question. The data would not be missing at random if the missing values occurred because older respondents refused to state their ages. The missing at random assumption is not violated if missing values on one variable are dependent on the values of another variable. In practice, it is difficult or impossible to determine whether the data

are missing at random. However, multiple imputation has been shown to be quite robust even when the missing at random assumption is violated.[232]

Multiple imputation assumes the variables that have missing data are normally distributed. In this thesis, non-normal variables were not transformed because multiple imputation has also been shown to be robust to departures from normality.[210;233;234] Additionally, the algorithms of the conditional Gaussian model allow categorical variables to be treated in their original state, rather than as continuous or normal.[210]

3.2.2.3. Computer Software

SAS v8.2 (The SAS Institute, Cary, NC) was used to conduct the non-response bias, reliability, descriptive, and regression analyses. S-Plus v6.1 (Insightful Corporation, Seattle, WA) was used to impute the missing values.

The methods for collecting data in the physician study have been discussed in the above sections. Similar methods, presented below, were used to collect data in the caregiver study.

3.3. Caregiver Questionnaire

3.3.1. Caregiver Questionnaire - From Sample Selection and Design to Bias Assessment

3.3.1.1. Sample

The Alzheimer Society of Montréal (ASM) and the Alzheimer Groupe

Incorporated (AGI) provide advocacy and support services to caregivers and patients in metropolitan Montréal. Since these organizations are in direct contact with unpaid caregivers of AD patients, they were invited to help recruit caregivers for the study. The ASM and AGI compiled a combined list of 375 caregivers, all of whom participated in support group meetings over the two-year period immediately prior to the start of the study. These caregivers formed the study sample, and questionnaires (described in Section 3.3.1.2 below) were mailed to each person in the sample.

The study population was restricted to metropolitan Montréal for two reasons. First, there was no comprehensive regional or national caregiver roster from which to draw a sample. Organizations that do maintain lists of caregivers tend to be local in scope and heterogeneous in nature. Contacting such a collage of organizations and coordinating an inter-regional mass mailing would have imposed excessive time and cost constraints on the ability to conduct the caregiver portion of the thesis. Second, to guard the anonymity of caregivers, the ASM and the AGI insisted on conducting the questionnaire mailings themselves. Adequate supervision of the questionnaire's administration could not be guaranteed unless the researchers and organizations were in close geographic proximity to one another. Expanding the study population beyond metropolitan Montréal would have increased the difficulty of maintaining adequate quality control because other organizations would have also been likely to require that the mailings be conducted in-house.

As a result of the need to restrict the study population, 375 was the maximum number of caregivers who could be sent a questionnaire. If all 375 caregivers

were to respond, then an odds ratio of at least 1.30 would be detectable at 80% power and a 5% level of significance. If 300 caregivers were to respond, then an odds ratio of at least 1.40 would be detectable with the same power and level of significance. If 200 caregivers were to respond, then an odds ratio of at least 1.50 would be detectable at the aforementioned power and level of significance. These calculations assume a 50% probability of prescribing a ChEI at the mean value of a continuous main effect variable.

3.3.1.2. Development and Content

The first step in developing the caregiver questionnaire was to use the information from the literature to select possible question topics. The literature review, described in Chapter 2, was supplemented by the recommendations of the neuroepidemiologist and geriatrician who had reviewed the physician questionnaire. Question wording was again guided by the principles of questionnaire design.[211;212]

3.3.1.2.1. Pre-test

No one involved in the design or review of the questionnaire was a caregiver. Consequently, a formalized pre-test was needed to ensure that the final version of the questionnaire had relevant, clearly written questions and a visually pleasing appearance.

The pre-test method was based on cognitive interviewing and consensus panels. Cognitive interviewing is a terminology that refers to a large spectrum of data collection methods.[235] For the purpose of this thesis, cognitive interviewing was operationalized as the use of one-on-one interviews to ask participants about the meaning and clarity of survey questions. Participants could also suggest question modifications,

additions, or deletions. This feedback is intended to create more 'user-friendly' surveys, which are designed to reduce the number of unanswered questions and raise overall response rates.[198] The interview procedure can be concurrent, where participants describe their thoughts to the interviewer as they answer each survey question. The concurrent approach is often called a 'think aloud'. The interview procedure can also be retrospective, where the interviewer asks participants a series of probes after the entire questionnaire is completed. Cognitive interviewing has been shown to be appropriate for pre-testing questionnaires about new or poorly understood healthcare issues.[236-240] Caregiver expectations from AD drug treatments clearly falls into this category.

However, there are challenges associated with cognitive interviewing. The process can be time consuming and expensive, and results are not generalizable. Additionally, feedback is limited to what participants are willing to share. Finally, in retrospective cognitive interviewing, participants may not remember if they had problems with one or more questions.[238;241;242] Nevertheless, for the pre-test of the caregiver questionnaire, the disadvantages of cognitive interviewing were outweighed by the ability to probe caregivers and get direct feedback about question topics and wording, as well as overall questionnaire design.

To amplify the benefits of caregiver feedback through cognitive interviewing, the pre-test was organized around group interviews rather than through one-on-one interviews. Group interviews can lead to more insights than one-on-one interviews. As well, the group can help to identify extreme individual viewpoints and validate diverse individual viewpoints.[243]

The 'consensus panel' was judged to be the most suitable structure for conducting cognitive interviewing in a group setting. Consensus panels are similar to focus groups, as both are led by trained moderators who direct the activities of approximately six to eight participants. However, with respect to group interaction and tangential discussions, consensus panels are much more structured, formal, and limiting than focus groups. There is room for some group discussion in a consensus panel, but the moderator maintains strict control by using prepared topics or questions to guide the group.[244]

Conversely, focus groups are designed to seek a broad range of ideas around an open-ended topic. Therefore, moderators facilitate free discussion among group members.[225] Focus groups are suitable for generating initial conceptual approaches to a research topic, but they are too open-ended to provide feedback on a survey.

To pre-test the caregiver questionnaire, an experienced moderator was engaged to direct five pre-test groups using a prepared script. The script consisted of several probes (Table 3.1) that were designed to elicit group participants' viewpoints about the questionnaire. The probes were based on the cognitive interviewing literature.[235;245]

Pre-test group participants were chosen from AD caregivers attending support group meetings offered by the ASM or the AGI. Other research studies[246;246-249;249;250;250] in AD or dementia have also recruited caregivers from support groups.

The following procedure was used to assemble the pre-test groups:

- Leaders of support groups from the ASM and the AGI first provided

caregivers in their support groups with oral and written descriptions of the study and asked for volunteers.

- Forty caregivers (eight caregivers for each of five pre-test groups – four English speaking and one French speaking) were randomly selected from the total number of volunteers.

- Randomly selected caregivers provided days and times for which they were available. This information was used to schedule the group meetings and assign each caregiver to a specific meeting. Caregivers were telephoned two weeks prior to the meeting that they were asked to attend.

Table 3.1: Probes Used in the Caregiver Pre-test Groups

Type of Probe	Probe
General Probes (Apply to the survey as a whole, or to specific sections of the survey.)	1) Did you understand how to answer the questions? 2a) Was it clear whether you were supposed to answer part A, part B, or part C in section 2? 2b) Was it clear where to find the part you were supposed to answer? 3) Was the size of the print too big or too small? 4) Was there enough space between questions, or was everything 'bunched up'? 5) What did you think of the picture on the front? 6) Can you suggest something else that may be appropriate to put on the front (e.g., another picture)? 7) Did the questionnaire leave something out that you felt was important?
Multiple Question Probes (The same probe was used for more than one question.)	1) What, in your own words, did this question mean to you? 2) Did the answer choices include your answer?

Table 3.1: Probes Used in the Caregiver Pre-test Groups (continued)

Type of Probe	Probe
Specific Question Probes (The probe was used for only one question.)	1) What do you think we mean by "average annual income from all sources"? 2) Did you know the month and year of birth of the person under your care? 3) Were you able to estimate the average hours per week over the past three months that you devoted to caregiving? 4a) Was this a question that you felt uncomfortable answering? (The question asked: In the past 3 months, have you discussed the possibility of institutionalizing the person under your care with that person's doctor and/or relatives?) 4b) Would you keep the question in the questionnaire? 5) Are there other expectations that you may have for an Alzheimer's disease drug? 6) Should other side-effects be mentioned in this question? 7) Did you have trouble remembering back 12 months to answer the question about non-prescription drug use? 8) Is the question on prescribing cholinesterase inhibitors presented in a way that is easy to read?

- Reminder letters were mailed to participants approximately eight days before their meetings, and reminder phone calls were made one to two days in advance of the meetings.

Eight caregivers were chosen per group to increase the probability that at least six or seven would attend the meeting. According to the qualitative research literature, a group of six or seven participants is properly sized to allow for the expression of a variety of opinions without becoming disorderly or fragmented.[251]

The pre-test groups were held in meeting rooms on the premises of the ASM or

AGI. The moderator began each meeting with an explanation of the purpose of the pre-test. Caregivers were given copies of the questionnaire and asked to take 15 minutes to independently answer the questions. Once the questionnaires were completed, the moderator read the probes aloud and asked everyone to respond. Quieter caregivers were prompted for comments, and overly active caregivers were asked to give everyone a chance to speak. When diverse opinion existed about a probe, group discussion was encouraged to generate as many comments as possible.

The meetings were audio recorded to capture caregivers' comments in their own words. After considering each comment, one of three possible actions was taken: (1) no incorporation of the comment into the questionnaire; (2) incorporation leading to a minor modification of the questionnaire (e.g., reformulation of question wording, addition or deletion of response options, changing the font); or (3) incorporation leading to a major modification (e.g., addition/deletion of a question).

The first set of English speaking pre-test groups provided input on the first draft of the questionnaire, which was revised in accordance with group members' comments. The revised draft was presented to the second set of English speaking groups and further input was obtained to develop the final English version of the questionnaire. For each set of groups, one group was conducted at the ASM and the other group was conducted at the AGI.

A French speaking pre-test group was only held at the ASM since the AGI serves an exclusively English speaking clientele. The French speaking group received a translated version of the draft questionnaire that was used in the first set of

English speaking groups. The French speaking group was conducted in the same manner as the English groups.

Comments from the English and French pre-test groups were incorporated into the final English and French versions of the questionnaire. The final versions were inspected side-by-side to ensure harmonious translation. Care was taken to incorporate the French speaking group's comments on questionnaire translation into the final French version of the questionnaire.

3.3.1.2.2. Content

The final English and French questionnaires were comprised of two sections (Appendix F). The first section elicited information about the characteristics of caregivers and their loved ones with AD (e.g., age, sex). This section also contained questions about the caregiving experience. The second section asked caregivers about their attitudes and perceptions toward drug treatments for AD. Questions included the level of satisfaction with ChEIs, the use of medications for patient memory loss, loss of speech, or loss of independence, and the willingness to have patients continue on AD medications in the event of adverse effects. All questions were closed-ended.

3.3.1.3. Implementation

The caregiver questionnaire was implemented in a similar manner to the physician questionnaire (Section 3.2.1.3). The same colour of paper, use of logos, contents of a questionnaire package, and type of stamps were used. However, to strike a balance between reducing non-response and respecting the stressful and busy

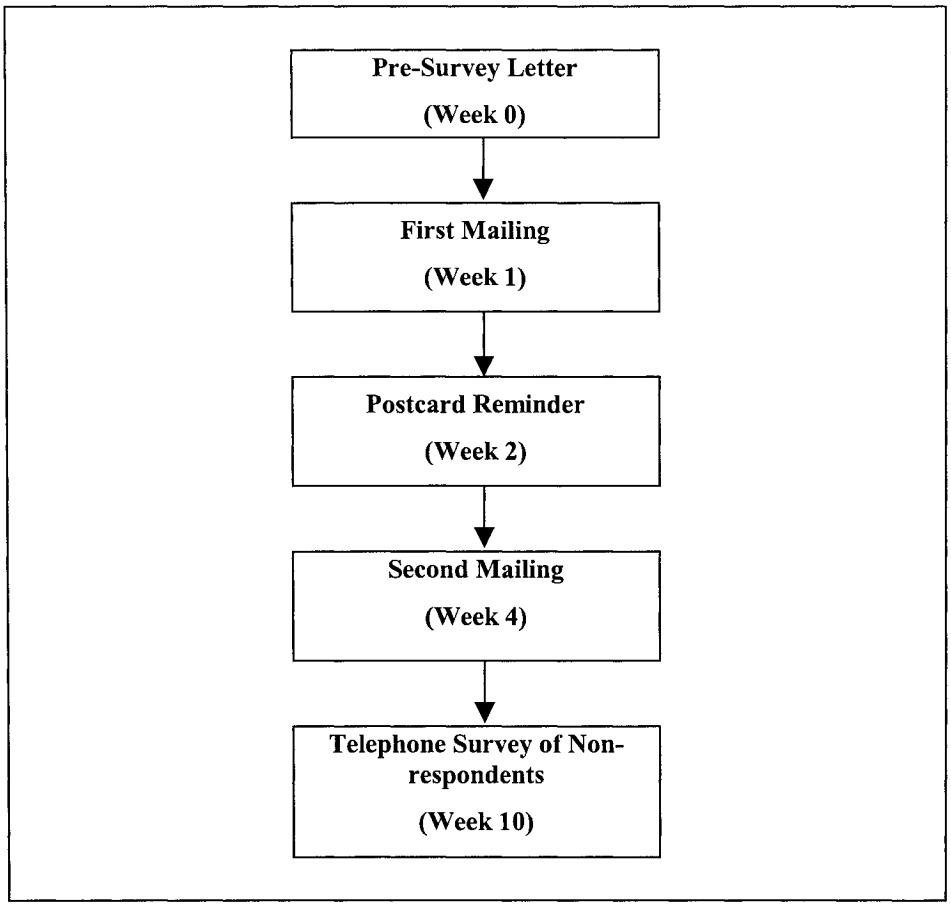
lives of persons who care for AD patients, five contacts (Figure 3.2) instead of six were employed over the course of the questionnaire's administration. The first contact was a 'pre-survey' letter that contained an explanation of the survey and an invitation to participate. One week later, questionnaire packages were mailed to the caregivers. Follow-ups of non-respondents included a postcard reminder that was sent two weeks after the pre-survey letter and a second questionnaire package that was sent four weeks after the pre-survey letter. A telephone follow-up of non-respondents was conducted ten weeks after the pre-survey letter (Appendix G). The third contact was a postcard reminder rather than a questionnaire package because a higher response rate can sometimes occur if the type of reminder is different from earlier contacts.[198] All contacts took place between July and September of 2003.

As a condition of participating in the research, the ASM and AGI insisted on maintaining the complete anonymity of caregivers. To this end, both organizations compiled lists of caregivers internally and assigned unique study identification numbers to the caregivers. The numbers were written on the questionnaires. At no time were the names of caregivers divulged to researchers. All survey materials were printed, collated, and mailed from the premises of the ASM or AGI. Caregivers were asked to use the pre-addressed, pre-stamped envelopes to return the questionnaires directly to the Centre for Clinical Epidemiology and Community Studies (CCECS) of the Jewish General Hospital. Caregiver addresses were not put on the return envelopes.

Upon receipt of a questionnaire at the CCECS, the identification number was communicated to the ASM or AGI. An employee of the ASM or AGI removed

the corresponding caregiver name from the mailing list. This process preserved the anonymity of caregivers and prevented caregivers from receiving follow-up material after returning a questionnaire.

Figure 3.2: Steps in the Administration of the Caregiver Questionnaire



Instructions on the cover letters directed the caregivers to tick off a box on the cover of the questionnaire if they did not wish to participate. The caregivers were then asked to return the blank questionnaire.

Caregivers who were not caring for an AD patient, or who were no longer providing care because the patient was deceased, were not expected to participate. These

caregivers were asked to tick off a box pertaining to their situation and to return the blank questionnaire.

3.3.1.4. Non-response Bias

3.3.1.4.1. Characteristics of Caregivers

Non-response bias was assessed by comparing the characteristics of caregivers who responded to the questionnaire with the characteristics of caregivers in the Canadian Study of Health and Aging (CSHA). The CSHA is a longitudinal study designed to provide information on the prevalence and incidence of dementia in Canada. A total of 10,263 community-dwelling or institutionalized persons aged 65 or over were representatively sampled from 36 communities across the country.[252] Data collection was performed at baseline (1991-1992), in 1996, and again in 2001. The study also investigated the burden of dementia on caregivers. Please visit http://www.csha.ca/about_study.asp for more information about the CSHA. The CSHA dataset was accessed through Dr. Christina Wolfson, who is the contact principal investigator for the Montréal site of the CSHA.

The last CSHA dataset, compiled after the final phase of data collection in 2001, contained 332 caregiver variables for a nation-wide cohort of 1,137 informal caregivers of community-dwelling CSHA study subjects. The variables covered a wide range of areas, including age and sex. Due to the national, weighted, stratified procedure that was used to recruit the CSHA study subjects,[252] the 1,137 caregivers closely approximated a group of Canadian caregivers of persons with dementia.

Fourteen variables that were available in the CSHA dataset were selected for this analysis because they were similar to variables that were available in the postal questionnaire. Five of the 14 variables were: caregiver sex, caregiver lives in the same house as the person with AD, caregiver health, positive aspects of caregiving, and household income. The nine other variables pertained to the amount of help patients required from caregivers in the following areas: eating, dressing, getting in and out of bed, taking baths and showers, using the toilet, using the telephone, preparing meals, doing housework, and taking medications. Fisher's exact test was used to compare the responses of the CSHA caregivers with the responses of the caregivers who participated in the current study.

3.3.1.4.2. Actual Questionnaire Responses

Non-response bias was also assessed by comparing the actual questionnaire responses of respondents to non-respondents and early respondents to late respondents. For respondents versus non-respondents, a sample of caregivers who did not return the questionnaire was randomly selected to participate in a telephone survey. The ASM and AGI compiled separate mailing lists of these caregivers. The lists were arranged alphabetically and numbered sequentially starting at 1. R v1.8.1 was used to select a random sample of 25 caregivers from the ASM list and 25 caregivers from the AGI list.

Calls to the 50 caregivers were placed from the offices of the ASM or AGI during daytime hours. Caregivers were asked to answer some of the more substantive questions from the original postal questionnaire (Appendix G). A prepared script that contained speaking points governed the conduct of the telephone survey (Appendix G).

Answers to the telephone survey were compared with answers to the postal questionnaire.

For both the respondent versus non-respondent and early respondent versus late respondent comparisons, answers to questions with categorical response options were compared using Fisher's exact test. Answers to questions with continuous response options were compared using the Wilcoxon rank sum test. All tests were two-tailed since the objective was to assess the presence of non-response bias by examining whether the answers provided by respondents and non-respondents were similar or dissimilar to one another. The level of significance was set at the 5% level.

3.3.1.5. Social Desirability Bias

To counter the potential for social desirability bias, the caregiver questionnaire was designed to be self-administered. Additionally, the questionnaire was introduced by a cover letter (Appendix F) that highlighted the importance of the data being collected. In the cover letter, caregivers were told their responses would help to guide the development and assessment of new AD medications.

3.3.1.6. Reliability

The test-retest reliability of the caregiver questionnaire was assessed by sending a shorter version of the questionnaire (Appendix H) to a random sample of 60 respondents. The sample was drawn as described in Section 3.2.1.6, although 30 respondents were selected from each of two lists. The first list contained all respondents who were initially recruited by the ASM and the second list contained all respondents who were initially

recruited by the AGI.

The short questionnaire and a cover letter (Appendix I) were mailed seven weeks after the final mailing of the original postal questionnaire. There was no attempt to conduct a follow-up mailing out of respect for the already heavy demands of caregiving.

The measure of test-retest reliability was the κ_w. For questions that were broken down into sub-questions, a separate κ_w was calculated for each sub-question.

3.3.2. Caregiver Questionnaire - Statistical Analyses

3.3.2.1. Descriptive Analysis

For the caregiver questionnaire, the descriptive analysis was the same as for the physician questionnaire (Section 3.2.2.1).

3.3.2.2. Regression Analysis

3.3.2.2.1. Explanation of Variables

A total of 16 variables were considered for inclusion in the regression analyses. In some cases, variables were transformed prior to analysis. Each variable is briefly described below.

Patient currently prescribed a ChEI (dependent variable): Caregivers were asked whether the AD patient for whom they were caring was currently being prescribed a ChEI. Three response options were available: yes, no, or do not know (section 2, question 18). The

'do not know' responses (n=4) were subsequently re-coded 'no.'

Index of caregiver requirements for improvements to domains affected by AD (main effect variable): Caregivers were asked to assume the AD patients for whom they were caring could be treated with a hypothetical new AD drug. Fifteen domains that are affected by AD were specified in the question. Caregivers were asked to rate the level of improvement that they would require in each domain before allowing their loved ones to start taking the new drug (section 2, questions 23, 32, 44). Response options were: not applicable (score=0), no improvement, but stabilization (score=1), fair improvement (score=2), good improvement (score=3), and excellent improvement (score=4).

Caregiver levels of importance for greater delays to institutionalization (main effect variable): Caregivers were again asked to assume the AD patients for whom they were caring could be treated with a hypothetical new AD drug. Caregivers were told the drug could delay the need to place loved ones in nursing homes. As a prelude to allowing patients to start taking the drug, caregivers were asked about the level of importance that they would attach to several different delays in nursing home placement, i.e., 1 to 6 months, 6 to 12 months, 1 to 2 years, and more than 2 years. For each delay, caregivers ranked the level of importance on a three-point scale: not at all important, somewhat important, very important (section 2, questions 24, 33, 45). A separate main effect variable for each delay was used in the regression modeling process.

Caregivers' willingness to accept adverse effects (main effect variable): Unlike the previous two main effect variables, caregivers were asked to assume patients were currently taking an AD medication. The medication could be either

hypothetical or real. A list of 11 common adverse effects was presented in the questionnaire. Caregivers were directed to indicate their willingness to have patients continue on drug treatment in the event that any one of the listed adverse effects occurred (section 2, questions 25, 34, 46). Three response categories were provided: not willing to continue treatment (score=1), somewhat willing to continue treatment (score=2), clearly willing to continue treatment (score=3). For nine of the 11 adverse effects, fewer than 10% of respondents fell into the 'clearly willing to continue treatment' category. Therefore, for regression analyses, the 'somewhat willing to continue treatment' and 'clearly willing to continue treatment' categories were combined into one category, which was called 'willing to continue treatment.'

Caregiver-physician discussions about drug treatments for AD (main effect variable): Caregivers were asked to indicate who first talked about the possibility of using a ChEI to treat AD. Four possible response options were provided: caregiver, doctor, someone else, do not remember. A space was given to allow caregivers selecting the 'someone else' response to indicate whether the person was a relative, friend, health care professional, etc. (section 2, questions 19, 29, 39b). Due to small numbers of responses in some categories, responses in the 'caregiver,' 'someone else', and 'do not remember' categories were combined into a single category for all regression analyses.

Caregiver pressure on physicians to prescribe AD medications (main effect variable): Caregivers were asked if they had ever put pressure on physicians to prescribe AD medications. The response option was dichotomous: yes or no (section 2, questions 22, 35, 40).

Non-prescription drugs for memory loss (covariate): Caregivers were asked if they had ever given AD patients non-prescription drugs such as vitamins to help overcome memory loss. The response option was dichotomous: yes or no (section 2, questions 26, 36, 47).

Non-prescription drugs for loss of speech (covariate): Caregivers were asked if they had ever given AD patients non-prescription drugs such as vitamins to help overcome loss of speech. The response option was dichotomous: yes or no (section 2, questions 26, 36, 47).

Non-prescription drugs for loss of independence (covariate): Caregivers were asked if they had ever given AD patients non-prescription drugs such as vitamins to help overcome loss of independence. The response option was dichotomous: yes or no (section 2, questions 26, 36, 47).

How informed is the caregiver about what drugs can do to treat AD? (covariate): Caregivers were asked: At the present time, how informed do you feel about what drugs can do to help treat AD? One of four responses could be chosen: well informed, somewhat informed, poorly informed, not at all informed (section 2, questions 28, 38, 42). Due to small numbers of responses in the 'poorly informed' and 'not at all informed' categories, these two categories were combined into one for all regression analyses.

Caregiver sex (covariate): The sex of the caregiver (section 1, question 1).

Caregiver age (covariate): The age of the caregiver (calculated from section 1, question 2). Calculated ages were minimum centred to address a problem of large regression coefficients and standard errors in some of the regression analyses. Minimum centring involved subtracting the lowest age (i.e., 18) from the age of each caregiver.

Caregiver overall physical health at the present time (covariate): Caregivers were asked to describe their overall physical health at the present time. Five possible responses were available: excellent, very good, good, fair, poor (section 1, question 5). 'Fair' and 'poor' responses were combined into one category for all regression analyses because of a small number of responses in the 'poor' category.

Sex of person for whom care is being provided (covariate): Sex of AD patient under caregiver supervision (section 1, question 6).

Age of person for whom care is being provided (covariate): Age of AD patient under caregiver supervision (section 1, question 7). The variable was minimum centred in the same manner, and for the reason, as caregiver age. The minimum age for centring was 56.

Primary caregiver (covariate): Is the caregiver the patient's primary caregiver? Dichotomous response - yes or no (section 1, question 11).

3.3.2.2.2. Model-building Procedure

Logistic regression was used to examine the following hypotheses: (1) more stringent caregiver requirements for improvements to domains that are affected by AD

are negatively associated with the current prescribing of ChEIs; (2) greater levels of importance attached by caregivers to delays to institutionalization are negatively associated with the current prescribing of ChEIs; (3) an increased willingness by caregivers to accept adverse effects is positively associated with the current prescribing of ChEIs; and (4) physician-initiated discussions about the use of drug therapy, as well as caregiver pressure on physicians to prescribe ChEIs, are positively associated with the current prescribing of ChEIs.

Goodness-of-fit assessments using the Hosmer-Lemeshow test, Pearson residuals, and deviance residuals indicated logistic regression models provided the best fit to the data. An examination of residual plots also demonstrated the appropriateness of logistic regression models. Due to the good fit of the logistic model, it was not necessary to estimate a dispersion parameter.

One set of models was constructed for each hypothesis. Model building was governed by the steps that were enumerated in Section 3.2.2.2.2. In brief, the steps were:

- A simple logistic regression analysis was conducted for each main effect variable or covariate and the dependent variable.
- Effect modification was assessed for covariates that had statistically significant associations with the dependent variable in the simple logistic regression analyses.
- Confounding was assessed for covariates that had statistically significant associations with the dependent variable in the simple logistic regression

analyses, but that were not effect modifiers.

- An initial full model (i.e., model 1) was built. The model contained the main effect variable and any relevant covariates (i.e., effect modifiers, confounders, and interaction terms).
- Other models were constructed and compared to one another and model 1, including:
    - A second full model (i.e., model 2) containing all independent variables;
    - A reduced model (i.e., model 3) composed only of the variables that were statistically significant in model 2;
    - A stepwise regression analysis (i.e., model 4) that was run on the variables in model 2; and
    - If necessary, a model that contained the main effect variable and any other covariate(s) that demonstrated some importance in at least one of the aforementioned four models.
- The best explanatory model was the model with the most precise estimate of the regression coefficient for the main effect variable (i.e., the estimate with the smallest standard error).
- The impact of deleting potential outliers and influential observations from the best explanatory model was examined.
- Linearity was assessed for all continuous variables in the best explanatory model.

3.3.2.2.3. Missing Data and Multiple Imputation

The primary source of missing data in the caregiver questionnaire was item non-response. To address this issue, the model-building procedure was carried out twice, once using listwise deletion and once using multiple imputation. Essentially, the rationale and use of multiple imputation were the same for both questionnaires. Please refer to Section 3.2.2.2.3 for an explanation of how multiple imputation was used in questionnaire analyses.

3.3.2.3. Computer Software

SAS v8.2 was used to conduct the non-response bias, reliability, descriptive, and logistic regression analyses. S-Plus v6.1 was used to impute the missing values.

4. RESULTS

This chapter contains the results of the physician and caregiver studies. The findings from the analysis of the physician questionnaire are presented first and include information on response rate, respondent characteristics, non-response bias, test-retest reliability, distribution of responses, and inferential statistical analyses. The findings from the caregiver questionnaire are presented second and in the same order.

4.1. Physician Questionnaire

4.1.1. Response Rate

The response rate to the physician questionnaire was 35.4%. The breakdown of the response rate according to physician specialty is presented in Table 4.1.

Table 4.1: Physician Questionnaire - Breakdown of Responses by Physician Specialty and Calculation of Response Rate

Response Category	**Geriatricians** n (%)	**Neurologists** n (%)	**Psychogeriat-ricians** n (%)	**General Practitioners** n (%)	**Other*** n (%)	**Overall** n (%)
Respondents	28 (57)	49 (23)	27 (51)	128 (26)	1 (100)	233 (29)
Non-respondents	10 (20)	86 (40)	15 (29)	171 (35)	0 (0)	281 (35)
Does not see AD patients	4 (8)	37 (17)	5 (10)	91 (19)	0 (0)	137 (17)
Does not wish to participate	6 (12)	42 (20)	5 (10)	91 (19)	0 (0)	144 (18)

Table 4.1: Physician Questionnaire - Breakdown of Responses by Physician Specialty and Calculation of Response Rate (continued)

Response Category	Geriatricians n (%)	Neurologists n (%)	Psychogeriat-ricians n (%)	General Practitioners n (%)	Other* n (%)	Overall n (%)
Invalid postal address	1 (2)	1 (<1)	1 (<1)	5 (1)	0 (0)	8 (1)
TOTAL	49 (99)†	215 (100)	53 (100)	486 (100)	0 (0)	803 (100)

RESPONSE RATE=35.4%

(233/233+281+144)=0.354

The calculation of the response rate excluded physicians who did not see AD patients or whose postal addresses were invalid.

*One respondent removed the unique study identification number from the questionnaire, thus rendering it impossible to determine his or her specialty.

†Percentage does not total 100 due to rounding error.

Notes: AD = Alzheimer's disease.

Overall, 233 completed questionnaires were received between weeks 1 through 7. Of these, 95 were received between the first and second mailings (weeks 1 through 4) and 82 were received between the second and third mailings (weeks 4 through 7). By the scheduled time of the telephone reminder (week 6), 26% (208/803) of the physicians had returned a completed or blank questionnaire. Attempts were made to phone the remaining 595 physicians and remind them about the survey. During the one week that was allotted to the telephone reminder, calls were placed to all of the geriatricians, psychogeriatricians, and neurologists who had not yet responded, as well as to all of the non-respondent GPs who had taken continuing medical education courses on the elderly (n=141). A total of 348 physicians (58% of 595) were telephoned during the allotted week, yielding an additional 56 completed questionnaires. Two hundred

forty-seven physicians, all of whom were GPs who did not take the courses, could not be telephoned during the allotted week.

4.1.2. Respondent Characteristics

Table 4.2 shows the characteristics of the 233 physicians who returned a completed questionnaire. The majority of physicians were male, their average age was 46 years, they lived in urban areas, and they were French speaking. Almost half of the physicians practiced in university-affiliated hospitals, one-quarter practiced in non-university-affiliated hospitals, and one-third had solo practices. Many physicians practiced in more than one location. Physicians reported obtaining their medical licenses in Québec an average of 20 years ago. The number of patients in physicians' practices, both overall and with AD, was highly variable. There was an average of about 1,000 patients in each practice, with the mean number of AD patients being substantially less at 57. Half of the AD patients were reported to be at the mild stage of disease, one-third at the moderate stage, and the remainder at the severe stage.

Table 4.2: Characteristics of Respondents to the Physician Questionnaire

Characteristic	n (%)
Sex	
Male	142 (61)
Female	90 (39)
Missing	1 (<1)
Age	mean=46, SD=10; median=46, range=26-79

Table 4.2: Characteristics of Respondents to the Physician Questionnaire (continued)

Characteristic	n (%)
Specialty	
Geriatrician	28 (12)
Psychogeriatrician	49 (21)
Neurologist	27 (12)
GP	128 (55)
Missing	1 (<1)
Place of Residence	
Urban	203 (87)
Rural	29 (12)
Missing	1 (<1)
Language	
French	210 (90)
English	23 (10)
Practice Settings*	
University-affiliated hospital	98 (42)
A hospital not affiliated with a university	55 (24)
CLSC	46 (20)
Solo practice	84 (36)
Same discipline group practice	18 (8)
Multi-discipline group practice	18 (8)
University-affiliated office-based practice	11 (5)
Ward or emergency work in a hospital (either university-affiliated or not)	29 (12)
Other	49 (21)
Years since obtaining a medical license in Québec	mean=20, SD=10; median=20, range=4-53 (n=43 missing)
Total Patients in Practice	mean=1034, SD=1240; median=500, range=8-8000 (n=36 missing)
Total Number of AD Patients in Practice	mean=57, SD=89; median=30, range=0-700 (n=12 missing)
% of Patients with Mild AD	mean=51, SD=24; median=50, range=0-100 (n=9 missing)
% of Patients with Moderate AD	mean=34, SD=17; median=30, range=0-100 (n=9 missing)
% of Patients with Severe AD	mean=15, SD=17; median=10, range=0-100 (n=9 missing)

*Physicians were permitted to select all categories that applied to them. The percentage of physicians who selected each category is shown in the table.

Notes: SD = standard deviation, GP = general practitioner, CLSC = *centre local de services communautaires* (local community services centre), AD = Alzheimer's disease.

4.1.3. Non-response Bias

4.1.3.1. Characteristics of Respondents versus Non-respondents

Four hundred twenty-five physicians were classified as non-respondents. This group included physicians who returned the questionnaire and indicated that they did not wish to participate, as well as physicians who did not respond at all (Table 4.1). The characteristics of respondents versus non-respondents were compared to help assess potential non-response bias. The distribution of only one characteristic (i.e., physician specialty) differed between the two groups (Table 4.3). A greater proportion of geriatricians and psychogeriatricians responded, while a greater proportion of neurologists and GPs did not respond.

Table 4.3: Non-response Bias - Comparison of Characteristics of Respondents versus Non-Respondents

Characteristic	**Respondents** n (%) Total: n=233	**Non-respondents** n (%) Total: n=425	**p-value**
Sex			0.0822†
Male	142 (61)	273 (64)	
Female	90 (39)	127 (30)	
Missing*	1 (<1)	25 (6)	
Specialty			<0.0001†
Geriatrician	28 (12)	16 (4)	
Psychogeriatrician	49 (21)	19 (4)	
Neurologist	27 (12)	128 (30)	
GP	128 (55)	262 (62)	
Missing*	1 (<1)	0 (0)	
Place of Residence			0.9033†
Urban	203 (87)	369 (87)	
Rural	29 (12)	56 (13)	
Missing*	1 (<1)	0 (0)	

Table 4.3: Non-response Bias - Comparison of Characteristics of Respondents versus Non-Respondents (continued)

Characteristic	Respondents n (%) Total: n=233	Non-respondents n (%) Total: n=425	p-value
Language			0.8901†
French	210 (90)	385 (91)	
English	23 (10)	40 (9)	
Missing*	0 (0)	0 (0)	
Years since obtaining a medical license in Québec	median=20, range=4-53 (n=38 missing*)	median=22, range=4-55 (n=126 missing*)	0.9183‡

*Missing values are not included in the computation of p-values.

†Fisher's exact test.

‡Wilcoxon rank sum test.

Notes: GP = general practitioner, SD = standard deviation.

4.1.3.2. Characteristics of Early Respondents versus Late Respondents

During the course of data collection, the time of receipt of questionnaires was monitored so that respondents could be classified as 'early' or 'late' respondents. Early respondents returned a completed questionnaire after the first mailing, while late respondents returned a completed questionnaire after the second or third mailing. The characteristics of early respondents versus late respondents were compared as another way to examine potential non-response bias. There were no statistically significant differences, although geriatricians, psychogeriatricians, and neurologists tended to respond early, while GPs tended to respond late (Table 4.4).

Table 4.4: Non-response Bias - Comparison of Characteristics of Early Respondents versus Late Respondents

Characteristic	Early Respondents n (%) Total: n=95	Late Respondents n (%) Total: n=138	p-value
Sex			1.0000†
Male	58 (61)	84 (61)	
Female	37 (39)	53 (39)	
Missing*	0 (0)	1 (<1)	
Specialty			0.1814†
Geriatrician	13 (14)	15 (11)	
Psychogeriatrician	22 (23)	27 (20)	
Neurologist	15 (16)	12 (9)	
GP	45 (47)	83 (61)	
Missing*	0 (0)	1 (<1)	
Place of Residence			0.8408†
Urban	84 (88)	119 (87)	
Rural	11 (12)	18 (13)	
Missing*	0 (0)	1 (<1)	
Language			0.6568†
French	87 (92)	123 (89)	
English	8 (8)	15 (11)	
Missing*	0 (0)	0 (0)	
Years since obtaining a medical license in Québec	median=20, range=4-53 (n=13 missing*)	median=20, range=4-47 (n=25 missing*)	0.8868‡

*Missing values are not included in the computation of p-values.

†Fisher's exact test.

‡Wilcoxon rank sum test.

Notes: GP = general practitioner, SD = standard deviation.

4.1.3.3. Responses to Questions - Respondents versus Non-respondents

Telephone interviews were conducted to assess whether respondents and non-respondents differed in their answers to the physician questionnaire. Randomly selected non-respondents were asked to answer 30 questions from the questionnaire

(Appendix C). The intent was to compare these answers to the answers of respondents. One hundred out of the 281 non-respondents (36%) who did not return a questionnaire were selected to be interviewed. The 144 physicians who returned a questionnaire and indicated that they did not wish to participate were not contacted for this assessment.

Only five of the 100 non-respondents were successfully interviewed. The other 95 were unreachable by phone or unwilling to participate. Given the small number of interviewees, this assessment of non-response bias did not yield informative results.

4.1.3.4. Responses to Questions - Early Respondents versus Late Respondents

For all of the questions in the physician questionnaire, the responses of early respondents were compared to the responses of late respondents. Statistically significant differences were found for only two questions: the extent to which a physician's familiarity with the patient would influence the decision to prescribe an AD medication and the minimum improvement in cognitive status that physicians would require before prescribing a hypothetical new AD medication. Familiarity appeared more likely to influence early respondents than late respondents ($p=0.038$). As well, early respondents appeared to require more stringent improvements to cognitive status than late respondents ($p=0.005$). However, given the number of questions that were compared, one might expect to find at least two statistically significant differences even if the null hypothesis were true.

4.1.3.5. Conclusion – Assessment of Non-Response Bias

There were few identifiable differences between respondents and non-respondents, or between early respondents and late respondents. Thus, there is little reason to believe that non-response bias has a major impact on the overall results of the physician study. However, the possibility of bias cannot be ruled out entirely. Two factors prevented a more thorough assessment of bias: (1) the low level of participation in the telephone interview and (2) the fact that 144 physicians could not be contacted, for ethical reasons, after expressly declining participation.

4.1.4. Test-retest Reliability

To assess the test-retest reliability of the physician questionnaire, a shorter version of the questionnaire (Appendix D) was mailed to a random sample of 100 respondents. The short questionnaire was posted five weeks after the third and final mailing of the original questionnaire. Seventy of these short questionnaires were returned within an 8-week waiting period. κ_ws, which were estimated to examine the agreement between responses to the original and short questionnaires, are shown in Table 4.5.

Table 4.5: Physician Questionnaire – Weighted Kappas for Test-retest Reliability

Questions on the Short Reliability Questionnaire	Weighted Kappa (95% CI)
Patient overall health status*	0.44 (0.25 to 0.64)
Patient's age*	0.55 (0.42 to 0.67)
Patient's current medication use*	0.34 (0.17 to 0.50)

Table 4.5: Physician Questionnaire – Weighted Kappas for Test-retest Reliability (continued)

Questions on the Short Reliability Questionnaire	Weighted Kappa (95% CI)
Patient lives in a nursing home*	0.45 (0.29 to 0.61)
Patient lives at home*	0.42 (0.25 to 0.59)
Past patient compliance to medication regimens*	0.34 (0.18 to 0.51)
Severity of patient's dementia*	0.33 (0.15 to 0.51)
Caregiver's current overall health status*	0.34 (0.18 to 0.50)
Caregiver pressure to prescribe a medication*	0.43 (0.26 to 0.60)
Caregiver's ability to tolerate patient behaviour*	0.21 (0.02 to 0.40)
How familiar you are with the patient*	0.47 (0.33 to 0.60)
How much time you have to devote to the patient*	0.17 (-0.01 to 0.34)
Ease of administration of the Alzheimer's drug*	0.30 (0.09 to 0.52)
Side-effect profile of the Alzheimer's drug*	0.33 (0.14 to 0.53)
Cost of the Alzheimer's drug*	0.48 (0.32 to 0.63)
Requirement to fill-out the 'Medicament d'exception' form*	0.58 (0.42 to 0.73)
Physician requirements for improvements to cognition	0.54 (0.34 to 0.75)
Physician requirements for improvements to behaviour and mood	0.32 (0.12 to 0.52)
Physician requirements for improvements to functional ability	0.41 (0.20 to 0.62)
Physician beliefs regarding improvements to cognition	0.44 (0.29 to 0.59)
Physician beliefs regarding improvements to behaviour and mood	0.44 (0.30 to 0.58)
Physician beliefs regarding improvements to functional ability	0.42 (0.28 to 0.56)

Table 4.5: Physician Questionnaire – Weighted Kappas for Test-retest Reliability (continued)

Questions on the Short Reliability Questionnaire	Weighted Kappa (95% CI)
Physician requirements for increased length of stabilization for mild AD patients	0.58 (0.40 to 0.75)
Physician requirements for increased length of stabilization for moderate AD patients	0.32 (0.04 to 0.60)
Physician beliefs regarding increased length of stabilization for mild AD patients	0.50 (0.35 to 0.64)
Physician beliefs regarding increased length of stabilization for moderate AD patients	0.54 (0.41 to 0.67)
Percentage of AD patients prescribed ChEIs – overall and by disease severity	0.53 (0.45 to 0.61)
Are MCI and 'other dementia' patients prescribed ChEIs? – Yes/No	0.74 (0.62 to 0.86)†
Percentage of MCI patients prescribed ChEIs	0.46 (0.14 to 0.78)
Percentage of patients with other forms of dementia prescribed ChEIs	0.35 (0.15 to 0.55)
Overall number of patients in a physician's practice	0.75 (0.62 to 0.88)
Number of AD patients in a physician's practice	0.63 (0.48 to 0.77)
Number of MCI patients in a physician's practice	0.47 (0.18 to 0.76)
Number of 'other dementia' patients in a physician's practice	0.53 (0.37 to 0.69)

*Factors influencing a physician's decision to prescribe ChEIs.

†Kappa, not weighted kappa, because the response option is dichotomous.

Notes: CI = confidence interval, AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, MCI = mild cognitive impairment.

Test-retest reliability was generally fair to moderate. Using the classification scheme of Landis and Koch,[253] the majority of the κ_ws (20 of 34) indicated moderate agreement beyond chance (i.e., $0.41 \leq \kappa_w \leq 0.60$). Three κ_ws indicated substantial agreement (i.e., $0.61 \leq \kappa_w \leq 0.80$), 10 κ_ws indicated fair agreement (i.e., $0.21 \leq \kappa_w \leq 0.40$),

and only one κ_w indicated poor agreement ($\kappa_w \leq 0.20$). Discrepancies in responses between the original questionnaire and the short reliability questionnaire could also be due to random error, which might lead to wider than expected confidence intervals for regression coefficients.

4.1.5. Descriptive Statistics – Distribution of Responses

4.1.5.1. Physician Questionnaire – Section 1: Factors Influencing Physicians' Decisions to Prescribe ChEIs to AD Patients

In the first section of the questionnaire, physicians were asked to indicate the extent to which each of sixteen factors might influence their decision to prescribe ChEIs to AD patients. Physicians could choose from among five responses: would not influence, probably would not influence, don't know, probably would influence, or would influence.

At least 87% of the physicians reported that the following factors 'probably would influence' or 'would influence' their decision to prescribe ChEIs:

- patient's current overall health status;
- dementia severity;
- ease of drug administration; and
- the adverse effect profile of the drug.

Between half and three-quarters of the physicians reported that the following factors 'probably would influence' or 'would influence' their decision:

- concurrent medication use by the patient;
- whether a patient lives at home or in a nursing home;
- patient compliance;
- cost of the medication; and
- caregiver ability to tolerate patient behaviour.

The majority of respondents reported that the following factors 'probably would not influence' or 'would not influence' their decision to prescribe:

- patient age;
- the degree of a physician's familiarity with a patient;
- the time a physician has available to devote to a patient; and
- the requirement to complete the *Médicament d'Exception* form.

For two factors, namely 'caregiver's current overall health status' and 'caregiver puts pressure on the physician to prescribe a medication,' responses were more or less evenly distributed across the response options. The distribution of responses for each of the 16 factors is shown in Appendix J.

4.1.5.2. Physician Questionnaire – Section 2: Physicians' Efficacy Requirements for Prescribing a Hypothetical New AD Medication

Section 2 of the physician questionnaire contained questions about physicians' efficacy requirements for prescribing a hypothetical new AD medication. The majority of respondents reported that they wanted patients' cognitive status to be at least permanently stabilized. On average, the physicians had a moderate level of belief in whether ChEIs could meet such an efficacy requirement. On the 'belief scale,' in which 1 indicates 'do not at all believe' and 10 indicates 'definitely believe,' the mean score was 6.

For behaviour and mood, as well as for the ability to perform basic activities of daily living, physicians generally required some degree of improvement, rather than permanent stabilization. Half of the physicians wanted to somewhat reduce further occurrences of problematic behaviours and moods. Almost equal numbers of physicians wanted to somewhat increase, or at least permanently prevent any further diminishment of, patients' ability to perform basic activities of daily living. The mean belief score for whether ChEIs could meet these requirements was 6.

In addition to permanent stabilization or improvement, another possibility for the hypothetical AD medication was to increase the length of time that patients would remain in their current disease state, following which it was presumed that deterioration would resume. To prescribe the hypothetical medication to patients with mild AD, physicians required a mean increase in length of stabilization of 15 months. For patients with moderate AD, the required increase was 11 months. In both cases, physicians held only a

modest level of belief that ChEIs could meet these requirements.

Responses to the requirements and belief questions are tabulated in Appendix J.

4.1.5.3. Physician Questionnaire – Section 3: Questions about the Actual Prescribing of ChEIs

Section 3 of the physician questionnaire contained questions concerning the actual prescribing of ChEIs. On average, physicians reported initiating prescriptions for almost two-thirds of the AD patients in their practices. Nearly all of these patients were in the mild or moderate stage of the disease. Ninety percent of physicians reported initiating at least one prescription for a ChEI. Most physicians who did not initiate a prescription said they would be likely to do so in the future. Physicians reported that nearly one in four caregivers pressured them to prescribe a ChEI to AD patients.

About one-third of physicians said they initiated ChEI prescriptions for patients with MCI and almost two-thirds said they did the same for patients with other dementias.

Physicians reported that the mean percentages of patients with adverse effects, and adverse effects severe enough to lead to a discontinuation of treatment, were highest for rivastigmine and lowest for donepezil.

To help address AD-related problems, most physicians initiated prescriptions for medications such as anti-depressants to an average of 46% of their AD patients. Also, one-quarter of physicians suggested to an average of 55% of their AD patients that over-the-counter medications be taken to help alleviate losses of memory, speech, or

independence.

Most physicians reported being very knowledgeable about the efficacy of donepezil, and the remainder had at least some knowledge. For rivastigmine and galantamine, at least half the physicians were very knowledgeable about the efficacy of the drugs and another third had some knowledge. The highest percentage of 'not knowledgeable' responses was for galantamine, which was approved for use in AD later than donepezil or rivastigmine. The top three primary sources of information regarding ChEIs were medical journal articles, scientific meetings, and continuing medical education courses given by academic institutions.

Responses to the questions about the prescribing of ChEIs are tabulated in Appendix J.

4.1.6. Inferential Statistical Analysis

4.1.6.1. Main Effect Variable: Index of Favourable Physician Efficacy Requirements for Prescribing

4.1.6.1.1. Simple Quasi-binomial Regression Analyses

A simple quasi-binomial regression analysis was conducted to examine the crude association between physicians' favourable efficacy requirements for prescribing and the proportion of AD patients who are currently prescribed ChEIs. Simple quasi-binomial regression analyses were also conducted to identify covariates that could be effect modifiers or confounders (Appendix K).

The crude odds ratios for physicians' favourable efficacy requirements were indicative of an inverse association with current prescribing (Table 4.6). This was consistent with the a priori hypothesis. However, the associations were not statistically significant.

Table 4.6: Physician Questionnaire: Simple Quasi-binomial Regression Analysis - Physicians' Favourable Efficacy Requirements for Prescribing and the Proportion of AD Patients Currently Prescribed ChEIs

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Physicians' favourable efficacy requirements for prescribing (listwise deletion)	-0.0932	0.0565	0.91 (0.82, 1.02)	0.0991
Physicians' favourable efficacy requirements for prescribing (multiple imputation)	-0.1010	0.0695	0.90 (0.79, 1.04)	0.1464

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval.

Turning to the covariates, 13 covariates were found to be statistically significantly associated with current prescribing when missing data were handled by listwise deletion, and 12 covariates were found to be statistically significantly associated with current prescribing when missing data were handled by multiple imputation (Appendix K). These covariates were assessed for potential effect modification or confounding in the manner described in Section 3.2.2.2.2.

As a prelude to the assessment of covariates, the correlations between similar covariates were examined to guard against multicollinearity. The three

covariates pertaining to the percentages of AD patients in a practice with mild, moderate, or severe disease (Appendix K) were moderately correlated with one another. Pearson correlation coefficients were -0.65 for mild versus moderate and for mild versus severe. For moderate versus severe, the correlation was 0.65. Turning to the four adverse effects variables that were statistically significant in the simple quasi-binomial regression analyses (Appendix K), Pearson correlation coefficients ranged from 0.64 to 0.91. In all subsequent model building, the percentage of patients in a practice with mild AD and the percentage of patients with adverse effects from rivastigmine were chosen to represent the two correlated groups of covariates. These covariates were chosen because the simple quasi-binomial regression models in which they appeared had the lowest Akaike Information Criterion values of any of the simple quasi-binomial regression models in the correlated groups.

After completing the simple quasi-binomial regression analyses, the best explanatory model for the main effect variable was developed in accordance with the procedure outlined in Section 3.2.2.2.2. Briefly, the procedure involved the use of four 'preliminary' models to build a final, best explanatory model. The preliminary models are described in Section 3.2.2.2.2.

4.1.6.1.2. Multiple Quasi-binomial Regression Analyses: Building the Final, Best Explanatory Model for Physicians' Favourable Efficacy Requirements

None of the covariates were found to be effect modifiers when either listwise deletion or multiple imputation was used to handle missing data. However, some of the covariates were found to be confounders: level of knowledge about ChEIs and

the prescribing index for other dementias (listwise deletion); the percentage of patients with mild AD and the percentage of patients who had adverse effects from rivastigmine (multiple imputation). Adjusting for the confounders reduced the standard error of physicians' favourable efficacy requirements by 2% (listwise deletion) and 19% (multiple imputation).

Following the assessments of effect modification and confounding, full, reduced, and stepwise models were constructed as part of the model-building process. In all of these adjusted models, the standard error of physicians' favourable efficacy requirements was higher than in the crude models. However, the construction of these models allowed for the identification of several covariates that were independent predictors of the current prescribing of ChEIs. These covariates are shown along with the confounders in Tables 4.7 and 4.8.

As per the steps enumerated in Section 3.2.2.2.2, another set of adjusted models was created to include the main effect variable and all important covariates. These covariates could be confounders or independent predictors of current prescribing. In this set of adjusted models, relative to the crude models, the standard error of physicians' favourable efficacy requirements decreased by 3% (listwise deletion) and 19% (multiple imputation). However, the odds ratios did not change by 10% or more. These adjusted models (Tables 4.7 and 4.8) were selected as the final, best explanatory models for physicians' favourable efficacy requirements because of the improvements to precision and the fact that important covariates were highlighted.

For listwise deletion, the final, best explanatory model contained physicians' favourable efficacy requirements, level of knowledge, prescribing index for other dementias, percentage of patients with mild AD, and the percentage of patients who had adverse effects from rivastigmine (Table 4.7).

Table 4.7: Physician Questionnaire - Final Model of Physicians' Favourable Efficacy Requirements for Prescribing and the Proportion of AD Patients Currently Prescribed ChEIs

Listwise Deletion (n=188)				
Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Intercept	-1.4197	0.4076	N/A	0.0005
Physicians' favourable efficacy requirements for prescribing	-0.0059	0.0550	0.99 (0.89, 1.11)	0.9141
Level of knowledge regarding the efficacy of ChEIs	0.1532	0.0654	1.17 (1.03, 1.33)	0.0192
Prescribing index - other dementias				
0%	Reference	N/A	1.00	N/A
1-99%	0.3980	0.1981	1.49 (1.01, 2.20)	0.0445
100%	0.4748	0.4039	1.61 (0.73, 3.55)	0.2397
Percentage of patients in a practice with mild AD	0.0135	0.0039	1.01 (1.01, 1.02)	0.0005

Table 4.7: Physician Questionnaire - Final Model of Physicians' Favourable Efficacy Requirements for Prescribing and the Proportion of AD Patients Currently Prescribed ChEIs (continued)

Listwise Deletion (n=188)				
Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Percentage of patients with adverse effects - rivastigmine	0.0332	0.0110	1.03 (1.01, 1.06)	0.0027
Prescribing indicator - rivastigmine*				
Riv prescribed - Yes	Reference	N/A	1.00	N/A
Riv prescribed - No	0.2185	0.2003	1.24 (0.84, 1.84)	0.2753

*For the percentage of patients with adverse effects from rivastigmine, values of 0% indicated no adverse effects. Values of 0 indicated rivastigmine was not prescribed. To distinguish between the zero values, the prescribing indicator was entered and kept in any model that contained the adverse effects variable. The indicator variable was assigned a value of 0 when rivastigmine was prescribed and a value of 1 when rivastigmine was not prescribed.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable, Riv = rivastigmine.

For multiple imputation, the final, best explanatory model contained physicians' favourable efficacy requirements, level of knowledge, percentage of patients with mild AD, percentage of patients who had adverse effects from rivastigmine, level of belief, and physician specialty (Table 4.8).

Table 4.8: Physician Questionnaire - Final Model of Physicians' Favourable Efficacy Requirements for Prescribing and the Proportion of AD Patients Currently Prescribed ChEIs

Multiple Imputation (n=233)				
Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Intercept	-1.5599	0.3970	N/A	0.0001

Table 4.8: Physician Questionnaire - Final Model of Physicians' Favourable Efficacy Requirements for Prescribing and the Proportion of AD Patients Currently Prescribed ChEIs (continued)

Multiple Imputation (n=233)

Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Physicians' favourable efficacy requirements for prescribing	-0.0821	0.0561	0.92 (0.83, 1.03)	0.1438
Level of knowledge regarding the efficacy of ChEIs	0.2018	0.0616	1.22 (1.08, 1.38)	0.0011
Percentage of patients in a practice with mild AD	0.0107	0.0037	1.01 (1.00, 1.02)	0.0042
Percentage of patients with adverse effects - rivastigmine	0.0201	0.0097	1.02 (1.00, 1.04)	0.0407
Prescribing indicator - rivastigmine*				
Riv prescribed - Yes	Reference	N/A	1.00	N/A
Riv prescribed - No	-0.1168	0.1932	0.89 (0.61, 1.30)	0.5455
Level of belief in the ability of ChEIs to meet physicians' efficacy requirements (index)	0.0352	0.0161	1.04 (1.00, 1.07)	0.0288
Physician Specialty				
GP	Reference	N/A	1.00	N/A
Psychogeriatrician	0.3373	0.0756	1.40 (1.21, 1.63)	<0.0001
Geriatrician	0.6746	0.1512	1.96 (1.46, 2.64)	<0.0001
Neurologist	1.0119	0.2268	2.75 (1.76, 4.29)	<0.0001

*For the percentage of patients with adverse effects from rivastigmine, values of 0% indicated no adverse effects. Values of 0 indicated rivastigmine was not prescribed. To distinguish between the zero values, the prescribing indicator was entered and kept in any model that contained the adverse effects variable. The indicator variable was assigned a value of 0 when rivastigmine was prescribed and a value of 1 when rivastigmine was not prescribed.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable, Riv = rivastigmine, GP = general practitioner.

Both final models were examined for outliers and influential observations. For

the listwise deletion model (n=188), 34 observations were flagged as outliers or influential observations. The model was re-run without the observations and no material changes were observed with respect to any of the parameter estimates or standard errors. Therefore, the observations were retained in the model. For the multiple imputation model, four observations in each of the five imputed datasets were flagged as possible outliers or influential observations. The observations were deleted and no material impact was observed on any of the parameter estimates or standard errors. Consequently, the observations were retained in the model.

The continuous variables in both models were assessed for linearity. The assessment did not show any violations of the linearity assumption.

4.1.6.1.3. Model Interpretation

Index for Physician Requirements-Favourable Outcomes for a Hypothetical New AD Medication

A 1-unit increase in the index for physician requirements--favourable outcomes for a hypothetical new AD medication--reduced the odds of currently prescribing a ChEI to AD patients by 1% (listwise deletion – odds ratio=0.99) or 8% (multiple imputation – odds ratio=0.92). Higher scores on the index represent more stringent requirements for favourable outcomes in the areas of cognitive status, behaviour and mood, and the ability to perform basic activities of daily living. The findings are in line with the hypothesis, which posits that more stringent requirements for a hypothetical new AD medication are associated with less current prescribing. However, the association is not significant at the

5% level.

Level of Knowledge Regarding the Efficacy of ChEIs

A 1-unit increase in the knowledge index regarding the efficacy of ChEIs--higher values indicate greater knowledge--increases the odds of prescribing ChEIs to current AD patients by 17% (listwise deletion) and 22% (multiple imputation). The association is statistically significant at the 5% level.

Prescribing Index - Other Dementias

Physicians who prescribe ChEIs to all (versus none) of their patients with other dementias have a 61% increased odds of prescribing ChEIs to current AD patients. This finding is not statistically significant at the 5% level. Physicians who prescribe ChEIs to between 1 and 99% (versus 0%) of their patients with other dementias have a 49% increased odds of prescribing ChEIs to current AD patients ($p<0.05$).

Percentage of Patients in a Practice with Mild AD

Physicians whose practices include higher percentages of AD patients in the mild stage of disease have a greater odds of currently prescribing ChEIs to AD patients. A 1% increase in the number of mild-stage AD patients increases the odds of prescribing by 1% (listwise deletion and multiple imputation). The percentage of mild AD patients in a practice is negatively correlated with the percentages of moderate and severe AD patients in a practice. Thus, greater percentages of patients in the moderate or severe stages of disease are associated with less current prescribing of ChEIs. The association is

statistically significant at the 5% level.

Percentage of Patients with Adverse Effects from Rivastigmine

A 1% increase in the percentage of AD patients with adverse effects from rivastigmine appears to increase the odds of currently prescribing ChEIs to AD patients by 3% (listwise deletion) or 2% (multiple imputation). The percentage of patients who have adverse effects from rivastigmine is positively correlated with the percentages of patients whose adverse effects from donepezil, rivastigmine, or galantamine led to a discontinuation of treatment. Thus, greater percentages of treatment discontinuations also appear to be positively associated with more current prescribing of ChEIs. Since the data are cross-sectional, these associations should not be interpreted to suggest that adverse effects or treatment discontinuations precede increases in prescribing. Rather, it is more likely to be the other way around: increased prescribing precedes a higher incidence of adverse effects and a higher incidence of treatment discontinuations on account of these adverse effects.

Level of Belief in the Ability of ChEIs to Meet Physicians' Efficacy Requirements (Index)

Not surprisingly, physicians who more strongly believe that ChEIs can meet their efficacy requirements for favourable outcomes are more likely to prescribe the medications. A 1-unit increase in the index of beliefs increases the odds of prescribing ChEIs to current AD patients by 4%. This variable was included in the multiple

imputation model only. The association is statistically significant at the 5% level.

Physician Specialty

Relative to GPs, the odds of currently prescribing ChEIs to AD patients are 40% greater for psychogeriatricians, 96% greater for geriatricians, and 275% greater for neurologists. This variable was included in the multiple imputation model only. The association is statistically significant at the 5% level.

In summary, the following covariates consistently showed positive associations with prescribing in the listwise deletion and multiple imputation models:

- level of knowledge;
- the percentage of patients with mild AD; and
- the percentage of patients who had adverse effects from rivastigmine.

In addition, the associations were similar in magnitude when compared across models.

The listwise deletion and multiple imputation models did yield some differences. The prescribing index for other dementias was included in the listwise deletion model only, while level of belief and physician specialty were included in the multiple imputation model only.

A comparison of the crude and final models indicates that the covariates did not confound the association between physicians' favourable efficacy requirements and

current prescribing. However, the final models provided more precise estimates of this association.

4.1.6.2. Main Effect Variable: Index of Physician Efficacy Requirements for Prescribing - Increased Length of Stabilization

4.1.6.2.1. Simple Quasi-binomial Regression Analyses

The crude association between physicians' efficacy requirements for increased length of stabilization and the current prescribing of ChEIs was negative (Table 4.9). Thus, more stringent requirements were associated with less current prescribing of ChEIs. This finding confirmed the a priori hypothesis. In both the listwise deletion and multiple imputation models, the associations were statistically significant at the 5% level, although the upper bound of the confidence intervals touched the null value when rounded to the nearest hundredth. Two hundred fifteen respondents contributed information to the listwise deletion analysis.

Table 4.9: Physician Questionnaire: Simple Quasi-binomial Regression Analysis - Physicians' Efficacy Requirements for Prescribing (Increased Length of Stabilization) and the Proportion of AD Patients Currently Prescribed ChEIs

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Physicians' efficacy requirements for prescribing (increased length of stabilization)	-0.0138	0.0060	0.99 (0.98, 1.00)	0.0210
(listwise deletion)				

Table 4.9: Physician Questionnaire: Simple Quasi-binomial Regression Analysis - Physicians' Efficacy Requirements for Prescribing (Increased Length of Stabilization) and the Proportion of AD Patients Currently Prescribed ChEIs (continued)

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Physicians' efficacy requirements for prescribing (increased length of stabilization)	-0.0134	0.0067	0.99 (0.97, 1.00)	0.0457
(multiple imputation)				

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval.

4.1.6.2.2. Multiple Quasi-binomial Regression Analyses: Building the Final, Best Explanatory Model for Physician Efficacy Requirements for Prescribing – Increased Length of Stabilization

None of the covariates (Appendix K) were found to be effect modifiers in the listwise deletion or multiple imputation analyses. For listwise deletion, none of the covariates were found to be confounders. For multiple imputation, five covariates were found to be confounders: total number of AD patients in a physician's practice, level of knowledge, percentage of patients with mild AD, suggestion index for over-the-counter medications, and percentage of patients who had adverse effects from rivastigmine.

To address confounding in the multiple imputation model, current prescribing was regressed on physicians' efficacy requirements and the five covariates. The odds ratio for the requirements variable did not change and two of the covariates, namely total number of AD patients in a physician's practice and suggestion index for over-the-counter medications, were not statistically significant at the 5% level. The analysis was re-run without the two non-significant covariates and the standard error of physicians' efficacy

requirements decreased from 0.0067 (crude) to 0.0056. The estimated regression coefficients for the requirements variable and the remaining covariates were not materially altered by the exclusions. The model without the two covariates was chosen as the better model to represent confounding because of the increased precision and the ability to communicate the same information using fewer variables.

In the model building that followed the examination of effect modification and confounding, only the stepwise procedure identified potentially important covariates. For listwise deletion, the percentage of patients with mild AD (p=0.0021) and the percentage of patients who had adverse effects from rivastigmine (p=0.0024) were selected and retained in the stepwise model. Physicians' efficacy requirements was non-significant (odds ratio=0.99; 95% CI=0.98 to 1.00; p=0.0751), although the odds ratio and confidence interval were unchanged from the crude model when rounded to the nearest hundredth. The standard error of the requirements variable increased from 0.0060 (crude) to 0.0064 (Table 4.10).

For multiple imputation, software limitations required five different stepwise analyses to be run, one for each imputed dataset. The five resulting models were quite similar to one another, with each containing level of knowledge, percentage of patients with adverse effects from rivastigmine, and physician specialty. Four of the models contained the percentage of patients with mild AD. Odds ratios for the physicians' efficacy requirements variable ranged from 0.97 to 1.00, and standard errors ranged from 0.0061 to 0.0102.

The crude and adjusted associations between physicians' efficacy requirements and current prescribing were consistent regardless of model. For listwise deletion, two models were adopted as final, best explanatory models. To represent the association between physicians' efficacy requirements and current prescribing, the crude model (Table 4.9) was adopted as the final model (intercept=0.6307). To reflect the impact on prescribing of the percentage of patients with mild AD and the percentage of patients who had adverse effects from rivastigmine, the adjusted model from the stepwise procedure (Table 4.10) was also chosen as a final model.

For multiple imputation, a new model (Table 4.11) was assembled to include physicians' efficacy requirements and the four covariates that were identified in the stepwise analyses. Three of these covariates had also been identified as confounders. For physician's efficacy requirements, there were only two differences between this new model and the crude model: first, the lower bound of the confidence interval was 0.98 instead of 0.97 (crude); second, the standard error decreased to 0.0055 from 0.0067 (crude). Given the improved precision, the new model was adopted as the final, best explanatory model. The new model had the added benefit of showing associations between several important covariates and current prescribing.

The final, best explanatory models in Tables 4.10 and 4.11 were examined for outliers and influential observations. For the listwise deletion model, 26 out of 196 observations were flagged as outliers or influential observations. The model was re-run without the 26 observations and the standard errors increased by 1 to 2% for all of the

variables except the percentage of patients who had adverse effects from rivastigmine.

Table 4.10: Physician Questionnaire - Final Model for Covariates in the Association between Physicians' Efficacy Requirements for Prescribing (Increased Length of Stabilization) and the Proportion of AD Patients Currently Prescribed ChEIs

Listwise Deletion (n=196)

Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Intercept	-0.2276	0.3283	N/A	0.4882
Physicians' efficacy requirements for prescribing (increased length of stabilization)	-0.0114	0.0064	0.99 (0.98, 1.00)	0.0751
Percentage of patients in a practice with mild AD	0.0135	0.0044	1.01 (1.01, 1.02)	0.0021
Percentage of patients with adverse effects - rivastigmine	0.0429	0.0142	1.04 (1.02, 1.07)	0.0024
Prescribing indicator - rivastigmine*				
Riv prescribed - Yes	Reference	N/A	1.00	N/A
Riv prescribed - No	-0.2355	0.2253	0.79 (0.51, 1.23)	0.2959

*For the percentage of patients with adverse effects from rivastigmine, values of 0% indicated no adverse effects. Values of 0 indicated rivastigmine was not prescribed. To distinguish between the zero values, the prescribing indicator was entered and kept in any model that contained the adverse effects variable. The indicator variable was assigned a value of 0 when rivastigmine was prescribed and a value of 1 when rivastigmine was not prescribed.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable, Riv = rivastigmine.

Table 4.11: Physician Questionnaire - Final Model of Physicians' Efficacy Requirements for Prescribing (Increased Length of Stabilization) and the Proportion of AD Patients Currently Prescribed ChEIs

Multiple Imputation (n=233)

Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Intercept	-1.1535	0.4074	N/A	0.0049
Physicians' efficacy requirements for prescribing (increased length of stabilization)	-0.0140	0.0055	0.99 (0.98, 1.00)	0.0111
Level of knowledge regarding the efficacy of ChEIs	0.1791	0.0605	1.20 (1.06, 1.35)	0.0032
Percentage of patients in a practice with mild AD	0.0125	0.0036	1.01 (1.01, 1.02)	0.0006
Percentage of patients with adverse effects - rivastigmine	0.0219	0.0095	1.02 (1.00, 1.04)	0.0237
Prescribing indicator - rivastigmine*				
Riv prescribed - Yes	Reference	N/A	1.00	N/A
Riv prescribed - No	-0.1524	0.1869	0.86 (0.60, 1.24)	0.4150
Physician Specialty				
GP	Reference	N/A	1.00	N/A
Psychogeriatrician	0.2881	0.0727	1.33 (1.16, 1.54)	<0.0001
Geriatrician	0.5762	0.1454	1.78 (1.34, 2.37)	<0.0001
Neurologist	0.8643	0.2181	2.37 (1.55, 3.64)	<0.0001

*For the percentage of patients with adverse effects from rivastigmine, values of 0% indicated no adverse effects. Values of 0 indicated rivastigmine was not prescribed. To distinguish between the zero values, the prescribing indicator was entered and kept in any model that contained the adverse effects variable. The indicator variable was assigned a value of 0 when rivastigmine was prescribed and a value of 1 when rivastigmine was not prescribed.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable, Riv = rivastigmine, GP = general practitioner.

The standard error for the percentage of patients who had adverse effects from rivastigmine did not change. The model with all 196 observations was more precise than the model without potential outliers and influential observations, so all of the observations were retained. For the multiple imputation model, four observations in each of the five imputed datasets were identified as possible outliers or influential observations. The observations were deleted and the standard error for physicians' efficacy requirements increased from 0.0055 (Table 4.11) to 0.0060. To avoid the loss of precision, the observations were retained in the model.

The continuous variables in both models were assessed for linearity. The assessment did not show any violations of the linearity assumption.

In summary, both the listwise deletion and multiple imputation final models showed negative associations of the same magnitude between physicians' efficacy requirements--increased length of stabilization and the proportion of patients currently prescribed ChEIs. This suggests more stringent requirements for a hypothetical new AD medication are associated with less current prescribing. Point estimates of the odds ratios for physicians' efficacy requirements were the same in the final and crude models.

In terms of the covariates, the percentage of patients in a practice with mild AD and the percentage of patients with adverse effects from rivastigmine were included in the listwise deletion and multiple imputation final models. The effects of each covariate were similar in both models. The final multiple imputation model included two additional covariates, namely level of knowledge and physician specialty.

4.1.6.2.3. Model Interpretation

Index of Physician Efficacy Requirements for Prescribing - Increased Length of Stabilization

For every 1-month overall increase in the length of patient stabilization that would be required to prescribe a hypothetical new AD medication, the odds of currently prescribing ChEIs to AD patients decreases by 1% (listwise deletion and multiple imputation). The unadjusted listwise deletion and multiple imputation associations are statistically significant at the 5% level, as is the adjusted multiple imputation association. Only the adjusted listwise deletion association is not statistically significant at the 5% level.

Level of Knowledge Regarding the Efficacy of ChEIs

A 1-unit increase in the knowledge index concerning the efficacy of ChEIs would increase the odds of currently prescribing ChEIs to AD patients by 20% (multiple imputation only; $p=0.0032$).

Percentage of Patients in a Practice with Mild AD

A 1% increase in the percentage of mild AD patients in a physician's practice would increase the odds of prescribing by 1% (listwise deletion and multiple imputation; $p<0.01$). The percentage of mild AD patients in a practice is negatively correlated with the percentages of moderate and severe AD patients in a practice. Thus, greater percentages of moderately or severely affected patients in a practice are associated with

less current prescribing of ChEIs.

Percentage of Patients with Adverse Effects from Rivastigmine

A 1% increase in patients who have adverse effects from rivastigmine appears to increase the odds of current prescribing by 4% (listwise deletion) or 2% (multiple imputation). The percentage of patients with adverse effects from rivastigmine was positively correlated with the percentages of patients whose adverse effects from donepezil, rivastigmine, or galantamine led to a discontinuation of treatment. Thus, greater percentages of treatment discontinuations appear to be positively associated with more current prescribing of ChEIs. As was the case when the main effect variable was physicians' favourable efficacy requirements, it is more likely that increased prescribing precedes a higher incidence of adverse effects and a higher incidence of treatment discontinuations on account of these adverse effects.

Physician Specialty

Relative to GPs, the odds of currently prescribing ChEIs to AD patients are 33% greater for psychogeriatricians, 78% greater for geriatricians, and 237% greater for neurologists (multiple imputation only; $p<0.0001$).

4.2. Caregiver Questionnaire

A questionnaire was sent to 375 caregivers who had attended support group meetings organized by the Alzheimer Society of Montréal or the Alzheimer Groupe Incorporated. The questionnaire was designed to elicit information on

caregivers' efficacy requirements for new AD medications, caregivers' willingness to accept the occurrence of adverse effects and have patients continue taking AD medications, and caregiver pressure on physicians to prescribe AD medications. Before the questionnaire was mailed to intended recipients, it was pre-tested on a series of small groups of caregivers.

4.2.1. Pre-test Results

The questionnaire pre-test involved 31 caregivers who participated in five groups (Table 4.12). In two of the groups, the optimal number of six to seven caregivers was not attained because some prospective participants had last minute scheduling conflicts. This did not adversely affect the contributions of the two groups, as the percentage of comments implemented was similar across all five groups (Table 4.13). What did affect the contributions was the iteration of the questionnaire being evaluated. The number of comments provided by the second set of English groups, who evaluated a revised version of the questionnaire, decreased relative to the number of comments provided by the first set of English groups and by the French group, both of whom evaluated the first version of the questionnaire (Table 4.13).

Table 4.12: Characteristics of Caregivers in the Pre-test Groups*

Characteristic	First Set Group # 1	First Set Group # 2	French Speaking Group	Second Set Group # 3	Second Set Group # 4
Total Participants (n)	8	5	8	6	4
Sex					
Female	2	3	7	6	2
Male	6	2	1	0	2
Mean Age	59 (range: 27-67)	66 (range: 60-77)	63 (range: 50-79)	58† (range: 45-75)	79 (range: 78-82)
Education (highest level)					
Elementary School	0	2	0	1	1
High School	5	2	0	0	3
Community College	0	0	3	0	0
Professional Degree	1	0	1	2	0
University Degree	2	1	4	3	0
Income					
≤15,000	0	0	1	2	0
15,001-25,000	0	2	2	0	0
25,001-35,000	3	1	2	0	2
35,001-45,000	2	1	1	1	0
>45,000	3	1	2	2	1
Did not report	0	0	0	1	1
The participant was caring for a...					
Parent	6	0	3	5	0
Spouse	2	4	4	1	4
Sibling	0	1	1	0	0

*Groups numbered 1-4 are English speaking.

†Mean age based on five caregivers (one did not provide this information).

Table 4.13: Type and Number of Pre-test Group Comments*†

Type of Comment (Theme)‡	First Set Group # 1	First Set Group # 2	French Speaking Group	Second Set Group # 3	Second Set Group # 4
	(Comments Implemented/Comments Suggested)				
Question Wording	9/9	5/7	2/6	5/5	1/1
Question Meaning	9/11	2/2	4/4	0/0	5/5
Question Response Categories	8/9	9/12	6/6	7/10	4/6
Questionnaire Instructions	3/4	7/7	1/1	2/2	4/4
Questionnaire Font	1/1	0/0	0/0	0/0	0/0
Questionnaire Appearance	1/2	1/3	2/2	1/1	0/1
General Comments (e.g., questionnaire is missing an important question)	4/6	7/8	6/7**	2/4	0/0
Total # Comments Implemented	35	31	21	17	14
Total # Comments Made	42	39	26	22	17
% Total Comments Implemented	83%	79%	81%	77%	82%

*Comments include suggestions for changing the questionnaire, not remarks made in support of the questionnaire. When more than one panel had the same comment, the comment was credited to each of the panels.

†Panels numbered 1-4 are English speaking.

‡Comments were classified into themes.

**Includes five comments on questionnaire translation, all of which were implemented.

Although two hours were allotted for each pre-test group meeting, the meetings lasted 85 minutes on average (range: 75-105 minutes). One hundred forty-six comments were accumulated over the five meetings, and 81% (118/146) were implemented. The comments were categorized into seven themes: wording, meaning, response categories, instructions, font, appearance, and general comments (Table 4.13).

To more clearly present the themes and how the questionnaire was revised, an example of each theme is provided. For question wording, two questions in the first draft of the questionnaire were designed to elicit caregiver efficacy requirements for a hypothetical new AD medication. However, some caregivers mistakenly thought that the questions asked about patients' past responses to ChEIs. To correct the misunderstanding, the questions were reworded to include the phrase "What if your loved one can be treated with a new Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects)..."

One item that evoked much commentary was the meaning of 'income' in the question about annual income. Caregivers were not sure if the word referred to employment income alone, or if retirement pensions, investment income, etc. were also included. Some caregivers claimed they did not have an income because their spouse was the sole wage earner in the family. To address the comments, the question was rephrased to ask about 'household income.' A definition of household income was provided with the question.

For response categories, caregivers identified problems with the available responses to the question about the acceptability of adverse effects from AD

medications. In the original question, caregivers were asked to provide responses for three classes of adverse effects: (1) minor adverse effects that would go away without the need to stop drug treatment (e.g., weight loss); (2) minor adverse effects that would go away if drug treatment were stopped (e.g., severe vomiting); and (3) major adverse effects that would require hospitalization (e.g., stomach bleeding). The examples were given to clarify what 'minor' and 'major' adverse effects meant. Caregivers felt the examples were inadequate. As a case in point, the caregivers did not see severe vomiting as a minor adverse effect. Also, most caregivers wanted more adverse effects listed in the question, rather than just the three original examples. Consequently, the three classes of adverse effects were replaced with a list of 11 common adverse effects, all of which were suggested by the caregivers.

Turning to instructions, font, and appearance, caregivers felt heavy use of bold print, and wrapped text boxes around each question, led to some cluttered and visually straining pages. The problems were alleviated by changing to a softer font (i.e., Franklin Gothic Book instead of Arial), eliminating all text boxes, and maintaining bold print only for the instructions.

Two of the most interesting general comments concerned caregiver time and caregiver 'connectedness' to the questionnaire. In the first version of the questionnaire, caregivers were asked to specify the minimum reduction in caregiving time that would be a relevant outcome for an AD medication. In the groups, caregivers were not comfortable with this question because they felt it implied a caregiver benefit, whereas

the focus should be on patient benefit. The question was deleted from the final version of the questionnaire.

Some caregivers did not feel "connected" to the first version of the questionnaire because it was not clearly applicable to cases where patients had been institutionalized. To correct the problem, questions were made applicable to these cases. For example, in the question asking whether respondents were primary caregivers, 'primary caregiver' was re-defined to include caregivers who bore responsibility for overseeing the legal or financial affairs of institutionalized patients.

'Connectedness' to the questionnaire was also threatened because the phrase "the person for whom you provide care" was used to refer to patients with AD. Caregivers felt this phrase was impersonal. Consequently, it was changed to "the loved one for whom you are caring."

4.2.2. Response Rate

The overall response rate to the caregiver questionnaire was 64.4%. The calculation of the response rate is shown in Table 4.14. One hundred fifty-one of the 201 respondents (75%) returned a completed questionnaire between the first and second mailings. The remaining 50 respondents (25%) returned a completed questionnaire after the second mailing. The one-week interval between the first mailing and the postcard reminder was too short to assess the impact of the postcard on prompting caregivers to answer and return the questionnaire.

Table 4.14: Caregiver Questionnaire - Calculation of Response Rate

	Respondents	Non-respondents	Does not wish to participate	Does not care for a person with AD or the person with AD is deceased	TOTAL
n (%)	201 (54)	88 (23)	23 (6)	63 (17)	375 (100)

RESPONSE RATE=64.4%

(201/201+88+23)=0.644

The calculation of the response rate excludes caregivers who do not care for a person with AD, or who no longer provide care because the person with AD is deceased.

Notes: AD = Alzheimer's disease.

4.2.3. Respondent Characteristics

Section 1 of the caregiver questionnaire contained questions on respondent characteristics (Table 4.15). Most respondents were women and just over half were English speaking; the average age was 63 years. The majority of caregivers completed at least high school, and the annual household income for almost half was greater than $55,000. Overall physical health was good or better for well over three-quarters of the caregivers. Ninety percent of caregivers were caring for a parent or a spouse, three-quarters considered themselves to be the primary caregiver, and almost two-thirds lived with their ailing loved one. Three-quarters of caregivers also felt they were somewhat or well informed about what ChEIs could do for patients. Caregivers reported 69% of patients were taking ChEIs at the time the questionnaire was completed. Caregivers also reported giving less than one-quarter of patients other medications for problems such as memory loss, loss of speech, or loss of independence. The average age of

patients was 80 years and three-quarters were female. Also, three-quarters of patients had been diagnosed with AD during the last 1 to 4 years.

Table 4.15: Characteristics of Respondents to the Caregiver Questionnaire

Characteristic	n (%*)
Caregiver Sex	
Male	44 (22)
Female	157 (78)
Caregiver age	mean=63, SD=13; median=61, range=18-90
Caregiver language	
English	108 (54)
French	93 (46)
Caregiver education (highest level achieved)	
Elementary school	15 (8)
High school	70 (35)
Community College or trade school	15 (17)
University (undergraduate or graduate)	68 (34)
Other	12 (6)
Missing	1 (<1)
Caregiver household income (annual)	
≤15,000	6 (3)
15,001-25,000	23 (11)
25,001-35,000	29 (14)
35,001-45,000	16 (8)
45,001-55,000	21 (10)
>55,000	84 (42)
Missing	22 (11)
Caregiver overall physical health	
Excellent	36 (18)
Very good	69 (34)
Good	64 (32)
Fair	25 (12)
Poor	3 (1)
Missing	4 (2)
Patient sex	
Male	67 (33)
Female	132 (66)
Missing	2 (1)

Table 4.15: Characteristics of Respondents to the Caregiver Questionnaire (continued)

Characteristic	n (%*)
Patient age	mean=80, SD=14; median=81, range=56-93 (n=4 missing)
Patient is caregiver's...	
Parent	92 (46)
Spouse	88 (44)
Other relative	13 (6)
Other	7 (3)
Missing	1 (1)
When was AD diagnosed	
<1 year ago	14 (7)
1-2 years ago	70 (35)
3-4 years ago	62 (31)
5-6 years ago	26 (13)
>6 years ago	24 (12)
Do not know	2 (1)
Missing	3 (1)
Patient's current living arrangements	
Lives with caregiver	122 (61)
Institutionalized	76 (38)
Missing	3 (1)
Respondent is primary caregiver	
Yes	151 (75)
No	47 (23)
Missing	3 (1)
Use of medications besides ChEIs for memory loss	
Yes	51 (25)
No	141 (70)
Missing	9 (4)
Use of medications besides ChEIs for loss of speech	
Yes	15 (7)
No	174 (87)
Missing	12 (6)
Use of medications besides ChEIs for loss of independence	
Yes	16 (8)
No	131 (65)
Missing	54 (27)

Table 4.15: Characteristics of Respondents to the Caregiver Questionnaire (continued)

Characteristic	n (%*)
How informed are caregivers about what ChEIs can do for patients?	
Well informed	52 (26)
Somewhat informed	103 (51)
Poorly informed	26 (13)
Not at all informed	13 (6)
Missing	7 (3)
Patient currently taking ChEI	
Yes	138 (69)
No	58 (29)
Do not know	4 (2)
Missing	1 (<1)

*Percentages do not always total 100 due to rounding error.

Notes: SD = standard deviation, AD = Alzheimer's disease, ChEI = cholinesterase inhibitor.

4.2.4. Non-response Bias

4.2.4.1. Caregiver Questionnaire Respondents versus Caregivers in the CSHA Dataset

To help assess whether non-response bias may have affected the results of the caregiver questionnaire, respondents' answers to 14 questions were compared to the answers of the nation-wide cohort of CSHA caregivers to 14 similar questions from the 2001 CSHA dataset (Section 3.3.1.4.1). Statistically significant differences were found in 11 of the comparisons (Table 4.16). For annual household income, caregiver questionnaire respondents generally had higher incomes, especially at the extremes of the income distribution. Annual income was greater than $45,000 for 59% of the caregiver questionnaire respondents and 41% of the CSHA caregivers. At the other end of the income scale, 3% of caregiver questionnaire respondents and 8% of CSHA caregivers had incomes below $10,000.

If higher incomes can facilitate access to drug treatments, then one would expect better access for caregiver questionnaire respondents. Better access, in turn, could lead to more opportunities to formulate opinions about AD drug treatments. For example, caregivers who know they can afford medications for their loved ones may be more likely to discuss drug treatments with physicians or do their own research. However, this may not translate into a substantial difference of opinion relative to lower income caregivers. Consequently, it is difficult to assess whether income disparities suggest the presence of non-response bias.

Table 4.16: Non-response Bias - Caregiver Questionnaire Respondents versus Caregivers in the CSHA Dataset

Characteristic	Fisher's Exact Test, two-sided p-value
Caregiver Sex	0.1397
Caregiver Annual Household Income	<0.0001
Patient Current Living Arrangements	0.0617
Caregiving is Rewarding	<0.0001
Caregiver Overall Physical Health	0.7833
Caregiver Helps Patient:	
Eat	<0.0001
Dress/Undress	<0.0001
Get in/out of Bed	<0.0001
Take Bath/Shower	<0.0001
Use the Toilet	<0.0001
Use the Telephone	<0.0001
Prepare Meals	<0.0001
Do Housework	<0.0001
Take Medications	<0.0001

Notes: CSHA = Canadian Study of Health and Aging.

The second comparison for which a statistically significant difference was found involved caregivers' opinions on whether caregiving was rewarding. Sixty-

five percent of caregiver questionnaire respondents felt caregiving was often or occasionally rewarding, while 90% of CSHA caregivers felt there were positive aspects to caregiving. The discrepancy in responses could be explained by the fact that the questions in each survey were not similar enough to be compared. In the caregiver questionnaire, respondents could select one of four responses to the 'reward question.' The responses were 'often,' 'occasionally,' 'rarely,' or 'never rewarding.' For the comparison with the CSHA caregivers, the four responses were dichotomized into 'often or occasionally' or 'rarely or never.' The CSHA question about whether caregivers thought there were positive aspects to caregiving had a 'yes' or 'no' response option. Given the lack of similarity between questions, the difference might not be indicative of non-response bias.

The remaining differences concerned the degree to which caregivers helped AD patients perform each of the nine tasks listed in Table 4.16 under the heading "caregiver helps patient." To enable comparisons, caregiver questionnaire responses were re-categorized to fit the categories used in the CSHA questionnaire. 'Help all the time' became 'completely unable,' 'frequent or occasional help' became 'with some help,' and 'no help' became 'without any help.' For all nine tasks, larger percentages of caregiver questionnaire respondents answered 'completely unable.' For five of the nine tasks, larger percentages of caregiver questionnaire respondents answered 'some help.' The aforementioned differences may be due to the underlying dissimilarity of the questions. However, the patients of caregiver questionnaire respondents did appear to require more help than the patients of CSHA caregivers. Perhaps caregiver questionnaire respondents

were therefore more likely to be interested in drug treatments, or more likely to want their loved ones treated with medications. It is not known if and how these attitudes might have affected responses to the caregiver questionnaire.

To summarize, comparing caregiver questionnaire respondents with CSHA caregivers yielded some statistically significant differences in question responses. However, the differences were not clearly indicative of the presence of non-response bias. Some of the data from both sets of caregivers might have been too dissimilar to permit adequate inter-group comparisons. In other cases, caregiver questionnaire respondents might have had more reason to have opinions on drug treatments, but there was no evidence that this would lead to non-response bias.

4.2.4.2. Responses to Questions - Respondents versus Non-respondents

Telephone interviews (Appendix G) were conducted to assess whether respondents and non-respondents differed in their answers to the caregiver questionnaire. Fifty of the 88 non-respondents (57%) were randomly selected to participate, and 11 were interviewed. Of the 39 non-respondents who were not interviewed, 20 could not be reached because they did not answer the phone or the telephone number was incorrect, 7 were not providing care for an AD patient, 2 were out of town, 1 claimed to have returned the questionnaire, 8 refused to be interviewed (without giving a reason for refusal), and 1 was no longer a caregiver because the person with AD had died.

Since only 11 non-respondents were interviewed, assessing non-response bias by comparing answers did not yield informative results. However, the act of

contacting non-respondents provided some insight into the possibility of bias. Persons who do not care for AD patients, or whose loved ones are deceased, are not AD caregivers and therefore not part of the study population. Also, caregivers who are out of town are probably away for reasons unrelated to the study. Therefore, none of these factors is likely to lead to non-response bias. Of course, the full extent to which these factors explain non-response in the case of the caregiver questionnaire is unknown, but their presence does lessen the possibility of non-response bias.

4.2.4.3. Responses to Questions - Early Respondents versus Late Respondents

For all 83 questions in the caregiver questionnaire, the responses of early respondents were compared to the responses of late respondents. The rationale was that late respondents, who returned a completed questionnaire after the second mailing, would probably have been non-respondents had the administration of the questionnaire been limited to a single mailing.

The responses for 11 questions were found to be statistically significantly different at the 5% level. However, there were no discernable patterns in these differences, which appeared to be random. For example, late respondents were less willing than early respondents to continue drug treatment in the event of headaches or nausea, but they were more willing to continue drug treatment in the event of a drop in blood pressure. The results of the response comparisons suggested that early and late respondents were not substantively different from one another.

The random nature of the differences is one indication of little or no bias. Another indication is the number of comparisons, which is large enough so that at least four of the differences might be statistically significant by chance alone. In effect, response bias, if present, is probably minimal.

4.2.4.4. Conclusion - Assessment of Non-response Bias

The evidence from comparing respondents to non-respondents and early respondents to late respondents suggests the impact of non-response bias is minimal. However, the possibility of some bias cannot be ruled out. A more thorough assessment of non-response bias was precluded by the low participation rate in the telephone interviews and by the difficulty of comparing caregiver questionnaire respondents with CHSA caregivers. As well, 23 non-respondents could not be contacted at all because they returned a blank questionnaire and expressly opted out of the study.

4.2.5. Test-retest Reliability

To assess the test-retest reliability of the caregiver questionnaire, a shorter version of the questionnaire (Appendix H) was mailed to a random sample of 60 respondents. The short questionnaire was sent seven weeks after the second and final mailing of the original questionnaire. Forty-seven short questionnaires were returned within an 8-week waiting period.

Test-retest reliability was generally fair to moderate (Table 4.17). Using the classification scheme of Landis and Koch,[253] the majority of the κ_ws (33 of 44) indicated

fair to moderate agreement beyond chance (i.e., $0.21 \leq \kappa_w \leq 0.60$). Two κ_ws indicated substantial agreement ($0.61 \leq \kappa_w \leq 0.80$), and nine κ_ws indicated poor agreement ($\kappa_w \leq 0.20$). Discrepancies in responses could be due to random error, which might lead to wider than expected confidence intervals for regression coefficients.

Table 4.17: Caregiver Questionnaire - Weighted Kappas for Test-retest Reliability

Questions on the Reliability Survey	Weighted Kappa (95% CI)
Presently, how much help does your loved one need from you to do the following tasks?	
Bathe	0.53 (0.20, 0.85)
Dress	0.58 (0.28, 0.88)
Move from bed to chair	0.41 (0.05, 0.78)
Go up/down stairs	0.33 (-0.11, 0.77)
Use the toilet	0.46 (0.05, 0.87)
Eat	0.46 (0.12, 0.80)
Cook	0.76 (0.54, 0.98)
Shop	0.69 (0.48, 0.91)
Clean house	0.49 (0.24, 0.73)
Use the telephone	0.41 (0.14, 0.68)
Take medication	0.31 (-0.02, 0.65)
For each of these areas, please indicate how much improvement you would require before letting your loved one start taking the new drug.	
Memory	0.32 (0.07, 0.57)
Speech	0.37 (0.10, 0.64)
Recognition of surroundings	0.37 (0.13, 0.62)
Wandering	0.23 (-0.07, 0.52)
Irritability	0.13 (-0.15, 0.41)
Depression	0.14 (-0.13, 0.41)
Anger	0.09 (-0.13, 0.31)
Mood swings	0.15 (-0.10, 0.41)
Eating	0.43 (0.12, 0.75)
Washing	0.33 (0.06, 0.60)
Dressing	0.40 (0.14, 0.66)
Stair climbing	0.37 (0.08, 0.65)
Getting in/out of chairs	0.22 (-0.07, 0.51)
Walking	0.15 (-0.16, 0.47)
Using the toilet	0.29 (0.04, 0.54)

Table 4.17: Caregiver Questionnaire - Weighted Kappas for Test-retest Reliability (continued)

Questions on the Reliability Survey	Weighted Kappa (95% CI)
For the four possibilities below, how important would each one be in your decision to let your loved one start taking the new drug?	
Delay institutionalization for 1-6 months	0.44 (0.20, 0.68)
Delay institutionalization for 7-12 months	0.44 (0.20, 0.67)
Delay institutionalization for 1-2 years	0.47 (0.19, 0.76)
Delay institutionalization for more than 2 years	0.58 (0.33, 0.82)
For each [adverse effect], please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs.	
Weight loss	0.35 (0.01, 0.69)
Appetite loss	0.39 (0.07, 0.70)
Headaches	0.52 (0.12, 0.92)
Dizziness	0.17 (-0.10, 0.43)
Nausea	0.60 (0.28, 0.91)
Diarrhea	0.59 (0.24, 0.94)
Vomiting	0.56 (0.22, 0.90)
Drop in blood pressure	0.50 (0.17, 0.82)
Insomnia	0.22 (-0.04, 0.47)
Muscle cramps	0.16 (-0.14, 0.46)
Stomach bleeding	0.61 (0.22, 1.00)
Have you ever given your loved one non-prescription drugs (example: vitamins) to help overcome any of the following three problems?	
Memory loss	0.50 (0.14, 0.85)
Loss of speech	-0.07 (-0.17, 0.02)
Loss of independence	-0.08 (-0.15, -0.01)

Notes: CI = confidence interval.

4.2.6. Descriptive Statistics – Distribution of Responses

Section 1 contained questions about the caregiving experience. Section 2 contained questions about drug therapy for AD and was divided into three sub-sections. Caregivers answered questions in the sub-section addressing whether their loved ones currently used, once used, or never used ChEIs. Caregivers who were uncertain about whether their loved ones had ever used ChEIs answered questions in the 'never used'

sub-section.

Responses concerning the caregiving experience are shown in Appendix L. Three-quarters of caregivers reported having started providing hands-on care within the last four years, while one-quarter reported never having had to provide hands-on care. Just under half of the caregivers were still providing hands-on care at the time of the study. The most common activity for caregivers was helping AD patients shop. Conversely, the least common activity was helping patients move from a bed to a chair. Slightly more than 80% of the caregivers found the caregiving experience to be occasionally or often difficult, yet at other times almost two-thirds found the experience to be occasionally or often rewarding. For one-third of the caregivers, the loved one with AD was already institutionalized; another one-third of the caregivers had thought about institutionalizing their sick loved ones. Overall, caregivers, physicians, and other third parties made all of the treatment decisions for just under half of the patients.

The distribution of responses to the second section of the caregiver questionnaire is shown in Appendix L. For caregivers (n=138) who indicated that patients under their care were currently using ChEIs, nine out of 10 caregivers reported that physicians were the first person to bring up the possibility of prescribing a ChEI. Only one in 10 caregivers felt the need to pressure physicians into prescribing ChEIs. Two-thirds of caregivers were somewhat or very satisfied with ChEIs, and almost three-quarters thought patients would benefit from continuing to take ChEIs. As a prerequisite to letting patients take a hypothetical new AD medication, almost three-quarters of the caregivers wanted the medication to bring about at least fair improvement to patients'

memory. Two-thirds of caregivers believed the ability to delay nursing home placement for one to two years would be a somewhat or very important prerequisite for prescribing the new medication. Most caregivers were willing to continue AD drug treatment in the event patients suffered weight or appetite loss. However, caregivers were generally not willing to continue treatment in the event of other adverse effects. The vast majority of caregivers reported that they did not give patients non-prescription drugs for AD-related problems such as loss of memory, speech, or independence. Caregivers' primary source of information about drug treatments for AD was the treating physician.

For caregivers (n=30) who indicated that the patients under their care used ChEIs in the past (but not currently), three-quarters reported that physicians were the first person to have brought up the possibility of prescribing a ChEI. Slightly less than one in five caregivers felt the need to pressure physicians into prescribing ChEIs. Just over one-third of the caregivers were somewhat or very satisfied with ChEIs, and only 13% thought patients would benefit from continuing to take ChEIs. As a prerequisite to letting patients take a hypothetical new AD medication, most caregivers wanted the medication to bring about at least fair improvement, rather than stabilization, in nine of the 15 domains that could be affected by AD. A little more than half of the caregivers believed the ability to delay nursing home placement for one to two years would be a somewhat or very important prerequisite for prescribing the new medication. A majority of caregivers were not willing to accept adverse effects and continue patients on drug treatment. Most caregivers did not give patients non-prescription drugs for AD-related problems such as loss of memory, speech, or independence. Caregivers' primary sources of information

about drug treatments for AD were the physicians who were treating patients. Nearly half of the caregivers also obtained information from personal research (Appendix L).

For caregivers (n=32) who indicated that the patients under their care had never used ChEIs, or who were uncertain about whether the patients had ever used ChEIs, 60% reported that no discussions had occurred with physicians in the past year concerning the prescribing of ChEIs. In other cases, physicians were generally the first person to bring up the possibility of prescribing a ChEI. Few caregivers pressured physicians to prescribe ChEIs. Nearly half of the caregivers did not know if patients would benefit from taking a ChEI. As a prerequisite to letting patients take a hypothetical new AD medication, most caregivers wanted the drug to bring about at least fair improvement, rather than stabilization, in six of the 15 domains that could be affected by AD. Thirty-eight percent of caregivers believed any delay to nursing home placement would be a very important prerequisite for prescribing the new medication. Almost half of the caregivers were somewhat willing to accept weight loss and allow AD drug treatment to continue. For appetite loss, there was an almost even split between caregivers who would and who would not accept the adverse effect and allow drug treatment to continue. For the remaining adverse effects, most caregivers would not allow drug treatment to continue. Roughly three-quarters or more of the caregivers did not give patients non-prescription drugs for AD-related problems such as loss of memory, speech, or independence. Caregivers had two primary sources of information about drug treatments for AD, namely the physicians who were treating patients and brochures (Appendix L).

4.2.7. Inferential Statistical Analysis

4.2.7.1. Main Effect Variable: Caregiver-Physician Discussions about Drug Treatments for AD

4.2.7.1.1. Simple Logistic Regression Analyses

A simple logistic regression analysis was conducted to examine the crude association between caregiver-physician discussions about drug treatments for AD and whether caregivers' loved ones were currently being prescribed a ChEI. A positive association was found, meaning that caregivers' loved ones were more likely to be currently prescribed a ChEI when physicians were the first to discuss the possibility of using medications to treat AD. However, in the listwise deletion and multiple imputation models (Table 4.18), the confidence intervals for the main effect variable included the null value.

Simple logistic regression analyses were also conducted to identify covariates that would be assessed as potential effect modifiers or confounders of the crude associations shown in Table 4.18. For listwise deletion and multiple imputation, none of the

Table 4.18: Caregiver Questionnaire: Simple Logistic Regression Analysis - Caregiver-Physician Discussions about Drug Treatments for AD and the Current Prescribing of ChEIs to AD Patients

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Caregiver-physician discussions about drug treatments for AD				
Caregiver or someone else	Reference	N/A	1.00	N/A
Physician	0.7621	0.4812	2.14 (0.83, 5.50)	0.1132
(listwise deletion)				

Table 4.18: Caregiver Questionnaire: Simple Logistic Regression Analysis - Caregiver-Physician Discussions about Drug Treatments for AD and the Current Prescribing of ChEIs to AD Patients (continued)

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Caregiver-physician discussions about drug treatments for AD				
Caregiver or someone else	Reference	N/A	1.00	N/A
Physician	0.6783	0.4672	1.97 (0.78, 5.00)	0.1506
(multiple imputation)				

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, N/A = not applicable, CI = confidence interval.

covariates were statistically significantly associated with current prescribing (Appendix M). Therefore, according to the methods presented in Section 3.2.2.2.2, these covariates should not be assessed as potential effect modifiers or confounders. However, since different combinations of covariates can affect the parameter estimates of a main effect variable, the covariates in Appendix M were assessed for effect modification or confounding (see Section 4.2.7.1.2 below).

Three covariates in Appendix M, namely caregivers giving patients non-prescription drugs for memory loss, loss of speech, or loss of independence, were moderately correlated with one another. Pearson correlation coefficients ranged from 0.50 to 0.80. The covariate for loss of independence had the largest correlations (i.e., approximately 0.80) with the other two covariates, so it was chosen to represent all three in subsequent model-building exercises and statistical models.

4.2.7.1.2. Multiple Logistic Regression Analyses: Building the Final, Best Explanatory Model for Caregiver-Physician Discussions about Drug Treatments for AD

None of the covariates were found to be effect modifiers in analyses involving listwise deletion or multiple imputation. Caregiver age was shown to be the only confounder in the listwise deletion analysis. The adjusted odds ratio for caregiver-physician discussions after adding caregiver age to the model was 2.37, an increase of 11% over the crude odds ratio of 2.14. None of the covariates were found to be confounders in the multiple imputation analysis.

The construction of full, reduced, and stepwise models did not yield any important covariates in addition to caregiver age. That is, none of the other covariates were shown to be confounders or independent predictors of the dependent variable. Consequently, for listwise deletion, the association between caregiver-physician discussions and the current prescribing of ChEIs was best represented by a final model (Table 4.19) that included one covariate (i.e., caregiver age) and the main effect variable. For multiple imputation, the final model was the crude model (Table 4.18), with an intercept of 0.2299.

Both the listwise deletion and multiple imputation final models were examined for the impact of outliers and influential observations. Twelve observations in the listwise deletion dataset, and 146 out of 1,005 observations in the five imputed datasets, were identified as possible outliers or influential observations. After deleting these

Table 4.19: Caregiver Questionnaire - Final Model of Caregiver-Physician Discussions about Drug Treatments for AD and the Current Prescribing of ChEIs to AD Patients

Listwise Deletion (n=172)				
Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Intercept	1.5394	0.9788	N/A	0.1158
Caregiver-physician discussions about drug treatments for AD				
Caregiver or someone else	Reference	N/A	1.00	N/A
Physician	0.8607	0.4949	2.37 (0.90, 6.24)	0.0820
Caregiver age	-0.0145	0.0150	0.99 (0.96, 1.02)	0.3331

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

observations and re-running the models, no material changes in estimated regression coefficients or standard errors were observed. Consequently, all of the observations were retained in the models.

Caregiver age was assessed for linearity in the listwise deletion model. The assessment did not show any violations of the linearity assumption.

4.2.7.1.3. Model Interpretation

Caregiver-Physician Discussions about Drug Treatments for AD

The odds of an AD patient being currently prescribed a ChEI are greater when a physician is the first person to discuss the possibility of using ChEIs to treat AD. This is in comparison to situations where the caregiver, or someone other than a physician or the

caregiver, is the first person to discuss using ChEIs to treat AD. However, the confidence interval for the population parameter includes the null value.

Caregiver Age

For every 1-year increase in a caregiver's age, the odds of an AD patient being currently prescribed a ChEI decrease by 1% (listwise deletion only). However, the confidence interval for the population parameter includes the null value.

4.2.7.2. Main Effect Variable: Caregiver Pressure on Physicians to Prescribe AD Drugs

4.2.7.2.1. Simple Logistic Regression Analyses

A simple logistic regression analysis showed that caregiver pressure on physicians to prescribe AD drugs was positively associated with the current prescribing of ChEIs to AD patients. However, in the listwise deletion and multiple imputation models (Table 4.20), the confidence intervals for the population parameter contained the null value.

Table 4.20: Caregiver Questionnaire: Simple Logistic Regression Analysis - Caregiver Pressure on Physicians to Prescribe AD Drugs and the Current Prescribing of ChEIs to AD Patients

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Has the caregiver ever put pressure on a physician to prescribe an AD drug?				
No	Reference	N/A	1.00	N/A
Yes	0.2231	0.4714	1.25 (0.50, 3.15)	0.6360
(listwise deletion)				

Table 4.20: Caregiver Questionnaire: Simple Logistic Regression Analysis - Caregiver Pressure on Physicians to Prescribe AD Drugs and the Current Prescribing of ChEIs to AD Patients (continued)

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Has the caregiver ever put pressure on a physician to prescribe an AD drug?				
No	Reference	N/A	1.00	N/A
Yes	0.1964	0.4765	1.22 (0.48, 3.11)	0.6806
(multiple imputation)				

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

4.2.7.2.2. Multiple Logistic Regression Analyses: Building the Final, Best Explanatory Model for Caregiver Pressure on Physicians to Prescribe AD Drugs

Although there were no statistically significant associations between any of the covariates and current prescribing (Appendix M), the covariates were still assessed for effect modification or confounding. For listwise deletion, none of the covariates were found to be effect modifiers, although three were found to be confounders: caregiver sex, caregiver overall physical health, and caregivers give patients non-prescription drugs for loss of independence. For multiple imputation, none of the covariates were found to be effect modifiers or confounders.

The development of full, reduced, and stepwise models indicated that two covariates were independent predictors of current prescribing when listwise deletion was used to handle missing data. These covariates were patient age and the extent to which caregivers feel they are informed about what drugs can do to treat AD. Conversely, when

multiple imputation was used to handle missing data, no covariates were found to be independent predictors of current prescribing.

Since several covariates were identified as confounders or independent predictors in the listwise deletion analyses, a new model was formed containing caregiver pressure, caregiver sex, caregiver overall physical health, caregivers give patients non-prescription drugs for loss of independence, patient age, and the extent to which caregivers feel they are informed about what drugs can do to treat AD. In the 'new' model, none of these covariates confounded the association between caregiver pressure and current prescribing. The only covariate that was a statistically significant independent predictor of current prescribing was the extent to which caregivers feel they are informed about what drugs can do to treat AD. Removal of the covariates from least-to-most significant did not have any impact on the odds ratio for caregiver pressure. Therefore, all but one of the covariates were dropped from the model. The exception was the extent to which caregivers feel they are informed about what drugs can do to treat AD, which was retained in a final, listwise deletion model (Table 4.22) with caregiver pressure because of its importance as an independent predictor of current prescribing.

When the extent to which caregivers feel they are informed about what drugs can do to treat AD was included in a model with caregiver pressure, the standard error of the regression coefficient for caregiver pressure increased by 8% (from 0.4714 to 0.5068). Therefore, to most precisely explain the association between caregiver pressure and current prescribing, the crude model (Table 4.20) was also adopted as a final model.

Table 4.21: Caregiver Questionnaire - Final Model of Caregiver Pressure on Physicians to Prescribe AD Drugs and the Current Prescribing of ChEIs to AD Patients

	Listwise Deletion (n=186)			
Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Intercept	0.1326	0.3344	N/A	0.6918
Caregiver pressure on physician to prescribe AD drugs				
No	Reference	N/A	1.00	N/A
Yes	0.2811	0.5068	1.33 (0.49, 3.58)	0.5791
Extent to which caregivers feel they are informed about what drugs can do to treat AD				
Poorly/not informed	Reference	N/A	1.00	N/A
Somewhat informed	0.8678	0.4016	2.38 (1.08, 5.23)	0.0307
Very informed	0.9726	0.4686	2.65 (1.06, 6.63)	0.0380

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

For multiple imputation, the final, best explanatory model was the crude model (Table 4.20; intercept=0.7716) because none of the covariates were shown to be effect modifiers, confounders, or independent predictors of current prescribing.

The listwise deletion and multiple imputation final models were examined for the impact of outliers and influential observations. Twelve observations in the listwise deletion dataset, and 41 out of 1,005 observations in the five imputed datasets, were suspect. After deleting these observations and re-running the models, there were no material changes in the estimated regression coefficients or standard errors for any of the variables. Therefore, all of the observations were retained in the models.

Linearity was not assessed because there were no continuous variables in the final models.

4.2.7.2.3. Model Interpretation

Caregiver Pressure on Physicians to Prescribe AD Drugs

The odds of an AD patient being currently prescribed a ChEI increase by 25% (listwise deletion) or 22% (multiple imputation) when a caregiver has put pressure on a physician to use an AD drug to treat the patient. This is in comparison to situations where the caregiver has not put pressure on a physician. However, the confidence interval for the population parameter includes the null value.

Extent to which caregivers feel they are informed about what drugs can do to treat AD

In the listwise deletion model only, the odds of an AD patient being currently prescribed a ChEI increase by 238% when a caregiver is somewhat informed about what drugs can do to help treat AD (versus poorly or not at all informed; $p<0.05$). The odds increase by 265% when a caregiver is well informed (versus poorly or not at all informed; $p<0.05$).

4.2.7.3. Main Effect Variables: Levels of Importance Caregivers Attach to Delays to Institutionalization

4.2.7.3.1. Simple Logistic Regression Analyses

Simple logistic regression analyses were performed to study the crude associations between the current prescribing of ChEIs to AD patients and the

levels of importance caregivers attach to delays to institutionalization. Four temporal delays to institutionalization were modeled separately as main effect variables: 1 to 6 months, 7 to 12 months, 1 to 2 years, and more than 2 years (Table 4.22).

Table 4.22: Caregiver Questionnaire: Simple Logistic Regression Analyses - Levels of Importance Caregivers Attach to Delays to Institutionalization and the Current Prescribing of ChEIs to AD Patients

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
1 to 6 month delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.1978	0.5469	1.22 (0.42, 3.56)	0.7176
Very important	0.3615	0.4330	1.44 (0.61, 3.35)	0.4038
7 to 12 month delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.1542	0.5844	1.17 (0.37, 3.67)	0.7920
Very important	0.3285	0.5420	1.39 (0.48, 4.02)	0.5445
1 to 2 year delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.2891	0.5445	1.34 (0.46, 3.88)	0.5954
Very important	0.09542	0.4956	1.82 (0.69, 4.80)	0.2280
More than 2 year delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	1.2528	0.9940	3.50 (0.50, 24.56)	0.2076
Very important	0.7321	0.8032	2.08 (0.43, 10.04)	0.3620
(listwise deletion)				
1 to 6 month delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.1064	0.2441	1.11 (0.67, 1.84)	0.6668
Very important	0.2128	0.4882	1.24 (0.45, 3.39)	0.3752
7 to 12 month delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.0733	0.2461	1.08 (0.66, 1.75)	0.7665
Very important	0.1466	0.4922	1.16 (0.44, 3.06)	0.5270
1 to 2 year delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.1990	0.2547	1.22 (0.73, 2.04)	0.4395
Very important	0.3980	0.5094	1.49 (0.53, 4.18)	0.1683

Table 4.22: Caregiver Questionnaire: Simple Logistic Regression Analyses - Levels of Importance Caregivers Attach to Delays to Institutionalization and the Current Prescribing of ChEIs to AD Patients (continued)

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
More than 2 year delay				
Not important	Reference	N/A	1.00	N/A
Somewhat important	0.0939	0.2615	1.10 (0.66, 1.84)	0.7199
Very important	0.1878	0.5230	1.21 (0.43, 3.38)	0.7919
(multiple imputation)				

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

All of the associations were positive and the majority were stronger for the 'very important' category versus the 'somewhat important' category. However, all of the confidence intervals contained the null value of the parameter. In a comparison of the listwise deletion and multiple imputation models, the associations were stronger in the listwise deletion models, although each listwise deletion odds ratio was not statistically significantly different from the corresponding multiple imputation odds ratio.

4.2.7.3.2. Multiple Logistic Regression Analyses: Building the Final, Best Explanatory Models for Levels of Importance Caregivers Attach to Delays to Institutionalization

Although simple logistic regression analyses failed to show statistically significant associations between any of the covariates and current prescribing (Appendix M), the covariates were still assessed for possible effect modification or confounding.

For listwise deletion, none of the covariates were found to be effect modifiers. However, several covariates were found to be confounders, including caregiver sex, caregiver age, caregiver overall physical health, patient age, primary

caregiver, caregivers give patients non-prescription drugs for loss of independence, and the extent to which caregivers feel they are informed about what drugs can do to treat AD. Since each main effect variable had a different mix of these confounders, the optimal mix was chosen by forming a series of models, each of which contained one main effect variable and all of the confounding covariates for that main effect variable. Covariates were removed separately in order of least-to-most significant. If the removal of a covariate changed the odds ratio of a main effect variable by at least 10%, then the covariate was re-inserted and kept in future iterations of the model in question. If the change was less than 10%, then the covariate was kept out of future iterations of the model. Optimal combinations of confounders were caregiver sex and caregivers give patients non-prescription drugs for loss of independence (1 to 6 month delays), the extent to which caregivers feel they are informed about what drugs can do to treat AD (7 to 12 month delays), primary caregiver and caregivers give patients non-prescription drugs for loss of independence (1 to 2 year delays), and patient age and the extent to which caregivers feel they are informed about what drugs can do to treat AD (delays of more than 2 years).

For multiple imputation, none of the covariates were found to be effect modifiers. Furthermore, in three of the four models, none of the covariates were found to be confounders. The exception was patient age in the model for delays of more than 2 years.

The construction of full, reduced, and stepwise models yielded three additional confounders (listwise deletion): patient sex (1 to 6 month delays); primary caregiver and caregivers give patients non-prescription drugs for loss of independence (7 to

12 month delays). As well, four other covariates were identified as independent predictors of current prescribing through the model-building process (listwise deletion). These covariates were caregiver sex, patient sex, patient age, and the extent to which caregivers feel they are informed about what drugs can do to treat AD. For multiple imputation, the construction of full, reduced, and stepwise models did not yield any additional confounders or independent predictors.

The confounders and independent predictors from the listwise deletion analyses were contained in disparate models. Since no one model was an obvious selection as the best model for any main effect variable, a new set of models was constructed. Each model in this new set contained one of the main effect variables and all of the covariates that were found to be confounders or independent predictors of that main effect variable. Covariates were removed from these models in order of least-to-most significant: if the odds ratio of a main effect variable changed by at least 10% following the removal of a covariate, then the covariate was re-inserted and retained in all further iterations of the model in question. Otherwise, the covariate was kept out of all further iterations of the model. The final, best explanatory models that were developed as a result of this process are shown in Table 4.23 (listwise deletion).

For multiple imputation, the final, best explanatory models are shown in Table 4.24. With the exception of the model for delays to institutionalization of more than 2 years, the final models are the crude models.

Table 4.23: Caregiver Questionnaire - Final Models of Levels of Importance Caregivers Attach to Delays to Institutionalization and the Current Prescribing of ChEIs to AD Patients

Listwise Deletion (n=102-131 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
1 to 6 month delay (n=131)				
Intercept	1.5511	0.9000	N/A	0.0848
1 to 6 month delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	0.1985	0.5744	1.22 (0.40, 3.76)	0.7297
Very important	0.4900	0.4672	1.63 (0.65, 4.08)	0.2942
Patient sex				
Female	Reference	N/A	1.00	N/A
Male	-0.7311	0.4414	0.48 (0.20, 1.14)	0.0977
Patient age	-0.0633	0.0306	0.94 (0.88, 1.00)	0.0383
Informed*				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.0485	0.5203	2.85 (1.03, 7.91)	0.0439
Well informed	0.7530	0.5770	2.12 (0.69, 6.58)	0.1918
7 to 12 month delay (n=102)				
Intercept	-0.5450	0.7970	N/A	0.4941
7 to 12 month delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	0.2238	0.6832	1.25 (0.33, 4.77)	0.7433
Very important	0.1878	0.6519	1.21 (0.34, 4.33)	0.7733
Primary caregiver				
No	Reference	N/A	1.00	N/A
Yes	-0.3317	0.4995	0.72 (0.27, 1.91)	0.5067
Non-prescription drugs†				
No	Reference	N/A	1.00	N/A
Yes	-0.7621	0.7289	0.47 (0.11, 1.95)	0.2958
Informed*				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.4891	0.6104	4.43 (1.34, 14.67)	0.0147
Well informed	1.4560	0.6754	4.29 (1.14, 16.12)	0.0311

Table 4.23: Caregiver Questionnaire - Final Models of Levels of Importance Caregivers Attach to Delays to Institutionalization and the Current Prescribing of ChEIs to AD Patients (continued)

Listwise Deletion (n=102-131 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
1 to 2 year delay (n=113)				
Intercept	-1.6694	0.7728	N/A	0.0308
1 to 2 year delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	1.0900	0.7483	2.97 (0.69, 12.89)	0.1452
Very important	1.2438	0.6610	3.47 (0.95, 12.67)	0.0599
Non-prescription drugs†				
No	Reference	N/A	1.00	N/A
Yes	-1.0817	0.6953	0.34 (0.09, 1.33)	0.1198
Informed*				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.3602	0.5520	3.90 (1.32, 11.50)	0.0137
Well informed	1.5124	0.6467	4.54 (1.28, 16.12)	0.0194
More than 2 year delay (n=105)				
Intercept	0.3068	1.2905	N/A	0.8121
More than 2 year delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	1.0579	1.0793	2.88 (0.35, 23.88)	0.3270
Very important	0.5866	0.8792	1.80 (0.32, 10.07)	0.5047
Patient age	-0.0557	0.0353	0.95 (0.88, 1.01)	0.1148
Informed*				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.9705	0.6356	7.17 (2.06, 24.93)	0.0019
Well informed	1.3672	0.6525	3.92 (1.09, 14.10)	0.0362

*Extent to which caregivers are informed about what drugs can do to treat AD.

†Caregivers give patients non-prescription drugs for loss of independence.

Notes: ChEI = cholinesterase inhibitor, AD = Alzheimer's disease, CI = confidence interval, N/A = not applicable.

Table 4.24: Caregiver Questionnaire - Final Models of Levels of Importance Caregivers Attach to Greater Delays to Institutionalization and the Current Prescribing of ChEIs to AD Patients

	Multiple Imputation (n=201)			
Model Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
1 to 6 month delay				
Intercept	0.5616	0.5698	N/A	0.3332
1 to 6 month delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	0.1064	0.2441	1.11 (0.67, 1.84)	0.6668
Very important	0.2128	0.4882	1.24 (0.45, 3.39)	0.3752
7 to 12 month delay				
Intercept	0.6225	0.6135	N/A	0.3124
7 to 12 month delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	0.0733	0.2461	1.08 (0.66, 1.75)	0.7665
Very important	0.1466	0.4922	1.16 (0.44, 3.06)	0.5270
1 to 2 year delay				
Intercept	0.3195	0.6325	N/A	0.6163
1 to 2 year delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	0.1990	0.2547	1.22 (0.73, 2.04)	0.4395
Very important	0.3980	0.5094	1.49 (0.53, 4.18)	0.1683
More than 2 year delay				
Intercept	1.7956	1.1609	N/A	0.1224
More than 2 year delay				
Not at all important	Reference	N/A	1.00	N/A
Somewhat important	-0.0056	0.3080	0.99 (0.54, 1.82)	0.9855
Very important	-0.0112	0.6160	0.99 (0.29, 3.32)	0.7892
Patient age	-0.0410	0.0277	0.96 (0.91, 1.01)	0.1395

Notes: ChEI = cholinesterase inhibitor, AD = Alzheimer's disease, CI = confidence interval, N/A = not applicable.

In all but one of the eight final, best explanatory models (Tables 4.23 and 4.24), the importance caregivers attach to delays to institutionalization was positively associated with the current prescribing of ChEIs to AD patients. The exception was the multiple imputation model for delays of greater than 2 years, where the association was negative. The point estimates for the listwise deletion odds ratios were greater than the corresponding point estimates for the multiple imputation odds ratios, but the differences in point estimates were not statistically significant. It should be noted that the confidence intervals for all eight associations contained the null value.

For listwise deletion, the association between the main effect variable and current prescribing was stronger for the 'very important' category in two models and stronger for the 'somewhat important' category in two models. For multiple imputation, the association was stronger for the 'very important' category in three models and equivalent between categories in one model.

No effect modification was found in the final models for listwise deletion or multiple imputation. Conversely, confounders were present in all four listwise deletion models. The covariate pertaining to the extent to which caregivers are informed about what drugs can do to treat AD was a confounder in all four models. Patient age was a confounder in two of the four models, and caregivers give patients non-prescription drugs for loss of independence was a confounder in the other two models. Patient sex and primary caregiver were confounders in one model each. For multiple imputation, three of the four models had no confounders. The exception was the model for delays of more than 2 years, where the confounder was patient age.

In all of the final models, possible outliers and influential observations were identified; the models were re-run without the observations and there were no material changes in the estimated regression coefficients or standard errors of any of the main effect variables. Therefore, all observations were retained in the models.

Patient age, the only continuous covariate in any of the models, was assessed for linearity. The assessment did not show any violations of the linearity assumption.

4.2.7.3.3. Model Interpretation

1 to 6 Month Delay to Institutionalization

The odds of an AD patient being currently prescribed a ChEI increase by 63% (listwise deletion) or 24% (multiple imputation) when a caregiver believes delaying nursing home placement by 1 to 6 months is very important versus not at all important. The odds increase by 22% (listwise deletion) or 11% (multiple imputation) when the delay is considered somewhat important versus not at all important.

7 to 12 Month Delay to Institutionalization

The odds of an AD patient being currently prescribed a ChEI increase by 21% (listwise deletion) or 16% (multiple imputation) when a caregiver believes delaying nursing home placement by 7 to 12 months is very important versus not at all important. The odds increase by 25% (listwise deletion) or 8% (multiple imputation) when the delay is considered somewhat important versus not at all important.

1 to 2 Year Delay to Institutionalization

The odds of an AD patient being currently prescribed a ChEI increase by 347% (listwise deletion) or 49% (multiple imputation) when a caregiver believes delaying nursing home placement by 1 to 2 years is very important versus not at all important. The odds increase by 297% (listwise deletion) or 22% (multiple imputation) when the delay is considered somewhat important versus not at all important.

More than 2 Year Delay to Institutionalization

The odds of an AD patient being currently prescribed a ChEI increase by 80% (listwise deletion) or decrease by 1% (multiple imputation) when a caregiver believes delaying nursing home placement by more than 2 years is very important versus not at all important. The odds increase by 288% (listwise deletion) or decrease by 1% (multiple imputation) when the delay is considered somewhat important versus not at all important.

All Length of Delay Variables

For the four length of delay variables, all of the confidence intervals include the null value for the population parameter.

Patient Sex

Patient sex is in the model for delays of 1 to 6 months and current prescribing (listwise deletion only). In the model, the odds of an AD patient being currently prescribed a ChEI decrease by 52% if the patient is male. However, the confidence

interval for the population parameter includes the null value.

Patient Age

Patient age is in the models for current prescribing and two main effect variables, namely delays of 1 to 6 months and delays of more than 2 years. In the model with delays of 1 to 6 months, every 1-year increase in the age of an AD patient decreases the odds of the patient being currently prescribed a ChEI by 6% (listwise deletion only). For delays of more than 2 years, the decrease in odds is 5% (listwise deletion) or 4% (multiple imputation). In the listwise deletion and multiple imputation models for delays to institutionalization of more than 2 years, the confidence intervals for the population parameter include the null value.

Extent to which caregivers feel they are informed about what drugs can do to treat AD

The 'informed' covariate is in all four listwise deletion models. The odds of an AD patient being currently prescribed a ChEI increase when a caregiver is somewhat or well informed about what drugs can do to help treat AD (versus poorly or not at all informed). The magnitude of the increases in odds is reported in Table 4.23. In the model for delays of 1 to 6 months, the confidence interval for the 'well informed' category contains the null value for the population parameter.

Primary Caregiver

Primary caregiver is in the model for delays of 7 to 12 months and current prescribing (listwise deletion only). The odds of an AD patient being currently

prescribed a ChEI decrease by 28% if the caregiver is the primary caregiver. However, the confidence interval for the population parameter includes the null value.

Caregivers give patients non-prescription drugs for loss of independence

The impact of caregivers giving patients non-prescription drugs for loss of independence is in the models for two main effect variables, namely delays of 7 to 12 months and delays of 1 to 2 years (listwise deletion only). According to the model for 7 to 12 month delays to institutionalization, when caregivers give AD patients non-prescription drugs for loss of independence, the odds of these patients being currently prescribed a ChEI decrease by 53%. For delays of 1 to 2 years, the odds decrease by 66%. However, the confidence intervals for the population parameter include the null value.

4.2.7.4. Main Effect Variables: Caregivers' Required Improvements to Domains Affected by AD

4.2.7.4.1. Simple Logistic Regression Analyses

Simple logistic regression analyses were conducted to study the crude associations between the current prescribing of ChEIs to AD patients and caregivers' required improvements to each of 15 domains affected by AD. To avoid the unwieldy situation of constructing 15 separate regression models to examine these associations, three index variables were created as follows:

- The 15 domains were ranked in descending order by strength of association with

the dependent variable (simple regression – p-value – Wald X^2);

- Three statistically significant domains, i.e., eating, washing, and dressing, were placed into one group, three close-to-significant domains ($0.05<p \leq 0.20$), i.e., memory, speech, and using the toilet, were placed into a second group; and nine moderately to highly non-significant domains ($p>0.20$), i.e., depression, irritability, walking, anger, stair climbing, mood swings, wandering, recognition of surroundings, and getting in or out of chairs, were placed into a third group;

- The top-ranked domain in each group was assigned a weight of 1.0, the next highest ranked domain was assigned a weight of 0.9, the third highest ranked domain was assigned a weight of 0.8, and the other domains were assigned weights of 0.7, 0.6, etc., all based on descending order of ranking;

- For each domain, a weighted score was obtained by multiplying the response values (i.e., 1, 2, 3, 4, 5) corresponding to actual caregiver responses by the specific weight assigned to the domain; and

- The weighted scores for all of the domains in a group were added together to get a single group score. In the regression models, each group was represented by an index variable, and the group score was the value for the index variable. The index variables were continuous with numerical ranges of 0 through 13.5 for the indices with three underlying domains and 0 through 27 for the index with nine underlying domains. The larger range for the latter index is a function of the

greater number of underlying domains. Higher values along the ranges indicate greater required levels of improvement.

The construction of index variables can lead to two problems. First, meaningful effects can be mixed with null effects. This possibility was avoided by constructing separate indices for significant and non-significant domains. The non-significant domains were also divided into two groups based on p-value: one group consisted of close-to-significant domains ($0.05<p \leq 0.20$) and the other group consisted of moderately to highly non-significant domains ($p>0.20$). Second, opposite effects can be mixed together. The potential impact of this problem appears to be minimal because all 15 domains were positively correlated with one another (*r* range: 0.50 to 0.82), thereby suggesting uni-directional effects. Any residual consequences from the mixing of effects would probably result in a bias to the null.

Simple logistic regression analyses involving the index variables showed that the odds of an AD patient being currently prescribed a ChEI were lower when caregivers required greater levels of improvement to the domains that are affected by AD (Table 4.25).

Table 4.25: Caregiver Questionnaire: Simple Logistic Regression Analyses – Index Variables for Levels of Improvement that Caregivers Require to Domains Affected by AD and the Current Prescribing of ChEIs to AD Patients

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Index Variable 1*	-0.2084	0.0619	0.81 (0.72 to 0.92)	0.0008

Table 4.25: Caregiver Questionnaire: Simple Logistic Regression Analyses – Index Variables for Levels of Improvement that Caregivers Require to Domains Affected by AD and the Current Prescribing of ChEIs to AD Patients (continued)

Main Effect Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Index Variable 2*	-0.1466	0.0733	0.86 (0.75 to 1.00)	0.0453
Index Variable 3*	-0.0003	0.0340	1.00 (0.94 to 1.07)	0.9929
Index Variable 1†	-0.1634	0.0534	0.85 (0.76 to 0.94)	0.0023
Index Variable 2†	-0.1375	0.0669	0.87 (0.76 to 0.99)	0.0412
Index Variable 3†	-0.0129	0.0318	0.99 (0.93 to 1.05)	0.6850

*Listwise deletion.

†Multiple imputation.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, index variable 1 = eating/washing/dressing, index variable 2 = memory/speech/using the toilet, index variable 3 = depression, irritability, walking, anger, stair climbing, mood swings, wandering, recognition of surroundings, and getting in or out of chairs.

4.2.7.4.2. Multiple Logistic Regression Analyses: Building the Final, Best Explanatory Models for Caregivers' Required Improvements to Domains Affected by AD

There were no statistically significant associations between any of the covariates and current prescribing (Appendix M). However, the covariates were still assessed as potential effect modifiers or confounders. For listwise deletion, the assessment did not yield any effect modifiers or confounders. For multiple imputation, none of the covariates were found to be effect modifiers, and only one covariate, whether or not the caregiver is the primary caregiver, was found to be a confounder. The confounding was limited to index variable 1, whose odds ratio changed from 0.85 in the crude

model to 0.74 in the model with the 'primary caregiver' covariate (i.e., a 13% decrease). See the notes to Table 4.25 for the list of domains for index variables 1, 2, and 3.

For listwise deletion, the construction of full, reduced, and stepwise models did not lead to the identification of any effect modifiers or confounders. Three covariates, though, were identified as independent predictors of current prescribing when they were included in models with two of the index variables. These covariates and index variables were the extent to which caregivers feel they are informed about what drugs can do to treat AD (index variables 1 and 2), patient age (index variables 1 and 2), and patient sex (index variable 2). In the absence of effect modification and confounding, the final, best explanatory model for each index variable was the crude model. To more fully present the range of factors that impact upon current prescribing, a second pair of final models was presented for index variables 1 and 2. These additional models contained the aforementioned independent predictors (Table 4.26).

For multiple imputation, the model-building exercise failed to identify any effect modifiers, but the following variables were found to be confounders or independent predictors: primary caregiver (index variables 1, 2, and 3); the extent to which caregivers feel they are informed about what drugs can do to treat AD (index variables 1, 2, and 3); patient age (index variables 1 and 2); and caregiver sex (index variables 2 and 3). Since different combinations of covariates occurred in different models, and no one model for any index variable was evident as a best model, a new set of models was constructed. Each model in this new set contained an index variable and all of the confounders or independent predictors related to that index variable. Covariates were

selected for inclusion in final models by the least-to-most significant removal procedure, which was described in Section 4.2.7.3.2 above. The final, best explanatory models for index variables 1 and 2 contained at least one covariate in addition to the main effect variable, while the final model for index variable 3 was the crude model (Table 4.27).

Table 4.26: Caregiver Questionnaire – Index Variables for Levels of Improvement that Caregivers Require to Domains Affected by AD and the Current Prescribing of ChEIs to AD Patients (Final Models)

Listwise Deletion (n=118-127 [range])

Model Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Index Variable 1				
Intercept (crude)	1.8206	0.4077	N/A	<0.0001
Index variable 1 (crude)	-0.2084	0.0619	0.81 (0.72 to 0.92)	0.0008

Intercept (adjusted)	2.5826	1.0239	N/A	0.0117
Index variable 1 (adjusted)	-0.2382	0.0694	0.79 (0.69 to 0.90)	0.0006
Informed (adjusted)*				
Poorly/not informed	Reference	N/A	1.00	N/A
Somewhat informed	1.2635	0.6164	3.54 (1.06 to 11.84)	0.0404
Well informed	1.4826	0.6840	4.41 (1.15 to 16.83)	0.0302
Patient age (adjusted)	-0.0744	0.0331	0.93 (0.87 to 0.99)	0.0245
Index Variable 2				
Intercept (crude)	1.5314	0.4613	N/A	0.0009
Index variable 2 (crude)	-0.1466	0.0733	0.86 (0.75 to 1.00)	0.0453

Intercept (adjusted)	2.5213	1.0928	N/A	0.0210
Index variable 2 (adjusted)	-0.1970	0.0838	0.82 (0.70 to 0.97)	0.0187

Table 4.26: Caregiver Questionnaire – Index Variables for Levels of Improvement that Caregivers Require to Domains Affected by AD and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Listwise Deletion (n=118-127 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Index Variable 2 (continued)				
Informed (adjusted)*				
Poorly/not informed	Reference	N/A	1.00	N/A
Somewhat informed	1.5575	0.5877	4.75 (1.51 to 15.03)	0.0080
Well informed	1.5940	0.6517	4.92 (1.38 to 17.64)	0.0144
Patient age (adjusted)	-0.0747	0.0341	0.93 (0.87 to 0.99)	0.0308
Patient sex (adjusted)				
Female	Reference	N/A	1.00	N/A
Male	-1.0260	0.4607	0.36 (0.15 to 0.88)	0.0259
Index Variable 3				
Intercept (crude)	0.7088	0.3801	N/A	0.0622
Index variable 3 (crude)	-0.0003	0.0340	1.00 (0.94 to 1.07)	0.9929

*Extent to which caregivers are informed about what drugs can do to treat AD.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

The deletion of outliers and influential observations did have a material impact on the standard error of index variable 1 in the multiple imputation analysis. Thirty-nine observations were deleted from the five imputed datasets and the standard error decreased by 32%, from 0.0953 in the model with all observations to 0.0647 in the model without the 39 observations. To improve precision, the 39 observations in question were omitted from the final reported model for index variable 1. All observations were retained in the other models. Linearity was confirmed for each of the index variables and patient age.

Table 4.27: Caregiver Questionnaire – Index Variables for Levels of Improvement that Caregivers Require to Domains Affected by AD and the Current Prescribing of ChEIs to AD Patients (Final Models)

	Multiple Imputation (n=201)*			
Model Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Index Variable 1				
Intercept	1.6789	0.3445	N/A	<0.0001
Index variable 1	-0.3020	0.0953	0.74 (0.61 to 0.89)	0.0016
Primary caregiver				0.0789
No	Reference	N/A	1.00	
Yes	0.1110	0.0632	1.12 (0.99 to 1.26)	
Index Variable 2				
Intercept	-0.9444	0.8911	N/A	0.2912
Index variable 2	-0.0183	0.0980	1.02 (0.81 to 1.19)	0.8521
Caregiver sex				0.0073
Female	Reference	N/A	1.00	
Male	1.8385	0.6749	6.29 (1.66 to 23.87)	
Primary caregiver				0.0333
No	Reference	N/A	1.00	
Yes	-0.1481	0.0682	0.86 (0.75 to 0.99)	
Informed†				0.0192
Poorly/not informed	Reference	N/A	1.00	
Somewhat informed	0.5890	0.2513	1.80 (1.10 to 2.95)	
Well informed	1.1780	0.5026	3.25 (1.21 to 8.70)	
Index Variable 3				
Intercept	0.9345	0.3615	N/A	0.0103
Index variable 3	-0.0129	0.0318	0.99 (0.93 to 1.05)	0.6850

*39 observations were deleted from the final model for index variable 1 to improve the precision of the main effect estimate.

†Extent to which caregivers are informed about what drugs can do to treat AD.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

4.2.7.4.3. Model Interpretation

Index Variable 1

A 1-unit increase in the index variable representing caregivers' required improvements to patients' ability to dress, wash, and eat is associated with a 19% (listwise deletion – crude model) or a 26% (multiple imputation) reduction in the odds of an AD patient being currently prescribed a ChEI ($p<0.01$). This finding supports the hypothesis that more stringent caregiver requirements for new AD medications are negatively associated with the current prescribing of ChEIs. Caregivers, realizing the limitations of ChEIs, may be less inclined to want patients treated with ChEIs when they have big expectations from drug treatment.

Index Variable 2

A 1-unit increase in the index variable representing caregivers' required improvements to patients' memory, speech, and ability to use the toilet is associated with a 14% reduction (listwise deletion – crude model) or a 2% increase (multiple imputation) in the odds of an AD patient being currently prescribed a ChEI. In the multiple imputation model, the confidence interval for index variable 2 contains the null value for the population parameter. The results from the listwise deletion model support the hypothesis, while the results from the multiple imputation model are more equivocal.

Index Variable 3

A 1-unit increase in the index variable representing caregivers' required

improvements to patients' ability to recognize surroundings, walk, climb stairs, and get in or out of chairs, as well as the extent to which caregivers require a diminishment of patients' problems with wandering, irritability, depression, anger, and mood swings, is not associated with the current prescribing of ChEIs to AD patients (listwise deletion OR=1.00; 95% CI=0.94 to 1.07; multiple imputation OR=0.99; 95% CI=0.93 to 1.05).

Extent to which caregivers feel they are informed about what drugs can do to treat AD

The 'informed' covariate is in two listwise deletion models and one multiple imputation model. In these models, the odds of an AD patient being currently prescribed a ChEI increase when a caregiver is somewhat or well informed about what drugs can do to help treat AD (versus poorly or not at all informed; $p<0.05$). The magnitudes of the increases are shown in Tables 4.26 and 4.27.

Patient Age

Patient age is in the listwise deletion models for index variables 1 and 2. In both cases, a 1-year increase in the age of an AD patient decreases the odds of the patient being currently prescribed a ChEI by 7% ($p<0.05$).

Patient Sex

Patient sex is in the listwise deletion model for index variable 2. The odds of an AD patient being currently prescribed a ChEI decrease by 64% if the patient is male ($p<0.05$).

Caregiver Sex

Caregiver sex is a confounder in the multiple imputation model for index variable 2. The odds of an AD patient being currently prescribed a ChEI increase by 629% if the caregiver is male ($p<0.01$).

Primary Caregiver

Primary caregiver is a confounder in the multiple imputation models for index variables 1 and 2. In the model for index variable 1, the odds of an AD patient being currently prescribed a ChEI increase by 12% if the caregiver is the primary caregiver. However, the confidence interval includes the null value for the population parameter. In the model for index variable 2, the odds of an AD patient being currently prescribed a ChEI decrease by 14% if the caregiver is the primary caregiver ($p<0.05$).

4.2.7.5. Main Effect Variables: Caregivers' Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment

4.2.7.5.1. Simple Logistic Regression Analyses

Positive, crude associations were found between the willingness of caregivers to accept adverse effects and continue patients on drug treatment and the current prescribing of ChEIs to AD patients (Table 4.28). The associations were strong in the listwise deletion analyses: odds ratios for the 11 adverse effect variables ranged from 2.35 to 6.06. For nine of the variables, the confidence intervals did not contain the null value. For all 11 variables, the confidence intervals were relatively wide. Similar results were found in the multiple imputation analyses, although the range of odds ratios

was narrower (i.e., 1.76 to 3.53) and the confidence intervals were not as wide. The findings agreed with the hypothesis that the willingness to accept adverse effects was positively associated with current prescribing.

Table 4.28: Caregiver Questionnaire: Simple Logistic Regression Analyses – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients

Main Effect Variable*	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Weight loss†	1.2278	0.3577	3.41 (1.69 to 6.88)	0.0006
Appetite loss†	1.1619	0.3425	3.20 (1.63 to 6.25)	0.0007
Headaches†	1.1402	0.3857	3.13 (1.47 to 6.66)	0.0031
Dizziness†	1.5145	0.4716	4.55 (1.80 to 11.46)	0.0013
Nausea†	1.0943	0.4099	2.99 (1.34 to 6.67)	0.0076
Diarrhea†	1.0780	0.4510	2.94 (1.21 to 7.11)	0.0168
Vomiting†	0.8531	0.5231	2.35 (0.84 to 6.54)	0.1029
Drop in blood pressure†	1.0080	0.3749	2.74 (1.31 to 5.71)	0.0072
Insomnia†	1.4395	0.3931	4.22 (1.95 to 9.12)	0.0003
Muscle cramps†	1.4319	0.3947	4.19 (1.93 to 9.08)	0.0003
Stomach bleeding†	1.8016	1.0549	6.06 (0.77 to 47.9)	0.0877
Weight loss‡	1.1567	0.3483	3.18 (1.60 to 6.30)	0.0009
Appetite loss‡	0.9956	0.3255	2.71 (1.43 to 5.12)	0.0022
Headaches‡	1.1080	0.3535	3.03 (1.51 to 6.06)	0.0018
Dizziness‡	1.2617	0.4860	3.53 (1.31 to 9.51)	0.0142
Nausea‡	0.9543	0.4185	2.60 (1.12 to 6.00)	0.0264
Diarrhea‡	0.9419	0.4551	2.56 (1.03 to 6.41)	0.0440
Vomiting‡	0.5634	0.4517	1.76 (0.72 to 4.29)	0.2144
Drop in blood pressure‡	0.8343	0.3650	2.30 (1.12 to 4.74)	0.0238

Table 4.28: Caregiver Questionnaire: Simple Logistic Regression Analyses – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (continued)

Main Effect Variable*	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Insomnia‡	1.2521	0.3550	3.50 (1.74 to 7.02)	0.0004
Muscle cramps‡	1.2596	0.3635	3.52 (1.73 to 7.20)	0.0006
Stomach bleeding‡	1.2174	0.6808	3.38 (0.88 to 13.04)	0.0706

*Each main effect variable is dichotomous. The reference category is 'caregiver is not willing to continue drug treatment for AD in the event the adverse effect occurs'; the category for which odds ratios have been estimated is 'caregiver is willing to continue drug treatment for AD in the event the adverse effect occurs.'

†Listwise deletion.

‡Multiple imputation.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval.

4.2.7.5.2. Multiple Logistic Regression Analyses: Building the Final, Best Explanatory Models for Caregivers' Willingness to Accept Adverse Effects and Continue Patients on Drug Treatment

None of the covariates had statistically significant associations with current prescribing (Appendix M). However, the covariates were still assessed as possible effect modifiers or confounders of the associations between the adverse effect variables and current prescribing. A separate multiple logistic regression model was constructed for each adverse effect variable. Index variables were not used because caregivers' tolerance for adverse effects from AD medications has received attention from other researchers.[27;28] The use of separate regression models facilitated comparisons between this study and the findings of these researchers.

For listwise deletion, two covariates were shown to be effect modifiers: caregiver overall physical health (weight loss) and patient age (dizziness and nausea).

Confounders were more abundant. Eight of the adverse effect variables had at least one confounder. The exceptions were diarrhea, insomnia, and muscle cramps. The following covariates were identified as confounders, sometimes alone in a model with one of the adverse effect variables, and sometimes in combination with other covariates: caregiver sex, caregiver overall physical health, patient age, giving AD patients non-prescription drugs to help overcome loss of independence, and the extent to which caregivers are informed about what drugs can do for AD patients. For multiple imputation, none of the covariates were shown to be effect modifiers. The only confounder was caregiver overall physical health, which intensified the association between stomach bleeding and current prescribing by 17.5%, from an odds ratio of 3.38 to 3.97.

For listwise deletion, the construction of full, reduced, and stepwise models led to the identification of one additional covariate, patient sex, which confounded the associations between most of the adverse effect variables and current prescribing. For multiple imputation, the model-building exercise yielded four other confounders: patient age, patient sex, the extent to which caregivers feel they are informed about what drugs can do to treat AD, and giving AD patients non-prescription drugs to help overcome loss of independence.

To decide which covariates to retain and which to discard, a new set of models was constructed. Each model contained an adverse effect variable and all six of the covariates that were identified as confounders in previous analyses. The covariates were removed in order of least-to-most significant; covariates whose removal changed the odds ratio of an adverse effect variable by at least 10% were retained in the

model in question, while covariates whose removal did not change the odds ratio by at least 10% were discarded. The reduced models obtained through this procedure were compared to the crude models. If the odds ratio of an adverse effect variable differed by at least 10% from the corresponding odds ratio in the crude model, then the reduced model was chosen as the best explanatory model for that variable. Otherwise, the crude model was chosen as the best explanatory model.

The final model for each adverse effect variable is shown in Tables 4.29 and 4.30. The deletion of outliers and influential observations did not have a material impact on any of the results, so the models are reported with all observations intact. Linearity was assessed and verified for the only continuous covariate in any of the models, namely patient age.

Table 4.29: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models)

Listwise Deletion (n=132-179 [range])

Model Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Weight Loss				
Intercept	1.0574	0.6129	N/A	0.0846
Weight loss*	-0.7934	1.0232	0.45 (0.06 to 3.36)	0.4381
Caregiver overall physical health				
Excellent	Reference	N/A	1.00	N/A
Very good	-0.5701	0.5687	0.57 (0.19 to 1.72)	0.3162
Good	-1.8760	0.7696	0.15 (0.03 to 0.69)	0.0148
Fair or poor	-1.9198	0.9975	0.15 (0.02 to 1.04)	0.0543
Weight loss x Caregiver overall physical health	0.8507	0.4043	2.34 (1.06 to 5.17)	0.0353

Table 4.29: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Listwise Deletion (n=132-179 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Appetite Loss				
Intercept	0.7337	0.8554	N/A	0.3910
Appetite loss*	0.8727	0.3963	2.39 (1.10 to 5.21)	0.0277
Loss of independence†				
No	Reference	N/A	1.00	N/A
Yes	-0.7801	0.6153	0.46 (0.14 to 1.53)	0.2049
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.6557	0.5479	5.24 (1.79 to 15.33)	0.0025
Well informed	0.5479	0.5926	4.35 (1.36 to 13.88)	0.0132
Patient age	-0.0845	0.0308	0.92 (0.87 to 0.98)	0.0061
Headaches				
Intercept	0.4132	0.1966	N/A	0.0356
Headaches*	1.1402	0.3857	3.13 (1.47 to 6.66)	0.0031
Dizziness				
Intercept	2.0010	0.9943	N/A	0.0442
Dizziness*	-2.3534	1.6453	0.10 (0.00 to 2.38)	0.1526
Loss of independence†				
No	Reference	N/A	1.00	N/A
Yes	-0.8090	0.6380	0.45 (0.13 to 1.56)	0.2048
Patient sex				
Female	Reference	N/A	1.00	N/A
Male	-0.8752	0.4605	0.42 (0.17 to 1.03)	0.0573
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	2.0207	0.6138	7.54 (2.27 to 25.12)	0.0010
Well informed	2.1230	0.6641	8.36 (2.27 to 30.71)	0.0014
Patient age	-0.1333	0.0393	0.88 (0.81 to 0.95)	0.0007
Dizziness x Patient age	0.1553	0.0711	1.17 (1.02 to 1.34)	0.0291

Table 4.29: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Listwise Deletion (n=132-179 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Nausea				
Intercept	1.9687	0.8709	N/A	0.0238
Nausea*	-1.7300	1.3502	0.18 (0.01 to 2.50)	0.2001
Patient sex				
Female	Reference	N/A	1.00	N/A
Male	-0.4663	0.3850	0.63 (0.30 to 1.33)	0.2258
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.0210	0.4577	2.78 (1.13 to 6.81)	0.0257
Well informed	1.0541	0.5090	2.87 (1.06 to 7.78)	0.0384
Patient age	-0.0846	0.0323	0.92 (0.86 to 0.98)	0.0088
Nausea x Patient age	0.1123	0.0559	1.12 (1.00 to 1.25)	0.0445
Diarrhea				
Intercept	0.5596	0.1809	N/A	0.0020
Diarrhea*	1.0780	0.4510	2.94 (1.21 to 7.11)	0.0168
Vomiting				
Intercept	-0.2197	0.3780	N/A	0.5611
Vomiting*	0.6022	0.5370	1.83 (0.64 to 5.23)	0.2621
Caregiver sex				
Female	Reference	N/A	1.00	N/A
Male	1.0004	0.5061	2.72 (1.01 to 7.33)	0.0481
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	0.9698	0.4369	2.64 (1.12 to 6.21)	0.0264
Well informed	0.9857	0.4898	2.68 (1.03 to 7.00)	0.0442

Table 4.29: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Listwise Deletion (n=132-179 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Drop in Blood Pressure				
Intercept	0.5636	0.8373	N/A	0.5009
Drop in blood pressure*	1.1533	0.4246	3.17 (1.38 to 7.28)	0.0066
Loss of independence†				
No	Reference	N/A	1.00	N/A
Yes	-0.9075	0.6308	0.40 (0.12 to 1.39)	0.1503
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.6902	0.5752	5.42 (1.76 to 16.74)	0.0033
Well informed	1.5669	0.6159	4.79 (1.43 to 16.02)	0.0110
Patient age	-0.0769	0.0302	0.93 (0.87 to 0.98)	0.0109
Insomnia				
Intercept	0.3522	0.1945	N/A	0.0702
Insomnia*	1.4395	0.3931	4.22 (1.95 to 9.12)	0.0003
Muscle Cramps				
Intercept	0.3429	0.1971	N/A	0.0819
Muscle cramps*	1.4319	0.3947	4.19 (1.93 to 9.08)	0.0003

Table 4.29: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Listwise Deletion (n=132-179 [range])

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Stomach Bleeding				
Intercept	2.2697	1.1365	N/A	0.0458
Stomach bleeding*	2.1158	1.1617	8.30 (0.85 to 80.62)	0.0686
Caregiver overall physical health				
Excellent	Reference	N/A	1.00	N/A
Very good	-0.1275	0.5743	0.88 (0.29 to 2.71)	0.8243
Good	-0.8021	0.5757	0.45 (0.15 to 1.39)	0.1636
Fair or poor	-1.0029	0.8617	0.37 (0.07 to 1.99)	0.2445
Patient sex				
Female	Reference	N/A	1.00	N/A
Male	-0.6748	0.4691	0.51 (0.20 to 1.28)	0.1503
Loss of independence†				
No	Reference	N/A	1.00	N/A
Yes	-0.6235	0.4691	0.54 (0.16 to 1.86)	0.3250
Informed‡				
Not/poorly informed	Reference	N/A	1.00	N/A
Somewhat informed	1.5494	0.6314	4.71 (1.37 to 16.23)	0.0141
Well informed	1.6057	0.6745	4.98 (1.33 to 18.68)	0.0173
Patient age	-0.1066	0.0343	0.90 (0.84 to 0.96)	0.0019

*Adverse effect variables are dichotomous. The reference category is 'caregiver is not willing to continue drug treatment for AD in the event the adverse effect occurs'; the category for which odds ratios have been estimated is 'caregiver is willing to continue drug treatment for AD in the event the adverse effect occurs.'

†Caregiver gives AD patient non-prescription drugs to help overcome loss of independence.

‡The extent to which caregivers are informed about what drugs can do for AD patients.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

Table 4.30: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models)

	Multiple Imputation (n=201)			
Model Variable	**Parameter Estimate**	**Standard Error**	**Odds Ratio (95% CI)**	**p-value**
Weight Loss				
Intercept	-0.0064	0.2799	N/A	0.9818
Weight loss*	1.1567	0.3483	3.18 (1.60 to 6.30)	0.0009
Appetite Loss				
Intercept	0.1581	0.2545	N/A	0.5345
Appetite loss*	0.9956	0.3255	2.71 (1.43 to 5.12)	0.0022
Headaches				
Intercept	0.3709	0.4539	N/A	0.0280
Headaches*	1.1080	0.3535	3.03 (1.51 to 6.06)	0.0018
Dizziness				
Intercept	0.4663	0.1904	N/A	0.0152
Dizziness*	1.2617	0.4860	3.53 (1.31 to 9.51)	0.0142
Nausea				
Intercept	0.5184	0.1885	N/A	0.0062
Nausea*	0.9543	0.4185	2.60 (1.12 to 6.00)	0.0264

Table 4.30: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Multiple Imputation (n=201)

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
Diarrhea				
Intercept	2.5133	0.8255	N/A	0.0024
Diarrhea*	1.0599	0.4717	2.89 (1.11 to 7.48)	0.0299
Overall caregiver physical health				0.0630
Excellent	Reference	N/A	1.00	
Very good	-0.3298	0.1772	0.72 (0.51 to 1.02)	
Good	-0.6596	0.3544	0.52 (0.26 to 1.04)	
Fair or poor	-0.9894	0.5316	0.37 (0.13 to 1.05)	
Patient age	-0.0485	0.0249	0.95 (0.91 to 1.00)	0.0518
Vomiting				
Intercept	0.6968	0.1723	N/A	<0.0001
Vomiting*	0.5634	0.4517	1.76 (0.72 to 4.29)	0.2144
Drop in Blood Pressure				
Intercept	-0.0505	0.9200	N/A	0.9562
Drop in blood pressure*	0.7175	0.3815	2.05 (0.96 to 4.37)	0.0628
Caregiver sex				
Female	Reference	N/A	1.00	N/A
Male	0.6447	0.4299	1.91 (0.82 to 4.43)	0.1338
Overall caregiver physical health				0.0998
Excellent	Reference	N/A	1.00	
Very good	0.4051	0.2459	1.50 (0.93 to 2.43)	
Good	0.8102	0.4918	3.00 (1.86 to 4.86)	
Fair or poor	1.2153	0.7377	4.50 (2.79 to 7.29)	
Patient age	-0.0248	0.0243	0.98 (0.93 to 1.02)	0.3077
Insomnia				
Intercept	0.3466	0.1917	N/A	0.0706
Insomnia*	1.2521	0.3550	3.50 (1.74 to 7.02)	0.0004

Table 4.30: Caregiver Questionnaire – Willingness to Accept Adverse Effects and Continue AD Patients on Drug Treatment and the Current Prescribing of ChEIs to AD Patients (Final Models) (continued)

Model Variable	Parameter Estimate	Standard Error	Odds Ratio (95% CI)	p-value
		Multiple Imputation (n=201)		
Muscle Cramps				
Intercept	0.8307	1.0666	N/A	0.4363
Muscle cramps*	1.1514	0.3775	3.16 (1.50 to 6.65)	0.0025
Caregiver sex				0.1488
Female	Reference	N/A	1.00	
Male	0.6509	0.4507	1.92 (0.79 to 4.64)	
Overall caregiver physical health				0.1000
Excellent	Reference	N/A	1.00	
Very good	-0.2974	0.1808	0.74 (0.52 to 1.06)	
Good	-0.5948	0.3616	0.55 (0.27 to 1.12)	
Fair or poor	-0.9822	0.5424	0.37 (0.13 to 1.08)	
Informed†				0.1771
Not/poorly informed	Reference	N/A	1.00	
Somewhat informed	0.3410	0.2525	1.41 (0.86 to 2.31)	
Well informed	0.6820	0.5050	2.82 (1.72 to 4.62)	
Patient age	-0.0350	0.0254	0.97 (0.92 to 1.01)	0.1682
Stomach Bleeding				
Intercept	1.3720	0.4497	N/A	0.0023
Stomach bleeding*	1.3800	0.7051	3.97 (0.98 to 16.18)	0.0539
Overall caregiver physical health				0.1027
Excellent	Reference	N/A	1.00	
Very good	-0.2873	0.1758	0.75 (0.53 to 1.06)	
Good	-0.5746	0.3516	0.56 (0.28 to 1.12)	
Fair or poor	-0.8619	0.5274	0.42 (0.15 to 1.19)	

*Adverse effect variables are dichotomous. The reference category is 'caregiver is not willing to continue drug treatment for AD in the event the adverse effect occurs'; the category for which odds ratios have been estimated is 'caregiver is willing to continue drug treatment for AD in the event the adverse effect occurs.'

†The extent to which caregivers are informed about what drugs can do for AD patients.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, CI = confidence interval, N/A = not applicable.

4.2.7.5.3. Model Interpretation

Adverse Effect Variables

For the most part, the final models in Tables 4.29 and 4.30 indicate that the odds of an AD patient being currently prescribed a ChEI increase when caregivers are willing (versus not willing) to continue drug treatment following an adverse effect. These positive associations support the hypothesis, i.e., a willingness by caregivers to accept adverse effects is positively associated with the current prescribing of ChEIs. The associations were quite strong, with estimated odds ratios ranging from 1.83 to 8.30 (listwise deletion) and 1.76 to 3.53 (multiple imputation). Six adverse effect variables in the listwise deletion analyses, and eight in the multiple imputation analyses, were statistically significant at the 5% level.

In the listwise deletion analysis, effect modification was present for weight loss, dizziness, and nausea. Caregiver overall physical health modified weight loss; patient age modified dizziness and nausea. Except for one instance, effect modification produced negative associations between the three adverse effects and current prescribing. For weight loss, the odds of current prescribing increased by 6% when caregivers were willing to continue drug treatment in the face of the adverse effect, provided caregiver overall physical health was excellent. If health was very good, then the odds decreased by 40%. If health was good, then the odds decreased by 84%; if fair or poor, then 85%. For dizziness, the odds of current prescribing decreased by 90% when caregivers were willing to continue drug treatment and age remained constant. If age increased by one year, then the decrease in odds would be 90.3%; if age increased by 10 years,

then the decrease would be 88%. For nausea, the odds of current prescribing decreased by 82% when caregivers were willing to continue drug treatment and age remained constant or increased by only one year. If age increased by 10 years, then the odds decreased by 77%. There was no effect modification in the multiple imputation analyses.

Caregiver Overall Physical Health

Besides its role as an effect modifier of the association between weight loss and current prescribing, caregiver overall physical health appeared as a confounder in one listwise deletion model and four multiple imputation models. In every model except the multiple imputation model for a drop in blood pressure, the odds of an AD patient being currently prescribed a ChEI decreased progressively when caregivers reported very good, good, or fair or poor health (relative to excellent health). For a drop in blood pressure, the odds increased progressively as caregivers reported lower levels of health relative to excellent health. However, in all but two instances, the confidence intervals included the null value for the population parameter.

Non-prescription Drugs for Loss of Independence

This covariate appeared as a confounder in four listwise deletion models, where the odds of an AD patient being currently prescribed a ChEI decreased when caregivers gave AD patients non-prescription drugs to help overcome loss of independence (versus not giving patients such drugs). However, the confidence intervals contained the null value for the population parameter.

Extent to which caregivers feel they are informed about what drugs can do to treat AD

The 'informed' covariate appeared as a confounder in six listwise deletion models and one multiple imputation model. In all models, the odds of an AD patient being currently prescribed a ChEI increased when a caregiver was somewhat or well informed about what drugs can do to help treat AD (versus poorly or not at all informed). All associations were statistically significant at the 5% level except for the one involving the 'somewhat informed' category in the multiple imputation model for muscle cramps.

Patient Age

Besides its role as an effect modifier in two listwise deletion models, patient age was a confounder in another three listwise deletion models and in three multiple imputation models. In these six latter models, a 1-year increase in the age of an AD patient decreased the odds of the patient being currently prescribed a ChEI by 2 to 10%. The confidence intervals did not include the null value for the population parameter in the case of the listwise deletion models, but they did include the null value in the case of the multiple imputation models.

Patient Sex

This covariate appeared as a confounder in three listwise deletion models. The odds of an AD patient being currently prescribed a ChEI decreased by an average of 48% when the patient was male. However, all of the confidence intervals included the null value for the population parameter.

Caregiver Sex

Caregiver sex was a confounder in one listwise deletion model and two multiple imputation models. When the caregiver was male, the odds of an AD patient being currently prescribed a ChEI increased by 272% (listwise deletion) and by 91% or 92% (multiple imputation). The association was statistically significant at the 5% level in the listwise deletion model, but not in either multiple imputation model.

4.3. Summary of Regression Results

The results of the regression analyses were presented separately for the physician and caregiver parts of the study. As a prelude to the discussion, the results will be summarized in tandem (Table 4.31).

According to the results, the directions of association between the main effect variables and the current prescribing of ChEIs to AD patients supported a priori hypotheses for physicians' efficacy requirements (favourable requirements and increases in length of stabilization), caregiver-physician discussions, and caregiver pressure. Conversely, the directions of association did not support some a priori hypotheses for delays to institutionalization, caregivers' required improvements to domains affected by AD, and caregivers' willingness to accept adverse effects (Table 4.31).

Overall, 22 main effect variables were studied in regression analyses. When missing values were handled by listwise deletion, nine variables were found to be statistically significantly associated with current prescribing at the 5% level. When

missing values were handled by multiple imputation, 10 variables were found to be statistically significantly associated with current prescribing at the 5% level. Some main effect variables were consistently significant, or not significant, in both sets of models. Conversely, other main effect variables were significant in one set of models, but not in the other set of models.

Effect sizes for the main effect variables ranged from small for physicians' efficacy requirements to anywhere from small to large for the caregiver variables. Many of the moderate to strong effects were not statistically significant at the 5% level, probably due to a lack of power to detect smaller true effects or to the absence of a true effect in the study population. Several of the moderate to strong effects were also accompanied by wide confidence intervals, which were likely to have resulted from random error in questionnaire responses (Sections 4.1.4 and 4.2.5).

Several covariates were confounders or independently associated with current prescribing. Six such covariates were found in analyses of the physician questionnaire (Table 4.32), and eight such covariates were found in analyses of the caregiver questionnaire (Table 4.33).

Table 4.31: Summary of Regression Results – Physician and Caregiver Questionnaires

Main Effect Variables →	Physicians' Favourable Efficacy Requirements	Physicians' Efficacy Requirements – Increased Length of Stabilization	Caregiver-Physician Discussions	Caregiver Pressure	Caregiver Importance - Delays to Institutionalization	Caregivers' Required Improvements to Domains Affected by AD	Caregivers' Willingness to Accept Adverse Effects and Continue Drug Treatment
Direction of association (main effect)	Negative NS	Negative SS	Positive NS	Positive NS	Negative (1 MI) Positive (4 LD, 3 MI) NS	Negative (2 LD, 2 MI) Positive (1 MI) Null (1 LD) SS (2 LD, 1 MI) NS (1 LD, 2 MI)	Positive (except 3 LD models with effect modification [negative]) SS (6 LD, 8 MI) NS (5 LD, 3 MI)
Direction agrees with hypothesis	Yes	Yes	Yes	Yes	Yes (if negative) No (if positive)	Yes (if negative) No (if positive or null)	Yes (if positive) No (if negative)
Effect size (odds ratios - main effect)	Small (0.99 [LD] or 0.92 [MI])	Small (0.99 [LD and MI])	Strong (2.37 [LD] or 1.97 [MI])	Moderate (1.33 [LD] or 1.22 [MI])	Small to strong (1.21 to 3.47 [LD] or 0.99 to 1.49 [MI])	Small to moderate (0.79 to 1.00 [LD] or 0.74 to 1.02 [MI])	Strong (0.10 to 8.30 [LD]) (1.76 to 3.53 [MI])
Reasons for statistical non-significance (main effect)	Lack of power	N/A	Lack of power or no true effect	Lack of power or no true effect	Lack of power or no true effect	No true effect	Lack of power or no true effect
Width of confidence intervals (main effect)	Random error in responses could have widened the CIs	N/A	Wide CIs could have resulted from random error in responses	Wide CIs could have resulted from random error in responses	Wide CIs (LD model) could have resulted from random error in responses	Most confidence intervals are not wide, so the effect of random error is minimal	Wide CIs could have resulted from random error in responses

Table 4.31: Summary of Regression Results – Physician and Caregiver Questionnaires (continued)

Main Effect Variables →	Physicians' Favourable Efficacy Requirements	Physicians' Efficacy Requirements – Increased Length of Stabilization	Caregiver-Physician Discussions	Caregiver Pressure	Caregiver Importance - Delays to Institutionalization	Caregivers' Required Improvements to Domains Affected by AD	Caregivers' Willingness to Accept Adverse Effects and Continue Drug Treatment
Covariates	Many covariates were found to be associated with current prescribing, although only in models with other covariates. No one variable explains current prescribing, but variables come together to explain why physicians might prescribe ChEIs.	Some covariates were found to be associated with current prescribing. No one variable explains current prescribing, but variables come together to explain why physicians might prescribe ChEIs.	Only one covariate was found to be a confounder (i.e., caregiver age in the LD model).	Only one covariate was found to be a confounder (i.e., the extent to which caregivers are aware of what drugs can do to treat AD [LD model only]).	Several covariates acted as confounders in LD models, but not in MI models.	Several covariates acted as confounders in models for index variables 1 and 2, but no covariates acted as confounders in models for index variable 3.	Several covariates acted as confounders, and there was effect modification for three adverse effect variables (LD only).

Table 4.31: Summary of Regression Results – Physician and Caregiver Questionnaires (continued)

Main Effect Variables →	Physicians' Favourable Efficacy Requirements	Physicians' Efficacy Requirements – Increased Length of Stabilization	Caregiver-Physician Discussions	Caregiver Pressure	Caregiver Importance - Delays to Institutionalization	Caregivers' Required Improvements to Domains Affected by AD	Caregivers' Willingness to Accept Adverse Effects and Continue Drug Treatment
Listwise deletion versus multiple imputation	LD and MI models were similar to one another in terms of the variables included in the models and the magnitude of the effects of these variables. This suggests minimal bias due to missing values.	Besides the main effect variable, the same two covariates were statistically significant in both the LD and MI models. Also, two additional covariates were in the MI model, suggesting a possible bias due to missing values.	Odds ratio in LD model was 20% greater than odds ratio in MI model, although the difference was not statistically significant. Bias is still possible because the association was not as strong among observations with missing data.	LD and MI models were similar to one another, thereby suggesting minimal bias due to missing values.	Odds ratios in LD models were larger than odds ratios in MI models, although the differences between LD and MI odds ratios were not statistically significant. Bias is still possible because associations between delays and current prescribing were attenuated in observations with missing data.	Index variable 1: different covariates in LD and MI models (bias); effect of index variable was the same in both models (no bias) Index variable 2: most covariates in LD and MI models differ (bias); no association between index variable and current prescribing in MI model (bias) Index variable 3: no differences in LD and MI models (no bias)	In the MI models, fewer covariates acted as confounders and there was no effect modification. 7 MI models had no covariates (versus 4 LD). Bias? → perhaps caregivers with missing values were more 'average,' so their inclusion in the MI models eliminated the effects of many covariates.

Notes: AD = Alzheimer's disease, NS = not statistically significant, SS = statistically significant, LD = listwise deletion, MI = multiple imputation, N/A = not applicable, CI = confidence interval, ChEI = cholinesterase inhibitor.

Table 4.32: Covariates Appearing in Regression Models: Physician Questionnaire

Covariate	Number of Models in which Covariate Appears	
	Listwise Deletion (Total # Models=2)	Multiple Imputation (Total # Models=2)
Level of knowledge regarding the efficacy of ChEIs	1	2
Prescribing index – other dementias	1	0
Percentage of patients in a practice with mild AD	2	2
Percentage of patients with adverse effects – rivastigmine	2	2
Level of belief in the ability of ChEIs to meet physicians' efficacy requirements (index)	0	1
Physician specialty	0	2

Notes: ChEIs = cholinesterase inhibitors, AD = Alzheimer's disease.

Table 4.33: Covariates Appearing in Regression Models: Caregiver Questionnaire

Covariate	Number of Models in which Covariate Appears	
	Listwise Deletion (Total # Models=20)	Multiple Imputation (Total # Models=20)
Extent to which caregivers feel they are informed about what drugs can do to treat AD	13	2
Patient sex	5	0
Patient age	9	4
Primary caregiver	1	2
Caregivers give patients non-prescription drugs for loss of independence	6	0
Caregiver sex	1	3
Caregiver age	1	0
Caregiver overall physical health	2	3

Notes: AD = Alzheimer's disease.

For analyses of the physician questionnaire, more covariates appeared in the multiple imputation rather than listwise deletion models, although the net difference was only one covariate more in the multiple imputation models. For analyses of the caregiver questionnaire, the situation was reversed. More covariates appeared in the listwise deletion models, and there was a greater imbalance between covariates across both sets of models. Each of the eight covariates appeared in at least one listwise deletion model, while only five covariates appeared in at least one multiple imputation model. For example, the extent to which caregivers feel they are informed about what drugs can do to treat AD appeared in 13 listwise deletion models and in only two multiple imputation models.

A bias due to missing values could explain the different mixes of covariates between the listwise deletion and multiple imputation models. The missing values, which ranged from 0 to approximately 50% depending on the covariate in question (see Appendices J and L), obscured the effects of some covariates and amplified the effects of others. The bias can also explain differences in the magnitude of the odds ratios for certain main effect variables. In the analyses for caregiver-physician discussions, as well as in the analyses for delays to institutionalization, the odds ratios were larger in the listwise deletion models. This suggests weaker associations for respondents with missing values. However, the impact of any bias in these models was probably minimal because the estimated odds ratios in the listwise deletion models were relatively similar to the estimated odds ratios in the multiple imputation models.

There were no substantial differences between the listwise deletion and multiple imputation models for three main effect variables, namely physicians' favourable efficacy requirements, caregiver pressure, and index variable 3 for caregivers' required improvements to domains affected by AD. In these models, the discrepancies involving covariates and odds ratios were minimal. Therefore, these models were unlikely to have been affected by a bias due to missing values.

In the next chapter, the study results will be discussed in the context of the overall objective of the thesis, i.e., to broaden the understanding of the physician and caregiver perspectives on the use of medications in AD.

5. DISCUSSION

5.1. Overall Objective of Thesis and Overview of Chapter

The overall objective of this thesis research was to provide an understanding of physician and caregiver perspectives on the use of drugs to treat AD. This involved the collection of data in several domains, including physician and caregiver efficacy requirements for using new AD medications, caregiver opinions on adverse effects and institutionalization, and the caregiver-physician relationship. As well, the association between each of these domains and the prescribing of ChEIs was estimated to study prescribing behaviour. Since the current literature has little or no information on any of these domains, the major contribution of this thesis is new data that can be applied to improving the understanding of the physician and caregiver perspectives. In this chapter, the results of the research are discussed within the context of this understanding, the strengths and limitations of the thesis are examined, new areas of research are considered, and the final conclusions are presented.

5.2. Discussion of Physician and Caregiver Efficacy Requirements

According to the results, physicians would require, as a prerequisite to prescribing, that a hypothetical new AD drug be able to permanently stabilize cognition, reduce further occurrences of problematic behaviours and moods, or improve or prevent further diminishment of a patient's ability to perform activities of daily living. Moreover, physicians reported that a mean increase of 15 months in the mild stage of AD would be

a prerequisite to prescribing a drug aimed at prolonging the time patients spend in this stage. Physicians reported that the mean increase would be 11 months for patients in the moderate stage of AD.

The findings from the caregiver survey showed that a majority of caregivers would require good or excellent improvement in memory before they would agree to have their loved ones treated with a hypothetical new AD drug. For many of the other 14 domains affected by AD, 30-40% of caregivers required good or excellent improvement. For delays to institutionalization, 35-43% of caregivers claimed that any delay would be a very important potential outcome for an AD medication. For adverse effects, most caregivers were willing to continue drug treatment in the event patients suffered weight or appetite loss. However, caregivers were not generally willing to continue drug treatment in the event of other adverse effects.

5.2.1. Physician and Caregiver Efficacy Requirements as Benchmarks for Drug Development and Assessment

The utility of eliciting physician and caregiver efficacy requirements is that these requirements can be used as benchmarks for drug development and assessment. Researchers developing new AD medications, especially medications that will alter the course of disease rather than treat only symptoms, can use the information to help identify clinically relevant targets for drug action (e.g., levels of improvement in cognition or behaviour). As well, the information on increases to length of stabilization can be used to specify minimum clinically meaningful differences for planned clinical

trials of drugs whose symptomatic impact on AD is better than that of the ChEIs.

In relation to drug assessment, new medications can be evaluated in phase IV studies or through systematic reviews to determine if physicians' and caregivers' efficacy requirements have been attained in standard practice settings. This step is important for understanding drug utilization. Medical opinion makers (e.g., eminent physicians in a particular specialty or the principal investigators who conduct clinical trials) may view a new drug that comes on the market favourably, perhaps because the change in score on an outcome measurement scale such as the ADAS-cog or CIBIC-plus (Sections 2.1.2.1 and 2.1.2.2) was found to be statistically significant in a trial. However, the clinical relevance of what are often small changes in scale score is not always clear, so AD drugs that appear efficacious in trials might not receive widespread use in everyday medical practice. By eliciting physician efficacy requirements, a body of benchmark efficacy data has been generated to help evaluate the performance and use of new drugs in AD.

Caregivers, who are generally omitted from consideration in clinical trials, and who were found in this research (Section 4.1.5.1) to have only an equivocal influence on physicians' prescribing decisions, are nevertheless the gatekeepers between the intent to treat AD patients with medications and the actual use of medications by these patients. Even at relatively early stages of disease, it is often caregivers who take direct responsibility for administering medications. Thus, when it comes to developing and evaluating drug treatments for AD, caregivers' efficacy requirements are just as important as physicians' efficacy requirements. For example, caregivers who are dissatisfied with drug performance may not want patients treated with a

certain medication, and they may even restrict patient access to the medication, regardless of whether a physician has prescribed the drug.

Caregiver opinions on adverse effects from AD medications are also important. This is because the impact of dealing with adverse effects often adds to caregiver burden. As the burden increases, it is possible that some caregivers might seek relief by stopping drug therapy. Also, since caregivers often decide to institutionalize patients in response to burden,[29] it is conceivable that difficult to manage adverse effects could contribute to the decision to institutionalize. This possibility is contrary to the standard view of drug treatments in AD, namely that medications will lessen the burden of caring and reduce the need to institutionalize.[29] Data from the caregiver study indicate that most caregivers would not want to continue drug treatment if patients suffered from any one of a series of common adverse effects (Section 4.2.6). Only in the case of weight or appetite loss would a majority of caregivers be willing to continue drug treatment.

The elicitation of physician and caregiver efficacy requirements responds to researchers who have called for a broad group of stakeholders to be given a voice in defining goals for AD treatment.[25;26;28;30] The public expression of these requirements can promote a therapeutic alliance[32] (Section 1.4.3) between physicians and caregivers. This is because both groups are given a means to better understand one another's viewpoints. Such an understanding can allow physicians and caregivers to work together and plan therapeutic strategies for patients.

5.2.2. *Efficacy Requirements – Lack of Concordance between Questionnaire Responses and Actual Behaviour*

A concern that arises in research where questionnaires are used is that there may be a difference between what people say they do and what they really do. The difference may occur because of social desirability bias.[216] In this research, two steps were taken to minimize social desirability bias (Sections 3.2.1.5 and 3.3.1.5): postal questionnaires rather than in-person interviews were used to collect data[217-219] and the importance of the research was stressed in the cover letters that accompanied the questionnaires.[221]

To examine the extent of discordance between answers to the questionnaires and prescribing behaviour, multiple regression analyses were conducted to investigate the associations between physician and caregiver requirements on the one hand and the reported current prescribing of ChEIs to AD patients on the other hand. Since the efficacy of ChEIs has been shown to be limited to the symptomatic treatment of AD for periods of six months to one year, it was hypothesized that respondents with more stringent requirements for a hypothetical new AD medication would be less likely to currently prescribe ChEIs or care for patients who are currently prescribed ChEIs. It was thought these respondents would not want patients treated with what to them must seem like an inferior class of drugs.

Referring back to Table 4.31, there were inverse associations in half (9/18) of the models involving current prescribing and physicians' efficacy requirements, the level of importance caregivers attach to delays to institutionalization, or caregivers' required improvements to domains affected by AD. The associations were positive in the other

half of the models. In 13 of the 18 models, the associations were not statistically significant at the 5% level of significance, so there could well have been no true associations in some instances. Due to these results, it is not possible to determine whether respondents' answers to the requirements questions reflect physicians' and caregivers' actual behaviours.

Unlike the models discussed above, the models for caregivers' willingness to accept adverse effects do provide some indication as to whether respondents' behaviour would match their answers to the questionnaire. The results in 19 out of 22 adverse effect models agreed with the hypothesis, which was that an increased willingness to accept an adverse effect would be positively associated with current prescribing. Additionally, 13 of the models featured associations that were statistically significant at the 5% level of significance. Thus, there was evidence showing that caregiver-respondents 'practice what they preach' where adverse effects are concerned. In the three adverse effect models that were not in agreement with the hypothesis, effect modification was present and the associations were negative.

5.3. Discussion of other Caregiver Analyses: Caregiver-Physician Discussions about Drug Treatments for AD and Caregiver Pressure

When studying the use of drug treatments in AD from the caregiver perspective, one cannot neglect the fact that prescriptions for medications are obtained from physicians. Caregivers may want patients treated with an AD medication, but a physician must first write the prescription. Since caregivers act as advocates and as proxy decision makers for patients, it is important to investigate whether caregivers can

influence the prescribing decisions of physicians. Until now, there had been no examination of the physician-caregiver relationship in the area of drug treatments for AD. An unbalanced relationship could make a therapeutic alliance[32] between physicians and caregivers difficult to achieve. The lack of such an alliance, and the concomitant potential for fragmented approaches to treatment, could prevent patients from receiving optimal therapy.

The physician-caregiver relationship was examined using multiple logistic regression models. The main effect variables were 'the person who raised the possibility of using drug therapy' and 'caregiver pressure on physicians to prescribe AD drugs.' A priori hypotheses posited that current prescribing would be greater when physicians were the first to raise the possibility of using drug therapy and also when caregivers put pressure on physicians to prescribe AD medications.

The results of these regression analyses (Sections 4.2.7.1 and 4.2.7.2) were inconclusive. Current prescribing was positively associated with physicians being the first persons to talk about using drug therapy and with caregiver pressure to prescribe. The directions of association seemed to confirm the hypotheses and the estimated odds ratios were moderate to strong in magnitude. However, the same odds ratios were not statistically significant at the 5% level of significance.

5.4. Discussion of Important Covariates

Several covariates were examined as possible effect modifiers or confounders of the primary associations under investigation. Although there was little

evidence of effect modification, some covariates were found to be confounders. In the regression models, a few of these covariates were also found to be statistically significantly associated with the current prescribing of ChEIs. It is evident from Tables 4.32 and 4.33 that a small number of covariates were of recurring importance in the regression analyses. Since no a priori hypotheses were formulated about the relations between these covariates and current prescribing, the associations observed in the regression models should be taken as hypothesis generating. What can be said at this point is that some covariates appear to have good explanatory value with respect to the current prescribing of ChEIs. This is especially so for the covariate 'extent to which caregivers are informed about what drugs can do to treat AD.' More thorough interpretations of the findings for the covariates should follow further research wherein a priori hypotheses are formulated for these covariates. The covariates could then be evaluated as main effect variables in regression models.

Several covariates (e.g., caregiver age, primary caregiver, patient age and sex) were found to be confounders of the associations between the main effect variables in the caregiver study and the current use of ChEIs. The direction and magnitude of the impact of these covariates was variable. In some cases, the presence of one or more confounding covariates amplified an association between a main effect variable and the current use of ChEIs, and in other cases the association was attenuated. The effect of the covariates was also influenced by the interplay with other covariates in the same model.

One interesting pair of covariates from the caregiver perspective was 'primary caregiver' and patient status as institutionalized or not. Primary and

secondary caregivers may have different views on AD drugs, as may caregivers of institutionalized versus non-institutionalized patients. It is possible that secondary caregivers have less direct experience with drug treatments, and drugs have not generally been targeted to more severely affected, institutionalized patients. Since about 25% of caregiver respondents were not primary caregivers, and 38% were caring for institutionalized patients, it is possible that some of the inconclusive findings (e.g., delays to institutionalization) could have been due to the heterogeneity of the caregiver sample. Indeed, 'primary caregiver' was shown to be a confounder in some models (there was no adjustment done for whether a patient was institutionalized). The potential impact of sample heterogeneity suggests that a future course of research would be to conduct exploratory analyses that are stratified by primary versus secondary caregiver or caregivers of institutionalized patients versus caregivers of non-institutionalized patients.

Similar comments can be made about the physician sample, with heterogeneity defined in terms of physician specialty or GPs who attended courses on geriatrics and the elderly versus GPs who did not. However, physician specialty was not shown to be a confounder (although it was shown to be independently associated with current prescribing in some models). Therefore, it was not necessary to conduct an exploratory analysis of the association between physicians' efficacy requirements and current prescribing after having first stratified by specialty. In future research, it would be interesting to investigate whether the results would differ in the sub-population of GPs if there was stratification according to attendance or non-attendance at continuing medical education courses.

5.5. Study Results and Published Data

The results of this study pertain to areas that have received little attention in the AD literature. Therefore, only a few comparisons can be made with published data. The comparisons that can be made relate to delays to institutionalization and caregivers' willingness to accept adverse effects. Karlawish et al.[27] asked 40 caregivers to indicate the importance of a one-year delay before placing an AD patient in a nursing home. Answers were given on a six-point scale ranging from 'not at all important' (score=0) to 'extremely important' (score=5). Most caregivers answered 'extremely important.' This matches well with the results from the thesis, where over half of the responding caregivers, excluding persons with missing values, reported that each of the four delays to institutionalization was 'very important' (Appendix L). Clearly, caregivers place a great deal of value on outcomes that involve delays to institutionalization.

Karlawish et al.[27] also asked their sample of 40 caregivers to assume that the hypothetical AD medication carried a risk of GI bleeding. The caregivers were required to express, in terms of percentages, their risk tolerance for each of three increasingly severe levels of GI bleeding. For minimal bleeding that stops when the drug is no longer taken, caregivers said they would allow their relatives with AD to take the drug as long as the chance of occurrence of GI bleeding was no more than an average of 62%. For bleeding requiring hospitalization and possible transfusion or surgery, the chance was no more than an average of 25%. For bleeding resulting in death, the chance was no more than an average of 8%. In a subsequent study,[28] Karlawish et al. asked 102 caregivers about their willingness to use two hypothetical AD medications. The first

drug was risk-free, while the second drug carried a three percent annual risk of GI bleeding that could lead to hospitalization, transfusion, or surgery. Seventeen (17%) of the caregivers said they would refuse to use the risk-free drug and half said they would refuse to use the riskier version. These findings suggest caregivers are less willing to accept increasingly severe adverse effects and have patients continue on drug treatment. Results leading to the same conclusion were found in the current caregiver study. A majority of respondents, excluding persons with missing values, reported they would be somewhat or clearly willing to accept weight or appetite loss and allow patients to continue receiving drug treatment. Conversely, only 15 respondents (18%) would be somewhat or clearly willing to accept the most serious adverse effect, i.e., stomach bleeding, and allow patients to continue receiving drug treatment (Appendix L).

The results of the caregiver study also add to the literature on adverse effects because caregivers were asked about their willingness to accept 11 adverse effects, rather than just one adverse effect as in the Karlawish et al. studies. A majority of caregivers reported they would not be willing to accept nine of the 11 adverse effects, including moderate effects such as headaches or nausea. Many of the moderate adverse effects are common to ChEIs, and it is telling from the descriptive results (Appendix L) that the vast majority of respondents who were not currently using ChEIs, or who had never used ChEIs, were not willing to accept many of the moderate adverse effects. Multiple logistic regression analyses (Section 4.2.7.5; Table 4.31) also indicated generally positive associations between caregivers' willingness to accept adverse effects and the current prescribing of ChEIs. It would appear that caregivers' willingness to accept adverse

effects has an influential impact on whether patients receive medications for AD.

In summary, the findings of this study were consistent with published material[27;28] on delays to institutionalization and the willingness to accept adverse effects. The remainder of the findings for this study were in areas that until now have not been extensively researched, despite an identified need for such research.[25;26;28;30;31]

5.6. Study Strengths

This study has three major strengths. First, it is focused primarily on areas for which there is no information in the published literature, save for the work of Karlawish et al.[27;28] Consequently, considering the findings of this study can enhance understanding of many issues surrounding the use of drug treatments in AD. For example, the regression analyses discussed in the previous chapter are the first to show associations between certain variables (e.g., physicians' and caregivers' efficacy requirements) and the prescribing of ChEIs.

The second strength is that the study's results are timely given ongoing research into new AD medications. This is especially so given the recent approval of memantine in Canada, where data on physician and caregiver efficacy requirements can be used to assess the performance of the drug in actual clinical settings.

The third strength is the methodological rigour with which the study was conducted. The questionnaires were developed with expert input and pre-tested on intended recipients; a hybrid cognitive interview-consensus panel format was used to pre-

test the caregiver questionnaire. The questionnaires were designed to encourage a high response rate through consideration of appearance and font, colour and type of paper, and use of first-class stamps on return envelopes. Additionally, the questionnaires were administered in multiple mailings.

A comprehensive approach was adopted for the statistical analysis. Two sets of regression models (i.e., listwise deletion and multiple imputation) were built for each main effect variable to investigate the impact of missing data. The thrust of the statistical analysis was to develop a best explanatory model for each main effect variable. Covariates were also considered as possible effect modifiers, confounders, or independent explanatory variables for the current use of ChEIs.

5.7. Study Limitations

5.7.1. Cross-sectional Design

The study data were cross-sectional, so in the case of the regression analyses one cannot assume that respondents' requirements preceded the prescribing of ChEIs. The specification of requirements could have been a reaction to the observed efficacy of ChEIs. For example, some respondents might have been dissatisfied with the performance of ChEIs and therefore specified stringent requirements. The issue of the temporal sequence in cross-sectional studies can produce reverse-causality bias.[254] There is no way to know with certainty if this bias is present and to what extent it may have had an impact on the results of this study. Caution must therefore be exercised when

interpreting the regression models.

Reverse-causality bias is less likely to affect the models for caregiver-physician discussions and caregiver pressure because a degree of temporality is built into these two models. The underlying questions that were used to form variables for the models required that caregivers indicate who first talked about the possibility of prescribing ChEIs and whether pressure ever had to be put on a physician to treat a patient with an AD drug. The implied temporal context in both questions is the period before ChEIs were initially prescribed.

In spite of the potential for reverse-causality bias, the study contains a wealth of data that has never before been elicited in research on AD medications. Also, the regression analyses can be regarded as tools to generate hypotheses rather than to confirm hypotheses. Indeed, cross-sectional studies are ideally suited for hypothesis generation, and they are a fitting first step in situations where phenomena have not been previously studied.[254]

Another important issue to consider is the feasibility of collecting data with a study design that avoids the problem of reverse-causality bias. A prospective study is an option, but the moderately high prevalence of patients who are prescribed ChEIs (Sections 4.1.5.3 and 4.2.3) would make it difficult to assemble samples of physicians and caregivers who are not initially involved with prescribing. Also, to examine the association between any of the main effect variables in this study and the future prescribing of a disease altering AD medication, a prohibitively long follow-up would be

required because no such drug is close to being developed. A cross-sectional design served as the most expedient means of proceeding with this study.

5.7.2. Selection Bias

5.7.2.1. Physician Sample

Physicians who were most likely to see AD patients were targeted for inclusion in the study. Such targeting might be regarded as biased sampling; however, this was necessary to ensure that the questionnaire would reach persons for whom the subject matter was relevant. It was unnecessary (and indeed undesirable) to assemble a simple random sample of physicians because such a sample would likely include many physicians with no experience or interest in AD. Since targeted physicians were sent a questionnaire, all eligible physicians were offered the opportunity to participate. Thus, the sample frame was constructed to reflect the physician population of interest.

There were different response rates across physician specialties (i.e., 64% geriatricians, 57% psychogeriatricians, 33% GPs, 28% neurologists). A simple explanation could be that greater percentages of geriatricians and psychogeriatricians, relative to GPs and neurologists, had an interest in completing the questionnaire. As long as this interest was only related to whether physicians treated AD patients, selection bias would be unlikely because the relevant portion of the sample responded. If other factors were involved, such as differing opinions on drug therapy among the specialities, then pooling results could lead to effect modification or confounding, with greater weight

placed on the responses of GPs and psychogeriatricians.

5.7.2.2. Caregiver Sample

The selection of caregivers for a study is more complicated than choosing physicians. There are no published caregiver rosters, so caregivers must be recruited through patients at doctors' offices or memory clinics, through media advertisements, or through advocacy organizations. For this study, two advocacy organizations (i.e., ASM and AGI) compiled mailing lists of caregivers who had attended support group meetings in the two-year period immediately prior to the study. The time frame was short enough to ensure that the lists would be as accurate as possible regarding caregivers' addresses and caregiving status (i.e., the person was caring for an AD patient at the time of the study). All of the caregivers on the lists were sent a questionnaire and given the opportunity to participate. Therefore, as with the physicians, the caregiver sample frame was constructed to minimize the potential for selection bias.

5.7.2.3. Non-response Bias

Non-response bias, a form of selection bias, arises in questionnaire research when respondents are not representative of all of the persons who were initially sent a questionnaire.[254] Based on the assessments of non-response bias in Sections 4.1.3 and 4.2.4, the impact of said bias appears to be minimal in both the physician and caregiver studies. However, a more thorough assessment of non-response bias was precluded by obstacles such as the low level of participation in the telephone surveys and by the use of late respondents as a form of proxy for non-respondents. Late respondents, in

spite of when they returned a questionnaire, are still respondents and they are likely to be more similar to early respondents than to non-respondents. Additionally, there were 144 physicians (18%) and 23 caregivers (6%) in the original samples who could not be approached for a telephone interview because they had returned a blank questionnaire to clearly indicate a refusal to participate.

Bias assessment was further precluded in the caregiver study because the questions on the caregiver questionnaire (Appendix F) were different from the questions on the CHSA survey. As well, sample characteristics were unavailable for non-respondent caregivers because there was no master database containing such information, and the ASM and AGI did not disclose their mailing lists to the researchers.

While some physicians and caregivers did not respond for reasons that were unlikely to result in bias, such as not treating AD or not caring for an AD patient, the complete number within these categories is not available. Thus, the study's results must be interpreted with the possibility of bias in mind.

Future survey research of physicians and caregivers should involve the use of supplemental techniques, in addition to what was already used, to minimize non-response. Possible techniques include token monetary incentives (where permitted by institutional review boards), package tracking, and first class outward mailing.[255]

5.7.3. Test-retest Reliability

Test-retest reliability was assessed by sending short versions of the questionnaires

to randomly selected sub-samples of physician- and caregiver-respondents (Sections 4.1.4 and 4.2.5). For both groups, test-retest reliability was found to be fair to moderate. This can be considered minimally acceptable because the discrepancies in responses between the original and short versions of the questionnaires were mainly the result of random error, which can produce wider than expected confidence intervals. While wide confidence intervals were observed in five of the seven sets of regression models (Table 4.31), the estimated odds ratios themselves were not biased by the discrepancies in responses.

5.7.4. Power

With approximately 200 respondents per questionnaire, a post hoc power calculation indicated that the study had 80% power to detect an odds ratio of at least 1.50. This calculation was based on two assumptions: (1) the probability of prescribing a ChEI was 50% at the mean value of a continuous main effect variable and (2) 12 covariates were included in a model along with the main effect variable. For categorical main effect variables, the minimum detectable odds ratio was approximately 25% larger (i.e., 1.80). Many of the estimated odds ratios in the regression analyses (Table 4.31) were below these thresholds. Thus, the study was underpowered to detect statistically significant small effects.

5.7.5. Generalizability

5.7.5.1. Physician Sample

The physician sample was drawn entirely from Québec to preclude potential confounding by regional variations in practice patterns. As practice patterns and access to drug treatments differ across provinces or countries, the views of physicians in this study may not be completely generalizable to physicians outside of Québec.

Almost half of the responding physicians practiced in university hospitals. This can be explained by the fact that many specialists in the sample frame practiced in these hospitals. For example, most geriatricians worked in urban centres where the major hospitals are university affiliated. Thus, the number of respondents is an appropriate reflection of the sampling frame.

5.7.5.2. Caregiver Sample

The caregiver sample was composed of persons who participated in support groups. These persons may differ from caregivers who have not participated in support groups with respect to level of knowledge about AD, level of knowledge about drug therapy for AD, and level of involvement in patient care. Furthermore, caregivers who responded to the questionnaire might be more educated and wealthier than caregivers in general because a large number of respondents possessed a post-secondary education and an annual income above $45,000 (Table 4.15). Readers should be aware of these differences before attempting to generalize the study's results to other groups of

caregivers (e.g., caregivers identified during patient visits to a memory clinic).

5.8. Final Conclusions

This study was undertaken to examine the physician and caregiver perspectives on the use of drug treatments in AD. Postal questionnaires were used to collect data on several important issues that are encompassed by these perspectives. The issues, which have received little attention in the literature, include:

1. The degree to which certain factors (e.g., patient's or caregiver's current overall health status, physician's degree of familiarity with the patient, the adverse effects profile of an AD drug) may influence physician prescribing;

2. Physician and caregiver efficacy requirements for using hypothetical new medications in the AD population;

3. The impact of the caregiver-physician relationship on prescribing, specifically caregiver-physician discussions about drug treatment and caregiver pressure on physicians to prescribe AD medications; and

4. Caregivers' willingness to accept adverse effects and continue patients on drug therapy.

The information obtained in this study can be used to establish benchmarks to guide drug development and assessment. This is timely given the large amount of ongoing research into drug therapies for AD. The information has also provided many

non-medical insights into the prescribing of AD medications. For example, at least half of the physicians who responded to the questionnaire reported that their decision to prescribe a ChEI is influenced by the living arrangements of the patient in question (e.g., living at home or institutionalized). Also, the prescribing decision is influenced by the caregiver's reported ability to tolerate patient behaviour. Conversely, most physicians indicated that the degree of familiarity with a patient does not influence prescribing decisions. Caregivers stated that physicians were the primary source of information on drug treatments for AD, and many reported that physicians were the first to discuss the possibility of using medications to treat patients. These findings are important for understanding the use of AD medications. The reported safety and efficacy of a drug do not completely explain why the drug may or may not be prescribed to AD patients.

Regression analyses were performed to investigate whether physicians' and caregivers' reported efficacy requirements reflected what respondents would do in actual situations. Half of the associations were in agreement with a priori hypotheses, suggesting some concordance between what respondents say and what they do. However, the confidence intervals for a majority of the associations included the null value. Due to a confluence of factors, such as low power and random error, it was difficult to determine whether these confidence intervals suggested a lack of true effects, or whether some true effects were not being detected.

The regression analyses showed that several covariates were associated with the current prescribing of ChEIs. Examples of these covariates are physician specialty and

the extent to which caregivers feel they are informed about what drugs can do to treat AD. These findings provide further insight into prescribing in AD.

The results of this research have generated several possibilities for future research, six of which are highlighted here:

1. Attempt to reconcile whether the current published evidence for the efficacy of ChEIs matches physicians' and caregivers' requirements as specified in this research.

2. Investigate other possible influences on prescribing. For example, one-third of physicians prescribed ChEIs for MCI, even though there is an absence of evidence for using these drugs to treat the condition. Could it be that physicians who write these prescriptions are participating in clinical trials? Or, could they be prescribing ChEIs off label because they feel that the drugs might have some positive benefit for MCI patients?

3. Develop a priori hypotheses for covariates of interest (e.g., physician specialty, the extent to which caregivers feel they are informed about what drugs can do to treat AD [Table 4.32; Table 4.33]), use questionnaires to collect additional data on these covariates, broaden the scope of data collection beyond Québec, and conduct regression analyses to investigate associations between these covariates and prescribing in AD.

4. Conduct surveys of drug researchers and healthcare policy makers to investigate whether the physician and caregiver data from this

thesis can be expected to help guide drug development and assessment. If so, then how? If not, then why? A negative response would not necessarily mean the data are unusable. Perhaps the data are useful yet presented in a manner that is unsuited to the needs of other healthcare stakeholders. To facilitate knowledge transfer and evidence-based practice, it is important to investigate the transmissibility of data across different disciplines.

5. Examine the patient perspective by obtaining patients' efficacy requirements for using new AD medications. This recognizes that patients who are competent to make decisions are also more likely to show awareness of their symptoms, prognosis, and diagnosis, and therefore are more likely to play a role in treatment decision making.[256]

6. Design a single questionnaire, or a series of questionnaires with overlapping components, for physicians, caregivers, and patients so that information on the same set of requirements can be obtained from all three groups. This would allow for direct comparisons between the groups. Of course, such an undertaking would pose some challenges:

    a. Question wording would have to be developed that is appropriate for all three groups;

    b. Three samples of sufficient size would have to be assembled to satisfy power requirements; and

c. Strategies would have to be implemented to minimize non-response (e.g., length and appearance of questionnaire, Dillman's Tailored Design Method, monetary incentives).

As a final comment, the overall goal of this thesis was to provide an understanding of the physician and caregiver perspectives on the use (i.e., prescribing) of drugs to treat AD. This goal was accomplished by examining several facets of the two perspectives, including physician and caregiver efficacy requirements for using new AD medications, caregiver opinions on adverse effects and institutionalization, the caregiver-physician relationship, and the association between each of these domains and the prescribing of ChEIs. It is hoped that studying the physician and caregiver perspectives will help define clinically important outcomes in AD, provide benchmark efficacy data to facilitate drug development and assessment, and promote a better understanding among physicians and caregivers of each others' attitudes to treating AD.

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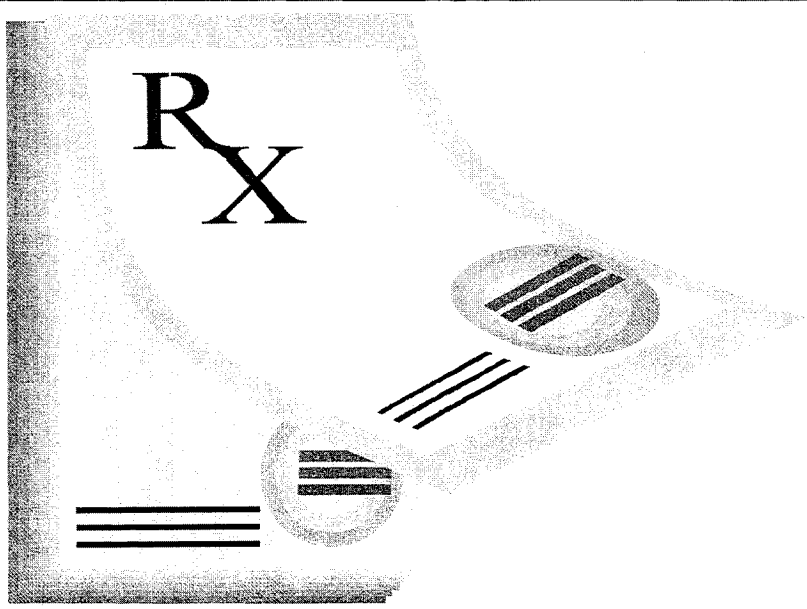
Appendix A: PHYSICIAN QUESTIONNAIRE (ENGLISH & FRENCH)

«STUDY_ID_»

Jewish General Hospital
Montreal, Quebec

McGill University
Montreal, Quebec

THE PMAD (PHYSICIANS' USE OF MEDICATIONS FOR ALZHEIMER'S DISEASE) STUDY



Section 1. Factors Influencing the Selection of Drug Therapy as a Treatment Option for Alzheimer's Disease Patients

Please complete this section whether or not you presently prescribe donepezil (Aricept), rivastigmine (Exelon), or galantamine (Reminyl) to treat Alzheimer's patients.

To what extent would each of the factors below influence your decision to treat the average Alzheimer's patient with a medication developed specifically for Alzheimer's disease (such as donepezil, rivastigmine, or galantamine)?

For each factor, please check the most appropriate box.

FACTORS	Would not influence	Probably would not influence	Don't know	Probably would influence	Would influence
Patient's current overall health status					
Patient's age					
Patient's current medication use					
Patient lives in a nursing home					
Patient lives at home					
Past patient compliance to medication regimens					
Severity of patient's dementia					
Caregiver's current overall health status					
Caregiver pressure to prescribe a medication					
Caregiver's ability to tolerate patient behaviour					
How familiar you are with the patient					
How much time you have to devote to the patient					
Ease of administration of the Alzheimer's drug					
Side-effect profile of the Alzheimer's drug					
Cost of the Alzheimer's drug					
The requirement to fill out the 'Medicament d'exception' form					

Section 2. Requirements and Beliefs for Using Medications to Treat Alzheimer's Patients

In this section, we are interested in knowing your efficacy requirements for initiating prescriptions for a hypothetical, newly developed Alzheimer's disease medication ('Drug A'). When responding to questions 1a and 2a below, think from the perspective of a clinician who is considering whether or not to use Drug A to treat her/his Alzheimer's patients. Assume that adverse effects are minimal and that the medication is on the provincial formulary.

In questions 1b and 2b below, we would like to know whether or not you believe existing Alzheimer's disease medications (i.e., donepezil, rivastigmine, galantamine) can meet these requirements.

1a. Assume Drug A has been shown to have a positive impact on any or all of the following areas: cognitive status, behaviour and mood, and/or the ability to perform basic activities of daily living. Taking each area separately, what is the minimum effect that you would require the drug to have on the average patient before you would consider prescribing the medication to your own patients? Please circle one choice per area.

Cognitive status – required minimum effect would be...

a) To permanently stabilize the level of cognition (i.e., no decline in Folstein/MMSE score, but no improvement either)
b) To somewhat reverse the degree of cognitive impairment (i.e., 1-3 point increase in Folstein/MMSE score)
c) To substantially reverse the degree of cognitive impairment (i.e., > 3 point increase in Folstein/MMSE score)

Behaviour and mood – required minimum effect would be...

a) To somewhat reduce further occurrences of problematic behaviours and moods (e.g., up to 25% reduction in incidence of problematic behaviours and moods)
b) To substantially reduce further occurrences of problematic behaviours and moods (e.g., more than 25% reduction in incidence of problematic behaviours and moods)
c) To permanently prevent further occurrences of problematic behaviours and moods (e.g., no more bouts of agitated behaviour, no more depressive episodes)

Ability to perform basic activities of daily living – required minimum effect would be...

a) To permanently prevent further diminishment of a patient's ability to perform basic activities of daily living
b) To somewhat increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 1-2 basic activities)
c) To substantially increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 3 or more basic activities)

1b. Given your responses to question 1a above, how strongly do you believe existing Alzheimer's medications (i.e., donepezil, rivastigmine, galantamine) can meet your requirements? For each of the three areas below, please circle the number that best reflects your opinion.

Cognitive status

I do not at all believe									I definitely believe
1	2	3	4	5	6	7	8	9	10

Behaviour and mood

I do not at all believe									I definitely believe
1	2	3	4	5	6	7	8	9	10

Ability to perform basic activities of daily living

I do not at all believe									I definitely believe
1	2	3	4	5	6	7	8	9	10

2a. Assume Drug A does not halt or reverse the impact of Alzheimer's disease. Instead, the drug stabilizes the patient for a lengthened period of time, after which decline recommences. What is the minimum increase in length of stabilization that you would require in order to consider prescribing the medication to your patients? Please express your answers in months.

For patients in the mild state of Alzheimer's disease, I would require an increase in length of stabilization of at least ____ months
(Mild state Folstein/MMSE score range: 21-26)

For patients in the moderate state of Alzheimer's disease, I would require an increase in length of stabilization of at least ____ months
(Moderate state Folstein/MMSE score range: 11-20)

2b. Given your responses to question 2a above, how strongly do you believe existing Alzheimer's medications (i.e., donepezil, rivastigmine, galantamine) can meet your requirements? For each of the disease states below, please circle the number that best reflects your opinion.

Mild state

I do not at all believe									I definitely believe
1	2	3	4	5	6	7	8	9	10

Moderate state

I do not at all believe									I definitely believe
1	2	3	4	5	6	7	8	9	10

Section 3. Prescribing Alzheimer's Disease Medications

The following questions ask about your prescribing practices with respect to Alzheimer's disease medications. There are no right or wrong answers. For each question, please circle or write the response you feel is most appropriate. Or, if the question asks for a percentage, then please provide a 'best guess' estimate.

1. For the Alzheimer's patients you see in your practice, have you ever initiated prescriptions for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

a) No
b) Yes

If you answered 'no', then please go to question 2.
If you answered 'yes', then please skip question 2 and go directly to question 3.

2. Would you consider initiating prescriptions for a cholinesterase inhibitor in the future?

a) Will not do so
b) Unlikely to do so
c) Toss-up
d) Likely to do so
e) Will do so

If you answered question 2, then please skip questions 3 and 4; go directly to question 5.

3a. For what percentage of your Alzheimer's patients have you initiated a prescription for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)? _____%

Please break down this overall percentage by stage of disease. The percentages you specify for the three stages should add up to this overall percentage.

Mild stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 21-26)
Moderate stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 11-20)
Severe stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 0-10)

3b. For the patients with mild cognitive impairment (MCI) that you see in your practice, have you ever initiated prescriptions for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

a) No
b) Yes → If 'yes,' then to what percentage of these patients have you initiated prescriptions for these medications?
_____%

3c. For the patients with other forms of dementia besides Alzheimer's disease (e.g., vascular, Lewy body, frontal-temporal) that you see in your practice, have you ever initiated prescriptions for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

a) No
b) Yes → If 'yes,' then to what percentage of these patients have you initiated prescriptions for these medications?
_____%

4a. What percentage of your patients developed adverse effects (AEs) while using a cholinesterase inhibitor? Please answer separately for each medication below. Leave the line blank if you do not prescribe the medication in question.

donepezil _____% rivastigmine _____% galantamine _____%

4b. For what percentage of your patients were the AEs severe enough for you to discontinue the medication? Please answer separately for each medication below. Leave the line blank if you do not prescribe the medication in question.

donepezil _____% rivastigmine _____% galantamine _____%

5. For Alzheimer's patients you see in your practice, do you initiate prescriptions for other medications besides cholinesterase inhibitors to help address Alzheimer-related problems in areas such as cognition, behaviour and mood, performing activities of daily living, etc.?

a) No
b) Yes
- What percentage is prescribed other medications? _____%
- To what classes do these medications belong (e.g., NSAIDs, antidepressants)?

_____

6. Do you suggest that your Alzheimer's patients take over-the-counter medications (OTCs) such as vitamin E or ginkgo biloba to address symptoms or behaviours related to Alzheimer's disease (e.g., memory loss)?

a) No
b) Yes
- To what percentage do you suggest taking OTCs? _____%
- What types of OTCs are they?

_____

7. How knowledgeable are you with respect to the efficacy* of...

donepezil	rivastigmine
a) Not knowledgeable	a) Not knowledgeable
b) Somewhat knowledgeable	b) Somewhat knowledgeable
c) Very knowledgeable	c) Very knowledgeable

galantamine

a) Not knowledgeable
b) Somewhat knowledgeable
c) Very knowledgeable

(*Efficacy: In controlled trials, the effect of these medications with respect to delaying further cognitive impairment.)

If you circled 'a' for ALL three medications, then please skip question 8 and go directly to question 9.

8. What is the primary source of your information on donepezil, rivastigmine, and/or galantamine? (*Circle one*)

a) Medical journal articles
b) Scientific meetings
c) Advertisements in medical journals
d) Observations of your patients' responses to these drugs
e) Your colleagues' opinions
f) Representatives of pharmaceutical companies
g) Continuing medical education courses given by an academic institution
h) Continuing medical education courses given by a pharmaceutical company
i) Electronic media (e.g., Internet, CD-ROM)

9. What percentage of caregivers* put pressure on you to prescribe donepezil, rivastigmine, or galantamine for Alzheimer's disease?

_____%

(*'Caregiver' refers to an unpaid, primary caregiver, who is usually a family member/relative or friend of an Alzheimer's patient.)

Section 4. Demographic Information

The following information will be used to describe the characteristics of our respondents. For each question, please circle or write the appropriate response.

1. What is your sex?

a) Male
b) Female

2. What is your age?

|_____|

3. In what year did you obtain your medical license?

|_____|

4. In what settings do you practice (circle all that apply)?

a) University-affiliated hospital
b) A hospital not affiliated with a university
c) CLSC
d) Solo practice
e) Same discipline group practice
f) Multi-discipline group practice
g) University-affiliated office-based practice
h) Ward or emergency work in a hospital (either university-affiliated or not)
i) Other (specify _____)

5. Approximately how many patients **in total** do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients in total: _____

6a. Approximately how many **Alzheimer's** patients do you currently have in your practice (provide a **'best guess'** estimate)?

Number of Alzheimer's patients: _____

6b. Approximately how many patients with **mild cognitive impairment** (MCI) do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients with mild cognitive impairment: _____

6c. Approximately how many patients with **other forms of dementia besides Alzheimer's disease** (e.g., vascular, Lewy body, frontal-temporal) do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients with other forms of dementia: _____

7. What percentage of your Alzheimer's patients is at each stage of disease severity? Please provide **'best guess'** estimates for each of the following stages.

Mild stage of disease severity (Folstein/MMSE score range: 21-26) _____%

Moderate stage of disease severity (Folstein/MMSE score range: 11-20) _____%

Severe stage of disease severity (Folstein/MMSE score range: 0-10) _____%

TOTAL 100 %

(MMSE = Mini-Mental State Examination)

THE QUESTIONNAIRE IS NOW COMPLETE

THANK YOU VERY MUCH FOR YOUR TIME

Please return the questionnaire in the enclosed, self-addressed stamped envelope.

Or, fax the completed questionnaire to Mr. Mark Oremus at (514)340-7564.

If you do not intend to respond to the questionnaire, then please check one of the following boxes; return the questionnaire in the enclosed, self-addressed stamped envelope. This will prevent follow-up material from being sent to you.

I do not wish to participate. ☐

I do not see Alzheimer's patients in my practice. ☐

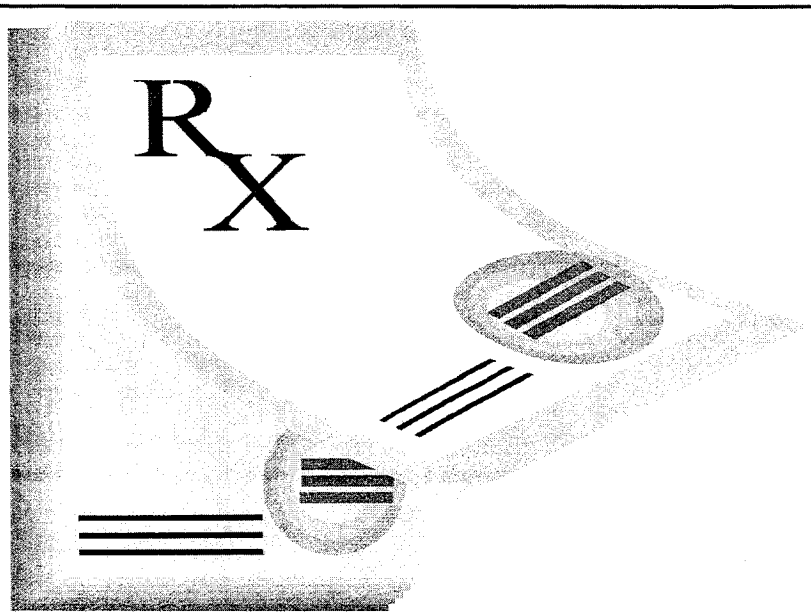
I do not wish to be re-contacted for the validation substudy. ☐

«STUDY_ID_»

Hôpital général juif
Montréal (Québec)

Université McGill
Montréal (Québec)

ÉTUDE UMMA (UTILISATION PAR LES MÉDECINS DE MÉDICAMENTS SERVANT AU TRAITEMENT DE LA MALADIE D'ALZHEIMER)



Section 1. Facteurs influant sur le choix d'une pharmacothérapie servant à traiter les personnes atteintes de la maladie d'Alzheimer

Veuillez remplir cette section que vous prescriviez ou non présentement le donépézil (Aricept), la rivastigmine (Exelon) ou la galantamine (Reminyl) pour traiter les personnes atteintes de la maladie d'Alzheimer.

Comment chacun des facteurs suivants influerait-il sur votre décision de traiter le patient moyen atteint de la maladie d'Alzheimer à l'aide d'un médicament spécialement conçu pour traiter la maladie (donépézil, rivastigmine ou galantamine)? Pour chaque facteur, veuillez cocher la case la plus appropriée.

FACTEURS	Aucune influence	Influence peu probable	Ne sais pas	Influence probable	Influence certaine
État de santé général actuel de la personne					
Âge de la personne					
Médicaments présentement utilisés par la personne					
La personne vit dans une maison de soins infirmiers					
La personne vit chez elle					
Observance antérieure de la personne d'autres traitements médicamenteux					
Gravité de la démence de la personne					
État de santé général actuel de l'aidant					
Pression exercée par l'aidant pour prescrire un médicament					
Tolérance de l'aidant envers le comportement de la personne					
Vos rapports personnels avec la personne					
Temps que vous pouvez consacrer à la personne					
Facilité d'administration du médicament					
Effets secondaires du médicament					
Coût du médicament					
Obligation de remplir le formulaire « Médicament d'exception »					

Section 2. Exigences et vues sur l'utilisation de médicaments pour traiter les personnes atteintes de la maladie Alzheimer

Nous désirons à présent connaître vos exigences en matière d'efficacité avant de commencer à prescrire un nouveau médicament hypothétique pour traiter la maladie d'Alzheimer (médicament A). Répondez aux questions 1a et 2a ci-dessous du point de vue d'un clinicien se demandant s'il doit ou non employer le produit A pour traiter des personnes atteintes. Supposons que les effets secondaires sont minimes et que le médicament figure sur le formulaire provincial.

Pour les questions 1b et 2b, nous désirons savoir si vous croyez ou non que les médicaments servant présentement à traiter la maladie d'Alzheimer (donépézil, rivastigmine, galantamine) satisfont à ces exigences.

1a. Supposons qu'on a démontré que le médicament A a un effet favorable sur un ou plusieurs domaines suivants : l'état cognitif, le comportement et l'humeur ou la capacité d'exécution des principales activités quotidiennes. En considérant chaque domaine séparément, quel effet minimum exigeriez-vous du médicament sur le patient moyen avant de le prescrire à vos propres patients? Veuillez encercler un choix par domaine.

État cognitif – L'effet minimum requis serait le suivant :

a) Stabiliser de façon permanente le niveau de compréhension (p. ex., ni baisse du résultat au test Folstein/MMSE, ni amélioration).
b) Inverser plus ou moins le degré de déficience intellectuelle (p. ex., hausse de 1 à 3 points au test Folstein/MMSE).
c) Inverser considérablement le degré de déficience intellectuelle (p. ex., hausse supérieure à 3 points au test Folstein/MMSE).

Comportement et humeur – L'effet minimum requis serait le suivant :

a) Réduire plus ou moins d'autres occurrences de conduites et d'humeurs problématiques (p. ex., réduction jusqu'à 25 % des occurrences de conduite agitée ou d'épisode dépressif).
b) Réduire considérablement d'autres occurrences de conduites et d'humeurs problématiques (p. ex., réduction supérieure à 25 % des occurrences de conduite agitée ou d'épisode dépressif).
c) Prévenir de façon permanente d'autres occurrences de conduites et d'humeurs problématiques (p. ex., ni conduite agitée ni épisode dépressif).

Capacité d'exécution des principales activités quotidiennes – L'effet minimum requis serait le suivant :

a) Arrêter de façon permanente la diminution de la capacité d'une personne d'exécuter les principales activités quotidiennes.
b) Accroître plus ou moins la capacité d'une personne d'exécuter les principales activités quotidiennes (p. ex., reprise d'une ou deux activités de base).
c) Accroître considérablement la capacité d'une personne d'exécuter les principales activités quotidiennes (p. ex., reprise de 3 activités ou plus).

1b. Selon vos réponses à la question 1a ci-dessus, à quel point estimez-vous que les médicaments actuels contre la maladie d'Alzheimer (donépézil, rivastigmine, galantamine) satisfont à vos exigences? Pour chaque domaine ci-dessous, veuillez encercler le chiffre qui reflète le mieux votre point de vue.

État cognitif

Je n'y crois pas du tout									**J'y crois entièrement**
1	2	3	4	5	6	7	8	9	10

Comportement et humeur

Je n'y crois pas du tout									**J'y crois entièrement**
1	2	3	4	5	6	7	8	9	10

Aptitude à exécuter les principales activités quotidiennes

Je n'y crois pas du tout									**J'y crois entièrement**
1	2	3	4	5	6	7	8	9	10

2a. Supposons que le médicament A n'arrête ni n'inverse l'effet de la maladie d'Alzheimer, mais qu'il stabilise la personne pendant une période prolongée, avant que recommence le déclin. Quelle durée accrue minimum de stabilisation exigeriez-vous avant de songer à prescrire le médicament à vos patients? Veuillez indiquer votre réponse en mois.

Pour les personnes à la phase initiale, j'exigerais une durée accrue de stabilisation d'au moins ____ mois.
(Résultat de 21-26 au test Folstein/MMSE, à la phase initiale)

Pour les personnes à la phase intermédiaire, j'exigerais une durée accrue de stabilisation d'au moins ____ mois.
(Résultat de 11-20 au test Folstein/MMSE, à la phase intermédiaire)

2b. Selon vos réponses à la question 1a ci-dessus, à quel point estimez-vous que les médicaments actuels contre la maladie d'Alzheimer (donépézil, rivastigmine, galantamine) satisfont à vos exigences? Pour chaque phase de la maladie ci-dessous, veuillez encercler le chiffre qui reflète le mieux votre point de vue.

Phase initiale

Je n'y crois pas du tout									**J'y crois entièrement**
1	2	3	4	5	6	7	8	9	10

Phase intermédiaire

Je n'y crois pas du tout									**J'y crois entièrement**
1	2	3	4	5	6	7	8	9	10

Section 3. Ordonnance de médicaments servant à traiter la maladie d'Alzheimer

Les questions suivantes concernent vos pratiques de prescription de médicaments servant à traiter la maladie d'Alzheimer. Il n'y a pas de bonne ou de mauvaise réponse. Pour chaque question, veuillez encercler ou donner la réponse qui vous semble la plus appropriée. Si la question concerne un pourcentage, veuillez alors fournir votre meilleure estimation.

1. Aux personnes atteintes de la maladie d'Alzheimer que compte votre pratique, avez-vous jamais commencé à prescrire un inhibiteur de la cholinestérase (donépézil, rivastigmine ou galantamine)?

a) Non
b) Oui

Si vous avez répondu non, veuillez passer à la question 2.
Si vous avez répondu oui, veuillez sauter la question 2 et répondre à la question 3.

2. Songeriez-vous à commencer à prescrire un inhibiteur de la cholinestérase à l'avenir?

a) Non
b) Probablement que non
c) Ne peux décider
d) Probablement que oui
e) Oui

Si vous avez répondu à la question 2, veuillez sauter les questions 3 et 4, et répondre à la question 5.

3a. À quel pourcentage de vos patients atteints de la maladie d'Alzheimer avez-vous jamais commencé à prescrire un inhibiteur de la cholinestérase (donépézil, rivastigmine ou galantamine)? _____ %

Veuillez répartir le pourcentage global selon la phase de la maladie. Les pourcentages indiqués devraient totaliser le pourcentage global.

Phase initiale de la maladie d'Alzheimer _____ %
(Résultat de 21-26 au test Folstein/MMSE)

Phase intermédiaire de la maladie d'Alzheimer _____ %
(Résultat de 11-20 au test Folstein/MMSE)

Phase avancée de la maladie d'Alzheimer _____ %
(Résultat de 0-10 au test Folstein/MMSE)

3b. Aux personnes souffrant de déficience cognitive légère (DCL) que compte votre pratique, avez-vous jamais commencé à prescrire un inhibiteur de la cholinestérase (donépézil, rivastigmine ou galantamine)?

a) Non
b) Oui → Dans ce cas, à quel pourcentage de ces personnes avez-vous prescrit ces médicaments?
_____ %

3c. Aux personnes qui présentent d'autres formes de démence que la maladie d'Alzheimer (p. ex, vasculaire, corps de Lewy, frontale-temporale) que compte votre pratique, avez-vous jamais commencé à prescrire un inhibiteur de la cholinestérase (donépézil, rivastigmine ou galantamine)?

a) Non
b) Oui → Dans ce cas, à quel pourcentage de ces personnes avez-vous prescrit ces médicaments?
_____ %

4a. Quel pourcentage de ces personnes ont développé des effets indésirables (EI) durant l'utilisation d'un inhibiteur de la cholinestérase? Veuillez indiquer une réponse pour chaque médicament ci-dessous. Ne rien écrire si vous ne prescrivez pas ce médicament.

Donépézil _____ % Rivastigmine _____ % Galantamine _____ %

4b. Pour quel pourcentage de personnes les EI étaient-ils suffisamment graves pour cesser la médication? Veuillez indiquer une réponse pour chaque médicament ci-dessous. Ne rien écrire si vous ne prescrivez pas ce médicament.

Donépézil _____ % Rivastigmine _____ % Galantamine _____ %

5. Aux personnes atteintes de la maladie d'Alzheimer que compte votre pratique, prescrivez-vous d'autres médicaments que les inhibiteurs de la cholinestérase pour soigner des problèmes liés à la maladie dans des domaines comme la cognition, le comportement et l'humeur, l'exécution des activités quotidiennes, etc.?

a) Non
b) Oui →
   - À quel pourcentage prescrivez-vous d'autres médicaments? _____ %
   - À quelles classes ces médicaments appartiennent-ils (AINS, antidépresseurs)?

     _____

6. Suggérez-vous à vos patients atteints de la maladie d'Alzheimer de prendre des produits grand public (PGP) comme la vitamine E ou le ginkgo biloba pour atténuer des symptômes ou des comportements liés à la maladie (p. ex., perte de mémoire)?

a) Non

b) Oui

→ À quel pourcentage suggérez-vous les PGP _____ %

→ De quels types de PGP s'agit-il?

_____

7. Que savez-vous de l'efficacité* des produits suivants:

Donépézil	Rivastigmine
a) Pas informé	a) Pas informé
b) Plus ou moins informé	b) Plus ou moins informé
c) Très bien informé	c) Très bien informé

Galantamine

a) Pas informé

b) Plus ou moins informé

c) Très bien informé

(* Efficacité : dans les essais contrôlés, l'effet de ces médicaments quant au ralentissement de la déficience cognitive.)

Si vous avez encerclé 'a' dans LES TROIS CAS, veuillez sauter la question 8 et répondre à la question 9.

8. Quelle est votre principale source d'information sur le donépézil, la rivastigmine ou la galantamine? (*Encerclez une seule réponse*)

a) Articles de publications médicales

b) Réunions scientifiques

c) Annonces dans les publications médicales

d) Vos propres observations des réponses des patients qui prennent ces médicaments

e) Opinions de collègues

f) Représentants de sociétés pharmaceutiques

g) Formation médicale continue offerte par un établissement universitaire

h) Formation médicale continue offerte par une société pharmaceutique

i) Médias électroniques (Internet, CD-ROM)

9. Quel pourcentage d'aidants* exercent une pression sur vous afin de prescrire le donépézil, la rivastigmine ou la galantamine à des personnes atteintes de la maladie d'Alzheimer?

_____ %

(* « Aidant » désigne un pourvoyeur de soins de premier recours non rémunéré, habituellement un membre de la famille, un parent ou un ami de la personne atteinte.)

Section 4. Données démographiques

L'information suivante servira à décrire les caractéristiques de nos répondants. Pour chaque question, veuillez encerclez ou fournir la réponse appropriée.

1. Votre sexe

a) Homme
b) Femme

2. Votre âge

|_____|

3. En quelle année avez-vous obtenu votre licence de médecine?

|_____|

4. Où pratiquez-vous (veuillez encercler toutes les réponses appropriées)?

a) Centre hospitalier universitaire
b) Hôpital non affilié à une université
c) CLSC
d) Pratique privée
e) Médecine de groupe dans une même discipline
f) Médecine de groupe multidisciplinaire
g) Pratique privée affiliée à une université
h) Service ou urgence dans un centre hospitalier (affilié ou non à une université)
i) Autre (veuillez préciser) _____

5. Approximativement combien de patients **au total** votre pratique compte-t-elle à l'heure actuelle (veuillez indiquer la **meilleure estimation possible**)?

Nombre de personnes au total : _____

6a. Approximativement combien de personnes atteintes de **la maladie d'Alzheimer** votre pratique compte-t-elle à l'heure actuelle (veuillez indiquer la **meilleure estimation possible**)?

Nombre de personnes atteintes de la maladie d'Alzheimer : _____

6b. Approximativement combien de personnes souffrant de **déficience cognitive légère** (DCL) votre pratique compte-t-elle à l'heure actuelle (veuillez indiquer la **meilleure estimation possible**)?

Nombre de personnes souffrant de déficience cognitive légère : _____

6c. Approximativement combien de personnes souffrant **d'autres formes de démence que la maladie d'Alzheimer** (p. ex, vasculaire, corps de Lewy, frontale-temporale) votre pratique compte-t-elle à l'heure actuelle (veuillez indiquer la **meilleure estimation possible**)?

Nombre de personnes souffrant d'autres formes de démence : _____

7. Quel pourcentage des personnes atteintes de la maladie d'Alzheimer que compte votre pratique est à chaque stade de gravité de la maladie? Veuillez indiquer la **meilleure estimation possible** dans chaque cas.

Phase initiale de la maladie (résultat de 21-26 au test Folstein/MMSE) : _____ %

Phase intermédiaire de la maladie (résultat de 11-20 au test Folstein/MMSE) : _____ %

Phase avancée de la maladie (résultat de 0-10 au test Folstein/MMSE) : _____ %

TOTAL 100 %

(MMSE = mini-examen de l'état mental)

FIN DU QUESTIONNAIRE

NOUS VOUS REMERCIONS POUR VOTRE TEMPS

Veuillez retourner le questionnaire dans l'enveloppe pré-adressée affranchie,

ou le retourner par télécopieur, à l'attention de M. Mark Oremus, au 514-340-7564.

Si vous ne désirez pas répondre au questionnaire, veuillez cochez une des cases ci-dessous, puis le retourner dans l'enveloppe pré-adressée affranchie. Vous éviterez ainsi de recevoir toute autre matériel de suivi.

Je ne désire pas y participer. ☐

Ma pratique ne compte pas de personnes atteintes de la maladie d'Alzheimer. ☐

Je ne souhaite pas être contacté de nouveau pour l'étude complémentaire de validation. ☐

Appendix B: PHYSICIAN QUESTIONNAIRE COVER LETTERS (ENGLISH & FRENCH)

The PMAD (Physicians' Use of Medications for Alzheimer's Disease) Study

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Date

Name and Address
X
X
X
X

Dear Dr. _____:

We are conducting a research project on the use of medications to treat Alzheimer's disease (AD). As part of this study, we will be asking Quebec physicians to share their views on these medications. In approximately one week, you will receive a brief questionnaire in the mail, and we kindly ask that you take a few minutes of your time to complete it. Given that approximately 8,000 Quebecers develop AD annually, and research into new and improved medications is ongoing, your input will be timely and it will help to guide future drug development and assessment.

We hope that you will participate in the survey. Your cooperation will be essential to the success of this project.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology and
Biostatistics
McGill University

Note: This research study is <u>not</u> funded by any pharmaceutical companies.

The PMAD (Physicians' Use of Medications for Alzheimer's Disease) Study

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Date

Name and Address
X
X
X
X

Dear Dr. _____:

We are conducting a research project on the use of medications to treat Alzheimer's disease (AD). As part of this project, we are asking Quebec physicians to share their views on these medications. Given that approximately 8,000 Quebecers develop AD annually, and research into new and improved medications is ongoing, your input will be timely and it will help to guide future drug development and assessment.

We kindly ask you to take a few minutes of your time to complete the attached, brief questionnaire. Once completed, please return the questionnaire in the enclosed self-addressed, stamped envelope. Your responses will remain confidential.

If you do not wish to participate for any reason, or if you do not see Alzheimer's patients in your practice, then please check the appropriate box at the end of the questionnaire and return it to us to avoid receiving follow-up material. As part of a validation substudy, you may be re-contacted within three months and asked a few questions. If you would prefer that we do not contact you again, then please check the appropriate box at the end of the questionnaire. Your name and address will be deleted from our database at the end of the study.

If you have any questions, then please do not hesitate to contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717, or at ADsurvey@epid.jgh.mcgill.ca.

Thank you in advance for participating in our survey. Your cooperation is essential to the success of this project.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology and
Biostatistics
McGill University

The PMAD (Physicians' Use of Medications for Alzheimer's Disease) Study

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Date

Name and Address
X
X
X
X

Dear Dr. _____:

We are conducting a research project on the use of medications to treat Alzheimer's disease (AD). As part of this project, we have been asking Quebec physicians to share their views on these medications. You were recently sent a brief questionnaire asking for your views, but we have not yet received a reply.

In case you do not have at your disposal the questionnaire that we mailed to you, we have enclosed another copy. Please take a few minutes of your time to complete the questionnaire, and then return it in the enclosed self-addressed, stamped envelope. Your responses will remain confidential.

If you do not wish to participate for any reason, or if you do not see Alzheimer's patients in your practice, then please check the appropriate box at the end of the questionnaire and return it to us to avoid receiving follow-up material and a follow-up telephone call. As part of a validation substudy, you may be re-contacted within three months and asked a few questions. If you would prefer that we do not contact you again, then please check the appropriate box at the end of the questionnaire. Your name and address will be deleted from our database at the end of the study.

If you have any questions, then please do not hesitate to contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717, or at ADsurvey@epid.jgh.mcgill.ca.

Thank you in advance for participating in our survey. Your cooperation is essential to the success of this project.

Sincerely,

Howard Bergman, MD
Director and Professor,
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McGill University and Jewish General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology and
Biostatistics

The PMAD (Physicians' Use of Medications for Alzheimer's Disease) Study

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Date

Name and Address
X
X
X
X

Dear Dr. _____:

We are conducting a research project on the use of medications to treat Alzheimer's disease (AD). As part of this project, we have been asking Quebec physicians to share their views on these medications. You were recently sent, on two separate occasions, a brief questionnaire asking for your views, but we have not yet received a reply. We also tried to reach you by telephone, but were unsuccessful.

In case you do not have at your disposal either questionnaire that we had sent earlier, we have enclosed another copy. Please take a few minutes of your time to complete the questionnaire, and then return it in the enclosed self-addressed, stamped envelope. Your responses will remain confidential.

If you do not see Alzheimer's patients in your practice, then please check the appropriate box at the end of the questionnaire and return it to us. As part of a validation substudy, you may be re-contacted within three months and asked a few questions. If you would prefer that we do not contact you again, then please check the appropriate box at the end of the questionnaire. Your name and address will be deleted from our database at the end of the study.

If you have any questions, then please do not hesitate to contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717, or at ADsurvey@epid.jgh.mcgill.ca.

Thank you in advance for participating in our survey. Your cooperation is essential to the success of this project.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology and
Biostatistics

Étude UMMA (Utilisation par les médecins de médicaments servant au traitement de la maladie d'Alzheimer)

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Date

Nom et adresse
X
X
X
X

Docteure, Docteur,

Nous réalisons présentement un projet de recherche sur l'utilisation de médicaments servant au traitement de la maladie d'Alzheimer (MA). Dans le cadre de cette étude, nous demanderons à des médecins du Québec d'exprimer leurs vues sur ces médicaments. Dans une semaine environ, vous recevrez un bref questionnaire par la poste, et nous vous demandons de bien vouloir prendre quelques minutes pour le remplir. Étant donné que quelque 8 000 Québécoises et Québécois développent la MA chaque année et que la recherche sur les médicaments nouveaux et améliorés est continue, votre avis sur la question sera opportun et nous aidera à orienter le développement et l'évaluation futurs de médicaments.

Nous espérons que vous participerez au l'étude. Votre collaboration est essentielle à la réussite du projet.

Recevez nos salutations distinguées.

Howard Bergman, M.D.
Directeur et professeur titulaire,
Division de gériatrie
Université McGill et Hôpital général juif

Christina Wolfson, Ph.D.
Directrice, Centre d'épidémiologie clinique et de recherche en santé publique
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Université McGill

Note : Cette recherche <u>n'est financée par aucune</u> société pharmaceutique.

Étude UMMA (Utilisation par les médecins de médicaments servant au traitement de la maladie d'Alzheimer)

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Date

Nom et adresse
X
X
X
X

Docteure Docteur,

Nous réalisons présentement un projet de recherche sur l'emploi de médicaments servant au traitement de la maladie d'Alzheimer (MA). Dans le cadre de cette étude, nous avons demandé à des médecins du Québec d'exprimer leur vue sur ces médicaments. Nous vous avons envoyé récemment un bref questionnaire pour recueillir vos vues sur la question mais n'avons pas encore eu de réponse.

Si vous n'avez plus le questionnaire, veuillez utiliser l'exemplaire ci-inclus. Nous vous prions de prendre quelques minutes pour le remplir et de nous le renvoyer dans l'enveloppe pré-adressée affranchie ci-jointe. Vos réponses demeureront confidentielles.

Si, pour une raison ou pour une autre, vous ne désirez pas participer à l'étude ou que vous ne comptez pas de personnes atteintes de la maladie d'Alzheimer parmi votre clientèle, veuillez cocher la case appropriée au bas du questionnaire et nous le retourner afin de ne plus recevoir de matériel de suivi. De plus, étant donné que nous prévoyions effectuer une étude complémentaire de validation, il est possible que nous communiquions de nouveau avec vous, environ trois mois suite au premier questionnaire, pour vous poser quelques questions. Si vous préférez que l'on ne vous contacte pas de nouveau pour la courte étude de validation, veuillez simplement cocher la case appropriée au bas du questionnaire. Nous supprimerons vos nom et adresse de notre base de données à la fin de l'étude.

Si vous avez des questions, n'hésitez pas à communiquer avec le coordonnateur de l'étude, M. Mark Oremus, au 514-340-8222, poste 4717, ou à ADsurvey@epid.jgh.mcgill.ca.

Nous vous remercions à l'avance de votre participation à notre l'étude. Votre collaboration est essentielle à la réussite du projet.

Recevez nos salutations distinguées.

Howard Bergman, M.D.
Directeur et professeur titulaire,
Division de gériatrie

Christina Wolfson, Ph.D.
Directrice, Centre d'épidémiologie
clinique et de recherche en santé publique

Étude UMMA (Utilisation par les médecins de médicaments servant au traitement de la maladie d'Alzheimer)

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Date

Nom et adresse
X
X
X
X

Docteure, Docteur,

Nous réalisons présentement un projet de recherche sur l'emploi de médicaments pour traiter la maladie d'Alzheimer. Dans le cadre de cette étude, nous avons demandé à des médecins du Québec d'exprimer leur vue sur ces médicaments. Nous vous avons envoyé à deux reprises un bref questionnaire pour recueillir vos vues, mais n'avons toujours pas eu de réponse. Nous avons aussi tenté de vous joindre par téléphone, sans y parvenir.

Si vous n'avez plus le ou les questionnaires, veuillez utiliser l'exemplaire ci-inclus. Nous vous prions de prendre quelques minutes pour le remplir et de nous le renvoyer dans l'enveloppe pré-adressée affranchie ci-jointe. Vos réponses demeureront confidentielles.

Si vous ne comptez pas de personnes atteintes de la maladie d'Alzheimer parmi votre clientèle, veuillez cocher la case appropriée au bas du questionnaire et nous le retourner. De plus, étant donné que nous prévoyions effectuer une étude complémentaire de validation, il est possible que nous communiquions de nouveau avec vous, environ trois mois suite au premier questionnaire, pour vous poser quelques questions. Si vous préférez que l'on ne vous contacte pas de nouveau pour la courte étude de validation, veuillez simplement cocher la case appropriée au bas du questionnaire. Nous supprimerons vos nom et adresse de notre base de données à la fin de l'étude.

Si vous avez des questions, n'hésitez pas à communiquer avec le coordonnateur de l'étude, M. Mark Oremus, au 514-340-8222, poste 4717, ou à ADsurvey@epid.jgh.mcgill.ca.

Nous vous remercions à l'avance pour votre participation à notre l'étude. Votre collaboration est essentielle à la réussite du projet.

Recevez nos salutations distinguées.

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général juif

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clinique et de recherche en santé publique
Hôpital général juif
Professeure titulaire, Département
d'épidémiologie et de biostatistique

Appendix C: PHYSICIAN QUESTIONNAIRE - TELEPHONE NON-RESPONSE SURVEY & SCRIPT (ENGLISH)

Secretary's Voice Mail

Hello, this is _____. I'm working on a study of medications to treat Alzheimer's disease. We recently mailed Dr. _____ a questionnaire on this subject but we did not get a response. I am wondering if it would be possible to ask Dr. _____ a few of the questions from this survey over the telephone. It should not take longer than five to eight minutes. Please have Dr. _____ contact me at _____. Thank you.

Speaking Directly to Secretary

Hello, this is _____. I'm working on a study of medications to treat Alzheimer's disease. We recently mailed Dr. _____ a questionnaire on this subject but we did not get a response. Does Dr. _____ treat Alzheimer's patients?

1) IF S/HE DOES TREAT AD PATIENTS: I am wondering if it would be possible to ask Dr. _____ a few of the questions from this survey over the telephone. It should not take longer than five to eight minutes. Is she (he) there now? **[If you can't get to speak to the**

physician, then → Please have Dr. _____ contact me at _____. Thank you.]

2) IF S/HE DOES NOT TREAT AD PATIENTS: Thank you. Have a good day.

Physician's Voice Mail

Hello, this is _____. I'm working on a study of medications to treat Alzheimer's disease. We recently mailed you a questionnaire on this subject but we did not get a response. I am wondering if it would be possible to ask you a few of the questions from this survey over the telephone. It should not take longer than five to eight minutes. Please contact me at _____. Thank you.

Speaking Directly to Physician

Hello, this is _____. I'm working on a study of medications to treat Alzheimer's disease. We recently mailed you a questionnaire on this subject but we did not get a response. Do you treat Alzheimer's patients in your practice?

1) IF S/HE DOES TREAT AD PATIENTS: I am wondering if it would be possible to ask you a few of the questions from this survey over the

telephone. It should not take longer than five to eight minutes. Would you have some time now?

a. **If the physician says that 'now' is not a good time, then →** When would be a good time to contact you?
b. **If the physician does not want to participate →** If you should reconsider, please contact me at _____. Thank you.
c. **If the physician wants to take your number, then →** You may contact me at _____. Thank you.

2) IF S/HE DOES NOT TREAT AD PATIENTS: I see, thank you very much. Have a good day.

IF THE PHYSICIAN SHOULD ASK WHAT THE STUDY IS ABOUT, YOU MAY RESPOND:

The study* is being undertaken to investigate the prescribing of medications for Alzheimer's disease. We hope the results will help guide future drug development and assessment. The study is funded from a FRSQ grant to a geriatric research team; no funding is coming from the pharmaceutical industry.

* PMAD--Physicians' Use of Medications for Alzheimer's Disease--Study

Script – Telephone Nonresponse Survey – The Questions

Physician Study ID #: _____

I am now going to ask you a few short questions.

Please note that your responses will remain confidential.
Your name is not written on the response sheet in front of me and the people doing data entry and analysis will not know who you are.

Question 1

For what percentage of your Alzheimer's patients have you initiated a prescription for a cholinesterase inhibitor such as donepezil, rivastigmine, or galantamine? _____%

(A percentage between 1 and 100 must be provided. If the physician has never initiated a prescription, the answer is 0%.)

Question 2

Do you see patients with mild cognitive impairment (MCI) in your practice?
Yes |__| No |__|

If 'no,' then go to question 3.

If 'yes,' then ask the portion below.

For what percentage of these MCI patients have you initiated prescriptions for a cholinesterase inhibitor such as donepezil, rivastigmine, or galantamine?
_____%

(A percentage between 1 and 100 must be provided. If the physician has never initiated a prescription, the answer is 0%.)

Question 3

Do you see patients with other forms of dementia such as vascular, Lewy body, or frontal-temporal in your practice?
Yes |__| No |__|

If 'no,' then go to question 4.

If 'yes,' then ask the portion below.

For what percentage of these patients have you initiated prescriptions for a cholinesterase inhibitor such as donepezil, rivastigmine, or galantamine?
_____%

(A percentage between 1 and 100 must be provided. If the physician has never initiated a prescription, the answer is 0%.)

Question 4

For this question, I'm going to list a series of factors.

To what extent would each factor influence your decision to treat the average Alzheimer's patient with a medication developed specifically for the disease? Cholinesterase inhibitors would be examples of such medications.

For each factor, you may select one of the following responses:
-would not influence
-probably would not influence
-don't know
-probably would influence
-would influence

(Read each factor [see next page] individually to the physician and tick off the box matching the response option that s/he provides. Then move to the next factor.)

Let's start with the factors...

FACTORS	Would not influence	Probably would not influence	Don't know	Probably would influence	Would influence
Patient's current overall health status					
Patient's age					
Patient's current medication use					
Patient lives in a nursing home					
Patient lives at home					
Past patient compliance to medication regimens					
Severity of patient's dementia					
Caregiver's current overall health status					
Caregiver pressure to prescribe a medication					
Caregiver's ability to tolerate patient behaviour					
How familiar you are with the patient					
How much time you have to devote to the patient					
Ease of administration of the Alzheimer's drug					
Side-effect profile of the Alzheimer's drug					
Cost of the Alzheimer's drug					
The requirement to fill out the 'Medicament d'exception' form					

Question 5

This question concerns a hypothetical, newly developed Alzheimer's disease medication, which we will call 'Drug A'.

Please assume Drug A has been shown to have positive effects on cognitive status, behaviour and mood, and the ability to perform basic activities of daily living.

You may also assume that adverse effects are minimal and that the medication is on the provincial formulary.

I am now going to ask what minimum effects you would require of Drug A before you would consider prescribing it to your patients.

[Read each response option and circle the response provided by the physician.]

For cognitive status, the required minimum effect would be which one of the following three options:

a) To permanently stabilize the level of cognition such that a patient would not show any further decline on the Folstein/MMSE scale, but at the same time would not improve either OR

b) To somewhat reverse the degree of cognitive impairment such that a patient would show a 1 to 3 point increase in score on the Folstein/MMSE scale OR

To substantially reverse the degree of cognitive impairment such that a patient would show a greater than 3 point increase on the Folstein/MMSE score.

For behaviour and mood, the required minimum effect would be which one of the following three options:

a) To permanently prevent further occurrences of problematic behaviours and moods, such as no more bouts of agitated behaviour or no more depressive episodes OR

b) To reduce further occurrences of problematic behaviours and moods by up to 25% OR

c) To reduce further occurrences of problematic behaviours and moods by more than 25%.

For the ability to perform basic activities of daily living, the required minimum effect would be which one of the following three options:

a) To permanently prevent any further diminishment of a patient's ability to perform basic activities of daily living OR

b) To allow a patient to resume 1 to 2 basic activities of daily living OR

c) To allow a patient to resume 3 or more basic activities of daily living.

Question 6

For this question, please assume Drug A does not halt or reverse the impact of Alzheimer's disease. Instead, the drug stabilizes the patient for a certain length of time, and then decline resumes again.

What is the minimum length of stabilization that you would require in order to consider prescribing Drug A to your patients? Please express your answers in months.

For patients in the mild state of Alzheimer's disease, I would require a minimum length of stabilization of at least ____ months

[Mild state of AD: Folstein/MMSE score range = 21-26]

For patients in the moderate state of Alzheimer's disease, I would require a minimum length of stabilization of at least ____ months
[Moderate state of AD: Folstein/MMSE score range = 11-20]

The Wrap-Up

The questionnaire is almost complete. I would just like to obtain some demographic information.

1. What is your age? _____

2. In what year did you receive your license to practice medicine? _____

3. Approximately how many patients do you have in your practice?
   _____

4. Approximately how many Alzheimer's disease patients do you have in your practice? _____

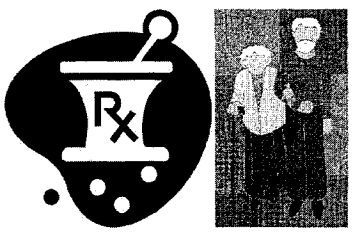
We are finished. Thank you very much for participating. Good day.

Appendix D: PHYSICIAN QUESTIONNAIRE - TEST-RETEST RELIABILITY SURVEY (ENGLISH)

Thank you for taking the time to complete this questionnaire. Your willingness to provide this information once again is very much appreciated. If there is anything else you would like to mention about this study, then please do so in the space provided below.

If you have any questions, then please contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717. Please return your completed questionnaire in the envelope provided to:

Centre for Clinical Epidemiology and Community Studies
Jewish General Hospital
3755 Cote Ste. Catherine Road
Montreal, Qc
H3T 1E2



THE PMAD (PHYSICIANS' USE OF MEDICATIONS FOR ALZHEIMER'S DISEASE) STUDY

McGill University
&
Jewish General Hospital
Montreal, Qc

Please return your completed questionnaire in the enclosed envelope to:

CENTRE for CLINICAL EPIDEMIOLOGY and COMMUNITY STUDIES
JEWISH GENERAL HOSPITAL
3755 COTE STE. CATHERINE ROAD
MONTREAL, Qc
H3T 1E2

Question 1. Factors Influencing the Selection of Drug Therapy as a Treatment Option for Alzheimer's Disease Patients

Please complete this section whether or not you presently prescribe donepezil (Aricept), rivastigmine (Exelon), or galantamine (Reminyl) to treat Alzheimer's patients.

To what extent would each of the factors below influence your decision to treat the average Alzheimer's patient with a medication developed specifically for Alzheimer's disease (such as donepezil, rivastigmine, or galantamine)?

For each factor, please check the most appropriate box.

FACTORS	Would not influence	Probably would not influence	Don't know	Probably would influence	Would influence
Patient's current overall health status					
Patient's age					
Patient's current medication use					
Patient lives in a nursing home					
Patient lives at home					
Past patient compliance to medication regimens					
Severity of patient's dementia					
Caregiver's current overall health status					
Caregiver pressure to prescribe a medication					
Caregiver's ability to tolerate patient behaviour					
How familiar you are with the patient					
How much time you have to devote to the patient					
Ease of administration of the Alzheimer's drug					
Side-effect profile of the Alzheimer's drug					
Cost of the Alzheimer's drug					
The requirement to fill out the "Medicament d'exception" form					

5. Approximately how many patients **in total** do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients in total: _____

6a. Approximately how many **Alzheimer's** patients do you currently have in your practice (provide a **'best guess'** estimate)?

Number of Alzheimer's patients: _____

6b. Approximately how many patients **with mild cognitive impairment** (MCI) do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients with mild cognitive impairment: _____

6c. Approximately how many patients **with other forms of dementia besides Alzheimer's disease** (e.g., vascular, Lewy body, frontal-temporal) do you currently have in your practice (provide a **'best guess'** estimate)?

Number of patients with other forms of dementia: _____

4a. For what percentage of your Alzheimer's patients have you initiated a prescription for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

_____%

Please break down this overall percentage by stage of disease. The percentages that you report should add up to the overall percentage that you specified above.

Mild stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 21-26)

Moderate stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 11-20)

Severe stage of Alzheimer's disease _____%
(Folstein/MMSE score range: 0-10)

4b. For the patients with mild cognitive impairment (MCI) that you see in your practice, have you ever initiated prescriptions for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

a) No

b) Yes → If 'yes,' then to what percentage of these patients have you initiated prescriptions for these medications?
_____%

4c. For the patients with other forms of dementia besides Alzheimer's disease (e.g., vascular, Lewy body, frontal-temporal) that you see in your practice, have you ever initiated prescriptions for a cholinesterase inhibitor (i.e., donepezil, rivastigmine, or galantamine)?

a) No

b) Yes → If 'yes,' then to what percentage of these patients have you initiated prescriptions for these medications?
_____%

Questions 2 and 3. Requirements and Beliefs for Using Medications to Treat Alzheimer's Patients

We are interested in knowing your efficacy requirements for initiating prescriptions for a hypothetical, newly developed Alzheimer's disease medication ('Drug A'). When responding to questions 2a and 3a below, think from the perspective of a clinician who is considering whether or not to use Drug A to treat her/his Alzheimer's patients. Assume that adverse effects are minimal and that the medication is on the provincial formulary.

In questions 2b and 3b below, we would like to know whether or not you believe existing Alzheimer's disease medications (i.e., donepezil, rivastigmine, galantamine) can meet these requirements.

2a. Assume Drug A has been shown to have a positive impact on any or all of the following areas: cognitive status, behaviour and mood, and/or the ability to perform basic activities of daily living. Taking each area separately, what is the minimum effect that you would require the drug to have on the average patient before you would consider prescribing the medication to your own patients? Please circle one choice per area.

Cognitive status – required minimum effect would be…

a) To permanently stabilize the level of cognition (i.e., no decline in Folstein/MMSE score, but no improvement either)
b) To somewhat reverse the degree of cognitive impairment (i.e., 1-3 point increase in Folstein/MMSE score)
c) To substantially reverse the degree of cognitive impairment (i.e., > 3 point increase in Folstein/MMSE score)

Behaviour and mood – required minimum effect would be…

a) To somewhat reduce further occurrences of problematic behaviours and moods (e.g., up to 25% reduction in incidence of problematic behaviours and moods)
b) To substantially reduce further occurrences of problematic behaviours and moods (e.g., more than 25% reduction in incidence of problematic behaviours and moods)
c) To permanently prevent further occurrences of problematic behaviours and moods (e.g., no more bouts of agitated behaviour, no more depressive episodes)

Ability to perform basic activities of daily living – required minimum effect would be…

a) To permanently prevent further diminishment of a patient's ability to perform basic activities of daily living
b) To somewhat increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 1-2 basic activities)
c) To substantially increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 3 or more basic activities)

2b. Given your responses to question 2a above, how strongly do you believe existing Alzheimer's medications (i.e., donepezil, rivastigmine, galantamine) can meet your requirements? For each of the three areas below, please circle the number that best reflects your opinion.

Cognitive status

I do not at all believe									**I definitely believe**
1	2	3	4	5	6	7	8	9	10

Behaviour and mood

I do not at all believe									**I definitely believe**
1	2	3	4	5	6	7	8	9	10

Ability to perform basic activities of daily living

I do not at all believe									**I definitely believe**
1	2	3	4	5	6	7	8	9	10

3a. Assume Drug A does not halt or reverse the impact of Alzheimer's disease. Instead, the drug stabilizes the patient for a lengthened period of time, after which decline recommences. What is the minimum increase in length of stabilization that you would require in order to consider prescribing the medication to your patients? Please express your answers in months.

For patients in the mild state of Alzheimer's disease, I would require an increase in length of stabilization of at least ____ months

(Mild state Folstein/MMSE score range: 21-26)

For patients in the moderate state of Alzheimer's disease, I would require an increase in length of stabilization of at least ____ months

(Moderate state Folstein/MMSE score range: 11-20)

3b. Given your responses to question 3a above, how strongly do you believe existing Alzheimer's medications (i.e., donepezil, rivastigmine, galantamine) can meet your requirements? For each of the disease states below, please circle the number that best reflects your opinion.

Mild state

I do not at all believe									**I definitely believe**
1	2	3	4	5	6	7	8	9	10

Moderate state

I do not at all believe									**I definitely believe**
1	2	3	4	5	6	7	8	9	10

Appendix E: PHYSICIAN QUESTIONNAIRE - TEST-RETEST RELIABILITY SURVEY COVER LETTERS (ENGLISH & FRENCH)

The PMAD (Physicians' Use of Medications for Alzheimer's Disease) Study

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Date

Name and Address
X
X
X
X

Dear Dr. _____:

Recently you were kind enough to respond to a questionnaire on the use of medications to treat Alzheimer's disease (AD). We would like to thank you very much for participating in our study.

In order to verify the reliability of the questionnaire before analyzing the data, we are asking a random sample of respondents to answer a few of the same questions a second time. We would appreciate it if you could spare approximately five minutes to complete the enclosed short questionnaire, which can then be returned in the accompanying self-addressed stamped envelope.

Your responses will remain confidential because data entry and analysis are conducted blind as to identity.

Please rest assured that we will not contact you for more information. Your participation in this study will end after the enclosed questionnaire is returned.

If you have any questions, then please do not hesitate to contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717 or at ADsurvey@epid.jgh.mcgill.ca.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology and
Biostatistics
McGill University

Note: This research study is <u>not</u> funded by any pharmaceutical companies.

Étude UMMA (Utilisation par les médecins de médicaments servant au traitement de la maladie d'Alzheimer)

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Date

Nom et adresse
X
X
X

Docteure, Docteur _____,

Récemment, vous avez eu l'obligeance de répondre à un questionnaire sur l'utilisation de médicaments pour traiter la maladie d'Alzheimer (MA). Nous profitons de l'occasion pour vous remercier de votre participation à l'étude.

Afin de vérifier la fiabilité du questionnaire et avant d'en analyser les données, nous posons de nouveau certaines des mêmes questions à un échantillon aléatoire de répondants. Auriez-vous la gentillesse de prendre environ cinq minutes pour remplir le questionnaire abrégé ci-joint, puis de le renvoyer dans l'enveloppe adressée et affranchie incluse.

Vos réponses demeureront confidentielles étant donné que l'entrée et l'analyse des données s'effectuent à l'insu quant à l'identité.

Ayez l'assurance que nous ne communiquerons plus avec vous pour obtenir d'autres renseignements. Votre participation à l'étude prend fin une fois que le questionnaire ci-joint nous est retourné.

Si vous avez des questions, n'hésitez pas à vous adresser au coordonnateur de l'étude, M. Mark Oremus, au 514-340-8222, poste 4717, ou à ADsurvey@epid.jgh.mcgill.ca.

Recevez nos salutations distinguées.

Howard Bergman, MD
Directeur et professeur titulaire,
Division de gériatrie
Université McGill et Hôpital
général juif

Christina Wolfson, PhD
Directrice, Centre d'épidémiologie
clinique et de recherche en santé publique
Hôpital général juif
Professeure titulaire, Département
d'épidémiologie et de biostatistique
Université McGill

Note : Cette recherche <u>n'est financée par aucune</u> société pharmaceutique.

Appendix F: CAREGIVER QUESTIONNAIRE AND COVER LETTERS (ENGLISH & FRENCH)

Jewish General Hospital
Montreal, Quebec

McGill University
Montreal, Quebec

THE DRUG TREATMENTS FOR ALZHEIMER'S DISEASE STUDY

This questionnaire is for caregivers of Alzheimer's disease patients. Please read the instructions below carefully.

This questionnaire is asking caregivers like <u>you</u> for <u>your</u> opinions on the use of drugs to treat Alzheimer's disease. Please answer the following questions whether or not you are caring for someone who takes these drugs. <u>Please answer even if he or she is institutionalized</u>. The information we get will help researchers guide future drug development and assessment.

Please mail back the completed questionnaire in the enclosed, self-addressed, stamped envelope. The questionnaire should take you about 15 minutes to answer.

Some questions will ask about your caregiving experiences. If you are sharing caregiver duties with others, then please answer these questions with <u>your</u> contribution in mind.

<u>If you do not wish to participate</u>, then please mark an 'X' in this box → ☐ and return the blank questionnaire in the enclosed, self-addressed, stamped envelope.

<u>If you are not a caregiver for an Alzheimer's disease patient, or the person for whom you were providing care is now deceased</u>, then you do <u>not</u> have to complete this questionnaire. Please mark an 'X' in this box → ☐ and return the blank questionnaire in the enclosed, self-addressed, stamped envelope.

Section 1. Demographic and Caregiving Information

The following information will provide us with information about you and your caregiving experiences. There are no right or wrong answers. For each question, please mark an 'X' in the box (☐) next to the choice that applies to you, or fill-in the blanks.

1. **What is your sex?**
   - Female ☐1
   - Male ☐2

2. **What is your month and year of birth?**
   - Month _____ Year _____

3. **What is the highest education level or degree that you have <u>completed</u>?**
   - Elementary school ☐1
   - High school ☐2
   - Community college, CEGEP ☐3
   - Trade school ☐4
   - Undergraduate university degree ☐5
   - Graduate university degree ☐6
   - Other (Specify _____) ☐7

4. **What is your average annual <u>household</u> income from all sources (including wages or salary, government or company pension, disability pension, investment income, etc.)?**
   - Less than $15,000 ☐1
   - $15,001-$25,000 ☐2
   - $25,001-$35,000 ☐3
   - $35,001-$45,000 ☐4
   - $45,001-$55,000 ☐5
   - More than $55,000 ☐6

5. **How would you describe your overall physical health at the present time?**

Excellent ☐1
Very good ☐2
Good ☐3
Fair ☐4
Poor ☐5

6. **What is the sex of the loved one for whom you are caring?**
NOTE: You would still be considered as providing care if your loved one were institutionalized and you were responsible for managing his or her legal or financial affairs.

Female ☐1
Male ☐2

7. **What is the age of the loved one for whom you are caring?**

_____ years old → If you know his or her month and year of birth, then please write them below:

Month_____, Year_____

8. **Is your loved one your...?**

Parent ☐1
Spouse ☐2
Son or daughter ☐3
Brother or sister ☐4
Other relative (Specify _____) ☐5
Friend ☐6
Other (Specify _____) ☐7

9. **How long ago was your loved one diagnosed with Alzheimer's disease?**

Less than 1 year ago ☐1
1-2 years ago ☐2
3-4 years ago ☐3
5-6 years ago ☐4
More than 6 years ago ☐5
Do not know ☐6

10. **Which of the following best describes your loved one's <u>current</u> living arrangements?**

My loved one lives with me ☐1
My loved one lives with someone else ☐2
My loved one lives alone ☐3
My loved one is institutionalized (e.g., nursing home) ☐4
My loved one is hospitalized ☐5

11. **Do you consider yourself to be your loved one's primary caregiver?**
NOTE: You would be the primary caregiver if you are the only caregiver, or if you devote more time to your loved one than any of his or her other caregivers. If your loved one is institutionalized or hospitalized, and you look after his or her legal or financial affairs, then you would also be the primary caregiver.

Yes ☐1
No ☐2

12a. **When (if ever) did <u>you</u> start providing at least some hands-on care for your loved one?**
NOTE: Hands-on care is what you have to provide because your loved one has Alzheimer's disease. It may include helping your loved one move around, eat, bathe, etc. Before your loved one had Alzheimer's disease, you did not have to help with tasks like these.

Less than 1 year ago ☐1
1-2 years ago ☐2
3-4 years ago ☐3
5-6 years ago ☐4
More than 6 years ago ☐5
I never had to provide hands-on care for my loved one ☐6

12b. **When did <u>you</u> stop providing this hands-on care for your loved one? (For example, you may have stopped when he or she was placed in a nursing home.)**

Less than 1 year ago ☐1
1-2 years ago ☐2
3-4 years ago ☐3
5-6 years ago ☐4
More than 6 years ago ☐5
I still provide hands-on care for him or her ☐6

13. **Presently, how much help does your loved one need from <u>you</u> to do the following tasks? PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> TASK.**
NOTE: If someone else helps your loved one with a task, but you <u>do not</u>, then choose 'No help.' If your loved one does not need help at all with a task, then choose 'No help.'

	Help all the time ▼	Frequent help ▼	Occasional help ▼	No help ▼
Bathe	☐1	☐2	☐3	☐4
Dress	☐1	☐2	☐3	☐4
Move from bed to chair	☐1	☐2	☐3	☐4
Go up/down stairs	☐1	☐2	☐3	☐4
Use the toilette	☐1	☐2	☐3	☐4
Eat	☐1	☐2	☐3	☐4
Cook	☐1	☐2	☐3	☐4
Shop	☐1	☐2	☐3	☐4
Clean house	☐1	☐2	☐3	☐4
Use the telephone	☐1	☐2	☐3	☐4
Take medication	☐1	☐2	☐3	☐4

14. **Presently, how would you describe your caregiving experiences?**
- Often difficult ☐1
- Occasionally difficult ☐2
- Rarely difficult ☐3
- Never difficult ☐4

15. **Some people feel that caregiving is rewarding. For example, they get a sense of satisfaction from helping a loved one. Do you feel that caregiving is...**
- Often rewarding ☐1
- Occasionally rewarding ☐2
- Rarely rewarding ☐3
- Never rewarding ☐4

16. **Which of the following statements best describes how your loved one currently makes treatment decisions? Choose only <u>one</u> statement.**
- He or she makes all treatment decisions alone ☐1
- He or she is primarily responsible for making all treatment decisions, but he or she gets help from family members, doctors, a legal guardian, friends, etc. ☐2
- Family members, doctors, a legal guardian, friends, etc., and my loved one, have equal input into all treatment decisions ☐3
- Family members, doctors, a legal guardian, friends, etc. are primarily responsible for making all treatment decisions, but my loved one helps ☐4
- Family members, doctors, a legal guardian, friends, etc. make all treatment decisions alone ☐5
- None of the above ☐6

17. **At this stage in the life of your loved one, have you talked with anyone about, or maybe just thought about, institutionalizing him or her?**
- Yes ☐1
- No ☐2
- The person is already institutionalized ☐3

Section 2. Drug Treatments for Alzheimer's Disease

This section asks about drug treatments for Alzheimer's disease. There are no right or wrong answers. For each question, please mark an 'X' in the box (☐) next to the choice that applies to you.

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18. These are the names of some drugs for Alzheimer's disease – Aricept, Exelon, Reminyl. Is your loved one currently taking any one of them?

Yes ☐1
No ☐2 → If "No", then please answer the question in the box.
Do not know ☐3

Has your loved one ever taken one or more of them?

Yes ☐1 No ☐2

IMPORTANT

Please read the following instructions carefully to see if you should answer the questions in Part A, Part B, or Part C of Section 2.

- **If your loved one is currently taking Aricept, Exelon, or Reminyl, then please complete questions 19-28 in Part A on pages 8-11.**
- **If your loved one has taken one or more of these drugs in the past (but not now), then please complete questions 29-38 in Part B on pages 12-15.**
- **If your loved one has never taken one or more of these drugs, or you do not know if he or she has ever taken one or more of these drugs, then please complete questions 39-47 in Part C on pages 16-19.**

Part A - Answer this part only if your loved one is currently taking Aricept, Exelon, or Reminyl.

---

19. Who first talked about the possibility of prescribing Aricept, Exelon, or Reminyl to the loved one for whom you provide care?

You ☐1
A doctor ☐2
Someone else (Who? _____) ☐3
Do not remember ☐4

20. At this time, are you satisfied with your loved one's response to drug treatment?

Very satisfied ☐1
Somewhat satisfied ☐2
Neutral ☐3
Somewhat dissatisfied ☐4
Very dissatisfied ☐5

21. Do you think it is possible for your loved one to benefit from continuing to take an Alzheimer's disease drug?

Yes ☐1
No ☐2
Do not know ☐3

22. Have you ever put pressure on a doctor to treat your loved one with an Alzheimer's disease drug?

Yes ☐1
No ☐2

23. **Below are several areas affected by Alzheimer's disease. What if your loved one can be treated with a new Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For each of these areas, please indicate how much improvement you would require before letting your loved one start taking the new drug.**
PLEASE PROVIDE AN ANSWER FOR EACH OF THE FOLLOWING AREAS.

	No improvement, but stabilization	Fair improvement	Good improvement	Excellent improvement	Not applicable
Memory	☐1	☐2	☐3	☐4	☐5
Speech	☐1	☐2	☐3	☐4	☐5
Recognition of surroundings	☐1	☐2	☐3	☐4	☐5
Wandering	☐1	☐2	☐3	☐4	☐5
Irritability	☐1	☐2	☐3	☐4	☐5
Depression	☐1	☐2	☐3	☐4	☐5
Anger	☐1	☐2	☐3	☐4	☐5
Mood swings	☐1	☐2	☐3	☐4	☐5
Eating	☐1	☐2	☐3	☐4	☐5
Washing	☐1	☐2	☐3	☐4	☐5
Dressing	☐1	☐2	☐3	☐4	☐5
Stair climbing	☐1	☐2	☐3	☐4	☐5
Getting in/out of chairs	☐1	☐2	☐3	☐4	☐5
Walking	☐1	☐2	☐3	☐4	☐5
Using the toilet	☐1	☐2	☐3	☐4	☐5

24. **Again, what if your loved one can be treated with a new Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For the four possibilities below, how important would each one be in your decision to let your loved one start taking the new drug?**
PLEASE PROVIDE AN ANSWER FOR EACH OF THE FOUR POSSIBILITIES.
If your loved one is currently in an institution, then please answer by imagining how you would feel if they were still at home.

The drug can delay the need to place your loved one in a nursing home for...	Not at all important	Somewhat important	Very important
1-6 months	☐1	☐2	☐3
7-12 months	☐1	☐2	☐3
1-2 years	☐1	☐2	☐3
More than 2 years	☐1	☐2	☐3

25. **Alzheimer's disease drugs occasionally cause side-effects. Several possible side-effects are listed below. For each, please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs.**
PLEASE PROVIDE AN ANSWER FOR EACH OF THESE SIDE-EFFECTS.

	Not willing to continue treatment	Somewhat willing to continue treatment	Clearly willing to continue treatment
Weight loss	☐1	☐2	☐3
Appetite loss	☐1	☐2	☐3
Headaches	☐1	☐2	☐3
Dizziness	☐1	☐2	☐3
Nausea	☐1	☐2	☐3
Diarrhea	☐1	☐2	☐3
Vomiting	☐1	☐2	☐3
Drop in blood pressure	☐1	☐2	☐3
Insomnia	☐1	☐2	☐3
Muscle cramps	☐1	☐2	☐3
Stomach bleeding	☐1	☐2	☐3

26. **Have you ever given your loved one non-prescription drugs (example: vitamins) to help overcome any of the following three problems?**
PLEASE PROVIDE AN ANSWER FOR EACH OF THE THREE PROBLEMS.

	Yes ▼	No ▼
Memory loss	☐1	☐2
Loss of speech	☐1	☐2
Loss of independence	☐1	☐2

27. **Who or what are your main sources of information about drug treatments for Alzheimer's disease?**
(You may select more than one answer.)

- The doctor treating your loved one ☐1
- Fellow caregivers and/or Alzheimer's patients ☐2
- Family, friends ☐3
- Your own research in a library, on the internet, etc. ☐4
- Information brochures from a health clinic, support group, alternative medicine group, etc. ☐5
- The popular media (newspapers, television, etc.) ☐6
- Advertisements from pharmaceutical companies ☐7
- You do not have any sources of information on these drugs ☐8

28. **At the present time, how informed do you feel about what drugs can do to help treat Alzheimer's disease?**

- Well informed ☐1
- Somewhat informed ☐2
- Poorly informed ☐3
- Not at all informed ☐4

THE QUESTIONNAIRE IS NOW COMPLETE

THANK YOU VERY MUCH FOR YOUR TIME

Please mail back the questionnaire in the enclosed, self-addressed stamped envelope.

(Do not answer Part B or Part C.)

Part B - Answer this part only if your loved one has taken Aricept, Exelon, or Reminyl in the past.

29. **Who first talked about the possibility of prescribing Aricept, Exelon, or Reminyl to the loved one for whom you provide care?**

- You ☐1
- A doctor ☐2
- Someone else (Who? _____) ☐3
- Do not remember ☐4

30. **Over the course of your loved one's treatment with one or more of these drugs, were you satisfied with his or her response to treatment?**

- Very satisfied ☐1
- Somewhat satisfied ☐2
- Neutral ☐3
- Somewhat dissatisfied ☐4
- Very dissatisfied ☐5

31. **Do you think it is possible for your loved one to benefit if he or she were to resume taking an Alzheimer's disease drug?**

- Yes ☐1
- No ☐2
- Do not know ☐3

32. **Below are several areas affected by Alzheimer's disease. What if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For each of these areas, <u>please indicate how much improvement you would require before letting your loved one start taking the new drug</u>.**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOLLOWING AREAS.

	No improvement, but stabilization	Fair improvement	Good improvement	Excellent improvement	Not applicable
Memory	☐1	☐2	☐3	☐4	☐5
Speech	☐1	☐2	☐3	☐4	☐5
Recognition of surroundings	☐1	☐2	☐3	☐4	☐5
Wandering	☐1	☐2	☐3	☐4	☐5
Irritability	☐1	☐2	☐3	☐4	☐5
Depression	☐1	☐2	☐3	☐4	☐5
Anger	☐1	☐2	☐3	☐4	☐5
Mood swings	☐1	☐2	☐3	☐4	☐5
Eating	☐1	☐2	☐3	☐4	☐5
Washing	☐1	☐2	☐3	☐4	☐5
Dressing	☐1	☐2	☐3	☐4	☐5
Stair climbing	☐1	☐2	☐3	☐4	☐5
Getting in/out of chairs	☐1	☐2	☐3	☐4	☐5
Walking	☐1	☐2	☐3	☐4	☐5
Using the toilet	☐1	☐2	☐3	☐4	☐5

33. **Again, what if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For the four possibilities below, <u>how important would each one be in your decision to let your loved one start taking the new drug</u>?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOUR POSSIBILITIES.
If your loved one is currently in an institution, then please answer by imagining how you would feel if they were still at home.

The drug can delay the need to place your loved one in a nursing home for...	Not at all important	Somewhat important	Very important
1-6 months	☐1	☐2	☐3
7-12 months	☐1	☐2	☐3
1-2 years	☐1	☐2	☐3
More than 2 years	☐1	☐2	☐3

34. **For this question, please assume that your loved one is currently taking an Alzheimer's disease drug, which (like all drugs) could cause side-effects. Several possible side-effects are listed below. For each side-effect, <u>please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs</u>.**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THESE SIDE-EFFECTS.

	Not willing to continue treatment	Somewhat willing to continue treatment	Clearly willing to continue treatment
Weight loss	☐1	☐2	☐3
Appetite loss	☐1	☐2	☐3
Headaches	☐1	☐2	☐3
Dizziness	☐1	☐2	☐3
Nausea	☐1	☐2	☐3
Diarrhea	☐1	☐2	☐3
Vomiting	☐1	☐2	☐3
Drop in blood pressure	☐1	☐2	☐3
Insomnia	☐1	☐2	☐3
Muscle cramps	☐1	☐2	☐3
Stomach bleeding	☐1	☐2	☐3

35. **Did you ever put pressure on a doctor to treat your loved one with an Alzheimer's disease drug?**
Yes ☐1
No ☐2

36. **Have you ever given your loved one non-prescription drugs (example: vitamins) to help overcome any of the following three problems?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE THREE PROBLEMS.

	Yes	No
Memory loss	☐1	☐2
Loss of speech	☐1	☐2
Loss of independence	☐1	☐2

37. **Who or what were (are) your main sources of information about drug treatments for Alzheimer's disease? (You may select more than one answer.)**

- The doctor treating your loved one ☐1
- Fellow caregivers and/or Alzheimer's patients ☐2
- Family, friends ☐3
- Your own research in a library, on the Internet, etc. ☐4
- Information brochures from a health clinic, support group, alternative medicine group, etc. ☐5
- The popular media (newspapers, television, etc.) ☐6
- Advertisements from pharmaceutical companies ☐7
- You do not have any sources of information on these drugs ☐8

38. **At the present time, how informed do you feel about what drugs can do to help treat Alzheimer's disease?**

- Well informed ☐1
- Somewhat informed ☐2
- Poorly informed ☐3
- Not at all informed ☐4

THE QUESTIONNAIRE IS NOW COMPLETE

THANK YOU VERY MUCH FOR YOUR TIME

Please mail back the questionnaire in the enclosed, self-addressed stamped envelope.

(Do <u>not</u> answer Part A or Part C.)

Part C - Answer this part <u>only</u> if your loved one has <u>never</u> taken Aricept, Exelon, or Reminyl, or you <u>do not know</u> if he or she has ever taken one or more of these drugs.

39a. **In the past 12 months, have you and the doctor treating the loved one for whom you provide care discussed using Aricept, Exelon, or Reminyl to treat the Alzheimer's disease?**

- Yes ☐1
- No ☐2

- **If you answered 'yes', then please answer question 39b below.**
- **If you answered 'no', then please go to question 40 below (and <u>skip</u> question 39b).**

39b. **Who <u>first</u> talked about the possibility of using Aricept, Exelon, or Reminyl to treat the disease?**

- You ☐1
- A doctor ☐2
- Someone else (Who? _____) ☐3
- Do not remember ☐4

40. **Have you ever put pressure on a doctor to treat your loved one with an Alzheimer's disease drug?**

- Yes ☐1
- No ☐2

41. **Who or what are your main sources of information about drug treatments for Alzheimer's disease?**
(You may select more than one answer.)

- The doctor treating your loved one ☐1
- Fellow caregivers and/or Alzheimer's patients ☐2
- Family, friends ☐3
- Your own research in a library, on the Internet, etc. ☐4
- Information brochures from a health clinic, support group, alternative medicine group, etc. ☐5
- The popular media (newspapers, television, etc.) ☐6
- Advertisements from pharmaceutical companies ☐7

42. **At the present time, how informed do you feel about what drugs can do to help treat Alzheimer's disease?**

Well informed ☐1
Somewhat informed ☐2
Poorly informed ☐3
Not at all informed ☐4

43. **Do you think it is possible for your loved one to benefit from taking an Alzheimer's disease drug?**

Yes ☐1
No ☐2
Do not know ☐3

44. **Below are several areas affected by Alzheimer's disease. What if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For each of these areas, <u>please indicate how much improvement you would require before letting your loved one start taking the new drug</u>.**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOLLOWING AREAS.

	No improvement, but stabilization ▼	Fair improvement ▼	Good improvement ▼	Excellent improvement ▼	Not applicable ▼
Memory	☐1	☐2	☐3	☐4	☐5
Speech	☐1	☐2	☐3	☐4	☐5
Recognition of surroundings	☐1	☐2	☐3	☐4	☐5
Wandering	☐1	☐2	☐3	☐4	☐5
Irritability	☐1	☐2	☐3	☐4	☐5
Depression	☐1	☐2	☐3	☐4	☐5
Anger	☐1	☐2	☐3	☐4	☐5
Mood swings	☐1	☐2	☐3	☐4	☐5
Eating	☐1	☐2	☐3	☐4	☐5
Washing	☐1	☐2	☐3	☐4	☐5
Dressing	☐1	☐2	☐3	☐4	☐5
Stair climbing	☐1	☐2	☐3	☐4	☐5
Getting in/out of chairs	☐1	☐2	☐3	☐4	☐5
Walking	☐1	☐2	☐3	☐4	☐5
Using the toilet	☐1	☐2	☐3	☐4	☐5

45. **Again, what if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For the four possibilities below, <u>how important would each one be in your decision to let your loved one start taking the new drug</u>?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOUR POSSIBILITIES.
If your loved one is currently in an institution, then please answer by imagining how you would feel if they were still at home.

The drug can delay the need to place your loved one in a nursing home for...	Not at all important ▼	Somewhat important ▼	Very important ▼
1-6 months	☐1	☐2	☐3
7-12 months	☐1	☐2	☐3
1-2 years	☐1	☐2	☐3

46. **For this question, please assume that your loved one is currently taking an Alzheimer's disease drug, which (like all drugs) could cause side-effects. Several possible side-effects are listed below. For each side-effect, <u>please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs</u>.**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THESE SIDE-EFFECTS.

	Not willing to continue treatment ▼	Somewhat willing to continue treatment ▼	Clearly willing to continue treatment ▼
Weight loss	☐1	☐2	☐3
Appetite loss	☐1	☐2	☐3
Headaches	☐1	☐2	☐3
Dizziness	☐1	☐2	☐3
Nausea	☐1	☐2	☐3
Diarrhea	☐1	☐2	☐3
Vomiting	☐1	☐2	☐3
Drop in blood pressure	☐1	☐2	☐3
Insomnia	☐1	☐2	☐3
Muscle cramps	☐1	☐2	☐3
Stomach bleeding	☐1	☐2	☐3

47. **Have you ever given your loved one non-prescription drugs (example: vitamins) to help overcome any of the following three problems?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE THREE PROBLEMS.

	Yes ▼	No ▼
Memory loss	☐1	☐2
Loss of speech	☐1	☐2
Loss of independence	☐1	☐2

THE QUESTIONNAIRE IS NOW COMPLETE

THANK YOU VERY MUCH FOR YOUR TIME

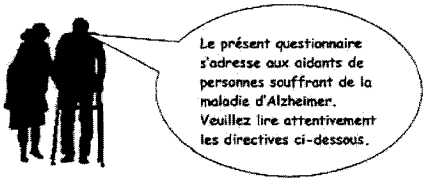
Please mail back the questionnaire in the enclosed, self-addressed stamped envelope.

(Do <u>not</u> answer Part A or Part B.)

Hôpital général juif
Montréal (Québec)

Université McGill
Montréal (Québec)

ÉTUDE SUR LES MÉDICAMENTS PRESCRITS POUR LE TRAITEMENT DE LA MALADIE D'ALZHEIMER



Le présent questionnaire vous demande, ainsi qu'à d'autres aidants comme vous, vos vues et opinions sur l'utilisation de médicaments prescrits pour le traitement de la maladie d'Alzheimer. Veuillez répondre aux questions suivantes que vous soyez ou non l'aidant d'une personne à qui l'on a prescrit ces médicaments. Veuillez répondre même si la personne est institutionnalisée. Les renseignements aideront les chercheurs à orienter la mise au point et l'évaluation de futures médicaments.

Veuillez nous retourner le questionnaire dûment rempli dans l'enveloppe-réponse ci-jointe. Répondre aux questions ne devrait prendre qu'une quinzaine de minutes.

Certaines questions concernent votre expérience en tant qu'aidant. Si vous partagez vos tâches avec une autre personne, veuillez nous faire part de votre contribution.

Si vous ne désirez pas participer à l'étude, veuillez cocher cette case → ☐ et retourner le questionnaire non rempli dans l'enveloppe-réponse ci-jointe.

Si vous n'êtes pas l'aidant d'une personne souffrant de la maladie d'Alzheimer ou que la personne dont vous preniez soin est décédée, ne remplissez pas le questionnaire. Veuillez cocher cette case → ☐ et retourner le questionnaire non rempli dans l'enveloppe-réponse ci-jointe.

Section 1. Renseignements personnels et concernant l'aide fournie

Les renseignements suivants nous renseigneront sur vous et sur votre expérience en tant qu'aidant. Il n'y a pas de bonne ou de mauvaise réponse. Pour chaque question, veuillez cocher la case (☐) qui s'applique ou remplissez les espaces blancs.

1. **Votre sexe**
   - Femme ☐1
   - Homme ☐2

2. **Votre date de naissance**
   - Mois_____ année_____

3. **Niveau de scolarité atteint ou diplôme obtenu**
   - École primaire ☐1
   - École secondaire ☐2
   - Cégep ou collège communautaire ☐3
   - École de métiers ☐4
   - Diplôme de premier cycle ☐5
   - Diplôme de deuxième cycle ☐6
   - Autre (précisez_____) ☐7

4. **Quel est le revenu annuel moyen de votre ménage en provenance de toutes sources (incluant salaires et traitements, pension de l'État ou d'entreprise, prestations d'invalidité, revenu de placement, etc.)?**
   - Inférieur à 15 000 $ ☐1
   - 15 001 $ - 25 000 $ ☐2
   - 25 001 $ - 35 000 $ ☐3
   - 35 001 $ - 45 000 $ ☐4
   - 45 001 $ - 55 000 $ ☐5
   - Supérieur à 55 000 $ ☐6

5. **Comment décririez-vous votre état de santé actuel?**

Excellent ☐1
Très bon ☐2
Bon ☐3
Passable ☐4
Mauvais ☐5

6. **Sexe de l'être cher dont vous prenez soin**
REMARQUE : On considérera que vous êtes un aidant même si l'être cher est institutionnalisé et que vous vous occupez de ses affaires juridiques ou financières.

Femme ☐1
Homme ☐2

7. **Âge de l'être cher dont vous prenez soin**

_____ ans → Si vous connaissez sa date de naissance, veuillez l'indiquer ci-dessous:

Mois_____ Année_____

8. **L'être cher est-il**

un parent ☐1
votre conjoint ☐2
votre fils ou fille ☐3
votre frère ou soeur ☐4
un autre membre de la famille (précisez_____) ☐5
un ami ☐6
autre (précisez _____) ☐7

9. **À quand remonte le diagnostic de maladie d'Alzheimer de l'être cher?**

Moins d'un an ☐1
1 - 2 ans ☐2
3 - 4 ans ☐3
5 - 6 ans ☐4
Plus de 6 ans ☐5
Ne sais pas ☐6

10. **Parmi les choix suivants, lequel s'applique le mieux aux conditions de logement de l'être cher?**

L'être cher habite avec moi ☐1
L'être cher habite avec une autre personne ☐2
L'être cher habite seul ☐3
L'être cher est institutionnalisé (p. ex., centre de soins de longue durée) ☐4
L'être cher est hospitalisé ☐5

11. **Vous considérez-vous comme le principal aidant de l'être cher?**
REMARQUE : Vous êtes considéré comme le principal aidant si vous êtes le seul aidant ou que vous consacrez plus de temps à l'être cher que tout autre aidant. Si l'être cher est institutionnalisé ou hospitalisé et que vous vous occupez de ses affaires juridiques et financières, vous êtes alors considéré comme l'aidant principal.

Oui ☐1
Non ☐2

12a. **Quand (si cela est le cas) avez-vous commencé à fournir des soins directs à l'être cher?**
REMARQUE : Les soins directs sont ceux que vous devez fournir parce que l'être cher souffre de la maladie d'Alzheimer (l'aider à se déplacer, à se nourrir, à faire sa toilette, etc.). Avant que l'être souffre de la maladie d'Alzheimer, vous ne l'aidiez pas à accomplir ces tâches.

Moins d'un an ☐1
1 - 2 ans ☐2
3 - 4 ans ☐3
5 - 6 ans ☐4
Plus de 6 ans ☐5
Je n'ai jamais eu à fournir de soins directs à l'être cher ☐6

12b. **Quand avez-vous cessé de fournir des soins directs à l'être cher? (Par exemple, vous avez cessé de lui fournir ces soins au moment où il a été admis dans un centre de soins de longue durée.)**

Moins d'un an ☐1
1 - 2 ans ☐2
3 - 4 ans ☐3
5 - 6 ans ☐4
Plus de 6 ans ☐5
Je continue de fournir des soins directs à l'être cher ☐6
Je n'ai jamais eu à fournir de soins directs à l'être cher ☐7

13. **Présentement, quel type d'aide devez-vous fournir à l'être cher pour ce qui est des tâches suivantes?**
VEUILLEZ DONNER UNE RÉPONSE POUR CHAQUE TÂCHE.
REMARQUE : Si une autre personne aide l'être cher à accomplir une tâche à laquelle vous ne participez pas, veuillez choisir « Aucune aide ». Si l'être cher n'a pas besoin d'aide pour accomplir la tâche, indiquez « Aucune aide ».

	Aide constante ▼	Aide fréquente ▼	Aide occasionnelle ▼	Aucune aide ▼
Faire sa toilette	☐1	☐2	☐3	☐4
S'habiller	☐1	☐2	☐3	☐4
Se déplacer du lit au fauteuil	☐1	☐2	☐3	☐4
Monter ou descendre l'escalier	☐1	☐2	☐3	☐4
Faire ses besoins	☐1	☐2	☐3	☐4
S'alimenter	☐1	☐2	☐3	☐4
Faire la cuisine	☐1	☐2	☐3	☐4
Faire des courses	☐1	☐2	☐3	☐4
Faire le ménage	☐1	☐2	☐3	☐4
Téléphoner	☐1	☐2	☐3	☐4
Prendre ses médicaments	☐1	☐2	☐3	☐4

14. **Présentement, comment décririez-vous votre expérience en tant qu'aidant?**
- Souvent difficile ☐1
- Parfois difficile ☐2
- Rarement difficile ☐3
- Jamais difficile ☐4

15. **Certaines personnes estiment que le travail d'aidant est enrichissant. Par exemple, aider un être cher leur procure une grande satisfaction. Pour vous, être aidant est...**
- Souvent enrichissant ☐1
- Parfois enrichissant ☐2
- Rarement enrichissant ☐3
- Jamais enrichissant ☐4

16. **Parmi les énoncés suivants, lequel décrit le mieux la façon dont l'être cher prend des décisions au sujet des soins? Ne choisissez qu'un seul énoncé.**
- L'être cher prend lui-même toutes les décisions concernant les soins ☐1
- L'être cher est la principale personne qui prend les décisions concernant les soins, avec l'aide d'autres (membres de la famille, médecins, mandataire légal, amis, etc.) ☐2
- Membres de la famille, médecins, mandataire légal ou amis ainsi que l'être cher prennent conjointement les décisions concernant les soins ☐3
- Membres de la famille, médecins, mandataire légal ou amis prennent les décisions concernant les soins, mais l'être cher participe au processus ☐4
- Membres de la famille, médecins, mandataire légal ou amis prennent toutes les décisions concernant les soins ☐5
- Aucune de ces réponses ☐6

17. **Au stade actuel de la vie de l'être cher, avez-vous abordé avec lui la question de l'institutionnalisation, ou y avez-vous réfléchi?**
- Oui ☐1
- Non ☐2
- La personne est déjà institutionnalisée ☐3

Section 2. Médicaments prescrits pour le traitement de la maladie d'Alzheimer

La présente section concerne les médicaments prescrits pour traiter la maladie d'Alzheimer. Il n'y a pas de bonne ou de mauvaise réponse. Pour chaque question, veuillez cocher la case (☐) qui s'applique à votre situation.

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18. Les médicaments suivants sont prescrits pour le traitement de la maladie d'Alzheimer – Aricept, Exelon ou Reminyl. L'être cher prend-il l'un d'eux à l'heure actuelle?

Oui ☐1 → Si la réponse est « oui », veuillez répondre à la question suivante

Non ☐2

Ne sais pas ☐3

L'être cher a-t-il déjà pris un ou plusieurs de ces médicaments?

Oui ☐1 Non ☐2

IMPORTANT

Veuillez lire attentivement les directives pour déterminer si vous devez répondre aux questions de la partie A, B ou C de la section 2.

- **Si l'être cher prend <u>présentement</u> Aricept, Exelon ou Reminyl, <u>veuillez répondre aux questions 19 à 28 de la partie A, pages 8-11</u>.**
- **Si l'être cher a déjà pris un ou plusieurs de ces médicaments <u>dans le passé</u> (mais pas présentement), <u>veuillez répondre aux questions 29 à 38 de la partie B, pages 12-15</u>.**
- **Si l'être cher n'a <u>jamais</u> pris un de ces médicaments, ou que <u>vous ne le savez pas</u>, <u>veuillez répondre aux questions 39 à 47 de la partie C, pages 16-19</u>.**

Partie A Répondez aux questions de cette partie <u>seulement</u> si l'être cher prend <u>présentement</u> Aricept, Exelon ou Reminyl.

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19. Qui a abordé le premier la possibilité de prescrire Aricept, Exelon ou Reminyl à l'être cher dont vous prenez soin?

Moi ☐1

Un médecin ☐2

Une autre personne (précisez _____) ☐3

Ne me souviens pas ☐4

20. À l'heure actuelle, êtes-vous satisfait de la réaction de l'être cher à la pharmacothérapie?

Très satisfait ☐1

Assez satisfait ☐2

Neutre ☐3

Assez insatisfait ☐4

Très insatisfait ☐5

21. Selon vous, serait-il bénéfique à l'être cher de continuer à prendre un médicament prescrit pour le traitement de la maladie d'Alzheimer?

Oui ☐1

Non ☐2

Ne sais pas ☐3

22. Avez-vous déjà fait pression sur un médecin pour qu'il prescrive à l'être cher un médicament pour le traitement de la maladie d'Alzheimer?

Oui ☐1

Non ☐2

23. **Nous présentons ci-dessous plusieurs domaines affectés par la maladie d'Alzheimer. Supposons que l'être cher peut être traité au moyen d'un <u>nouveau</u> médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour chaque domaine, <u>veuillez indiquer le degré d'amélioration que vous exigeriez avant de l'administrer à l'être cher.</u>**
VEUILLEZ FOURNIR UNE RÉPONSE POUR <u>CHACUN</u> DES DOMAINES SUIVANTS.

	Etat stable: pas d'amélioration ▼	Faible amélioration ▼	Bonne amélioration ▼	Excellente amélioration ▼	Ne s'applique pas ▼
Mémoire	☐1	☐2	☐3	☐4	☐5
Parole	☐1	☐2	☐3	☐4	☐5
Reconnaissance des lieux	☐1	☐2	☐3	☐4	☐5
Errance	☐1	☐2	☐3	☐4	☐5
Irascibilité	☐1	☐2	☐3	☐4	☐5
Dépression	☐1	☐2	☐3	☐4	☐5
Colère	☐1	☐2	☐3	☐4	☐5
Sautes d'humeur	☐1	☐2	☐3	☐4	☐5
S'alimenter	☐1	☐2	☐3	☐4	☐5
Faire sa toilette	☐1	☐2	☐3	☐4	☐5
S'habiller	☐1	☐2	☐3	☐4	☐5
Monter un escalier	☐1	☐2	☐3	☐4	☐5
S'asseoir et se lever	☐1	☐2	☐3	☐4	☐5
Marcher	☐1	☐2	☐3	☐4	☐5
Faire ses besoins	☐1	☐2	☐3	☐4	☐5

24. **De nouveau, supposons que l'être cher peut être traité au moyen d'un <u>nouveau</u> médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour les quatre possibilités ci-dessous, <u>quelle importance aurait chacune dans votre décision d'administrer le nouveau médicament à l'être cher</u>?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR <u>CHACUNE</u> DES QUATRE POSSIBILITÉS.
Si l'être cher est présentement institutionnalisé, que répondriez-vous si la personne était encore à la maison.

Grâce au médicament, on pourrait reporter l'institutionnalisation de l'être cher dans un centre de soin longue durée de:	Pas important ▼	Assez important ▼	Très important ▼
1 - 6 mois	☐1	☐2	☐3
7 - 12 mois	☐1	☐2	☐3
1 - 2 ans	☐1	☐2	☐3
Plus de deux ans	☐1	☐2	☐3

25. **Les médicaments pour le traitement de la maladie d'Alzheimer entraînent parfois des effets secondaires, dont certains sont énumérés ci-dessous. Pour chacun, <u>veuillez indiquer votre disposition à ce que l'être cher continue d'employer le médicament si cet effet se manifeste.</u>**
VEUILLEZ FOURNIR UNE RÉPONSE POUR <u>CHAQUE</u> EFFET SECONDAIRE.

	Pas disposé à continuer la pharmacothérapie ▼	Plutôt disposé à continuer la pharmacothérapie ▼	Entièrement disposé à continuer la pharmacothérapie ▼
Perte de poids	☐1	☐2	☐3
Perte d'appétit	☐1	☐2	☐3
Maux de tête	☐1	☐2	☐3
Étourdissements	☐1	☐2	☐3
Nausée	☐1	☐2	☐3
Diarrhée	☐1	☐2	☐3
Vomissements	☐1	☐2	☐3
Baisse de la tension artérielle	☐1	☐2	☐3
Insomnie	☐1	☐2	☐3
Crampes musculaires	☐1	☐2	☐3

26. **Avez-vous déjà administré à l'être cher des médicaments sans ordonnance (comme des vitamines) pour aider à soulager un des trois problèmes suivants?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR <u>CHACUN</u> DES TROIS PROBLÈMES.

	Oui ▼	Non ▼
Perte de mémoire	☐1	☐2
Perte de la parole	☐1	☐2
Perte d'autonomie	☐1	☐2

27. **Quelles sont vos principales sources d'information concernant les médicaments prescrits pour le traitement de la maladie d'Alzheimer? (Vous pouvez indiquer plus d'une réponse.)**

- Le médecin qui soigne l'être cher ☐1
- Aidants ou autres personnes souffrant de la maladie d'Alzheimer ☐2
- Parents et amis ☐3
- Vos propres recherches à la bibliothèque, sur Internet, etc. ☐4
- Brochures d'une clinique, groupe de soutien, groupe de médecine alternatif, etc. ☐5
- Les médias (journaux, télévision, etc.) ☐6
- Publicité de sociétés pharmaceutiques ☐7
- Vous n'avez aucune source d'information concernant ces médicaments ☐8

28. **À l'heure actuelle, quel est, selon vous, votre niveau de connaissance des médicaments susceptibles d'aider à traiter la maladie d'Alzheimer?**

- Bien informé ☐1
- Assez informé ☐2
- Mal informé ☐3
- Aucunement informé ☐4

LE QUESTIONNAIRE EST TERMINÉ.

MERCI D'AVOIR PRIS LE TEMPS D'Y RÉPONDRE.

Veuillez placer le questionnaire dans l'enveloppe-réponse ci-jointe et le poster.

(Ne répondez pas aux parties B ou C.)

Partie B Répondez aux questions de cette partie <u>seulement</u> si l'être cher a pris Aricept, Exelon ou Reminyl <u>dans le passé</u>.

29. **Qui a abordé le premier la possibilité de prescrire Aricept, Exelon ou Reminyl à l'être cher dont vous prenez soin?**

- Moi ☐1
- Un médecin ☐2
- Une autre personne (précisez _____) ☐3
- Ne me souviens pas ☐4

30. **Pendant que l'être cher a pris un ou plusieurs de ces médicaments, avez-vous été satisfait de sa réaction au traitement?**

- Très satisfait ☐1
- Assez satisfait ☐2
- Neutre ☐3
- Assez insatisfait ☐4
- Très insatisfait ☐5

31. **Selon vous, serait-il bénéfique à l'être cher de recommencer à prendre un médicament prescrit pour le traitement de la maladie d'Alzheimer?**

- Oui ☐1
- Non ☐2
- Ne sais pas ☐3

32. **Nous présentons ci-dessous plusieurs domaines affectés par la maladie d'Alzheimer. Supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour chaque domaine, veuillez indiquer le degré d'amélioration que vous exigeriez avant de l'administrer à l'être cher.**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUN DES DOMAINES SUIVANTS.

	État stable: pas d'amélioration ▼	Faible amélioration ▼	Bonne amélioration ▼	Excellente amélioration ▼	Ne s'applique pas ▼
Mémoire	☐1	☐2	☐3	☐4	☐5
Parole	☐1	☐2	☐3	☐4	☐5
Reconnaissance des lieux	☐1	☐2	☐3	☐4	☐5
Errance	☐1	☐2	☐3	☐4	☐5
Irascibilité	☐1	☐2	☐3	☐4	☐5
Dépression	☐1	☐2	☐3	☐4	☐5
Colère	☐1	☐2	☐3	☐4	☐5
Sautes d'humeur	☐1	☐2	☐3	☐4	☐5
S'alimenter	☐1	☐2	☐3	☐4	☐5
Faire sa toilette	☐1	☐2	☐3	☐4	☐5
S'habiller	☐1	☐2	☐3	☐4	☐5
Monter un escalier	☐1	☐2	☐3	☐4	☐5
S'asseoir et se lever	☐1	☐2	☐3	☐4	☐5
Marcher	☐1	☐2	☐3	☐4	☐5
Faire ses besoins	☐1	☐2	☐3	☐4	☐5

33. **De nouveau, supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour les quatre possibilités ci-dessous, quelle importance aurait chacune dans votre décision d'administrer le nouveau médicament à l'être cher?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUNE DES QUATRE POSSIBILITÉS.
Si l'être cher est présentement institutionnalisé, que répondriez-vous si la personne était encore à la maison.

Grâce au médicament, on pourrait reporter l'institutionnalisation de l'être cher dans un centre de soin longue durée de:	Pas important ▼	Assez important ▼	Très important ▼
1 - 6 mois	☐1	☐2	☐3
7 - 12 mois	☐1	☐2	☐3
1 - 2 ans	☐1	☐2	☐3
Plus de deux ans	☐1	☐2	☐3

34. **Pour cette question, veuillez supposer que l'être cher prend actuellement un médicament prescrit pour le traitement de la maladie d'Alzheimer, lequel (comme tous les médicaments) peut entraîner des effets secondaires. Certains effets secondaires sont énumérés ci-dessous. Pour chacun, veuillez indiquer votre disposition à ce que l'être cher continue d'employer le médicament si cet effet se manifeste.**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHAQUE EFFET SECONDAIRE.

	Pas disposé à continuer la pharmacothérapie ▼	Plutôt disposé à continuer la pharmacothérapie ▼	Entièrement disposé à continuer la pharmacothérapie ▼
Perte de poids	☐1	☐2	☐3
Perte d'appétit	☐1	☐2	☐3
Maux de tête	☐1	☐2	☐3
Étourdissements	☐1	☐2	☐3
Nausée	☐1	☐2	☐3
Diarrhée	☐1	☐2	☐3
Vomissements	☐1	☐2	☐3
Baisse de la tension artérielle	☐1	☐2	☐3
Insomnie	☐1	☐2	☐3
Crampes musculaires	☐1	☐2	☐3
Hémorragies stomacales	☐1	☐2	☐3

35. **Avez-vous déjà fait pression sur un médecin pour qu'il prescrive à l'être cher un médicament pour le traitement de la maladie d'Alzheimer?**

Oui ☐1
Non ☐2

36. **Avez-vous déjà administré à l'être cher des médicaments sans ordonnance (comme des vitamines) pour aider à soulager un des trois problèmes suivants?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUN DES TROIS PROBLÈMES.

	Oui ▼	Non ▼
Perte de mémoire	☐1	☐2
Perte de la parole	☐1	☐2
Perte d'autonomie	☐1	☐2

37. **Quelles étaient (sont) vos principales sources d'information concernant les médicaments prescrits pour le traitement de la maladie d'Alzheimer?**
(Vous pouvez indiquer plus d'une réponse.)

Le médecin qui soigne l'être cher ☐1
Aidants ou autres personnes souffrant de la maladie d'Alzheimer ☐2
Parents et amis ☐3
Vos propres recherches à la bibliothèque, sur Internet, etc. ☐4
Brochures d'une clinique, groupe de soutien, groupe de médecine alternatif, etc. ☐5
Les médias (journaux, télévision, etc.) ☐6
Publicité de sociétés pharmaceutiques ☐7
Vous n'avez aucune source d'information concernant ces médicaments ☐8

38. **À l'heure actuelle, quel est, selon vous, votre niveau de connaissance des médicaments susceptibles d'aider à traiter la maladie d'Alzheimer?**

Bien informé ☐1
Assez informé ☐2
Mal informé ☐3
Aucunement informé ☐4

LE QUESTIONNAIRE EST TERMINÉ.

MERCI D'AVOIR PRIS LE TEMPS D'Y RÉPONDRE.

Veuillez placer le questionnaire dans l'enveloppe-réponse ci-jointe et le poster.

(Ne répondez pas aux parties A ou C.)

Partie C Répondez aux questions de cette section seulement si l'être cher n'a jamais pris Aricept, Exelon ou Reminyl, ou que vous ne savez pas si cela est le cas.

39a. **Au cours des 12 derniers mois, est-ce que le médecin traitant et vous avez abordé la question de la prescription d'Aricept, d'Exelon ou de Reminyl pour le traitement de la maladie d'Alzheimer?**

Oui ☐1
Non ☐2

➨ Si « oui », veuillez répondre à la question 39b ci-dessous.
➨ Si « non », veuillez sauter la question 39b et répondre à la question 40 ci-dessous.

39b. **Qui a en premier abordé la possibilité de prescrire Aricept, Exelon ou Reminyl pour le traitement de la maladie?**

Moi ☐1
Un médecin ☐2
Une autre personne (précisez _____) ☐3
Ne me souviens pas ☐4

40. **Avez-vous déjà fait pression sur un médecin pour qu'il prescrive à l'être cher un médicament pour le traitement de la maladie d'Alzheimer?**

Oui ☐1
Non ☐2

41. **Quelles sont vos principales sources d'information concernant les médicaments prescrits pour le traitement de la maladie d'Alzheimer?**
(Vous pouvez indiquer plus d'une réponse.)

Le médecin qui soigne l'être cher ☐1
Aidants ou autres personnes souffrant de la maladie d'Alzheimer ☐2
Parents et amis ☐3
Vos propres recherches à la bibliothèque, sur Internet, etc. ☐4
Brochures d'une clinique, groupe de soutien, groupe de médecine alternatif, etc. ☐5
Les médias (journaux, télévision, etc.) ☐6
Publicité de sociétés pharmaceutiques ☐7
Vous n'avez aucune source d'information concernant ces médicaments ☐8

42. À l'heure actuelle, quel est, selon vous, votre niveau de connaissance des médicaments susceptibles d'aider à traiter la maladie d'Alzheimer?

Bien informé ..... ☐1
Assez informé ..... ☐2
Mal informé ..... ☐3
Aucunement informé ..... ☐4

43. Selon vous, serait-il bénéfique à l'être cher de prendre un médicament prescrit pour le traitement de la maladie d'Alzheimer?

Oui ..... ☐1
Non ..... ☐2
Ne sais pas ..... ☐3

44. Nous présentons ci-dessous plusieurs domaines affectés par la maladie d'Alzheimer. Supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour chaque domaine, veuillez indiquer le degré d'amélioration que vous exigeriez avant de l'administrer à l'être cher.
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUN DES DOMAINES SUIVANTS.

	État stable; pas d'amélioration ▼	Faible amélioration ▼	Bonne amélioration ▼	Excellente amélioration ▼	Ne s'applique pas ▼
Mémoire	☐1	☐2	☐3	☐4	☐5
Parole	☐1	☐2	☐3	☐4	☐5
Reconnaissance des lieux	☐1	☐2	☐3	☐4	☐5
Errance	☐1	☐2	☐3	☐4	☐5
Irascibilité	☐1	☐2	☐3	☐4	☐5
Dépression	☐1	☐2	☐3	☐4	☐5
Colère	☐1	☐2	☐3	☐4	☐5
Sautes d'humeur	☐1	☐2	☐3	☐4	☐5
S'alimenter	☐1	☐2	☐3	☐4	☐5
Faire sa toilette	☐1	☐2	☐3	☐4	☐5
S'habiller	☐1	☐2	☐3	☐4	☐5
Monter un escalier	☐1	☐2	☐3	☐4	☐5
S'assoir et se lever	☐1	☐2	☐3	☐4	☐5
Marcher	☐1	☐2	☐3	☐4	☐5
Faire ses besoins	☐1	☐2	☐3	☐4	☐5

45. De nouveau, supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour les quatre possibilités ci-dessous, quelle importance aurait chacune dans votre décision d'administrer le nouveau médicament à l'être cher?
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUNE DES QUATRE POSSIBILITÉS.
Si l'être cher est présentement institutionnalisé, que répondriez-vous si la personne était encore à la maison.

Grâce au médicament, on pourrait reporter l'institutionnalisation de l'être cher dans un centre de soin longue durée de:

	Pas important ▼	Assez important ▼	Très important ▼
1 - 6 mois	☐1	☐2	☐3
7 - 12 mois	☐1	☐2	☐3
1 - 2 ans	☐1	☐2	☐3
Plus de deux ans	☐1	☐2	☐3

46. Pour cette question, veuillez supposer que l'être cher prend actuellement un médicament prescrit pour le traitement de la maladie d'Alzheimer, lequel (comme tous les médicaments) peut entraîner des effets secondaires. Certains effets secondaires sont énumérés ci-dessous. Pour chacun, veuillez indiquer votre disposition à ce que l'être cher continue d'employer le médicament si cet effet se manifeste.
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHAQUE EFFET SECONDAIRE.

	Pas disposé à continuer la pharmacothérapie ▼	Plutôt disposé à continuer la pharmacothérapie ▼	Entièrement disposé à continuer la pharmacothérapie ▼
Perte de poids	☐1	☐2	☐3
Perte d'appétit	☐1	☐2	☐3
Maux de tête	☐1	☐2	☐3
Étourdissements	☐1	☐2	☐3
Nausée	☐1	☐2	☐3
Diarrhée	☐1	☐2	☐3
Vomissements	☐1	☐2	☐3
Baisse de la tension artérielle	☐1	☐2	☐3
Insomnie	☐1	☐2	☐3
Crampes musculaires	☐1	☐2	☐3
Hémorragies stomacales	☐1	☐2	☐3

47. **Avez-vous déjà administré à l'être cher des médicaments sans ordonnance (comme des vitamines) pour aider à soulager un des trois problèmes suivants?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUN DES TROIS PROBLÈMES.

	Oui ▼	Non ▼
Perte de mémoire	☐1	☐2
Perte de la parole	☐1	☐2
Perte d'autonomie	☐1	☐2

LE QUESTIONNAIRE EST TERMINÉ.

MERCI D'AVOIR PRIS LE TEMPS D'Y RÉPONDRE.

Veuillez placer le questionnaire dans l'enveloppe-réponse ci-jointe et le poster.

(Ne répondez pas aux parties A ou B.)

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Alzheimer Society or
Alzheimer Groupe
symbol here

The Drug Treatments for Alzheimer's Disease Study

Date

Name and Address
X
X
X
X

Dear _____:

We are asking for your participation in a study of what caregivers think about drug treatments for Alzheimer's disease. We believe you and other caregivers can provide information to help guide the development and assessment of new Alzheimer's drugs.

You are being contacted at random from a sample of caregivers provided by the Alzheimer Society of Montreal {Alzheimer Groupe Inc.}, which has mailed this questionnaire package on our behalf.

Your participation in the study is voluntary; however, you can help us very much by taking a few minutes to complete the enclosed questionnaire. That is all you have to do. Your answers will remain completely confidential and the Alzheimer Society of Montreal {Alzheimer Groupe Inc.} will not release your name or address to us, so you will never be connected to your answers.

If for some reason you prefer not to respond, or you are not caring for an Alzheimer's disease patient, please let us know by putting an 'X' in the appropriate box on page 1 of the questionnaire. Whether you complete the questionnaire or not, please mail it back to us in the enclosed, self-addressed, stamped envelope.

If you have any questions or comments, please contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717. Thank you very much for helping with this important study.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish
General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology
and Biostatistics, McGill University

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

Alzheimer Society or
Alzheimer Groupe
symbol here

The Drug Treatments for Alzheimer's Disease Study

Date

Name and Address
X
X
X
X

Dear _____:

Three weeks ago we sent you a questionnaire about your opinions on drug treatments for Alzheimer's disease. To the best of our knowledge, your questionnaire has not yet been returned.

The caregivers who have already responded provided very good comments about Alzheimer's drug treatments. We think the results are going to be quite useful to researchers who are trying to find better treatments for Alzheimer's disease.

We are writing again because your questionnaire is important for helping us to get accurate results. It is only by hearing from everyone in the sample that we can be sure the results are truly representative.

A few people have written that they do not wish to participate, and some people who are not caregivers have inadvertently received a questionnaire. If either of these situations applies to you, please let us know by putting an 'X' in the appropriate box on page 1 of the questionnaire, and then return the blank questionnaire in the enclosed, self-addressed, stamped envelope.

A comment on our study procedures. A number is printed on the questionnaire. When we receive your questionnaire, we provide the Alzheimer Society of Montreal {Alzheimer Groupe Inc.} with the number, and they check your name off the study mailing list. At no time is your name shared with us, and we do not share your answers with the Alzheimer Society {Alzheimer Groupe Inc.}. This way, you can never be connected to your answers. Protecting your confidentiality is very important to us, as well as to the Alzheimer Society {Alzheimer Groupe Inc.} and McGill University.

We hope that you will fill out and return the questionnaire today. Please return it in the enclosed envelope. If you have any questions, then please feel free to contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish
General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies,
Jewish General Hospital
Professor, Department of Epidemiology
and Biostatistics, McGill University

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Alzheimer Society or
Alzheimer Groupe
symbol here

Étude sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer

Date

Nom et adresse
X
X
X

Madame, Monsieur,

Par la présente, nous vous demandons de participer à une étude pour obtenir les vues et opinions d'aidants sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer. Les renseignements recueillis serviront à orienter la mise au point et l'évaluation de nouveaux médicaments destinés à traiter la maladie.

Votre nom, qui a été choisi au hasard, figure sur une liste d'aidants que la Société Alzheimer de Montréal {Alzheimer Groupe Inc.} nous a fournie et qui vous a envoyé le présent questionnaire en notre nom.

Votre participation est bénévole, mais vous pouvez nous aider grandement en prenant quelques minutes pour remplir le questionnaire ci-joint. Nous ne vous en demandons pas plus. Vos réponses seront entièrement confidentielles. La Société Alzheimer de Montréal {Alzheimer Groupe Inc.} ne nous communiquera pas vos nom et adresse, de sorte qu'il sera impossible de vous identifier grâce à vos réponses.

Si vous décidez, pour une raison ou une autre, de ne pas participer à l'étude, ou que vous ne prenez présentement pas soin d'une personne souffrant de la maladie d'Alzheimer, veuillez l'indiquer en cochant la case appropriée de la page 1 du questionnaire. Que vous remplissiez le questionnaire ou non, veuillez nous le retourner dans l'enveloppe-réponse incluse.

Si vous avez des questions ou des commentaires, n'hésitez pas à communiquer avec le coordonnateur de l'étude, M. Mark Oremus, au (514)340-8222, poste 4717. Nous vous remercions de votre collaboration.

Veuillez agréer nos salutations distinguées.

Howard Bergman, MD
Directeur et professeur titulaire
Division de gériatrie
Université McGill et Hôpital général juif

Christina Wolfson, PhD
Directrice, Centre d'épidémiologie clinique et de recherche en santé publique, Hôpital général juif
Professeure titulaire, Département d'épidémiologie et de biostatistique
Université McGill

Étude sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

Alzheimer Society or Alzheimer Groupe symbol here

Date

Nom et adresse
X
X
X

Madame, Monsieur,

Il y a trois semaines, nous vous avons fait parvenir un questionnaire afin d'obtenir vos vues et opinions sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer. Selon nos dossiers, vous ne l'avez pas encore retourné.

Les aidants qui ont déjà répondu au questionnaire nous ont fourni d'excellents commentaires sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer. Nous croyons que les résultats seront très utiles aux chercheurs qui s'efforcent de mettre au point des médicaments plus efficaces pour traiter la maladie.

Nous vous écrivons de nouveau parce que vos réponses nous permettront d'obtenir des résultats précis. C'est grâce aux réponses de tous les participants que nous pourrons vraiment garantir la représentativité des résultats.

Certaines personnes ont exprimé leur désir de ne pas participer à l'étude, tandis que d'autres, qui ne sont pas aidants, ont reçu un questionnaire par inadvertance. Si cela est votre cas, veuillez l'indiquer en cochant la case appropriée, à la page 1 du questionnaire, puis retourner ce dernier, non rempli, dans l'enveloppe-réponse fournie à cette fin.

Vous aurez remarqué que le questionnaire est numéroté. Lorsque nous recevons un questionnaire, nous en communiquons le numéro à la Société Alzheimer de Montréal {Alzheimer Groupe Inc.}, qui coche alors le nom du répondant qui figure sur sa liste de diffusion. Nous ne connaissons pas l'identité des répondants et ne communiquons pas les résultats à la Société Alzheimer de Montréal {Alzheimer Groupe Inc.}. De cette manière, il est impossible d'établir de lien entre les réponses et les répondants. La Société Alzheimer de Montréal {Alzheimer Groupe Inc.}, l'Université McGill et nous tenons à ce que le processus soit entièrement confidentiel.

Nous espérons que vous remplirez le questionnaire et que vous nous le ferez parvenir dès aujourd'hui. Veuillez utiliser l'enveloppe-réponse prévue à cette fin. Si vous avez des questions, n'hésitez pas à communiquer avec le coordonnateur de l'étude, M. Mark Oremus, au (514)340-8222, poste 4717.

Veuillez agréer nos salutations distinguées.

Howard Bergman, MD
Directeur et professeur titulaire,
Division de gériatrie
Université McGill et Hôpital général juif

Christina Wolfson, PhD
Directrice, Centre d'épidémiologie clinique et de recherche en santé publique
Hôpital général juif
Professeure titulaire, Département d'épidémiologie et de biostatistique
Université McGill

Appendix G: CAREGIVER QUESTIONNAIRE - TELEPHONE NON-RESPONSE SURVEY & SCRIPT (ENGLISH & FRENCH)

Telephone Survey of Non-Respondents

Dear _____:

You were recently sent a questionnaire about caregiver opinions on drug treatments for Alzheimer's disease.

[NOTE: Even if the caregiver on the phone does not know anything about drug treatments for Alzheimer's disease, or the person with the disease does not take (or has never taken) these kinds of drugs, the caregiver can still answer the questions).

Did you receive the questionnaire?

We are contacting a small sample of people who either did not receive, or who did not return, the questionnaire. We would like to take a few minutes of your time to ask you some of the questions over the phone.

Do you agree to participate?

[If no, then ask why they do not wish to participate, thank them, and wish them a good day.]

[If yes, then proceed with the following...]

Are you providing care for a person with Alzheimer's disease?

[They would be considered as providing care if they engage in hands-on care--such as helping the patient with daily tasks like washing, walking, eating, etc.--or if they supervise the patient's legal/financial affairs (in the case of institutionalized patients).]

[If they are NOT a caregiver (none of the above apply), then they do not have to answer any questions. Thank them and wish them a good day.]

[If they are a caregiver, then proceed to the questions.]

[NOTE: If the patient for whom care was provided is deceased, then the caregiver on the phone does not have to answer the questions. Thank them and wish them a good day.]

Questions [Indicate whether the person you are talking to is a male or female - circle the word for whichever applies.]

[Read each question and the response categories to the person on the phone. Indicate his or her response.]

1. What is your current age? _____

2. What is the sex of the loved one for whom you are caring? M F

3. What is the age of the loved one for whom you are caring? _____

4. Is your loved one your...?

- Parent ☐1
- Spouse ☐2
- Son or daughter ☐3
- Brother or sister ☐4
- Other relative (Specify _____) ☐5
- Friend ☐6
- Other (Specify _____) ☐7

5. How long ago was your loved one diagnosed with Alzheimer's disease?

- Less than 1 year ago ☐1
- 1-2 years ago ☐2
- 3-4 years ago ☐3
- 5-6 years ago ☐4
- More than 6 years ago ☐5
- Do not know ☐6

6. Which of the following best describes your loved one's current living arrangements?

- My loved one lives with me ☐1
- My loved one lives with someone else ☐2
- My loved one lives alone ☐3
- My loved one is institutionalized (e.g., nursing home) ☐4
- My loved one is hospitalized ☐5

7. Do you consider yourself to be your loved one's primary caregiver?

NOTE: You would be the primary caregiver if you are the only caregiver, or if you devote more time to your loved one than any of his or her other caregivers. If your loved one is institutionalized or hospitalized, and you look after his or her legal or financial affairs, then you would also be the primary caregiver.

- Yes ☐1
- No ☐2

8. At this stage in the life of your loved one, have you talked with anyone about, or maybe just thought about, institutionalizing him or her?

[NOTE: Ask question 8 only if the loved one is not institutionalized. If institutionalized, then tick point # 3.]

- Yes ☐1
- No ☐2
- The person is already institutionalized ☐3

9. **Presently, how much help does your loved one need from <u>you</u> to do the following tasks?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> TASK.
NOTE: If someone else helps your loved one with a task, but you <u>do not</u>, then choose 'No help.' If your loved one does not need help at all with a task, then choose 'No help.'

	Help all the time ▼	Frequent help ▼	Occasional help ▼	No help ▼
Bathe	☐1	☐2	☐3	☐4
Dress	☐1	☐2	☐3	☐4
Move from bed to chair	☐1	☐2	☐3	☐4
Go up/down stairs	☐1	☐2	☐3	☐4
Use the toilette	☐1	☐2	☐3	☐4
Eat	☐1	☐2	☐3	☐4
Cook	☐1	☐2	☐3	☐4
Shop	☐1	☐2	☐3	☐4
Clean house	☐1	☐2	☐3	☐4
Use the telephone	☐1	☐2	☐3	☐4
Take medication	☐1	☐2	☐3	☐4

10. **These are the names of some drugs for Alzheimer's disease – <u>Aricept, Exelon, Reminyl</u>. Is your loved one <u>currently</u> taking <u>any</u> one of them?**

Yes ☐1
No ☐2
Do not know ☐3

If 'no', then please answer the question in the box.

Has your loved one ever taken one or more of them?
Yes ☐1 No ☐2

11. **Below are several areas affected by Alzheimer's disease. What if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For each of these areas, <u>please indicate how much improvement you would require before letting your loved one start taking the new drug.</u>**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOLLOWING AREAS.

	No improvement, but stabilization ▼	Fair improvement ▼	Good improvement ▼	Excellent improvement ▼	Not applicable ▼
Memory	☐1	☐2	☐3	☐4	☐5
Speech	☐1	☐2	☐3	☐4	☐5
Recognition of surroundings	☐1	☐2	☐3	☐4	☐5
Wandering	☐1	☐2	☐3	☐4	☐5
Irritability	☐1	☐2	☐3	☐4	☐5
Depression	☐1	☐2	☐3	☐4	☐5
Anger	☐1	☐2	☐3	☐4	☐5
Mood swings	☐1	☐2	☐3	☐4	☐5
Eating	☐1	☐2	☐3	☐4	☐5
Washing	☐1	☐2	☐3	☐4	☐5
Dressing	☐1	☐2	☐3	☐4	☐5
Stair climbing	☐1	☐2	☐3	☐4	☐5
Getting in/out of chairs	☐1	☐2	☐3	☐4	☐5
Walking	☐1	☐2	☐3	☐4	☐5
Using the toilet	☐1	☐2	☐3	☐4	☐5

12. **Again, what if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For the four possibilities below, <u>how important would each one be in your decision to let your loved one start taking the new drug</u>?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOUR POSSIBILITIES.
If your loved one is currently in an institution, then please answer by imagining how you would feel if they were still at home.

The drug can delay the need to place your loved one in a nursing home for...	Not at all important ▼	Somewhat important ▼	Very important ▼
1-6 months	☐1	☐2	☐3
7-12 months	☐1	☐2	☐3
1-2 years	☐1	☐2	☐3
More than 2 years	☐1	☐2	☐3

13. **Alzheimer's disease drugs occasionally cause side-effects. Several possible side-effects are listed below. For each, <u>please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs</u>.**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THESE SIDE-EFFECTS.

	Not willing to continue treatment ▼	Somewhat willing to continue treatment ▼	Clearly willing to continue treatment ▼
Weight loss	☐1	☐2	☐3
Appetite loss	☐1	☐2	☐3
Headaches	☐1	☐2	☐3
Dizziness	☐1	☐2	☐3
Nausea	☐1	☐2	☐3
Diarrhea	☐1	☐2	☐3
Vomiting	☐1	☐2	☐3
Drop in blood pressure	☐1	☐2	☐3
Insomnia	☐1	☐2	☐3
Muscle cramps	☐1	☐2	☐3
Stomach bleeding	☐1	☐2	☐3

1. **Quelle âge avez-vous?** _____

2. **Sexe de l'être cher dont vous prenez soin.** H F

3. **Âge de l'être cher dont vous prenez soin** _____

4. **L'être cher est-il ...**
un parent ☐1
votre conjoint ☐2
votre fils ou fille ☐3
votre frère ou soeur ☐4
un autre membre de la famille (précisez_____) ☐5
un ami ☐6
autre (précisez _____) ☐7

5. **À quand remonte le diagnostic de maladie d'Alzheimer de l'être cher?**
Moins d'un an ☐1
1 - 2 ans ☐2
3 - 4 ans ☐3
5 - 6 ans ☐4
Plus de 6 ans ☐5
Ne sais pas ☐6

6. **Parmi les choix suivants, lequel s'applique le mieux aux conditions de logement de l'être cher?**
L'être cher habite avec moi ☐1
L'être cher habite avec une autre personne ☐2
L'être cher habite seul ☐3
L'être cher est institutionnalisé (p. ex., centre de soins de longue durée) ☐4
L'être cher est hospitalisé ☐5

7. **Vous considérez-vous comme le principal aidant de l'être cher?**
REMARQUE : Vous êtes considéré comme le principal aidant si vous êtes le seul aidant ou que vous consacrez plus de temps à l'être cher que tout autre aidant. Si l'être cher est institutionnalisé ou hospitalisé et que vous vous occupez de ses affaires juridiques et financières, vous êtes alors considéré comme l'aidant principal.
Oui ☐1
Non ☐2

8. Au stade actuel de la vie de l'être cher, avez-vous abordé avec lui la question de l'institutionnalisation, ou y avez-vous réfléchi?

[NOTE: Ask question 8 only if the loved one is not institutionalized. If institutionalized, then tick point # 3.]

Oui ☐1

Non ☐2

La personne est déjà institutionnalisée ☐3

9. Présentement, quel type d'aide devez-vous fournir à l'être cher pour ce qui est des tâches suivantes?

VEUILLEZ DONNER UNE RÉPONSE POUR CHAQUE TÂCHE.

RÉMARQUE : Si une autre personne aide l'être cher à accomplir une tâche à laquelle vous ne participez pas, veuillez choisir « Aucune aide ». Si l'être cher n'a pas besoin d'aide pour accomplir la tâche, indiquez « Aucune aide ».

	Aide constante ▼	Aide fréquente ▼	Aide occasionnelle ▼	Aucune aide ▼
Faire sa toilette	☐1	☐2	☐3	☐4
S'habiller	☐1	☐2	☐3	☐4
Se déplacer du lit au fauteuil	☐1	☐2	☐3	☐4
Monter ou descendre l'escalier	☐1	☐2	☐3	☐4
Faire ses besoins	☐1	☐2	☐3	☐4
S'alimenter	☐1	☐2	☐3	☐4
Faire la cuisine	☐1	☐2	☐3	☐4
Faire des courses	☐1	☐2	☐3	☐4
Faire le ménage	☐1	☐2	☐3	☐4
Téléphoner	☐1	☐2	☐3	☐4
Prendre ses médicaments	☐1	☐2	☐3	☐4

10. Les médicaments suivants sont prescrits pour le traitement de la maladie d'Alzheimer – Aricept, Exelon ou Reminyl. L'être cher prend-il l'un d'eux à l'heure actuelle?

Oui ☐1 — Si la réponse est « non », veuillez répondre à la question dans l'encadré ci-dessous

Non ☐2

Ne sais pas ☐3

L'être cher a-t-il déjà pris un ou plusieurs de ces médicaments?

Oui ☐1 Non ☐2

11. Nous présentons ci-dessous plusieurs domaines affectés par la maladie d'Alzheimer. Supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour chaque domaine, veuillez indiquer le degré d'amélioration que vous exigeriez avant de l'administrer à l'être cher.

VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUN DES DOMAINES SUIVANTS.

	État stable : pas d'amélioration ▼	Faible amélioration ▼	Bonne amélioration ▼	Excellente amélioration ▼	Ne s'applique pas ▼
Mémoire	☐1	☐2	☐3	☐4	☐5
Parole	☐1	☐2	☐3	☐4	☐5
Reconnaissance des lieux	☐1	☐2	☐3	☐4	☐5
Errance	☐1	☐2	☐3	☐4	☐5
Irascibilité	☐1	☐2	☐3	☐4	☐5
Dépression	☐1	☐2	☐3	☐4	☐5
Colère	☐1	☐2	☐3	☐4	☐5
Sautes d'humeur	☐1	☐2	☐3	☐4	☐5
S'alimenter	☐1	☐2	☐3	☐4	☐5
Faire sa toilette	☐1	☐2	☐3	☐4	☐5
S'habiller	☐1	☐2	☐3	☐4	☐5
Monter un escalier	☐1	☐2	☐3	☐4	☐5
S'asseoir et se lever	☐1	☐2	☐3	☐4	☐5
Marcher	☐1	☐2	☐3	☐4	☐5
Faire ses besoins	☐1	☐2	☐3	☐4	☐5

12. **De nouveau, supposons que l'être cher peut être traité au moyen d'un nouveau médicament pour la maladie d'Alzheimer (médicament « miracle » sans effets secondaires déplaisants), et que la décision finale vous appartient. Pour les quatre possibilités ci-dessous, quelle importance aurait chacune dans votre décision d'administrer le nouveau médicament à l'être cher?**
VEUILLEZ FOURNIR UNE RÉPONSE POUR CHACUNE DES QUATRE POSSIBILITÉS.
Si l'être cher est présentement institutionnalisé, que répondriez-vous si la personne était encore à la maison.

Grâce au médicament, on pourrait reporter l'institutionnalisation de l'être cher dans un centre de soin longue durée de:	Pas important ▼	Assez important ▼	Très important ▼
1 - 6 mois	☐1	☐2	☐3
7 - 12 mois	☐1	☐2	☐3
1 - 2 ans	☐1	☐2	☐3
Plus de deux ans	☐1	☐2	☐3

13. **Les médicaments pour le traitement de la maladie d'Alzheimer entraînent parfois des effets secondaires, dont certains sont énumérés ci-dessous. Pour chacun, veuillez indiquer votre disposition à ce que l'être cher continue d'employer le médicament si cet effet se manifeste.**

VEUILLEZ FOURNIR UNE RÉPONSE POUR CHAQUE EFFET SECONDAIRE.

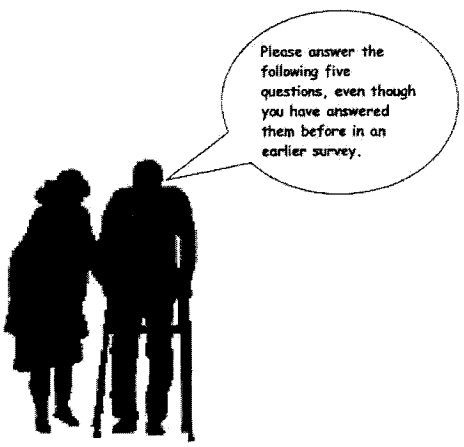
	Pas disposé à continuer la pharmacothérapie ▼	Plutôt disposé à continuer la pharmacothérapie ▼	Entièrement disposé à continuer la pharmacothérapie ▼
Perte de poids	☐1	☐2	☐3
Perte d'appétit	☐1	☐2	☐3
Maux de tête	☐1	☐2	☐3
Étourdissements	☐1	☐2	☐3
Nausée	☐1	☐2	☐3
Diarrhée	☐1	☐2	☐3
Vomissements	☐1	☐2	☐3
Baisse de la tension artérielle	☐1	☐2	☐3
Insomnie	☐1	☐2	☐3
Crampes musculaires	☐1	☐2	☐3
Hémorragies stomacales	☐1	☐2	☐3

Appendix H: CAREGIVER QUESTIONNAIRE - TEST-RETEST RELIABILITY SURVEY (ENGLISH)

Jewish General Hospital
Montreal, Quebec

McGill University
Montreal, Quebec

THE DRUG TREATMENTS FOR ALZHEIMER'S DISEASE STUDY



Page 1

1. **Presently, how much help does your loved one with Alzheimer's disease need from <u>you</u> to do the following tasks?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> TASK.
NOTE: If someone else helps your loved one with a task, but you <u>do not</u>, then choose 'No help.' If your loved one does not need help at all with a task, then choose 'No help.'

	Helps all the time ▼	Frequent help ▼	Occasional help ▼	No help ▼
Bathe	☐1	☐2	☐3	☐4
Dress	☐1	☐2	☐3	☐4
Move from bed to chair	☐1	☐2	☐3	☐4
Go up/down stairs	☐1	☐2	☐3	☐4
Use the toilette	☐1	☐2	☐3	☐4
Eat	☐1	☐2	☐3	☐4
Cook	☐1	☐2	☐3	☐4
Shop	☐1	☐2	☐3	☐4
Clean house	☐1	☐2	☐3	☐4
Use the telephone	☐1	☐2	☐3	☐4
Take medication	☐1	☐2	☐3	☐4

2. **What if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For the four possibilities below, <u>how important would each one be</u> in your decision to let your loved one start <u>taking the new drug</u>?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOUR POSSIBILITIES.
If your loved one is currently in an institution, then please answer by imagining how you would feel if they were still at home.

The drug can delay the need to place your loved one in a nursing home for...	Not at all important ▼	Somewhat important ▼	Very important ▼
1-6 months	☐1	☐2	☐3
7-12 months	☐1	☐2	☐3
1-2 years	☐1	☐2	☐3
More than 2 years	☐1	☐2	☐3

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3. **Below are several areas affected by Alzheimer's disease. Again, what if your loved one can be treated with a <u>new</u> Alzheimer's disease drug (a 'fantasy drug' that does not cause unpleasant side-effects), and the final decision to begin treatment is yours. For each of these areas, <u>please indicate how much improvement you would require before letting your loved one start taking the new drug.</u>**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE FOLLOWING AREAS.

	No improvement, but stabilization	Fair improvement	Good improvement	Excellent improvement	Not applicable
Memory	☐1	☐2	☐3	☐4	☐5
Speech	☐1	☐2	☐3	☐4	☐5
Recognition of surroundings	☐1	☐2	☐3	☐4	☐5
Wandering	☐1	☐2	☐3	☐4	☐5
Irritability	☐1	☐2	☐3	☐4	☐5
Depression	☐1	☐2	☐3	☐4	☐5
Anger	☐1	☐2	☐3	☐4	☐5
Mood swings	☐1	☐2	☐3	☐4	☐5
Eating	☐1	☐2	☐3	☐4	☐5
Washing	☐1	☐2	☐3	☐4	☐5
Dressing	☐1	☐2	☐3	☐4	☐5
Stair climbing	☐1	☐2	☐3	☐4	☐5
Getting in/out of chairs	☐1	☐2	☐3	☐4	☐5
Walking	☐1	☐2	☐3	☐4	☐5
Using the toilet	☐1	☐2	☐3	☐4	☐5

4. **Alzheimer's disease drugs occasionally cause side-effects. Several possible side-effects are listed below. For each, <u>please indicate your willingness to have your loved one continue on drug treatment in the event that it occurs.</u>**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THESE SIDE-EFFECTS.

	Not willing to continue treatment	Somewhat willing to continue treatment	Clearly willing to continue treatment
Weight loss	☐1	☐2	☐3
Appetite loss	☐1	☐2	☐3
Headaches	☐1	☐2	☐3
Dizziness	☐1	☐2	☐3
Nausea	☐1	☐2	☐3
Diarrhea	☐1	☐2	☐3
Vomiting	☐1	☐2	☐3
Drop in blood pressure	☐1	☐2	☐3
Insomnia	☐1	☐2	☐3
Muscle cramps	☐1	☐2	☐3
Stomach bleeding	☐1	☐2	☐3

5. **Have you ever given your loved one non-prescription drugs (example: vitamins) to help overcome any of the following three problems?**
PLEASE PROVIDE AN ANSWER FOR <u>EACH</u> OF THE THREE PROBLEMS.

	Yes	No
Memory loss	☐1	☐2
Loss of speech	☐1	☐2
Loss of independence	☐1	☐2

THE QUESTIONNAIRE IS NOW COMPLETE

THANK YOU VERY MUCH FOR YOUR TIME.

Please mail back the questionnaire in the enclosed, self-addressed, stamped envelope.

Appendix I: CAREGIVER QUESTIONNAIRE - TEST-RETEST RELIABILITY SURVEY COVER LETTERS (ENGLISH & FRENCH)

McGill University
Montreal, Quebec

Jewish General Hospital
Montreal, Quebec

LOGO

The Drug Treatments for Alzheimer's Disease Study

Date

Name and Address
X
X
X
X

Dear _____:

A few weeks ago we sent you a questionnaire about caregiver opinions on drug treatments for Alzheimer's disease. We would like to thank you for taking the time to respond. Your input has made an excellent contribution to our research.

We are kindly asking for your participation in one last phase of our study. After this, you will not be contacted again.

We would like you to answer the five questions in the attached survey. This should not take more than a few minutes. These questions were in the first questionnaire; however, we are asking you and other randomly selected caregivers to respond again because it occasionally happens that people's answers could be influenced by unusual events that might have taken place just before they filled-out a questionnaire. This could sometimes lead to answers that do not reflect how people really feel. The only way to see if this happened with our questionnaire is to ask a few caregivers to respond again.

As before, your participation is voluntary and your answers will remain completely confidential. The Alzheimer Society of Montreal {Alzheimer Groupe Inc.} will not release your name or address to us, so you will never be connected to your answers.

Once completed, please mail the questionnaire back to us in the enclosed, self-addressed, stamped envelope.

If you have any questions or comments, please contact the study coordinator, Mr. Mark Oremus, at (514)340-8222, ext. 4717. Thank you very much for once again helping with this important study.

Sincerely,

Howard Bergman, MD
Director and Professor,
Division of Geriatric Medicine,
McGill University and Jewish
General Hospital

Christina Wolfson, PhD
Director, Centre for Clinical
Epidemiology and Community Studies
Jewish General Hospital
Professor, Department of Epidemiology
and Biostatistics, McGill University

Université McGill
Montréal (Québec)

Hôpital général juif
Montréal (Québec)

LOGO

Étude sur les médicaments prescrits pour le traitement de la maladie d'Alzheimer

Date

Nom et adresse
X
X

Madame, Monsieur,

Il y a quelques semaines, nous vous avons fait parvenir un questionnaire concernant les vues des soignants sur les pharmacothérapies servant au traitement de la maladie d'Alzheimer. Nous aimerions vous remercier d'avoir pris le temps d'y répondre. Vos commentaires ont grandement contribué à notre recherche.

Nous désirons à présent vous demander de participer à la dernière phase de notre étude. Après cela, nous ne communiquerons plus avec vous.

Auriez-vous l'obligeance de répondre aux cinq questions du sondage ci-inclus. Cela ne devrait vous prendre que quelques minutes. Ces questions faisaient partie du premier questionnaire; nous vous demandons ainsi qu'à d'autres soignants choisis au hasard d'y répondre de nouveau, étant donné qu'il arrive parfois que les réponses des personnes interrogées soient influencées par des événements exceptionnels ayant pu se produire juste avant de remplir le questionnaire. Il arrive alors que les réponses ne reflètent pas véritablement les sentiments des personnes. La seule façon de vérifier si cela s'applique à notre questionnaire est de demander aux soignants d'y répondre de nouveau.

Comme auparavant, votre participation est bénévole et vos réponses seront entièrement confidentielles. La Société Alzheimer de Montréal ne nous communiquera pas vos nom et adresse, de sorte qu'il sera impossible de vous identifier grâce à vos réponses.

Après avoir rempli le questionnaire, veuillez nous le retourner dans l'enveloppe-réponse incluse.

Si vous avez des questions ou des commentaires, n'hésitez pas à communiquer avec le coordonnateur de l'étude, M. Mark Oremus, au (514) 340-8222, poste 4717. Nous vous remercions de votre collaboration.

Veuillez agréer nos salutations distinguées.

Howard Bergman, MD
Directeur et professeur titulaire
Division de gériatrie
Université McGill et Hôpital général juif

Christina Wolfson, PhD
Directrice, Centre d'épidémiologie clinique et de recherche en santé publique, Hôpital général juif
Professeure titulaire, Département d'épidémiologie et de biostatistique
Université McGill

Appendix J: PHYSICIAN QUESTIONNAIRE - DISTRIBUTION OF RESPONSES TO SECTIONS 1-3

Table J1: Physician Questionnaire - Distribution of Responses to Section 1 (16 Factors)*

	Would not influence n (%)	**Probably would not influence** n (%)	**Don't know** n (%)	**Probably would influence** n (%)	**Would influence** n (%)	**Missing** n (%)
Patient's current overall health status	5 (2)	22 (9)	1 (<1)	82 (35)	122 (52)	1 (<1)
Patient's age	49 (21)	84 (36)	3 (1)	62 (27)	27 (12)	8 (3)
Patient's current medication use	8 (3)	58 (25)	8 (3)	113 (49)	44 (19)	2 (1)
Patient lives in a nursing home	29 (12)	64 (27)	8 (3)	93 (40)	37 (16)	2 (1)
Patient lives at home	26 (11)	34 (15)	4 (2)	59 (25)	109 (47)	1 (<1)
Past patient compliance to medication regimens	6 (3)	36 (15)	12 (5)	109 (47)	66 (28)	4 (2)
Severity of a patient's dementia	4 (2)	10 (4)	7 (3)	67 (29)	144 (62)	1 (<1)
Caregiver's current overall health status	33 (14)	72 (31)	25 (11)	59 (25)	37 (16)	7 (3)
Caregiver puts pressure on physician to prescribe a medication	23 (10)	77 (33)	18 (8)	97 (42)	17 (7)	1 (<1)

Table J1: Physician Questionnaire - Distribution of Responses to Section 1 (16 Factors)* (continued)

	Would not influence n (%)	**Probably would not influence** n (%)	**Don't know** n (%)	**Probably would influence** n (%)	**Would influence** n (%)	**Missing** n (%)
Caregiver's ability to tolerate patient behaviour	16 (7)	58 (25)	21 (9)	107 (46)	30 (13)	1 (<1)
How familiar you are with the patient	72 (31)	71 (30)	21 (9)	49 (21)	19 (8)	1 (<1)
How much time you have to devote to the patient	79 (34)	88 (38)	15 (6)	34 (15)	14 (6)	3 (1)
Ease of administration of the Alzheimer's drug	3 (1)	16 (7)	2 (1)	121 (52)	88 (38)	3 (1)
Side-effect profile of the Alzheimer's drug	0 (0)	8 (3)	4 (2)	80 (34)	138 (59)	3 (1)
Cost of the Alzheimer's drug	19 (8)	57 (24)	14 (6)	82 (35)	60 (26)	1 (<1)
The requirement to fill out the 'Medicament d'exception' form	107 (46)	76 (33)	6 (3)	26 (11)	17 (7)	1 (<1)

*Percentages do not always total 100 due to rounding error.

Table J2: Physician Questionnaire - Distribution of Responses to Section 2 (Requirements and Beliefs Questions)*

Question	n (%)
Cognitive status – required minimum effect would be...	
To permanently stabilize the level of cognition	144 (62)
To somewhat reverse the degree of cognitive impairment	67 (29)
To substantially reverse the degree of cognitive impairment	20 (9)
Missing	2 (1)
Behaviour and mood – required minimum effect would be...	
To somewhat reduce further occurrences of problematic behaviours and moods	117 (50)
To substantially reduce further occurrences of problematic behaviours and moods	58 (25)
To permanently prevent further occurrences of problematic behaviours and moods	55 (24)
Missing	3 (1)
Ability to perform basic activities of daily living – required minimum effect would be...	
To permanently prevent further diminishment of a patient's ability to perform basic activities of daily living	105 (45)
To somewhat increase a patient's ability to perform basic activities of daily living	100 (43)
To substantially increase a patient's ability to perform basic activities of daily living	26 (11)
Missing	2 (1)
Level of belief - cognitive status	mean=6, SD=2; median=6, range=1-10 (n=2 missing)
Level of belief - behaviour and mood	mean=6, SD=2; median=6, range=1-10 (n=2 missing)
Level of belief - ability to perform basic activities of daily living	mean=6, SD=2; median=6, range=1-10 (n=2 missing)
Required increase in length of stabilization for patients in the mild stage of AD (in months)	mean=15, SD=10; median=12, range=1-60 (n=3 missing)
Required increase in length of stabilization for patients in the moderate stage of AD (in months)	mean=11, SD=6; median=12, range=1-36 (n=3 missing)
Level of belief - increase in length of stabilization (mild stage)	mean=6, SD=2; median=7, range=1-10 (n=3 missing)
Level of belief - increase in length of stabilization (moderate stage)	mean=5, SD=2; median=6, range=1-10 (n=3 missing)

*Percentages do not always total 100 due to rounding error.

Notes: SD = standard deviation, AD = Alzheimer's disease.

Table J3: Physician Questionnaire - Distribution of Responses to Section 3 (Questions about the Prescribing of ChEIs)*

Question	n (%)
Ever initiated prescription for a ChEI to AD patients?	
Yes	211 (91)
No	22 (9)
Missing	0 (0)
Will consider initiating prescriptions for ChEIs in the future?	
Will not do so	2 (<1)
Unlikely to do so	2 (<1)
Toss-up	2 (<1)
Likely to do so	6 (3)
Will do so	9 (4)
Not applicable (already initiated ≥1 prescription)	211 (91)
Missing	1 (<1)
Percentage of AD patients for whom a ChEI prescription was initiated	mean=63, SD=29; median=70, range=0-100 (n=23 missing)
Breakdown of percentage:	
Mild AD patients	mean=41, SD=24; median=40, range=0-100 (n=24 missing)
Moderate AD patients	mean=20, SD=16; median=18, range=0-72 (n=24 missing)
Severe AD patients	mean=2, SD=8; median=0 , range=0-100 (n=24 missing)
Ever initiated prescription for a ChEI to MCI patients?	
Yes	71 (30)
No	141 (61)
Missing	21 (9)
Percentage of MCI patients for whom a ChEI prescription was initiated	mean=45, SD=29; median=50, range=1-100
Ever initiated prescription for a ChEI to patients with dementias other than AD?	
Yes	142 (61)
No	70 (30)
Missing	21 (9)
Percentage of patients with dementias other than AD for whom a ChEI prescription was initiated	mean=47, SD=30; median=50, range=1-100 (n=1 missing)

Table J3: Physician Questionnaire - Distribution of Responses to Section 3 (Questions about the Prescribing of ChEIs)* (continued)

Question	n (%)
Percentage of patients developing adverse effects while using...	
donepezil (210 physicians prescribed donepezil)	mean=17, SD=16; median=10, range=0-100 (n=12 missing)
rivastigmine (124 physicians prescribed rivastigmine)	mean=27, SD=24; median=20, range=0-100 (n=17 missing)
galantamine (100 physicians prescribed galantamine)	mean=20, SD=23; median=10, range=0-100 (n=20 missing)
Percentage of patients who had adverse effects that were severe enough to lead to a discontinuation of...	
donepezil (210 physicians prescribed donepezil)	mean=10, SD=17; median=5, range=0-100 (n=12 missing)
rivastigmine (124 physicians prescribed rivastigmine)	mean=22, SD=27; median=10, range=0-100 (n=18 missing)
galantamine (100 physicians prescribed galantamine)	mean=15, SD=26; median=5, range=0-100 (n=21 missing)
Initiation of prescriptions for other medications besides ChEIs to help address AD-related problems	
Yes	193 (83)
No	40 (17)
What percentage of patients are prescribed other medications besides ChEIs to help address AD-related problems	mean=46, SD=25; median=50, range=2-100 (n=13 missing)
Physician suggests AD patients take OTC medications to address symptoms or behaviours related to AD	
Yes	64 (27)
No	169 (73)
To what percentage of AD patients is the suggestion made to take OTC medications	mean=55, SD=32; median=50, range=5-100 (n=1 missing)
Level of knowledge regarding donepezil	
Not knowledgeable	0 (0)
Somewhat knowledgeable	49 (21)
Very knowledgeable	183 (79)
Missing	1 (<1)
Level of knowledge regarding rivastigmine	
Not knowledgeable	15 (6)
Somewhat knowledgeable	78 (33)
Very knowledgeable	137 (59)
Missing	3 (1)

Table J3: Physician Questionnaire - Distribution of Responses to Section 3 (Questions about the Prescribing of ChEIs)* (continued)

Question	n (%)
Level of knowledge regarding galantamine	
Not knowledgeable	35 (15)
Somewhat knowledgeable	80 (34)
Very knowledgeable	116 (50)
Missing	2 (<1)
Primary source of information regarding ChEIs	
Medical journal articles	76 (33)
Scientific meetings	54 (23)
Advertisements in medical journals	2 (<1)
Observations of patient responses to ChEIs	8 (3)
Colleagues' opinions	2 (<1)
Representatives of pharmaceutical companies	10 (4)
CME courses given by an academic institution	42 (18)
CME courses given by a pharmaceutical company	20 (9)
Electronic media	4 (2)
Missing	15 (6)
Percentage of caregivers who pressure physicians to prescribe ChEIs for AD	mean=24, SD=24; median=30, range=0-100 (n=8 missing)

*Percentages do not always total 100 due to rounding error.

Notes: ChEI = cholinesterase inhibitor, SD = standard deviation, AD = Alzheimer's disease, MCI = mild cognitive impairment, OTC = over-the-counter, CME = continuing medical education.

Appendix K : PHYSICIAN QUESTIONNAIRE : SIMPLE QUASI-BINOMIAL REGRESSION ANALYSES – COVARIATES

Table K1 : Physician Questionnaire : Simple Quasi-binomial Regression Analyses – Covariates

Variable	Listwise Deletion		Multiple Imputation	
	p-value*	Decision†	p-value*	Decision†
Physician's primary source of information on ChEIs	0.1830	Do not retain	0.0707	Do not retain
Physician sex	0.7735	Do not retain	0.9802	Do not retain
Physician age	0.5791	Do not retain	0.6393	Do not retain
Total number of patients in a practice	0.3631	Do not retain	0.3294	Do not retain
Total number of AD patients in a practice	0.0008	Retain	0.0003	Retain
Level of knowledge regarding the efficacy of ChEIs	<0.0001	Retain	<0.0001	Retain
Percentage of patients in a practice with mild AD	0.0003	Retain	<0.0001	Retain
Percentage of patients in a practice with moderate AD	0.0453	Retain	0.0265	Retain
Percentage of patients in a practice with severe AD	0.0032	Retain	<0.0001	Retain
Prescribing index – other medications	0.8542	Do not retain	<0.0001	Retain
Suggestion index – over-the-counter medications	0.0621	Do not retain	0.0002	Retain

Table K1: Physician Questionnaire : Simple Quasi-binomial Regression Analyses – Covariates (continued)

Variable	Listwise Deletion		Multiple Imputation	
	p-value*	Decision†	p-value*	Decision†
Prescribing index - mild cognitive impairment	0.0015	Retain	0.8696	Do not retain
Prescribing index - other dementias	0.0016	Retain	0.0866	Do not retain
Percentage of patients with adverse effects – donepezil‡	0.1423	Do not retain	0.1073	Do not retain
Percentage of patients with adverse effects - rivastigmine‡	0.0017	Retain	0.0013	Retain
Percentage of patients with adverse effects - galantamine‡	0.0803	Do not retain	0.0673	Do not retain
Percentage of patients whose adverse effects led to treatment discontinuation - donepezil‡	0.0029	Retain	0.0002	Retain
Percentage of patients whose adverse effects led to treatment discontinuation - rivastigmine‡	0.0073	Retain	<0.0001	Retain
Percentage of patients whose adverse effects led to treatment discontinuation - galantamine‡	0.0451	Retain	0.0247	Retain
Level of belief in the ability of ChEIs to meet physicians' favourable efficacy requirements (index)	0.0172	Retain	0.0673	Do not retain
Level of belief in the ability of ChEIs to meet physicians' efficacy requirements for increased length of stabilization (index)	0.0172	Retain	0.0015	Retain
Physician specialty	<0.0001	Retain	<0.0001	Retain

*For categorical variables, the overall p-value (Wald X^2 test - type III analysis of effects) is given, not the p-value per category.

†Retain (if $p \leq 0.05$) or do not retain (if $p > 0.05$) as a potential effect modifier or confounder.

‡Simple quasi-binomial regression analysis includes a dichotomous prescribing indicator (Section 3.2.2.2.1).

Notes: ChEI = cholinesterase inhibitor, AD = Alzheimer's disease.

Appendix L: CAREGIVER QUESTIONNAIRE - DISTRIBUTION OF RESPONSES TO SECTIONS 1-2

Table L1: Caregiver Questionnaire - Distribution of Responses to Section 1 (Caregiving Experience)

Questions and Responses	n (%*)
When did caregiver start providing some hands-on care?	
<1 year ago	25 (12)
1-2 years ago	61 (30)
3-4 years ago	36 (18)
5-6 years ago	18 (9)
>6 years ago	10 (5)
Never had to provide care	46 (23)
Missing	5 (2)
When did caregiver stop providing hands-on care?	
<1 year ago	37 (19)
1-2 years ago	17 (9)
3-4 years ago	6 (3)
5-6 years ago	0 (0)
>6 years ago	1 (<1)
Still provides care	89 (44)
Never had to provide care	33 (16)
Missing	18 (9)
Caregiver helps loved one bathe	
All the time	27 (13)
Frequently	11 (6)
Occasionally	25 (12)
Never	125 (62)
Missing	13 (7)
Caregiver helps loved one dress	
All the time	20 (10)
Frequently	12 (6)
Occasionally	35 (17)
Never	118 (59)
Missing	16 (8)
Caregiver helps loved one move from bed to chair	
All the time	6 (3)
Frequently	5 (2)
Occasionally	10 (5)
Never	159 (79)
Missing	21 (10)

Table L1: Caregiver Questionnaire - Distribution of Responses to Section 1 (Caregiving Experience) (continued)

Questions and Responses	n (%*)
Caregiver helps loved one go up/down stairs	
All the time	16 (8)
Frequently	5 (2)
Occasionally	18 (9)
Never	143 (71)
Missing	19 (9)
Caregiver helps loved one use the toilet	
All the time	14 (7)
Frequently	7 (3)
Occasionally	11 (5)
Never	150 (75)
Missing	19 (9)
Caregiver helps loved one eat	
All the time	17 (8)
Frequently	7 (3)
Occasionally	28 (14)
Never	131 (65)
Missing	18 (9)
Caregiver helps loved one cook	
All the time	66 (33)
Frequently	10 (5)
Occasionally	16 (8)
Never	87 (43)
Missing	22 (11)
Caregiver helps loved one shop	
All the time	75 (37)
Frequently	22 (11)
Occasionally	21 (10)
Never	65 (32)
Missing	18 (9)
Caregiver helps loved one clean house	
All the time	56 (28)
Frequently	15 (7)
Occasionally	17 (8)
Never	91 (45)
Missing	22 (11)

Table L1: Caregiver Questionnaire - Distribution of Responses to Section 1 (Caregiving Experience) (continued)

Questions and Responses	n (%*)
Caregiver helps loved one use the telephone	
All the time	45 (22)
Frequently	18 (9)
Occasionally	29 (14)
Never	89 (44)
Missing	20 (10)
Caregiver helps loved one take medication	
All the time	62 (31)
Frequently	12 (6)
Occasionally	9 (4)
Never	64 (32)
Missing	54 (27)
Difficulty of caregiving experience	
Often difficult	60 (30)
Occasionally difficult	106 (53)
Rarely difficult	24 (12)
Never difficult	8 (4)
Missing	3 (1)
Caregiving is...	
Often rewarding	52 (26)
Occasionally rewarding	79 (39)
Rarely rewarding	53 (26)
Never rewarding	13 (6)
Missing	4 (2)
How does patient make treatment decisions?	
Patient makes decisions alone	6 (3)
Patient is primarily responsible for treatment decisions, but gets help from others	22 (11)
Patient and others have equal input into treatment decisions	22 (11)
Others are primarily responsible for treatment decisions, but patient helps	31 (15)
Others make all treatment decisions	85 (42)
None of the above	27 (13)
Missing	8 (4)
Caregiver has talked or thought about institutionalizing the patient	
Yes	72 (36)
No	55 (27)
Patient already institutionalized	70 (35)
Missing	4 (2)

*Percentages do not always total 100 due to rounding error.

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
First who talked about prescribing a ChEI			
Caregiver	12 (9)	5 (17)	1 (3)
Doctor	120 (87)	23 (77)	5 (16)
Someone else	4 (2)	0 (0)	2 (6)
Not applicable	0 (0)	0 (0)	19 (59)
Missing	2 (1)	2 (7)	5 (16)
Satisfied with ChEIs?			
Very satisfied	45 (33)	2 (7)	N/A
Somewhat satisfied	47 (34)	9 (30)	
Neutral	33 (24)	6 (20)	
Somewhat dissatisfied	9 (7)	5 (17)	
Very dissatisfied	4 (3)	6 (20)	
Is there a benefit from continuing to take a ChEI? (Or, is there a possible benefit from taking a ChEI?)			
Yes	100 (72)	4 (13)	4 (13)
No	6 (4)	18 (60)	10 (31)
Do not know	29 (21)	5 (17)	15 (47)
Missing	3 (2)	3 (10)	3 (9)
Has caregiver ever put pressure on physician to prescribe ChEIs?			
Yes	20 (14)	5 (17)	2 (6)
No	112 (81)	22 (73)	27 (84)
Missing	6 (4)	3 (10)	3 (9)
Required improvement in memory			
No improvement, but stabilization	33 (24)	3 (10)	2 (6)
Fair improvement	31 (22)	9 (30)	8 (25)
Good improvement	51 (37)	10 (33)	11 (34)
Excellent improvement	20 (14)	6 (20)	6 (19)
Not applicable	0 (0)	0 (0)	1 (3)
Missing	3 (2)	2 (7)	4 (13)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Required improvement in speech			
No improvement, but stabilization	21 (15)	2 (7)	2 (6)
Fair improvement	18 (13)	7 (23)	4 (13)
Good improvement	36 (26)	11 (37)	10 (31)
Excellent improvement	19 (14)	4 (13)	3 (9)
Not applicable	35 (25)	2 (7)	5 (16)
Missing	9 (7)	4 (13)	8 (25)
Required improvement in recognition of surroundings			
No improvement, but stabilization	22 (16)	3 (10)	3 (9)
Fair improvement	30 (22)	9 (30)	5 (16)
Good improvement	43 (31)	7 (23)	10 (31)
Excellent improvement	18 (13)	3 (10)	5 (16)
Not applicable	15 (11)	3 (10)	2 (6)
Missing	10 (7)	5 (17)	7 (22)
Required improvement in wandering			
No improvement, but stabilization	19 (14)	4 (13)	2 (6)
Fair improvement	13 (9)	3 (10)	3 (9)
Good improvement	29 (21)	4 (13)	9 (28)
Excellent improvement	20 (14)	6 (20)	3 (9)
Not applicable	48 (35)	8 (27)	7 (22)
Missing	9 (7)	5 (17)	8 (25)
Required improvement in irritability			
No improvement, but stabilization	17 (12)	2 (7)	1 (3)
Fair improvement	22 (16)	5 (17)	5 (16)
Good improvement	41 (30)	4 (13)	8 (25)
Excellent improvement	16 (12)	6 (20)	3 (9)
Not applicable	28 (20)	9 (30)	5 (16)
Missing	14 (10)	4 (13)	10 (31)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Required improvement in depression			
No improvement, but stabilization	23 (17)	4 (13)	2 (6)
Fair improvement	22 (16)	5 (17)	5 (16)
Good improvement	47 (34)	4 (13)	10 (31)
Excellent improvement	17 (12)	5 (17)	2 (6)
Not applicable	17 (12)	8 (27)	5 (16)
Missing	12 (9)	4 (13)	8 (25)
Required improvement in anger			
No improvement, but stabilization	19 (14)	6 (20)	0 (0)
Fair improvement	17 (12)	3 (10)	8 (25)
Good improvement	37 (27)	4 (13)	8 (25)
Excellent improvement	19 (14)	4 (13)	4 (13)
Not applicable	32 (23)	9 (30)	5 (16)
Missing	14 (10)	4 (13)	7 (22)
Required improvement in mood swings			
No improvement, but stabilization	15 (11)	4 (13)	0 (0)
Fair improvement	12 (9)	6 (20)	2 (6)
Good improvement	28 (20)	5 (17)	8 (25)
Excellent improvement	15 (11)	5 (17)	2 (6)
Not applicable	17 (12)	6 (20)	5 (16)
Missing	51 (37)	4 (13)	15 (47)
Required improvement in eating			
No improvement, but stabilization	14 (10)	3 (10)	1 (3)
Fair improvement	13 (9)	7 (23)	3 (9)
Good improvement	21 (15)	7 (23)	8 (25)
Excellent improvement	8 (6)	6 (20)	3 (9)
Not applicable	31 (22)	4 (13)	2 (6)
Missing	51 (37)	3 (10)	15 (47)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Required improvement in washing			
No improvement, but stabilization	14 (10)	2 (7)	1 (3)
Fair improvement	14 (10)	7 (23)	5 (16)
Good improvement	21 (15)	9 (30)	5 (16)
Excellent improvement	9 (7)	6 (20)	4 (13)
Not applicable	29 (21)	3 (10)	3 (9)
Missing	51 (37)	3 (10)	14 (44)
Required improvement in dressing			
No improvement, but stabilization	16 (12)	1 (3)	3 (9)
Fair improvement	14 (10)	7 (23)	4 (13)
Good improvement	22 (16)	8 (27)	6 (19)
Excellent improvement	5 (4)	6 (20)	2 (6)
Not applicable	30 (22)	3 (10)	3 (9)
Missing	51 (37)	5 (17)	14 (44)
Required improvement in stair climbing			
No improvement, but stabilization	17 (12)	4 (13)	2 (6)
Fair improvement	11 (8)	5 (17)	1 (3)
Good improvement	16 (12)	5 (17)	7 (22)
Excellent improvement	5 (4)	2 (7)	0 (0)
Not applicable	39 (28)	9 (30)	7 (22)
Missing	50 (36)	5 (17)	15 (47)
Required improvement in getting in/out of chairs			
No improvement, but stabilization	15 (11)	4 (13)	3 (9)
Fair improvement	11 (8)	5 (17)	2 (6)
Good improvement	20 (14)	4 (13)	7 (22)
Excellent improvement	6 (4)	3 (10)	0 (0)
Not applicable	37 (27)	9 (30)	5 (16)
Missing	49 (36)	5 (17)	15 (47)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A	**Part B**	**Part C**
	Person with AD Currently Uses ChEIs (n=138)	**Person with AD Used ChEIs in the Past (n=30)**	**Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Required improvement in walking			
No improvement, but stabilization	17 (12)	5 (17)	2 (6)
Fair improvement	11 (8)	5 (17)	1 (3)
Good improvement	18 (13)	4 (13)	6 (19)
Excellent improvement	4 (3)	4 (13)	1 (3)
Not applicable	38 (28)	7 (23)	7 (22)
Missing	50 (36)	5 (17)	15 (47)
Required improvement in using the toilet			
No improvement, but stabilization	15 (11)	2 (7)	2 (6)
Fair improvement	6 (4)	7 (23)	1 (3)
Good improvement	20 (14)	3 (10)	5 (16)
Excellent improvement	7 (5)	5 (17)	2 (6)
Not applicable	38 (28)	7 (23)	7 (22)
Missing	52 (38)	6 (20)	15 (47)
Importance of delaying nursing home placement for 1-6 months			
Not at all important	24 (17)	7 (23)	6 (19)
Somewhat important	18 (13)	5 (17)	3 (9)
Very important	53 (38)	8 (27)	12 (38)
Missing	43 (31)	10 (33)	11 (34)
Importance of delaying nursing home placement for 7-12 months			
Not at all important	12 (9)	4 (13)	3 (9)
Somewhat important	26 (19)	7 (23)	6 (19)
Very important	50 (36)	9 (30)	12 (38)
Missing	50 (36)	10 (33)	11 (34)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Importance of delaying nursing home placement for 1-2 years			
Not at all important	13 (9)	5 (17)	4 (13)
Somewhat important	27 (20)	5 (17)	9 (28)
Very important	63 (46)	12 (40)	12 (38)
Missing	35 (25)	8 (27)	7 (22)
Importance of delaying nursing home placement >2 years			
Not at all important	4 (3)	2 (7)	1 (3)
Somewhat important	14 (10)	2 (7)	1 (3)
Very important	61 (44)	10 (33)	12 (38)
Missing	59 (43)	16 (53)	18 (56)
Willingness to accept weight loss and continue drug treatment			
Not willing	24 (17)	13 (43)	11 (34)
Somewhat willing	61 (44)	10 (33)	15 (47)
Clearly willing	38 (28)	3 (10)	1 (3)
Missing	15 (11)	4 (13)	5 (16)
Willingness to accept appetite loss and continue drug treatment			
Not willing	31 (22)	15 (50)	13 (41)
Somewhat willing	60 (43)	10 (33)	12 (38)
Clearly willing	32 (23)	2 (7)	2 (6)
Missing	15 (11)	3 (10)	5 (16)
Willingness to accept headaches and continue drug treatment			
Not willing	65 (47)	21 (70)	22 (69)
Somewhat willing	41 (30)	4 (13)	6 (19)
Clearly willing	11 (8)	1 (3)	0 (0)
Missing	21 (15)	4 (13)	4 (13)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Willingness to accept dizziness and continue drug treatment			
Not willing	79 (57)	23 (77)	26 (81)
Somewhat willing	29 (21)	3 (10)	2 (6)
Clearly willing	15 (11)	1 (3)	0 (0)
Missing	15 (11)	3 (10)	4 (13)
Willingness to accept nausea and continue drug treatment			
Not willing	77 (56)	21 (70)	25 (78)
Somewhat willing	32 (23)	5 (17)	3 (9)
Clearly willing	13 (9)	1 (3)	0 (0)
Missing	16 (12)	3 (10)	4 (13)
Willingness to accept diarrhea and continue drug treatment			
Not willing	84 (61)	24 (80)	24 (75)
Somewhat willing	24 (17)	2 (7)	4 (13)
Clearly willing	12 (9)	1 (3)	0 (0)
Missing	18 (13)	3 (10)	4 (13)
Willingness to accept vomiting and continue drug treatment			
Not willing	98 (71)	23 (77)	27 (84)
Somewhat willing	13 (9)	2 (7)	1 (3)
Clearly willing	10 (7)	2 (7)	0 (0)
Missing	17 (12)	3 (10)	4 (13)
Willingness to accept a drop in blood pressure and continue drug treatment			
Not willing	68 (49)	20 (67)	23 (72)
Somewhat willing	41 (30)	6 (20)	5 (16)
Clearly willing	11 (8)	1 (3)	0 (0)
Missing	18 (13)	3 (10)	4 (13)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A **Person with AD Currently Uses ChEIs (n=138)**	**Part B** **Person with AD Used ChEIs in the Past (n=30)**	**Part C** **Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Willingness to accept insomnia and continue drug treatment			
Not willing	64 (46)	25 (83)	20 (63)
Somewhat willing	49 (36)	2 (7)	6 (19)
Clearly willing	11 (8)	1 (3)	1 (3)
Missing	14 (10)	2 (7)	5 (16)
Willingness to accept muscle cramps and continue drug treatment			
Not willing	62 (45)	21 (70)	24 (75)
Somewhat willing	48 (35)	5 (17)	4 (13)
Clearly willing	12 (9)	1 (3)	0 (0)
Missing	16 (12)	3 (10)	4 (13)
Willingness to accept stomach bleeding and continue drug treatment			
Not willing	101 (73)	25 (83)	26 (81)
Somewhat willing	4 (3)	0 (0)	2 (6)
Clearly willing	8 (6)	1 (3)	0 (0)
Missing	25 (18)	4 (13)	4 (13)
Ever given loved one non-prescription drugs for memory loss?			
Yes	37 (27)	8 (27)	6 (19)
No	98 (71)	20 (67)	23 (72)
Missing	3 (2)	2 (7)	3 (9)
Ever given loved one non-prescription drugs for loss of speech?			
Yes	10 (7)	2 (7)	3 (9)
No	122 (88)	26 (87)	26 (81)
Missing	6 (4)	2 (7)	3 (9)

Table L2: Caregiver Questionnaire - Distribution of Responses to Section 2 (Drug Therapies for AD) (continued)

Questions and Responses	n (%*)		
	Part A	**Part B**	**Part C**
	Person with AD Currently Uses ChEIs (n=138)	**Person with AD Used ChEIs in the Past (n=30)**	**Person with AD Never Used ChEIs or Caregiver is Uncertain about whether Person Ever Used ChEIs (n=32)**
Ever given loved one non-prescription drugs for loss of independence?			
Yes	9 (7)	3 (10)	3 (9)
No	83 (60)	24 (80)	26 (81)
Missing	46 (33)	3 (10)	3 (9)
Main sources of information about drug treatments for AD†			
Doctor treating loved one	120 (87)	22 (73)	14 (44)
Fellow caregivers or other AD patients	37 (27)	3 (10)	6 (19)
Family or friends	36 (26)	3 (10)	6 (19)
Personal research	43 (31)	13 (43)	9 (28)
Information brochures	65 (47)	15 (50)	14 (44)
Popular media	48 (35)	9 (30)	9 (28)
Advertisements from pharmaceutical companies	22 (16)	4 (13)	3 (9)
No sources of information	3 (2)	1 (3)	4 (13)

*Percentages do not always total 100 due to rounding error.

†Percentages do not total 100 because respondents could select more than one answer. n (%) is number (percentage) of respondents who consulted each source.

Notes: AD = Alzheimer's disease, ChEI = cholinesterase inhibitor, N/A = not applicable.

Appendix M: CAREGIVER QUESTIONNAIRE: SIMPLE LOGISTIC REGRESSION ANALYSES - COVARIATES AND THE CURRENT PRESCRIBING OF ChEIs TO AD PATIENTS

Table M1: Caregiver Questionnaire: Simple Logistic Regression Analyses - Covariates and the Current Prescribing of ChEIs to AD Patients

Variable	Listwise Deletion		Multiple Imputation	
	p-value	Decision*	p-value†	Decision*
Caregiver sex		Do not retain	0.0901	Do not retain
Female	Reference			
Male	0.0908			
Caregiver age	0.8440	Do not retain	0.8506	Do not retain
Caregiver overall physical health		Do not retain	0.1885	Do not retain
Excellent	Reference			
Very good	0.9038			
Good	0.2047			
Fair or poor	0.5293			
Patient sex		Do not retain	0.5665	Do not retain
Female	Reference			
Male	0.5865			
Patient age	0.0930	Do not retain	0.0789	Do not retain
Primary caregiver		Do not retain	0.5173	Do not retain
No	Reference			
Yes	0.5234			
Caregiver gives patient non-prescription drugs for loss of independence		Do not retain	0.3731	Do not retain
No	Reference			
Yes	0.5801			
Extent to which caregivers feel they are informed about what drugs can do to treat AD		Do not retain	0.0830	Do not retain
Poorly/not informed	Reference			
Somewhat informed	0.0631			
Well informed	0.0645			

*Retain or do not retain as a potential effect modifier or confounder based on the results of a simple logistic regression analysis.

†For categorical variables (multiple imputation only), the overall p-value (Wald X^2 test - type III analysis of effects) is given, not the p-value per category.

Notes: ChEI = cholinesterase inhibitor, AD = Alzheimer's disease.

Appendix N: CERTIFICATE OF ETHICS APPROVAL

McGill

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CERTIFICATION OF ETHICAL ACCEPTABILITY FOR RESEARCH
INVOLVING HUMAN SUBJECTS

The Faculty of Medicine Institutional Review Board consisting of:

LAWRENCE HUTCHISON, MD	
FRANCES ABOUD, PHD	GEOFFREY BLAKE, MD
MARK S. GOLDBERG, PHD	VINCENT GRACCO, PHD
GEORGE HOUSTON, BCL	MARIGOLD HYDE, BSC
ABBY LIPPMAN, PHD	HARVEY SIGMAN, MD
MICHAEL THIRLWELL, MD	SALLY TINGLEY, BCOM

has examined the research project **A10-B45-01B** entitled **"Use of Medications in the Alzheimer's Disease Population: Physician and Caregiver Perspectives"**

as proposed by: Dr. Christina Wolfson (Applicant) to _____ (Granting Agency, if any)

and consider the experimental procedures to be acceptable on ethical grounds for research involving human subjects.

October 30, 2001 (Date) — Chair, IRB — Dean of Faculty

Institutional Review Board Assurance Number: M-1458