Physicians' Efficacy Requirements for Prescribing Medications to Persons with Alzheimer's Disease*

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RÉSUMÉ

Des médecins ($N = 803$) ont été interrogés par sondage postal sur deux ensembles de critères de jugement de l'efficacité des traitements médicamenteux de la maladie d'Alzheimer : (a) la durée de la maladie d'intensité légère ou modérée et (b) les degrés de modification de la progression de la maladie sur les plans de la cognition, du comportement et de l'humeur, et la capacité d'accomplir les activités courantes élémentaires. Les médecins ont répondu qu'ils prescriraient un nouveau médicament hypothétique s'il permettait de maintenir l'état actuel de la maladie pendant 15 mois (maladie légère) ou 11 mois (maladie modérée). La plupart des médecins s'attendent à ce que le médicament freine de façon permanente la progression de la maladie ou que celle-ci recule avant de prescrire le médicament ; quelques-uns ne le prescriront que s'il fait reculer la maladie de façon remarquable. Des critères d'efficacité stricts influencent négativement le comportement de prescription actuel des médecins en ce qui concerne les inhibiteurs de la cholinestérase dans le maladie d'Alzheimer, quoique l'effet soit faible (ratio d'incidence approché = 0,99), ou non statistiquement significatif au niveau de cinq p. cent. Les résultats révèlent que les médecins qui appliquent des critères de jugement stricts aux paramètres d'efficacité d'importance clinique sont moins enclins à prescrire des inhibiteurs de la cholinestérase.

ABSTRACT

Physicians ($N = 803$) were contacted via postal survey and given two sets of efficacy measures for drug treatments in Alzheimer's disease: (a) the time that patients spend in a mild or moderate state of disease; (b) levels of modification to disease progression in the areas of cognition, behaviour, and mood, and ability to perform basic activities of daily living. Physicians reported that they would prescribe a hypothetical, new Alzheimer's disease medication if it would allow patients to remain in their current disease state for 15 (*mild*) or 11 (*moderate*) additional months. Most physicians required a permanent halt to, or some reversal of, disease progression as a prerequisite for prescribing; a few required substantial reversal. More stringent efficacy requirements were negatively associated with physicians' current prescribing of cholinesterase inhibitors to persons with Alzheimer's disease, although the effects were either small (odds ratio = 0.99) or not statistically significant at the 5 per cent level. The results suggest that physicians with stringent efficacy requirements for clinically relevant efficacy measures are less likely to prescribe cholinesterase inhibitors.

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Introduction

In clinical research, the efficacy of medications for Alzheimer's disease (AD) is assessed by the magnitude of changes in score on outcome measurement instruments. These instruments include the Alzheimer's Disease Assessment Scale (cognitive sub-scale)[1] and the Clinician Interview-Based Impression of Change.[2] In clinical practice, changes in scale score are, however, limited indicators of efficacy because they do not capture the impact of treatment on patient symptoms.[3] In light of the importance of medications in the treatment of AD, numerous researchers[3–7] have recognized that clinically relevant efficacy measures are needed to help physicians better appreciate treatment effects and make more informed prescribing decisions.

Despite the need for such measures, no work has been done to select particular measures or investigate whether specific values of these measures might have an impact on prescribing. For example, AD medications such as donepezil, rivastigmine, galantamine, tacrine, and memantine can have a modest symptomatic effect on cognition, behaviour, and function.[8–10] Therefore, one clinically relevant efficacy measure is the average length of time that patients on drug therapy can benefit from the symptomatic effects. The standard *benefit period* for these medications is reported to be 6 to 12 months.[8–10] This can have an impact on prescribing if physicians who require a longer or shorter benefit period alter their prescribing behaviour accordingly. Thus, physicians who require a longer benefit period might be less likely to prescribe because they believe the medications are not sufficiently efficacious for their patients.

This study was conducted to provide examples of clinically relevant efficacy measures in AD and to investigate the impact of these measures on prescribing.

Methods

Study Sample

A postal survey was sent to all of the province of Quebec's 49 geriatricians, 215 neurologists, and 53 psychogeriatricians. These specialists were chosen because they are the most likely physicians to treat AD and prescribe AD medications.

In recognition of the fact that general practitioners (GPs) are the next most likely group of physicians to treat AD, the survey was also sent to 486 (6%) of Quebec's 8,115 GPs. One hundred and ninety-one of the GPs were drawn from a list of physicians who had taken continuing medical education courses on geriatrics and elder care in 2001 or 2002. The remaining 295 GPs were randomly chosen from the master provincial list of GPs using R version 1.8.1 software.

Survey Administration

The survey was administered between August and October 2002. The text of all cover letters, the format and font of the survey, the colour and type of paper, the use of first-class stamps on return envelopes, and the use of multiple mailings followed recommendations for maximizing the number of respondents.[11–14]

A *pre-survey* letter was the first item mailed to the sample. The letter introduced the study and encouraged recipients to respond. One week later, survey packages were mailed to the sample. Each package contained a cover letter, survey questionnaire, and pre-addressed, pre-stamped return envelope. Identical packages were mailed to non-respondents at 3 and 6 weeks after the initial package. Between the follow-up mailings, non-respondents were also contacted by telephone and encouraged to respond.

Survey Questions

As a prelude to answering the questions, physicians were asked to assume that a new medication for AD

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had come on the market. They were told that the medication could prolong the time in months that patients would remain in a mild or moderate disease state, after which cognitive decline would recommence. Physicians were asked to specify the minimum number of months of prolongation that would be required as a prerequisite to prescribing the medication. Separate answers were sought for the mild and moderate states of AD.

In another question, physicians were asked to assume that the new medication could permanently halt or even reverse, rather than temporarily stabilize, a patient's condition. Physicians were asked to specify the minimum effect that they would require of the medication before they would prescribe the medication to their own patients. Answers were sought for effects in three separate domains: cognition, behaviour and mood, and ability to perform basic activities of daily living (Figure 1).

The survey also contained questions about clinical experience (e.g., proportion of persons with AD for whom a physician had initiated prescriptions for the cholinesterase inhibitors [ChEIs] donepezil, rivastigmine, or galantamine) and questions to elicit sample characteristics (e.g., physician age and sex, number of years since obtaining a medical licence). A copy of the survey is available upon request.

Statistical Analysis

Descriptive statistics were used to summarize survey responses: counts and percentages for categorical responses, means, standard deviations, and ranges for continuous responses.

Quasi-binomial regression was used to examine the hypothesis that more stringent efficacy requirements for prescribing a hypothetical, new AD medication would be associated with less reported prescribing of the ChEIs donepezil, rivastigmine, and galantamine. Given the modest benefits of ChEIs,[8] physicians who had strong treatment expectations for the hypothetical medication were anticipated to be less likely to prescribe ChEIs.

A quasi-binomial regression model is a generalized linear model with a scaled Bernoulli variance function and a logit link. In such a model, the dependent variable (in this study, the proportion of persons with AD for whom a physician prescribed donepezil, rivastigmine, or galantamine [*reported prescribing*]) is assigned a weight of 1. Several alternative generalized linear models, including logistic regression or unweighted binomial regression with a complementary log-log link or a negative binomial error structure, were also fitted to the data. Different weights were employed in the modelling process, including weights based on overall practice size or the number of persons with AD in a practice. However, the quasi-binomial model with the dependent variable weighted by 1 was shown to be the best means of fitting the data. Indeed, since reported prescribing was a proportion reported by physicians rather than computed from counts of dichotomous events, there was no reason a priori to believe that the

Cognitive status —required minimum effect would be … (choose one)

a) to permanently stabilize the level of cognition (i.e., no decline in Folstein/MMSE score, but no improvement either)
b) to somewhat reverse the degree of cognitive impairment (i.e., 1–3 point increase in Folstein/MMSE score)
c) to substantially reverse the degree of cognitive impairment (i.e., > 3 point increase in Folstein/MMSE score)

Behaviour and mood—required minimum effect would be … (choose one)

a) to somewhat reduce further occurrences of problematic behaviours and moods (e.g., up to 25% reduction in incidence of problematic behaviours and moods)
b) to substantially reduce further occurrences of problematic behaviours and moods (e.g., more than 25% reduction in incidence of problematic behaviours and moods)
c) to permanently prevent further occurrences of problematic behaviours and moods (e.g., no more bouts of agitated behaviour, no more depressive episodes)

Ability to perform basic activities of daily living— required minimum effect would be … (choose one)

a) to permanently prevent further diminishment of a patient's ability to perform basic activities of daily living
b) to somewhat increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 1–2 basic activities)
c) to substantially increase a patient's ability to perform basic activities of daily living (e.g., a resumption of 3 or more basic activities)

Figure 1: Response options for question about physicians' efficacy requirements for a hypothetical Alzheimer's disease medication that can improve patient condition

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dependent variable would follow a binomial or scaled binomial distribution (logistic regression). The estimated regression coefficients from a quasi-binomial regression model are interpreted as log odds ratios.

A separate set of regression models was built for each of two independent variables. The first variable was a synthetic index that was constructed by adding together the responses to the mild and moderate portions of the question about the minimum additional length of time that physicians would require patients to remain in a certain disease state. The second variable, also a synthetic index, was constructed by combining the responses to all three domains shown in Figure 1. The first step in combining these domains was to assign numerical values to responses in ascending order of stringency. Thus, responses identified by the letter 'a' in Figure 1 were given a value of 1, the letter 'b' a value of 2, and the letter 'c' a value of 3. For each respondent, the numerical values were summed to obtain a score that ranged from 3 to 9. Higher scores indicated more stringent efficacy requirements for prescribing a hypothetical new AD medication.

The following co-variates (Table 1) were assessed as potential effect modifiers or confounders of the association between physicians' efficacy requirements and reported prescribing:

- physician age and sex
- physician's primary source of information on ChEIs
- total number of patients in a practice
- total number of patients with AD in a practice
- proportions of patients in a practice with mild, moderate, or severe AD
- level of knowledge regarding the efficacy of ChEIs
- proportion of patients with mild cognitive impairment or another form of dementia besides AD who are prescribed ChEIs
- whether physicians use other medications (prescription or over-the-counter drugs) to treat the symptoms of AD
- proportion of patients in a practice with adverse effects from the ChEIs
- physician specialty

For each model, a co-variate was considered to be an effect modifier if the interaction term that was formed by the product of the co-variate and the independent variable was statistically significant at the 5 per cent level.[15] Co-variates that were not shown to be effect modifiers were considered to be confounders if their inclusion in the model changed the odds ratio of the independent variable by at least 10 per cent.[16]

Multiple imputation,[17,18] implemented according to the procedure of Schimert et al.,[19] was used to investigate whether the results of the regression analysis were biased due to item non-response on the survey. Bias was assessed by comparing the regression models obtained using casewise deletion (where observations with missing data were removed from the analysis) to the models obtained using multiple imputation (where all observations in the dataset were included in the analysis).

SAS version 8.2 was used to conduct the regression analysis. S-Plus version 6.1 was used to perform multiple imputation.

Ethics Approval

This study received ethics approval from the Institutional Review Board of McGill University and the Research Ethics Committee of the S.M.B.D. Jewish General Hospital.

Results

Survey Response Proportion and Respondent Characteristics

The proportion of the sample that responded to the survey was 0.354 (233/658). Excluded from the denominator were 137 physicians who returned a blank survey after indicating that they did not treat persons with AD. Also excluded were eight physicians whose postal addresses were invalid.

The majority of respondents were male, their average age was 46 years, they lived in urban areas, and they spoke French. Almost half of the respondents practised in university-affiliated hospitals, one quarter practised in non-university-affiliated hospitals, and one third had solo practices. Many respondents practised in more than one location, and they reported obtaining their medical licences in Quebec an average of 20 years ago. The number of patients in physicians' practices, both overall and with AD, was highly variable. There was an average of about 1,000 patients in each practice, although the mean number of patients with AD was substantially less, at 57. Half of the patients with AD were reported to be at the mild stage of disease, one third at the moderate stage, and the remainder at the severe stage (Table 1).

Respondents did not differ from non-respondents in terms of sex, urban/rural residence, language, or years since obtaining a medical licence in Quebec. However, there were differences with respect to physician specialty ($p < 0.001$). The proportion of geriatricians and psychogeriatricians who responded was greater than the proportion who did not respond.

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Table 1: Characteristics of respondents to the physician survey ($N = 233$)

Characteristic	*n* (%) [categorical]
Sex	
Male	142 (61)
Female	90 (39)
Missing[a]	1 (<1)
Specialty	
Geriatrician	28 (12)
Psychogeriatrician	49 (21)
Neurologist	27 (12)
General practitioner	128 (55)
Missing	1 (<1)
Urban/Rural Residence	
Urban	203 (87)
Rural	29 (12)
Missing	1 (<1)
Language	
French	210 (90)
English	23 (10)
Practice Settings[b]	
University-affiliated hospital	98 (42)
Hospital not university-affiliated	55 (24)
Community public health clinic	46 (20)
Solo practice	84 (36)
Same-discipline group practice	18 (8)
Multi-discipline group practice	18 (8)
University-affiliated office-based practice	11 (5)
Ward or emergency work in a hospital	29 (12)
Other	49 (21)
Primary Source of Information on ChEIs	
Medical journal articles	76 (33)
Scientific meetings	54 (23)
Advertisements in medical journals	2 (<1)
Observations of patient responses to ChEIs	8 (3)
Colleagues' opinions	2 (<1)
Representatives of pharmaceutical companies	10 (4)
CME courses given by an academic institution	42 (18)
CME courses given by a pharmaceutical company	20 (9)
Electronic media	4 (2)
Missing	15 (6)
Level of Knowledge Regarding the Efficacy of Donepezil	
Not knowledgeable	0 (0)
Somewhat knowledgeable	49 (21)
Very knowledgeable	183 (79)
Missing	1 (<1)

(Continued)

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Table 1: Continued

Characteristic	*n* (%) [categorical]
Level of Knowledge Regarding the Efficacy of Rivastigmine	
Not knowledgeable	15 (6)
Somewhat knowledgeable	78 (33)
Very knowledgeable	137 (59)
Missing	3 (1)
Level of Knowledge Regarding the Efficacy of Galantamine	
Not knowledgeable	35 (15)
Somewhat knowledgeable	80 (34)
Very knowledgeable	116 (50)
Missing	2 (<1)
Ever Initiated a Prescription for a ChEI	
Yes	211 (91)
No	22 (9)
Ever Initiated a Prescription for Another Medication to Treat the Symptoms of AD	
Yes	193 (83)
No	40 (17)
Ever Suggested That Patients Take over-the-Counter Medications to Treat the Symptoms of AD	
Yes	64 (27)
No	169 (73)
Characteristic	$M \pm SD$ **(range) [continuous]**
Age	46 ± 10 (26–79)
Years since obtaining a medical license in Quebec	20 ± 10 (4–53) ($n = 43$ missing)
Total number of patients in a practice	$1{,}034 \pm 1{,}240$ (8–8000) ($n = 36$ missing)
Total number of AD patients in a practice	57 ± 89 (0–700) ($n = 12$ missing)
Proportion of patients in a practice with mild AD	0.51 ± 0.24 (0.0–1.0) ($n = 9$ missing)
Proportion of patients in a practice with moderate AD	0.34 ± 0.17 (0.0–1.0) ($n = 9$ missing)
Proportion of patients in a practice with severe AD	0.15 ± 0.17 (0.0–1.0) ($n = 9$ missing)
Proportion of patients in a practice with MCI who are prescribed ChEIs	0.45 ± 0.29 (0.0–1.0)
Proportion of patients in a practice with other dementias who are prescribed ChEIs	0.47 ± 0.30 (0.0–1.0) ($n = 1$ missing)
Proportion of patients developing adverse effects on	
donepezil (210 physicians prescribed donepezil)	0.17 ± 0.16 (0.0–1.0) ($n = 12$ missing)
rivastigmine (124 physicians prescribed rivastigmine)	0.27 ± 0.24 (0.0–1.0) ($n = 17$ missing)
galantamine (100 physicians prescribed galantamine)	0.20 ± 0.23 (0.0–1.0) ($n = 20$ missing)
Proportion of patients who had adverse effects that were severe enough to lead to a discontinuation of	
donepezil (210 physicians prescribed donepezil)	0.10 ± 0.17 (0.0–1.0) ($n = 12$ missing)
rivastigmine (124 physicians prescribed rivastigmine)	0.22 ± 0.27 (0.0–1.0) ($n = 18$ missing)
galantamine (100 physicians prescribed galantamine)	0.15 ± 0.26 (0.0–1.0) ($n = 21$ missing)

a missing = number of respondents who did not answer the question
b percentages do not total 100 because respondents could practice in more than one setting
SD = standard deviation
ChEIs = cholinesterase inhibitors
CME = continuing medical education
AD = Alzheimer's disease
MCI = mild cognitive impairment

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Table 2: Physicians' reported efficacy requirements ($N = 233$)

Efficacy Requirement	***M* ± *SD* (range) [continuous]**
Additional required length of time (months)—mild stage of AD[a]	15 ± 10 (1–60) (n = 3 missing)
Additional required length of time (months)—moderate stage of AD[b]	11 ± 6 (1–36) (n = 3 missing)
Efficacy Requirement	**n (%) [categorical]**
Cognitive Status—Required Minimum Effect[c] Would Be	
To permanently stabilize the level of cognition	144 (62)
To somewhat reverse the degree of cognitive impairment	67 (29)
To substantially reverse the degree of cognitive impairment	20 (9)
Missing	2 (1)
Behaviour and Mood—Required Minimum Effect[c] Would Be	
To somewhat reduce further occurrences of problematic behaviours and moods	117 (50)
To substantially reduce further occurrences of problematic behaviours and moods	58 (25)
To permanently prevent further occurrences of problematic behaviours and moods	55 (24)
Missing	3 (1)
Ability to Perform Basic Activities of Daily Living—Required Minimum Effect[c] Would Be	
To permanently prevent further diminishment of a patient's ability to perform basic activities of daily living	105 (45)
To somewhat increase a patient's ability to perform basic activities of daily living	100 (43)
To substantially increase a patient's ability to perform basic activities of daily living	26 (11)
Missing	2 (1)

a additional required length of time in months for a patient to remain in the mild stage of AD versus what would be possible if the hypothetical new AD drug were not prescribed
b additional required length of time in months for a patient to remain in the moderate stage of AD versus what would be possible if the hypothetical new AD drug were not prescribed
c the minimum effect that a physician would require the hypothetical new AD medication to have on an average patient (the medication would have to demonstrate this minimum effect before the physician would consider prescribing it)
SD = standard deviation
AD = Alzheimer's disease

Conversely, the proportion of neurologists and GPs who responded was less than the proportion who did not respond.

Physicians' Efficacy Requirements

Respondents reported that they would prescribe a hypothetical, new AD medication to patients with mild AD if doing so would allow the patients to remain in the mild disease state for an average of 15 additional months over what would be possible if the drug were not prescribed. For patients with moderate AD, the requirement was an average of 11 additional months (Table 2).

Assuming the hypothetical medication could permanently halt or even reverse the course of disease, the majority of respondents reported wanting the hypothetical medication at least to permanently stabilize patients' cognitive status so that there would be no further decline. Half of the respondents wanted the medication to somewhat reduce further occurrences of problematic behaviours and moods. Almost equal numbers of respondents wanted the medication to somewhat increase or permanently prevent any further diminishing of patients' ability to perform basic activities of daily living (Table 2).

Quasi-binomial Regression Analysis

The regression models (Table 3) indicated that more stringent efficacy requirements for prescribing a hypothetical, new AD medication were negatively associated with the reported prescribing of donepezil, rivastigmine, or galantamine. However, the magnitudes of effects were relatively small and the estimated odds ratios for two out of the four models were not statistically significant at the 5 per cent level.

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Table 3: Associations between physicians' efficacy requirements and reported prescribing of ChEIs (donepezil, rivastigmine, galantamine)[a]

Efficacy Requirement	Casewise Deletion ($N = 230$) Odds Ratio (95% Confidence Interval)	Multiple Imputation ($N = 233$) Odds Ratio (95% Confidence Interval)
Additional required length of time in disease state	0.99 (0.98-1.00)[b, c]	0.99 (0.97-1.00) [b, c]
Permanently halting disease progression or reversing effects of disease	0.91 (0.82-1.02) [c]	0.90 (0.79-1.04) [c]

a dependent variable = reported prescribing (i.e., proportion of patients with Alzheimer's disease for whom a physician reported initiating a prescription for donepezil, rivastigmine, or galantamine)
b $p < 05$; upper bound of confidence interval is 100 because of rounding to the nearest hundredth
c unadjusted ChEIs = cholinesterase inhibitors

None of the co-variates were found to be effect modifiers or confounders in any model. Therefore, the unadjusted estimates of the odds ratios were regarded as the best estimates of the association between each efficacy requirements variable and reported prescribing. The estimated odds ratios did not materially change when multiple imputation instead of casewise deletion was used to handle missing data.

Discussion

This is the first study to respond to the need[3–7] to elicit data on clinically relevant outcomes for drug treatments in AD. Physicians were asked to specify their efficacy requirements for using a hypothetical, new AD medication. The first set of requirements was predicated on the assumption that the medication would prolong the time that patients remained in a mild or moderate disease state. The second set of requirements was based on the assumption that the medication would permanently halt or reverse the course of disease.

Physicians' requirements for prolongation of time in a certain disease state were stringent when compared with the efficacy of existing drug treatments for AD. While existing drugs can have symptomatic effects on cognition, behaviour, and function for 6 to 12 months, physicians' minimum requirements for the prolongation of time in the mild or moderate disease state exceeded an average of one year. Physicians were more modest with the second set of requirements. Rather than requiring cognitive impairment to be somewhat or substantially reversed, the majority reported wanting patients' cognitive status to be permanently stabilized. Also, half of the physicians required that the new medication somewhat reduce problematic behaviours and moods, while 25 per cent required a substantial reduction and only 24 per cent required a complete halt. For patients' ability to perform basic activities of daily living, almost 90 per cent of the physicians were split between requiring the permanent prevention of further loss of ability and the restoration of some ability. Just over one-tenth of physicians required a substantial increase in patients' ability. Physicians' responses to the second set of requirements may have been tempered by a recognition of the therapeutic limitations of existing AD medications. As well, the responses could have been moderated by the fact that disease-altering medications are still many years from coming to market.

Since some physicians did report stringent requirements that were unlikely to be met by existing medications (e.g., a complete halt to problematic behaviours and moods), it was hypothesized that these physicians would be less likely to prescribe ChEIs. The results of the regression analysis did show some evidence of a negative association, but the effects were weak and only half of the estimated odds ratios were statistically significant at the 5 per cent level. Perhaps many physicians regard stringent requirements as an ideal conception of the efficacy of an AD medication. In the absence of medications that can achieve ideal performance, however, physicians appear willing to prescribe medications that are currently available to treat AD.

As new drug treatments reach the market, physicians' efficacy requirements can be used to help explain prescribing. For example, researchers may view a new drug as efficacious because the results of a clinical trial show a statistically significant change in mean score on an outcome measurement scale, but prescribing of the new drug lags behind expectations. Perhaps this is the case because the drug does not meet the level of efficacy that physicians require on clinically relevant outcomes.

This study has numerous strengths. It is the first where physicians were asked to specify their efficacy

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requirements for clinically relevant drug outcomes. The eliciting of these requirements followed a rigorous methodological approach: The survey was guided by sound principles of design and administration, the potential for non-response bias was assessed, and a comprehensive modelling approach was used to build two sets of regression models (i.e., casewise deletion and multiple imputation) for each efficacy requirement.

Selection bias is unlikely to have had a major impact on the study's results. By identifying and sending questionnaires to all geriatricians, psychogeriatricians, and neurologists, as well as to all GPs who had taken continuing medical education courses in geriatrics and elder care, the vast majority of Quebec physicians with experience in AD were given the opportunity to participate in the study. Maximizing the number of eligible participants is one way to minimize selection bias.[20]

In any survey, the potential for non-response bias has to be considered. Some physicians probably did not respond to the survey of efficacy requirements for reasons that were unrelated to the topic, including being too busy with their practices or never as a rule participating in surveys.[21] While the number of physicians who fell into either category is unknown, 137 other physicians expressly declined to participate because they did not treat persons with AD. Evidence suggests that some other non-respondents also fell into the *do not treat* category. The proportions of geriatricians and psychogeriatricians who responded were greater than the proportions who did not respond, while the reverse was observed for neurologists and GPs. Geriatricians and psychogeriatricians see disproportionately greater numbers of AD patients than neurologists and GPs, so there appears to have been a link between non-response and non-treatment of persons with AD.

Item non-response, which occurs when a respondent does not answer every survey question, was the source of missing values in this study. However, the missing values were unlikely to bias the study's results for two reasons. First, the number of missing values was 3 or fewer for 17 of the 30 questions that had missing values. Included in these 17 questions were the 5 questions about physicians' efficacy requirements. The impact of bias decreases as the number of missing values decreases. Second, the use of different methods to handle missing values in the regression analysis produced nearly identical results.

The study has some limitations, including the fact that the data are cross-sectional. Therefore, the negative associations in the regression analysis cannot be taken to suggest that physicians' efficacy requirements precede or influence the prescribing of ChEIs. The requirements that were reported by physicians could have been a reaction to the observed efficacy of ChEIs. Physicians who were dissatisfied with the ChEIs may have provided stringent requirements in answer to the survey. Despite the cross-sectional data, the study results do serve as a tool for hypothesis generation, which is an essential first step in research where new topics are being explored.[20]

The data on physician prescribing were collected for three ChEIs—donepezil, rivastigmine, and galantamine—that were approved for use in Canada at the time of the study. Tacrine has never been approved in Canada and memantine had not yet been approved. Therefore, caution must be exercised when generalizing the regression results to other medications besides donepezil, rivastigmine, and galantamine.

The prescribing data were reported by physicians in answer to a question on the survey (''For what proportion of your AD patients have you initiated a prescription for a ChEI [i.e., donepezil, rivastigmine, or galantamine]?''). Most physicians were probably unsure of the exact proportion and provided a best-guess estimate. Any ensuing misclassification would probably be random and therefore bias the regression results to the null.

There are many opportunities for future research. Physicians in the study were asked to specify efficacy requirements for a given series of outcomes (e.g., prolongation of time in a certain disease state). There are undoubtedly other clinically relevant outcomes, and these should be elicited from physicians who are interested in AD. The efficacy requirements related to these outcomes should also be obtained from the physicians.

In conclusion, physicians were asked to specify efficacy requirements for prescribing a hypothetical, new AD medication. Physicians specified stringent requirements for outcomes that concerned the prolongation of time in the mild or moderate stage of AD. The requirements were more modest for outcomes that involved permanently halting or reversing the course of disease. There was a small, negative association between efficacy requirements and the reported prescribing of donepezil, rivastigmine, and galantamine.

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