

Alzheimer's Drug Therapy Initiative (ADTI): Research Report

UNIVERSITY OF VICTORIA

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GLOSSARY OF ACRONYMS

AD	Alzheimer's disease
ADRD	Alzheimer's disease and related dementias
ADS	Adult Day Services
ADTI	Alzheimer's Drug Therapy Initiative
AL	Assisted Living
B.C.	British Columbia
CAS	Caregiver Appraisal Study
CCD	Continuing Care Data
CCIMS	Continuing Care Information Management System
CDMI	Chronic Disease Management Initiative
CDT	Clock-Drawing Test
CER	Clinical Evidence Review
CG/P	Caregiver and patient
ChEI	Cholinesterase inhibitors (donepezil/Aricept, galantamine/Reminyl, rivastigmine/Exelon)
CIHI	Canadian Institute for Health Information
Clin Epi	Clinical Epidemiology Project
CRS	Community Rehab Services
DAD	Hospital Discharge Abstract Database
DSM-IV	Diagnostic and statistical manual of mental disorders
GDS	Global Deterioration Scale
GEE	Generalized Estimating Equation
HAs	Health Authorities
HCC	Home and Continuing Care
HCCMRR	Home and Community Care Minimum Reporting Requirements
HDPS	High dimensional propensity scores
HNS	Home Nursing Services
HSS	Home Support Services
LTC	Long-term care
MoH	B.C. Ministry of Health
MSP	Medical Services Plan
OPAR	Overall Patient Assessment Rating
OT	Occupational therapy
PHNs	Personal Health Numbers
PNet	PharmaNet
PSD	Pharmaceutical Services Division

PT	Physiotherapy
RC	Respite Care
RCR	Respite Care - Residential
RCT	Randomized Control Trials
SA	Special Authority form(s)
SMMSE	Standardized Mini-Mental State Examination
SMS	Seniors' Medication Study
TICS	Telephone Interview for Cognitive Status
U&C	Utilization and Cost Project
UBC	University of British Columbia
UVic	University of Victoria

KEY POINTS

The **Seniors' Medication Study** showed Standardized Mini-Mental State Examination (SMMSE) scores submitted by physicians on Special Authority forms (SA) correlated quite well (~0.65) with the Clock-Drawing Test (CDT) and Telephone Interview for Cognitive Status (TICS), similar to correlations for the reliability of blood pressure measurements.

The **Clinical Epidemiology Project** showed SMMSE scores and other cognitive function measures fluctuated considerably between enrolment and first SA renewal, even among 'non-naïve' patients. After various adjustments, the average change in SMMSE score among naïve patients (new to a cholinesterase inhibitor [ChEI]), by 6 months was +1.6 points, consistent with observations in randomized clinical trials (e.g., +0.8 in the AD2000 trial). This average change is small compared to the natural fluctuation between first and second SMMSE in individual patients (standard deviation of ± 3.5 points; 95% of fluctuations falling within ± 7 points). SMMSE response could not be predicted from available data nor were there differences in outcomes for different types of ChEIs. There was indirect evidence that a drop in SA-measured cognitive function was associated with early stopping of ChEIs. These findings are limited by lack of a valid comparison group and large loss to follow-up (approximately 40%).

The **Utilization and Cost Project** revealed no change in trends of utilization or costs of health services after ADTI introduction, except for a shift in drug costs to PharmaCare from other payers, and a small increase in costs of services by general practitioners (\$3.70/patient). Direct comparisons of ChEI users with non-users, among patients with Alzheimer's disease and related dementias (ADRD) demonstrated increased costs of health services in patients with low-moderate costs (up to \$1.50/day) but decreased costs in those with heavy costs (up to \$10/day). ChEI users had longer survival in the first 2 years, then similar survival, dropping to shorter survival in patients alive at the beginning of the 5th years since diagnosis. When examining monthly trends, ChEI use was associated with a growth in mortality rates from month to month during the 7 years following diagnosis compared with a slow decline in non-users. ChEI use was associated with increased long-term care entrance compared to non-use. Due to the nature of the data and the observational study design, the results are inconclusive; causation cannot be imputed. They are suggestive only, and additional research is warranted.

The **Caregiver Appraisal Study** revealed differential findings depending on the measure used. The benefit perceived was small and inconsistent. Caregivers thought patients were calmer and disease progression slowed but saw little improvement in abilities or behaviour. Caregivers were unblinded, and a placebo effect could not be calculated. Caregivers' appraisals of patients' improvement or deterioration did not correlate well with clinicians' assessments on SA.

Summary. There is insufficient evidence to support coverage of ChEIs based on the findings from these 4 studies. The indication of possible increased mortality among ChEI users is uncertain and warrants further research. If coverage of ChEIs continues, the SA process should be maintained to ensure standardized clinical assessments over time, allowing clinicians to recommend stopping the medications in patients who are deteriorating. If coverage of ChEIs is stopped or restricted, the impact should be measured by delaying the policy change in some areas and comparing patients' rates of entry into long-term care between comparable areas.

EXECUTIVE SUMMARY

The Alzheimer's Drug Therapy Initiative (ADTI) was announced in October, 2007, consisting of three concurrent programs: drug coverage, education, and research. The PharmaCare program covered cholinesterase inhibitors (ChEIs) with approval of a Special Authority form (SA) submitted by physicians. A dementia education strategy for physicians offered professional development between November 2007 through June 2012. The research program consisted of 4 studies conducted from the University of Victoria (UVic) and 1 from the University of British Columbia (UBC). This report contains the results from the 4 UVic studies and concludes with comments to inform policy in British Columbia (B.C.). The ADTI drug coverage and research constitute a program of 'Coverage with Evidence Development'.

Dementia is a clinical diagnosis based on a constellation of symptoms showing deterioration in previous mental capacities. As a result, reliable and valid measurement of dementia is difficult and complex with wide variation from person to person.

Seniors' Medication Study (SMS)

The SMS was a prospective longitudinal observational study. It sought to understand outcomes of ChEI-patients with an initial indeterminate response and to assess the adequacy of the Standardized Mini-Mental State Examination (SMMSE) on the SA.

1. *To improve the understanding of the outcomes of ChEI use among patients having an initial indeterminate response to treatment.*

a. In patients who experience little improvement from the first 6 months of ChEI therapy, are times-to-clinical events lengthened if the medications are continued past 6 months, compared with similar patients who stop at 6 months and can demographic factors predict outcomes?

About a third of the SMS patients experienced little improvement from the first 6 months of ChEI therapy—defined as having an indeterminate response measured by change in SMMSE score and taking into account natural progression of the disease. When using the Global Deterioration Scale (GDS) to measure treatment response, three quarters of SMS patients were classified as indeterminate responders—initially and over time. With the Overall Patient Assessment Rating (OPAR), half of SMS patients were indeterminate at 6 months and this number rose to three quarters at subsequent renewals. Almost all of these SMS patients continued on the medication at their first 6-month renewal with the exception of 6 patients so a predictive model to see if clinical outcomes were lengthened past 6 months among those who stayed on drug compared with those who stopped could not be conducted. We observed, however, that for those who remained on treatment, the majority of the subjects (over 60%) continued to be for up to 2 years, while patients with an indeterminate response to ChEI after 6 months who continued on the drug, had fewer residential care placements (26% vs. 74%) but more hospitalizations (64% vs. 36%).

b. Is there any benefit from switching to another type of ChEI if the patient has not responded to the first type in 6 months, taking type of ChEI into account?

Just over a tenth of the SMS patients switched from 1 type of ChEI to another type after 6 months of use but of those switchers only 14 patients were assessed as having no response to the drug. These patients did not do better on the SMMSE or on the GDS 6 months later but did show slight improvement according to the OPAR. Therefore, there does not appear to be any benefit from switching to another type of ChEI among patients who did not respond to the first type of ChEI in 6 months. The number of switchers was too small for any meaningful subgroup analyses by type of ChEI.

2. To assess how well physicians and PharmaCare can determine, using the existing measurement methods for Special Authority forms, whether a particular patient is one of those who has benefited from the program.

a. Validate the reproducibility¹ of measures of cognitive status on the SA form in order to assist in the analyses and interpretation of the two studies: Utilization & Cost and Clinical Epidemiology.

Correlation analyses among the different measures of cognitive status used on the SA initially and over time, revealed that the SMMSE and Telephone Interview for Cognitive Status (TICS) had the highest concordance relative to the other tools, with correlation coefficients of about 0.65. This is similar to correlations from studies of the reliability of blood pressure measurements. In addition, future research is required on the OPAR as its association with other assessment tools was weak. These results were replicated when examining the correlations between the assessment tools within the Clinical Epidemiology Project (Clin Epi) cohort.

Evaluation of how well the SAs were completed by clinicians with patients enrolled in the SMS was generally positive. The GDS and SMMSE were almost always completed in full, as these measures were required for coverage approval. The OPAR in contrast had a high frequency of incomplete data and errors, likely because this was optional. Qualitative data (focus groups with physicians) suggested that physicians found overall the ADTI provided a good framework for chronic disease management through ongoing systematic assessment of patients with Alzheimer's disease and related dementias (ADRD) over time.

The findings concerning Question 1 cannot be generalized beyond this small population of real-world ChEI users; there was no control group. As a result, it is possible that patients not doing well on the drug dropped out and because we are only observing those in the study (without a comparator) they thus might be skewed to show positive results. Further, the study was limited by varying timeframes in data collection that were in some cases outside of study protocols. This made it difficult to standardize timeframes (e.g., 6 months) in which to define patient benefit from ChEI use. As Question 2 did not require a control group, the SMS provided more conclusive data on the reliability of measurements by physicians.

¹ The SMS performed correlations to assess agreement between instruments; it did not test reproducibility, which calls for repeated measurements with third party independent observation.

An important value of the SMS was to demonstrate the reliability of SMMSE scores as measured by general practitioners in routine practice and recorded on SA. If real-world SMMSE scoring by physicians had had poor reliability, the entire basis of the ADTI program would have been undermined.

Clinical Epidemiological Project (Clin Epi)

This observational study drew on data from SA and provincial administrative datasets in order to examine response to ChEIs among those covered under the ADTI.

1. Study the cognitive, functional, behavioural, and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to the following:

a. Determine proportion of subjects who show a response or remain unchanged at different assessments.

In defining positive, negative, and indeterminate cognitive responses assessed by the SMMSE, we adjusted patients' changes in scores for the natural progression of the disease without ChEIs. Thus when referring to the SMMSE, it should be understood that a "positive" response actually means better than would be expected for patients not taking ChEIs, "negative" means worse than expected, and "indeterminate" means in the expected range.

i. Non-Naïve Patients: For assessing a *positive, negative, and indeterminate cognitive response (as assessed on the SMMSE)*, the non-naïve cohort served as an informal control group. As the non-naïve patients were already taking ChEIs, any changes in SMMSE scores between their first SA and renewal at 5-7 months could *not* have been due to the patients starting on the ChEI medications. Approximately 30% of the non-naïve cohort fit the definition of 'positive responder.' These are *false positives*. This estimate can serve as comparison with the cognitive (SMMSE) responses to the ChEIs of naïve patients.

ii. Naïve Patients: During the first 6 months following the initial ChEI prescription, between 33% (cognitive OPAR component) and 49% (SMMSE) of naïve patients showed an *apparent positive cognitive* response; there was no *apparent* impact on the *functional* scores; 20% of patients were assessed as having improved on the *behavioural* scores; and depending on which *global* measure was used, between 14% (GDS) and 43% (total OPAR) of naïve patients showed an *apparent* positive response. During the subsequent 3 6-month time intervals, the responses appeared to level out on the cognitive (at 15-30% of patients continuing to respond positively) and behavioural measures (11%). Again, the 2 global measures showed different patterns: the GDS indicated that larger percentages of patients appeared worse across assessments (about 17% showed a negative response while 10% showed a positive response) whereas a higher percentage (25%) of patients continued to be clinically assessed as having improved, based on total OPAR scores.

b. Determine time required for treatment onset to reach response for the maximum number of subjects.

This could not be satisfactorily answered due to the severe limitations of the SA data and the infeasibility of estimating the potential bias in the results produced by patients not having their SA renewals completed on a regular basis. For those patients who remained on the ChEIs and had their SA renewals completed at regular 6-month intervals, the largest proportion of patients showed a positive cognitive and behavioural response at 6 months. Patients did not change over time on the functional responses, and the global responses were inconsistent across measures and thus inconclusive.

c. Determine duration of persistent treatment response among responders.

About a quarter to a third of naïve patients who did not get worse and who remained in the study showed a better than expected response or were clinically assessed as having improved across consecutive 6-month assessments. For those patients who initially got worse but remained on the ChEI, between 16% and 63% (depending on the measure used) responded better than expected or improved, and between 33% and 71% remained stable since their last assessment. However, this may be because patients who deteriorated on consecutive assessments would have had their ChEIs terminated and thus discontinued from the study. Analysis of PharmaCare data suggested that approximately 30% of the entire cohort who no longer had SA coverage stayed on the medication; fully 73% of those without a SA renewal, continued on the medication for at least 5 months.

d. Determine rates of switching of ChEIs, tolerability, and nature of side effects.

About 14% of all naïve patients switched the ChEI within 2 years of their initial SA approval, with more than half switching within the first 10 months. Switching among types of ChEIs did not appear to differ across time. About 18% of all naïve patients stopped taking the ChEI within 2 years of initial SA approval, with half of these stopping within the first 6 months.

Physicians did not document side effects on the SA renewal forms.

e. Determine if global and cognitive response at 6 month or 12 month assessments predicts respective response at 2 year and 3 year assessments.

A patient's cognitive or global response at 6- or 12-month assessments did not predict his/her response on the respective measure 2 years later. Several variations of predictor variables were attempted, and failed. However, the null findings must remain inconclusive. Due to the inconsistent time frames when the cognitive and global assessments were conducted, the analyses were based on only 3.1% of the overall SA dataset.

2. Study the effect of age, gender, ethnicity, education, dementia asperity, baseline Standardized Mini-Mental State Examination (SMMSE) score, co-morbidities, use of other medications and physician category (specialist or general practitioner) as predictors of treatment response.

None of these variables showed a consistent response across all outcome measures and time intervals. Most of the associations were for the short term only (at 6 months), namely, patients

who were younger, male, and had lower baseline SMMSE scores showed a positive cognitive response, and those with non-European ancestry, higher education level, higher Romano scores (co-morbidities), and who were male tended to show a positive global response. In the long term (at 2 years), women tended to score better than expected on the cognitive measure (SMMSE); no other variables were related to the cognitive and global outcomes. The number of non-ChEI medications the patient took in the year immediately prior to their first ChEI did not have any relationship with the cognitive or global outcome measures, and data on physician category were not available for these analyses.

3. Determine the effect of ChEI on outcome measures such as mortality, service utilization, and nursing home placement among subjects receiving ChEI. (Note: These analyses were not conducted in conjunction with the U & Cost; as initially stipulated.)

In the absence of a control group, determining the effect of ChEIs on mortality was not possible. In comparing mortality rates for naïve versus non-naïve patients, mortality was slightly lower for naïve patients within the first 6 months of their initial ChEI and decreased over 2 years. Since naïve patients were on average about 4 years older when initially prescribed a ChEI and their age at death was very similar to non-naïve patients, we speculate that ChEI-prescribing patterns and/or diagnosing ADRD may have changed with the ADTI (a smaller percentage of naïve patients were diagnosed with Alzheimer's disease (AD) without any related diseases compared with non-naïve patients).

Over two-thirds of all naïve patients had received at least 1 Home and Community Care (HCC) service. The most highly utilized services were home support services followed by community rehabilitation (occupational therapy [OT] and physiotherapy [PT]). Over time (relative to their initial ChEI), fewer patients used HCC services, but those who did use the services used them with higher frequency and volume.

Similarly, over the course of the 2 years since their initial ChEI, about a quarter of naïve patients were placed into residential care or assisted living, with more than a third of these being placed within the first 6 months. These patients were, on average, more demented particularly in the non-naïve group. Patients diagnosed with AD (without related diseases) tended to be placed after 1 year on ChEIs in the naïve group, which occurred later than placement of non-naïve patients. Higher percentages of women, especially in the non-naïve group were placed into residential care or assisted living.

4. Develop reference graphs of SMMSE change over time based on age and baseline dementia asperity for subjects receiving ChEI.

Average SMMSE scores (with standard deviations) were plotted over time, for patients in 3 age cohorts (65-74 years, 75-84 years, and 85+ years old) and two levels of dementia asperity, early dementia (GDS=4) and moderate dementia (GDS=5). (There were insufficient data for the youngest cohort of 50-64 year olds, and for moderately severe dementia, GDS=6). The graphs showed: (a) as expected, overall lower scores for patients with moderate dementia compared with early dementia; (b) no differences between the three age cohorts; (c) slight but noticeable decrease in the SMMSE scores over time in each group, though this decrease was not as steep

as would have been expected with the natural progression of the disease (Tombaugh & McIntyre, 1992); (d) large variability in the scores within groups and time intervals; and (e) fluctuation across time intervals, particularly in the group of the oldest (85+) patients with moderate dementia.

Estimated impact of starting ChEIs on SMMSE scores: Adjusting for natural fluctuations and measurement errors by using the non-naïve cohort as an informal control group, we estimated the impact of the ChEIs in the naïve patients to be about a 1.6 points increase on the SMMSE scale (95% confidence interval: 1.4 to 1.9). This is consistent with observations in randomized clinical trials (e.g., +0.8 in the AD2000 trial). This estimate of average change is small compared to the fluctuation between first and second SMMSE measurements in individual patients (standard deviation of ± 3.5 points), such that a clinician would not be able to tell whether the cognitive improvement was due to treatment or natural fluctuation in the SMMSE or measurement error.

In summary, this study had no control group. Approximately 40% of the study cohort had no renewal forms; just under a third of the study cohort continued to be prescribed the medication for at least 5 months even though they had no SA renewal. Therefore it was difficult to draw conclusions concerning long-term outcomes.

This study supports existing research showing that a proportion of individuals likely have a small benefit from ChEIs but overall no strong conclusions can be drawn.

Utilization and Cost Project (U & C)

This series of studies draws on provincial administrative data to examine use of and costs of other health care services prior to and after the ADTI was launched and the effect of ChEI use on clinical outcomes and costs of health services. It applies rigorous methodology to account for limitations of the data and to minimize bias, including confounding.

1. What are the utilizations and costs of drugs and health services by patients with Alzheimer's disease (AD) before and after implementation of the ADTI for those with cholinesterase inhibitor (ChEI) coverage and those without?

We compared trends in utilization and costs of health services, prior to and after the ADTI (2004-2011) was launched, in two groups of patients: 129,600 newly-diagnosed AD patients and 424,604 similar controls that did not have the disease. ADRD patients were identified based on a single recorded diagnosis. Participants were followed until death, LTC entrance, or December 2011. Longer follow-up was available for controls, and to avoid a bias caused by differences in duration of follow-up we also examined trends when data were limited for the first 5 years of follow-up. Adjusted analysis revealed that overall trends were similar, supporting the absence of an effect of ADTI on utilization and costs of health services. A couple of main differences were:

1. a shift in costs from other payers to PharmaCare, essentially the cost of covering ChEIs, and
2. a small increase in costs of visits to general practitioners (\$3.7 per patient more after ADTI), likely fees associated with ADTI.

In a study of 28,185 ADRD patients who initiated any ChEI any time after diagnosis, longer persistence with ChEIs and higher rates of switching between these drugs were observed in patients who initiated treatment after ADTI introduction compared to earlier initiators. These findings were only partially related to drug coverage.

2. Is prescribing ChEIs for Alzheimer's disease patients cost effective?

Due to limitation of the data and methodology, we were unable to conduct a cost-effectiveness study, but rather examined the effect of ChEI use on clinical outcomes (death, entrance to long-term care) and costs of health services. Newly-diagnosed ADRD patients who were included in this study were identified using a more specific procedure compared with deliverable 1: we required either a hospital discharge diagnosis or two recorded diagnoses of ADRD within three months. Patients were identified from 2001 to the end of 2011, clinical outcomes were evaluated for the years 2001-2014, and cost outcomes were analyzed for the years 2004-2011.

In a series of studies in 71,635 ADRD patients, we compared those initiating ChEI early after diagnosis (ChEI users) to those who did not (non-users). Patients were divided into ChEI users and non-users based on a single dispensing record within the first three months after diagnosis was established. In an analysis of ADRD patients who were alive 6 months after first diagnosis, ChEI users had longer survival during the first 2 years, then similar in years 3 and 4, dropping to a shorter survival in patients alive at the beginning of the 5th year since diagnosis. When examining monthly trends, ChEI use was associated with a growth in mortality rates from month to month during the 7 years following diagnosis compared with a slow decline in non-users with ADRD diagnosis. In an analysis of ADRD patients who were alive in a community-dwelling setting 6 months after first diagnosis, ChEI users also had higher hazards of entering long-term care starting the second year after diagnosis. Differences in outcomes between users and non-users were adjusted for age, income level, gender, and general health status, using high-dimensional propensity score. However, due to the nature of the data and study design (observational study and patients divided to user groups early) the results are inconclusive; causation cannot be imputed. The findings are informative insofar as they signal a need for caution and further investigation but they do not imply certainty.

In an adjusted analysis examining costs of health services during months 7 to 30 after first diagnosis, ChEI use was associated with an increase of less than \$1.5 per day among the low-medium cost patients, which probably reflected the costs of ChEIs, but up to \$10 per day among the most costly patients. Due to the nature of the data and study design the results are inconclusive; causation cannot be imputed.

Another analysis explored perspectives on cost-effectiveness. We interviewed 22 individuals in Canada, the US, and the UK who had no relevant conflicts of interest. Overall, the interviewees recognized that ChEIs were widely prescribed to delay the progression of AD symptoms,

maintain quality of life, and postpone institutionalization, yet none of the participants believed that there is reliable, quality evidence supporting these outcomes. Nine of 22 interviewees (40%) were clinicians who often prescribed the drugs and an additional 9 participants were mostly concerned that the drugs' potential for harm likely exceeded their benefit. Most participants expressed the opinion that the bulk of public investments in the treatment of AD should go towards quality psycho-social supports, including caregiver education and support, respite care, home care, and appropriate long-term care.

Caregiver Appraisal Study (CAS)

This study included face-to-face interviews, province-wide, with just over 900 family caregivers to persons prescribed ChEIs and covered for the medications under PharmaCare.

1. Understand caregiver assessments of the effectiveness (and lack thereof) of ChEI for patients and for themselves.

The multiple areas explored suggest that some families see some benefit but it is neither overwhelming nor consistent. The greatest effect was perceived in terms of the patient being calmer and a slowing of disease progression with little improvement in abilities or behaviour. If a placebo effect were taken into account, the effectiveness would likely be underwhelming. We do not know if any perceived effect is due to greater attention from the caregiver due to taking these drugs or to the drug itself.

2. Identify which caregivers (gender, age, ethnicity, etc.) are more likely to identify which type of effect as beneficial and as not.

The data were unsuccessful in isolating a particular type or groups of caregivers who are more likely to perceive a benefit. Where type of ChEI taken was significant, it was those caring for persons taking donepezil who were more likely to perceive a benefit but this explained little of the variance. Whether this is due to a real effect of donepezil or a greater placebo effect due to the advertising of this ChEI cannot be determined with these data.

3. Compare caregiver subjective assessments with objective (using validated scales for burden and quality of life) measures of impact.

Only a few factors were related to caregiver quality of life (burden, self-esteem, anxiety, and depression). They were differential and not strong. Stronger relationships were evident when examining the perceived effects on the *caregiver's* mental and physical health and a perceived change in level of assistance required than perceived effects on the *patient*. Type of ChEI taken was not related.

4. Compare caregiver assessments of effectiveness for the patients with clinical assessments made by physicians.

At 6 months, physicians were less likely than caregivers to say the drug had helped the patient when asked about helping with memory, remembering, and reasoning. Contrarily, physicians'

ratings were more likely to fall between the same and improved in terms of the patient's concentration, losing things, and following instructions whereas caregivers were more likely to say between worse and no change when asked specifically in terms of concentration, especially in terms of losing things, or in terms of following instructions. Regarding the overall assessment of whether the ChEI helped, caregivers were more likely to say it did than physicians. There was no difference between the two groups when asked about change in mood or change in ability. Overall, physicians and caregivers often disagree on their assessment of the effectiveness of ChEIs.

5. Identify predictors of intention to institutionalize (note: predictors of actual institutionalization using caregiver data are to be assessed in U & C, focusing on service use).

Which ChEI the patient takes does not predict whether the caregiver intends to place the family member nor does it predict whether the patient is institutionalized 1 year after the 6 month assessment. Intention to place at 6 months is the strongest predictor of actual placement 1 year later. These data cannot speak to whether taking a ChEI delays institutionalization compared to not taking one.

6. Why were these drugs terminated?

The type of ChEI taken was not related to whether the patient stopped taking the drug. The strongest correlates of stopping related to caregivers' beliefs about whether the drug was helping.

These analyses point to the importance of multiple measures in this area and of not generalizing from 1 measure to other areas. These findings provide new insights into caregiver perceptions. They do not provide evidence in support of coverage of these drugs.

Because it was not possible to recruit a random sample, nor a comparison group of caregivers to those with dementia not taking ChEIs or those taking a sugar pill, the findings cannot be generalized nor can inferences be made about how caregivers to persons taking these drugs differ from those not taking ChEIs. That means the placebo effect of taking ChEIs cannot be determined. Nevertheless, this is the most comprehensive study of caregivers' assessment of ChEIs conducted to date.

Relevance of Findings for B.C. Policy

There is insufficient evidence to support coverage of ChEIs based on the findings from these 4 studies. They point to the importance of proper measurement and the collection of complete and detailed data. Given ADRD is a syndrome; it is not surprising that findings vary depending on the measurement used and that within patient variability in scores is so wide-ranging.

The indication of possible increased mortality among those taking ChEIs warrants further research before any conclusions are drawn in this regard.

In establishing the ADTI, the Ministry of Health (MoH) was informed by international experience of Coverage with Evidence Development (CED), also known as Access with Evidence Development. When evidence is absent or ambiguous, CED takes the stance that ‘benefit of the doubt’ should be neither wholly on the side of the funder (saving funds until the evidence from elsewhere is solidly in favour of coverage) nor wholly on the side of the recipient (receiving coverage until the evidence from elsewhere is solidly against coverage). CED involves sharing the ‘benefit of the doubt’ while producing evidence to reduce the doubt. Under objections from clinicians that a RCT would be unethical because it would withhold medications (considered the ‘standard of care’ at the time) from some individuals, the ADTI proceeded without this design. Given the experience and analyses of the ADTI, it appears that it would have been ethical for a randomized policy trial to have been conducted. If the MoH decides to curtail coverage of ChEIs, it would be ethical to do a Reduction in Coverage with Evidence Development using the ‘designed delay’ method previously used by PharmaCare in a restriction of coverage of respiratory medications in 1999.

If coverage of ChEIs were to remain in place it is strongly recommended that the SA be maintained in order to obtain valuable data and patient follow-up on a difficult category of patients, but that it be modified in the following ways:

- delete patient signature
- delete optional information
- delete requirement that a patient achieve specific scores on both the SMMSE and the GDS
- add the MOCA (best for relatively mildly impaired) or include it as an alternative to the SMMSE (better for moderate impairment) with the choice of which to use left to the physician
- add measures of function and behaviour
- renewals be stipulated as required between 3 and 12 months
- establish an ongoing evaluation process for the SA
- add a brief questionnaire for the caregiver to complete about their perceptions of the ChEI, to be discussed with the physician

If coverage is changed, evaluate it.

The scope of the ADTI did not include non-pharmacological treatments (such as caregiver education and support, respite care, home care, appropriate long term care, exercise, art, music, and social engagement), yet these alternatives need to be taken into account in decisions concerning the allocation of resources.

INTRODUCTION

With increasing numbers of older adults in British Columbia (B.C.) there has been a concomitant rise in dementia including the incidence of Alzheimer's disease (AD), the most common form of dementia. This trend will continue with the aging of the baby boom generation. While there is no cure for AD, acetylcholinesterase or cholinesterase inhibitors (ChEI) are widely prescribed as pharmacotherapy for modifying clinical manifestations of mild to moderate forms of the disease (Birks, 2006). Their acceptability as a treatment option is evidenced in the fact that all provinces except Newfoundland & Labrador and B.C. provided some form of coverage by 2005. However, there is less agreement about the effectiveness of these drugs than this near consensus among the provinces would suggest. For example, the U.K. National Institute for Clinical Excellence (NICE) recommended the National Health Service no longer cover the drugs (Loveman, et al., 2004) but the consensus statement of the British Association for Psychopharmacology concludes that there is randomized control trial (RCT) evidence for the effectiveness of ChEIs for mild to moderate AD (Burns & O'Brien, 2006).

On at least 3 occasions between 1999 and 2005, B.C. PharmaCare's Drug Benefit Committee recommended that PharmaCare not cover ChEIs because of a lack of scientific evidence for their clinical effectiveness (B.C. Drug Benefit Committee of PharmaCare, 2005). However, in 2007, Premier Gordon Campbell announced a province-wide study, the Alzheimer's Drug Therapy Initiative (ADTI) (B.C. Government, 2007). During the study, PharmaCare was to cover the three ChEIs (donepezil, rivastigmine, galantamine) on a trial basis, and the decision whether or not ChEIs would be added to the 'benefit list' was postponed until the end of the study.

The inconclusiveness found in existing studies helps explain the differing historical positions of B.C. and most other Canadian provinces on this issue. There are scientific reviews available from several countries including the U.K., the U.S., and Germany; they conclude that there is limited evidence for the outcome effectiveness of ChEIs even within RCTs and, among those arguing for positive effects, there is widespread recognition that the effects are small (Hansen, et al., 2008; Hansen, Gartlehner, Lohr, & Kaufer, 2007; Kaduszkiewicz, Zimmerman, Beck-Bornholdt, & van den Bussche, 2005; Ringman & Cummings, 2006). For example, a recent review of 22 RCTs that compared the 3 ChEI drugs with placebo (Luckman, 2006) concluded that while there is current consensus that "... they probably have a small positive effect on cognitive function, and possibly behavior [sic], in some patients ... the clinical significance of the effect may be marginal.... Clinicians ... must struggle with how to identify responders to cholinesterase inhibitors, how long to treat, and whether a trial of medication is cost-effective."

Birks and Harvey (2006) draw similar conclusions from their meta-analysis of 15 trials of donepezil (the drug most often studied among the three) as does Birks (2006) after a review of 10 randomized, double-blind, placebo controlled trials of donepezil - treatment effects are not large. (See Birks & Harvey, 2009 for similar conclusions from a later review.) The most recent reviews (Bond, 2012; Clinical Evidence Review, 2014) arrive at the same conclusion, asking whether or not the clinical benefit is meaningful. Herrmann (2007), however, concludes that donepezil may be more beneficial than the other two ChEIs and Knowles (2006) argues there is

strong evidence for its efficacy especially in terms of improvement or less deterioration in global outcomes and cognition in the short to medium term. Persons (2006) though argues that on the basis of cost, limited benefit and side effects, donepezil should not be used.

For all 3 ChEIs the evidence in favour of use appears strongest for cognitive function, less conclusive when examining outcome measures other than cognition. Mixed findings are reported for global outcome measures, functioning, behaviour, and mood (Loveman, et al., 2006; Ringman & Cummings, 2006; Rockwood, Fay, Song, MacKnight, & Gorman, 2006). Studies that examine quality of life yield conflicting results, with some suggesting benefits (Caramelli et al., 2014; Loveman, et al., 2006; Jones, et al., 2009; Kavanagh, Van Baelen, & Schäuble, 2011), while others do not find any significant benefits (Birks, 2006; Courtney, et al., 2004; Raina, et al., 2008; Takeda, et al., 2006). Methodological problems include the inability of standard psychometric tools to document all the relevant treatment effects; the short time line of most trials (6 months), and the lack of data on many critical aspects of these drugs (Burns & O'Brien, 2006; Hogan, 2007; Knowles, 2006; Messinger-Rapport, McCallum, & Hujer, 2006; Raina, et al., 2008). The effect of ChEIs on mortality is no more conclusive. A review by Winblad, et al. (2008) suggested galantamine has a slight increase in mortality over 24 months, whereas a meta-analysis by Feldman, et al. (2009) did not find any significant increase in mortality with galantamine. Most other studies did not find increased mortality with ChEI use (Román, et al., 2010; Russ & Morling, 2012; Winblad, 2009).

Little is known about the optimum duration of use of ChEIs for treatment of patients diagnosed with mild to moderate Alzheimer's disease and related dementias (ADRD) among community dwelling individuals. Further, there is limited understanding about what assessment tools are effective in measuring treatment response for this particular class of drugs and disease initially and over time. In addition, while the ADAS-Cog and global function rating such as CDR or CGIC have become standard requirements for FDA approval of any drug for dementia, these scales are long and complex, and not very practical or feasible for general use in a busy clinic. Yet, clinical scales that are brief enough for clinical use may not be sensitive enough to detect changes in patients.

There are limited data on such potentially important factors as: the identifying characteristics of those who benefit from taking these drugs, those who do not benefit, and those most likely to experience adverse events; the effect of switching from one form of ChEI to another form; the cost-effectiveness of the drug; whether taking the drug delays institutionalization by a significant amount; whether taking the drug decreases caregiver burden and the factors affecting that burden such as stage of disease; patient and caregiver age, gender, and ethnicity; and whether current outcome measures are the most appropriate.

The dearth of studies that include caregiver assessment of drug effects and of consequences for caregivers themselves, is a criticism lodged by local Alzheimer organizations against assessments conducted in jurisdictions such as B.C. and the U.K. Caregivers observe patients in situations and in an ongoing manner not available to clinicians. In addition, since caregivers are a critical aspect of care for persons with AD (potentially administering medications, deciding whether to institutionalize, etc.), perceived consequences for their own lives are also critical to

understand. Caregivers to those with ADRD suffer from high rates of anxiety and depression (Livingston, Regan, Cooper, Orrell, & Katona, 2007) and are often the main person making the decision about institutionalizing the patient. Little is known about caregivers' perceptions of the effectiveness of ChEIs either for the patient or for their own well-being (Jönsson, 2003). The few studies comparing clinician and caregiver assessments suggest differences of opinion between the two groups, whether in terms of assessed effect after the patient was taking the drug or expectations prior to beginning the medication (Anderson, Silvius, Slaughter, Dalziel, & Drummond, 2008; Rockwood, Black, Bédard, Tran, & Lussier, 2007; Rockwood, et al., 2006; Sinforiani, Pasotti, Chiapella, Malinverni, & Zucchella, 2010)

Studies on caregivers only, note that ChEIs can be a source of hope for families (Smith, Kobayashi, Chappell, & Hoxley, 2011) and some such as Franchi, Arosio, Djade, Porro, and Nobili (2013) conclude that caregivers perceive little benefit (see also Huizing, Berghmans, Widdershoven, & Verhey, 2006). Smith, Chur-Hansen, Neale, and Symon (2008) report that caregivers perceive a slowing of decline in short-term memory although most could not discern an appreciable benefit for the patient's quality of life. Schoenmakers, Buntinx, and Delepeleire's (2009) review of 8 studies concludes that the use of ChEIs seems to lower caregiver burden (mean difference 0.23) and the time caregivers spend providing care (mean difference 41.65 minutes/ day), irrespective of the actual effect of these drugs on the person with dementia. Lingler, Martire, and Schulz (2005) also conclude there are small benefits for burden after reviewing 4 drug trials that include caregiver burden as an outcome. Most recently, Levy, Lanctot, Farber, Li, and Herrmann's (2012) review also concludes that the medications are associated with a decrease in burden in some studies but that it is unclear whether this is due to changes in the behavioural and psychological symptoms of dementia or cognition and function. We know little about how the perception of ChEI effectiveness varies by the gender, stage of disease, quality of the caregiver-patient relationship, or other factors that potentially confound any relationship between taking a ChEI and perceived effectiveness (Messinger-Rapport, et al., 2006).

That is, little is known about caregivers' perceptions of the effectiveness of ChEIs (confirmed by the Clinical Evidence Review (2013) conducted at UBC).

Within the ADTI, the PharmaCare program covers ChEIs through approval of a Special Authority form (SA) submitted by physicians. This SA determines eligibility. Participants are residents of B.C. who have a primary diagnosis of AD based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) and National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related disorders Association (NINCDS-ADRDA) criteria. Other etiologies of dementia in which AD (according to the DSM-IV criteria) is the main etiology were also included (i.e., vascular, Parkinsonian, other). For coverage, the initial scores for participants on the Standardized Mini-Mental State Examination (SMMSE) were to be between 10 and 26, inclusive, and their scores on the Global Deterioration Scale (GDS) 4, 5, or 6. Individuals were to be excluded from the ADTI if they had contraindications to the use of ChEIs, if they could not take medications safely, or lacked the necessary social support to allow for reliable medication administration. Mandatory assessment every 6 months was to be performed on all participants.

A Note on Dementia

Dementia is a syndrome, a constellation of symptoms resulting in a change of ability from previous capacity. Because mixed dementia is common and often clinically challenging to identify the components, reference is made to ADRD. It is generally a clinical diagnosis based on a description of changes in cognition, function, and behaviour. Collateral information is required from someone who knows the person well. Diagnostic tests including CT scans and blood tests rule out extenuating problems. Longitudinal follow up is appropriate. At the present time, there is no diagnostic test per se. The cause is poorly understood (although there are some genes known to cause the disease and some genes known to indicate risk, but there is no specific treatment for the disease); there is only symptomatic treatment. Because ADRD is a syndrome, measurement is complex; the disease manifestations vary considerably from person to person.

To address the lack of definitive measurement tools and the complexity of the syndrome, the primary cognitive measure chosen was the SMMSE, a well-established test, not diagnostic in itself, but a screening tool. The GDS is also a well-established test for overall status. Measures of function and behaviour were limited and are included in the sub-measures of the Overall Patient Assessment Rating (OPAR) and were included in longitudinal follow up with the physician asked to judge overall, whether there were changes in the patient over the previous 6 months. In establishing the SA, the researchers were very cognizant of potential compliance of physicians who were completing it, their tolerance for learning new measures, and their understanding of ADRD. Administrative data available only include diagnoses; the bases for diagnoses can only be assumed.

Over time individuals with ADRD worsen, the nature of neurodegenerative disease. While the trajectory of this change varies from person to person, within the study the endeavour was to include enough subjects to mitigate variability and show trends. For example, there is reasonable literature on what happens to the SMMSE over time; this is taken into consideration in the analyses.

Coverage with Evidence Development

As in all real world research, numerous events unfolded within the duration of the ADTI, having unknown effects on the data. A number of changes in the policy context within B.C. also occurred prior to or during the ADTI.

The Evolution of the ADTI

2007 – The ADTI was announced in October. The ADTI consists of 3 concurrent programs: research, drug coverage, and education. Professional development offerings started in November 2007 and continued through June 2012. Topics included: ADTI clinical package and SA approval, cognitive impairment guidelines, ChEIs for AD, cognitive impairment in

treatment of mild to moderate AD, distinguishing mild cognitive impairment from early dementia, regional dementia conferences, and psychiatry and dementia. In April 2008, offerings were expanded to include case-based workshops on: mild cognitive impairment & progression of symptoms of dementia, dementia & driving, dementia & living at risk, and late stage dementia & admission to a nursing home. The workshops were held across B.C. and funding was extended to 2013.

2007 – In November, the B.C. Medical Association (BCMA, now Doctors of BC) directed their members to refrain from completing the ADTI SA. By October 2008 the research was put on hold. The BCMA reversed their position in May 2009 when they agreed to partner with the Pharmaceutical Services Division (PSD) and endorse the ADTI.

2007 – In December, the ADTI International Peer Review Committee approved the research protocol.

2008 – Donepezil was once daily oral dose; in 2008 extended release galantamine became available, allowing the prescription of one pill for this ChEI as well.

2009 – The Exelon patch was added to ADTI SA coverage plan in February.

2012 – On June 26, the University of Victoria (UVic) and the Ministry of Health (MoH) were prepared to link the province data for ADTI analyses; none arrived. In September, the university received notification from the MoH that work was to halt on the ADTI. During this period the validation of OPAR, which was to be undertaken at UBC since it is not a validated tool, was also stopped and the opportunity to continue this study was lost. It was to be part of The Clinical Meaningfulness in Alzheimer's Disease Treatment Response Study to Acetylcholinesterase Inhibitor Treatment (CLIMAT), initially part of the ADTI but conducted out of the University of British Columbia (UBC) rather than UVic. This study addresses the need for clinically meaningful measures for evaluating dementia therapy and is reported on separately.

2012 – In October, permission was received to continue with primary data collection only (allowing 2 of the studies, the SMS and the CAS to proceed with these aspects).

2014 – In June provincial files were released to PEG. In September, the ADTI had full access to provincial data.

Other Contextual Factors

2003 – Introduction of Fair PharmaCare, wherein deductibles are based on family income not individual incomes, making studying subsets of drug prescriptions (i.e., seniors) difficult. Prescription drug use below the deductible levels was not included in the PharmaCare SA database. These changes in deductibles were in response to reductions in income during the economic downturn of 2008.

2004 to 2012 – The Continuing Care Information Management System (CCIMS) implemented reporting requirement changes moving from the Community Care Data (CCD) to Home and Community Care Minimum Reporting Requirements (HCCMRR). Health Authorities (HAs) differentially adopted the changes, resulting in difficulties with comparability of Continuing Care data over time.

2004 – The BCMA’s Council on Health Promotion formally called for a coordinated dementia strategy and the MoH introduced the Complex Care Management initiative which provides additional compensation to physicians working with patients experiencing 2 or more chronic conditions including neurological diseases such as AD.

2007 – The MoH released “Cognitive Impairment in the Elderly – Recognition, Diagnosis and Management Guidelines and Protocols”. In October, the MoH released the B.C. Clinical Practice Guidelines on Cognitive Impairment in the Elderly (also referred to as the Clinical Practice Guidelines) which were regularly revised through July 2014. Shortly after the release of the Clinical Practice Guidelines the BCMA’s Guidelines and Protocols Advisory committee along with the MoH released the GPAC handbook on how to best use the Clinical Practice Guidelines.

2008 – The Community-based Mental Health Initiative started, providing additional fee items for physicians to complete care plans for patients with serious mental health issues, including cognitive impairment, and living in the community.

2008 – The Exelon patch was approved by Health Canada.

2009 – The Frequency of Dispensing Policy was implemented by PharmaCare, intended to manage dispensing activities of pharmacists to address issues of patient stock-piling, vacation dispensing, and pharmacy ordering habits. Through 2010 and into 2011, a policy audit found a 93.3% non-compliance rate. Policy clarifications and refinements were implemented in late 2012.

2009 – Pfizer applied to the FDA in the U.S. for Aricept 23 (the patent for Aricept 5 and 10 mg doses was set to expire in November 2010) and in August 2010 it was introduced to market with a 3-year extension. (A class action suit against Pfizer and Eisai was launched in 2015).

2012 – The Pharmaceutical Services Act (PSA) created a framework for the MoH to regulate and lower prescription drug prices (between 2001 and 2011/12 the PharmaCare budget increased by 74%).

Throughout: it is unknown how many or how often physicians provided free manufacturers’ samples of ChEIs to patients. Other instruments became available for physician use (such as the Montreal Cognitive Assessment [MOCA]), free of charge. Marketing campaigns by the drug manufacturers were ongoing. Many individuals continued to take ChEIs but without coverage from Fair PharmaCare.

The ADTI Research Program

The ADTI research program at the University of Victoria consists of 4 studies:

Seniors' Medication Study (SMS)

1. To improve the understanding of the outcomes of ChEI use among patients receiving treatment.
2. To assess how well physicians and PharmaCare can determine, using the existing measurement methods for SA forms, whether a particular patient has benefited from the program. More specifically, the research questions are:
 - a. In patients who experience little improvement from the first 6 months of ChEI therapy, are times-to-clinical events lengthened if the medications are continued past 6 months, compared with similar patients who stop at 6 months and can demographic factors predict outcomes?
 - b. Is there any benefit from switching to another type of ChEI if the patient has not responded to the first type in 6 months, taking type of ChEI into account?
 - c. Validate the reproducibility of measures of cognitive status on the SA form in order to assist in the analyses and interpretation of the U & C and the Clin Epi.

Principal Investigator: Ging-Yuek Robin Hsiung, MD, MHSc, FRCPC

Co-Investigators: K. Malcolm Maclure, ScD; Neena Chappell, PhD, FRSC, FCAHS

Research Staff: Carren Dujela, MA; Guiping Liu, PhD; Kristine Votova, PhD

Clinical Epidemiological Project (Clin Epi)

1. Study the cognitive, functional, behavioural, and global scores of subjects with mild to moderate AD/DRD receiving ChEI with respect to the following:
 - a. determine proportion of subjects who show a response or remain unchanged at different assessments,
 - b. determine time required for treatment onset to reach response for the maximum number of subjects,
 - c. determine duration of persistent treatment response among responders,
 - d. determine rates of switching of ChEIs, tolerability, and nature of side effects,
 - e. determine if global and cognitive response at 6 month or 12 month assessments predicts respective response at 2 year and 3 year assessments.
2. Study the effect of age, gender, ethnicity, education, dementia asperity, baseline Standardized Mini-Mental State Examination (SMMSE) score, co-morbidities, use of other medications, and physician category (specialist or general practitioner) as predictors of treatment response.

3. Determine the effect of ChEI on outcome measures such as mortality, service utilization, and nursing home placement among subjects receiving ChEI. (These analyses will be conducted in conjunction with the U & Cost.)
4. Develop reference graphs of SMMSE change over time based on age and baseline dementia asperity for subjects receiving ChEI.

Principal Investigator: B. Lynn Beattie, MD, FRCPC

Co-Principal Investigators: K. Malcolm Maclure, ScD; Neena L. Chappell, PhD, FRSC, FCAHS; Colin Dormuth, ScD

Statistical Advisor: Ken Bassett, MD, PhD

Research Staff: Helena Kadlec, PhD; Carren Dujela, MA; Guiping Liu, PhD

Utilization and Cost Project (U & C)

1. What are the utilizations and costs of drugs and health services by patients with Alzheimer's disease (AD) before and after implementation of the ADTI for those with cholinesterase inhibitor (ChEI) coverage and those without?
2. Is prescribing ChEIs for Alzheimer's disease patients cost effective? This study involved secondary analysis of administrative data.

Co-Principal Investigators: Colin Dormuth, ScD; Neena L. Chappell, PhD, FRSC, FCAHS; B. Lynn Beattie, MD, FRCPC

Co-Investigator: K. Malcolm Maclure, ScD

Statistical Advisor: Ken Bassett, MD, PhD

Research Staff: Greg Carney, BSc; Anat Fisher, MD, MHA, PhD; Richard Morrow, MA; Carren Dujela, MA

Caregiver Appraisal Study (CAS)

1. Understand caregiver assessments of the effectiveness (and lack thereof) of ChEI for patients and for themselves.
2. Identify which caregivers (gender, age, ethnicity, etc.) are more likely to identify which type of effect as beneficial and as not.
3. Compare caregiver subjective assessments with objective (using validated scales for burden and quality of life) measures of impact.
4. Compare caregiver assessments of effectiveness for the patients with clinical assessments made by physicians.
5. Identify predictors of intention to institutionalize (note: predictors of actual institutionalization using caregiver data are to be assessed in U & C, focusing on service use).
6. Why were these drugs terminated?

Principal Investigator: Neena L. Chappell, PhD, FRSC, FCAHS

Co-Investigators: André Smith, PhD; Kaitlyn Roland, PhD

Research Staff: Carren Dujela, MA; Helena Kadlec, PhD; Guiping Liu, PhD

These research projects were to provide input for PharmaCare's decision regarding changing the policy for who is eligible to have their drugs covered and whether ChEI can be targeted more effectively to those who will benefit from the drug, and to provide the MoH with cost-effectiveness data.

The Data for the Four Studies

Provincial data:

- Hospital Discharge Abstract Database (DAD), April 1 2001 to December 31 2013
- Home and Continuing Care (HCC), January 1 2001 to March 31 2013
- Medical Services Plan (MSP), April 1 2001 to December 31 2013
- PharmaNet (PNet), April 1 2001 to December 31 2013

Primary data for the SMS:

- Triage data: screening questions including whether or not the ChEI impacted the patient's mood, memory, and physical health
- Telephone Interview for Cognitive Status (TICS): completed by study staff, collected up to 4 times (every 6 months up to 24 months)
- Clock-Drawing Test (CDT): completed optionally by the physician, collected up to 3 times (every six months up to 18 months), to coincide with SA renewal
- Special Authority form (SA): completed optionally by the physician with payment by PSD, collected between October 2007 and December 2012

Primary data for the CAS:

- Triage data: screening questions including whether or not the ChEI impacted the CR's mood, memory, and physical health
- Focus groups and in-depth interviews with caregivers to prepare for the structured face-to-face interviews
- Face-to face interview when patients had been taking ChEI for 6 months
- Follow-up face-to-face interview 1 year later

The studies are presented here starting with the SMS in order to test the reliability of the SMMSE, used to measure cognitive status in all of the ADTI projects. The Clin Epi then presents scores over time and compares naïve with non-naïve ChEI users. The U & C assesses impacts of taking ChEI on the use and cost of other services. The CAS examines family caregiver perceptions of the effectiveness of ChEI.

Uniqueness of the ADTI

The 4 studies comprising the ADTI, both singly and together, offer new insights into the use of ChEI among those with dementia and increase our understanding of research with ADRD patients. Combining administrative data with primary data from multiple sources was a major strength.

The SMS provides insight into physician (generalist and specialist) use of the SA process for drug coverage for community-dwelling patients with ADRD. It provides an overview of what physicians are willing to tolerate in terms of completing additional documentation related to the clinical visit. The SMS is Canada's first real-world effectiveness study of ChEIs among a community dwelling group of individuals with ADRD, composed of a reasonable number of patients (~200). It is the first to provide repeated measurement of patient perspectives of 'benefit' compared to physician's standardized assessment across cognition, function, and behaviour. Consistent with the literature, it confirms that the SMMSE correlates well with cognitive performance for this group of patients.

The Clin Epi is unique in analyzing clinical data collected on the SA in such a large population-based sample, gathered over time, and linked to utilization and PharmaCare data for patients with ADRD. The submission of the SA every 6 months permitted a wealth of analyses examining cognitive, functional and behavioural response to the medication, switching, stopping, and institutionalization and to do so over time, that has not been conducted previously. The findings in the Clin Epi accounted for the natural progression of the disease, thus removing the confounding effect in most studies where an indeterminate/no change response can signify a 'benefit' because the natural progression of the disease would lead one to expect a deterioration rather stabilization. It included a new clinical instrument, the OPAR, which is not related to patient literacy levels and focuses on change in status over the previous 6 months.

The U & C was the first to estimate health services utilization and costs associated with a drug coverage policy and the first study in ChEI patients to estimate the effect of drug coverage on ChEI persistence and switching. The association of ChEI use with long term (up to 13 years since diagnosis) mortality or LTC entrance has not been previously studied. Of note, 3 observational studies have been published between 2004-6 with no studies since that time: Becker, Andel, Rohrer, and Banks (2006) examined the risk of LTC in ChEI users vs. non users with decreased risk of 28% and 21% during the first 12 and 18 months of use. Risks were non-statistically significant for longer durations of use. Beusterien, et al. (2004) followed patients up to 2 years, rivastigmine vs. non users subjects (hazard ratio [HR] = 2.71; 95% CI 1.82, 4.03), and vs. donepezil (hazard ratio = 1.23; 95% CI 0.89, 1.71). Gillette-Guyonnet, et al. (2006) reported that patients treated with ChEIs for at least 1 year had a significant decrease in the risk of institutionalization (odds ratio = 0.20, 95% CI, 0.08–0.48) during the first year. That odds ratio is in the realm of unbelievable.

The CAS is the largest study of caregiver perceptions of the effects of ChEI conducted to date with a sample of just over 900. It included a vast array of areas (derived from focus groups with

caregivers themselves prior to conducting the interviews) that could potentially be effected by the drugs but not previously measured. The findings indicate the need to examine symptomatology in addition to cognition when studying ADRD. Caregivers made their assessments over time, 1 year apart. Comparisons were made with assessments by physicians in multiple areas. The CAS was also unique in that it studied both intention to institutionalize and actual institutionalization 1 year later.

SENIORS' MEDICATION STUDY (SMS)

Participants and Methods

Study Design

The SMS is a prospective observational longitudinal study with a cohort defined by their exposure to physician-prescribed ChEI. Data were collected at baseline and every 6 months thereafter until attrition or study end, whichever came first. The first SMS participant enrolled in 2008 and the last enrolled in 2011.

Primary data were collected from the patient, through consultation with their prescribing physician, and when consented, linked with caregiver primary data collected via the CAS.

Data Collection Instruments

Assessments of cognitive and functional status and global clinical impression were completed using 6 scales administered at baseline and/or each time point over the course of the SMS. The SMMSE and GDS were mandatory scales for SA coverage. The OPAR was an optional section on the SA renewals. The CDT was an add-on instrument completed by physicians with payment provided by PSD for completion, and the TICS was administered by study staff. Details of each of the 6 data collection instruments including site of administration, type of domains tested, and metrics are provided in the SMS Technical Analyses Report (available upon request).

Special Authority Drug Coverage and Data Collection Points

Initial coverage for ChEIs was assessed by prescribing physicians using the Algorithm for Initial Coverage of Cholinesterase Inhibitors for Mild to Moderate Alzheimer's Disease (Appendix 1). Every 6 months thereafter prescription renewal coverage was dependent on a physician completing the SA renewal including the SMMSE and GDS unless indicated that the patient was functionally illiterate.

Potential SMS participants were screened prior to the 6-month renewal of ChEI in order to allow for consent to be established prior to the 1st SA renewal visit. Those eligible and who consented to participate were then interviewed by research staff at 6, 12, and 18 months in order to coincide with SA renewals. Those stopping the medication prior to this time continued to complete TICS, however, no further data was provided by physicians and SA assessments stopped. As shown in Figure 1, the number of participants at each time period varies, as a function of attrition and missing data.

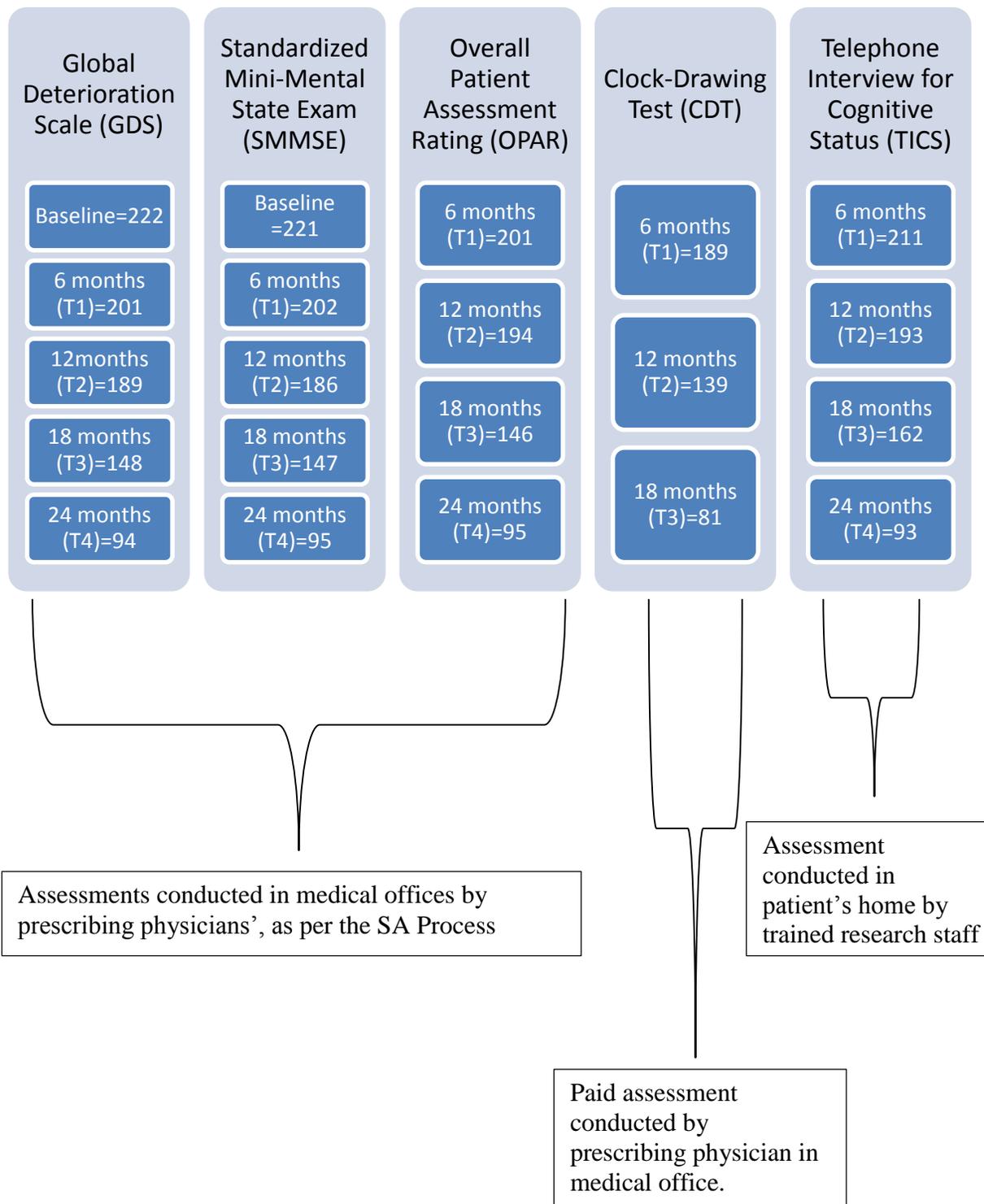


Figure 1. Number of Completed Assessment Forms for the SMS Participants at Each Time Period

Inclusion Criteria

To be included in the SMS, participants had to meet specific eligibility requirements. At first point of contact, patients and/or family members were triaged to assess for potential eligibility and then reviewed twice more to ensure the following were met (see Figure 2):

- Has ADTI SA coverage in place and taking a ChEI
- Has a family/caregiver who agreed to facilitate interviews
- Has an attending physician who agreed to participate in the study and complete the SA and SMS forms with each prescription renewal
- Has signed caregiver and participant informed consent on file

Participants were recruited into the SMS through physician referral, MoH contact, or a public recruitment campaign. For this report, data analysis is restricted to those patients who consented to link primary, SA, and province data (referred to as “PHN-consented SMS participants”).

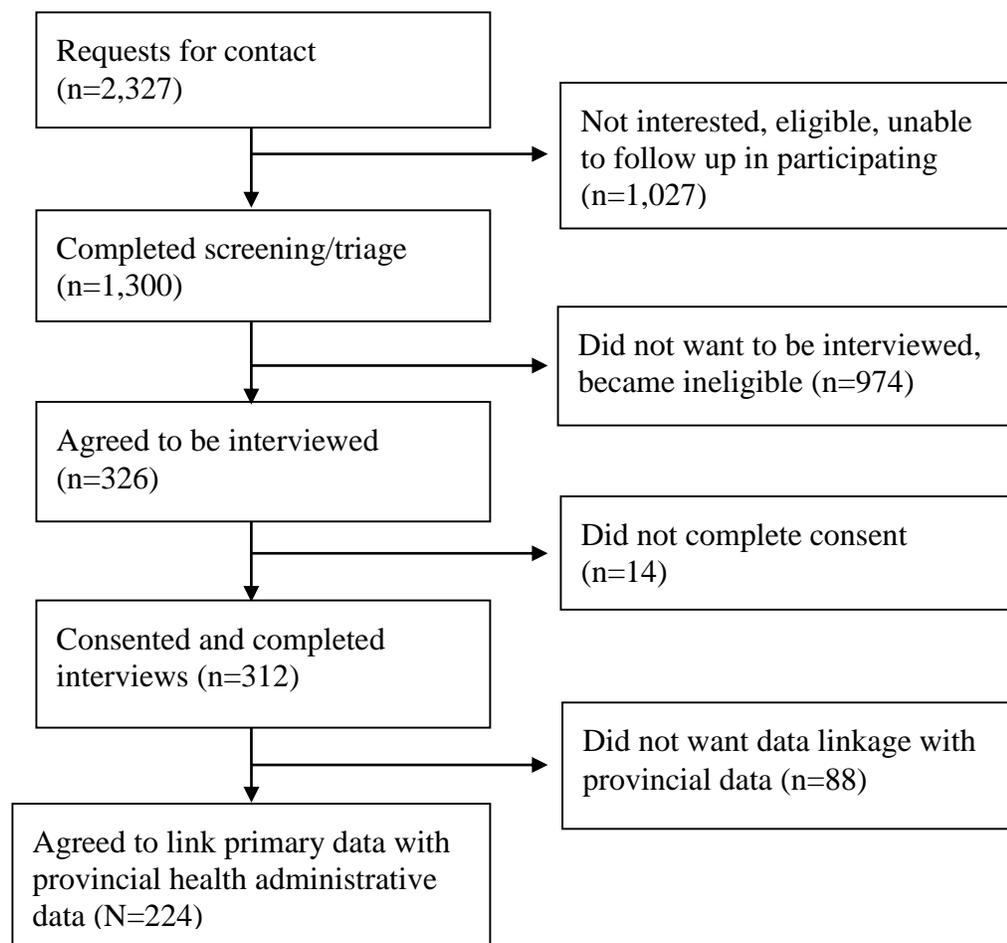


Figure 2. Flowchart of Seniors' Medication Study (SMS) Enrollment

Sample

The sample consists of individuals who have ADTI SA coverage, and agreed to be interviewed and to have their data linked via their PHN with the provincial administrative data (N=224).

The gender breakdown of the SMS participants is somewhat equal with slightly higher proportion of males in each of the four time points (see Table 1). The sample is almost entirely of European descent (n=211, 99%).

Table 1. Distribution of Gender at 6, 12, 18, and 24 Months, n (%)

Renewal	Male	Female	Total
6 month	121 (54.0)	103 (46.0)	224 (100.0)
12 month	119 (54.8)	98 (45.2)	217 (100.0)
18 month	109 (54.8)	90 (45.2)	199 (100.0)
24 month	84 (59.2)	58 (40.9)	142 (100.0)

About 20% of SMS participants have less than a grade 8 education. The remaining 80% are split about equally between those having a grade 12 education or less and those having some or completed post-secondary education. These educational differences seen across the SMS participants are similar to those found in the B.C. population in general. Education was optionally provided at initial SA only; there was a 99.1% completion rate.

As reported by family caregivers, the most frequent type of cognitive diagnosis among the SMS participants is AD with approximately 60% of the sample across all time points. AD with vascular components is the second most frequent diagnosis for this group, characterizing about a quarter of all diagnoses in the SMS group. AD with Parkinsonian features was the third largest of the 4 groups with about 13% of patients' caregivers reporting that diagnosis and AD with other components making up less than 2%.

The average age of participants and number of chronic conditions suggest that this is a relatively older group with an average age of 79 years. Most have complex health conditions with caregivers reporting the patient having on average 5 chronic conditions. Many participants enrolled into the SMS after having lived with their diagnosis for at least 2 years. Most are in their late seventies, but there are a handful of early-onset participants in their forties and fifties.

Cholinesterase Inhibitor Drug Therapy Profiles of the SMS Participants

Almost all of the SMS participants were naïve to ChEIs at the 6-month assessment (see Table 2A). That is, 94% (n=210) were new to the ChEI therapy in the 6 months prior to their initial SA coverage. Across all 4 time points, the percentage of SMS patients who expressed an interest in the study but stopped the ChEI drug therapy after enrolling in the study was less than 5%. In Table 2B, SMS linked PNet data show that of the 179 SMS participants for whom we

have these linked data the actual number of patients who actually stopped taking the drug all together.

Table 2. Drug Status at 6-Month Assessment Intervals, n (%)

A. Naïve vs Non-naïve Patients

Renewal	Drug status		
	Non-naïve	Naïve	Total ¹
6 months	4 (1.8)	210 (93.8)	224 (100.0)
12 months	4 (1.8)	207 (95.4)	217 (100.0)
18 months	4 (2.0)	191 (96.0)	199 (100.0)
24 months	3 (2.1)	136 (95.8)	148 (100.0)

Note: ¹Includes missing data.

B. Number of Stoppers at Time Interval, SMS Linked with PNet Data (n=197)

Renewal	Drug-status	
	Renewed ChEI since previous SA	Stopped ChEI since previous SA
0-4 months	197 (100.0)	0 (0)
5-7 months	177 (89.8)	20 (10.2)
11-14 months	185 (93.9)	12 (6.1)
15-20 months	180 (91.4)	17 (8.6)
21-28 months	168 (85.3)	29 (14.7)

SMS participants were taking at least 1 of 3 types of ChEI: donepezil, galantamine, and rivastigmine (oral or transdermal patch) (see Table 3). Based on the linked PNet data, we observe that the most common type of ChEI in current use at each 6-month interval for SMS participants was donepezil. Galantamine use was the second most common type of ChEI in use, followed by rivastigmine.

Table 3. Type of Cholinesterase Inhibitor, n (%)

Renewal	Taking Donepezil	Taking Galantamine	Taking Rivastigmine (oral or patch)	Total
6 month	114 (51.4)	59 (28.4)	40 (19.3)	208 (100.0)
12 month	102 (47.0)	58 (28.3)	40 (19.5)	205 (100.0)
18 month	93 (46.7)	49 (25.3)	37 (19.6)	189 (100.0)
24 month	64 (43.2)	39 (29.1)	27 (20.2)	134 (100.0)

Statistical analysis: Defining Treatment Response

For all univariate and bivariate analyses, descriptive frequency counts were used. Pearson Chi-square tests were used to analyze treatment response.

For analyses of change over time, as shown in Table 4, we defined treatment response to ChEI drug therapy using three different outcomes: 1) change in scores between renewal time points using SMMSE, 2) change in scores between renewal time points in the GDS and 3) the stand-alone OPAR score (Atchison, Bradshaw, & Massman, 2004; Clark, et al., 1999; Doody, Massman, & Dunn, 2001). Negative/worse than expected were categorized as the *non-responders*, depending upon their change in score from initial to renewal. *Indeterminate* responders had neither a positive nor negative change in cognition, function, or behaviour at each renewal assessment and any changes in those domains may be attributed to the natural progression of the disease. In contrast, positive/better than expected responders demonstrated a positive change, as assessed by a better score in assessment than the previous one and are called *positive responders*. These analyses take into account the natural progression of the disease for scores on the SMMSE; indeterminate therefore does NOT indicate stabilization and therefore less decline than expected. (The same definitions are used in Clin Epi)

Table 4. Definition of “Treatment Response” for the SMMSE, Global Deterioration Scale (GDS), and OPAR Outcome Measures

	Type of Treatment Response		
	Negative / Worse than Expected (non-responder)	Indeterminate / Within Expected Range of Progression (indeterminate responder)	Positive / Better than Expected (positive-responder)
SMMSE: Initial to 1 st renewal (6 months) change of	-5 or less	-4.9 to 0	Greater than 0.1
SMMSE: Initial to 2 nd renewal (12 months) change of	-5 or less	-4.9 to 0	Greater than 0.1
SMMSE: Initial to 3 rd renewal (18 months) change of	-7.5 or less	-1 to -7.4	Greater than -0.9
SMMSE: Initial to 4 th renewal (24 months) change of	-10 or less	-2 to -9.9	Greater than -1.9
GDS: Initial to next (6, 12, 18, or 24 months) renewal change of	+1 to +6	0	-1 to -6
OPAR: Clinician assessment of the patient’s change since last visit (on the SA form)	-2 to -4	-1 or 0	+1 to +4

Results

Deliverable One

Change in scores over time following 6-months of treatment

The results assessing treatment response of SMS participants by three different outcome measures SMMSE, GDS, and OPAR are presented by cross-tabulations using the parameters outlined in Table 5 to define the type of treatment response. For each outcome measure, we present the (i) frequency of response of SMS participants within each of the three types of treatment response for that assessment tool (*non-responder, indeterminate responder, positive-responder*). These results are in subsections a-c. Details regarding the mean score of the other tests cross-tabulated against each of the 3 outcomes measures are in the SMS Technical Analyses Report.

In addition, we examine whether times-to-clinical events (i.e., hospitalization, residential care placement, and mortality) are delayed if the medications are continued past 6 months, compared with similar patients who stop at 6 months. We also examine whether patients who switch to another type of ChEI at the 6-month renewal has any demonstrated benefit over the subsequent 6 month period. These results are presented in subsections d and e.

Defining treatment response as change in SMMSE scores

Table 5 illustrates participants grouped into 3 classes defined by their change in SMMSE score (non-responder, indeterminate responder, positive responder). At first renewal (6 months), the majority were *positive responders* (56.5%) followed by *indeterminate responders* (37.5%). This proportion changed at second renewal (12 months) with equal numbers of *indeterminate responders* (45%) and *positive responders* (44%). However, at the 18 month point (3rd renewal) and at later time periods, the percentage of *positive responders* increases by more than double and surpasses the *indeterminate responders*, in terms of frequency. Specifically, by 24 months, there are 63% (n=59/93) *positive responders* compared to 32% (n=30/93) *indeterminate responders*. Thus, when treatment response is defined by change in SMMSE score the majority of SMS participants are *positive responders*. It should be noted that only participants who have SA can be analyzed. If those who dropped out were non-responders, the findings will be positively skewed. On the other hand, since the study is a rolling enrolment, the small numbers with longer duration follow up could be due to participants entering the study at a late phase and did not have as long a duration of observation as those who entered the study at an earlier time point.

Table 5. Frequency of Treatment Response within SMMSE Categories, n (%)

Renewal	Worse than Expected (non-responder)	Within Expected Range of Progression (indeterminate responder)	Better than Expected (positive-responder)	Total
6 months	12 (6.0)	75 (37.5)	113 (56.5)	200 ¹ (100.0)
12 months	20 (10.9)	83 (45.1)	81 (44.0)	184 (100.0)
18 months	8 (6.2)	43 (33.1)	79 (60.8)	130 (100.0)
24 months	4 (4.3)	30 (32.3)	59 (63.4)	93 (100.0)

Note: ¹Missing 24 SMMSE scores.

Defining treatment response as change in GDS score

When SMS participants are grouped into 3 classes defined by their change in GDS score (*non-responder, indeterminate responder, positive responder*) from initial assessment (baseline) to subsequent time points (6, 12, 18, and 24 months), we see that almost two-thirds of the participants are classified as *indeterminate responders* initially and over time (Table 6). That is, at the first renewal, the SMS participant’s treatment response is best described as falling within the range of progression for the disease, with neither positive nor negative changes in the GDS assessment. As the duration on ChEI-drug therapy lengthens, the number of *positive responders* increases, relative to a decrease in the number of *non-responders*, indicating that when treatment response is defined by GDS scores, SMS participants are seen as either staying the same or improving over time.

Table 6. Frequency of Treatment Response within GDS Categories, n (%)

Renewal	Negative Response	Indeterminate Response	Positive Response	Total
6 month	37 (18.6)	135 (67.8)	27 (13.6)	199 (100.0)
12 month	36 (19.3)	113 (60.4)	38 (20.3)	187 (100.0)
18 month	24 (16.4)	86 (59.0)	36 (24.7)	146 (100.0)
24 month	13 (14.1)	57 (62.0)	22 (23.9)	92 (100.0)

Defining treatment response as change in OPAR score

When patients were classified by their OPAR score into the 3 response categories (*non-responder, indeterminate, positive responder*), the indeterminate responders make up the largest proportion and this remains true for all time points, except at the first 6 months when there were slightly more positive than indeterminate responders (see Table 7).

Table 7. Frequency of Treatment Response within OPAR Categories¹, n (%)

Renewal	Negative Response	Indeterminate Response	Positive Response	Total
6 month	4 (2.0)	94 (46.8)	103 (51.2)	201 (100.0)
12 month	5 (2.6)	116 (59.8)	73 (37.6)	194 (100.0)
18 month	2 (1.4)	103 (70.6)	41 (28.1)	146 (100.0)
24 month	5 (5.3)	74 (77.9)	16 (16.8)	95 (100.0)

Note: ¹Optional completion

In terms of average SMMSE score over time, we noted that the average SMMSE score is highest among *positive responders* across all time points (approximate \bar{x} =24.3). Furthermore, we observed a moderate increase in mean SMMSE within this treatment response group from first to last assessment by 1.5 points. *Non-responders* have the lowest SMMSE score across all assessments, dropping 3 SMMSE points from first to last assessment.

Indeterminate treatment response, stopping status, and clinical outcomes

For the SMS participants defined as indeterminate responders² at the first 6-month renewal (n=83) we observed 6 months of clinical outcomes between the first and second renewal (12 months) and compared stoppers with non-stoppers. There are only 6 SMS participants who were indeterminate responders at first renewal and who stopped taking the ChEI. Of those indeterminate responder-stoppers only 1 patient (17%) was placed in residential care and the other 5 (83%) were not. In contrast, however, all 6 indeterminate responder-stoppers had at least 1 hospitalization in the 6 months following the first assessment.

Within the cohort of indeterminate responders, as assessed at first renewal, there were 77 patients who continued on the medication (93%). Of these indeterminate responder non-stoppers, 20 patients (26%) were placed in residential care compared to 57 (74%) who were not. There were 49 (64%) indeterminate responder non-stoppers who had at least 1 hospitalization in the 6-month period compared with 28 (36%) patients who did not. Based on these frequency counts, we observe that patients with an indeterminate response to ChEI after 6 months and who continue on the drug have fewer residential care placements but more hospitalizations.

Due to the limited number of indeterminate responders who stopped taking the ChEI at the first renewal (n=6) it is not possible to do regression analyses to determine if the clinical outcomes were related to (or predicted by) demographic or health status of the individual patient or to evaluate comparisons among stoppers and non-stoppers beyond descriptive analyses.

Treatment response and switched or renewed status

Within the SMS cohort, there were 35 participants (16%) who switched from 1 type of ChEI to another type after 6 months of use. There were 14 indeterminate responders who switched ChEI

² When treatment response is defined by OPAR score.

at 6-months and who, at the time that they switched, were defined as being an indeterminate responder to the ChEI type they had just switched from.

Table 8 shows the mean values of 3 assessment tools of the patients who switched and those who renewed (i.e., did not switch ChEI type) at their 6- and 12-month assessments. For patients who switched from 1 ChEI type to another, they did not do better on the SMMSE or on the GDS 6 months later but did show slight improvement according to the OPAR. We conclude, therefore, that based on the descriptive analyses of this very small sample of patients who switched, that there does not appear to be any benefit from switching to another type of ChEI among patients who did not respond to the first type of ChEI in 6 months.

Table 8. Mean SMMSE, GDS, and OPAR Values at the 6 and 12 Months for Indeterminate Responders

Time	Switched			Renewed		
	n	Mean	Std Dev	n	Mean	Std Dev
SMMSE score						
6 months	14	21.93	5.44	78	21.62	4.49
12 months	12	21.58	4.96	68	21.63	4.79
GDS score (higher values indicate worse condition)						
6 months	14	9.79	19.36	79	5.37	8.18
12 months	14	18.00	34.32	77	13.01	27.38
OPAR score						
6 months	14	2.50	0.52	79	2.67	0.47
12 months	12	2.67	0.65	73	3.00	1.00

Deliverable Two

How well do physicians use the existing measurement methods for Special Authority to assess patient benefit from ChEI drug therapy?

The focus of this section is on determining how well physicians use the existing cognitive, behavioural, and functional assessment tools to evaluate a patient’s treatment response. We broadened the scope of the deliverable to include different perspectives of understanding physicians’ utility of the SA and actual accuracy of the assessment tools themselves. We include quantitative results and qualitative findings in 3 sub-sections (a, b, c) as follows. First, we present results that show how the assessment tools are correlated with each other. That is, does a score on the SMMSE have any association with a performance score on any other tool, such as the CDT? We comment on the direction and strength of the association, if any.

Second, we examine the accuracy of and compliance with the SA by examining missing and/or incomplete data. This exercise demonstrates what information is not being collected by

physicians and extrapolates to the broader objective of determining how well physicians use the existing measurement methods in the ADTI SA process. Third, we present qualitative data from separate focus groups and interviews with physicians and caregivers reflecting the many perspectives on the SA process itself and evaluation of drug coverage for this disease and cohort of community dwelling persons with ADRD on ChEIs.

Deliverable 2a: How well are the existing measurement methods for Special Authority correlated?

In order to compare the SMMSE and GDS with other scales (OPAR, CDT, and TICS), we performed Pearson or Spearman Correlations between each of the assessment tools. For each assessment tool, we examined 2 correlation matrices. The first included all SMS participants, then to relax the assumption of missing or attrition at random we re-ran the correlations selecting only those participants whose data we have for repeated assessments; in other words, the same cohort of patients over time. (Details in the SMS Technical Analyses Report).

The overall finding from the correlations of assessment tools used in the evaluation process for measuring drug benefit is that the SMMSE and the TICS have the highest linear association, relative to all the other assessment tools, and that the association is relatively good (e.g., Pearson=.63, $p<.001$). This association is statistically significant across all time periods. The association between the CDT and the SMMSE were also found to be statistically significant with each other and across time periods; yet the strength of these relationships was weaker relative to the strength of association found between SMMSE and TICS. In contrast, the OPAR has a weak to no association with existing assessment tools, including the SMMSE, GDS, and TICS, and not all of these associations were statistically significant.

Deliverable 2b: Physician Accuracy and Compliance with Completion of the SA

To assess how accurate and compliant physicians are with completing the SA, we examined both the common errors made by physicians in completing the forms and the overall compliance with submitting forms under the SA process. The collection of ChEI SA for coverage allowed for the (i) collection of evidence for funding purposes and (ii) systematic tracking of disease progression. (Refer to Appendix 1 for the SA forms: initial and renewal). While clinical workflow at each prescribing physician's office differs, the majority of physicians used Medical Office Assistants to assist with the fax and/or electronic transmission of patient information from their office to the MoH, PharmaCare program.

For all SAs, regardless of initial or renewal coverage, this information was mandatory:

- Prescriber Information (Section 1)
- Patient Information (Section 2)
- Medication Requested (Section 3)
- Clinical Information (SMMSE and GDS only)

It is interesting to note when interpreting these results that about 75% of the time the prescribing physician—the one completing the renewal SA—was the same doctor from the

initial SA and/or previous renewals. This is helpful in that accuracy and compliance with the SA represents for the most part the same group of doctors managing these dementia patients in their practices.

SA: Required clinical information

With regard to presumptive diagnosis, this was filled in quite well by physicians with ‘unsure’ selected in only 1% of completed initial SA.

SA: Required policy coverage information

The ADTI policy dictated range for number of days between SA renewals was between 150 and 210 days. At first renewal, the mean number of days is 229, this number drops at second renewal to 218 days but is still outside of acceptable policy range. At third and fourth renewal the number of days is within acceptable policy range, but remains at the high end of what is deemed an acceptable number of days between SAs.

It is unclear whether the number of days between SAs is outside of policy due to factors that are: patient driven (i.e., patient is showing up to prescribing physician at longer intervals than recommended); data driven/outliers (e.g., highest in the range is 883 days); practice driven in that prescribing physicians are submitting forms with delays (i.e., patient has come and gone but form is not submitted right away); or policy driven (i.e., most SA requests are due in 12-month intervals).

The same observation is seen with number of days that patients are on the ChEI. The mean number of days at first renewal is 229 which is outside of the policy window of 150-210 days.

SA: Required clinical assessment information

Of the 3 assessment tools on the SA, the SMMSE and GDS were asked on both initial and renewal. The GDS was completed 100% of the time on the initial SA, but over time the frequency of completion for GDS dropped somewhat at first renewal (7% not completed) but this improved with subsequent renewals. The frequency of missing SMMSE score was highest at first renewal, but improved slightly with subsequent renewals (2-5%).

Overall, OPAR had a higher frequency of incomplete data relative to SMMSE and GDS. The OPAR was only asked at renewal and if left incomplete the SA was not returned by PSD to physicians for additional information, unlike SMMSE and GDS. For the total OPAR score, at first renewal, 11% of doctors did not complete the total score, but again this number decreased with renewal time (range: 6-4%). In only 1 case was it reported that the patient could not complete the assessment, across all renewals. The frequency of incomplete data observed in the total OPAR score is consistent within each of the 4 different components that make up the total OPAR score (i.e., cognition, function IDL, function ADL, behaviour). Again, time demonstrates that accuracy of completion increased with renewals.

SA: Optional supplementary information

Optional supplementary information includes a range of questions related to socio-demographic and selected physical ability information. Some questions were asked only on the initial SA. In those cases, in about 30% of all initial SAs (n=245), physicians did not complete information about ethnic ancestry, years of education, presence of hearing/vision problems, and/or language barriers. We do not know whether the missing data are because the physician did not record his or her observations or if the patient opted not to respond to the physician's clinical inquiry.

Supplementary information about patient's living arrangement and physical status (height and weight) were asked at initial and renewal. Living arrangement consisted of two separate questions, 1. Lives alone, and 2. Resides in a facility where medical care is provided. Information was filled out by doctors approximately 75% of the time on the initial SA but at each renewal the percentage of incomplete information on living arrangement increased to about 38-45%. On the initial SA, almost half of completed forms included information on height (53.1%) and weight (58.0%); yet with each renewal this information was provided less often but was still being filled in about 40%-46% of the time for height and 46-49% for weight.

The overwhelming majority of patients did not sign the SA at initial (96%) or subsequent renewals (range: 95-98%); this was also noted as optional.

Deliverable 2c: Qualitative findings from physicians and caregivers on the SA process specifically and on drug coverage evaluation generally

Focus groups and guided interviews were conducted with physicians and family caregivers on the lower Mainland and Vancouver Island. Physicians were known to the SMS, either having attended a previous focus group or had patients enrolled in the SMS. Physicians were contacted via fax and offered an honorarium for attending. Family caregivers were enrolled in the CAS and their family member was enrolled in the SMS. The purpose of these interviews was to investigate the process of discontinuing ChEIs. Findings discussed here are unsolicited comments related to the ADTI.

In total, 19 physicians participated in the focus groups, 5 geriatricians were interviewed face-to-face, and an additional 25 face-to-face interviews with caregivers of family members who stopped taking ChEIs were conducted. The purpose of the interviews with geriatric specialists was the same as that with general practitioners. Family caregivers were asked about their own personal views and experiences with having their family member stop a ChEI. Names have been removed to protect the privacy of respondents.

Focus group interviews with 19 general practitioners with an interest in geriatric care
Each focus group was approximately 2 hours in length and most physicians had a familiarity with one another. Several themes emerged from the data.

Theme 1: Physicians want to be paid

The physicians in these focus groups expressed reluctance to provide services that are not compensated and that take them away from clinical activities that are reimbursed on a meaningful fee schedule.

- “[\$15 for optional section on SA] is better than nothing.” [1]
- “... the time required to do an MMSE - you’re looking at, well, you might be able to do one in 15 minutes but it’s probably closer to 20 minutes to do and you don’t get paid for it, and so with 20 people sitting in the waiting room there is a fair bit of pressure to get moving here.” [2]

Theme 2: Resistance to research

Partially stemming from the BCMA directive to not complete ADTI SA, there was general resistance to the ADTI. Focus group attendees expressed resistance in terms of how to fit the additional work into everyday practice and cynicism about how funding is driving the drug research and whether the research really captures the complexities of care.

- “Well, if you have to do this form every 6 months, ... why do clinicians have to jump through these hoops?” [1]
- “... the conversations around who do you start, who do you stop - they are so complex and studies never capture that. ‘cause it’s all about numbers.” [3]
- “And it would be so interesting to know, had there been a placebo arm as well, what the percentages would be? ... the power of placebo as a perception-measure...” [4]
- “None of the databases is reliable.” [1]

Theme 3: SA could be improved

Physicians shared their view that the SA needs to focus on assessment regarding functioning in the patient’s real-world context, rather than scores on a measurement scale. They reported reservations about relying only on scores of SMMSE because it is cognition only, and that it misses cases that should be covered by the SA. Others preferred the MOCA (not available when the ADTI began) to SMMSE; while some felt that the GDS was useful but perhaps categorizations too broad.

- “I do the MOCA and the Mini-mental are slightly different in terms of which target audiences, if you will. The MOCA tends to sort out the more subtle start-ups of the dementia; the mini-mental is, I think, a much blunter tool and more useful as the progress goes to its finality.” [2]
- “I think it’s very subjective. There are no objective measurements, really.” [1]
- “[The GDS] it is too broad.” [2]
- “[Including caregiver assessment of functional activity and relationships] that sure would be good.” [6]

Theme 4: Benefits of SA coverage

Even though a number of physicians expressed issues with the instruments used in the SA, others had more positive reactions.

- “[The OPAR] it makes people think about it [cognition, functioning, and behaviour].” [6]
- “[what will happen] if you don’t have that trigger of the Special Authority to re-evaluate... [interviewer] “It would slide...in my practice, I think, it would slide. We have some stuff filled in but...” [7]

Theme 5: Concerns about drug funding in general, and ChEIs in particular

There is a conflict between drug funding and best practice of care for the patient. Physicians expressed concern regarding the moral and ethical issues of prescribing and funding medication.

- “... it all comes down to an issue of cost, and I’m not sure if cost should really play a role when deciding medication treatment.” [8]
- [discussion regarding the idea of ChEI giving family members hope] “That’s unethical. That’s false hope.” [9]; “That’s completely unethical. That’s a placebo.” [10]; “I much rather give them a placebo that costs nothing then to give them a drug that can cause harm.” [11]

Theme 6: Systemic problems

Physicians are quick to identify issues within the MoH with regards to SA approvals, paper-flow, Ministry staff, billing complexities, and policy development.

- “I had a patient who’s got a diagnosis under every letter of the alphabet and we needed Special Authorization for I forget now which drug. A standard issue. I spent 45 minutes on the phone with this young lady at PharmaCare who said to me, I understand where you’re coming from but you need to write a letter. Dumb me, wrote 5-page letter...It came back with a stamp ‘not enough information’. [1]
- “I think part of the problem for frustration is when I apply for Special Authority on something I know that a Grade 12 Summer student has got a book in front of her and if the magic words aren’t spelled exactly as it is required it won’t work.” [2]
- “And I just see this new initiative as another layer of complexity. You just called them in for their chronic care visit for diabetes, and COPD or...but you can’t do this one because it says in there you can’t bill them on the same day. So, now you’re gonna bring them back again, what for? Care or for financial reasons, so, we’re moving away from what’s right for the patient to what’s right for the practice.” [10]

Theme 7: Support for including ADRD in the Chronic Disease Management Initiative (CDMI)

Physicians were asked how they believed including ADRD in the CDMI would impact care. Overall, the idea was well received.

- “... if there were the Chronic Disease Management issued, I think it would encourage us to bring in people as a general cohort and start screening and then we might pick up some of this earlier....” [12]
- “But if we end up having this kind of a chronic disease initiative, that’s usually always on your file, on your EMR and that pop-up date when that is due is always visible....” [13]

- “See, under preventative care, people would make the effort to look for it. They document it, they treat it. And then you have the criteria that you go by, everybody would follow them, make sure you’ve done everything correctly. I think that would make a big difference. [14]
- “I would disagree with that. ... what I would like to see is not another layer of complexity ... I’d like to see this all turn back to based upon people’s ACB classification, which is done for every single person with a care card in the province.” [10]

Face to face interviews with five geriatric specialists

Geriatric specialists saw benefits to the SA and the ADTI. Overall, this group of physicians felt the SA improved the amount and type of follow-up with patients covered by SA. Some specific benefits mentioned by the specialists included:

- better assessment of drug efficacy as ADTI patients are to be followed in a standardized fashion
- changes are noticed because of scheduled follow ups, especially given that so much change can take place in a year and given issues with self-isolating associated with the disease. With the use of clear-cut tools, follow up can be provided by auxiliary services: GPs, health practitioners, nurses, etc.
- pushed physicians to adopt the chronic disease management model where patients were seen at dedicated visits at specific times
- positively impacted physician perceptions about ChEI efficacy by having to complete SA and note change over time (e.g., regular appointments and objective scores from standardized instruments)

Face to face interviews with 25 family caregivers whose family member had stopped cholinesterase inhibitors

Caregivers understood the SA as the doctor requiring permission from the B.C. government to prescribe the medication. Caregivers also understood that family members had to meet point system requirements in order to be considered for drug coverage.

Discussion

SMS Limitations

There are a number of research limitations that impact on the generalizability of these findings. First, there were difficulties in obtaining data in a timely manner. For example, SA renewals were often not submitted systematically by the individual physician offices to PharmaCare. This led to varying timeframes for the first and subsequent renewals that were in some cases outside of study protocols. We do not know if the extended delays between SA renewals were due to patient or physician factors. We have accounted for these time-related differences in renewal period in the analyses for the most part; however, a lack of a defined 6-month mark between assessments/renewals will make comparisons with other ChEI studies difficult.

Additionally, not included in our study are those patients who were given free samples of ChEIs, or those in the higher income bracket who did not bother to apply for coverage as they would not benefit from Fair PharmaCare financially (i.e., deductibles too high); therefore any clinical improvement derived from these ChEI users will not be included in these analyses as we do not have SA information for these patients. Also not included in the analyses are those patients who switched out of the SA program and into a different third-payer arrangement but did not stop taking ChEI. Finally, we did not complete the SMS among participants who stopped taking the drug and/or those who continued to take ChEIs but did so without ADTI coverage (i.e., paid-out-of-pocket).

Conclusion

The SMS had 2 main objectives. The first was to measure association among the assessment tools being used to monitor changes in cognition, function, and behaviour among a group of community dwelling older adults with mild to moderate ADRD taking ChEIs. The second objective was to understand in more detail how effective the SA process and its associated assessment tools were for measuring benefit from drug and overall health of these patients.

For the first objective, the data suggest the majority of SMS participants show some benefit in SMMSE and TICS for up to 2 years in those we have SMS data for. As most studies follow patients only for 6 months, this adds to the literature revealing small effects for some patients (Birks & Harvey, 2009; Clinical Evidence Review, 2014). However, without data on those who did not follow up (since those who did not renew their medications are not required to provide a SA), there may be a bias over-representing the number of positive responders overall (i.e., those who renewed the SA and continue to take the medications are more likely to be positive responders). Without a control group, we cannot determine the degree of ‘natural progression’ that is inherent to this disease for similar patients not on ChEI. It is to be noted though, that our analyses of the SMMSE did take natural progression of the disease into account.

The most common type of ChEI used by the participants is donepezil. This is likely due to prescribing preferences. Donepezil was the first ChEI introduced to the market and its launch predates the extended release version of the other drugs. Since donepezil is to be taken one time per day whereas the other 2 ChEI were 2 times per day until the newer extended release formulation became available, the once-a-day medication has an advantage of convenience. The delayed regulatory approval of the rivastigmine patch also influenced how long the other types of ChEIs were taken. Arguably, Pfizer—the pharmaceutical company that marketed donepezil—was the most aggressive in providing free samples and this might have contributed to it being the most frequently prescribed ChEI, as shown in other studies (Findlay, 2001).

As for the second objective, physicians had mixed reviews about the SA process and specific measurement tools. Most felt that the additional paperwork is time-consuming and that they were not appropriately compensated for the time. On the other hand, most also agreed that the SA forced them to have regular assessments and follow up with the patients who were placed on these medications. There were some physicians who attended the focus groups and

expressed their view that the measurement tools being used in the ADTI could be different. Our analyses showed that among the different tools being used to measure treatment response to ChEI there is an association between the SMMSE and the TICS and the CDT, similar to correlations for the reliability of blood pressure measurements. All other associations among these and the other assessment tools were weakly or not at all associated. Overall, however, we can expect considerable variation in performance on these assessment tools and in turn observe variations in treatment response when quantifying ‘benefit’ from ChEI use.

ADRD is a syndrome with a constellation of symptoms with a variable mix of underlying pathologies. Realistically therefore, we can expect that there would be a constellation of measurements required to assess change in various aspects of domains most impacted by this disease. Relatedly we can expect variability in scores across the measurements, and over time, and as a result, poor correlations between the tests. However, the combination of SMMSE and GDS seems appropriate and adequate at the moment. The OPAR shows promise as a tool that captures a wider range of constructs, but it requires further validation to be properly implemented in future studies.

CLINICAL EPIDEMIOLOGICAL PROJECT (CLIN EPI)

Participants and Methods

Inclusion criteria for patients in this study were: (1) they received SA approval; (2) they were prescribed a ChEI; and (3) they were at least 50 years old on January 1, 2001. The total number of patients in this sub-population in B.C. was 19,307. For some of the deliverables in this study, we used only patients whose initial prescription for the ChEI occurred after the initial date of the ADTI, October 1, 2007. We refer to this group as the naïve group (n=15,388); eligible patients who took ChEIs prior to this date are labeled non-naïve (n=3,919).

Outcome Measures

For Deliverables 1 and 2, the outcome measures were obtained from the patients scores as documented on their initial and renewal SAs; viz.,

- Cognitive response: the SMMSE scores and the cognitive component of the OPAR (Step 2A on the SA renewal). Higher scores on the SMMSE indicate better performance. The OPAR components are scored as +1 (improved since 6 months ago), 0 (no change from 6 months ago), or -1 (worse than 6 months ago). Note that OPAR was not on the initial SA.
- Functional response: the OPAR score (Step3), and the function B and C components of the OPAR (Step 2B, 2C);
- Behavioural response: the behavioural component of the OPAR (Step 2D); and
- Global response: the score on the GDS (Step 1); higher scores indicate deterioration.³

For Deliverables 1a, 1b, 1c, 1e, and 2, the study was to assess “treatment response”. This was defined, based on each outcome measure, by categorizing the patients’ change in scores across time (e.g., from initial to first SA renewal) into 3 general categories (note that the different terms used in this report reflect differences in interpretation):

1. Positive response (GDS, OPAR components, and total OPAR) or better than expected response (SMMSE, which took into account decreasing scores due to natural disease progression) (Molloy & Standish, 1997);
2. No change (GDS, OPAR) or an expected response (SMMSE); or
3. Negative response (GDS, OPAR) or worse than expected response (SMMSE).

³ The SMMSE, OPAR, and the GDS measure slightly different aspects of the patients’ cognitive and functional health. Within the present subpopulation of naïve patients, the SMMSE and GDS were moderately correlated with each other ($r=-.305$ at baseline, $-.224$ at first renewal; recall that the GDS is a measure where higher scores indicate greater patient deterioration, hence the negative correlation coefficients). The correlation between the SMMSE change score from initial to 1st renewal and the cognitive component of the OPAR, both measuring the patient’s change in cognition, was moderately strong ($r=.425$). Change in the GDS score and the cognitive component of the OPAR were less strongly correlated ($r=-.125$), as were the change in the GDS and overall OPAR ($r=-.113$), likely due to the small variability in both the GDS and the OPAR component scores (most patients’ GDS scores ranged from 4 to 6, and the OPAR components only have 3 possible values, -1, 0, or +1).

Three outcome measures for Deliverable 1d were:

- Switching: rates of switching from 1 ChEI to another were estimated using PNet dispensing data;
- Tolerability: this was assessed by examining the number of patients who stopped taking the drug within time windows. Data from both SA and PNet were used to estimate when patients stopped taking the ChEI; and
- Side effects: were assessed based on written comments on the SA completed by physicians.

Outcome measures for Deliverable 3 were:

- Mortality: mortality rate estimates are reported as percentages of deceased patients in each consecutive 6-month time interval; we also analyzed the length of time from their initial ChEI to their date of death;
- Service utilization: reported as the number (and percent) of individual patients receiving the services, and the number of services per patient, within each 6-month time interval, for the following services:
 - home nursing services (including the average number of visits per month),
 - home support services,
 - community rehab services,
 - adult day services, and
 - respite care services.
- Nursing home placements: reported as the number of patients who received either assisted living or residential care services within each 6-month time interval.

Mortality rates were estimated using the SA dataset (because it contained everyone's data). Service utilization and nursing home placements were analyzed using the CCD and HCCMRR datasets.

The outcome measure for Deliverable 4 was the SMMSE. Group averages are plotted across time intervals for separate age groups and baseline dementia asperity (as given by the GDS score on the initial SA approval). The SMMSE scores that were available in the SA database were used.

Definitions of Time Intervals

During the analyses, it was discovered that the SA renewals were conducted at widely ranging time intervals; for example, only 48.2% of first renewals took place within 7 months of the initial approval, as mandated by the guidelines (12.6% had their "first" renewals completed beyond 1 year). Because the research questions were about patients' responses over time, to keep the time intervals consistent across patients we based the analyses on patients whose data fell within the 6 (+/-1) month time windows; see Figure 1 (note that the time windows were expanded to accommodate the +/-1 month flexibility for each successive time interval). This

substantially reduced the number of data points, but kept the time intervals in the proper ranges across patients. There is no reason to suspect that there were any systematic factors that would have led to patients having their SA renewals completed beyond 7 months, thus we do not believe this data selection protocol introduced a sample selection bias.

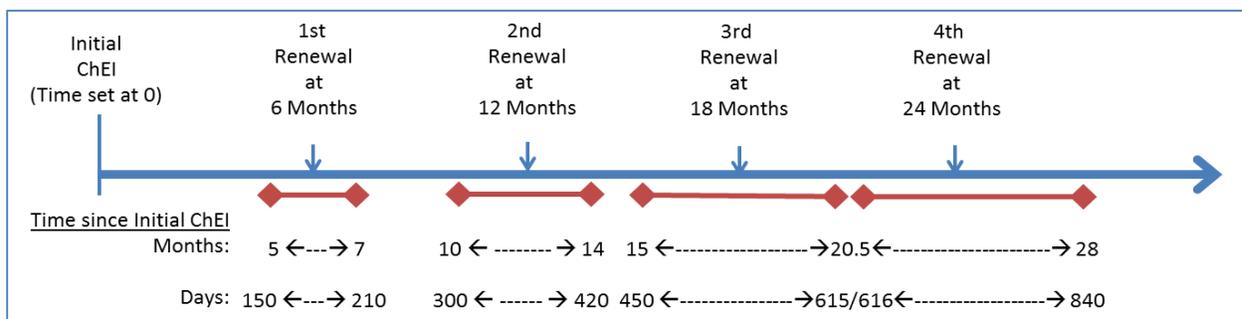


Figure 3. SA Renewal Time Intervals Used in the Analyses

Results

Table 9 shows the description of all patients selected for this study.

Table 9. Demographic Description of Patients in Clin Epi

	Naïve Patients Only		Non-Naïve Patients Only		All Patients	
	n	%	n	%	N	%
OVERALL	15,388	79.7	3,919	20.3	19,307	100.0
Sex:						
Male	5,991	38.9	1,450	37.0	7,441	38.5
Female	9,385	61.0	2,464	62.9	11,849	61.4
Age at first ChEI:						
M	81.1		78.0		80.4	
SD	7.1		7.1		7.2	
Education (Years):						
M	8.2		8.2		8.2	
SD	4.4		4.4		4.4	
Baseline SMMSE:						
M	21.2		19.5		20.8	
SD	4.1		4.7		4.3	
Baseline GDS:						
M	4.5		4.8		4.6	
SD	0.6		0.7		0.7	
Age at first Diagnosis:						
M	78.9		78.4		78.8	
SD	8.0		7.7		8.0	
ADTI Diagnosis:						
Alzheimer's disease (AD)	9,887	64.3	2,718	69.4	12,606	65.3
AD with Parkinson's	872	5.7	227	5.8	1,099	5.7
AD with Vascular	4,399	28.6	909	23.2	5,308	27.5
AD with Other	229	1.5	65	1.7	294	1.5

Deliverable 1a

Study the cognitive, functional, behavioural and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to the proportion of subjects who show a response or remain unchanged at different assessments.

i. Non-naïve Cohort and Estimating False Positives For assessing whether naïve patients responded to the ChEI *better than expected* on the SMMSE, the non-naïve cohort can serve as an informal control group. Because the non-naïve patients were already taking ChEIs, their improvement in SMMSE scores from initial SA to first renewal at 6-months could *not* have been due to starting the medications. For a subsample of non-naïve patients who scored in the middle of the SMMSE scale (SMMSE score of 20), we found that 30% showed an increase in their SMMSE score, presumably due to a combination of natural fluctuations in cognitive function (good days and bad days), plus measurement error. We consider these to be “*false positives*” in this context. The same analysis of a subsample of naïve patients found that SMMSE scores increased for 55% at 6-months. The difference of 25% (55-30%) thus gives us the proportion of naïve patients whose increase in SMMSE scores can potentially be attributed to their starting the ChEI. In other words, due to the fluctuations of the SMMSE scores and measurement error, only about half of the positive responders may be “true” positive responders; this needs to be taken into consideration when interpreting the following results.

ii. Naïve Cohort Using only assessments that fell within the 6-month time windows,⁴ during the first 6 months following the initial ChEI prescription:

- Almost half (48.7%) of the naïve patients showed a better than expected cognitive response on the SMMSE, and a third (32.7%) were assessed as having improved on the cognitive component of the OPAR by their physicians;
- There did not seem to be much of an impact on the functional scores (over 80% of patients were assessed as not having changed on the function ADL and IDL components of the OPAR);
- Almost 20% of patients were assessed as having improved on the behavioural component of the OPAR; and
- With regard to global clinical assessments, 13.5% showed a positive response on the GDS while 42.9% were assessed by their physicians as overall having improved on the total OPAR score since the previous visit.

During the subsequent 3 6-month time intervals, the responses appeared to level out on the cognitive (15-30% of patients continued to show a better than expected/positive responses) and behavioural measures (about 11% of patients continued to be assessed as improved). However, based on the GDS, larger percentages (17-18%) of patients were clinically assessed with a worse score compared with those assessed with an improved GDS score (9-11%), from

⁴ In the analyses of all data across consecutive SA renewals irrespective of the time windows, the overall patterns were similar, although there were proportionally fewer better than expected responders and more worse than expected responders on the SMMSE, and similarly more negative responders as assessed on the GDS and the total OPAR.

assessment to assessment. This is in contrast to the total OPAR measure, where 21-28% of patients continued to be clinically assessed as having overall improved (compared with the previous visit) across subsequent renewals.

Deliverable 1b

Study the cognitive, functional, behavioural and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to the time required for treatment onset to reach response for the maximum number of subjects.

Issues with data and SA compliance limited the ability to satisfactorily answer this research question. Several factors played a role.

To determine the time required for a particular treatment response (negative/worse than expected, indeterminate/within expected range, or positive/better than expected) for the maximum number of subjects, patients needed to be categorized by the type of response by month or some other time interval, consistently across all patients. (We chose a month, but the same issue would apply to any time interval chosen.) The number of patients within each 1 month interval thus served as the basis for computing the percentages. However, the percentages could only be based on the number of patients who had their SA renewal completed; in other words, patients who “dropped out”, for whatever reason (except those who died, but these were considered separately), could not be included in the analyses to obtain the estimates. This potentially biased the results toward more positive outcomes, because the percentage of negative responders is likely underestimated as these patients presumably would be more likely to drop out and/or not return to the physician to have their next SA renewed. As we report below for Deliverable 1c, however, just because a patient did not have a SA renewal completed did not mean that they had stopped taking the medication. Using PNet dispensing data, we found that 23.1% of the 6,162 patients without any SA renewals had continued to have ChEIs dispensed for at least 24 months since their initial SA. The continued ChEI dispensation without SA renewal suggests that their responses to the medication were likely not predominantly negative, possibly lessening the impact of the drop-out bias.

We also considered a number of ways of estimating the size of the “drop out” bias. However, several factors made this unfeasible. First, the percentage of patients for whom data on the “next” renewal were not available was very large (in the 30% range), prohibiting the use of techniques for estimating/modeling their “missing” responses (e.g., multiple imputation or estimating the responses under a variety of assumed scenarios). Second, given that the renewal-to-renewal time intervals were so variable and unpredictable across both patients and renewals, it was impossible to make reasonable assumptions about when the patients dropped out and align the dates with the dates of the outcome measure assessments. Third, it was not feasible to restrict the analysis for this deliverable to only those patients for whom we had a complete set of data on 4 SA renewals and/or 24 month time period, because the number of these patients became too small to analyze - particularly once they were divided into the regular time (monthly) intervals. Thus, the best we could do for this deliverable was to estimate the proportions of the 3 types of responders across time, but interpret the findings with the caveat that the estimates are based on only those patients who remained on a ChEI up to and including

their most recent SA renewal. We note, however, that when we compared subgroups of patients with only 1, only 2, or only 3 renewals, they did not differ from each other on any of the demographic or baseline clinical variables.

Given the above caveats, the analyses showed the following:

For cognitive responses,

- During the first year, the largest proportion of positive responders and lowest percentages of negative responders appeared to be at 5-6 months, as determined by the SMMSE scores adjusted for the natural disease progression (50.5% better than expected; 4.9% worse than expected) and by the cognitive component of the OPAR (34.1% were assessed by their physician as having improved; 16.3% as having deteriorated when assessed at 5-6 months). The percentages of patients with a positive response dropped across the course of the first year (to about 44% on the SMMSE and 19% on the cognitive component of the OPAR at the end of the first year), while the percentage of negative responders appeared to increase slightly (to an estimated 11% to 13% on the SMMSE and 21% to 24% on the cognitive component of the OPAR at the end of the first year).
- In the second year, the 2 cognitive measures showed divergent results: Based on the SMMSE, the majority of patients who had their SAs renewed (51% to 71% of patients) responded better than expected, whereas small percentages (1% to 7%) responded worse than expected; however, on the cognitive component of the OPAR, only 15% to 22% of the remaining patients were assessed by their physicians as cognitively improved (since their last visit) while 19% to 31% were assessed as having deteriorated (since their last visit).

A similar pattern was observed for the behavioural response: Based on the behavioural component of the OPAR, the largest percentage of patients clinically assessed as having improved (21%) and smallest percentage of patients who were assessed as having deteriorated (4%) were observed at the earliest (5-6 month) time point. From there, the percentage of the improved patients dropped over the course of the first year and levelled out at about 6% to 14% in the second year, while the percentages of deteriorating patients remained relatively constant across time at 4% to 7%.

The global response showed different patterns, depending on which outcome measure was employed. Based on the GDS, the percentage of patients who showed a globally positive response increased steadily over the course of the 2 years, from about 15% at 5-6 months to about 31-39% at 2 years. The number of indeterminate responders correspondingly decreased, while the percentage of negative responders appeared to remain relatively steady across the 2 year period at about 13-15%. Based on the total OPAR scores, however, the percentage of patients who were globally clinically assessed by their physicians as having improved since their last visit decreased from 46% at 5-6 months to about 23-25% at 2 years. The percentage of patients clinically assessed as not having changed overall increased in the first year (from 48% at 5-6 months to an estimated 68% at one year) and then levelled off in this range (between 62% and 76% during the second year), while the percentage of patients assessed as having deteriorated overall fluctuated between 5% and 12% across the 2 year period. Analyses of the individual components of the OPAR indicated that this pattern is primarily due to the cognitive and to a smaller extent the behavioural components of the OPAR.

With regard to the functional responses, the 2 components of the OPAR (function ADL and IDL) did not evidence any notable changes over time.

Deliverable 1c

Study the cognitive, functional, behavioural, and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to the duration of persistent treatment response among responders.

For all naïve patients, 6,162 patients (40.0%) did not have any SA renewal completed, so could not be used in these analyses.⁵ Conversely, only 16.4% of patients had at least 4 SA renewals (ostensibly for 24 months).⁶ To obtain estimates of persistence of treatment response, which are based on time and repeated SA renewals, we examined the 3 treatment response categories on each of the relevant outcome measures (viz., better than expected (SMMSE)/positive (GDS and OPAR); indeterminate/no change; and worse than expected/negative) using only naïve patients' SA renewals that fell in the 6 (+/-1) month time windows (note the substantially smaller n's).

Specifically, the persistence of responses was examined by looking at how different responders, categorized on their first renewal, fared on subsequent renewals. For each outcome measure, persistence of response from first to second renewal is shown in Figure 4, and from second to third renewal in Figure 5. In both of these sets of graphs, the persistent response is shown with the percentage bolded. For example in Figure 4, in the SMMSE panel, 21.1% of patients who responded better than expected on the first renewal continued to respond better than expected (relative to the natural disease progression) on their second renewal. These figures also show how the responders changed from renewal to renewal; for example, based on the SMMSE, 63.0% of patients who had responded worse than expected on their first renewal reversed their trend and responded better than expected on their second renewal.

⁵ Of those 6,162 patients without any renewals, a total of 4,840 patients (78.5%, or 31.5% of the original 15,388 naïve patients) died within 24 months of their initial SA, and these are discussed in Deliverable 3 below. Patients who did not have SA renewals but who did not die (the “stoppers”, based on their not having their SA renewed) did not appear to differ on their demographics or baseline clinical assessments from those who did have SA renewals. Furthermore, not having a SA renewal completed was not indicative of the patient having stopped taking the ChEI: we verified this using patients' dispensing data in the PNet database. Stopping, as a treatment response, is discussed further in Deliverable 1d, under the subheading of “Tolerability”.

⁶ To use as much of the SA data as possible, we used data from patients who had at least 2 renewals.

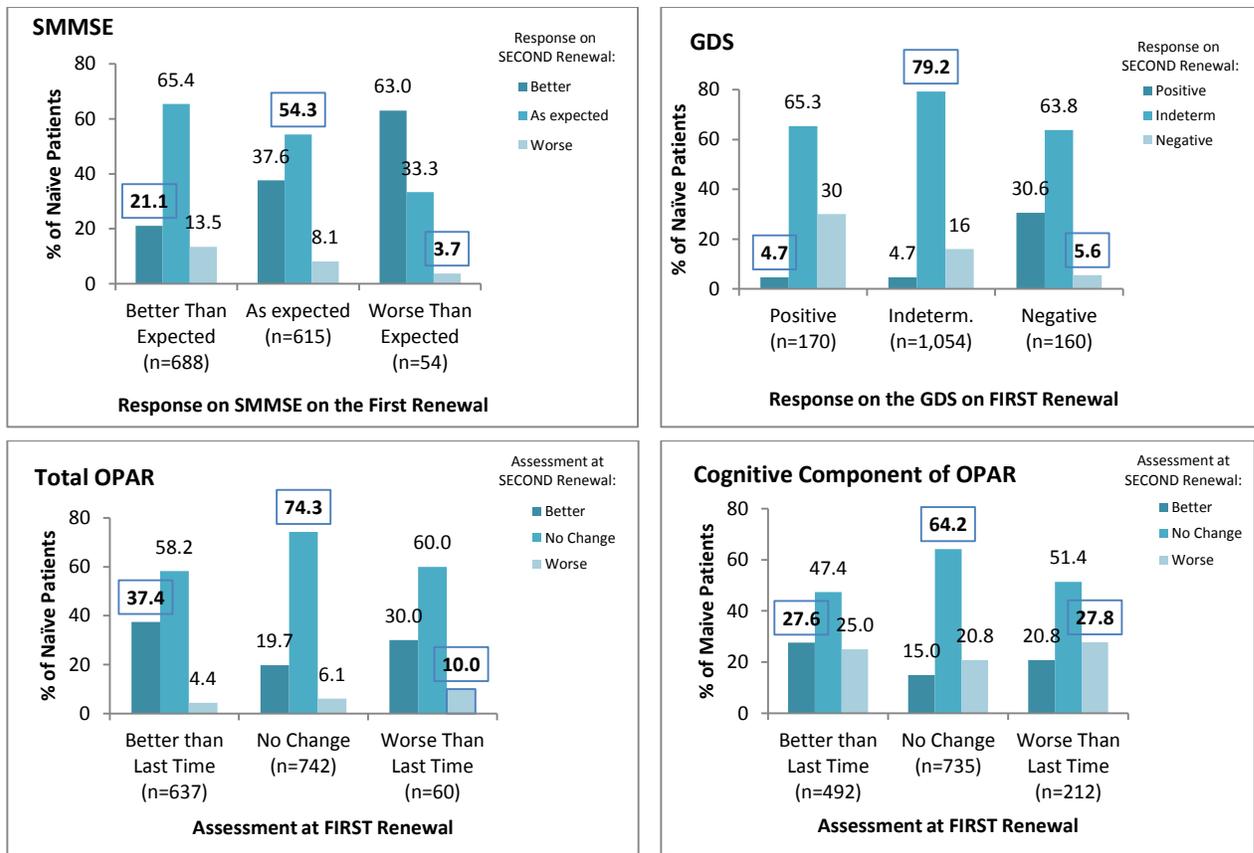


Figure 4. Persistence of Response to ChEI from First (5-7 Months) to Second (10-14 months) Renewal

Paucity of data within the time windows precluded assessment of the persistence of response across 3 subsequent renewals. We did, however, examine this using data from all naive patients who had at least 3 SA renewals (disregarding the time intervals between assessments) and found:

- On the SMMSE (n=3,177):
 - 56 (1.8%) of patients showed a better than expected response across all 3 renewals;
 - 495 (15.6%) responded consistently within the expected range; and
 - None showed a worse than expected response across all 3 renewals.
- On the GDS (n=3,262):
 - 2 (0.1%) showed a positive response across the 3 renewals;
 - 1,310 (40.2%) had an indeterminate response; and
 - None showed a repeatedly negative response across all 3 renewals.
- On the total OPAR (n=3,518):
 - 294 (8.4%) were assessed as showing an improvement across all 3 renewals,
 - 987 (28.1%) were assessed as showing no change; and
 - 8 (0.2%) were assessed as having deteriorated across all 3 renewals.

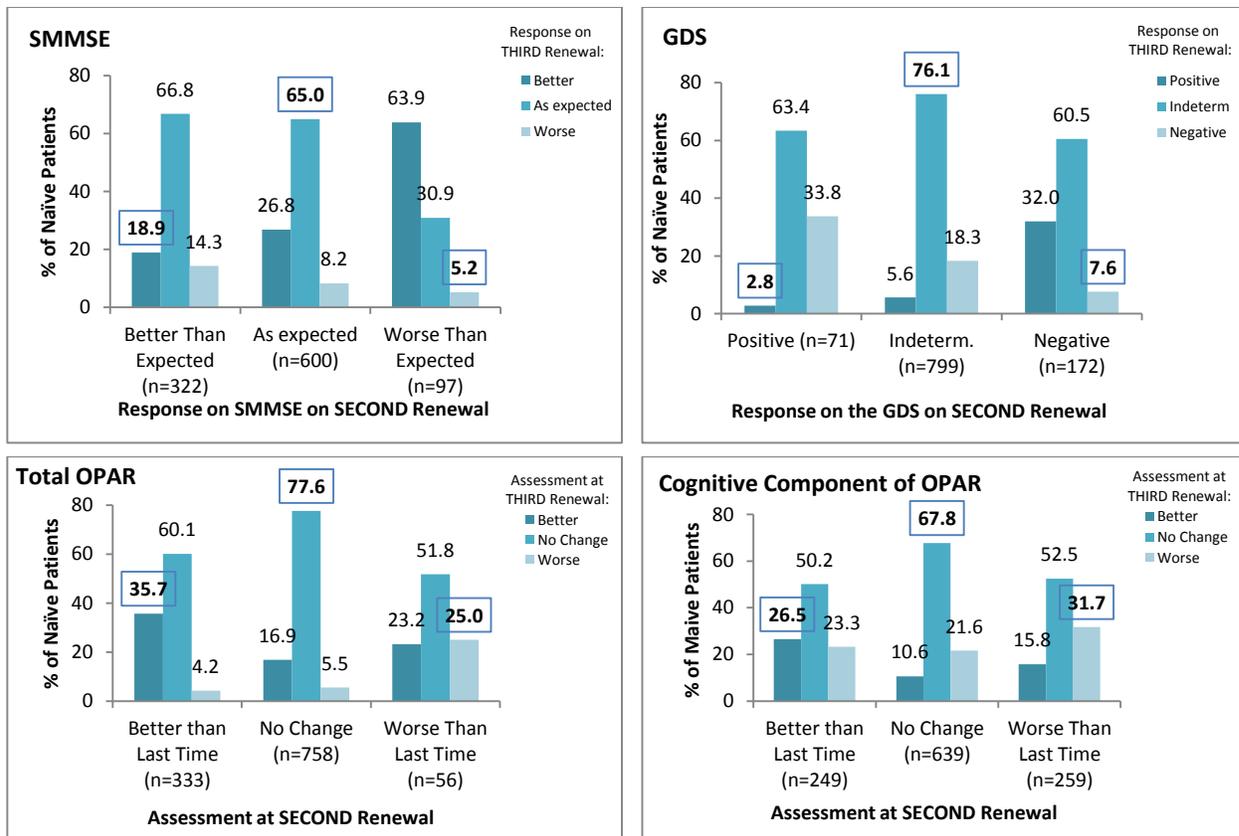


Figure 5. Persistence of Response to ChEI from Second (10-14 Months) to Third (15-20 months) Renewal

Deliverable 1d

Study the cognitive, functional, behavioural, and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to the rates of switching of ChEIs, tolerability, and nature of side effects.

Switching⁷

Two sets of analyses were conducted, 1 based on the SA data and 1 based on PNet. Only first switches are considered; fewer than 2.4% of all naïve patients switched 2 or more times.

Analyses using SA data were based on the subset of naïve patients whose renewal forms were completed within the SA 6 month (+/- 1 month) time windows, so we could determine approximately when the switching occurred. Rates of switching across the 3 types of ChEIs appeared to increase across the 2 renewals, with about 15% of patients switching at first

⁷ The findings reported here do not take into account free samples that may have been given to patients, for example, Pfizer marketing campaign offered free samples (see Coverage with Evidence section).

renewal, and about 20-22% switching at each subsequent renewal. The remaining patients continued taking the same type of ChEI as initially prescribed.

The switching rates by type of ChEI for this subset of naïve patients showed that:

- At first renewal, 17.9% of patients on donepezil, 15.7% of patients on galantamine, and 7.0% of patients on rivastigmine⁸ switched.
- Across time, responses to donepezil and galantamine were quite similar and remained relatively steady over time: 17-19% of patients on donepezil switched and 16-18% of patients on galantamine switched at each renewal.
- Rivastigmine (patch and capsule were not distinguished; see footnote 8) showed a different overall pattern over time. A low percentage of patients (7.0%) switched at the first renewal, but increasingly higher percentage switched at each subsequent renewal (24.8% at second renewal; 29.6% at third renewal, and 36.3% at fourth renewal).

The PNet ChEI dispensing data allowed for finer grained estimates of when the switching occurred, relative to the patients' initial ChEI prescription. Based on these data, 2,243 (14.6%) naïve patients switched their ChEI within 28 months of their initial SA (we used 28 months because of the potential variability allowed for completion of the 4th renewal - Figure 3). Of these, more than half (57%, or 8.3% of all naïve patients) switched within the first 10 months: specifically, 637 patients (4.1% of all naïve patients) switched within the first 5 months (following their initial SA but prior to what would have been their first renewal) and another 644 (4.2%) patients switched between 5 and 10 months (prior to what would have been their second renewal). The switching rate then dropped to 2.4% of patients switching between 10 and 15 months and 3.8% switching between 15 and 28 months.⁹

With regard to the specific ChEIs, the pattern of switching among them was the same for all time intervals. Of those who switched, patients initially prescribed donepezil were about equal in switching to galantamine (49.6% of patients) as to rivastigmine (50.4%). Those initially given galantamine were slightly more likely to switch to rivastigmine (55.5%) than to donepezil (44.5%). And those initial prescribed rivastigmine were more likely to be switched to donepezil (67.7%) than to galantamine (32.2%).

Tolerability

Of all naïve patients, 6,162 (40.0%) did not have any SA renewals completed. Of these, 4,840 (78.5%, or 31.5% of the original 15,388 naïve patients) died within 24 months of their initial SA (these are discussed further below in Deliverable 3). Those who were not renewed but who did not die (the “stoppers”, based on their not having their SA renewed) did not appear to differ from those who continued to have SA renewals on their demographics or baseline clinical assessments.

⁸ In these analyses, rivastigmine refers to both the capsules and transdermal patch. Although we understand that patients responded to the 2 versions of this ChEI differently, the analyses do not take this into account because the transdermal patch was not available in B.C. until Feb. 2009.

⁹ If we use 6-month time intervals without the +/- 1 month adjustments, the switching rates were: 5.1% of patients switched in 0-6 months; 4.3% in 6-12 months; 2.6% in 12-18 months; and 1.8% in 18-24 months. The total number of naïve patients who switched between 0 and 24 months was 2,125 or 13.8% of all naïve patients.

Lack of a SA renewal, however, was not indicative of a patient having stopped taking ChEI. Verification using dispensing data in the PNet database confirmed that 1,423 patients (23.1% of those without any SA renewals) had ChEIs dispensed to them for at least 24 months following their initial SA without any SA renewals completed; hence these were not considered stoppers.

Using the PNet data, 2,807 patients (18.2% of all naïve patients) had stopped taking the ChEI within the first 2 years of their initial ChEI SA. Of these, about half (52.9%) stopped within the first 5 months (1,485 patients, or 9.7% of all naïve patients). And the number of stoppers then dropped considerably for the next 3 time windows to 407 (2.6% of all naïve) patients stopping between 5 and 10 months, 345 (2.2%) stopping between 10 and 15 months, and 570 (3.7%) stopping between 15 and 28 months.

Side Effects

Only a small number of patients (n=99, or 0.64% of all naïve patients) had comments about the any type of effects of the medications written on the completed SA renewal. This suggests that physicians were not recording them, and therefore the low percentage of recorded effects should not be interpreted as an indication of the extent of side-effects (negative or otherwise) of these medications.

The 75 different side effects, or more generally effects related to the medications, that were recorded were categorized into 14 distinct categories. Of these, gastro-intestinal/stomach issues (n=36, 35.4%) and general intolerances (n=20, 20.2%) were the most frequently noted, across all 3 types of ChEIs.

Deliverable 1e

Study the cognitive, functional, behavioural, and global scores of subjects with mild to moderate ADRD receiving ChEI with respect to determining if global and cognitive response at 6 month or 12 month assessments predicts respective response at 2 year and 3 year assessments.

Logistic regression models were estimated to assess whether or not a patient's response on an earlier assessment (on the SMMSE, GDS, and the cognitive component of the OPAR) predicted his or her response at 2 years. As predictors, we used change scores, response categories, and the actual scores from the initial SA and first and second renewals as predictors of future responses on each respective outcome measure.

Using data from patients within the proper time windows (and in this analysis, only patients for whom all 4 renewals fell in the windows as per Figure 1, otherwise there would be too much unknown variability; n=480, or 3.1% of all naïve patients), the analyses revealed that:

- None of the earlier change scores or response categories, whether taken as the difference between initial and 6 month, initial and 12 month, or 6 and 12 month scores, predicted

the patients' response at 2 years on the SMMSE or the cognitive component of the OPAR;

- For the SMMSE scores and the cognitive component of the OPAR, none of the actual scores or assessments at baseline, first and/or second renewals (alone or in combination) predicted the patients' response at 2 years on the respective outcome measure; and
- For the GDS, only the actual GDS score on the second renewal predicted the patients' response on the GDS at 2 years (4th renewal).

Deliverable 2

Study the effect of age, sex, ethnicity, education, dementia asperity, baseline Standardized Mini-Mental State Examination (SMMSE) score, co-morbidities, use of other medications and physician category (specialist or general practitioner) as predictors of treatment response.

Information about physician category was not available. Information about ethnic ancestry was limited, so we dichotomized this variable into European versus non-European ancestry.

Responses on SMMSE were influenced by the patient's:

- age at initial ChEI, with older patients tending to score lower, but only at 6 months;
- sex, with a higher proportion of men scoring somewhat better than expected at 6 months, and a higher proportion of women scoring better than expected at 2 years; and
- baseline SMMSE score, with higher baseline scores being associated with worse than expected responses at 6 months, but not at 2 years.

Responses on the GDS were influenced by the patient's:

- sex but only at 6 months, with higher percentages of men showing an improved (i.e., lower) score;
- ethnic ancestry, only at 6 months, with non-Europeans showing proportionally higher positive responses;
- dementia asperity (i.e., baseline GDS), with higher percentages of naïve patients with higher baseline scores (i.e., showing moderately severe dementia) showing a negative response, at both 6 months and 2 years; and
- co-morbidities, with higher Romano scores being associated with negative response at 6 months.

Responses on the OPAR (total score) were influenced by the patient's:

- age at initial ChEI, with older patients tending to be assessed as worse by their physician but only at 6 months;
- education level at 6 months, with more education being associated with more positive physician assessments; and
- co-morbidities, with higher Romano scores being associated with the patient being assessed as improved at 6 months.

Responses on the cognitive component of the OPAR were influenced by the patient's:

- age at initial ChEI, with older patients tending to be assessed by their physicians as being cognitively worse but again only at 6 months.

The only variable that did not show any relationship with any of these 4 treatment response measures, both at 6-months and at 2-years, was the number of non-ChEI medication that the patient had dispensed in the 12-months prior to their first ChEI.

Deliverable 3

Determine the effect of ChEI on outcome measures such as mortality, service utilization, and nursing home placement among subjects receiving ChEI.

In the absence of a control group of non-users among patients with SA, we could not assess the *immediate* effect of *current* use of ChEIs versus non-use. However, we compared these outcome measures for naïve versus non-naïve patients. Such analyses have the potential to assess the cumulative effect of *past* use of ChEIs, because naïve patients have no past use, at least during their first interval of use. Interpretation of such analyses are challenging because non-naïve patients not only have used ChEIs longer, but are likely to have a diagnosis of ADRD longer and, at enrolment into the study, to have greater dementia. Also, as naïve patients steadily increase their cumulative intake of ChEIs (and become steadily “less naïve”), sustained differences between the naïve and non-naïve cohorts are less explainable as being due to differences in the history of ChEI intake, and more explainable as due to differences in stage of progression of the illness.

Mortality

For all ChEIs combined, the mortality rate was slightly lower for naïve patients within the first 6 months of initial ChEI (14.8% for naïve and 21.7% for non-naïve) and the mortality rate appeared to drop over the course of the 2 year period. With regard to the 3 types of ChEIs, the mortality rate estimates were similar for donepezil and galantamine, for both naïve and non-naïve patients. For rivastigmine, the initial mortality rate (within the first 6 months) was slightly higher than for the other 2 drugs but then dropped to similar rates in the subsequent time intervals.

Compared to the description of all patients in the study, those who died within the first 2 years of their initial ChEI, whether naïve or non-naïve, were more likely to be male, and were less likely to be diagnosed with AD only. Naïve patients were less severely demented (as indicated by lower initial GDS scores), but initial dementia asperity did not appear to have a differential impact on the mortality rates across time. With regard to the SMMSE, naïve patients had higher initial scores (similarly indicating higher cognitive function), but in this case, both naïve and non-naïve patients with higher scores tended to die later.

Service Utilization

Through HCC, information was available for the following service categories: Home Nursing Services (HNS), Home Support Services (HSS); Community Rehab Services (CRS); Adult Day Services (ADS); and Respite Care-Residential (RCR) services. Of all 15,388 naïve patients, 10,574 (68.7%) naïve patients had received at least 1 of these services.

For these service categories, both the number of patients and the number of service episodes decreased over time. However, the average number of service episodes utilized per patient increased fairly steadily and consistently over time. The most highly utilized service, in terms of the number of service episodes, the number of patients, and the average number of services per patients was HSS (an average of 2.29 services per patient and 2,017 patients utilized this service in the first 6 months; this rose to 3.01 services per patient for 1,300 patients in 18-24 months). Second highest utilized service category was CRS (1.79 services per patient on average with 1,631 patients utilizing this services in the first 6 months, rising to 2.11 services per patient and 1,155 patients in the 18-24 months). RCR had on average 2.34 services per patient rising to 2.92 services per patient, but the number of patients utilizing this service category was comparatively much smaller (406 patients in first 6 months dropping to 352 patients in the 18-24 month period). Utilization of HNS and ADS had very similar patterns, with an average of about 1.5 services per patient and just over 1,000 patients using these services in the first 6 months rising to an average of about 1.8 services per patient and about 500 patients utilizing these services in the 18-24 month period.

For HNS and CRS, the number of visits per episode was also analyzed. The distribution was highly positively skewed, so we report the medians. For patients who received HNS services, the median number of visits per month per service episode increased from 4.3 in the first 6 months to 5.5 visits per month in the 6-12 month time period, and then leveled off at 5.0 visits per month in the second year. The median number of visits for CRS remained constant across time at 1.7 to 1.8 visits per month over 2 years.

Nursing Home Placements

The findings here are based on analyses of patients' first occurrence of receiving residential care (RC) and assisted living (AL) services. Placements of naïve and non-naïve patients into RC and AL differed. For naïve patients, the placement rate (RC and AL combined) was highest during the first 6 months, at 10.0% of patients, and dropped over time to 6.4% during the 18-24 month time period. Overall, over the course of the two years since their initial ChEI, a total of 26.7% of naïve patients were placed into RC or AL. The pattern was the opposite for non-naïve patients, with 4.4% being placed during the first 6 months rising to 6.4% during the 18-24 month period, for an overall 15.2% of non-naïve patients being placed in RC or AL. (We observed that this pattern was similar for all 3 ChEI types.)

Patients placed in RC or AL facilities during the first 2 years of their initial ChEI were, on average, more demented (higher baseline GDS scores and lower baseline SMMSE scores), and this was particularly noticeable for the non-naïve group. Higher percentages of patients diagnosed with AD only tended to be placed after 1 year on ChEIs in the naïve group, but

placement appeared to occur earlier (in the 6-12 month time interval) for the non-naïve group. The average age at placement was higher for the naïve group, although this reflects the overall age difference between these 2 groups and was not statistically significant. Higher percentages of women, especially in the non-naïve group were placed in RC or AL, at each time interval and overall (65.2% of naïve and 73.3% of non-naïve female patients were placed in RC or AL).

Deliverable 4

Develop reference graphs of SMMSE change over time based on age and baseline dementia asperity for subjects receiving ChEI.

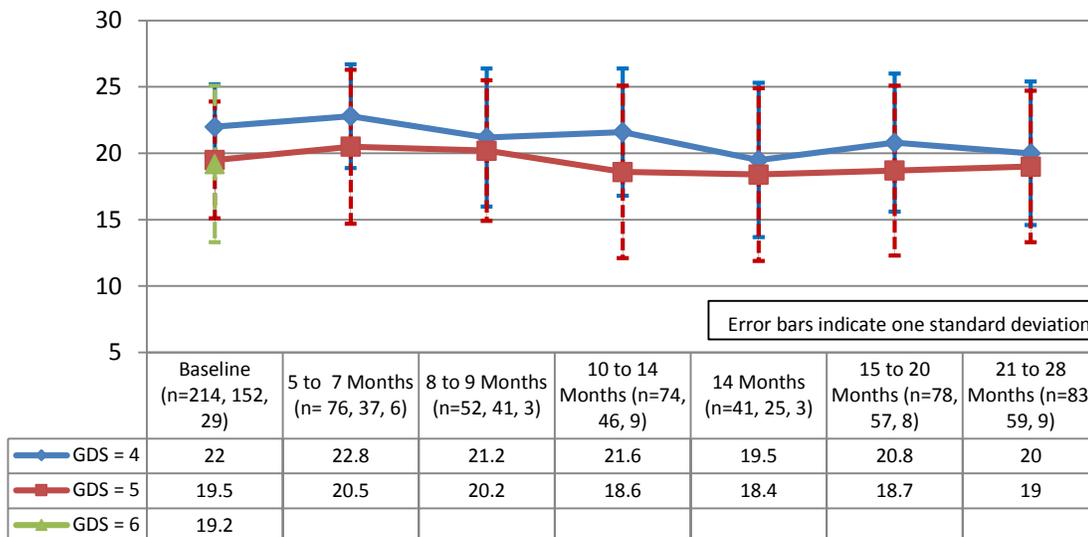
To use as much of the data as possible, all SMMSE scores were used regardless of which SA renewal they came from; the SMMSE scores were grouped by the date on which they were obtained. Naïve patients were grouped by their GDS score (only the eligible scores of 4, 5, and 6 were considered) as well as by age group based on their age of first being on the ChEI: (1) 50 to 64 years old, (2) 65 to 74 years old, (3) 75 to 84 years old, and (4) 85 years or older patients.

The 3 panels of Figure 6 show the means and standard deviations¹⁰ on the SMMSE for naïve patients who had not died within the 24 months from their initial ChEI date. Arguably, these means represent a healthier subset of patients. Each figure shows the means for 1 age group. Means for groups and time points where the number of scores were too small (typically less than 15) are not shown. Specifically, there were insufficient numbers to plot the means for the 50-64 year old age group hence these are not shown.

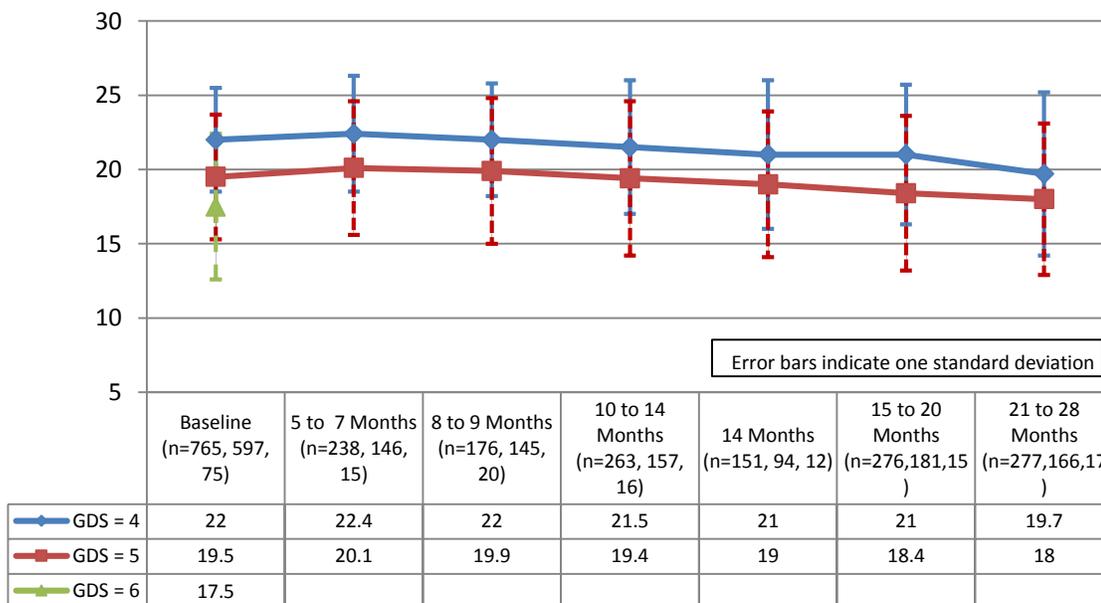
In addition to the graphs of the average SMMSE scores over time, using the non-naïve cohort as an informal control group, we estimated the impact of starting ChEIs on SMMSE scores within the first 6 months as an increase of 1.6 points on the SMMSE scale (95% confidence interval from 1.4 to 1.9 points).

¹⁰ Standard deviations are more appropriate in this context because they do not depend on sample size.

**Average SMMSE Scores across Time by Dementia Disparity:
65-74 Year Old ADRD Patients (Not Died within 24 Months of Initial
ChEI)**



**Average SMMSE Scores across Time by Dementia Disparity:
75-84 Year Old ADRD Patients (Not Died within 24 Months of Initial
ChEI)**



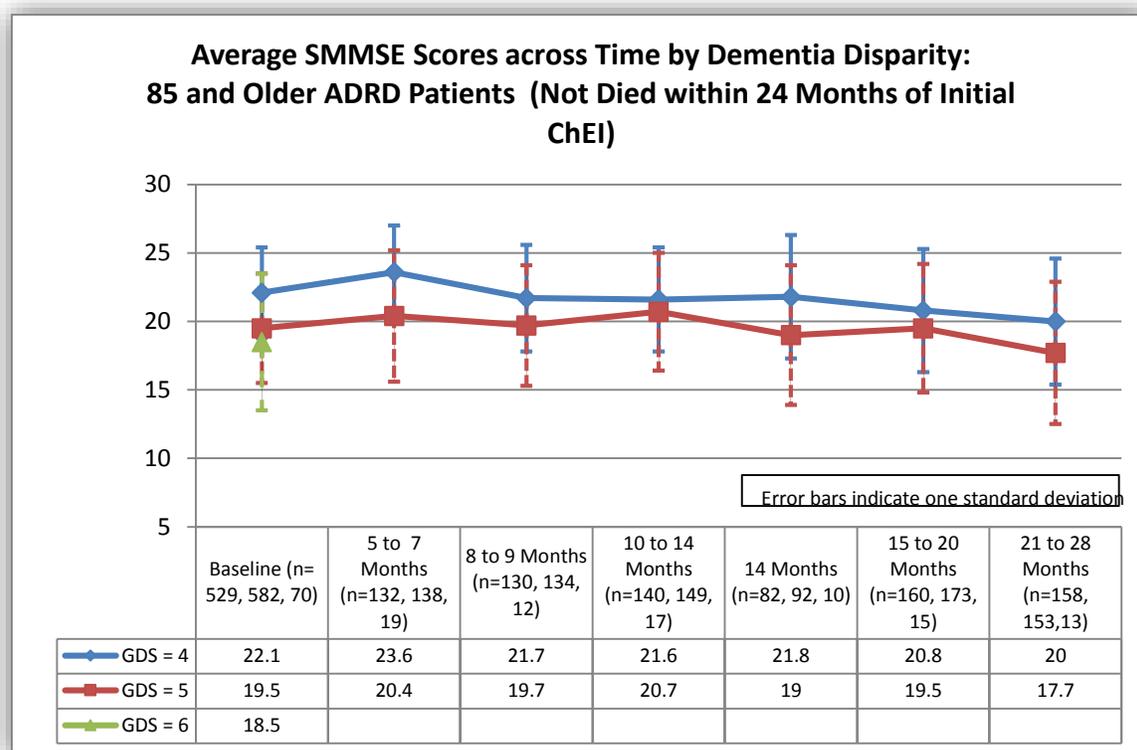


Figure 6. Average SMMSE Scores across Time for Naïve Patients Who Were 65 to 74 Years Old when Initially Approved for a ChEI (top graph), 75 to 84 Years Old (middle graph), and 85 Years Old or Older (bottom graph)

Notes:

- (1) GDS scores are the patient’s initial GDS score: 4=Early Dementia; 5=Moderate Dementia; 6=Moderately Severe Dementia
- (2) Time interval labels on the horizontal axis correspond to the intervals defined in Figure 3, and were computed using days from initial SA (and 30 day months). The initial time interval of 0-4 months is not plotted (typically the numbers were too small); instead, we include the baseline values.
- (3) The number of scores that each mean and standard deviation is based on is given in the parentheses on the labels for the x-axis, in the order of GDS scores of 4, 5, and 6.
- (4) The number of cases for GDS scores of 6 was too small and thus their means are not plotted.

Discussion

The key dataset for Clin Epi that contained assessments of patients’ cognitive, functional, behavioural, and global responses (the outcome measures of interest for Deliverables 1, 2, and 4) was severely limited by 2 factors that make the conclusions drawn from analyses of this dataset tentative. We believe that we were able to minimize the impact of 1 factor, the widely ranging irregularity in the completions of the renewals, by using the actual dates of the SA renewals rather than simply their order. This created analytic challenges, gaps in the data across time and in some analyses considerably smaller sample sizes on which the analyses could be performed, but we can be confident that the time intervals are consistent across consecutive

assessments. However, the second factor, that the SA renewals were not completed even though we verified that a large proportion of patients continued to have ChEIs dispensed, creates a potential “drop out” bias in the findings.¹¹ While those without SA renewals who continued to take the ChEIs did not appear to be superficially demographically and clinically different from those who did have SA renewals completed, we cannot rule out the possibility that patients with more negative responses to the ChEIs dropped out at higher rates than others. In other words, all conclusions based on this study are based on only those patients who remained well enough to continue in the study.

For Deliverable 1, ADRD patients’ response to the ChEI treatment over time, as assessed by cognitive, functional, behavioural, and global scores, was mixed. Cognitive measures appeared to improve during the first 6 months, as assessed by both the SMMSE and the cognitive component of the OPAR. Almost half of the naïve patients showed a response that was better than expected based on natural disease progression on first SA renewal to 6 months. Similarly, but to a lesser extent, patients also appeared to improve on their behavioural scores in the first 6 months. Over the subsequent 3 6-month time intervals, the observed cognitive and behavioural improvement appeared to level off. Patients’ functional scores did not appear to change across the 2 years following initial ChEI.

Using global measures to assess treatment response provided a murky picture, and depended on which global measure was used. Based on the GDS, a relatively small percentage of patients improved on their GDS scores from initial assessment to first renewal in the first 6 months and then the percentage increased somewhat from renewal to renewal over the course of the 2 years; at the same time, the number of indeterminate responders correspondingly decreased and the percentage of negative responders appeared to remain relatively steady across the 2 year period. However, based on the total OPAR scores, the conclusions are slightly different. Initially, a relatively large percentage of patients (similar percentage as the percentage of patients who scored better than expected on the SMMSE) were assessed by their physicians as having improved during the first 6 months, and then this percentage decreased across assessments over the course of 2 years, while the percentage of patients clinically assessed as not having changed overall increased in the first year and then leveled off while the percentage of patients assessed as having deteriorated remained relatively even across time. It is unclear why the conclusions based on the 2 global measures differed, although we note that the OPAR is a different type of measure (it is the clinician’s assessment of the change in the patient over the previous 6 months) and has not been validated as an assessment tool. The total OPAR score is the sum of four different clinical assessments, and as such it does not assess a single dimension (e.g., a total OPAR score of 2 represents several different constellations of patient symptoms).

Patients’ positive or indeterminate cognitive and global responses to the ChEI tended to persist across assessments (Deliverable 1c). Regardless of what response a patient had on an assessment, most patients tended to show an expected (SMMSE), indeterminate (GDS), or no change (total OPAR and cognitive component of the OPAR) response on their next assessment,

¹¹ Reasons for not completing a patient’s SA renewal may include third party payers, Fair PharmaCare, as well as a variety of unknown reasons.

reflecting a kind of “regression to the mean” phenomenon. However, this is expected because with a “good” score on an earlier assessment (e.g., a 25 on the SMMSE) a patient can only score higher by a relatively smaller amount (due to a ceiling effect) and thus is more likely to have a score in the same general range. Furthermore, 3 consecutive improvements on the GDS (with patient scores ranging mostly between 4 and 6) are not even possible in the present context (i.e., a patient would have had to score a 6 initially, then a 5 and then a 4 on the GDS to show a persistence of a positive response across three assessments). Even with these limitations, about a quarter to a third of naïve patients who did not get worse and who remained in the study were clinically assessed as cognitively better than expected compared with the natural disease progression on the SMMSE, cognitive component of the OPAR, and the total OPAR across consecutive assessments. For those patients who did show a worse response or were clinically assessed as worse on a previous visit, large percentages showed either an improvement or at least did not deteriorate further (but it’s likely that those patients who deteriorated on consecutive assessment would have had their ChEIs terminated and thus dropped from the study).

How patients tolerated, or rather stopped, the ChEIs and rates of switching ChEIs (Deliverable 1d) was examined using dispensing data from PNet. These analyses showed that about 18% of all patients stopped taking the ChEI within 2 years of the initial SA, with half of these stopping within the first 6 months (i.e., at what would have been the time of their first renewal). Another 14% of all naïve patients switched the ChEI within 2 years of their initial ChEI approval, again with more than half switching within first 10 months (about 5% of all naïve patients switched within first 5 months, with another 4% switched between 5 and 10 months). Switching among types of ChEIs did not appear to differ across time: Overall, patients initially prescribed donepezil were equally likely to be switched to galantamine as to rivastigmine; those initially given galantamine were slightly more likely to switch to rivastigmine than to donepezil; and those initially prescribed rivastigmine were twice as likely to be switched to donepezil as to galantamine.

Attempts to determine what predicted a positive or negative response to the ChEI were not successful (Deliverables 1e and 2). We examined several versions of predicting a patient’s cognitive or global response 2 years later, based on their earlier assessments, but found earlier cognitive responses did not predict later cognitive response, and only the most recent global response weakly predicted the later global response. These null findings, however, must remain inconclusive because they were based on a very small fraction of the overall dataset (3.1%) after we selected only those patients who had at least 4 SA renewals with each one falling within the “proper” time window at 6-month renewal intervals. In terms of the demographic and clinical variables and how these may predict patients’ cognitive, behavioural, functional, or global responses, we found that only some were weakly associated with improvements in the cognitive and global responses, these influences were observed almost exclusively in the short term (at 6 months). None of these variables showed a consistent response across all outcome measures and across time. In the short term (at 6 months), patients who were younger, male, and had lower baseline SMMSE scores showed a positive cognitive response, and those with non-European ancestry, higher education level, higher Romano scores (co-morbidities), and who were male tended to show a positive global response. In the long term (at 2 years), women

tended to score better than expected on the cognitive measure (SMMSE), and no other variables were related to the cognitive and global outcomes.

In the absence of a control group, determining the effect of ChEIs on mortality was not possible. We did, however, compare the mortality rates for naïve versus non-naïve patients. The mortality rate was slightly lower for naïve patients within the first 6 months of their initial ChEI and appeared to drop over the course of the 2 year period.¹² This finding is somewhat at odds with the naïve patients being on average about 4 years older when they were initially prescribed a ChEI and their age at death was very similar (about 85.5 years old in both groups).^{13,14} Possible explanations may lie in how non-naïve patients were initially prescribed ChEIs and/or how they were diagnosed prior to the ADTI: we noticed that a smaller percentage of naïve patients were diagnosed with AD (without related diseases) compared with non-naïve. Naïve patients were also less severely demented as indicated by lower initial GDS scores (although initial dementia asperity did not appear to have a differential impact on the mortality rates across time) and by higher initial SMMSE scores (and in this case, both naïve and non-naïve patients with higher SMMSE scores tended to die later). If ChEIs are associated with slowing down the progression of cognitive decline (e.g., as assessed on the SMMSE), then potentially patients could live longer; however, to draw such a conclusion would require a randomized control trial.

Over two-thirds of all naïve patients had received at least 1 HCC service over the course of the 2 years since their initial SA.¹⁵ Over time (relative to each patient's initial SA date), the number of patients and the overall number of service episodes decreased, however, the average number of service episodes per patient increased steadily and consistently. Within 2 years of their initial ChEI, about a quarter of naïve patients were placed into residential care or assisted living, with more than a third of these being placed within the first 6 months. These patients were, on average, more demented particularly in the non-naïve group. Patients diagnosed with AD (without related diseases) tended to be placed after 1 year on ChEIs in the naïve group, which occurred later than placement of non-naïve patients. Higher percentages of women, especially in the non-naïve group were placed into RC or AL.

Reference graphs were constructed for the average SMMSE scores over time, for patients in three age cohorts (65-74 years, 75-84 years, and 85+ years old) and 2 levels of dementia asperity, early dementia (initial GDS score of 4), and moderate dementia (GDS score of 5)

¹² With regard to the 3 types of ChEIs, the mortality rate estimates were similar for donepezil and galantamine, for both naïve and non-naïve patients. For rivastigmine, the initial mortality rate (within the first 6 months) was slightly higher than for the other 2 drugs but then dropped to similar rates in the subsequent time intervals.

¹³ In a separate analysis examining the longevity of those who died (since their initial ChEI date), we found that non-naïve patients lived about 2 to 7 months longer (depending on sex and age group) than naïve patients.

¹⁴ This is very similar to the overall average age at death in B.C., which is 80 for men and 84 for women in 2007-2009; Statistics Canada: <http://www.statcan.gc.ca/tables-tableaux/sum-som/101/cst01/health26-eng.htm>.

¹⁵ The analyses of the HCC dataset were fraught with its own challenges. For example, it required the merging of 2 separate datasets, the older CCD and the newer HCCMRR. Issues that arose and were addressed included the different health regions migrating from the CCD to the HCCMRR at different times and the variables of interest and the coding services not matching exactly. Duplication of patients' service coverage was assessed and eliminated when discovered, but some duplication cannot be ruled out.

(Deliverable 4). The graphs showed: (a) as expected, overall lower scores for patients with moderate dementia compared to those with early dementia; (b) no differences between the three age cohorts, (c) slight but noticeable drops in the SMMSE scores over time in each group, (d) large variability in the scores within groups and time intervals (standard deviations ranged from about 4 to 7 points on the SMMSE 30-point scale); and (e) some fluctuation across times intervals, particularly in the group of oldest (85+) patients with moderate dementia. The variability in the scores was also expected. The SMMSE scores are sensitive to many influences, including daily fluctuations of patient factors such as sleep, fatigue, stress level, and so on. Whereas there may be an expectation that such variability would be relatively random across subjects and assessments, and thus cancel out, the relatively small numbers of patients on whose scores these means are based weaken this assumption.

Interestingly, the relative flatness of these graphs over time is consistent with the increasing percentages of positive responders on the SMMSE over time discussed in Deliverable 1. Following Tombaugh and McIntyre (1992), we had accounted for the natural disease progression in the SMMSE scores, as would be expected for patients not taking ChEIs, by defining a change in the SMMSE scores of 0 to -5 points in 6 months and a change between -2 and -10 points in 2 years as an “expected response” (i.e., no better or worse than expected based on the natural progression of the disease). The reference SMMSE graphs developed for Deliverable 4 show that there is about a 2-point average drop in SMMSE scores in 2 years (for all age groups and both early and moderate dementia), and the large variability in the SMMSE scores indicates that there are large numbers of patients who scored above the average as well as below. Patients with SMMSE score differences of -2 or less (i.e., above -2) were classified as positive responders whereas patients with SMMSE score differences of -2 or more (below -2, and up to and including a difference of -10) would be classified as “expected” responders; furthermore, to be classified as a negative responder, the difference in a patient’s SMMSE scores would need to be at least -11. Therefore, the observation that higher proportions of patients responded better than expected over time (in Deliverable 1) is consistent with the slow decrease in the SMMSE means over time in the reference graphs (in Deliverable 4). Together, these findings suggest that patients’ SMMSE scores are decreasing less rapidly over the 2 years than would be expected had they not been taking the ChEI. But as before, this conclusion must remain tentative as these means are based only on those patients who remained in the study and we do not know the impact of the potential bias introduced by patients who dropped out of the study.

In a separate analysis, starting ChEIs increased naïve patients’ SMMSE scores by 1.6 points within the first 6 months. This is consistent with observations in randomized clinical trials (e.g., +0.8 in the AD2000 trial). However, the estimate of the average impact of ChEIs of 1.6 point increase in SMMSE score is small compared to the natural fluctuation between first and second SMMSE measurements in individual patients, where we estimated a standard deviation of ± 3.5 points. In other words, the SMMSE has a high ‘noise-to-signal ratio’: the ‘noise’ from natural fluctuations and measurement error (3.5) is relatively much larger than the ‘signal’ due to the actual average treatment effect (1.6) such that a clinician usually could not know whether an improved score in a patient 6 months later is due to the treatment or natural fluctuation or measurement error. This is a similar dilemma posed by the high fluctuations of blood pressure measurements within individual hypertensive patients across time.

Conclusions

Given the limitations of the data, the conclusions from this study remain tentative. It appears that a substantial proportion of patients who remain on the ChEI and have their SA renewed score better than expected on the cognitive measures (SMMSE, and positively on the cognitive component of the OPAR measure) and to a lesser extent on the behavioural measure, and furthermore the largest proportion of patients experience the positive response within the first 6 months of their initial SA. Assessments of patients on the functional measures (function ADL and IDL) do not appear to be change over time. The 2 global measures (GDS and total OPAR) each provide what may appear as 2 different and somewhat inconsistent pictures of the patient, but these 2 global measures are fundamentally different: The GDS is a single overall score of the patient's level of dementia, whereas the total OPAR score (which has not yet been validated) is the sum of the physician's assessment of the patient's change on 4 different dimensions (in the previous 6 months), and as such the same score on the total OPAR may represent vastly different patterns of responses. The greater benefit on cognitive measures in this study is consistent with some previous research (Loveman, et al., 2006; Rockwood, et al., 2006) but inconsistent with the review of recent studies by the Clinical Evidence Review (2014).

About 18% of patients stopped taking the ChEI within 2 years, and about 14% switched between different ChEIs with more than half of these switching within the first 10 months. The switching showed similar patterns for donepezil and galantamine, but rivastigmine was different which could be due to the introduction of the transdermal patch partway through the study (February 2009).

In comparison with non-naïve patients who had been on the ChEIs prior to the ADTI, it also appears that the naïve ADRD patients lived longer, with the collateral association that they utilize more HCC services (including nursing home placements), particularly in the second year of being on the ChEI. The differences in mortality rates and health services use could be attributable to non-naïve patients having greater cumulative intake of ChEIs in the past, or being at a later stage and severity of illness, or both. More research with a stronger research design is required to establish and explore these associations further.

UTILIZATION AND COST PROJECT (U & C)

Participants and Methods

Data Source

Data from B.C. MoH administrative databases – MSP payment, DAD, and PNet - were used in this project.

Study cohorts

ADRD cohort

This cohort included newly-diagnosed ADRD patients aged 50 and older, based on first in-patient encounter or out-patient physicians' diagnosis of ADRD¹⁶ between January 2001 and December 2011. We excluded patients without continuous provincial MSP enrollment during the pre-study period, those with ADRD diagnosis (including non-physician encounters) or at least 1 dispensing record of ADRD drugs¹⁷, and patients who were enrolled in PharmaCare Plan B or P¹⁸ anytime during an 18 month pre-study period. We also excluded patients with unknown sex. Cohort entry was the date of the first ADRD diagnosis between January 2001 and December 2011. Patients were followed until death, gap in MSP enrollment of 14 days or longer, first enrollment in PharmaCare Plans B or P, or 31 December 2011, whichever came earlier.

Control Cohort

We selected a control cohort of people without ADRD from the general B.C. population enrolled in the provincial MSP roster for the years 2001-2011. We identified all people born in 1961 or before, with known sex and 1 or more eligibility days as the source population. Persons enlisted in the control cohort were selected based on sampling twice. First, we identified all dates of health encounters during the years 2001-2011 based on MSP physician visits or hospital discharge records for the source population. For each year, starting in 2001, we selected a random visit for each person; we exclude patients under 50 years old at the time of the randomly-selected visit and those who were already selected as controls. Using stratified sampling (age/sex for each calendar year) we chose potential controls up to 10 times the number of ADRD patients in the stratum. We excluded people based on the exclusion criteria applied in constructing the ADRD cohort: (i.e., no continuous provincial MSP enrollment

¹⁶ We used the following diagnosis codes based on published validation studies: International Classification of Diseases, version 9, clinical modification (ICD-9-CM) codes 331, 290, 294 and 797 and the parallel ICD-10 codes F00, F01, F02, F03, F05, F06, G30, G31, R54. These codes had a sensitivity of 0.86 and specificity of 0.86, with positive predictive value of 0.78 and negative predictive value of 0.91. Requiring a second diagnosis decreased the sensitivity to 0.77 (Taylor Jr., Fillenbaum, & Ezell, 2002; Taylor Jr., Sloan, & Doraiswamy, 2004).

¹⁷ Donepezil, galantamine, rivastigmine, or memantine

¹⁸ Plan P is PharmaCare Palliative Care Drug Plan (Plan P) and Plan B covers Permanent Residents of Licensed Residential Care Facilities (British Columbia Ministry of Health, 2014); status was assigned based on first dispensing record under these plans.

during the 18-month pre-study period, ADRD diagnosis or drugs during this period and enrollment in PharmaCare Plan B or P anytime during the pre-study period). Cohort entry was the date of a health encounter selected during our first sampling. Patients were followed until death, gap in MSP enrollment of at least 14 days, first enrollment in PharmaCare Plans B or P, first ADRD diagnosis or ADRD drug dispensing, or 31 December 2011, whichever came earlier. People had to be enlisted in the control cohort for at least 30 days during Study 1 period (January 2004-December 2011) to be included in the potential control pool. In order to obtain similar ages in the ADRD and control cohorts, we conducted a second stratified sampling on the potential controls pool¹⁹. In the second sampling, strata were based on year of entry and age (5 categories), and we selected up to 5 times the ADRD patients for each stratum.

ChEI cohorts

Patients aged 50 and older were identified based on first in-patient encounter or out-patient physicians' diagnosis of ADRD²⁰ between January 2001 and December 2011. We excluded patients without continuous provincial MSP enrollment during the 18-month pre-study period, those with ADRD diagnosis or at least one dispensing records of ADRD drugs during this period, and patients who were enrolled in PharmaCare Plan B or P anytime during an 18-month pre-study period. We also excluded patients with unknown sex. Cohort entry was the date of the first ADRD diagnosis.

To increase the specificity of patients included in the cohort we required either hospital discharge diagnosis or a second diagnosis record. That is, all patients with ADRD diagnosis in an in-patients record from acute care facilities were included. From patients who were identified based on an out-patient physician encounter in MSP payment database, only those who had second diagnosis within 90 days (in-patients or out-patient) and no ChEI dispensing before the date of the second diagnosis were included. Patients were followed for 90 days after hospital discharge or second ADRD diagnosis record and were divided into ChEI users and non-users, based on at least 1 ChEI dispensing in this 90-day period.

Study design and statistical analysis

Study 1: The effect of ADTI on U & C

ADRD patients were included in Study 1 if they were enlisted in the ADRD cohort for at least 30 days during the study period (January 2004-December 2011).

The study consisted of a series of analyses conducted using interrupted time series methodology²¹ (Penfold & Zhang, 2013; Wagner, Soumerai, Zhang, & Ross-Degnan, 2002).

¹⁹ The potential controls pool was established after applying all exclusion criteria, including duration of follow-up.

²⁰ The following diagnosis codes were used based on published validation studies: International Classification of Diseases, version 9, clinical modification (ICD-9-CM) codes 331, 290, 294 and 797 and the parallel ICD-10 codes F00, F01, F02, F03, F05, F06, G30, G31, R54.

²¹ Interrupted time series is a before-and-after study design, in which data are collected at multiple instances over time before and after an intervention /interruption. The goal of this design is to test whether the intervention had an

We explored the association between ADTI introduction and multiple costs and utilization outcomes, for drugs, out-patient encounters, and in-patient services in acute care facilities²²:

- Utilization measures were the use of service at least once a month and count measures, i.e., the number of drug days, the number of out-patient encounters, or the length of hospital stay²³.
- Drug cost was defined as total (PharmaCare and not PharmaCare) product cost and indexed to 2014 costs based on B.C. Prescribed Medication Index (Statistics Canada website, 2015).
- Out-patient cost was corrected for increased costs associated with the Complex Care Management Initiative²⁴ and indexed to 2014 prices, based on the B.C. Health Care Services Index (Statistics Canada website, 2015).
- Acute in-patient costs were calculated based on Resource Intensity Weights (RIW)²⁵.
- Direct medical cost was an overall measure of drug, acute in-patients, and out-patient costs, indexed to 2013 prices.

For this study we analyzed data between January 2004 and December 2011, a period during which we identified relative stability of drug costs²⁶. We used generalized estimating equation (GEE) methodology that allowed accounting for the correlation between monthly observations of the same patient. We selected variable distribution that was dependent on the nature of outcome (normal, binomial, or Poisson). We set the interruption to November 1st, 2007, which was approximately the time of ADTI policy's introduction (October 22, 2007). We excluded from all analyses data from the first 6 months following ADTI introduction, to allow for adoption of the new policy.

The analysis consisted of two stages. The first stage estimated the effect of ADTI on ADRD patients using a single time series analysis. The independent variables in the crude model were *month*, *segment*, *month since ADTI*, and *calendar month*. *Month* was the time in months from the start of the study period, *segment* indicated whether month *t* was pre-ADTI (segment=0) or

effect significantly greater than the underlying secular trend (Ramsay, Matowe, Grilli, Grimshaw, & Thomas, 2003).

²² "Extended" level of care data was excluded, since these, in large part, were records referring to stay in long-term care facilities which were attached to acute care facilities.

²³ Length of hospital stay was defined as the number of nights the patients was in hospital.

²⁴ This initiative was launched in April 2007 (British Columbia Ministry of Health website, 2008) and was found in a preliminary analysis to have a major effect on costs, especially of visits in general practitioner offices. We observed large variation in the costs of out-patient services, with increased variation from 2007 and onwards as a result of the Complex Care Payment Management Fee (British Columbia Ministry of Health website, 2008; General Practice Services Committee (GPSC) website, 2009)

²⁵ RIWs are relative values calculated by the Canadian Institute for Health Information based on case mix groups (Canadian Institute for Health Information (CIHI) website, 2014). The MoH assigns dollar estimates for RIWs based mainly on hospital funding and its total number of RIWs. We used a value of CAN \$5500 for 1 RIW that was estimated by the MoH for the fiscal year 2013/2014.

²⁶ Before mid-2003 the provincial drug plan underwent many changes until the introduction of Fair PharmaCare (PharmaCare, British Columbia Ministry of Health website, 2004). This was associated with instability in drug utilization and cost. We also observed a significant decrease in drug cost in 2012, due to Pharmaceutical Services Act: drug pricing regulation and a decrease in pricing of generic drugs (B.C. Laws website, 2012). To allow the reader to compare utilization and cost of different measures, we used the same analytic period for all analyses.

post-ADTI (segment=1), and *calendar month* was an indicator of the calendar month, to correct for seasonality. We were specifically interested in the change in level after ADTI and the change in slope after ADTI. The adjusted model also included multiple clinical and demographic covariates. As a result of a large sample size, multiple data points for analysis for each patient, and subsequent computation challenges, we analyzed a random sample from the ADRD cohort (N=51,843).

In the second stage, we compared the effect of ADTI between ADRD patients and controls. Due to computation challenges, we used a stratified random sample of ADRD patients and similar controls, based on entry year, age, sex and propensity score strata (N=48,732, 50% were ADRD patients). The independent variables in this model included *month*, *segment*, *month since ADTI*, and *calendar month* and also *series* which allowed us to compare ADRD patients with controls, which were B.C. residents without ADRD that had similar characteristics. To test for the effect of ADTI on ADRD patients, compared with controls, we were interested in the difference in the change in level after ADTI between ADRD patients and controls and the difference in the change in slope after ADTI comparing ADRD patients and controls. The adjusted model included the time-dependent variables age, Romano score (Quan, et al., 2005; Romano, Roos, & Jollis, 1993), and income level as well as high dimensional propensity score (HDPS) deciles.

Study 2: The effect of ChEI persistence and switching

This study analyzed community dwelling ADRD patients. Patients in long-term care (LTC) facilities were excluded or censored. Analysis of all ChEI users in B.C., including LTC residents, can be accessed as manuscripts in submission (Fisher, Carney, Bassett, & Chappell, 2015a; Fisher, Carney, Bassett, & Chappell, 2015b).

From a cohort of ChEI new-users constructed in the analyses presented in the manuscripts mentioned above (Fisher, et al., 2015a; Fisher, et al., 2015b), we selected a subset of new-users of ChEI that included in the ADRD cohort, age 50 or older, and started ChEI treatment between the date of ADRD cohort entry and end of follow-up in this cohort. Discontinuation was ascertained based on the earliest drug-free gap of 90 days after exhaustion of dispensed days, allowing at any point stockpiling of no more than 90 days, and adjusting the dispensing date to the end of the previously dispensed days. Patients who switched to another ChEI, added on additional drug, or changed dose were not considered discontinuers. End of ChEI course was set to end of follow-up in the ADRD cohort or end of dispensed days, whichever was earliest. Follow-up and ChEI course were censored when a patient had entered LTC facility or palliative care.

For persistence analysis, we created 3 levels of an event-type variable: discontinuation, death, and censoring. Persistence was measured from first ChEI dispensing date until discontinuation, death, or censoring. We compared 2 groups of ChEI new-users: pre-ADTI initiators were patients who started their ChEI before 1 November 2007 and post-ADTI initiators were those who started later (regardless of ADTI coverage status). Multivariate regression analysis included demographics and proxies for clinical status, AD severity, and the first ChEI. Since

death and discontinuation are mutually exclusive and not independent events²⁷, we treated death as a competing risk. We presented a plot of time to discontinuation or death, crude cumulative incidence for discontinuation²⁸ and the results of Cox regression analysis, accounting for competing risk (Fine & Gray, 1999)²⁹.

For analysis of switching rates, from a cohort of ChEI new-users constructed in the analysis presented in the manuscript mentioned above (Fisher, et al., 2015a) we selected a subset of patients that were included in the ADRD cohort, age 50 or older, and started ChEI treatment between the date of ADRD cohort entry and end of follow-up in this cohort. Follow-up was censored as of the first occurrence of (1) end of follow-up in the ADRD cohort; (2) discontinuation, defined based on the first drug-free gap of 90 days; or (3) 5 years of continuous treatment with an individual ChEI. Switching was defined as the first dispensing of a second ChEI during continuous sequence of dispensing of the first drug. Patients were censored after their first switching event. Patients who added a second ChEI were considered switchers.

We tested for the effect of 2 main independent variables: duration of use and ADTI introduction. Follow-up was divided into 5 analytic periods corresponding to duration of drug use: less than 6 months, 6 to 12 months, year 2, year 3, and years 4-5. Patients contributed follow-up time to each period until they were censored or experienced the study outcome. We compared pre- with post-ADTI initiators, regardless of the time of ADRD diagnosis. We controlled for demographics and clinical status by a propensity score³⁰. We conducted GEE regression analysis with Poisson distribution and autoregressive correlation matrix. By including a variable for the period and interaction terms between duration of drug use and initiation relative to ADTI we were able to individualize the rates for the 5 use periods.

Study 3: The effect of ChEI on mortality

From the ChEI cohorts, we selected patients who were enlisted for at least 181 days between January 2001 and December 2014. The study outcome – death – was determined from the client roster. Since we had access only to month and year of death, we set death date to the 15 of each month. Patients were assigned an event if they died before the end of follow-up and were censored otherwise.

High dimensional propensity scores (HDPS) were calculated to control for confounders of the association between ChEI use and death within 3 years (Herrinton, et al., 2011; Rassen & Schneeweiss, 2012; Schneeweiss, et al., 2009) and asymmetrically trimmed out the study cohort based on the extreme tails. In a preliminary analysis that was conducted using survival analysis methodology, we observed crossing hazards, which reflected the invalidity of the proportional

²⁷ Specifically, discontinuation, as defined in this analysis, was conditional on the patient been alive at least 90 days after the exhaustion of the drug dispensed.

²⁸ We accounted death as competing risk, using SAS CIF macro (Lin, So, & Johnston, 2012). Cumulative incidence is defined as the probability that discontinuation has occurred before a given time.

²⁹ We used method A described by Lunn and McNeil (1995).

³⁰ Due to convergence issues caused by the size of our sample, we calculated propensity scores of post-ADTI initiation compared with pre-ADTI. The predictors included were similar to the independent variables included in the persistence analysis.

hazard assumptions and hence inappropriateness of conduction Cox regression for the full study period. Therefore we presented results by year since diagnosis.

Study 4: The effect of ChEI on LTC entrance

From the ChEI cohorts, we selected patients who were followed up for at least 181 days between January 2001 and December 2014. Patients who died or entered LTC³¹ earlier were excluded. LTC entrance date was determined as the earliest date of a dispensing record with PharmaCare Plan B during the follow-up. Patients were assigned 2 types of events: LTC or death; otherwise, their follow-up was censored.

HDPS were calculated to control for confounders of the association between ChEI use and LTC entrance within 3 years (Herrinton, et al., 2011; Rassen & Schneeweiss, 2012; Schneeweiss, et al., 2009) and asymmetrically trimmed out the study cohort based on the extreme tails. We compared risks of LTC entrance using survival analysis methodology with accounting for death as a competing risk and determined invalidity of the proportional hazard assumptions and hence inappropriateness of conduction Cox regression for the full study period. Therefore we presented results by year since diagnosis.

Study 5: The effect of ChEI on direct medical costs

We used a methodology similar a previous study (Dormuth, et al., 2012) to analyze cost data for January 2004-December 2011. From the ChEI cohorts, we selected only those patients included also in the ADRD cohort (i.e., had costs data during the analytic period). We tested the effect of ChEI use on direct medical costs starting in month 7 after diagnosis. We analyzed 8 quarters: months 7-9 after diagnosis, months 10-11 and so on, until month 30. Costs were selected from MSP, DAD, and PNet databases, indexed to 2013 prices and presented as CAD per day. We excluded quarterly data for patients who were listed less than 30 days during the quarter. We analyzed 2 types of costs: total (publicly and privately funded) and public (publicly funded), and the difference was only in drug costs.

HDPS were calculated to control for confounders of the association between ChEI use and costs higher than median (Herrinton et al., 2011; Rassen & Schneeweiss, 2012; Schneeweiss et al., 2009) and asymmetrically trimmed out the study cohort based on the 5% extreme values (Sturmer, Rothman, Avorn, & Glynn, 2010). We observed skewed distribution of costs with a few patients with extremely high costs. This meant that the average did not represent the population, and was largely influenced by these outliers. Therefore, we conducted analysis using Quantile regression³² (Koenker & Hallock, 2001).

³¹ LTC entrance was defined as first dispensing record under Plan B or admission to acute hospital with level of care “extended”.

³² While linear regression is used to estimate mean change, it presents limitations when analyzing costs data in this study due to skewed data. In Quantile regression we estimated the quantile for different groups and compared them, i.e., the 10th quantile of costs in ChEI users compared with the 10th quantile in non-users. By examining the full range of quantiles (from 5th to 95th) an effect over the whole range of costs can be observed.

Study 6: Perspectives on cost-effectiveness

In another analysis to explore perspectives on cost-effectiveness, over 40 potential interviewees were located who published studies and commentaries, written in English, which expressed perspectives on the value of the ChEIs. Of these we interviewed 22 individuals in Canada, the US, and UK who had no relevant conflicts of interest and were available for a 30 minute telephone interview. Ten questions were used to explore the interviewee's perspectives on effectiveness, safety, and cost-effectiveness of the drugs.

Results

Deliverable 1

What are the utilizations and costs of drugs and health services by patients with Alzheimer's disease (AD) before and after implementation of the ADTI for those with cholinesterase inhibitor (ChEI) coverage and those without?

The primary focus of the U & C is to consider the ADTI program comparing patients with ADRD before and after the ADTI, with a control group of seniors matched by risk factors for ADRD contained in the administrative databases (i.e., propensity score matching).

We designed 2 studies to answer this deliverable. In Study 1 we explored the effect of ADTI on utilization and cost of all ADRD patients, and also in comparison with similar controls. In Study 2 we explored the effect of ADTI policy and coverage on the utilization of ChEI.

Study 1: The effect of ADTI on utilization and cost

The ADRD cohort included in this study was 129,600 patients; a majority of them (67,575) were diagnosed before ADTI. Patients diagnosed after ADTI introduction were older, with lower income, and sicker (Table 10). The control cohort included 424,604 people; the study sample included 48,732 people; half of them ADRD patients. The difference in baseline characteristics between ADRD patients and controls diminished in the study sample compared with the full cohorts (Table 11) as a result of the stratified sampling we applied.

The trends of utilization and cost before and after ADTI in ADRD patients are summarized in Table 12. Since this analysis did not include a comparison group, we were unable to conclude whether any difference we observed was due to ADTI, or to other coinciding factors. In the analyses summarized in Table 13, we used the controls as a baseline to correct for other factors. The assumption was that most changes that occurred over time (policy, clinical practice, prices, etc.) influenced ADRD patients and controls similarly; the ADTI policy, on the other hand, affected only ADRD patients. Table 13 demonstrated that most cases in which we observed a difference in levels of utilization and cost before and after ADTI (Table 12) were probably unrelated to ADTI, because similar differences in levels were seen in controls.

Baseline levels of utilization and cost of multiple services were higher in ADRD patients than controls, despite the study design having selected 'similar' patients (Table 13). For drugs, we

observed an increase in PharmaCare costs in ADRD patients without a change in overall drug cost. Overall drug costs did not change because of a shift from other payers to PharmaCare presumably due to ChEI coverage. We observed no specific effect of ADTI on drugs used for mental symptoms (anxiolytics, antipsychotics, antidepressants, or hypnotics). However, there were different trends in the use of statins between ADRD patients and controls, that could be explained by the possible association between cardiovascular disease or cardiovascular risk factors and AD (de Bruijn & Ikram, 2014; Ferreira, et al., 2014; Firoz, et al., 2015) and the lack of adjustment for cardiovascular diseases in our model.

For out-patient services, we observed a small increase in costs of general practitioners. This finding could reflect the costs associated with ADTI, e.g., the new mental health service fee for GPs a year after the ADTI, or additional visits for SA renewals (British Columbia Ministry of Health website, 2015). In additional analysis we identified 7 fee items relevant to the ADTI:

- a. 97001 ADTI INITIAL COVERAGE
- b. 97002 ADTI 6-MONTH RENEWAL
- c. 97003 ADTI TERMINATION OF COVERAGE
- d. 97004 ADTI PATIENT REFERRAL TO SENIORS' MEDICATION STUDY
- e. 97005 ADTI PATIENTS IN SMS AT 6 MONTHS
- f. 97006 ADTI ASSESSMENT AT 6, 12, 18, AND 24 MONTHS
- g. 97007 ADTI PATIENT STOPS MEDICATION

During 2009-2013, there were 9574 visits with these codes, with a total paid cost of \$178,272

Differences observed in in-patient services in acute care facilities were primarily the result of differences in duration of follow-up. They disappeared when data was limited to the first 60 months since diagnosis. Differences in trend of number of acute hospitalizations between ADRD patients and controls were observed even when data was limited to 60 months of follow-up. While no change was observed over time in controls, we estimated a pre-ADTI decline in hospitalizations in ADRD patients of 0.3% (95% CI: 0.1% to 0.5%) fewer hospitalizations per month, as compared a post-ADTI growth of 0.3% (95% CI: 0.2% to 0.5%) more hospitalizations per month. This observation was not accompanied by a change in average length of stay per month (number of days in hospital), nor average in-patients costs.

In comparing ADRD patients and controls, we observed higher baseline direct medical costs in ADRD patients. Before ADTI, direct medical costs declined in ADRD patients, regardless of the type of costs – total or publicly-funded. No change was observed in controls. No difference was observed in the effect of ADTI on costs for ADRD patients or controls. ADTI introduction was associated with a reduction in overall level of costs but a positive trend in monthly costs in both groups. This finding could be an expression of the limitation of the methodology. By allowing an interruption, and then fitting a slope afterwards, a positive slope afterwards can produce a negative initial level after the interruption point, which is partially an artifact of the fitting procedure. In adjusted analysis, the slope changed from zero to positive (a growth) in controls, and from negative (a decline) to zero (stable level) in ADRD patients in adjusted analysis.

Table 10. Baseline Characteristics - ADRD Patients

Characteristics at cohort entry	ADRD cohort N=129,600	
	Entry before ADTI	Entry after ADTI
Number of patients	67,575	62,025
Follow-up (months) mean \pm SD, median	50.4 \pm 34.0, 50	18.4 \pm 13.7, 16
Age at entry mean \pm SD, median	77.2 \pm 10.6, 79	77.7 \pm 10.7, 80
Female, %	56.3	55.0
Low/medium income level ¹ , %	16.6%	27.5
Heavy users of:		
Drugs (> 9 different drugs), %	29.8	34.6
In-patients services (> 14 days), %	9.2	9.5
Physician visits (> 29), %	39.1	43.8
Specialists visits (> 13), %	29.3	38.4
Higher Romano score ² (> 10), %	0.2	0.2

Notes: ¹ Values were defined based on data from the 3 months preceding cohort entry.

² Quan, et al., 2005; Romano, et al., 1993

Table 11. Baseline Characteristics - ADRD Patients and Controls

Characteristics at cohort entry	Full study cohort N = 554,204		Study sample n=48,732	
	Controls	ADRD patients	Controls	ADRD patients
Number of patients	424,604	129,600	24,366	24,366
Follow-up (months); mean \pm SD, median	53.8 \pm 34.9, 49	35.1 \pm 30.8, 27	49.8 \pm 34.9, 44	43.2 \pm 33.1, 35
Age at entry: mean \pm SD, Median	70.8 \pm 9.2, 71	77.4 \pm 10.7, 79	72.9 \pm 9.6, 72	74.1 \pm 10.1, 76
Female, %	52.6	55.7	56.5	54.5
Low/medium income level, %	22.9	21.4	23.5	22.9
Heavy users of:				
Drugs (> 9 different drugs), %	15.6	32.2	19.2	22.4
In-patients services (> 14 days), %	1.4	9.3	1.4	3.1
Physician visits (> 29), %	13.4	41.4	18.0	23.0
Specialists visits (> 13), %	13.8	33.7	18.0	21.7
Higher Romano score (> 10), %	0.03	0.18	0.03	0.07

Table 12. ADRD Cohort: Association between ADTI on Utilization and Cost

	Measure	Pre-ADTI slope	Level change associated with ADTI	Effect of ADTI on the slope (direction toward)
DRUGS				
	Dispensing events	↑	↑	↓
Cost	Pharmacare cost		↑	
	Total cost	↑	↑ product cost	↑ in drug-related cost
Antipsychotics	Use			↓
	Days		↓	↓
	Drug costs			
Anxiolytics	Use	↓		↑
	Days	↓		↑
Hypnotics	Use			
	Days	↑		
	Drug costs	↑	↓	↑
Antidepressants	Use	↑		
	Days	↑	↓	
	Drug costs	↓	↓	↑
Drugs for incontinence	Use	↑	↓	
	Days	↑	↓	
	Drug costs	↑		
Statins	Use	↑		↓
	Days	↑	↓	↓
	Drug costs	↑	↑	↓
ChEI	Use	↓	↑	↑
	Days	↓	↑	↑
	Drug costs	↓	↑	↑
OUT-PATIENT SERVICES				
Cost	Overall cost	↓	↓	↑
Physician visits	Count			
	Cost of visits	↓	↓	↑
General practitioners	Count	↓	↑	
	Cost of visits	↓	↓	↑
Specialists	Count	↓		↑
	Cost of visits	↓	↓	↑

	Measure	Pre-ADTI slope	Level change associated with ADTI	Effect of ADTI on the slope (direction toward)
Mental diagnoses	Count	↓		↑
Neurological disorders	Count			
IN-PATIENT SERVICES (Table continues on next page)				
Costs	Overall cost	↓		↑ to stable level
Utilization	Hospital stay	↓		↑ to a smaller decline
	Hospital use	↓	↓	↑ to a small growth
Mental diagnoses	Hospital stay			
Neurological disorders	Hospital stay	↓		
Ischemic stroke	Hospital stay			
DIRECT MEDICL COSTS				
	Total costs	↓		↓
	Public costs	↓		↓

Notes: Empty cells=no change
 Shaded cells=no association with ADTI
 Cost - total (PharmaCare and not PharmaCare) product cost
 Count - number of encounters
 Days - number of drugs days that were dispensed for this therapeutic group
 Hospital use - at least 1 discharge from in-patients services
 Hospital stay - the number of nights in hospital
 Use - at least 1 dispensing record of drugs from this group

Table 13. ADRD Patients Compared with Cohort: Association of ADTI with Utilization and Costs of Health Services

	Measure	Baseline level	Pre-ADTI slope in	Post ADTI level change	Effect of ADTI on the slope
DRUGS					
Dispensing events	Dispensing events	↑			
Cost	PharmaCare cost		↑ in drug-related costs	↑	
	Total cost	↑			
Antipsychotics	Use	↑			
	Days	↑			
	Drug costs	↑			↓ ¹

	Measure	Baseline level	Pre-ADTI slope in	Post ADTI level change	Effect of ADTI on the slope
Anxiolytics	Use Days	↑			
Hypnotics	Use Days Drug costs				
Antidepressants	Use Days Drug costs	↑ ↑ ↑			
Statins	Use Days Drug costs	↑		↑ ↑	↓ ↓
OUT-PATIENT SERVICES (Table continues on next page)					
Cost	Overall cost	↑			
Physician visits	Count Cost of visits	↑ ↑			
General practitioners	Count Cost of visits	↑ ↑		↑	
Specialists	Count Cost of visits	↑ ↑	↓ ↓		
Mental diagnoses	Count	↑			
Neurological disorders	Count	↑	↓ ²		
IN-PATIENT SERVICES					
Costs	Overall cost	↑	↓ ³		
Utilization	Hospital stay Hospital use	↑ ↑	↓	↑ ⁴	↑
Mental diagnoses	Hospital stay	↑	↓ ^{2, 5}		↑ ⁶
Neurological disorders	Hospital stay	↑			
Ischemic stroke	Hospital stay				
DIRECT MEDICAL COSTS					
	Total costs	↑	↓		
	Public costs	↑	↓		

General Notes:

All values are in ADRD patients compared with controls

Empty cells=the same as controls
Shaded cells=no association with ADTI
Cost - total (PharmaCare and not PharmaCare) product cost
Count - number of encounters
Days - number of drugs days that were dispensed for this therapeutic group
Hospital use - at least 1 discharge from in-patients services
Hospital stay - the number of nights in hospital
Use - at least 1 dispensing record of drugs from this group

Notes:

- ¹ Small difference with no impact on budget
- ² Decline in ADRD patients compared with no change in controls
- ³ Larger decline in ADRD patients compared with controls
- ⁴ Level gain in ADRD patients compared with no change in controls
- ⁵ Differences disappeared when data were limited to the first 60 months of follow-up
- ⁶ Growth in ADRD patients compared with decline in controls

Study 2: The effect of ChEI persistence and switching

Persistence with ChEI

The final cohort for this analysis included 28,185 patients. Overall 12,639 patients (45%) initiated ChEI before ADTI (pre-ADTI initiators), and a total of 14,580 patients (51.7%) discontinued ChEI during the study period. An additional 2,858 (10.1%) patients died while on the drug. Persistence until discontinuation or death was longer in post-ADTI initiators (Figure 7) with adjusted hazard ratio of 0.869 (95% CI 0.837, 0.903). Estimated crude median persistence in pre-ADTI initiators was 14.8 (95% CI 13.8, 15.7) months and in post-ADTI initiators 23.2 (21.8, 24.4) months.

We observed lower risk for discontinuation in post-ADTI initiators (cumulative incidence plots in Figure 8, and Gray's Test for Equality of Cumulative Incidence Functions p-value <0.0001). Adjusted hazard ratio for ChEI discontinuation, comparing post-ADTI initiators with pre-ADTI initiators, accounting for death as competing risks, was 0.840 (95% CI 0.806, 0.876).

We also tested for the effect of ADTI coverage on discontinuing ChEI, accounting for death as a competing risk. We observed decreased hazard for discontinuation in covered³³ post-ADTI initiators compared with non-covered post-ADTI initiators; adjusted hazard ratio 0.836 (95% CI 0.802, 0.873) and in non-covered post-ADTI initiators compared with pre-ADTI initiators; adjusted hazard ratio 0.891 (0.849, 0.935), respectively. These findings suggested that ChEI coverage was not the only reason why ADTI prolonged persistence. Alternative influences could include patients' selection contributed to education, increase in frequency of visits that had been shown to prolong persistence (Cramer, Scheyer, & Mattson, 1990; Natarajan, Putnam, Yip, & Frail, 2007; Patel, Crismon, Miller, & Johnsrud, 2005), professional development for MDs, and differences in population diagnosed with ADRD before and after ADTI introduction.

³³ Covered initiators were defined as post-ADTI initiators that their first dispensing was flagged for SA.

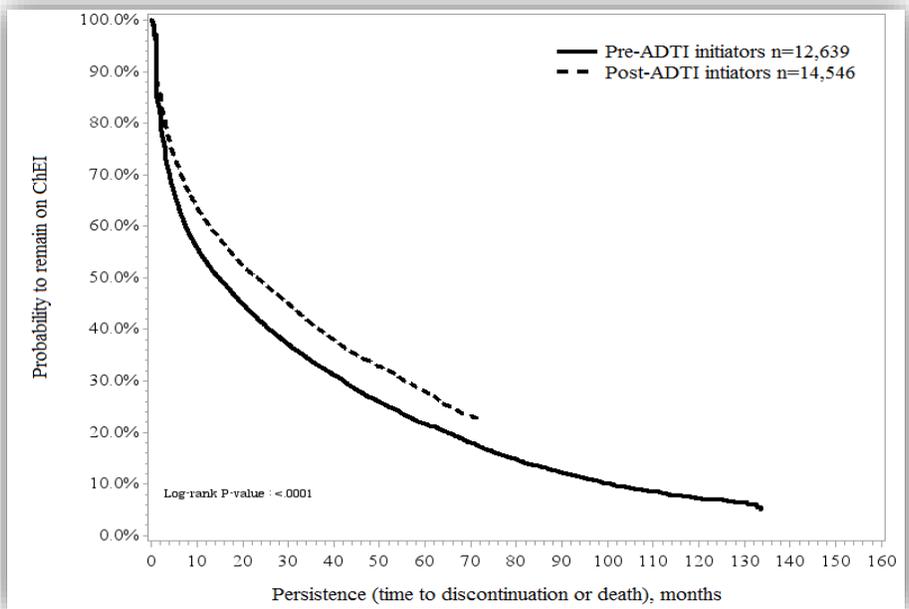


Figure 7. ChEI Users: Time to Discontinuation or Death

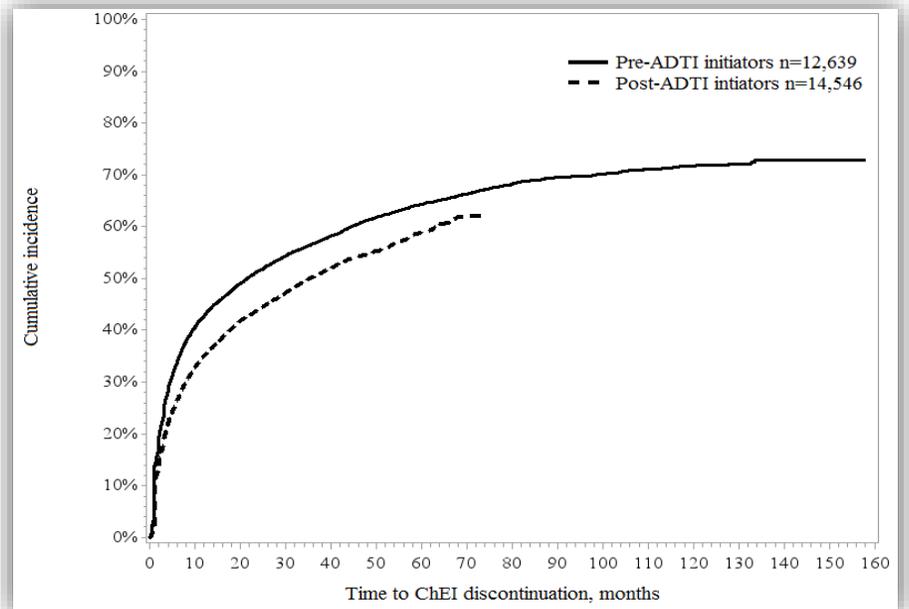


Figure 8. ChEI Discontinuation: Cumulative Incidence Plot

Note: The vertical axis represents the percentages of patients who experienced discontinuation

Switching between ChEIs

The study cohort included 27,572 patients. Number of participants, person-years of follow up, and number of switching events per analytic period are presented in Table 14. We observed significantly higher rates of switching in the first 2 years in post-ADTI initiators (Figure 9). Later the rate ratio became insignificant; however, the number of patients included in later periods became smaller and we could not rule out that these findings were caused by insufficient power to detect a difference.

Table 14. Patients Included in Analysis of Switching Rates

Period (months from treatment initiation)	All participants			Pre-ADTI initiator			Post-ADTI initiator		
	Number of patients	Patient-years	Number of first time switchers	Number of patients	Patient-years	Number of first time switchers	Number of patients	Patient-years	Number of first time switchers
0-6	27,572	10,411	1,413	12,129	4,482	483	15,443	5,929	930
7-12	16,521	7,234	653	6,990	3,053	231	9,531	4,181	422
13-24	12,736	10,101	608	5,360	4,334	242	7,376	5,767	366
25-36	7,826	5,956	279	3,468	2,806	142	4,358	3,150	137
37-60	4,318	5,015	182	2,226	3,004	114	2,092	2,012	68

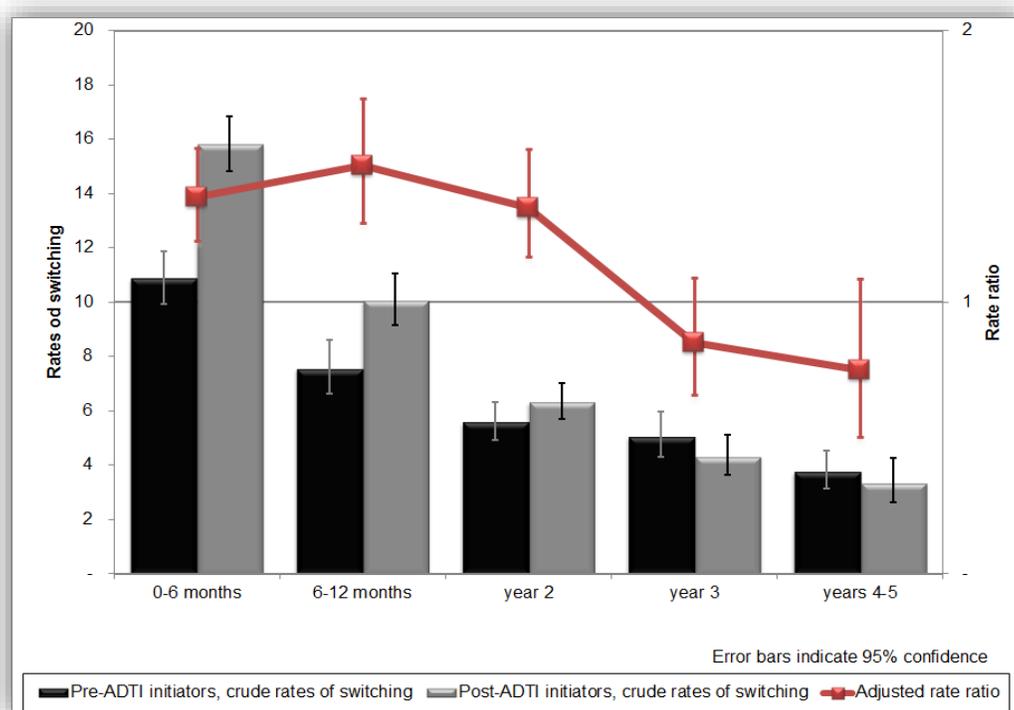


Figure 9. Switching between ChEI Discontinuation: Crude Rates and Adjusted Rate Ratios per Period

Deliverable 2

Is prescribing ChEIs for Alzheimer's disease patients cost effective?

In order to answer this question, we designed 3 studies: studies 3 and 4 examine clinical outcomes (mortality and LTC entrance) and study 5 examines cost outcomes. Study 5 posed challenges due to real world patterns of ChEI use, and incomplete adherence to treatment. Furthermore, early in our analysis we found unstable and contradictory effects of ChEI use (in studies 3 and 4) and therefore questioned the validity of cost-effectiveness estimates based on these data.

Study 3: The effect of ChEI on mortality

The study cohort included 71,635 patients; 7,159 of them were ChEI users (Table 15). Newly-diagnosed ADRD patients who were included in this study were identified between 2001-2011 using a more specific procedure compared with deliverable 1 – either hospital discharge, diagnosis, or 2 recorded diagnoses of ADRD within 3 months. The association between ChEI use and mortality in ADRD patients was dependent on time since diagnosis. We observed crossing hazards in Kaplan Meier survival curve (Figure 10). This finding highlighted the invalidity of the proportional hazard assumption, and therefore Cox regression was inappropriate.

We plotted crude mortality per 100 people at-risk, by quarter since diagnosis, starting in the third quarter in Figure 11. There were different trends for the groups: the risk in ChEI users increased during the first 7 years, after which it started to decline, while the mortality was mostly stable in non-users until the 7th year, after which we observed a decline. Due to computation limitations, adjusted monthly rates were not estimated. When plotting data of a subset of patients with the highest likelihood to be treated, based on HDPS deciles, the differences in pattern of mortality rates became smaller (data not shown).

Last, we calculated crude and adjusted annual hazard ratio for death for patients who were alive and followed each anniversary since first diagnosis (Figure 12). Hazard ratios for year 4, for example, were calculated only for patients who were alive and followed at the beginning of this period. Patients who did not die or censor before the end of year 4 were censored at the end of this period. While ChEI users had longer survival during the first 2 years of follow-up,³⁴ ChEI use was associated with shorter survival in ADRD patients who were alive at the beginning of year 5. We were unable to compare these results to previous research, since no previous study has presented mortality rates in ADRD patients, either ChEI users or non-users, as a function of time since diagnoses. Due to the nature of the data and study design (observational study) the results are inconclusive and warrant additional research.

³⁴ Note that all included patients had to be alive 6 months after diagnosis

Table 15. Baseline Characteristics – Study 3

Characteristics at cohort entry	ChEI users	Non-users
Number of patients	7,159	64,476
Follow-up (months) median	55.1	50.8
Age at entry: mean \pm SD, median	79.6 \pm 7.4, 80	78.3 \pm 10.4, 80
Female, %	59.9	54.9

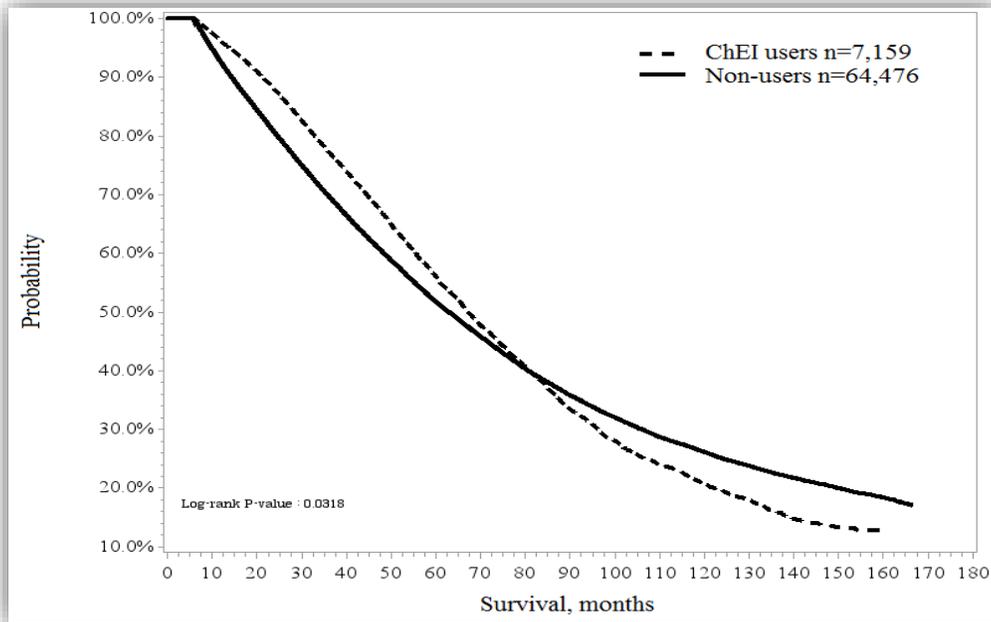


Figure 10. Survival Curve for ChEI Users and Non-users

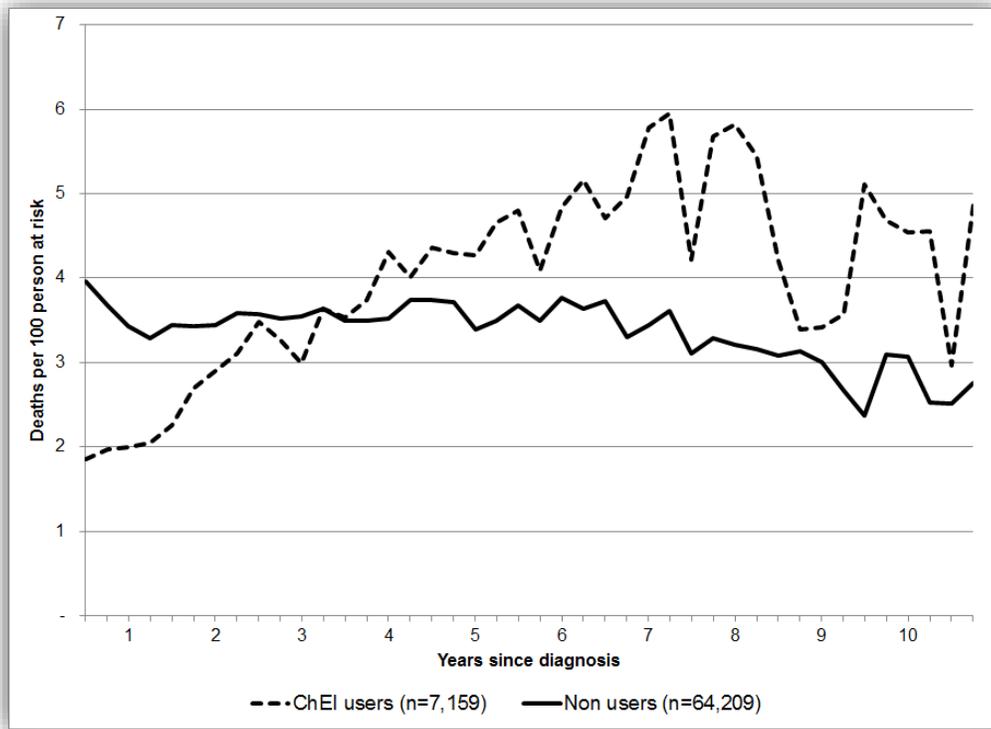


Figure 11. Mortality by Duration of Follow-up

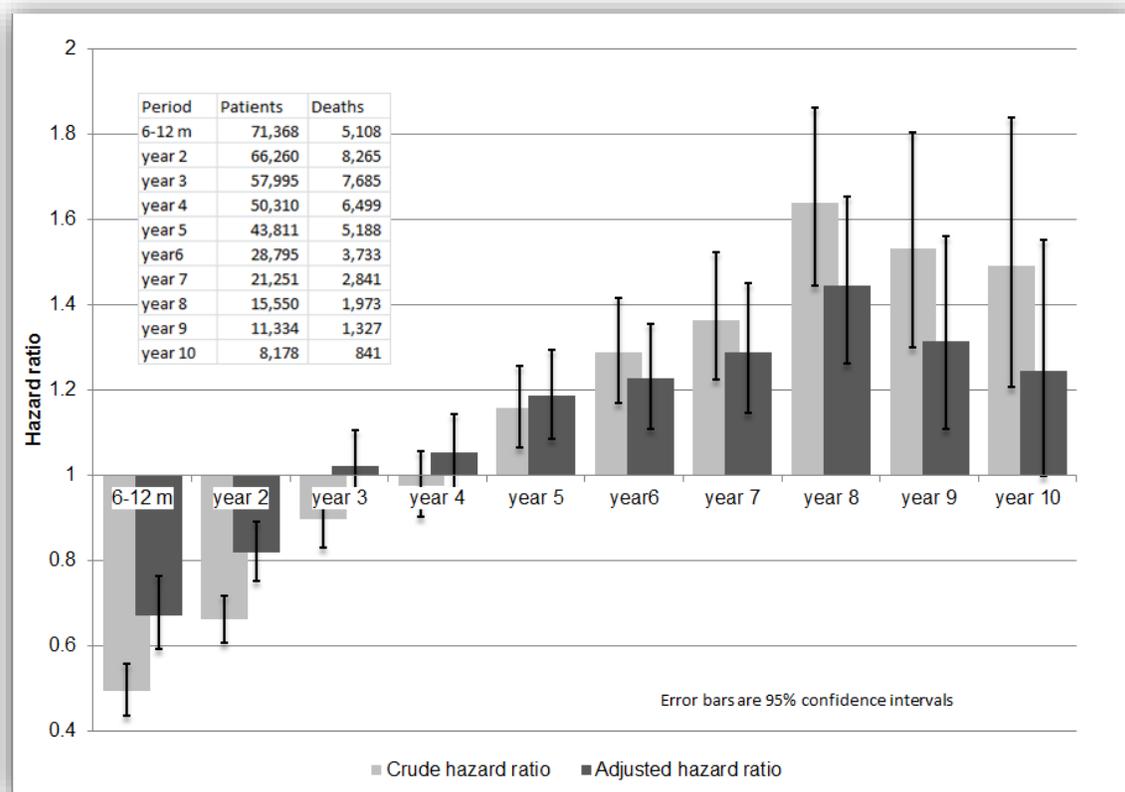


Figure 12. Hazard Ratios for Mortality Comparing ChEI Users and Non-users, by Year since First Diagnosis

Study 4: The effect of ChEI on LTC entrance

The study cohort included 57,521 patients; 4,879 were ChEI users. During follow-up, 16,670 patients entered LTC, and an additional 23,167 patients died before entering LTC. We accounted for death as a competing risk and observed higher incidence of LTC entrance in patients treated with ChEI compared to non-ChEI users (Figure 13).

During the first 3 years following diagnosis, we observed an increase in rates of LTC entrance in the ChEI cohort (Figure 8), similar to the increased mortality rates. It could represent a “last resort” ChEI initiation in patients awaiting LTC. Later the rates decreased, in comparison to continuous increase in mortality rate. LTC entrance rates declined in non-users throughout the follow-up period. When plotting rates for patients who were highly likely to be treated with ChEI, we observed smaller differences between the users groups (data not shown).

Crude and adjusted annual hazard ratio for LTC entrance for patients who were alive and followed each anniversary since first diagnosis revealed that ChEI users had higher hazards of entering long-term care starting the second year following diagnosis (see Figure 15).

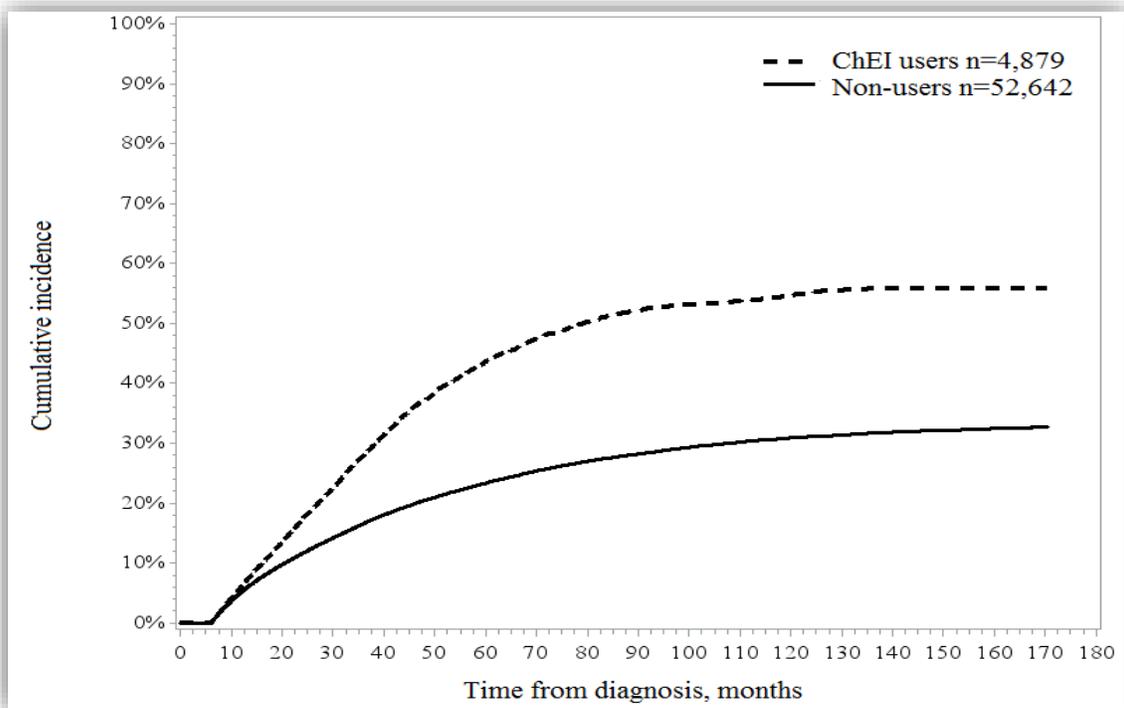


Figure 13. LTC Entrance in ADRD Patients by ChEI Use: Cumulative Incidence Plot

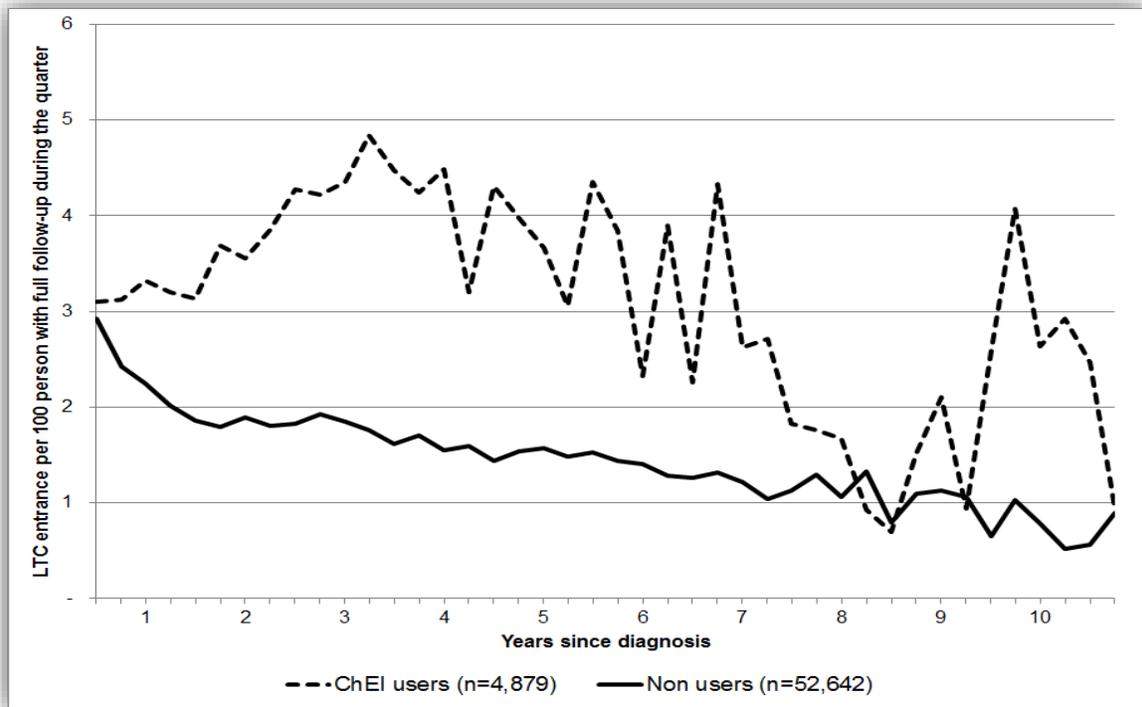


Figure 14. LTC Entrance Rates by Duration of Follow-up

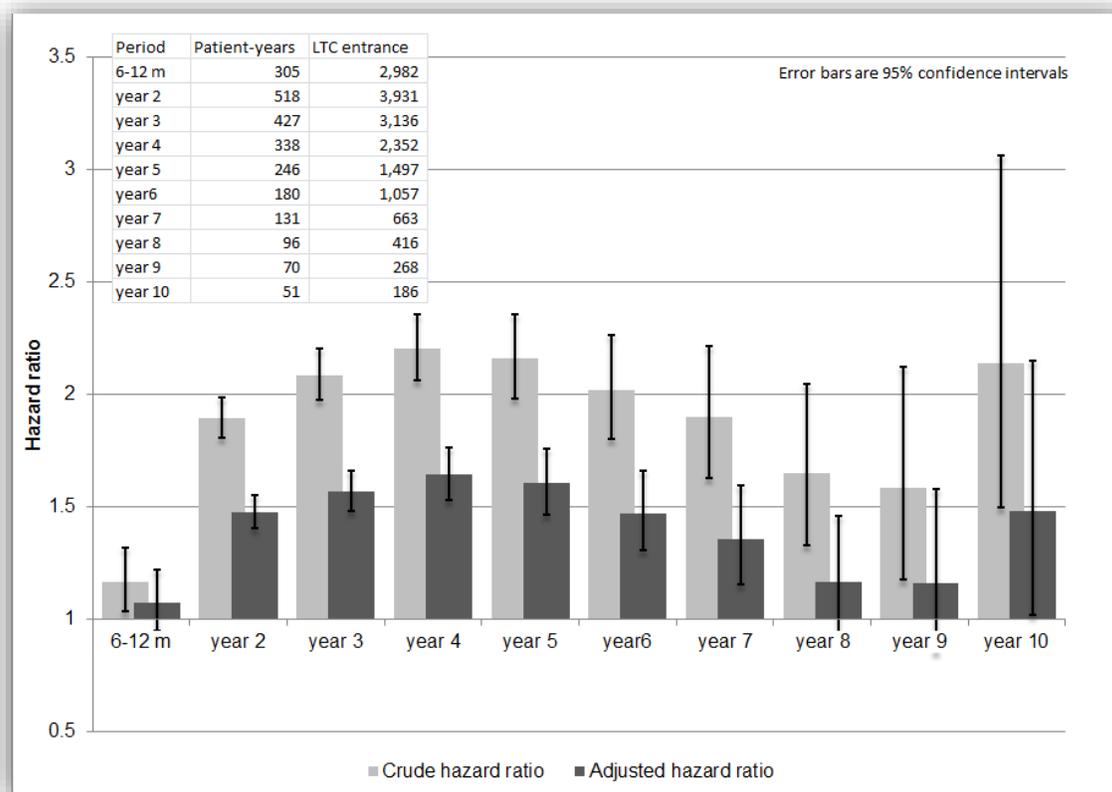


Figure 15. Hazard Ratios for LTC Entrance Comparing ChEI Users and Non-users, by Year since First Diagnosis

Study 5: The effect of ChEI on direct medical costs

The study cohort included 64,154 patients; 6,553 of them were ChEI users. We demonstrated that in patients with low medical costs, the use of ChEI was associated with a subsequent increase in costs, during months 7-30 after the first diagnosis. In patients with high medical costs (85th quantile and above), ChEI use was associated with subsequent decreased costs. An example of the pattern observed is plotted in Figure 16.

The increased costs in ChEI users in the lower quantiles could reflect the cost of ChEIs. The decreased costs in users in the highest quantiles could be an expression of a sicker population who is treated with ChEIs compared with non-users, or the pattern of initiating ChEIs in high users of health services. It could also be an expression of residual confounding or costs associated with adverse effects of the drugs.

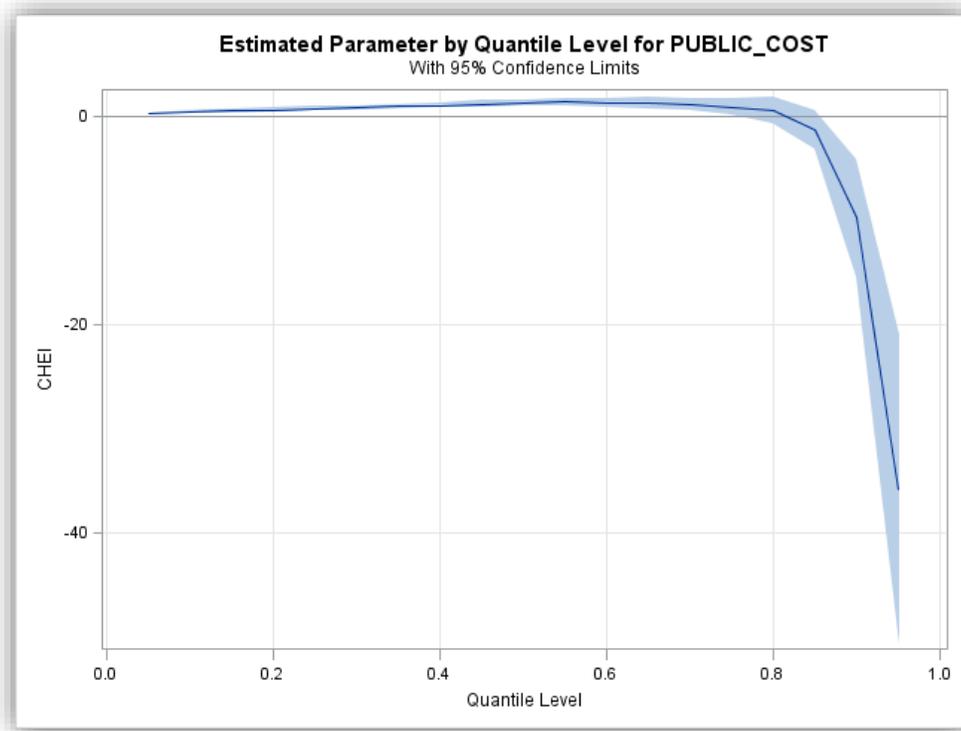


Figure 16. Results of Quantile Regression, Quarter 3, Total Cost

Note: Values on the vertical axis are the difference in dollars per patients per day between ChEI users and non-users and values on the horizontal axis are quantiles of patients in the group. For quantile 0.2, for example, 20% of the patients in the group had costs lower than that cost level. When comparing the value in ChEI users and non-users, users had a value which was significantly (but very small) larger than non-users. By examining the full range of quantiles (from 5th to 95th) we can observe an effect over the whole range of costs. In the middle to right hand of the plot, we estimated differences in middle-low cost patients and observed lower costs in ChEI users (difference > 0). In the right hand of the plot, we estimated differences in high cost patients and observed higher costs in ChEI users (difference < 0).

Study 6: Perspectives on cost-effectiveness

Overall, the 22 interviewees recognized that ChEIs were widely prescribed to delay the worsening of AD symptoms, maintain quality of life, and postpone institutionalization, yet none of the participants believed that there is reliable, quality evidence supporting these outcomes. Most of the interviewees were aware of the array of potential adverse effects related to the ChEIs, including gastrointestinal upset, muscle spasms, leg cramps, syncope, falls, and heart arrhythmia. The interviewees possessed critical and mostly negative perspectives on the value of these drugs; their opinions were classified under three headings: Willing, Reluctant, and Unwilling. Nine of 22 interviewees (40%), deemed “Willing”, were clinicians who often prescribed the drugs. “Reluctants” (4/22, 20%) were those who only reluctantly agreed to a limited trial of ChEIs in a small numbers of patients where they believed using the drug might be rational but where such a decision was not supported by published evidence. The “Unwilling” (9/22), who made up the last 40% of the cohort, were mostly concerned that the drugs’ potential for harm likely exceeded their benefit. Some of those physicians emphasized

that prescribing ChEIs in most patients contradicts the precautionary principle. The majority of these interviewees would favour very limited use and little public funding for ChEIs. Most expressed the opinion that the bulk of public investments in the treatment of AD should go towards quality psycho-social supports, including caregiver education and support, respite care, home care, and appropriate long-term care.

Discussion

U & C Limitations

Deliverable 1

In a preliminary study we observed that different populations were identified as ADRD in the time period before and after ADTI. In the studies reported herein, this was seen as differences in baseline characteristics between patients diagnosed before and after ADTI. That is, post-ADTI patients were older, sicker, and had lower income. Differences between pre- and post-ADTI initiators persisted (i.e., there was ‘residual confounding’ effects) despite statistical adjustments for all recognizable differences between the groups. A HDPS was unable to balance the study groups because the groups were separated over a time period in which multiple changes in coding and data collection occurred, and therefore we discarded the plan to use it in the analysis.

During the analysis, we observed multiple co-interventions and additional events (price change, addition of new drugs) that could have influenced utilization and cost patterns. We adjusted for known events and changes. However, it is likely that additional unknown factors have influenced the study samples over time. To account for some of this the conclusions ignored patterns observed from a single interrupted time-series (ADRD cohort). Instead, we draw conclusions comparing two time-series – ADRD patients versus controls.

As so many patients switched status from covered to non-covered and back, we were unable to incorporate the ChEI coverage status into our models. Instead, we compared the effect of ADTI on ADRD patients (regardless of ChEI coverage status) versus controls in the B.C. population.

We were unable to select historic ADRD controls as planned, considering the requirement to avoid correlation between participants in the 2 cohorts and the available data. Instead, we selected controls that were non-ADRD patients and active (had medical encounters) in the period of study. However, the ADRD cohort was much older than the overall population over 50. To compensate we ran an algorithm to ensure selecting control patients with an appropriate age range. We were unable to use matching due to limitations of the regression method we used³⁵.

³⁵ We were unable to account for 2 levels of clusters: the lowest was observations of the same patient and the higher level was patients within the same matching set (Stoner, Leroux, & Puumala, 2010).

Deliverable 2

In spite of rigorous methodology, due to the nature of the data and study design, it is possible that patients who initiated ChEIs were different from non-ChEI users (i.e., residual confounding). Therefore observed differences, such as the increased hazard of LTC entrance for ChEI users or differences in mortality, could be the result of differences in the user groups and not due to the exposure to ChEIs. Examples may include factors such as the degree of supporting environment (caregiver) or availability of LTC. However, these results signal possible harm associated with ChEI use (mortality after 5 years) and possible added cost (LTC entrance), and therefore further research is warranted. Published RCTs followed patients for a short period of time (up to 1 year), hence were not designed to detect delayed differences in mortality or institutionalization patterns.

In these studies of the effect of ChEIs, adherence to ChEIs was poor with patients repeatedly discontinuing and restarting treatment. Therefore, we defined use based on a single ChEI dispensing. Additionally, we observed inconsistencies in ADTI payment for drugs, with some dispensing covered and others not for the same patient.

Conclusions

ADTI policy was not associated with a change in patterns of health care utilization and cost, except for a shift in costs from other payers to PharmaCare, essentially the cost of covering ChEIs. In addition, a small increase in costs of visits to general practitioners was observed, likely reflecting fees associated with ADTI, e.g., the new mental health service fee for GPs a year after the ADTI, or additional visits for SA renewals. Longer persistence with ChEIs and higher rates of switching between these drugs were observed after ADTI introduction, and these findings were only partially related to drug coverage.

During the first 2 years following diagnosis, ChEI use was associated with longer survival. However, among patients alive at the beginning of the fifth year following diagnosis, ChEI users had a short survival. This adds to the few studies on mortality and ChEI where findings at present are inconsistent; Feldman and colleagues' (2009) review concludes there is no significant increase in mortality (looking only at galantamine) but others have reported increased mortality with ChEI use (Román, et al., 2010; Russ & Morling, 2012; Winblad, 2009). In addition, ChEI users had higher hazards of entering long-term care starting in the second year after diagnosis. In adjusted analysis examining costs of health services, ChEI use was associated with an increase of less than \$1.5 per day among the low-medium cost patients, which probably reflected the costs of ChEIs, but a decrease of up to \$10 per day among the most costly patients. Due to the nature of the data and study design (observational study) the results are inconclusive; causation cannot imputed and additional research is warranted.

In another analysis to explore perspectives on cost-effectiveness, we interviewed 22 individuals in Canada, the US, and UK who had no relevant conflicts of interest. Overall, the interviewees recognized that ChEIs were widely prescribed to delay the worsening of AD symptoms, maintain quality of life, and postpone institutionalization, yet none of the participants believed

that there is reliable, quality evidence supporting these outcomes. Most participants expressed the opinion that the bulk of public investments in the management of AD should go towards quality psycho-social supports, including caregiver education and support, respite care, home care, and appropriate long-term care.

CAREGIVER APPRAISAL STUDY (CAS)

Participants and Methods

While a random sample of caregivers to those with coverage through PharmaCare for their ChEI would have been ideal, this was not an option. Recruitment proved challenging. Ultimately, several methods were implemented including extensive multi-media coverage, appeals to physicians and a variety of seniors' organizations, and PharmaCare phone calls informing the family coverage of the drug was approved, informing them of the study and asking whether they were interested in receiving information or being forwarded to the study phones. The sample, therefore, is not representative.

The most successful strategy was PharmaCare phone calls. Overall 2,327 referrals were received, 1,243 (53%) were eligible, of these 68% came from the PharmaCare phone calls and 23% were referred by physicians. Others referrals came from self and staff.

Eligibility was assessed when the patient had been taking the ChEI for 6 months, to coincide with the time clinicians assess whether the patient should continue, switch, or stop using the drug. Those eligible and consenting to participate, were interviewed (T₁) and interviewed again 1 year later (T₂) when the patient had been taking the drug for 18 months. Those stopping the medication prior to this time were interviewed about their decision to stop. A structured interview schedule was devised after focus groups were conducted with caregivers about their perceptions of the effectiveness of ChEIs. For all except rural and remote areas of the province, interviewers were hired locally and trained; face-to-face interviews were conducted. For more rural and remote areas, interviews were conducted by telephone by the trained interviewers.

Data were collected on: socio-demographic variables (such as age, gender, formal education, and living arrangements of the caregiver and the care recipient); disease characteristics (such as diagnosis, stage of disease, and functioning); ChEI usage (such as length of time taking the drug, type of ChEI, whether they have switched type, or stopped usage); use of formal health care services (which ones); caregiver perceptions of the effects of the ChEI on the care recipient (both good and bad); caregiver perceptions of the effects of the ChEI on themselves as caregivers; health of the caregiver; quality of life, and at T₁, intention to institutionalize and at T₂, whether the care recipient has been institutionalized. (The CAS Technical Analyses Report is available on request.)

The Sample

Of the 1,243 caregivers eligible to participate after Triage, 906 (72.9%) completed T₁ interviews; 751 (60.4%) caregivers consented to use of province data; 689 (55.4%) care recipients consented to use of province data; 759 (83.8%) of T₁ caregivers completed T₂ interviews. On average, interviews lasted 97.26 minutes at T₁, 84 minutes at T₂.

At Triage, caregivers were asked for their perceptions of the impact of ChEIs on the care recipient’s memory, physical health, and mood. On the basis of their responses to these three questions, care recipients can be loosely classified as positive, indeterminate, no effect, or negative responders. How many fall into each category varies depending on its operationalization.

Positive responders:

positive to all 3	n=38	4.2%
positive to at least 1 and no negative responses	n=321	35.4%

Indeterminate responders:

indeterminate to all 3	n=107	11.3%
indeterminate and 1 positive and 1 negative	n=289	31.9%

Negative responders:

negative to all 3	n=19	2.1%
any negative and no	n=216	23.8%

No effect:

no effect to all 3	n=78	8.6%
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That is, if liberal operationalizations are used, approximately a third of caregivers would be classified as caring for positive responders, with fully two thirds indeterminate, no effect, or negative responders. Almost a third of care recipients are indeterminate responders and over a fifth are negative. If indeterminate responders are combined with those perceiving no effect, fully 40% are neither positive nor negative responders. How much of these caregiver perceptions are due to a placebo effect is unknown.

In total 539 or 59.4% were caregivers to naïve care recipients and 284 or 31.3% were caregivers to non-naïve care recipients.

As seen in Table 16, most caregivers are women living with the care recipient; more are wives than husbands or daughters or sons, providing care on average for 24.7 hours/week. Care recipients are split evenly between men and women (50.3% and 49.7% respectively), are overwhelmingly Caucasian (95.5%) with an average age of 79.5 years, and an average household monthly income between \$2,500 and \$2,749/month. They take donepezil (46.3%) or galantamine (32.3%) only for their dementia although 6.1% also take another drug simultaneously.

Table 16. Sample Characteristics, T₁

CG gender: Female	69.3%
CG/CR relationship:	
Wives caring for husband	45.0%
Husbands caring for wives	22.6%
Daughters caring for parent	20.6%
Sons caring for parent	8.1%
CG and CR live together	74.1%
Hours of care per week	24.7 hours
CG average age	68.8 years
CR average age	79.5 years
Average age at diagnosis	76.6 years
CG household income ¹	\$3,250.00 - \$3,499.00/mo.
CR household income ¹	\$2,500.00 - \$2,749.00/mo.
CR gender: Female	49.7%
Ethnicity: Caucasian	95.5%
Diagnosis: % Alzheimer's disease	58.8%
Cholinesterase Inhibitor:	
Donepezil	46.3%
Galantamine	32.3%
ChEI with another drug	6.1%
CR has depression	71.6%
CR uses formal services:	
None	22.3%
One only	26.4%

Note: ¹2010 average household income per month in B.C. \$5,580/month (\$66,700/year).
 Statistics Canada website, 2012 <http://www.statcan.gc.ca/tables-tableaux/sum-som/101/cst01/famil108a-eng.htm>

Just over half (54.1%) of caregivers believe the Fair PharmaCare program has made a financial difference to them personally, either somewhat or more typically 'yes'; more, 70.0% believe the program has made a financial difference to the care recipient. These two are correlated at .65 ($p < .000$), that is, those who believe it has made a difference to themselves also believe it has made a difference to the care recipient.

Results

Deliverable 1

Understanding caregiver assessments of the effectiveness (and lack thereof) of ChEI for patients and for themselves.

Several questions relating to caregivers' assessments of the effectiveness of ChEIs were asked at T₁ and T₂. A summative scale of 8 items ($\alpha = .86$) originally derived from a factor analysis referred to whether ChEIs helped in the following areas: communication skills;

remembering daily activities; doing daily activities; thinking more clearly (reasoning); being intimate in relationships; being settled or calmer; relating more or better with others; and recognizing people. Responses ranged from 0 (did not help in any of the 8 areas) to 8 (helped in all 8 areas) with a mean score of 3.28 at T₁; that is, on average caregivers believed the medications helped in less than half the areas and in all but 2 areas <50% of caregivers believed that ChEIs helped. By T₂, caregivers assessed the medications as helping less in all areas except recognizing people, where more believed the drug helped in this area. We refer to this scale as ‘helped with life’.

Three items not in this scale refer to cognition: slowing disease progression, slowing memory loss, and stabilizing them where they are. The items were summed ($\alpha = .79$); 17.4% said it helped in none of these areas, 33.4% in 1 or 2, and 45.8% in all 3. By T₂, the percent saying it helped in none had risen to 26.3% and it helped in all 3 had dropped to 35.5%.

The same general pattern emerges when asked an open-ended question about the effects of the medications on the patient. When asked to think generally about the physical effects of the medication, good and bad, over half (53.4%) reported no *positive* physical effects while 20.0% report 1; 13.6% 2, 8.6% 3, 3.7% 4 or more. Over half (56.1%) also report no *negative* effects of the medication; 24.6% reported 1, 10.8% reported 2, 4.8% 3, 3.7% 4 or more. (Note: this question was not asked at T₂.)

In addition, caregivers were asked a series of 17 questions in terms of potential problem areas where the care recipient might have improved, stayed the same, or become worse since taking the medication. A factor analysis revealed 2 interpretable factors. The first, labelled *effects on abilities* is comprised of 10 items that, when summed, produce a strong internal consistency coefficient ($\alpha = .89$); the second, labelled *effects on behaviour* is comprised of 9 items and, when summed, has acceptable internal consistency ($\alpha = .74$). The first factor consists of effects on the areas of: supervision generally, mobility, communication, concentration, interest, initiative, repetition, losing things, and instructions. The second factor consists of effects on the areas of: supervision, wandering, waking, demanding, impulsivity, socially inappropriate, denial, and hallucinating. Of a possible high score of 20 and 18 respectively (higher indicating a better effect), the mean for the sample is 6.79 (ranging from 0 to 20) and 6.56 (ranging from 0 to 15) respectively, revealing by and large little perceived improvement in the areas queried. Both means fall well below the mid-point. By 18 months, more caregivers perceive a decline in the effect of the ChEI in all areas with a greater proportion of caregivers saying the care recipient is worse and fewer noticing improvement.

Caregivers were also asked about the effect on themselves as caregivers of the family member taking a ChEI, specifically about the effect of the medication on their relationship with the family member; the effect on the caregiving experience, and the effect on the family member’s ability to relate to them. Most caregivers say it either had no effect (44.2%) or a positive effect (42.3%) on their relationship with the family member; similarly 45.7% say it had no effect and 44.3% say it had a positive effect on the caregiving experience. By T₂, the responses are similar, with somewhat fewer seeing positive effects on the caregiving experience. The responses, however, differ when asked about the effect on the family member’s ability to relate

to them. Here over half, 53.3% see no change at all while fewer, 28.6%, perceive positive changes. By T₂, many more perceive a negative effect (29.6% compared with 7.2% at T₁) and many fewer perceive positive effects (9.9% compared with 28.6% at T₁).

When asked whether the level of assistance required by the family member had changed since taking the medications, caregivers are split between no change (46.5%) and requiring greater assistance (45.2%), with the remainder (8.3%) seeing a decrease in the need for assistance. This question was not asked at T₂.

Caregivers were also asked whether their family member being on ChEI helped their own physical and mental health. Few said it did, more so for mental (13.7%) than for physical health (6.5%). Most said it remained the same, more so in terms of their physical than their mental health. By T₂, considerably more perceived a decline in physical health and considerably fewer believed the care recipient has remained the same; the perception of the effects on mental health changed little.

The data reported here, on caregiver perceptions of ChEIs is more extensive and nuanced than in any previous study. The focus groups prior to the construction of the interview schedule allowed the formulation of extensive areas where the medications might reach, not captured in clinical assessments. The inclusion of open-ended questions ensured caregivers could raise other areas if they believed it important. Overall, the data suggest caregivers see some benefit to ChEI use but it is neither overwhelming nor consistent. How strong these findings are, depends to some extent on whether it is believed 'no change' is a benefit. The areas of greatest improvement relate to the care recipient being calmer and a perceived slowing of disease progression and memory loss; there is little improvement perceived in terms of abilities and behaviour. However, these data cannot comment on the extent to which caregiver perceptions are influenced by a placebo effect. Although placebo effects among caregivers are understudied, some have reported them in the 30% range (Schoenmakers, et al., 2009; Teri, et al., 2000), which would mean there is basically no perceived benefit in these data.

Deliverable 2

Which caregivers (gender, age, ethnicity, etc.) are more likely to identify which type of effect as beneficial?

In order to query whether particular subgroups of caregivers were more or less likely to assess the medications as beneficial, several characteristics of both the caregiver and the care recipient were examined in multiple regression analyses (logistic regressions were used when the dependent variable was a dichotomy). Socio-demographic characteristics of the caregiver included: gender, age, education, marital status, adequacy of income, religion, and distance from the care recipient. Several characteristics of the caregiving were also included: hours/week of caregiving, sum of specific tasks of caregiving, whether the caregiver was able to take breaks when needed, whether the caregiver received help, and their perception of emotional support. In addition, caregiver health was measured by self-rated health and the number of chronic conditions the caregiver had as well as what they had hoped of the medications prior to the care

recipient beginning them. The following care receiver characteristics were examined: gender, age, education, income, has pets, the receipt of formal services, type of dementia, stage of dementia, type of ChEI, whether they had stopped taking ChEI, chronic conditions, ADLs, IADLs, depression, and receipt of emotional support. Multicollinearity was handled by either creating new variables or running those so affected in separate regressions.

The variables noted in the previous section on caregiver perceptions of effects of the medications on the care recipient were the dependent variables.

Few correlates of perceived effectiveness emerge and those that do are not especially strong. That is, among caregivers to those taking a ChEI, no subgroup of caregivers seems to be more or less at risk of identifying positive or negative effects of the drugs.

Only 3 variables are related to whether the medications helped with various *life skills*. Those who hoped it would help in more of the areas, those taking donepezil rather than either of the other 2 ChEIs (galantamine, rivastigmine), and those who are more religious tend to perceive that the drug helped in more life areas. The strongest predictor is what they had hoped for, suggesting support for a strong placebo effect in these data.

Whether the medications helped with *cognition* is related to taking donepezil rather than one of the other ChEIs (galantamine, rivastigmine) and the caregiver's ability to take a break when needed. Taking donepezil is the strongest of the 2 predictors. That is, donepezil is more likely to be perceived beneficial when compared with the other drugs, not in comparison with those not taking any ChEI.

In terms of the *positive* effects of the medications, caregivers who are younger, caring for someone taking donepezil, who had hoped it would help, are more religious, and caring for someone receiving more formal services are more likely to perceive a greater number of benefits.

Of note, little of the variance is explained even by those factors that are statistically significant. Nevertheless, taking donepezil rather than galantamine, or rivastigmine is a significant predictor in 3 instances: helped with life, helped with cognition, and number of positive effects perceived. Specifically, those taking donepezil are more likely to list 2 or more areas in which life was helped rather than none or 1, to perceive that the medication helped for all 3 questions relating to cognition rather than to none, 1 or 2 questions, and to name 2 or more physical effects rather than none or 1.

The factors related to whether the caregiver perceived *negative* effects, the perceived effects on *abilities* of the care recipient, the perceived effects on *behaviours*, perceived *benefits for themselves and their relationship* with the care recipient, perceived *change in the level of assistance required* by the care recipient did not include the type of ChEI being taken (and little

of the variance was explained by the factors that were significant – see the CAS Technical Analyses Report).

That is, these data suggest no subgroups are more or less likely than others to perceive a benefit of ChEI. While taking donepezil is related to three areas of perceived benefit, little of the variance is explained. Why donepezil is related is unknown although Smith and Guerra (2013) and Smith (2013) note the more extensive and comprehensive media campaigns for this medication aimed at both clinicians and families of those with dementia. Again, these data cannot compare those taking ChEIs with those not taking this medication, only those taking one type of ChEI compared with other types of ChEI (limited to donepezil, galantamine, and rivastigmine).

Deliverable 3

Compare caregiver subjective assessments with objective measures of impact.

Objective measures of burden and quality of life included standard valid and reliable measures often used in gerontological research. The short Zarit Burden interview (Bédard, et al., 2001) is a well-established measure of burden, developed specifically for use with caregivers to older adults. In the CAS, $\alpha=.89$. The Rosenberg Self-Esteem scale is similarly long-established in the gerontological literature (Morris Rosenberg Foundation, 2003; Robins, Hendin, & Trzesniewski, 2001). In the CAS, $\alpha=.88$. The Hospital Anxiety and Depression Scale (HAD) consists of both a depression and an anxiety scale (Mykletun, Stordal, & Dahl, 2001; Snaith, 2003). In the CAS, the overall scale $\alpha=.83$. The depression sub-scale has an $\alpha=.71$. The anxiety sub-scale has an $\alpha=.83$.

These 4 measures of quality of life of the caregiver are correlated with the measures noted in the section on caregivers' perceptions of the effectiveness of the ChEI, but differentially. Burden is the narrowest of the concepts, focused on the caregiver role. Perceptions of the drug helping with various areas of *life* and as having *positive* effects for the care recipient are both unrelated to burden. However, caregivers who think that it helped little or not at all with *cognition, abilities, or behaviour* and see more *negative* effects are also more likely to experience more burden.

Each of self-esteem, anxiety, and depression are broader concepts that extend beyond the caregiver role, encompassing potentially all of the caregiver's involvements. Only perceiving whether the ChEI helped with *cognition* was related to caregiver self-esteem; those perceiving less effect, report lower self-esteem. However, perceived effects on cognition is unrelated to either anxiety or depression. Those seeing more *negative* effects on the care recipient and few or no effects on *abilities* or *behaviour* have greater anxiety and more depression. In addition, those perceiving that the drug helped with life and saw more *positive* physical effects are also more anxious, whereas those who thought the drug helped less with life are more depressed; whether they saw positive effects is unrelated to depression.

That is, the caregivers' perceptions of how the ChEI affects the care recipient have little relationship to their own self-esteem. It is related to their levels of anxiety and depression as well as burden, but not strongly. For these 3 outcomes, it is perceiving negative effects, and seeing no or fewer effects on abilities and behaviour that is related to all 3. For helped with life, helped with cognition, and seeing positive effects, the association varies depending on the outcome. In all instances, the relationships are not especially strong, with the strongest being between effects on abilities and burden, explaining only 4% of the variance. That is, caregiver perceptions are somewhat related to the caregiver's quality of life, but not in a major way.

The correlations between perceived effects on the caregiver (rather than the care recipient) reveal that caregivers who think the ChEI has worsened their own physical health and their own mental health experience more burden, lower self-esteem, more anxiety, and more depression. That is, their perceptions of the effects of their family member taking a ChEI on themselves tends to be more related to the outcomes than the effects they think it has on the care recipient, suggesting an emphasis to be included in future research. Furthermore, the variance explained in some instances (but not all) is higher, for example, the relationship between perceived changes in their own mental health correlates $-.34$ with burden and change in level of assistance correlates $.36$ with depression explaining 12% and 13% of the variance respectively, fairly high for 1 factor.

Deliverable 4

Compare caregiver assessments of effectiveness for the patients with clinical assessments made by physicians.

Physician assessments were coded from the SA submitted by physicians to PSD as part of the ADTI. The data are dependent on whether physicians completed the items; not all did so. To assess change after 6 months, the data include only those who had a renewal submitted, as otherwise the SA was not required.

In this sample, using SMMSE scores, about a quarter (24.2%) would be classified as normal at the 6 month assessment with almost half (45.4%) classified as having mild dementia. Another quarter (23.7%) have moderate dementia and very few (.8%) have severe dementia. In this regard, caregivers differ significantly from the clinical assessment with none classifying their family member as normal. However, the interview only asked caregivers whether the doctor considered the patient to be at the mild, moderate, or severe stage of dementia. No question was asked about whether the patient could be considered as not having dementia. Among caregivers, fewer classified the patient as having mild dementia than did physicians (35.8%), while 25.5% classified the patient as having moderate dementia and only a few classified the person as having severe dementia (6.3%). A third (32.4%) said they did not know the stage of dementia of their family member (note: not knowing did not correlate with a normal score on the SMMSE).

Recognizing ADRD as a syndrome, other information on the SA helped explain why these patients were diagnosed with dementia and prescribed a ChEI. Both the OPAR and GDS scores

were examined. At baseline, when coverage was first requested for these patients (i.e., not at 6 months when the caregiver data were collected and coverage was renewed), fewer of the sample were classified as normal on the SMMSE (16.0% vs 24.2% at 6 months). Of the 105 patients classified as normal, all but 2 scored 4 or higher (early dementia) on the GDS (98.1% of those classified as ‘normals’ on the SMMSE), with 5 patients scoring 6 (moderately severe dementia). That is, physicians in this instance seem to weight the GDS score for their diagnosis, despite the instructions on the SA: “INITIAL ELIGIBILITY CRITERIA: Diagnosis of Alzheimer’s Disease with SMMSE of ≥ 10 to ≤ 26 and Global Deterioration Scale ≥ 4 to ≤ 6 ”.

Returning to 6 month data, t-tests compared assessments by physicians and by caregivers (caregivers who answered ‘do not know’ to the question concerning stage of dementia were omitted from these analyses as were physicians who scored the patient as normal on the SMMSE, unless otherwise specified). Overall, caregivers assess care recipient stage of disease much more severely than do physicians. However, physicians and caregivers do not differ when asked the extent of change in the patient after taking the ChEI for 6 months, i.e., whether the patient is worse, the same (or unsure), or has improved, nor in terms of GDS stage.

What about the effectiveness of the ChEI? Physicians noted whether the drug helped the patient or not in terms of memory, reasoning, and perception at 1st renewal. They were less likely to say the drug had helped the patient in these areas than caregivers were when asked about helping with memory, remembering, and reasoning. Contrarily, when physicians noted whether the patient’s concentration, losing things, and following instructions had become worse, there was no change or it had improved at 1st renewal, they were more likely to fall between the same and improved whereas caregivers were more likely to say between worse and no change when asked specifically in terms of concentration, especially in terms of losing things, or in terms of following instructions. Regarding the overall assessment of whether the ChEI helped, caregivers were more likely to say it did than physicians. There was no difference between the 2 groups when asked about change in mood or change in ability.

Perhaps more than anything, these data point to the importance of collecting data with more than 1 measure and that measurement counts; depending on what is asked, the answer can vary. This is not surprising given that ADRD is a syndrome, presenting differently in different individuals. It is also clear, at least within these data, physicians and caregivers often do not agree on their assessments of the effects of the ChEI.

Deliverable 5

Identify predictors of intention to institutionalize.

At the 6 month interview, caregivers were asked about their intention to institutionalize the care recipient. One year later, they were asked whether the family member had in fact been institutionalized. At T₁, a third of the sample (34.6%) said they had considered placement in a nursing home; most (65.4%) had not. By T₂, less than a quarter (22.2%) had been institutionalized, 71.8% remained in the community, and 6.1% had passed away. More of those who intended to institutionalize at T₁ had done so by T₂ (30.3% compared with 5.1%).

Several independent variables were entered into a logistic regression analyses to determine the predictors of intent to institutionalize. They included the following caregiver variables: gender; marital status; living arrangements; monthly household income; perceived income; age; education; who is cared for (spouse or parent); hours per week of care; help received from others; whether they need family to be more involved; whether they believe the care recipient would be better off in a nursing home; loneliness; feeling appreciated; fears of disease progression; self-esteem; pleasure derived from caregiving; whether they can take a break when needed; perceived health; number of chronic conditions; anxiety; depression; receipt of emotional support from others; expressive support from others; assessment of prior relationship with care recipient; whether the ChEI effected the caregiving experience; and burden. The following care recipient variables were included: age; gender; education; age at diagnosis; AD or other type of dementia; type of ChEI; whether the medication helped with: life, cognition, behaviour, or physically; number of positive effects; number of negative effects; effect on abilities; effect on behaviour; ADLs, IADLs; number of chronic conditions; formal services received; and agitation.

A limited number of variables were significantly correlated with intention to institutionalize. Caring for a parent rather than a spouse or other family member, feeling a need for family to help more, more burden, caring for someone with more functional disability, and receiving more formal services correlated with *intention* to place the care recipient. Taking one type of ChEI rather than another was not correlated.

Only those participants interviewed at both time periods are included in the analyses of T₁ predictors of *placement* at T₂. In addition to those independent variables noted above, caregivers were also asked several questions about what they took into consideration in making their decision. These variables were also examined as potential predictors of T₂ placement. The ChEI the care recipient is taking was not significant. T₁ predictors were: they intended to place; if the care is provided by an adult child rather than a spouse; if the care recipient has worse functioning in terms of basic ADLs; if the caregiver says they do not take their own physical health or the care recipient's aggressive behaviour into consideration in deciding to place the family member; and if the caregiver says they take their own exhaustion into account then the family member is more likely to be placed by T₂. That is, the condition of both the care recipient and the caregiver are considered in the decision to institutionalize. Intention to institutionalize at T₁ is the strongest predictor of actual institutionalization at T₂. Fully 94.9% of those not intending to place the care recipient did not do so, while only 5.1% did. Of those intending to institutionalize, 69.7% had done so by 1 year later while 30.3% had not.

Because the overwhelming proportion of caregivers did not institutionalize the care recipient by T₂, and the results noted above can be influenced by the majority who did not do so, a random sample of 171 of those who did not place was drawn and compared with those who did place the patient (n=339). In this case, if the caregiver is an adult child, feels alone and isolated, the care recipient has worse functioning in terms of basic ADLs, and intent to place are the significant predictors, similar to the analyses noted above (Chappell, 2014). In no instance did the type of ChEI taken emerge as significant.

Deliverable 6

Why are these drugs terminated?

In total, 65 care recipients stopped taking a ChEI by T₂. The largest category of stoppers were being cared for by their wives (44.6%), followed by those cared for by their daughters (26.2%), then husbands (20.0%), and sons (7.7%). That is, not surprisingly, most caregivers were female (72.3%) but only half (53.7%) of care recipients were female (44.6% were husbands, 20.0% wives, 30.8% mothers, 3.1% fathers, and 1.5% other). Those they were caring for suffered from mild (24.6%), moderate (33.8%), and severe (15.4%) dementia. Most had taken donepezil (66.2%), many galantamine (43.1%), and fewer rivastigmine (26.6%). On average, these caregivers were providing 24.94 hours of care per week.

When asked why the family member stopped taking the ChEI, 60.0% said it was because of negative side effects of the ChEI. Under a third (27.0%) said because it was not working. Caregivers were also asked who made the decision to stop taking the ChEI; 26.3% said it was the family, 28.2% said it was the family and physician together, and 45.6% said it was the physician. At the time of the interview, the average length of time since the family member had stopped taking the medication was 17.3 weeks with a range of 1 to 52 weeks. Before stopping, family members had been taking the medication for an average of 51.6 weeks with a range of 1 to 676 weeks.

To determine whether we could identify who was most likely to stop drug use, a random sample of 100 was drawn from the T₁ caregivers to those who had continued taking the drug and compared with this sample of stoppers. A comparison of the ChEI taken previously by the stoppers and currently by the continuers revealed no differences by drug taken. T-tests revealed the strongest ($p < .000$) bivariate correlations were all with caregivers' beliefs concerning whether the ChEIs were beneficial to care recipients. When caregivers believed the drug was helping, the care recipient was more likely to continue on the drug than to stop taking it. The data do not address whether the drugs are benefitting the care recipient, only the caregivers' perceptions. That is, these data cannot rule out a placebo effect.

In addition, the PSD within the MoH identified all patients who had received SA for ChEI but who had not been renewed (note they may have continued taking the drug but it was without SA coverage). All those known to be deceased were removed from the records. All others were sent a letter in early 2012 requesting a return by June 2012, asking them to fill out a 1-page survey listing a number of possible reasons for stopping use of the drug. They could check as many as applied. Of 6,555 letters mailed, 1,578 (24.1%) were returned of which 54.8% or 865 had stopped taking the ChEI (34.5% were still taking it, 5.9% did not know, 2.3% were deceased, and 2.4% had never filled the prescription). Among those who had stopped the medication, 37.1% said they could not tolerate the side effects, 36.2% said it did not improve their day-to-day life, 35.5% said the physician said it was not helping them anymore, 24.6% said it was no longer working. Other categories that were checked were done so by no more than 5.7% of respondents.

Conclusions

The CAS was initiated to learn about family caregivers' perceptions of ChEIs. Because it was not possible to recruit a random sample, nor a comparison group of caregivers to those with dementia but not taking ChEI or taking a sugar pill, the findings cannot be generalized nor can inferences be made about how caregivers to persons taking these drugs differ from those not taking ChEI. That means the placebo effect of taking ChEI cannot be determined. Nevertheless, this is the most comprehensive study of caregivers' assessment of ChEI conducted to date.

The multiple areas explored suggest that some families see some benefit but it is neither overwhelming nor consistent. This is consistent with existing studies in the area Franchi, et al., 2013; Huizing, et al., 2006). The greatest effect was perceived in terms of the patient being calmer and a slowing of disease progression with little improvement in abilities or behaviour. Especially if a 30% placebo effect is assumed, then the effectiveness is underwhelming. In addition, as noted in Smith and colleagues (2011), we do not know if any perceived effect is due to greater attention from the caregiver due to taking these drugs or to the drug itself.

The data were unsuccessful in isolating a particular type or groups of caregivers who are more likely to perceive a benefit. Where type of ChEI taken was significant, it was those caring for persons taking donepezil who were more likely to perceive a benefit. However, this explained little of the variance. Whether this is due to a real effect of donepezil or a greater placebo effect due to the marketing of this ChEI cannot be determined with these data (e.g., hand-outs provided to physicians for caregivers, advertising).

Of the several areas of potential effect, only a few were related to caregiver quality of life, and were differentially and not strongly related depending on whether burden, self-esteem, anxiety, or depression was examined. Stronger relationships were evident when examining the perceived effects on the *caregiver's* mental and physical health and a perceived change in level of assistance required rather than perceived effects on the patient.

These analyses point to the importance of multiple measures in this area and of not generalizing from one measure to other areas. They do not provide strong evidence in support of ChEIs but rather support the weak evidence in the clinical literature that for some patients, ChEIs may have a mild benefit.

While caregiver and physician understandings of the stage of dementia of the care recipient are correlated, they also differ quite dramatically. A quarter of physicians score patients normal on the SMMSE while almost of third of caregivers do not know the stage of dementia of the family member. Importantly, almost all of those scoring normal on the SMMSE score poorly on the GDS. At 6 months, physicians were less likely to say the drug had helped the patient when asked about helping with memory, remembering, and reasoning. Contrarily, physicians were more likely to fall between the same and improved in terms of the patient's concentration, losing things, and following instructions whereas caregivers were more likely to say between worse and no change when asked specifically in terms of concentration, especially in terms of

losing things, or in terms of following instructions. Regarding the overall assessment of whether the ChEI helped, caregivers were more likely to say it did than physicians. There was no difference between the two groups when asked about change in mood or change in ability.

Once again, measurement matters. Overall, physicians and caregivers often disagree on their assessment of the effectiveness of ChEIs, confirming existing studies (Rockwood, et al., 2007; Rockwood, et al., 2006; Sinforiani, et al., 2010).

Which ChEI the patient takes does not predict whether the caregiver intends to place the family member nor does it predict whether the patient is institutionalized 1 year after the 6 month assessment. Intention to place at 6 months is the strongest predictor of actual placement 1 year later. These data cannot speak to whether taking a ChEI delays institutionalization compared to not taking one.

The type of ChEI taken was not related to whether the patient stopped taking the drug. The strongest correlates of stopping related to caregivers' beliefs about whether the drug was helping.

These findings provide new insights into caregiver perceptions. They do not provide evidence in support of coverage of these drugs.

Note: From the beginning of the ADTI, it was agreed the researchers would try to leverage the studies to produce additional findings whether from within the ADTI data or through new funding for related studies. The CAS Technical Analyses Report elaborates on this additional work related to the CAS.

GAPS AND FUTURE DIRECTIONS

Despite the uniqueness of the ADTI and the knowledge gained from its studies, much remains to be accomplished.

Three of the studies did not include a comparison of non-ChEI users. The SMS did not have a control group to compare changes in cognition, behaviour, or function as they pertain to drug status (on ChEI or not on ChEI). All of the patients and their caregivers knew they were on the drug, so drug effect due to placebo or real efficacy (or lack thereof) could not be measured. Clin Epi, constructed around the SA, similarly included only patients prescribed ChEI. This was also the case for the CAS. No comparison group of caregivers caring for persons with dementia but not taking ChEI or those taking a ‘sugar pill’ could be obtained so caregiver perceptions of drug effects could have been due to a placebo effect.

None of the studies included alternative treatment strategies, either pharmacological or non-pharmacological. The absence of comparison to pharmacological strategies, with the inclusion of either biological or neurobiological data (such as blood samples or brain imaging, apolipoprotein E genotype, cerebrospinal fluid biomarkers and medical imaging), limits the ability to comment on physiological changes related to ADRD that may influence the variability among the measures reported across cognition, behaviour, and function. Including these data, however, would increase the cost considerably. Furthermore, the absence of comparison to non-pharmacological treatments means that even if or where ChEI are effective, whether they are more effective than other treatments cannot be determined.

An ideal design would be a large randomized trial that includes patients who are new to ChEI therapeutics and enrolled from general practice, specialist, and memory clinics. The comparator trial would have 3 study arms and be sufficiently powered to assess treatment effect of ChEIs for ADRD including: continue the same ChEI; stop the ChEI altogether; and no ChEI treatment (adding a 4th arm of those on a placebo would be ideal). Although preferable, a RCT was not implemented in the ADTI because physicians refused to comply in part because ChEIs were already available publicly. For the RCT to work, people must not be able to obtain the treatment any other way than be in a RCT. If a drug is available, people with a terminal disease will try to obtain it regardless of evidence to support its use or not. To enable RCT evidence, the MoH and regulatory bodies must not approve the drug until all the evidence has been gathered. Once a drug is approved, research is basically restricted to epidemiological type evidence.

After a drug has been approved, and in the absence of evidence that it is beneficial, there is an option of a Reduction in Coverage with Evidence Development using the ‘designed delay’ method previously used by PharmaCare in a restriction of coverage of respiratory medications in 1999. In this instance, impact could be measured by delaying the policy change in some areas and comparing patients’ rates of entry into long-term care between areas. The areas where the change was implemented immediately and those where there was a delay would have to be comparable for valid comparisons.

Incorporating comparisons with non-pharmacological treatments in either of these designs is highly desirable. Without it, even where a drug is found beneficial, one does not know whether an alternative treatment is more beneficial.

Finding a way to maintain data collection after stoppage of ChEI is important. Data over the long-term is important (more than 10 years).

Further evaluation of the OPAR is warranted along with future consideration of more robust measures for function and behavior.

Additional study of mortality in relation to ChEI use is warranted, particularly over the long term (well over 2 years).

Exploration of how the SA can be used to complement and assist chronic disease care provision in B.C. rather than being viewed as burdensome by some physicians is warranted.

There is some evidence that the ADTI program overall improved dementia care in the province. Efforts should be made to maintain these gains.

POLICY RELEVANCE

The ADTI provides insufficient evidence to support of coverage for ChEIs.

The **Seniors' Medication Study** (SMS) revealed Standardized Mini-mental State Examination (SMMSE) scores submitted by physicians on Special Authority forms (SA) correlated quite well (~0.65) with the Clock-Drawing Test (CDT) and Telephone Interview for Cognitive Status (TICS), similar to correlations for the reliability of blood pressure measurements. Physicians did participate, with adequate incentives. A positive effect was noted for some but the data did not reveal who these were. These subjects did relatively well, likely due to the fact that they were better cared for, received more attention, etc. due to the small nature of the study and regular contact. The sample though refers to a select non-representative group taking cholinesterase inhibitors (ChEI).

The **Clinical Epidemiology Project** (Clin Epi) showed SMMSE scores and other cognitive function measures fluctuated considerably between enrolment and first SA renewal, even among 'non-naïve' patients. After various adjustments, the average change in SMMSE score among naïve patients (new to ChEI), by 6 months was +1.6 points, consistent with observations in randomized clinical trials (e.g., +0.8 in the AD2000 trial). This average change is small compared to the natural fluctuation between first and second SMMSE in individual patients (standard deviation of ± 3.5 points; 95% of fluctuations falling within ± 7 points). SMMSE response could not be predicted from available data nor were there differences in outcomes for different types of ChEIs. There was indirect evidence that a drop in SA-measured cognitive function was associated with early stopping of ChEIs. These findings are limited by lack of a valid comparison group, large loss to follow-up (approximately 40%), and the many 'stoppers' (no longer covered) still taking the medication (30%), were problematic.

The **Utilization and Cost Project** (U & C) revealed no change in trends of utilization or costs of health services after ADTI introduction, except for a shift in drug costs to PharmaCare from other payers, and a small increase in costs of services by general practitioners (\$3.70/patient). Direct comparisons of ChEI users with non-users, among patients with Alzheimer's disease and related dementias (ADRD) demonstrated increased costs of health services in patients with low-moderate costs (up to \$1.50/day) but decreased costs in those with heavy costs (up to \$10/day). ChEI users had longer survival in the first 2 years, then similar survival, dropping to shorter survival in patients alive at the beginning of the 5th years since diagnosis. When examining monthly trends, ChEI use was associated with a growth in mortality rates from month to month during the 7 years following diagnosis compared with a slow decline in non-users. ChEI use was associated with increased long-term care entrance compared to non-use. Due to the nature of the data and the observational study design, the results are inconclusive; causation cannot be imputed. They are suggestive only; additional research is warranted.

The **Caregiver Appraisal Study** (CAS) is the most comprehensive study of caregiver perceptions of the effects of ChEIs. The multiple areas explored suggest that some families see some benefit but it is neither overwhelming nor consistent. If a placebo effect is assumed, the

perceived effectiveness is underwhelming. Caregivers' appraisals of patients' improvement or deterioration did not correlate well with clinicians' assessments on Special Authority forms (SA).

Measurement matters, both the Clin Epi and the CAS demonstrate the tremendous importance of measuring different aspects of this syndrome and that findings vary depending on the measurement used.

Both the Clin Epi and the SMS accounted for disease progression in their computation of response using the SMMSE. Therefore, indeterminate should not be interpreted as a positive effect of the ChEI on the argument that the disease progresses naturally (i.e., within these data indeterminate responses do not indicate stabilization). Only positive responders can be interpreted as a desirable response to the ChEI.

RECOMMENDATIONS

In establishing the ADTI, the Ministry of Health (MoH) was informed by international experience of Coverage with Evidence Development (CED), also known as Access with Evidence Development. When evidence is absent or ambiguous, CED takes the stance that ‘benefit of the doubt’ should be neither wholly on the side of the funder (saving funds until the evidence from elsewhere is solidly in favour of coverage) nor wholly on the side of the recipient (receiving coverage until the evidence from elsewhere is solidly against coverage). CED involves sharing the ‘benefit of the doubt’ while producing evidence to reduce the doubt. Under objections from clinicians that a randomized controlled trial (RCT) would be unethical because it would withhold the medications that were considered standard practice at the time from some individuals, the ADTI proceed without this design. Given the experience and analyses of the ADTI, it appears that a randomized policy trial would have been ethical. If the MoH decides to curtail coverage of cholinesterase inhibitors (ChEIs), it would be ethical to do a Reduction in Coverage with Evidence Development using the ‘designed delay’ method previously used by PharmaCare in a restriction of coverage of respiratory medications in 1999. In this instance, impact could be measured by delaying the policy change in some areas and comparing patients’ rates of entry into long-term care between comparable areas.

If coverage of ChEIs were to remain in place, it is strongly recommended that the Special Authority forms (SA) be maintained in order to obtain valuable data and patient follow-up on a difficult category of patients but that it be modified:

- delete patient signature
- delete optional information
- delete requirement that a patient achieve specific scores on both the SMMSE and the GDS
- add the MOCA (best for relatively mildly impaired) or include it as an alternative to the SMMSE (better for moderate impairment) with the choice of which to use left to the physician
- add measures of function and behaviour
- renewals be stipulated as required between 3 and 12 months
- establish an ongoing evaluation process for the SA
- add a brief questionnaire for the caregiver to complete about their perceptions of the ChEI, to be discussed with the physician.

If coverage is changed, evaluate it.

The scope of the ADTI did not include non-pharmacological treatments (such as caregiver education and support, respite care, home care, appropriate long term care, exercise, art, music, and social engagement), yet these alternatives need to be taken into account in decisions concerning the allocation of resources.

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APPENDIX 1: SPECIAL AUTHORITY FORMS (INITIAL AND RENEWAL)



**SPECIAL AUTHORITY REQUEST
CHOLINESTERASE INHIBITORS
INITIAL COVERAGE (6 MONTHS)
ALZHEIMER'S DRUG THERAPY INITIATIVE**

Fax requests to 1 800 609-4884 (toll free)

OR mail requests to: PharmaCare, Box 9652 Stn Prov Govt, Victoria, BC V8W 9P4

This facsimile is Doctor-Patient privileged and contains confidential information intended only for PharmaCare. Any other distribution, copying or disclosure is strictly prohibited. If you have received this fax in error, please write "MISDIRECTED" across the front of the form and fax toll-free to 1 800 609-4884, then destroy the pages received in error.

Should approval be granted for this Special Authority request, PharmaCare's authorization is solely for the purpose of providing prescription benefit for the cost of the requested medication. PharmaCare makes no representation about the suitability of the requested medication for the patient's medical condition or any other problem.

Forms with information missing will be returned for completion.

INITIAL ELIGIBILITY CRITERIA: Diagnosis of Alzheimer's Disease with SMMSE of ≥ 10 to ≤ 26 and Global Deterioration Scale ≥ 4 to ≤ 6

SECTION 1 - PRESCRIBER INFORMATION

NAME & MAILING ADDRESS <input type="checkbox"/> MAIL CONFIRMATION	APPLICATION DATE YYYY MM DD	PREScriBER'S TEL # AREA CODE
	PREScriBER'S COLLEGE ID #	PREScriBER'S FAX # AREA CODE

SECTION 2 - PATIENT INFORMATION

PERSONAL HEALTH NUMBER (PHN)	PATIENT (FAMILY) NAME
DATE OF BIRTH (YYYY / MM / DD)	PATIENT (GIVEN) NAME(S)

SECTION 3 - MEDICATION REQUESTED (MONTHLY FILLS)

	STARTING DOSE	TITRATION AS TOLERATED	EFFECTIVE RANGE
<input type="checkbox"/> DONEPEZIL	5 mg daily (2.5 mg if frail) for 4 to 6 weeks	increase by 5 mg	5 to 10 mg daily
<input type="checkbox"/> GALANTAMINE	8 mg ER daily for 4 to 6 weeks	increase by 8 mg	16 to 24 mg daily
<input type="checkbox"/> RIVASTIGMINE (divided dose)	1.5 mg twice daily for 2 to 4 weeks	increase by 1.5 to 3 mg twice daily	6 to 12 mg daily
<input type="checkbox"/> RIVASTIGMINE (patch)	1 patch (5 cm ² /9 mg) once daily for 4 to 6 weeks	increase to 1 patch (10 cm ² /18 mg) once daily	1 patch (5 cm ² /9 mg) to 1 patch (10 cm ² /18 mg) once daily

SECTION 4 - CLINICAL INFORMATION (ALL THREE SECTIONS MUST BE COMPLETED)

PRESUMPTIVE DIAGNOSIS <input type="checkbox"/> ALZHEIMER'S DISEASE (AD) <input type="checkbox"/> AD WITH PARKINSONIAN FEATURES (LEWY BODIES) <input type="checkbox"/> AD WITH VASCULAR COMPONENT <input type="checkbox"/> AD WITH OTHER (SPECIFY):	SMMSE ≥ 10 TO ≤ 26 OR: <input type="checkbox"/> UNABLE TO COMPLETE BECAUSE OF FUNCTIONAL ILLITERACY	GDS (GLOBAL DETERIORATION SCALE) ≥ 4 TO ≤ 6
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Personal information on this form is collected for the operations of the Ministry of Health. The Ministry will use the information in the decision to provide PharmaCare benefits for the medication requested, and for implementation, monitoring, evaluation and research of this and other Ministry programs, and for the management and planning of the health system generally. Personal information will be used and disclosed in accordance with the privacy protection provisions of the Freedom of Information and Protection of Privacy Act. If you have any questions about the collection of this information, call Health Insurance BC from Vancouver at 604-683-7151 or from elsewhere in BC toll free at 1-800-663-7100 and ask to consult a pharmacist concerning the Special Authority process.

I have discussed with the patient the purpose of the release of the patient's information to PharmaCare to obtain Special Authority for prescription benefit and for the purposes set out above.

Signature of Prescriber (Mandatory)

Patient Signature (Optional)

PharmaCare may request additional documentation to support this Special Authority request.

PHARMACARE USE ONLY

STATUS	EFFECTIVE DATE
	DURATION OF COVERAGE
	TERMINATION DATE

HLTH 5369 2012/09/14



**SPECIAL AUTHORITY REQUEST
CHOLINESTERASE INHIBITORS
RENEWAL/SWITCHING COVERAGE (6 MONTHS)
ALZHEIMER'S DRUG THERAPY INITIATIVE**

Fax requests to 1 800 609-4884 (toll free)
OR mail requests to: PharmaCare, Box 9652 Stn Prov Govt, Victoria, BC V8W 9P4

This facsimile is Doctor-Patient privileged and contains confidential information intended only for PharmaCare. Any other distribution, copying or disclosure is strictly prohibited. If you have received this fax in error, please write "MISDIRECTED" across the front of the form and fax toll-free to 1 800 609-4884, then destroy the pages received in error. Should approval be granted for this Special Authority request, PharmaCare's authorization is solely for the purpose of providing prescription benefit for the cost of the requested medication. PharmaCare makes no representation about the suitability of the requested medication for the patient's medical condition or any other problem.

Forms with information missing will be returned for completion.

<input type="checkbox"/> RENEWAL Eligibility criteria: Diagnosis of Alzheimer's Disease with SMMSE \geq 10, GDS 4 to 6, Overall Patient Assessment Rating of positive responder or indeterminate responder.
<input type="checkbox"/> SWITCHING FOR LACK OF EFFECTIVENESS Eligibility criteria: Diagnosis of Alzheimer's Disease with SMMSE \geq 10, GDS 4 to 6.

SECTION 1 – PRESCRIBER INFORMATION

NAME & MAILING ADDRESS	<input type="checkbox"/> MAIL CONFIRMATION	APPLICATION DATE YYYY MM DD	PRESCRIBER'S TEL # AREA CODE
		PRESCRIBER'S COLLEGE ID #	PRESCRIBER'S FAX # AREA CODE

SECTION 2 – PATIENT INFORMATION

PERSONAL HEALTH NUMBER (PHN)	PATIENT (FAMILY) NAME
DATE OF BIRTH (YYYY / MM / DD)	PATIENT (GIVEN) NAME(S)

SECTION 3 – MEDICATION REQUESTED (MONTHLY FILLS)

	STARTING DOSE	TITRATION AS TOLERATED	EFFECTIVE RANGE
<input type="checkbox"/> DONEPEZIL	5 mg daily (2.5 mg if frail) for 4 to 6 weeks	Increase by 5 mg	5 to 10 mg daily
<input type="checkbox"/> GALANTAMINE	8 mg ER daily for 4 to 6 weeks	Increase by 8 mg	16 to 24 mg daily
<input type="checkbox"/> RIVASTIGMINE (divided dose)	1.5 mg twice daily for 2 to 4 weeks	Increase by 1.5 to 3 mg twice daily	6 to 12 mg daily
<input type="checkbox"/> RIVASTIGMINE (patch)	1 patch (5 cm ² /9 mg) once daily for 4 to 6 weeks	Increase to 1 patch (10 cm ² /18 mg) once daily	1 patch (5 cm ² /9 mg) to 1 patch (10 cm ² /18 mg) once daily

SECTION 4 – SWITCHING FOR LACK OF EFFECTIVENESS (IF APPLICABLE)

CHOLINESTERASE INHIBITOR BEING DISCONTINUED	DATE TREATMENT STOPPED (YYYY / MM / DD)	DOSE
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TO PAGE 2 →

PharmaCare may request additional documentation to support this Special Authority request.

PHARMACARE USE ONLY

STATUS	EFFECTIVE DATE
	DURATION OF COVERAGE
	TERMINATION DATE

CHOLINESTERASE INHIBITORS RENEWAL/SWITCHING COVERAGE (6 MONTHS)

PATIENT NAME	PHN	DATE OF BIRTH (YYYY / MM / DD)
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SECTION 5 – PATIENT ASSESSMENT FOR RENEWING OR SWITCHING FOR LACK OF EFFECTIVENESS

STEP 1	PREVIOUS SMMSE SCORE (WITHIN LAST 4-6 MONTHS)	CURRENT SMMSE SCORE	DIFFERENCE	<input type="checkbox"/> UNABLE TO COMPLETE SMMSE BECAUSE OF FUNCTIONAL ILLITERACY	CURRENT GDS STAGE								
STEP 2	ASSESS THE CHANGE IN ABILITY OVER THE LAST SIX MONTHS.												
	COGNITION A. MEMORY, REASONING AND PERCEPTION (E.G. NAMES, TASKS, SMMSE)	_____			(+1 = IMPROVED, 0 = NO CHANGE, -1 = WORSE)								
	FUNCTION B. INSTRUMENTS OF DAILY LIVING (E.G. TELEPHONE, SHOPPING, MEAL PREPARATION)	_____			(+1 = IMPROVED, 0 = NO CHANGE, -1 = WORSE)								
	BEHAVIOUR C. BASIC ACTIVITIES OF DAILY LIVING (E.G. BATHING, DRESSING, HYGIENE AND TOILETING)	_____			(+1 = IMPROVED, 0 = NO CHANGE, -1 = WORSE)								
	BEHAVIOUR D. NEUROPSYCHIATRIC SYMPTOMS (E.G. AGITATION, DELUSIONS, HALLUCINATION, APATHY)	_____			(+1 = IMPROVED, 0 = NO CHANGE, -1 = WORSE)								
	TOTAL SCORE (A+B+C+D): _____												
STEP 3	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr><th>TOTAL SCORE</th></tr> <tr><td>+4</td></tr> <tr><td>+3 OR +2</td></tr> <tr><td>+1</td></tr> <tr><td>0</td></tr> <tr><td>-1</td></tr> <tr><td>-2 OR -3</td></tr> <tr><td>-4</td></tr> </table>	TOTAL SCORE	+4	+3 OR +2	+1	0	-1	-2 OR -3	-4	CLINICAL JUDGMENT →	OVERALL PATIENT ASSESSMENT RATING		RECOMMENDATION
TOTAL SCORE													
+4													
+3 OR +2													
+1													
0													
-1													
-2 OR -3													
-4													
			<input type="checkbox"/> VERY MUCH IMPROVED <input type="checkbox"/> MUCH IMPROVED <input type="checkbox"/> MINIMALLY IMPROVED <input type="checkbox"/> NO CHANGE <input type="checkbox"/> MINIMALLY WORSE <input type="checkbox"/> MUCH WORSE <input type="checkbox"/> VERY MUCH WORSE	POSITIVE RESPONDER INDETERMINATE RESPONDER NON-RESPONDER	CONTINUE TREATMENT; RE-EVALUATE PATIENT EVERY 6 MONTHS CONTINUE TREATMENT; RE-EVALUATE PATIENT EVERY 8 MONTHS (CONSIDER SWITCHING CHOLINESTERASE INHIBITOR). STOP TREATMENT OF CURRENT CHOLINESTERASE INHIBITOR (CONSIDER SWITCHING CHOLINESTERASE INHIBITOR).								
ELIGIBILITY CRITERIA: PRESUMPTIVE DIAGNOSIS OF ALZHEIMER'S DISEASE WITH SMMSE ≥ 10, GDS 4 TO 6, OVERALL PATIENT ASSESSMENT RATING OF POSITIVE RESPONDER OR INDETERMINATE RESPONDER. PLEASE NOTE SMMSE SCORES OVER 26 INDICATE POSITIVE RESPONDER.													

Personal information on this form is collected for the operations of the Ministry of Health. The Ministry will use the information in the decision to provide PharmaCare benefits for the medication requested, and for implementation, monitoring, evaluation, and research of this and other Ministry programs, and for the management and planning of the health system generally. Personal information will be used and disclosed in accordance with the privacy protection provisions of the Freedom of Information and Protection of Privacy Act. If you have any questions about the collection of this information, call Health Insurance BC from Vancouver at 604-683-7151 or from elsewhere in BC toll free at 1-800-663-7100 and ask to consult a pharmacist concerning the Special Authority process.

I have discussed with the patient the purpose of the release of the patient's information to PharmaCare to obtain Special Authority for prescription benefit and for the purposes set out above.

Signature of Prescriber (Mandatory)

Patient Signature (Optional)

SUPPLEMENTARY INFORMATION (required for payment of MSP fee item 97002)

To be used by BC researchers in a study to improve the care and treatment of individuals affected by Alzheimer's disease.

PATIENT LIVES ALONE <input type="checkbox"/> YES <input type="checkbox"/> NO RESIDES IN A FACILITY WHERE MEDICAL CARE IS PROVIDED <input type="checkbox"/> YES <input type="checkbox"/> NO	HEIGHT: _____ CM OR _____ IN WEIGHT: _____ KG OR _____ LBS <i>IF UNABLE TO MEASURE, PLEASE PROVIDE ESTIMATE</i>
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APPENDIX 2: ADTI PUBLICATIONS REPORT

Co-Principal Investigators

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K. Malcolm Maclure, ScD, Professor and B.C. Academic Chair in Patient Safety, Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia

Articles Published in Referred Journals

Roland, K. P., & Chappell, N. L. (2015). Relationship and stage of dementia differences in caregiver perspectives on the meaning of activity. *Dementia: The International Journal of Social Research and Practice*. Published on-line.

<http://dem.sagepub.com/content/early/2015/05/20/1471301215586287.full.pdf?ijkey=DurIc8b6pC5SJzN&keytype=finite>

Roland, K. P., & Chappell, N. L. (2015). Meaningful activity for persons with dementia: Family caregiver perspectives. *American Journal of Alzheimer's Disease & Other Dementias*. Published on-line, pp. 1-10. doi: 10.1177/1533317515576389

Roland, K., & Chappell, N. L. (2014). A typology of caregiving across neurodegenerative disease presenting with dementia. *Ageing & Society*. Published on-line, pp. 1-23. doi: 10.1017/S0144686X1400066X

Chappell, N. L., Dujela, C., & Smith, A. P. (2014). Spouse/adult child differences in caregiving burden. *Canadian Journal on Aging*, 33(Spec. Issue 4), 462-472. doi: 10.1017/S0714980814000336

Chappell, N. L., Dujela, C., & Smith, A. (2014). Caregiver well-being: Intersections of relationship and gender. *Research on Aging*. Published on-line doi: 10.1177/0164027514549258

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- Maclure, M. (2009). Explaining pragmatic trials to pragmatic policy-makers. *Journal of Clinical Epidemiology*, 62(5), 476-478.
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- Fisher, A., Carney, G., Bassett, K., & Chappell, N. (2015a). Cholinesterase inhibitors utilization: The impact of provincial drug policy on discontinuation [in submission]. Unpublished manuscript.
- Fisher, A., Carney, G., Bassett, K., & Chappell, N. (2015b). Switching between cholinesterase inhibitors: Effects of a new drug coverage plan and duration of use [in submission]. Unpublished manuscript.
- Smith, A., Dujela, C., & Chappell, N. (under review). Who do you start, who do you stop?: Physicians' experiences with managing long-term cholinesterase inhibitor therapy.

Reports

- Chappell, N. L., Beattie, B. L., Hsiung, G-Y. R., & Dormuth, C. (2014). *Alzheimer's Drug Therapy Initiative (ADTI) Progress Report*. June.
- Chappell, N. L., Beattie, B. L., Hsiung, G-Y. R., & Dormuth, C. (2014). *Alzheimer's Drug Therapy Initiative (ADTI) Progress Report*. March.
- Chappell, N. L., Beattie, B. L., Jacova, C., Lee, P., Hsiung, G-Y. R., & Rabheru, K. (2013). *Alzheimer's Drug Therapy Initiative (ADTI) Annual Progress Report*. November.
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- PharmacoEpidemiology Group (2010). ADTI Utilization and Cost Project, Quarterly Report: Time Trends of Drug Utilization. March.
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- Chappell, N. L., Maclure, M., Jacova, C., Rabheru, K. & Lee, P. (2009). *Alzheimer's Drug Therapy Initiative (ADTI) PSD-SMS Recommendation Report*. December.
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Presentations

- Dujela, C. E., & Chappell, N. L. (2015, May). *The role of pets in the lives of those living with dementia in the community*. 9th Annual International Conference on Sociology, Athens, Greece, May.

- Roland, K. & Chappell, N. L. (2014, November). *Meaningful activity for person with dementia: Caregiver perspectives*. Paper presented at Gerontological Society of America, Washington DC.
- Roland, K., & Chappell, N. L. (2014, October). *Meaningful activity differences in spouse compared with adult-children dementia caregivers*. Canadian Association on Gerontology, Niagara Falls, ON.
- Roland, K., & Chappell, N. L. (2014, September). *The role of symptom presentation in dementia caregiver burden and self-esteem*. International Conference of Alzheimer's Disease and Dementia, Valencia, Spain.
- Chappell, N. L. (2014, October). *Intersecting inequalities, implications for caregivers*. 6th International Social & Applied Gerontology Symposium; Aging & Caregiving in the 21st Century, Antalya, Turkey.
- Chappell, N. L. (2014, August). *Why caregiver's institutionalize family members; Examining gender and relationship intersections*. European Society for Health and Medical Sociology, Helsinki, Finland.
- Chappell, N. L., Dujela, C., & Smith, A. P. (2013, November). *Caregiver quality of life: The differential importance of caregiver burden*. Gerontological Society of America, New Orleans, LA.
- Smith, A. P., Kobayashi, K., & Chappell, N. L. (2013, November). *The rhetoric of claims-making: The case of cholinesterase inhibitors*. Poster. Gerontological Society of America, New Orleans, LA.
- Smith, A. P., Kobayashi, K., & Chappell, N. L. (2013, November). *Persistent cholinesterase inhibitor prescribing in dementia: Physician and specialists' experiences*. Gerontological Society of America, New Orleans, LA.
- Smith, A. P., Kobayashi, K., & Chappell, N. L. (2013, October). *Long-term use of cholinesterase inhibitors in dementia care: Physicians and specialists' experiences*. Canadian Association on Gerontology, Halifax, NS.
- Chappell, N. L., Dujela, C., & Smith, A. P. (2013, June). *Spouse and adult child differences in caregiving burden*. International Symposium on Aging Families, Victoria, BC.
- Kadgien, C., Dujela, C., Chappell, N. L. (2012, October). *Time to test? Thoughts on and images from caregiver-administered clock-drawing tests*. Poster. Canadian Association on Gerontology annual Scientific and Educational meetings, Vancouver, BC.
- Hsiung, G-Y. R., & Dujela, C. (2012, October). In the mind of the beholder: How well do self-assessments of function in early Alzheimer's Disease correlate with standardized test scores in a cohort of cholinesterase inhibitor users over time?. Canadian Association on Gerontology annual Scientific and Educational meetings, Vancouver, BC.
- Smith, A., Kobayashi, K., Chappell, N. L. (2012, October). *Discontinuing cholinesterase inhibitor therapy: Connecting caregivers' experiences to clinical practice*. Canadian Association on Gerontology annual Scientific and Educational meetings, Vancouver, BC.
- Chappell, N. L., & Maclure, M. (2012, August). *The gendered nature of caregiver perceptions of the effectiveness of cholinesterase inhibitors (ChEIs) for those with dementia*. International Sociological Association Forum of Sociology, Argentina.

- Votova, K., Dujela, C., & Hsiung, G-Y, R. (2012, July). Assessing cognition and function in Alzheimer's disease pharmacotherapy: A comparison of self-assessment by ChEI users and standardized test-scores. Alzheimer's Association International Conference, Vancouver, BC.
- Smith, A., Kobayashi, K., & Chappell, N. L. (2012, July). Examining the discontinuation of cholinesterase inhibitor therapy from the perspectives of Alzheimer's disease caregivers and physicians. Alzheimer's Association International Conference, Vancouver, BC.
- Smith, A., Kobayashi, K., & Chappell, N. L. (2012, March). *The controversial promises of cholinesterase inhibitors for dementia: A qualitative study of caregiver's experiences*. Applied Research Colloquium, Centre on Aging, Victoria, BC.
- Chappell, N. L. (2012, February). *A social perspective on dementia: Research advances and promising directions*. Keynote address, 1st International Symposium on Alzheimer's Disease and Related Disorders, French National Foundation on Alzheimer's Disease, Paris.
- Smith, A., Kobayashi, K., & Chappell, N. L. (2011, November). The controversial promises of cholinesterase inhibitors for dementia: A qualitative study of caregiver's experiences. The Gerontological Society of America, Boston.
- Chappell, N. L., Outcalt, L., & Maclure, M. (2011, October). *Can Pharmaceutical Research be Conducted without the Influence of the Pharmaceutical Industry?*. Canadian Association on Gerontology annual meetings jointly with the Pan American Congress, Ottawa.
- Chappell, N. L., Kobayashi, K., & Smith, A. (2011, March). *What caregivers think of cholinesterase inhibitors*. 26th International Conference of Alzheimer's Disease International, Toronto.
- Chappell, N. L., Kobayashi, K., Maclure, M. (2010, December). Caregiver perceptions of medications for dementia; Do they make a difference to caregiver burden and quality of life?. Canadian Association on Gerontology, Montreal.
- Chappell, N. L., Kobayashi, K., Maclure, M. (2010, November). *Caregiver perceptions of the effectiveness of dementia drugs*. Gerontological Society of America, New Orleans.
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- Maclure, M., Green, C. J., Jacova, C., Hsiung, G-Y. R., Dujela, C. E., Gerber, M., Hudson, R., & Chappell, N. L. (2009, August). Poster. *Pragmatic randomized trial of continuing cholinesterase inhibitors among indeterminate responders*. ISPE, Orlando, FL.

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