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Cholinesterase Inhibitor Utilization: The Impact of Provincial Drug Policy on Discontinuation

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ABSTRACT

Background: In October 2007, British Columbia started to cover the cost of cholinesterase inhibitors (ChEIs)—donepezil, galantamine, and rivastigmine—for patients with mild to moderate dementia and prominent Alzheimer's disease. **Objectives:** To examine the impact of this policy on persistence with ChEIs. **Methods:** A population-based cohort study was conducted using British Columbia administrative health data. We examined 45,537 new ChEI users aged 40 years and older between 2001 and 2012; 20,360 (45%) started the treatment after the coverage policy was launched. Patients were followed until treatment discontinuation, defined as a ChEI-free gap of 90 days, death, or December 2013. Persistence on ChEIs was estimated using survival analysis and competing risk approach. Hazards of discontinuation were compared using competing risk Cox regression with propensity adjustment. **Results:** Patients who started ChEI therapy after the introduction of the coverage policy had a significantly longer persistence. Median ChEI persistence until discontinuation or death was 9.37 months (95% confidence interval [CI] 9.0–39.7) and 17.6 months (95% CI 16.9–18.3) in patients who started therapy before and after the new policy, respectively. The propensity-adjusted hazard ratio for discontinuing therapy was 0.91 (95% CI 0.88–0.94). Similar patterns were observed for persistence with the first ChEI (propensity-adjusted hazard ratio of 0.94; 95% CI 0.91–0.98). In rivastigmine users, the hazard ratio was insignificant (0.98; 95% CI 0.92–1.02). **Conclusions:** The British Columbia ChEI coverage policy was associated with significantly prolonged persistence with donepezil and galantamine, but not rivastigmine.

Keywords: cholinesterase inhibitors, dementia, drug policy, persistence.

Introduction

In October 2007, the British Columbia public drug insurance plan, PharmaCare, initiated coverage of three cholinesterase inhibitors (ChEIs) used in Alzheimer's disease: donepezil, rivastigmine, and galantamine [1]. ChEIs were previously not covered by PharmaCare because clinical trials had not adequately addressed the effects on day-to-day function but rather focused on the effects on cognitive abilities [2]. To address this perceived evidence gap, ChEI coverage was provided as part of a research program using the coverage with evidence development concept [3]. The combined coverage-research program, known as the Alzheimer's Drug Therapy Initiative (ADTI), was designed to address gaps in knowledge on safety, effectiveness, and appropriate use of ChEIs.

The new ADTI program provided coverage to patients who demonstrated mild to moderate cognitive decline and Alzheimer's disease or other dementia with prominent Alzheimer's disease [4]. Mild to moderate cognitive decline was defined as a score of 10 to 26 on the Standardized Mini-Mental State Examination and 4 to 6 on the Global Deterioration Scale. Patients underwent reassessment every 6 to 7 months. Patients lost their eligibility for reimbursement if the score on the Standardized Mini-Mental State Examination was lower than 10 or the score on the Global Deterioration Scale was higher than 6 or lower than 4. Memantine, another medication marketed for Alzheimer's disease, was not covered because it works by a different mechanism of action and has a different indication (moderate to severe dementia). Furthermore, evidence on memantine's effectiveness was considered to be insufficient to justify drug coverage [5]. The new ChEI coverage policy was implemented subject to cost-sharing levels that were part of the larger PharmaCare plan; ChEI users had to share prescription costs in a manner that depended on family income and the total annual cost of their medications [6].

Conflicts of interest: All inferences, opinions, and conclusions drawn in this publication are those of the Alzheimer's Drug Therapy Initiative (ADTI) researchers, and do not reflect the opinions or policies of the British Columbia Ministry of Health.

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Included in the ADTI research program were several assessments of the impact of drug coverage on health service utilization. Because the new drug coverage policy started about 10 years after the first ChEI, donepezil, was licensed in Canada [7], it was possible to compare utilization before and after its implementation. This study examined ChEI persistence, a common measure of drug utilization, which is defined as the time from drug initiation to discontinuation [8]. Lack of efficacy and harmful events are the most common causes of drug discontinuation [9]; cost, however, is also a factor [10–12]. Given the new coverage policy introduced criteria for ChEI discontinuation, we hypothesized that it led to shorter persistence, despite the decrease in out-of-pocket fees. The goal of this study was to examine the effect of new ChEI coverage policy on persistence and risk of discontinuing ChEIs in the Canadian province of British Columbia.

Methods

Data Source and Study Cohort

We conducted a population-based cohort study, using data from the British Columbia Ministry of Health administrative claim databases. We analyzed data on prescription dispensing, demographic characteristics, enrollment in the provincial Medical Service Plan, fee-for-service payments to physicians and alternative providers, and hospital separations. Data were linked using de-identified unique patient numbers. The study protocol was approved by the Clinical Research Ethics Board, University of British Columbia, and the Human Research Ethics Board, University of Victoria.

We identified new users of donepezil, galantamine, or rivastigmine between January 1, 2001, and December 31, 2012. We excluded patients with a pharmacy refill for any ChEI in the year before entering the cohort, as well as those without continuous enrollment in the provincial health program for at least 1 year. Patients younger than 40 years at cohort entry and those with *combination therapies*, defined as refills of two or more different ChEIs at cohort entry, were also excluded. Patients were included as new users only once. They were followed until the earliest occurrence of December 31, 2013, or a gap of more than 14 days in continuous provincial health plan enrollment. Patients without a diagnosis of Alzheimer's disease and those in long-term care facilities were not excluded, but these factors were controlled for in the adjusted analysis.

Outcomes

We analyzed two types of outcomes: ChEI persistence, measured until discontinuation of any ChEI, and persistence with the first ChEI. For ChEI persistence, we extracted the ChEI refill records of the study cohort. We aggregated refills on the same date and selected the largest days-supply recorded regardless of the specific ChEI dispensed. Days supplied in each refill were limited to 90 because a very large number of days could mean an error in recording. *ChEI discontinuation* was defined as a failure to refill any ChEI prescription within 90 days of the exhaustion of the medication supply in earlier refills (i.e., 90-day ChEI-free gap). We allowed stockpiling of not more than 90 days and adjusted the dispensing date to the end of the previously days-supply dispensed. Stockpiling was managed this way because new prescriptions occasionally preceded the exhaustion of drug supply from earlier prescriptions. The end of course was the date of exhaustion of the refilled ChEI or the end of follow-up data, whichever was earliest. Three mutually exclusive events determined the latest "on-treatment" date: 1) discontinuation, when the ChEI-free gap ended before the end of follow-up data; 2) death, when the patient died before the end of the ChEI-free gap; or 3) censoring, when follow-up data ended before discontinuation or death. ChEI persistence was measured from cohort entry until discontinuation, death, censoring, or end of refilled days, whichever was the earliest.

In a subsequent analysis of persistence with only the first ChEI, switching between ChEI was considered discontinuation. *Switching* was defined as the first pharmacy refill of a second ChEI during treatment or before the end of the ChEI-free gap, and patients who added a second ChEI (combination therapy) were also considered "switchers." For switchers, the end of course was set to the switching date or the exhaustion of the first ChEI, whichever was earlier.

Exposure, Covariates, and Possible Confounders

We compared two groups of ChEI new users. Prepolicy new users were patients who entered the cohort before November 1, 2007, and postpolicy new users were patients who entered the cohort after this date. In multivariate regression analyses we controlled for demographic characteristics and proxies for clinical factors that may have confounded the association between the policy exposure and the persistence outcome (see Table S1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.03.1832). We controlled for age, sex, income, geographical residence, Alzheimer's diagnosis, and disease duration, as well as long-term care residence, comorbidities (Romano score [13,14]), and number of physician visits, hospital days, and different generic drugs refilled in the year before cohort entry. In addition, the models included a series of dichotomous variables to indicate the use of statins, antipsychotics, anxiolytics, hypnotics, antidepressants, and nonsteroidal anti-inflammatory drugs in the year before cohort entry. We also adjusted for prescriber specialty and the first drug prescribed (donepezil, galantamine, or rivastigmine). We did not control for combination therapy with memantine at cohort entry because less than 1% of the patients had a dispensing of memantine within the 3 months before cohort entry.

To further reduce bias and improve the validity of our comparison estimates, we calculated high-dimensional propensity scores (HDPSs) [15,16] for ChEI discontinuation within the first 3 years of treatment. We used data from the year before the entry date. The HDPS method searches through all variables in a database to identify and adjust for those unanticipated variables that may confound the main analysis. The method is described in detail elsewhere [15]. The HDPS included all the aforementioned variables in addition to the 200 variables that were captured by the HDPS algorithm. A large separation of the HDPS distributions between the comparison groups was found (c-statistics 0.960), meaning that the prepolicy and postpolicy new users were very different. We trimmed approximately 10% of the new users who had extreme, nonoverlapping scores [17]. This trimming allowed us to include in the analysis only those patients who had the potential to be treated both before and after the new coverage policy, and therefore to increase the validity relative risk estimates. The remaining 45,537 patients constituted the study cohort.

Statistical Analysis

Persistence, or time to discontinuation, was estimated and compared using survival analysis, and death, which was frequent in the study cohort, was approached as a competing risk [18]. In this study, death and discontinuation are not independent events because discontinuation required the patient to be alive at least 90 days after the exhaustion of the refilled drug. We undertook a three-phase approach. First, we considered either