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Featured Article

Comparison of cholinesterase inhibitor safety in real-world practice

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Abstract

Introduction: Cholinesterase inhibitors (ChEIs) are widely used to treat mild to moderate Alzheimer's disease and related dementia. Clinical trials have focused on placebo comparisons, inadequately addressing within-class comparative safety.

Methods: New users of ChEIs in British Columbia were categorized into five study cohorts: low-dose donepezil, high-dose donepezil, galantamine, rivastigmine patch, and oral rivastigmine. Comparative safety of ChEIs assessed hazard ratios using propensity score adjusted Cox regression.

Results: Compared with low-dose donepezil, galantamine use was associated with a lower risk of mortality (adjusted hazard ratio: 0.84, 95% confidence interval: 0.60–1.18), cardiovascular serious adverse events (adjusted hazard ratio: 0.78, 95% confidence interval: 0.62–0.98), and entry into a residential care facility (adjusted hazard ratio: 0.72, 95% confidence interval: 0.59–0.89).

Discussion: Given the absence of randomized trial data showing clinically meaningful benefit of ChEI therapy in Alzheimer's disease, our study suggests preferential use of galantamine may at least be associated with fewer adverse events than treatment with donepezil or rivastigmine.

Keywords: Cholinesterase inhibitor; Alzheimer's disease; Dementia; Log-binomial regression; Cox proportional hazard; Propensity score; Epidemiology

1. Introduction

Alzheimer's disease and related dementia (ADRD) is a growing problem in Canada, affecting an estimated 747,000 people in 2012, with 25,000 new cases diagnosed every year [1]. In British Columbia, cholinesterase inhibitors (ChEIs) are commonly prescribed for treatment of ADRD, where the B.C. Ministry of Health requires a baseline cognitive assessment as part of its Special Authority process [2]. Because little data exist beyond the 6-month to one-year clinical trials and this group of medications is frequently prescribed to patients with ADRD, there is an opportunity for observational data to assess longer-term safety and effectiveness [3].

ChEIs increase cholinergic function by preventing the breakdown of acetylcholine, a neurotransmitter that supports communication among nerve cells when its levels are sufficiently high. Acetylcholinesterase is an enzyme involved in the rapid hydrolysis of acetylcholine. Through inhibition of acetylcholinesterase, ChEIs, such as donepezil, rivastigmine, and galantamine, allow acetylcholine to accumulate. The rationale for prescribing ChEIs for treating symptoms of ADRD is to increase acetylcholine levels, which increases neuronal activity. However, this is a strategy that has low effectiveness [4], and there is no evidence that ChEIs prevent the underlying dementing process [5].

ChEIs have additional pharmacological actions. Rivastigmine inhibits butyrylcholinesterase with a similar

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affinity to acetylcholinesterase. The therapeutic effect and resulting clinical consequences of this is unknown [6,7]. Galantamine potentiates the action of acetylcholine on nicotinic receptors, which may influence neuronal processes, such as synaptic efficacy and neuroprotection [8,9]. Evidence suggests the cholinergic adverse effects of these drugs may cause gastrointestinal, neurological, cardiovascular, and urinary disorders [10,11]. In severe instances, these drugs may increase vagal tone and, thereby, precipitate bradycardia [12]. Multiple U.S. Food and Drug Administration safety alerts have raised concerns of increased mortality and serious cardiovascular adverse events in patients taking ChEIs for mild cognitive impairment versus placebo-treated patients [13].

A Cochrane database systematic review (Russ [14]) found no significant difference in progression to dementia between ChEIs and placebo at 12 months. They found ChEIs increased overall adverse events compared with placebo but found no significant differences between the groups for serious adverse events, cardiac problems, depression, or death. Earlier systematic reviews found small improvements or unchanged cognitive benefits with ChEIs versus placebo [15]. In addition, some trials within the systematic reviews showed an unexplained increased death rate.

Effective October 22, 2007, the British Columbia Ministry of Health began providing financial coverage of the ChEIs through the Alzheimer's Drug Therapy Initiative to address clinical knowledge gaps around the safety and effectiveness of these drugs [16]. Patients receiving a baseline assessment score on the Standardized Mini–Mental State Examination of mild to moderate cognitive impairment are eligible for full financial coverage of a ChEI.

We investigated the risk of mortality between the ChEIs for new users during the Alzheimer's Drug Therapy Initiative. Serious cardiovascular events were investigated as a secondary outcome. We also looked at time to entry into a residential care facility. Supporting people with ADRD to function in their own homes for as long as possible is a stated priority of the B.C. Provincial Guide to Dementia Care [17].

2. Methods

2.1. Data

We obtained access to the B.C. Ministry of Health administrative health claims database through a secure access environment. The database contains linkable, but deidentified, health service records containing all prescriptions dispensed at community pharmacies, physician services, hospital separations, and vital statistics data in British Columbia. We assume that the completeness and accuracy of the data is comparable to other administrative databases [18,19].

2.2. Study design and source population

We conducted a retrospective, propensity score–adjusted cohort study. The source population for the study was all B.C. residents between October 2007 and March 2016 who were registered in the provincial universal medical services plan. Federally insured patients, such as indigenous people, federal police officers, and members of the armed forces and their families, were excluded from the source population because they are not included in the data set. Excluded patients composed about 7% of the provincial population. The source population numbered 4.42 million in 2016 [20].

2.3. Study cohorts

New users of ChEIs were identified during the study period as having no ChEI prescription in the previous 365 days. New users were categorized into 5 exposure groups based on their first prescription: (1) low-dose donepezil ($\leq$7.5 mg/day), (2) high-dose donepezil (>7.5 mg/day), (3) galantamine, (4) rivastigmine patch, and (5) rivastigmine oral. Low-dose donepezil was defined based on receiving a dose equivalent to, or below, the World Health Organization's Defined Daily Dose. Low-dose donepezil, the most frequently prescribed ChEI, was assigned as the reference drug, providing four comparison cohorts instead of a single multinomial regression approach.

The date of each patient's first ChEI dispensing was defined as the index date. Patients were excluded from the study cohorts if they were under 50 years old on the index date, in a residential care facility in the 2-year period before index date, did not have continuous medical insurance in the 1-year period before index date, or dispensed more than one ChEI on index date.

2.4. Study outcomes

Our primary outcome was all-cause mortality. Secondary outcomes were (1) composite cardiovascular serious adverse events and (2) entry into a residential care facility. Composite cardiovascular events consisted of a hospital admission for myocardial infarction (ICD-9: 410), coronary artery disease (ICD-9: 411-414), heart failure (ICD-9: 428), arrhythmia (including atrial fibrillation) (ICD-9: 427), and peripheral arterial or vascular disease (ICD-9: 443.9, 440). Entry into a residential care facility was determined by the presence of a government-subsidized prescription under the residential care benefit plan.

2.5. Data analysis

Safety of ChEIs was compared using time-to-event Cox proportional regression. Four drug comparisons were made: (1) low-dose donepezil versus high-dose donepezil, (2) low-dose donepezil versus galantamine, (3) low-dose donepezil versus rivastigmine patch, and (4) low-dose donepezil versus oral rivastigmine. Patient follow-up was censored at the earliest occurrence of our study outcome, death, end of the study period (31 March 2016), emigration from BC, therapy discontinuation, or crossover to another study cohort. Sensitivity analyses used log-binomial regression to

estimate relative risk at 6-month and 12-month fixed follow-up periods [21]. All outcome models were adjusted for history of prior cardiovascular events, smoking, and high-dimensional propensity scores meant to capture other confounding factors. The high-dimensional propensity score methods have been previously described in detail here [22].

2.6. Confounders

Potential confounders were measured before exposure to a ChEI using hospital and physician diagnostic codes, dispensed prescription records, and patient demographic records. The following covariates were included in the outcome model if they occurred within two years before index date: arrhythmia (ICD-9: 427; ICD-10: I49), myocardial infarction (ICD-9: 410; ICD-10: I21), stroke (ICD-9: 430-434, 436; ICD-10: I60, I61, I64, I63), angina (ICD-9: 413; ICD-10: I20), congestive heart failure (ICD-9: 428; ICD-10: I50), cerebrovascular disease (ICD-10: I60-I69), coronary artery disease (ICD-9: 411, 412, 414; ICD-10: I22-I25, Z95.1, Z95.5, Z98.61), peripheral arterial disease (ICD-9: 440, 443.9; ICD-10: I70, I73.9), or diabetes (ICD-9: 250; ICD-10: E10-E14). Other covariates included sex, age group (50–64, 65–74, 75–84 as reference, 85+), and smoking status (current or past smoker).

The following predefined demographic and diagnostic covariates were incorporated into the high-dimensional propensity score model: age group, sex, family income, index year, time since ADRD diagnosis, more than five distinct medications dispensed in previous year (yes/no), more than five physician visits in previous year (yes/no).

3. Results

There were 34,338 patients from the source population who initiated a ChEI between 22 October 2007 and 31 March 2016. Of those, 29,047 patients remained eligible for the study after exclusions for not meeting medical insurance eligibility criteria (5.4%), resident of a long-term care facility in prior two years (7.9%), initiating more than one ChEI on cohort entry date (1.8%), and age under 50 years (0.4%).

Baseline patient characteristics of the study cohorts (Table 1) were similar for average age of patients (80.5 years). The proportion of female patients was lowest in the oral rivastigmine (48%) cohort and highest in the low-dose donepezil (60%) cohort. Smokers, past or current, ascertained by the presence of a diagnosis of chronic obstructive pulmonary disease or use of a prescription smoking cessation therapy were similar among all cohorts. Galantamine users had the highest proportion of cardiovascular-related hospital admissions in the 2-year period before index date, including stroke, unstable angina, cerebrovascular disease, coronary artery disease, and peripheral arterial disease. Prior medication history was similar, other than prior use of antipsychotics, which was nearly double (19.5%) with oral rivastigmine compared with the low-dose donepezil cohort (10.0%).

Compared with low-dose donepezil, galantamine was associated with a 16% lower 3-year risk of mortality (adjusted hazard ratio [aHR]: 0.84, 95% confidence interval [CI]: 0.60–1.18). High-dose donepezil had similar risk (aHR: 0.97, 95% CI: 0.61–1.54), and the rivastigmine patch had 29% higher risk (aHR: 1.29, 95% CI: 0.93–1.79) (Table 2). The mortality differences were not statistically significant ($P < .05$).

Compared with low-dose donepezil, galantamine was associated with a lower risk of serious cardiovascular events (aHR: 0.78, 95% CI: 0.62–0.98) and entry into a residential care facility (aHR: 0.72, 95% CI: 0.59–0.89) (Table 2). Comparison with the oral rivastigmine could not be completed due to small-cell data restrictions.

In the 12-month fixed follow-up sensitivity analysis of cardiovascular events, galantamine was associated with an 18% lower risk (adjusted risk ratio [RR]: 0.82 (0.72–0.93) and rivastigmine patch was associated with a 15% higher risk (RR: 1.15 [1.01–1.32]), compared with low-dose donepezil. In the 6-month fixed follow-up analysis of cardiovascular events, there was no significant difference between low-dose donepezil and any of the study medications.

Compared with low-dose donepezil, galantamine was associated with a lower risk of mortality at 6 months (RR: 0.83, 95% CI: 0.69–1.01) and 12 months (RR: 0.82, 95% CI: 0.72–0.93), although the 6-month result was nonsignificant. The rivastigmine patch was associated with an increased risk of mortality at 6 months (RR: 1.21, 95% CI: 0.99–1.49) and at 12 months (RR: 1.15, 95% CI: 1.01–1.32), although the 6-month result was nonsignificant. Both formulations of rivastigmine, patch and oral, were also associated with a 12-month increased risk of entry into residential care (RR: 1.14, 95% CI: 1.03–1.26) and (RR: 1.275, 95% CI: 1.06–1.52), respectively (Tables 3 and 4).

4. Interpretation

This study compares ChEIs in terms of mortality, serious cardiovascular events, and entry into a residential care facility. Donepezil users were divided into low- and high-dose exposure groups based on WHO Defined Daily Dose. Nearly all users of galantamine and rivastigmine (98%) used the single WHO Defined Daily Dose.

The 3-year risk of serious cardiovascular events was 22% lower (aHR 0.78 CI: 0.62–0.98) and all-cause mortality was 16% lower (aHR 0.84 CI: 0.60–1.18) in galantamine versus low-dose donepezil, although the mortality results were not significant at the conventional α level of 0.05. Similar results were seen in both fixed follow-up sensitivity analyses. A Danish cross-national study comparing cardiovascular safety of dementia medications found similar benefits for galantamine (29% lower risk of heart failure [aHR 0.71 CI: 0.46–1.10]) [23].

Table 1
Baseline patient characteristics

Characteristics	Donepezil (low dose) N or mean (n = 15,586)	% or SD	Donepezil (high dose) N or mean (n = 2519)	% or SD	Galantamine N or mean (n = 5926)	% or SD	Rivastigmine (patch) N or mean (n = 4286)	% or SD	Rivastigmine (oral) N or mean (n = 730)	% or SD
Age (years), mean (IQR)	80.7 (76-86)		78.7 (74-85)		80.8 (77-86)		80.3 (76-85)		79.2 (75-84)	
Female, n (%)	9366	60	1305	52	3400	57	2319	54	347	48
Low family income* (<$30k), n (%)	3469	22	507	20	1389	23	1169	27	139	19
Year of study cohort entry, n (%)										
2007 (Oct 22–Dec 31)	323	2	97	4	229	4	-	0	64	9
2008	1763	11	437	17	1277	22	94	2	186	25
2009	1767	11	371	15	1277	22	558	13	120	16
2010	1966	13	375	15	1051	18	744	17	76	10
2011	2241	14	360	14	787	13	791	18	75	10
2012	2350	15	355	14	554	9	774	18	59	8
2013	2336	15	256	10	348	6	657	15	68	9
2014	2182	14	215	9	315	5	536	13	62	8
2015 (up to March 31)	658	4	53	2	88	1	132	3	20	3
Duration of ADRD (years), mean (SD)	1.04	2.3	1.02	2.3	1.07	2.4	1.10	2.3	1.09	2.2
High-dose first prescription†, n (%)	-	-	-	-	113	1.9	23	0.5	10	1.4
High-dose second prescription†, n (%)	3471	22	-	-	134	2.3	11	0.3	11	1.5
Follow-up time (years)‡, mean (SD)	3.41 (1.95)		3.86 (2.05)		4.14 (2.12)		3.28 (1.76)		3.95 (2.26)	
Smoker§ (past or current), n (%)	6955	45	1075	43	2660	45	1967	46	311	43
Number of hospital admissions in previous year										
0, n (%)	10,709	69	1777	71	4080	69	2768	65	482	66
1–2, n (%)	1778	11	288	11	729	12	523	12	108	15
3+, n (%)	3099	20	454	18	1117	19	995	23	140	19
Number of physician visits in previous year, mean (SD)	21 (18.2)		20.9 (16.7)		21 (17.2)		25.2 (21.6)		24.1 (19.8)	
Prior medical history¶ (2 years), n (%)										
Atrial fibrillation or flutter	2393	15.4	336	13.3	982	16.6	704	16.4	105	14.4
COPD, n (%)	2200	14.1	330	13.1	871	14.7	634	14.8	90	12.3
Diabetes mellitus	3834	24.6	621	24.7	1467	24.8	1160	27.1	183	25.1
Myocardial infarction	218	1.4	29	1.2	71	1.2	62	1.4	9	1.2
Hypertension	9545	61.2	1420	56.4	3701	62.5	2573	60.0	441	60.4
Prior hospital admission (2 years), n (%)										
Stroke	209	1.3	34	1.3	125	2.1	82	1.9	10	1.4
Unstable angina	113	0.7	19	0.8	54	0.9	30	0.7	5	0.7
Congestive heart failure	409	2.6	48	1.9	159	2.7	124	2.9	17	2.3
Cerebrovascular disease	303	1.9	55	2.2	165	2.8	112	2.6	19	2.6
Coronary artery disease	570	3.7	91	3.6	261	4.4	172	4.0	31	4.2
Peripheral arterial disease	70	0.4	6	0.2	32	0.5	11	0.3	2	0.3
Prior medication history (1 year), n (%)										
Other anticholinergics, n (%)	2491	16.0	374	14.8	952	16.1	732	17.1	150	20.5
Lipid-lowering agents, n (%)	6307	40.5	995	39.5	2546	43.0	1804	42.1	298	40.8
ACE inhibitors, n (%)	5146	33.0	718	28.5	2146	36.2	1375	32.1	268	36.7
ARBs, n (%)	2409	15.5	365	14.5	917	15.5	702	16.4	102	14.0
Beta-blockers, n (%)	3944	25.3	553	22.0	1563	26.4	1102	25.7	195	26.7
Antidepressants, n (%)	4898	31.4	711	28.2	1776	30.0	1482	34.6	255	34.9
Antipsychotics, n (%)	1565	10.0	235	9.3	569	9.6	592	13.8	142	19.5

(*Continued*)

Table 1
Baseline patient characteristics (*Continued*)

Characteristics	Donepezil (low dose)		Donepezil (high dose)		Galantamine		Rivastigmine (patch)		Rivastigmine (oral)	
	N or mean (n = 15,586)	% or SD	N or mean (n = 2519)	% or SD	N or mean (n = 5926)	% or SD	N or mean (n = 4286)	% or SD	N or mean (n = 730)	% or SD
Anxiolytics/sedatives/ hypnotics, n (%)	3717	23.8	605	24.0	1360	22.9	1181	27.6	208	28.5

Abbreviations: IQR, interquartile range; COPD, chronic obstructive pulmonary disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

*Net family income in Canadian dollars from the most recent income tax return (1 Canadian dollar ≈ .75 US dollar).

†High-dose defined as a dispensed daily dose on the first ChEI prescription that is higher than the WHO Defined Daily Dose (DDD).

‡Follow-up time shown for primary outcome (mortality).

§Smoking status based on history of diagnosed COPD or use of a smoking cessation medication (varenicline, Zyban, or nicotine replacement products).

¶Hospital separation record or physician visit diagnosis within 2 years before the index date.

Prior hospital admission for several cardiovascular conditions was highest among galantamine users. Although this usually suggests patients were at a higher risk of future cardiovascular events, an alternative explanation could be that these patients were more closely monitored and more aggressively treated for vascular risk factors, resulting in lower cardiovascular events.

Entry into residential care was studied as a co-secondary outcome as a measure of net benefit over harm. Our results show a 28% lower 3-year risk of entry into a residential care facility with galantamine versus low-dose donepezil (aHR: 0.72 CI: 0.62–0.98). These findings are also consistent with a net benefit of treatment over harm for galantamine and may also be related to a previous finding of longer persistence and better adherence for patients on galantamine versus donepezil [24].

Residual confounding is a possible limitation of our results because of the nonrandomized study design. Baseline characteristics of the study cohorts indicate comparable age, smoking status, and prior medical history. Low-dose donepezil had the highest proportion of females (60%). This was likely due to weight-based dosing. Rivastigmine users had the highest prior use of antipsychotics. There is a positive correlation between cognitive decline, progression of neurodegeneration, and psychosis in patients with ADRD [25]. Previous research has shown that rivastigmine users have a lower rate of antipsychotic prescriptions compared with donepezil patients in a base cohort of antipsychotic naïve patients [26]. These findings may influence physicians to preferentially prescribe rivastigmine over other ChEIs to patients with symptoms of psychosis. In addition, the Alzheimer's Drug Therapy Initiative required regular cognitive assessments; our study findings may not be generalizable to jurisdictions with alternative health care systems.

A significant strength of our study was the use of the B.C. Ministry of Health administrative claims database, which captures all prescriptions dispensed at a community pharmacy regardless of payer. Dispensed prescriptions are

Table 2
Cox proportional hazards for mortality, serious cardiovascular events, and entry into a residential care facility

	N	3 year		
		Cumulative mortality events	Crude rate per 100 PYs	Propensity score–adjusted hazard ratio
All-cause mortality, time-to-event, Cox proportional hazards				
Low-dose donepezil (reference)	15,586	147	5.80	
High-dose donepezil	2519	23	5.35	0.97 (0.61–1.54)
Galantamine	5926	51	5.29	0.84 (0.60–1.18)
Rivastigmine—patch	4286	86	10.82	1.29 (0.93–1.79)
Rivastigmine—oral	730	<5		0.49 (0.17–1.36)
Serious cardiovascular events, time-to-event, Cox proportional hazards				
Low-dose donepezil (reference)	15,586	331	5.84	
High-dose donepezil	2519	50	5.39	1.02 (0.75–1.39)
Galantamine	5926	106	5.32	0.78 (0.62–0.98)
Rivastigmine—patch	4286	128	10.91	0.98 (0.77–1.25)
Rivastigmine—oral	730	16	3.53	0.87 (0.51–1.48)
Entry into residential care, time-to-event, Cox proportional hazards				
Low-dose donepezil (reference)	15,586	447	5.86	
High-dose donepezil	2519	66	5.41	0.97 (0.74–1.28)
Galantamine	5926	135	5.34	0.72 (0.59–0.89)
Rivastigmine—patch	4286	182	10.97	1.16 (0.95–1.42)
Rivastigmine—oral	730	22	2.55	0.88 (0.56–1.37)

Table 3
Six-month fixed follow-up log-binomial regression

	N	Number of outcomes	Crude risk ratio (95% confidence interval)	Age-sex adjusted: Risk ratio (95% confidence interval)	*P*-value	Fully adjusted: Risk ratio (95% confidence interval)	*P*-value
Crude and adjusted odds ratio, all-cause mortality, 6-month fixed follow-up							
Low-dose donepezil (reference)	15,586	440					
High-dose donepezil	2519	53	0.75 (0.56–0.99)	0.81 (0.61–1.08)	0.147	0.83 (0.62–1.11)	0.209
Galantamine	5926	150	0.90 (0.75–1.08)	0.89 (0.74–1.06)	0.194	0.83 (0.69–1.01)	0.066
Rivastigmine—patch	4286	158	1.31 (1.09–1.56)	**1.31 (1.09–1.56)**	**0.003**	1.21 (0.99–1.47)	0.062
Rivastigmine—oral	730	17	0.82 (0.51–1.33)	0.88 (0.54–1.41)	0.585	0.74 (0.45–1.22)	0.243
Crude and adjusted odds ratios, cardiovascular events, 6-month fixed follow-up							
Low-dose donepezil (reference)	15,586	517					
High-dose donepezil	2519	79	0.95 (0.75–1.19)	1.00 (0.80–1.27)	0.637	1.09 (0.85–1.38)	0.500
Galantamine	5926	161	0.82 (0.69–0.98)	**0.81 (0.68–0.96)**	**0.017**	**0.79 (0.66–0.96)**	**0.015**
Rivastigmine—patch	4286	140	0.98 (0.82–1.18)	0.99 (0.82–1.19)	0.891	0.94 (0.77–1.15)	0.543
Rivastigmine—oral	730	27	1.12 (0.76–1.63)	1.16 (0.79–1.69)	0.447	0.90 (0.61–1.34)	0.606
Crude and adjusted odds ratios, entry to residential care, 6-month fixed follow-up							
Low-dose donepezil (reference)	15,586	920					
High-dose donepezil	2519	108	0.73 (0.60–0.88)	**0.81 (0.67–0.99)**	**0.037**	0.82 (0.67–1.01)	0.058
Galantamine	5926	298	0.85 (0.75–0.97)	**0.86 (0.76–0.97)**	**0.017**	**0.80 (0.70–0.92)**	**0.001**
Rivastigmine—patch	4286	301	1.19 (1.05–1.35)	**1.22 (1.08–1.39)**	**0.002**	**1.19 (1.03–1.36)**	**0.015**
Rivastigmine—oral	730	63	1.46 (1.15–1.87)	**1.62 (1.27–2.06)**	**0.0001**	1.26 (0.98–1.63)	0.077

Bold values indicate a confidence interval that does not include 1.

linkable to physician services, hospital discharge abstracts, and client demographic information via an encrypted patient identifier. The comprehensiveness of the databases for the B.C. population reduces the risk of exposure misclassification, which is known to substantially affect risk estimates in observational studies [27] and allows for generalizing results to a wide population.

Our study found that galantamine has a superior safety profile compared with low-dose donepezil and was associated with a lower risk of entry into a residential care facility. The rivastigmine patch was associated with a higher risk of mortality and a higher risk of entry into a residential care facility. High-dose donepezil had a similar safety and effectiveness profile compared with low-dose donepezil. Given the absence

Table 4
Twelve-month fixed follow-up log-binomial regression

	N	Number of outcomes	Crude risk ratio (95% confidence interval)	Age- and sex-adjusted: Risk ratio (95% confidence interval)	*P*-value	Prop. Score adjusted: Risk ratio (95% confidence interval)	*P*-value
Crude and adjusted odds ratio, all-cause mortality, 12-month fixed follow-up							
Low-dose donepezil (reference)	15,586	990					
High-dose donepezil	2519	134	0.84 (0.70–0.99)	0.90 (0.76–1.07)	0.244	0.93 (0.77–1.11)	0.408
Galantamine	5926	335	0.89 (0.79–1.00)	**0.88 (0.78–0.99)**	**0.032**	**0.82 (0.72–0.93)**	**0.002**
Rivastigmine—patch	4286	329	1.21 (1.07–1.36)	**1.21 (1.07–1.36)**	**0.002**	**1.15 (1.01–1.32)**	**0.031**
Rivastigmine—oral	730	48	1.04 (0.78–1.37)	1.08 (0.82–1.43)	0.589	0.97 (0.72–1.29)	0.815
Crude and adjusted odds ratios, cardiovascular events, 12-month fixed follow-up							
Low-dose donepezil (reference)	15,586	914					
High-dose donepezil	2519	125	0.85 (0.71–1.02)	0.90 (0.75–1.08)	0.264	0.96 (0.80–1.16)	0.708
Galantamine	5926	300	0.86 (0.76–0.98)	**0.86 (0.75–0.97)**	**0.016**	**0.83 (0.73–0.95)**	**0.007**
Rivastigmine—patch	4286	240	0.95 (0.83–1.10)	0.96 (0.84–1.10)	0.560	0.94 (0.81–1.09)	0.434
Rivastigmine—oral	730	40	0.93 (0.69–1.27)	0.98 (0.72–1.33)	0.898	0.85 (0.61–1.16)	0.305
Crude and adjusted odds ratios, entry to residential care, 12-month fixed follow-up							
Low-dose donepezil (reference)	15,586	1702					
High-dose donepezil	2519	218	0.79 (0.69–0.91)	0.88 (0.77–1.00)	0.051	0.90 (0.78–1.03)	0.117
Galantamine	5926	659	1.02 (0.94–1.11)	1.02 (0.94–1.11)	0.566	0.95 (0.87–1.04)	0.284
Rivastigmine—patch	4286	529	1.13 (1.03–1.24)	**1.16 (1.06–1.27)**	**0.001**	**1.14 (1.03–1.26)**	**0.011**
Rivastigmine—oral	730	113	1.42 (1.19–1.69)	**1.54 (1.30–1.83)**	**<.0001**	**1.27 (1.06–1.52)**	**0.011**

Bold values indicate a confidence interval that does not include 1.

of randomized trial data showing clinically meaningful benefit of ChEI therapy in ADRD, our study suggests that preferential use of galantamine may at least be associated with fewer adverse events than treatment with donepezil or rivastigmine and may also be associated with longer independent living before requiring a residential care facility.

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Disclaimer: All inferences, opinions, and conclusions drawn in this manuscript are those of the authors and do not reflect the opinions or policies of the Data Stewards.

Ethics approval: The study received ethics approval from the University of British Columbia (UBC CREB Number H16-02922).

Data sharing statement: Statistical code available from the corresponding author at Greg.Carney@ti.ubc.ca

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.trci.2019.09.011.

RESEARCH IN CONTEXT

1. A clinically meaningful improvement in cognitive function has not been established between cholinesterase inhibitors (ChEIs) and placebo in clinical trials of patients with Alzheimer's disease and related dementia, yet ChEIs are commonly prescribed.
2. Using population-based data during a government-sponsored reimbursement program, we examined the comparative safety of ChEIs. Compared with the most common treatment, low-dose donepezil, we found galantamine was associated with a lower risk of cardiovascular events and mortality. Galantamine use was also associated with longer independent living, delaying the need for a residential care facility.
3. Given the absence of randomized trial data showing clinically meaningful benefit of ChEI therapy, preferential use of galantamine may at least be associated with a superior safety profile compared with donepezil or rivastigmine.

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