Anticholinergic Drug Burden in Persons with Dementia Taking a Cholinesterase Inhibitor: The Effect of Multiple Physicians

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OBJECTIVES: To explore the association between the number of physicians providing care and anticholinergic drug burden in older persons newly initiated on cholinesterase inhibitor therapy for the management of dementia.

DESIGN: Population-based cross-sectional study.

SETTING: Community and long-term care, Ontario, Canada.

PARTICIPANTS: Community-dwelling (n = 79,067, mean age 81.0, 60.8% female) and long-term care residing (n = 12,113, mean age 84.3, 67.2% female) older adults (≥66) newly dispensed cholinesterase inhibitor drug therapy.

MEASUREMENTS: Anticholinergic drug burden in the prior year measured using the Anticholinergic Risk Scale.

RESULTS: Community-dwelling participants had seen an average of eight different physicians in the prior year. The odds of high anticholinergic drug burden (Anticholinergic Risk Scale score ≥ 2) were 24% higher for every five additional physicians providing care to individuals in the prior year (adjusted odds ratio = 1.24, 95% confidence interval = 1.21–1.26). Female sex, low-income status, previous hospitalization, and higher comorbidity score were also associated with high anticholinergic drug burden. Long-term care facility residents had seen an average of 10 different physicians in the prior year. After a sensitivity analysis, the association between high anticholinergic burden and number of physicians was no longer statistically significant in the long-term care group.

CONCLUSION: In older adults newly started on cholinesterase inhibitor drug therapy, greater number of physicians providing care was associated with higher anticholinergic drug burden scores. Given the potential risks of anticholinergic drug use, improved communication among physicians and an anticholinergic medication review before prescribing a new drug are important strategies to improve prescribing quality. **J Am Geriatr Soc 64:492–500, 2016.**

Key words: anticholinergic; dementia; older adults; physicians; cholinesterase inhibitors

Medications used to manage a variety of clinical conditions (e.g., urinary incontinence, depression, Parkinson's disease) have anticholinergic effects that can cause adverse events, including cognitive decline.[1–4] The use of drug therapies that might worsen cognitive status is especially troubling in older adults with preexisting cognitive deficits and age-related changes in pharmacodynamics that lead to heightened sensitivity to central anticholinergic adverse effects.[5,6]

Although prescribing anticholinergic drugs to persons with dementia is generally considered inappropriate,[7] it often happens in clinical practice.[8,9] Anticholinergic drug therapy combined with cholinesterase inhibitor drug therapy[10] is particularly troubling. In this case, the directly opposing action of the anticholinergic drugs may reduce or eliminate the cognitive benefits gained from cholinesterase inhibitors.[11]

Efforts to identify drug therapies that are potentially inappropriate have largely targeted individual drug therapies[12,13] rather than considering the cumulative burden of different drugs with similar mechanisms of action. It is important to consider how overall drug burden may contribute to adverse events. Anticholinergic drug therapies

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with varying degrees of anticholinergic activity illustrate this situation. Although the anticholinergic effects of the individual drug therapies are important, estimating the cumulative anticholinergic burden from all prescribed drug therapies may more accurately predict the risk of adverse events.

Having multiple prescribers has been linked to polypharmacy, potential drug interactions, and adverse events.[14–16] Older adults with dementia and multiple comorbid conditions are particularly vulnerable to inadvertent prescription of inappropriate drug combinations because they often receive care from multiple physicians. Poor communication among physicians caring for the same individual may lead to prescription of inappropriate drug combinations from different sources. Through the Choosing Wisely campaign, the American Geriatrics Society suggests a medication review before starting any new drug therapy to improve the quality of prescribing in vulnerable elderly adults.[17]

Given the potential risks of anticholinergic drug use in older adults, a better understanding of the causes of frequent prescription is needed. The objective of this study was to examine the relationship between the number of physicians providing care and anticholinergic drug burden in older adults newly initiated on cholinesterase inhibitor therapy for dementia. It was hypothesized that having more physicians involved in care would be associated with greater risk of high anticholinergic drug burden.

METHODS

Data Sources

Ontario administrative healthcare data from April 1, 2008, to March 31, 2013, were used to conduct a population-based cross-sectional study. Ontario, Canada's largest province, had a population of approximately 12 million residents during the study period. All older adults (≥65) in Ontario receive comprehensive health coverage under a universal health insurance program that includes most physician services, hospitalizations, and prescription medications. This study used five linked administrative healthcare databases: the Registered Persons Database for demographic data; the Ontario Health Insurance Plan for data on physician billing claims; the Ontario Drug Benefit (ODB) database for information on prescription drug claims; and the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD), and National Ambulatory Care Reporting System for information on hospitalizations and Same Day Surgery (SDS). These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences. *International Statistical Classification of Diseases, 10th Revision*, diagnosis codes and drug therapy claims were used to define the cohort, outcome definitions, covariates, and exclusion criteria. The research ethics board at Sunnybrook Health Sciences Centre approved the study.

Cohort Definition

The cohort consisted of all older Ontario residents who commenced treatment for dementia with a cholinesterase inhibitor (donepezil, galantamine, rivastigmine) between April 1, 2008, and March 31, 2013. Therapy with a cholinesterase inhibitor was considered new if there had been no cholinesterase inhibitor dispensed in the prior year. The date of initiation of cholinesterase inhibitor therapy was the index date. The cohort was divided into two groups: community-dwelling and long-term care (LTC). The analyses were stratified according to these two groups because community-dwelling and LTC residents typically experience different processes of care related to drug prescribing. Comorbidity was measured using the Charlson Comorbidity Index[18] (constructed from CIHI-DAD and SDS medical diagnoses in the past 5 years) and number of distinct drugs prescribed at the time of the index date.[19] Socioeconomic status was evaluated using a low-income flag on the ODB drug claim (net income <C$16,018[20]). Urban residence was defined as having a postal code in a community with more than 10,000 residents.

Outcome

The outcome was the Anticholinergic Risk Scale (ARS) score,[21] calculated based on the number of drug therapies prescribed to the individual in the prior year. Several anticholinergic drug scales are available,[21–24] and there are some differences in the rating of anticholinergic activity between them.[25] The ARS was selected because it provides a more-conservative estimate of anticholinergic burden than other anticholinergic drug therapy scales.[26,27] Higher ARS scores have been shown to have a significant association with anticholinergic adverse effects,[21] including memory decline.[28]

The ARS assigns each drug therapy a score according to its risk of anticholinergic adverse effects (0 = limited or none, 1 = moderate, 2 = strong, 3 = very strong). These points are added together to produce the individual's ARS score. For example, amitriptyline is assigned a score of 3, tolterodine a score of 2, and quetiapine a score of 1. An individual prescribed all three drugs would have an ARS score of 6. See Appendix 1 for the complete ARS drug list.

The ARS score calculated within the year before initial cholinesterase inhibitor use allows for exploration of the link between anticholinergic burden and development of cognitive impairment. ARS scores were also calculated based on overlapping anticholinergic drug therapy dispensed within 120 days before cholinesterase inhibitor prescription. This measured the concomitant use of cholinesterase inhibitor therapy and anticholinergic drug therapy in the cohort to allow for the exploration of therapeutic competition.[29,30]

Exposures

Number of unique physicians providing care was defined as the number of unique physicians submitting claims for an individual in the year before the index date. Physicians were separated into groups based on the setting where care was provided (inpatient or outpatient) and the type of physician (specialist or primary care). Specialists were further categorized based on their specialty. Diagnostic radiologists were excluded because they are unlikely to be prescribers. The number of hospitalizations and outpatient visits in the prior year were also measured.

Statistical Analysis

Baseline characteristics were described according to categories based on ARS scores. Baseline characteristics of community-dwelling individuals and LTC residents with ARS scores of 0, 1, 2, and 3 or more were compared using the chi-square test. After examining the similarities between the four groups, individuals were regrouped into two groups (ARS ≤ 1 vs ≥ 2). Standardized differences were then used to assess the relevant factors to include in further analysis.

The 10 most frequently dispensed anticholinergic drugs were identified according to sex for all individuals and for those with ARS scores of 2 or more in the community and LTC groups. The most common drug therapies that contributed 1, 2, or 3 points to the total score were considered to determine how anticholinergic burden may be attributed to drugs with different levels of anticholinergic activity.

A binary logistic regression model was used to estimate the association between the number of unique physicians providing care in the prior year and ARS scores. Odds ratios (ORs) for the association between having more physicians and the odds of having an ARS score of 2 or more were calculated (ORs were also expressed for the effect of 5 additional unique physicians on the ARS score). Other potential predictor variables of having a higher ARS score were adjusted for, including age, sex, socioeconomic status, Charlson Comorbidity Index, urban residence, outpatient visits, and hospitalizations within the prior year. Collinearity among variables was examined. A second regression model was used to examine the association with the number of unique inpatient and outpatient physicians and a third model to examine the association with the number of primary care and specialist providers. A sensitivity analysis that included non-anticholinergic drugs was conducted to see whether the number of drugs dispensed in the prior year mediated the above associations. All analyses were stratified based on place of residence (community or LTC). Analyses were performed using SAS statistical software version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Community-Dwelling Group

Community-dwelling older adults with incident claims for cholinesterase inhibitors between April 1, 2008, and March 31, 2013 were identified (n = 79,067). The demographic characteristics of these individuals are detailed in Table 1 according to ARS score. The mean age of older adults in the community cohort was 81.0 ± 6.5, 60.8% were female, and on average they were dispensed six unique prescribed drug therapies. Community-dwelling individuals saw an average of eight different physicians in 1 year, 53% of whom were specialists. Individuals with an ARS score of 3 or more were much more likely than those with a score of 0 to see neurologists (25.4% vs 12.6%), psychiatrists (21.7% vs 7.4%), or urologists (17.5% vs 10.5%).

Sixty-three percent of community-dwelling persons with dementia (n = 49,838) were dispensed no anticholinergic drug therapy in the prior year and had an ARS score of 0, 16% (n = 12,745) had a score of 1, 9% (n = 6,751) had a score of 2, and 12% (n = 9,733) had a score of 3 or greater. For those with an ARS score of 2 or more, the most commonly dispensed drug therapies were tolterodine (22%), amitriptyline (19%), trazodone (18%), and quetiapine (16%). Table 2 lists the 10 most frequently dispensed anticholinergic drug therapies according to sex in the entire cohort and in individuals with high anticholinergic burden (ARS score ≥ 2). Women were more likely to receive each of these anticholinergic drug therapies, with the exception of carbidopa with levodopa and quetiapine, which were more commonly prescribed to men.

Of the 16,484 individuals with an ARS score of 2 or more, 9,827 (60%) were taking two or more anticholinergic drugs. Twenty-three percent (n = 3,833) of persons with ARS scores of 2 or more had scores comprised exclusively of drugs that had an individual score of 1 (moderate anticholinergic risk).

The odds of having high anticholinergic burden (ARS ≥ 2) increased by 4% with each additional physician providing care in the year before a cholinesterase inhibitor was dispensed (adjusted OR (aOR) = 1.04, 95% CI = 1.04–1.05) (Table 3). Results were consistent when physicians were separated based on setting of care (outpatient: aOR = 1.01, 95% CI = 1.01–1.02; inpatient: aOR = 1.05, 95% CI = 1.04–1.05) and physician type (primary care: aOR = 1.08, 95% CI = 1.07–1.09); specialist: aOR = 1.03, 95% CI = 1.03–1.04). The odds of having a high anticholinergic drug burden increased by 24% (aOR = 1.24, 95% CI = 1.21–1.26) with each additional five physicians seen in the prior year. The relationship between more physicians providing care and increasing anticholinergic burden is further demonstrated in Figure 1. Female sex (aOR = 1.38, 95% CI = 1.33–1.44), low-income status (aOR = 1.29, 95% CI = 1.24–1.34), previous hospitalization (aOR = 1.19, 95% CI = 1.13–1.25), and a Charlson comorbidity score of 2 or greater (aOR = 1.08, 95% CI = 1.03–1.13) were also associated with high anticholinergic burden. No collinearity among covariates was detected. A sensitivity analysis including number of non-anticholinergic drugs revealed that the odds of having a high anticholinergic drug burden increased by 2% (aOR = 1.02, 95% CI = 1.02–1.03) with each additional physician seen in the prior year. Each additional non-anticholinergic drug (aOR = 1.08, 95% CI = 1.08–1.09) was independently associated with higher anticholinergic burden.

When anticholinergic prescriptions that overlapped with cholinesterase inhibitor therapy were examined in the community cohort, 27% of individuals who were newly prescribed a cholinesterase inhibitor were already taking at least one anticholinergic drug, and 12% had an ARS score of 2 or more.

LTC Group

Long-term care residents with incident claims for cholinesterase inhibitors (n = 12,113) (Table 1) had an average of 10 unique physicians providing care in the prior year, 47% of whom were specialists. Anticholinergic drug burden was greater in LTC residents (n = 3,473, 29% with an

Table 1. Characteristics of Older Adults with Dementia Dispensed Cholinesterase Inhibitor Drug Therapy According to ARS Score

	Total ARS Scores									
	Community					Long-Term Care				
Characteristic	0 (n = 49,838)	1 (n = 12,745)	2 (n = 6,751)	≥3 (n = 9,733)	Total (n = 79,067)	0 (n = 3,433)	1 (n = 3,017)	2 (n = 2,190)	≥3 (n = 3,473)	Total (n = 12,113)
Age, mean ± SD	81.0 ± 6.5	81.4 ± 6.5	81.0 ± 6.5	80.1 ± 6.6	81.0 ± 6.5	85.6 ± 6.5	84.7 ± 6.7	83.8 ± 7.0	83.0 ± 6.9	84.3 ± 6.8
Female, n (%)	29,630 (59.5)	7,666 (60.1)	4,270 (63.2)	6,473 (66.5)	48,039 (60.8)	2,349 (68.4)	2,020 (67.0)	1,449 (66.2)	2,327 (67.0)	8,145 (67.2)
Urban residence, n (%)	43,629 (87.5)	11,132 (87.3)	5,960 (88.3)	8,442 (86.7)	69,163 (87.5)	2,937 (85.6)	2,529 (83.8)	1,881 (85.9)	2,922 (84.1)	10,269 (84.8)
Low income, n (%)	10,511 (21.1)	3,227 (25.3)	1,739 (25.8)	2,637 (27.1)	18,114 (22.9)	1,192 (34.7)	1,016 (33.7)	785 (35.8)	1,228 (35.4)	4,221 (34.8)
Charlson Comorbidity Index										
Mean ± SD	0.9 ± 1.4	1.2 ± 1.6	1.2 ± 1.6	1.2 ± 1.6	1.0 ± 1.5	1.6 ± 1.8	1.8 ± 1.8	1.8 ± 1.8	1.8 ± 1.9	1.8 ± 1.8
No score, n (%)	14,620 (29.3)	2,931 (23.0)	1,308 (19.4)	1,674 (17.2)	20,533 (26.0)	701 (20.4)	514 (17.0)	370 (16.9)	400 (11.5)	1,985 (16.4)
0, n (%)	19,934 (40.0)	4,728 (37.1)	2,593 (38.4)	3,817 (39.2)	31,072 (39.3)	882 (25.7)	690 (22.9)	509 (23.2)	846 (24.4)	2,927 (24.2)
1, n (%)	6,754 (13.6)	2,087 (16.4)	1,169 (17.3)	1,746 (17.9)	11,756 (14.9)	709 (20.7)	651 (21.6)	496 (22.6)	830 (23.9)	2,686 (22.2)
≥2, n (%)	8,530 (17.1)	2,999 (23.5)	1,681 (24.9)	2,496 (25.6)	15,706 (19.9)	1,141 (33.2)	1,162 (38.5)	815 (37.2)	1,397 (40.2)	4,515 (37.3)
Number of drugs taken on index date, mean ± SD	5.2 ± 3.0	6.8 ± 3.3	7.4 ± 3.5	8.0 ± 3.7	6.0 ± 3.4	7.2 ± 3.4	8.2 ± 3.6	8.8 ± 3.5	9.8 ± 3.7	8.5 ± 3.7
Hospitalization										
Any hospitalization, n (%)	8,916 (17.9)	3,584 (28.1)	2,080 (30.8)	3,192 (32.8)	17,772 (22.5)	1,386 (40.4)	1,346 (44.6)	1,006 (45.9)	1,824 (52.5)	5,562 (45.9)
Number of inpatient days, mean ± SD	2.1 ± 7.9	4.5 ± 12.2	5.3 ± 13.8	5.9 ± 15.6	3.2 ± 10.6	14.1 ± 32.7	18.4 ± 40.1	19.8 ± 43.7	21.2 ± 40.4	18.2 ± 39.1
Physician contact in past year, mean ± SD										
Total physician, mean ± SD	6.7 ± 5.5	8.6 ± 6.9	9.3 ± 7.4	9.9 ± 7.6	7.6 ± 6.3	9.3 ± 7.5	10.1 ± 7.8	10.6 ± 8.2	11.4 ± 8.7	10.3 ± 8.1
Total specialist, mean ± SD	4.0 ± 4.2	5.2 ± 5.2	5.8 ± 5.5	6.0 ± 5.7	4.6 ± 4.7	5.1 ± 5.5	5.5 ± 5.8	5.9 ± 6.0	6.3 ± 6.2	5.7 ± 5.9
Inpatient physician, mean ± SD	3.4 ± 5.0	4.9 ± 6.5	5.4 ± 7.0	5.5 ± 7.1	4.1 ± 5.8	6.1 ± 6.9	7.1 ± 7.4	7.3 ± 7.6	7.8 ± 8.1	7.1 ± 7.6
Inpatient specialist, mean ± SD	2.1 ± 3.6	3.1 ± 4.7	3.5 ± 5.1	3.5 ± 5.2	2.6 ± 4.2	3.5 ± 4.9	4.1 ± 5.3	4.3 ± 5.5	4.5 ± 5.8	4.1 ± 5.4
Outpatient physician, mean ± SD	3.7 ± 3.8	4.2 ± 4.3	4.5 ± 4.6	5.0 ± 4.8	4.0 ± 4.1	3.8 ± 3.9	3.7 ± 3.9	4.0 ± 4.1	4.5 ± 4.3	4.0 ± 4.1
Outpatient specialist, mean ± SD	2.1 ± 2.7	2.4 ± 3.0	2.6 ± 3.1	2.9 ± 3.3	2.3 ± 2.9	1.8 ± 2.5	1.7 ± 2.4	1.9 ± 2.6	2.2 ± 2.7	1.9 ± 2.5
Outpatient PCP, mean ± SD	1.6 ± 1.7	1.8 ± 1.9	1.8 ± 2.0	2.1 ± 2.2	1.7 ± 1.8	2.0 ± 1.9	2.0 ± 2.0	2.1 ± 2.1	2.3 ± 2.2	2.1 ± 2.1
Neurology, n (%)	6,267 (12.6)	2,507 (19.7)	1,498 (22.2)	2,473 (25.4)	12,745 (16.1)	350 (10.2)	393 (13.0)	331 (15.1)	672 (19.3)	1,746 (14.4)
Psychiatry, n (%)	3,705 (7.4)	2,191 (17.2)	1,390 (20.6)	2,116 (21.7)	9,402 (11.9)	598 (17.4)	871 (28.9)	731 (33.4)	1,261 (36.3)	3,461 (28.6)
Urology, n (%)	5,222 (10.5)	1,526 (12.0)	1,224 (18.1)	1,703 (17.5)	9,675 (12.2)	284 (8.3)	262 (8.7)	194 (8.9)	431 (12.4)	1,171 (9.7)

ARS = Anticholinergic Risk Scale; SD = standard deviation; PCP = primary care provider.

Table 2. Top 10 Anticholinergic Drugs that Individuals in the Community and Long-Term Care Use Most Frequently

Drug Name	ARS Score	n (%)		
		Total	Male	Female
Overall				
Community dwelling				
Total		79,067	31,028	48,039
Trazodone HCL	1	5,628 (7.1)	1,949 (6.3)	3,679 (7.7)
Ranitidine HCL	1	4,572 (5.8)	1,733 (5.6)	2,839 (5.9)
Quetiapine fumarate	1	4,515 (5.7)	1,848 (6.0)	2,667 (5.6)
Tolterodine tartrate	2	3,633 (4.6)	1,213 (3.9)	2,420 (5.0)
Risperidone	1	3,522 (4.5)	1,218 (3.9)	2,304 (4.8)
Amitriptyline HCL	3	3,198 (4.0)	905 (2.9)	2,293 (4.8)
Carbidopa and levodopa	1	3,186 (4.0)	1,929 (6.2)	1,257 (2.6)
Mirtazapine	1	2,576 (3.3)	809 (2.6)	1,767 (3.7)
Paroxetine HCL	1	2,167 (2.7)	636 (2.0)	1,531 (3.2)
Oxybutynin Chloride	3	1,804 (2.3)	489 (1.6)	1,315 (2.7)
Long-term care facility				
Total		12,113	3,968	8,145
Trazodone HCL	1	3,140 (25.9)	1,069 (26.9)	2,071 (25.4)
Quetiapine fumarate	1	2,578 (21.3)	1,002 (25.3)	1,576 (19.3)
Risperidone	1	2,165 (17.9)	708 (17.8)	1,457 (17.9)
Olanzapine	2	1,117 (9.2)	405 (10.2)	712 (8.7)
Carbidopa and levodopa	1	899 (7.4)	447 (11.3)	452 (5.5)
Mirtazapine	1	899 (7.4)	236 (5.9)	663 (8.1)
Ranitidine HCL	1	810 (6.7)	241 (6.1)	569 (7.0)
Tolterodine tartrate	2	661 (5.5)	183 (4.6)	478 (5.9)
Loperamide HCL	2	466 (3.8)	118 (3.0)	348 (4.3)
Haloperidol	1	457 (3.8)	210 (5.3)	247 (3.0)
Persons with high anticholinergic burden (ARS score ≥2)				
Community dwelling				
Total		16,484	5,741	10,743
Tolterodine tartrate	2	3,633 (22.0)	1,213 (21.1)	2,420 (22.5)
Amitriptyline HCL	3	3,198 (19.4)	905 (15.8)	2,293 (21.3)
Trazodone HCL	1	2,960 (18.0)	1,013 (17.6)	1,947 (18.1)
Quetiapine fumarate	1	2,639 (16.0)	1,061 (18.5)	1,578 (14.7)
Ranitidine HCL	1	1,940 (11.8)	648 (11.3)	1,292 (12.0)
Risperidone	1	1,933 (11.7)	651 (11.3)	1,282 (11.9)
Carbidopa and levodopa	1	1,922 (11.7)	1,115 (19.4)	807 (7.5)
Oxybutynin chloride	3	1,804 (10.9)	489 (8.5)	1,315 (12.2)
Olanzapine	2	1,722 (10.4)	625 (10.9)	1,097 (10.2)
Mirtazapine	1	1,516 (9.2)	490 (8.5)	1,026 (9.6)
Long-term care facility				
Total		5,663	1,887	3,776
Trazodone HCL	1	2,270 (40.1)	794 (42.1)	1,476 (39.1)
Quetiapine fumarate	1	1,892 (33.4)	756 (40.1)	1,136 (30.1)
Risperidone	1	1,487 (26.3)	483 (25.6)	1,004 (26.6)
Olanzapine	2	1,117 (19.7)	405 (21.5)	712 (18.9)
Mirtazapine	1	730 (12.9)	193 (10.2)	537 (14.2)
Carbidopa and levodopa	1	715 (12.6)	360 (19.1)	355 (9.4)
Tolterodine tartrate	2	661 (11.7)	183 (9.7)	478 (12.7)
Ranitidine HCL	1	585 (10.3)	179 (9.5)	406 (10.8)
Loperamide HCL	2	466 (8.2)	118 (6.3)	348 (9.2)
Amitriptyline HCL	3	434 (7.7)	111 (5.9)	323 (8.6)

ARS = Anticholinergic Risk Scale; HCL = hydrochloride.

ARS score ≥3) than in community-dwelling individuals (n = 9,733, 12% with an ARS score ≥3). Sixty-one percent of LTC residents were taking at least one anticholinergic drug at the time of initiating cholinesterase inhibitor drug therapy. The most commonly used drugs in those with an ARS score of 2 or greater were trazodone (40%), quetiapine (33%), risperidone (26%), and olanzapine (20%) (Table 2). Figure 1 demonstrates ARS score distribution in the LTC group, in which there was substantially greater anticholinergic drug burden than in the community-dwelling group. The odds of having high anticholinergic drug burden (ARS score ≥2) in the LTC group increased by only 1% with each additional physician seen in the year before cholinesterase inhibitor initiation (aOR = 1.01, 95%

Table 3. Predictors of High Anticholinergic Risk Scale Scores (2 or 3+) in Older Adults with Dementia Dispensed a Cholinesterase Inhibitor

Predictor	Adjusted Odds Ratio (95% Confidence Interval) *P*-Value	
	Community	Long-Term Care
Each additional physician	1.04 (1.04–1.05) <.001	1.01 (1.00–1.02) <.001
Every 5 physicians	1.24 (1.21–1.26)	1.05 (1.02–1.08)
Age	0.98 (0.98–0.98) <.001	0.96 (0.96–0.97) <.001
Female	1.38 (1.33–1.44) <.001	1.06 (0.98–1.15) .16
Low income (Ontario Drug Benefit flag)	1.29 (1.24–1.34) <.001	1.14 (1.05–1.23) <.001
Urban residence	0.91 (0.86–0.96) <.001	0.96 (0.87–1.07) .47
Charlson score	1.08 (1.03–1.13) <.001	0.99 (0.92–1.07) .83
Previous hospitalization	1.19 (1.13–1.25) <.001	1.19 (1.09–1.31) <.001
Number of outpatient visits	1.01 (1.01–1.01) <.001	1.00 (1.00–1.01) <.001

Analysis adjusted for age, sex, low income, urban residence, Charlson score, previous hospitalization, and outpatient visits.

CI = 1.00–1.02) and 5% with each five additional physicians seen (aOR = 1.05, 95% CI = 1.02–1.08) (Table 3). Low income (aOR = 1.14, 95% CI = 1.05–1.23) and previous hospitalization (aOR = 1.19, 95% CI = 1.09–1.31) were also associated with higher anticholinergic burden. A sensitivity analysis found that number of non-anticholinergic drugs was independently associated with higher anticholinergic burden (aOR = 1.05, 95% CI = 1.04–1.05), but the association between high anticholinergic burden and each additional physician seen in the prior year was no longer statistically significant (aOR = 1.00, 95% CI = 0.99–1.01).

DISCUSSION

Higher anticholinergic drug burden scores in older adults newly dispensed cholinesterase inhibitors were significantly associated with more physicians providing care. The association persisted when there was adjustment for risk factors such as age, sex, higher comorbidity, outpatient visits, and previous hospitalization. Community-dwelling persons received care from an average of eight physicians in 1 year, whereas LTC residents received care from an average of 10 physicians in 1 year. These findings are consistent with U.S. data demonstrating that the typical Medicare beneficiary sees seven different physicians in 1 year, including five different specialists, and that beneficiaries with seven or more chronic conditions see an average of 11 physicians.[31] The results of the current study suggest that receiving care from multiple physicians may be partly responsible for the high anticholinergic drug burden in this population. This result is consistent with recent studies in the United States documenting greater risk of inappropriate medications prescribed to Medicare beneficiaries associated with seeing more prescribers.[32] Studies from Norway and Sweden also found that seeing more prescribers were associated with poorer-quality medication management and prescription.[33,34] This may be in part attributed to a lack of coordinated prescribing and informed decision-making among these physicians.[14] This is important because ongoing education and better communication between prescribing physicians is a potential area for intervention.

The current study demonstrates that high anticholinergic drug burden most commonly results from a combination of drugs, rather than a single drug with high anticholinergic activity. Although the use of drugs that have high ARS scores is troubling,[3] clinicians may be less likely to consider the cumulative burden of combinations of anticholinergic drugs when making prescribing decisions.[35] This is especially important for neurologists, psychiatrists, and urologists, who were identified as specialists whom those with high anticholinergic burden commonly see. Although drugs such as trazodone and ranitidine may have low anticholinergic activity, the cumulative anticholinergic activity from multiple drugs may add up to clinically significant drug burden; 23% of total ARS scores of 2 or greater in community-dwelling individuals were made up exclusively of a combination of apparently "safe" drugs that were assigned 1 point on the anticholinergic risk scale. A recent Australian study reported similar results, demonstrating that the use of multiple medicines with lower anticholinergic potency rather than the use of medicines with higher potency led to high anticholinergic medication burden.[36] Therefore, in reviewing an older adult's drug therapies for anticholinergic adverse effects, clinicians need to be mindful of the overall burden from all drugs with measurable anticholinergic activity, including the contribution from low-potency anticholinergic drugs.

Reviewing the anticholinergic burden of the current medication regimen of older adults with dementia is especially important when considering initiation of cholinesterase inhibitors because anticholinergic drug therapy may exacerbate confusion.[3,37] The current study demonstrated that 27% of older adults with dementia in the community and 61% in LTC were dispensed a cholinesterase inhibitor concurrently with at least one anticholinergic drug. These findings are in keeping with studies demonstrating that between 23%[9,38] and 37%[8,10] of persons with dementia receiving cholinesterase inhibitors were also prescribed drug therapy with clinically significant anticholinergic activity. Furthermore, 77% of anticholinergic drug therapies were not discontinued once cholinesterase inhibitors were started.[8] Given that drugs with anticholinergic actions reduce the effectiveness of cholinesterase inhibitors,[39] clinicians should aim to minimize anticholinergic burden before initiating cholinesterase inhibitor therapy.

The current study demonstrates that drugs with potentially safer alternatives, such as amitriptyline and oxybutynin, are still among the top 10 anticholinergic drug therapies prescribed to persons with dementia. In the LTC cohort, risperidone, quetiapine, and olanzapine were among the top four most frequently dispensed drug therapies in those with ARS scores of 2 or more, demonstrating continued high use of antipsychotic drugs in the LTC setting despite warnings of risk of cerebrovascular events and mortality when used in the management of dementia.[40,41] A study using Kentucky Medicaid data found that LTC residents were twice as likely as community-dwelling older

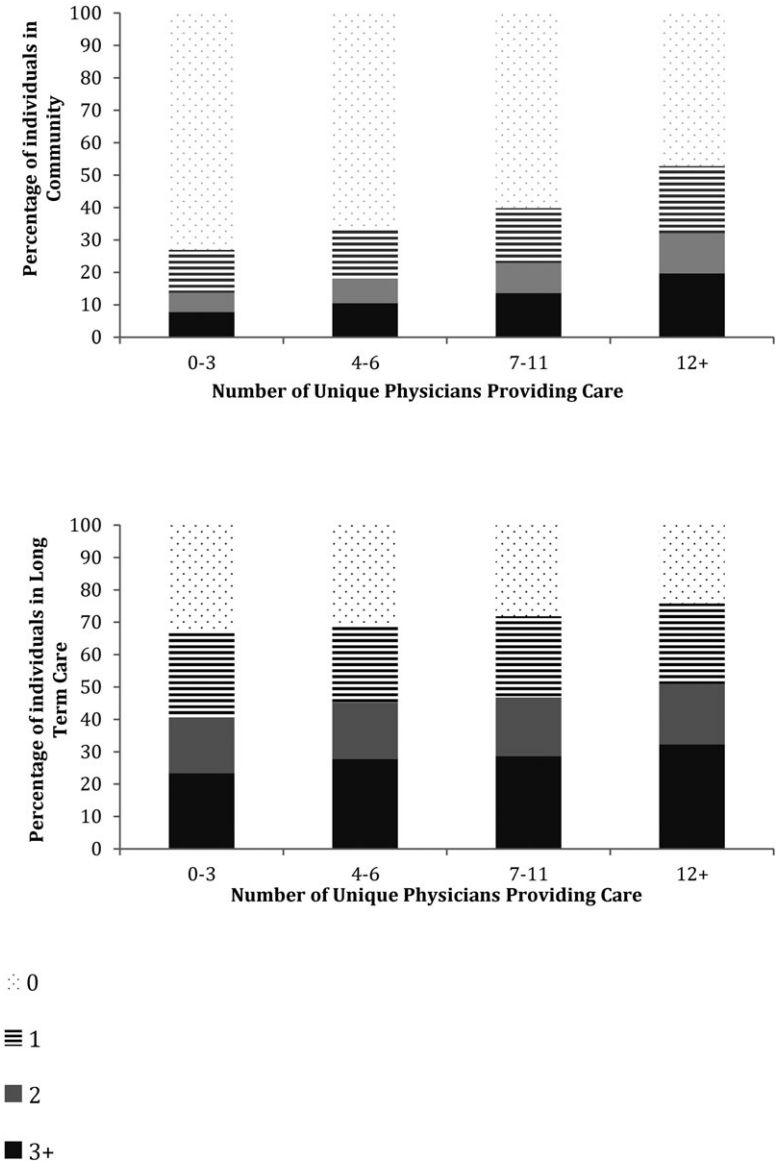

Figure 1. Relationship between increasing Anticholinergic Risk Scale scores (0, 1, 2, ≥3) in persons with dementia dispensed cholinesterase inhibitor drug therapy and increasing number of unique physicians providing care (0–3, 4–6, 7–11, ≥12).

adults to receive potentially inappropriate medications.[42] The current study results are consistent with these findings, with anticholinergic drug burden substantially greater in the LTC group than in the community.

There is a growing need for collaborative, innovative approaches to optimizing drug therapy for older adults with dementia. The American Geriatrics Society recognized this need in its ninth Choosing Wisely recommendation by highlighting a drug regimen review as an important quality indicator for prescribing in older adults.[17] Geriatric medicine consultation,[43] pharmacist interventions,[44] prescriber audits,[45] and computerized decision support[46] have also been shown to improve the appropriateness of prescribing in older adults. A mobile application has been developed that allows clinicians, patients, and caregivers to identify medications with potential adverse anticholinergic cognitive effects.[47]

This study had a number of strengths and limitations. One strength was access to comprehensive, linked data on health services use. Canada's universal healthcare system allows data to be obtained on all older adults dispensed cholinesterase inhibitors, not only those linked to an insurance plan or willing to enroll in a prospective cohort study. Furthermore, the coding accuracy and completeness of the drug exposure was excellent because the ODB has a low error rate of 0.7%.[48] There are also several limitations that merit attention. First, causal relationships could not be determined in this cross-sectional analysis. Second, as with all observational studies, unmeasured confounding variables are a possibility. This bias was minimized by carefully considering multiple risk factors and potential confounders and adjusting for them in the final analysis. A sensitivity analysis including non-anticholinergic drugs showed that the association between number of physicians and ARS score held in the community group, suggesting that these findings are robust. In LTC, the association between physicians and ARS score was no longer statistically significant, suggesting that the prescription of more

non-anticholinergic drugs is one of the main determinants of the finding in this group. Third, drug dosage effect on anticholinergic burden was not incorporated because the ARS measures burden based on affinity for the cholinergic receptor and does not consider drug dose. Finally, potential causes of overestimation of anticholinergic burden were identified, including the off-label use of low-dose trazodone for insomnia and the as-needed administration of some antipsychotics. Nevertheless, it is likely that burden was underestimated in the community-dwelling group because of frequently used over-the-counter (OTC) medications with anticholinergic properties that the prescription drug database did not capture. Highly anticholinergic oral histamines such as diphenhydramine ranked sixth on a list of commonly used prescription and OTC medications in an adult community-dwelling population.[49] This underlines the importance of including OTC drugs in medication review and management.

In conclusion, in older adults with dementia newly dispensed cholinesterase inhibitor drugs, having more physicians providing care was associated with higher anticholinergic drug burden scores. Medication reviews, as Choosing Wisely recommends, should consider the cumulative burden of combinations of anticholinergic drugs to inform prescribing decisions. Better communication among prescribing physicians and more-comprehensive medication review before prescribing cholinesterase inhibitor drug therapy are important strategies to improve prescribing practices.

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APPENDIX 1: ANTICHOLINERGIC RISK SCALE

3 points: amitriptyline hydrochloride, atropine products, benztropine mesylate, carisoprodol, chlorpheniramine maleate, chlorpromazine hydrochloride, cyproheptadine hydrochloride, dicyclomine hydrochloride, diphenhydramine hydrochloride, fluphenazine hydrochloride, hydroxyzine hydrochloride and hydroxyzine pamoate, hyoscyamine products, imipramine hydrochloride, meclizine hydrochloride, oxybutynin chloride, perphenazine, promethazine hydrochloride, thioridazine hydrochloride, thiothixene, tizanidine hydrochloride, trifluoperazine hydrochloride

2 points: amantadine hydrochloride, baclofen, cetirizine hydrochloride, cimetidine, clozapine, cyclobenzaprine hydrochloride, desipramine hydrochloride, loperamide hydrochloride, loratadine, nortriptyline hydrochloride, olanzapine, prochlorperazine maleate, pseudoephedrine hydrochloride-triprolidine hydrochloride, tolterodine tartrate

1 point: carbidopa-levodopa, entacapone, haloperidol, methocarbamol, metoclopramide hydrochloride, mirtazapine, paroxetine hydrochloride, pramipexole dihydrochloride, quetiapine fumarate, ranitidine hydrochloride, risperidone, selegiline hydrochloride, trazodone hydrochloride, ziprasidone hydrochloride

An individual's Anticholinergic Risk Scale (ARS) score is calculated as the sum of the ARS rankings assigned for each of the medications the patient is taking. Adapted from: Rudolph JL, Salow MJ, Angelini MC et al. The Anticholinergic Risk Scale and anticholinergic adverse effects in older persons. Arch Intern Med 2008;168:508–513.