ORIGINAL ARTICLE

Less Education Predicts Anticholinesterase Discontinuation in Dementia Patients

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ABSTRACT: ***Objective:*** We investigated patient socio-demographic, clinical and functional factors predicting cholinesterase inhibitor discontinuation by patients presenting to a memory clinic in Saskatoon, Saskatchewan. ***Methods:*** Data collection began in March 2004 at the Rural and Remote Memory Clinic where family physicians referred their non-institutionalized patients. Neurological and neuropsychological assessment, patient and caregiver questionnaires provided the socio-demographic, clinical and functional variables. Univariate logistic regression analysis was used to examine possible associations between each independent variable and the binary outcome variable of treatment discontinuation. Multivariate logistic regression was used to determine predictors of cholinesterase inhibitor discontinuation within six months of drug initiation. ***Results:*** Our sample consisted of the first 63 patients (60.3% female) for whom we prescribed a cholinesterase inhibitor. The mean age at clinic day was 74.56 years (SD=7.78). We found that years of formal education was the only variable significantly associated with cholinesterase inhibitor discontinuation by six months. The more years of formal education, the lower the rate of drug discontinuation by six months. ***Conclusions:*** Likelihood of cholinesterase inhibitor discontinuation by six months was predicted by fewer years of formal education.

RÉSUMÉ: Un niveau inférieur de scolarité prédit la cessation de la médication anticholinestérase chez les patients déments. ***Objectif :*** Nous avons étudié les facteurs sociodémographiques, cliniques et fonctionnels prédisant la cessation du traitement par un inhibiteur de la cholinestérase chez les patients qui sont suivis à une clinique de la mémoire à Saskatoon, en Saskatchewan. ***Méthode :*** La collecte des données a commencé en mars 2004 à la Rural and Remote Memory Clinic où des médecins de famille réfèrent des patients qui ne vivent pas en institution. Les variables sociodémographiques, cliniques et fonctionnelles ont été tirées des évaluations neurologiques et neuropsychologiques ainsi que des questionnaires remplis par les patients et les soignants. L'analyse de régression logistique univariée a été utilisée pour déterminer s'il existait une association entre chaque variable indépendante et la variable binaire identifiée comme étant l'arrêt du traitement. L'analyse de régression logistique multivariée a été utilisée pour déterminer les facteurs de prédiction de l'arrêt des inhibiteurs de la cholinestérase dans les six premiers mois de traitement. ***Résultats :*** Notre échantillon était constitué des 63 premiers patients, dont 60,3% étaient des femmes, chez qui nous avons prescrit un inhibiteur de la cholinestérase. L'âge moyen était 74,56 ans (écart type = 7,78 ans). Nous avons constaté que le nombre d'années de scolarité était la seule variable dont l'association avec l'arrêt du traitement dans les 6 premiers mois était significative. Plus le nombre d'années de scolarité était élevé, plus le taux d'arrêt de la médication dans les 6 premiers mois était faible. ***Conclusion :*** Un nombre d'années de scolarité inférieur était le facteur de prédiction de l'arrêt du traitement par un inhibiteur de la cholinestérase dans les six mois suivant le début du traitement.

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Canada is currently facing a dementia epidemic with approximately 500,000 Canadians suffering from the disorder. This number is expected to double within a generation. The current economic burden of dementia care is $15 billion and is expected to reach $153 billion within the next 30 years.[1] Our limited therapeutic armamentarium for dementia includes cholinesterase inhibitors. Patients with mild to moderate Alzheimer's Disease treated with these therapies may experience modest improvement in cognition, function, behavior, and/or global clinical state.[2]

Patients with dementia who are placed on cholinesterase inhibitors may symptomatically improve, in which case the medication is continued. They may also remain the same, or become symptomatically worse, in which case the medication is often discontinued. Some patients, whether or not they improve with medication, experience side effects such as gastrointestinal distress, light-headedness, or bradycardia, that necessitate discontinuation of therapy. In a retrospective cohort study assessing health data from Saskatchewan, Canada, it was found that, over 40 months, 84% of patients discontinued therapy with the one-year risk of discontinuation being 66.4%.[3] Such high rates underscore the importance of research examining predictors of cholinesterase inhibitor discontinuation so as to identify patients who are likely to respond to and continue on treatment with cholinesterase inhibitors and those who are less likely to respond or to have adverse effects.

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Saskatchewan, a western Canadian province of one million, has a large rural and aging population. In 2011, 39.1% of the Saskatchewan population lived in rural areas and small towns.[4] People aged 46-64 years in 2011 made up more than one quarter of the Saskatchewan population. One in five residents living in a rural area or small town is 65 years or older.[5] To address and alleviate the gaps in delivery of prompt dementia care to the aging population in rural Saskatchewan, we developed the Rural and Remote Memory Clinic (RRMC) in 2004. The separation of health care professionals and patients by distance is addressed through the use of telehealth videoconferencing. Follow-up appointments are delivered through telehealth to minimize the time, expense, and inconvenience of travel for patients and their caregivers. The Memory Clinic's goals are to provide an interdisciplinary assessment of dementia, reduce repeated patient travel to various health care professionals, and shorten time to diagnosis. It has proven to be a successful model in providing integrated, efficient, and tailored patient care. More information on the Rural and Remote Memory Clinic is available elsewhere.[6-9]

Studies examining predictors of cholinesterase inhibitor discontinuation have suggested that female gender, more severe cognitive impairment, and absence of social assistance predict a higher likelihood of discontinuation. Conversely, frequent physician visits, higher Chronic Disease scores and greater functional impairment predicted a lower likelihood of discontinuation.[3] A Japanese study suggested that patients with more severe cognitive impairment (CDR=3) discontinued therapy earlier than those with less severe impairment, with the most common reason being ineffectiveness of the medication.[10] Although some studies have been done to identify predictors and rates for the discontinuation of cholinesterase inhibitor therapy, more research is needed in this area. Furthermore, predictors may vary in different populations and settings. Thus, it is important to identify and compare them. The results of this research may help plan the treatment of patients with dementia. It may also benefit their caregivers and the health care systems that support these patients.

Methods

Data Collection and Ethical Consideration

Data Collection began in March 2004 at the Rural and Remote Memory Clinic (RRMC) in Saskatoon, Saskatchewan. Family physicians referred their non-institutionalized patients to the clinic. The University of Saskatchewan Behavioural Research Ethics Board granted ethical approval for this study. Prior to participation, all patients and their families gave informed consent. Due to the RRMC being directed toward patients with early stage memory loss, we assumed that most patients were competent to provide informed consent, although complete patient assessment must be conducted to confirm this assumption. Therefore, a family member was asked to witness the consent protocol for the patient, and the patient was aware that a family member co-signed the consent forms. The assessment began with a pre-clinic telehealth appointment followed by an in-person clinic visit several weeks later. During this visit, the patient and family members met with and were jointly interviewed by a neurologist, neuropsychology team, and physical therapist, following which clinic team members assessed the patient individually. A standardized neuropsychological battery was administered.[6] Family members completed a questionnaire that included measures of caregiver burden, distress, and health, and ratings of the patient's behaviors and functional ability. Patients also completed a questionnaire that included self-ratings of mood, memory, functional ability, and quality of life. Unless recent imaging had been done, all patients underwent computed tomography (CT) brain scans. Following an end-of-day team conference, the neurologist and neuropsychology team met with the patient and family members to discuss the diagnosis and make treatment recommendations. At this time, detailed education and counseling was given to patients and caregivers by the Memory Clinic team regarding action and expected effect of cholinesterase inhibitor therapy, as well as techniques to avoid side effects such as taking medication with food. Patients and caregivers were provided with ample time for questions and clarifications of the disease and treatment. Patients were seen in follow-up, either in person or over telehealth, at six weeks, 12 weeks, six months and annually thereafter. Additional appointments were scheduled as needed. At the six-month follow-up appointment, it was noted whether or not the patient was still on cholinesterase inhibitor therapy.

Participants

We included in the present study the first 318 individuals living in rural and remote areas in Saskatchewan who were referred to the RRMC. The participants included in this study were the 63 patients started on a cholinesterase inhibitor at clinic day and who attended a six-month follow up appointment. Those already taking a cholinesterase inhibitor at presentation as well as those who did not attend the six-month follow up appointment were not included in the present study.

Measures

Patient and caregiver questionnaires administered at the clinic day appointment provided the socio-demographic, clinical, and functional independent variables. Socio-demographic variables were age, sex, marital status, years of formal education, ethnicity, and number of other chronic diseases (Table 1). Clinical variables were smoking status, times per week of exercise and alcoholic drinks per week. Caregiver-rated functional status of the patient was assessed using various scales outlined below:

1. *Functional Assessment Questionnaire (FAQ):* The FAQ is a 10-item screening tool assessing independence in daily activities and universal skills among older adults.[11] The items are rated on a 4-point scale ranging from 0 (independence) to 3 (dependence). Overall scores range from 0-30, with a higher score signifying greater patient dependency.
2. *Neuropsychiatric Inventory Severity Scale (NPI-S):* The NPI measures behavioural changes in patients with dementia.[12] The NPI-S, one component of the NPI scale, was used for this study. This NPI-S is a 12-item scale in which each item is rated from 1 (mild) to 3 (severe). Overall scores range from 1-36, with a higher score signifying more severe psychiatric symptoms.

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Table 1: Socio-demographic, functional and clinical characteristics of patients at clinic day (baseline)

Continuous Variables	**Mean ± SD**	**Range**
Age	74.56 ± 7.78	54-89
Years of Formal Education	10.38 ± 2.79	5.00-17.00
MMSE – Mini-Mental State Exam	22.31 ± 3.68	13-29
FAQ- Functional Assessment Questionnaire	13.79 ± 7.31	0-28
IADL- Instrumental Activities of Daily Living, patient-rated	22.10 ± 4.64	10-27
BADL- Bristol Activities of Daily Living	7.60 ± 6.50	0.0-27.5
QOLPT- Quality of Life of patient as rated by patient	35.42 ± 5.51	21-48
QOLCG- Quality of Life of patient as rated by caregiver	32.35 ± 5.92	17-48
LC – Life Concerns Scale	4.66 ± 5.40	0-21
MEM- Self-rating of Memory Scale	-11.52 ± 6.82	-27-2
CES-D- Centre for Epidemiological Studies - Depressed Mood Scale	12.34 ± 9.57	0-42
NPI-S- Neuropsychiatric Inventory Severity	7.92 ± 5.61	1-30
Alcoholic Drinks per Week	1.32 ± 2.47	0.00-12.00
Categorical Variable		**n (%)**
Gender		
Male		25 (39.7)
Female		38 (60.3)
Ethnicity		
European		46 (73.0)
Other		11 (17.5)
Not completed by patient		6 (9.5)
Marital Status		
Married/Common-law		42 (66.7)
Single/Divorced/Separated/Widowed		20 (31.7)
Not completed by patient		1 (1.6)
Smoker		
Yes		10 (15.9)
No		26 (41.3)
Not completed by patient		27 (42.9)
Presence of Other Chronic Diseases		
≤ 2 conditions		10 (15.9)
3 conditions		12 (19.0)
4 conditions		11 (17.5)
5 or more conditions		29 (46.0)
Not completed by patient		1 (1.6)

3. *The Bristol Activities of Daily Living Scale (BADL):* The BADL is an instrument containing 20 daily living abilities in four areas: mobility, instrumental activities of daily living, self-care, and orientation.[13] The items are rated on a scale from 0 (independence) to 3 (dependence). Overall scores range from 0-60, with a higher score signifying greater dependence.
4. *Quality of Life of the Patient (caregiver rated) (QOLCG):* The QOLCG uses a 13-item scale that rates various aspects of the patient's life.[14] The items are rated on a scale from 1 (poor) to 4 (excellent). Overall scores range from 13-52, with a lower score signifying poorer quality of life of the patient.

Self-rated functional and lifestyle status of the patient was assessed using various scales outlined below:

1. *Quality of life of the Patient (patient rated) (QOLPT):* The QOLPT uses a 13-item scale that rates various aspects of the patient's life.[14] The items are rated on a scale from 1 (poor) to 4 (excellent). Overall scores range from 14-56, with a lower score signifying poorer quality of life of the patient.
2. *Center for Epidemiologic Studies-Depression Scale (CES-D):* The CES-D is a 20-item scale that assesses depressive symptoms.[15] The items are rated on a scale from 0 (rarely of none of the time) to 3 (most or all of the time). Overall scores range from 0-60, with a higher score signifying more depressive symptoms.
3. *Life Concerns Scale (LC):* The LC scale, a scale developed for the purpose of this study, assesses the patient's stress and concern with various aspects of his/her life. The 14 items are rated on a scale from 0 (no concern) to 4 (extreme concern), with a higher score signifying greater patient stress.
4. *Instrumental Activities of Daily Living (IADL):* The IADL is a 9-item scale that measures the ability of the patient to perform daily tasks.[16] The items are rated on a scale from 1 (being unable to perform the task independently) to 3 (being able to perform the task independently). Overall

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scores range from 9-27, with a higher score signifying greater level of function.

5. *Self-rating of Memory (MEM):* The MEM is a 15-item scale that assesses memory of the patient.[17] Each item is rated from -2 (much worse) to +2 (much better). Overall scores range from -30 to +30, with a lower or more negative score signifying worse memory symptoms.

Although multiple neuropsychological tests were administered, for the purposes of this study global cognitive impairment was assessed with the Mini-Mental State Exam (MMSE), as this test is required for coverage by the Saskatchewan Drug Plan.

Outcome: Discontinuation by six months

The dependent variable in this study was discontinuation of cholinesterase inhibitor therapy by six months. Switching from one cholinesterase inhibitor to another was not considered discontinuation.

Statistical Analysis

Data were analyzed using IBM SPSS version 19.0 software. Descriptive analysis was performed for all of the variables in order to characterize the sample. Categorical variables were described in terms of frequency and percentage. Continuous variables were described in terms of mean and standard deviation.

A univariate logistic regression analysis was carried out in order to examine the association between each potential independent variable and the binary outcome variable of discontinuation by six months. Based on bi-variable analysis, independent variables associated with the dependent variable with a $p<0.20$ became candidates for a multivariable logistic regression model. All variables that were significantly correlated with discontinuation of cholinesterase inhibitor therapy ($p<0.05$), as well as important individual factors (age and sex) were retained in the final multivariable model. The goodness of fit statistic for the final model was identified using the Hosmer and Lemeshow test. The strength of associations was presented by odds ratios and their 95% confidence intervals.

Results

Study Population

The total number of patients seen was 318. For many patients, a cholinesterase inhibitor was not considered due to

Table 2: Bivariate regression analysis

Variables	Odds Ratio (OR*)	95% CI	p value
Age	0.99	0.92-1.05	0.61
Gender[a]			
Female	1.19	0.39-3.60	0.76
Ethnicity[b]			
Other	0.70	0.16-3.03	0.64
Marital Status[c] Single/Divorced/Separated/Widowed	1.35	0.43-4.20	0.61
Years of Formal Education	0.77	0.61-0.98	0.03
Presence of Other Chronic Diseases[d]			
3 conditions	1.17	0.19-7.12	0.87
4 conditions	1.33	0.21-8.29	0.76
5 conditions	0.89	0.18- 4.31	0.88
Times per week of Exercise	1.00	0.86-1.16	0.98
Smoker[e]			
No	0.96	0.20-4.72	0.96
Alcoholic Drinks per Week	0.93	0.72-1.20	0.58
MMSE- Mini Mental State Exam	0.92	0.79-1.07	0.27
FAQ- Functional Assessment Questionnaire	1.06	0.98-1.14	0.15
IADL- Instrumental Activities of Daily Living, patient-rated	0.95	0.84-1.07	0.39
BADL- Bristol Activities of Daily Living	1.03	0.95-1.12	0.48
QOLPT- Quality of Life of patient as rated by patient	1.02	0.92-1.13	0.67
QOLCG- Quality of Life of patient as rated by caregiver	0.99	0.90-1.08	0.76
LC – Life Concerns Scale	1.00	0.91-1.11	0.95
MEM- Self-rating of Memory Scale	1.00	0.92-1.08	0.93
CES-D- Centre for Epidemiological Studies-Depressed Mood Scale	1.01	0.96-1.07	0.67
NPIS- Neuropsychiatric Inventory Severity	1.00	0.90-1.10	0.98
PS- Perceived Stress Scale	1.02	0.83-1.25	0.88

a. Gender (patient): reference is male; b. Ethnicity: reference is European; c. Marital Status: married/ common-law; d. Presence of other chronic diseases: reference is ≤ 2 conditions; e. Smoker: reference is yes; Notes: Variables with $p < 0.2$ become candidates for the multivariate logistic regression model. *OR=1 - No relationship; *OR<1 - Decreased risk of discontinuation; *OR>1 - Increased risk of discontinuation

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Table 3: Mean difference in clinic day MMSE scores between patients who discontinued treatment by six months and patients who continued treatment

Discontinued at 6 m		N	Mean	Std. Deviation	Std. Error Mean
MMSE /30	Yes	18	21.50	3.62	0.85
	No	43	22.65	3.70	0.56

Mean Difference = 1.15; Std. Error Difference = 1.03; p value = 0.27

diagnosis or contraindication. The final study sample consisted of 63 patients started on a cholinesterase inhibitor who met the requirements of being treatment naïve at presentation and attending a six-month follow up appointment. The mean patient age at clinic day for the study sample was 74.56 years (SD=7.78 years). The majority of patients were female (60.3%), over half were married or living with a common-law partner (66.7%), and most were of European ancestry (73.0%). The most common diagnosis was Alzheimer's Disease (83.6%), followed by Lewy Body dementia (8.2 %), mixed dementia (vascular/Alzheimer's) (5.5%), and vascular dementia (2.7%). Sixty-one patients were started on donepezil and two on galantamine. Subsequently, one was switched from donepezil to galantamine and one from donepezil to rivastigmine. Out of 63 patients, 19 (30.2%) had discontinued cholinesterase inhibitor therapy within six months. Reasons for discontinuation (n=19) were as follows: ineffectiveness of the drug (n=10), negative side effect(s) (n=6), and ineffectiveness of the drug plus negative side effect(s) (n=3). Negative side effects included nausea (n=6), vomiting (n=1), diarrhea (n=1), irritability (n=1), leg cramps (n=1), unpleasant dreams (n=1), and dramatic weight loss (n=1).

Bivariate and multivariate analyses

All independent variables underwent bivariate analysis with discontinuation of cholinesterase inhibitor therapy by or at six months as the dependent variable. Age, sex, marital status, ethnicity, smoking status, times per week of exercise, alcoholic drinks per week, MMSE clinic day scores and the presence of other health conditions were not significantly associated with discontinuation. The functional and lifestyle assessment scales (FAQ, IADL, BADL, QOLPT, QOLCG, LC, MEM, CES-D, and NPIS) were also not significantly associated with discontinuation in the bivariate analysis (Table 2). The mean difference in MMSE clinic day scores between patients who discontinued therapy by six months and those who continued was examined, but MMSE clinic day scores were not significantly different between the two groups of patients (p=0.27) (Table 3).

Years of formal education, which differed significantly between patients who continued or discontinued treatment, was selected from the bivariate analysis and used in the multivariate logistic regression analysis, where it remained significant ($p<0.05$). The greater the years of formal education, the lower the rate of discontinuation of therapy by six months. Age and sex, important individual factors and cited in the literature as significant, were also included in the multivariate logistic regression analysis. By including age and sex, we made sure that any effects of these variables were captured in the model (Table 4). The final selected model satisfied the goodness of test criteria (Chi Squared Statistics $\chi^2=10.43$, degrees of freedom=8, P value=0.24).

Discussion

The objective of this study was to obtain socio-demographic/economic, clinical, and functional predictors of cholinesterase inhibitor therapy discontinuation by six months. Knowing possible predictors for cholinesterase inhibitor discontinuation is valuable to clinicians, their patients, and to the health care system. A limitation of this study may be small sample size. Few studies have examined predictors of cholinesterase discontinuation beyond age, sex, and the type of cholinesterase inhibitor.[3] Studies comparing types of cholinesterase inhibitors have examined discontinuation rates

Table 4: Multiple logistic regression analysis

Variable	Odds Ratio (95% CI)	p value
Age (in years)	0.97 (0.90-1.05)	0.42
Gender (reference male)	1.07 (0.32-3.53)	0.91
Education (in years)	0.76 (0.59-0.96)	0.02

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between donepezil, galantamine, and rivastigmine[18,19], between galantamine and rivastigmine[20], and between two different doses of donepezil.[21] Further studies have looked at switching between cholinesterase inhibitors[22] and creating guidelines for cholinesterase inhibitor discontinuation.[23] The strengths of the current study include the sample, which consisted of non-institutionalized patients with heterogeneous ethnic backgrounds allowing for generalization to a larger population, and the extensive patient and caregiver variable data available on these patients.

Of the 63 patients started on a cholinesterase inhibitor, 19 had discontinued cholinesterase inhibitor therapy by six months. Our discontinuation rate of 30.2% (persistence/continuation rate of 69.8%) was consistent with the results of a retrospective cohort study from the Netherlands, which found that at six months, the cholinesterase inhibitor discontinuation rate was 30.8%.[20] Another study found that over 40 months, 84% of patients discontinued therapy with the one-year risk of discontinuation being 66.4%.[3] In a study from Quebec, persistence of cholinesterase inhibitor therapy at one year was found to be 45.3%.[24]

Using logistic regression analysis, we identified years of formal education as the only significant predictor of drug discontinuation. We found an inverse correlation between years of formal education and discontinuation by six months. Previous research has suggested that education plays a significant role in Alzheimer's disease and other dementias, pertaining to risk and progression of disease. It is interesting that we have found education to also be a predictor for dementia therapy persistence. We speculate that those with more years of formal education may better understand and appreciate the importance of continuing therapy. Negative side effects, which may be considered minor in comparison to the effects of the illness, may be dealt with more patiently for this reason, resulting in higher continuation rates among those with higher education.

None of the demographic variables or patient variables (FAQ, IADL, BADL, QOLPT, QOLCG, LC, MEM, CES-D, NPIS), predicted discontinuation of cholinesterase inhibitor therapy. Thus, in this study, ability to perform activities of daily living, patient quality of life, self-rated memory, mood, and behavioral symptoms did not have a major impact on discontinuation of anti-dementia drug treatment. Earlier studies have reported female gender, lower MMSE scores (higher level of cognitive impairment), and lack of social assistance as predictors of discontinuation.[3] We did not include income or social assistance in our study because the Saskatchewan Drug Plan covers the cost of cholinesterase inhibitor therapy, and almost all patients are covered. New patients are eligible for coverage if, during the three-month trial period, they exhibit an improvement from their initial MMSE by at least 2 points or their FAQ score by -1 point. The MMSE score must also remain above 10 to continue eligibility for drug coverage.[25] Patients who lose eligibility due to ineffectiveness would be likely to discontinue anyway, or if they are advised to continue, begin purchasing it themselves.

A retrospective cohort study using administrative health data from Saskatchewan found that higher chronic disease scores, FAQ scores of 9+ (indicating greater patient dependency), and frequent physician visits decreased the risk of discontinuation[3], but these factors were not important predictors in the current study, which had a smaller sample size but was able to examine a larger number of patient characteristics.

Our data shows that having more years of formal education decreases the risk of treatment discontinuation in dementia. This could be due to better understanding of treatment goals and higher compliance. Since patients with fewer years of formal education are at an increased risk of discontinuation, more time should be allotted for counseling about the possible positive and negative effects of treatment. Awareness about the effects of the illness in comparison to negative side effects of treatment should be raised with patients.

This study introduces areas for future research. The impact of education on treatment discontinuation needs to be examined further.

Disclosure

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