ORIGINAL INVESTIGATION

A Prescribing Cascade Involving Cholinesterase Inhibitors and Anticholinergic Drugs

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Background: The prescribing cascade model involves the misinterpretation of an adverse reaction to 1 drug and the subsequent, potentially inappropriate prescription of a second drug. We present a new example of the prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs used to manage urinary incontinence.

Methods: A population-based retrospective cohort study was carried out in Ontario, Canada. Participants included 44884 older adults with dementia (20491 were dispensed a cholinesterase inhibitor and 24393 were not), enrolled between June 1, 1999, and March 31, 2002. Subjects were observed until they received an anticholinergic drug, stopped the cholinesterase inhibitor treatment, died, or the study period ended (March 31, 2003). The main outcome measure was receipt of an anticholinergic drug to manage urinary incontinence.

Results: After adjusting for potential confounding factors, we observed that older adults with dementia who were dispensed cholinesterase inhibitors had an increased risk of subsequently receiving an anticholinergic drug (4.5% vs 3.1%; $P<.001$; adjusted hazard ratio, 1.55; 95% confidence interval, 1.39-1.72), relative to those not receiving cholinesterase inhibitors. This finding was consistent in a series of subgroup analyses.

Conclusions: Use of cholinesterase inhibitors is associated with an increased risk of receiving an anticholinergic drug to manage urinary incontinence. The use of an anticholinergic drug in this setting may represent a clinically important prescribing cascade. Clinicians should consider the possible contributing role of cholinesterase inhibitors in new-onset or worsening urinary incontinence and the potential risk of coprescribing cholinesterase inhibitors and anticholinergic drugs to patients with dementia.

Arch Intern Med. 2005;165:808-813

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Financial Disclosure: Dr Naglie has received speaker honorarium from Pfizer.

OPTIMIZING THE PRESCRIBING of medications for older adults remains a significant challenge for physicians and policy makers.[1] Efforts to improve prescribing have focused on potentially inappropriate drug use (ie, "errors of commission"),[2,3] the underuse of appropriate drugs (ie, "errors of omission"),[4-6] and drug interactions.[3] However, more subtle mechanisms of inappropriate prescribing may also be important. Adverse drug events in older adults can manifest in a variety of ways, and such events may not always be correctly identified. Fried et al[7] suggest that a misattribution model is a common illness presentation among older patients. Similarly, a "prescribing cascade" involves the misattribution of an adverse drug event to a new medical problem, leading to the inappropriate use of a second drug. Several examples of the prescribing cascade have been documented.[8] We document a newly recognized prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs.

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Cholinesterase inhibitors—including donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide—are increasingly being used to manage the symptoms of dementia. Through their effects on the autonomic nervous system, cholinesterase inhibitors can precipitate urge urinary incontinence.[9,10] To complicate matters, new-onset or worsening incontinence is commonly seen as part of the natural history of dementia. As a result, clinicians may misinterpret incontinence in patients with dementia as an unavoidable progression of their underlying disease, when it may in fact represent a potentially reversible drug-related adverse event.

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Urinary incontinence is common among frail older adults and is associated with significant morbidity.[11] As dementia is an important risk factor for the development or worsening of urinary incontinence,[12] the management of incontinence in this group is especially challenging. Although anticholinergic drugs (eg, oxybutynin chloride, tolterodine tartrate, and flavoxate hydrochloride) are often used to manage urge urinary incontinence, adverse drug events are common among frail older adults exposed to these agents. The risk of cognitive decline and delirium with anticholinergic drugs is particularly concerning in patients with dementia.[13-16] Thus, the prescription of anticholinergic drugs to patients with dementia is generally considered inappropriate.[2,3] Indeed, cholinesterase inhibitors and anticholinergic drugs can be viewed as having directly opposing actions.

The objective of this study was to examine the association between the use of cholinesterase inhibitors and the subsequent prescription of anticholinergic drugs to manage urge incontinence. This association may represent an important and underrecognized prescribing cascade.

METHODS

COHORT DEFINITION

The administrative health care databases of Ontario, Canada, allowed for identification of a group of older adults with a diagnosis of dementia and without a history of urinary incontinence. In Ontario, a universally funded health care program covers nearly all physician services, medications, and hospital services for patients 65 years and older. Encrypted unique identifiers that are common between databases were used to link anonymous information on demographics and health services utilization for patients in our study. The linked databases included computerized pharmacy records of the Ontario Drug Benefit (ODB) program, which records prescription drugs dispensed to all Ontario residents 65 years or older. Acute-care hospitalization records were obtained from the Canadian Institute for Health Information (CIHI) Discharge Abstract Database, which uses the *International Classification of Diseases, Ninth Revision* (*ICD-9*) nomenclature to provide detailed diagnostic records for all hospital admissions. The Ontario Health Insurance Plan (OHIP) records provided physician billing information for inpatient and outpatient services, and the Registered Persons Database (RPDB) contains basic demographic information and vital statistics for each patient. This study was approved by the ethics review board of Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario.

We identified the following 2 cohorts within the population of older adults with dementia (OHIP and *ICD-9* diagnosis codes 290, 331, and 797): those who were new users of cholinesterase inhibitors (the drug cohort) and those who were not dispensed cholinesterase inhibitors (the control cohort). In Ontario, the cholinesterase inhibitors donepezil, rivastigmine, and galantamine are available through the ODB program. We excluded patients who had evidence of urinary incontinence in the year prior to cohort entry, specifically, those with a diagnosis of incontinence (OHIP diagnosis codes 625 and 788; *ICD-9* codes 625.6 and 788.3), use of anticholinergic drugs (oxybutynin, tolterodine, or flavoxate), or documentation of a urodynamic procedure (OHIP procedure codes G192-194 and G475-477). Patients were enrolled into the cohorts in the entry event window between June 1, 1999, and March 31, 2002. To restrict our drug cohort to new users, we looked back 6 months from the first date of dispensation to ensure that subjects had not previously received any cholinesterase inhibitor. Frequency matching was used to match the control cohort to the drug cohort by date of cohort entry, within 1 month of the first date of dispensation. Members of the control cohort had no ODB claims for a cholinesterase inhibitor within 6 months of cohort entry or at any time during follow-up. Controls were also required to have evidence of other ODB claims during the entry event window to ensure that they were in contact with the health care system. The first ODB claim in the month of entry was the index date for control subjects.

PATIENT OBSERVATION

The surveillance period began on June 1, 1999, and extended to March 31, 2003. Drug exposure was considered to have continued as long as a subsequent prescription for a cholinesterase inhibitor was recorded in the ODB database within a period of 3 times the total days supplied after the anticipated end date of the last dispensation. Prescription duration for each dosage was defined as the drug quantity divided by the daily intake of drug recommended by the manufacturer in the 2003 Canadian *Compendium of Pharmaceuticals and Specialties*[17] (similar to the US *Physicians' Desk Reference*). This relatively long interval was used to account for the effects of pill splitting (eg, for patients dispensed 5-mg tablets but instructed to take only half a tablet or 2.5 mg/d) and the fact that many patients using cholinesterase inhibitors have been documented to have gaps in treatment of 6 weeks or more.[18]

OUTCOMES AND POTENTIAL CONFOUNDERS

The primary outcome in this study was receipt of an anticholinergic drug to manage urge urinary incontinence, as identified using the ODB database. Patients were observed until they were dispensed an anticholinergic drug, discontinued their cholinesterase inhibitor treatment, died, or the follow-up period ended (March 31, 2003). The coding accuracy of drug claims in the ODB database is excellent; an error rate of only 0.7% has been documented.[19] We were confident that most patients who were dispensed cholinesterase inhibitors and anticholinergic drugs received them for the indications of dementia and urinary incontinence, respectively; off-label use of these drugs is uncommon and discouraged by the use of "limited use" prescribing criteria.[20]

We controlled for factors that might influence the development of urge urinary incontinence and dispensation of anticholinergic drugs to manage this condition. These factors include age; sex; low-income status; residence in long-term care; medical conditions such as stroke and diabetes mellitus; overall comorbid disease burden; and the concomitant use of medications that might interfere with normal bladder function (such as neuroleptics, antidepressants, anticonvulsants, antiparkinsonian drugs, diuretics, and other drug classes with anticholinergic properties such as antihistamines). As an overall measure of comorbidity, we used the number of distinct drugs dispensed in the year prior to cohort entry,[21] a measure that performs as well as the Charlson comorbidity index[22] in risk adjustment. Finally, given the duration of our study and the potential for changes in patient care over this period, we controlled for the year of entry into the study.

STATISTICAL ANALYSIS

We conducted survival analyses using Cox proportional hazard models. All analyses were performed with SAS for UNIX, version 8.2 (SAS Institute Inc, Cary, NC).

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Table 1. Demographic Characteristics and Comorbidity in the Drug and Control Cohorts*

Characteristic	Drug Cohort (n = 20 491)	Control Cohort (n = 24 393)
Demographic		
Age, mean, y	81.3	82.4
Sex, % male	35.6	30.7
In long-term care	2578 (12.6)	11 717 (48.0)
Comorbidity		
Charlson comorbidity index, mean score	0.71	1.26
With prior stroke	312 (1.5)	593 (2.4)
With diabetes mellitus	2224 (10.9)	3475 (14.3)
Medication history, medications affecting urinary continence		
Medications per patient, mean (range), No.	5.8 (0-38)	7.9 (0-42)
Using neuroleptics		
High-potency typical	692 (3.4)	1710 (7.0)
Low-potency typical	537 (2.6)	1683 (6.9)
Atypical	2949 (14.4)	4442 (18.2)
Total†	3647 (17.8)	6755 (27.7)
Using antidepressants		
SSRIs	4429 (21.6)	5182 (21.2)
TCAs	1362 (6.7)	2264 (9.3)
Other	1459 (7.1)	2088 (8.6)
Total†	6266 (30.6)	8274 (33.9)
Using anticonvulsants	364 (1.8)	951 (3.9)
Using diuretics	5011 (24.5)	9074 (37.2)
Using antiparkinsonian drugs	828 (4.0)	1879 (7.7)
Using other anticholinergic drugs	296 (1.4)	369 (1.5)

Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

*Data are given as number (percentage) of patients unless otherwise specified.

†The total number of subjects dispensed neuroleptics is less than the sum of the different types of neuroleptics because some subjects were exposed to more than 1 type of neuroleptic. The same trend was seen for antidepressants.

Table 2. Event Rates and HRs for Main Analysis

Main Analysis (Full Cohorts)	Drug Cohort (n = 20 491)	Control Cohort (n = 24 393)
Total No. (%) of events (newly dispensed anticholinergic medications)	916 (4.5)	746 (3.0)
Duration of follow-up, mean ± SD, d	554 ± 364	641 ± 363
Crude event rate (No. of events per 1000 person-years)*	29.5	17.4
Unadjusted HR (95% CI)	1.66 (1.51-1.83)	1.00 (Referent)
Adjusted HR (95% CI)	1.55 (1.39-1.72)	

Abbreviations: CI, confidence interval; HR, hazard ratio (adjusted for potential confounding factors unless otherwise noted).

*Crude event rate = (number of events/total number of days per 365 days) × 1000.

RESULTS

STUDY POPULATION

The study population included 44 884 older adults with dementia. Of these patients, 20 491 were dispensed 1 of the 3 available cholinesterase inhibitors (the drug cohort), and 24 393 were not dispensed a cholinesterase inhibitor (the control cohort). The drug cohort included the following distribution of exposures: 95.6% of subjects were dispensed donepezil, 4.4% were dispensed rivastigmine, and fewer than 0.1% were dispensed galantamine. This distribution relates to the period analyzed and the timing of introduction of the different cholinesterase inhibitors onto the ODB formulary.

The demographic characteristics of these subjects are outlined in **Table 1**. In general, the demographic profile of the control cohort subjects suggested that they were slightly older and had more comorbid disease compared with the subjects in the drug cohort. The control cohort contained a larger proportion of women and long-term care residents compared with the drug cohort. The demographic characteristics of subjects who were excluded were generally comparable to those of subjects who were entered in the study. To indirectly compare the baseline risk of incontinence in the 2 groups, we examined the proportion of subjects in the drug and control cohorts who were excluded owing to evidence of incontinence in the year prior to study entry. We found that 11.6% of the subjects potentially eligible for the control cohort were excluded because of evidence of incontinence, compared with 10.9% of subjects potentially eligible for the drug cohort. This result suggests that the control cohort carried a similar baseline rate of incontinence as the drug cohort and might therefore have a similar propensity to receive an anticholinergic medication in follow-up.

There were 1662 new dispensations of anticholinergic drugs to patients during follow-up. Oxybutynin accounted for 67.6% of these dispensations, while tolterodine accounted for 22.3% and flavoxate for 10.1%. The distribution of individual anticholinergics was similar in the drug and control cohorts. Patients in the drug cohort were more likely to receive an anticholinergic medication in follow-up (4.5% vs 3.1%; $P<.001$).

In the unadjusted and multivariate analyses, older adults dispensed cholinesterase inhibitors were again found to have a higher risk of subsequently receiving an anticholinergic medication (unadjusted hazard ratio [HR], 1.66; 95% confidence interval [CI], 1.51-1.83; adjusted HR, 1.55; 95% CI, 1.39-1.72) (**Table 2**).

Given important baseline differences in our cohorts, we wanted to confirm that our results were consistent across specific subpopulations. Thus, we conducted 6 subgroup analyses. The findings for the main analysis were consistent with those in all 6 subgroups.

SUBGROUP ANALYSES

We conducted 6 subgroup analyses (**Table 3**). In the first analysis, we examined the subgroup of each cohort that was residing in long-term care. In this analysis, the HR for a receipt of an anticholinergic drug was again significantly higher for the drug cohort (HR, 1.94; 95% CI, 1.45-2.60). In the second analysis, we examined the subgroup of community-dwelling older adults. In this analysis, the HR for a receipt of an anticholinergic was again significantly higher for the drug cohort (HR, 1.47; 95% CI, 1.31-1.64). In the third analysis, we examined the sub-

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Table 3. Event Rates and HRs for Subgroup Analyses*

Subgroup	Drug Cohort	Control Cohort
Subgroup 1	n = 2578	n = 11 717
No. (%) of events†	63 (2.4)	189 (1.6)
Duration of follow-up, mean ± SD, d	440 ± 338	585 ± 364
Crude event rate‡	20.3	10.1
HR (95% CI)	1.94 (1.45-2.60)	1.00 (Referent)
Subgroup 2	n = 17 913	n = 12 676
No. (%) of events†	853 (4.8)	557 (4.4)
Duration of follow-up, mean ± SD, d	570 ± 364	692 ± 355
Crude event rate‡	30.5	23.2
HR (95% CI)	1.47 (1.31-1.64)	1.00 (Referent)
Subgroup 3	n = 13 202	n = 16 905
No. (%) of events†	609 (4.6)	532 (3.2)
Duration of follow-up, mean ± SD, d	553 ± 367	649 ± 365
Crude event rate‡	30.4	17.7
HR (95% CI)	1.50 (1.32-1.70)	1.00 (Referent)
Subgroup 4	n = 2062	n = 2502
No. (%) of events†	48 (2.3)	37 (1.5)
Duration of follow-up, mean ± SD, d	306 ± 136	370 ± 110
Crude event rate‡	27.8	14.6
HR (95% CI)	1.69 (1.07-2.67)	1.00 (Referent)
Subgroup 5	n = 17 721	n = 18 899
No. (%) of events†	741 (4.2)	548 (2.9)
Duration of follow-up, mean ± SD, d	559 ± 363	636 ± 359
Crude event rate‡	27.3	16.6
HR (95% CI)	1.47 (1.30-1.65)	1.00 (Referent)
Subgroup 6	n = 20 489	n = 20 489
No. (%) of events†	916 (4.5)	619 (3.0)
Duration of follow-up, mean ± SD, d	554 ± 364	679 ± 363
Crude event rate‡	29.5	16.2
HR (95% CI)	1.83 (1.62-2.07)	1.00 (Referent)

Abbreviations: CI, confidence interval; HR, hazard ratio.

*Data are presented for the following 6 subgroup analyses: subgroup 1: long-term care residents; subgroup 2: community-dwelling older adults; subgroup 3: women; subgroup 4: patients newly dispensed cholinesterase inhibitors in 2002 (Caremark program [providing the first 12-week supply of donepezil outside of the Ontario Drug Benefit program] took place between June 1999 and June 2001; new cholinesterase inhibitor users in 2002 were identified from first use in the Ontario Drug Benefit program); subgroup 5: patients not dispensed any anticholinergic medications at baseline (eg, tricyclic antidepressants, low-potency neuroleptics, antiparkinsonian drugs, or other medications with moderate or strong anticholinergic activity[23,24]); and subgroup 6: matched-pair analysis to assess effects of comorbidity on results.

†Newly dispensed anticholinergic medications.

‡Crude event rate (number of events per 1000 person-years) = (number of events/total number of days per 365 days) × 1000.

group of women in each of the cohorts. Again, the HR for receipt of an anticholinergic medication was higher among patients in the drug cohort (HR, 1.50; 95% CI, 1.32-1.70).

In the fourth subgroup analysis, we examined those patients who were newly prescribed a cholinesterase inhibitor in 2002. The rationale for this subgroup was the fact that patients dispensed donepezil between June 1999 and June 2001 received the first 12-week supply of the drug through a company called Caremark (Canada), with no record of this dispensation in the ODB database. As a result, we were concerned that patients considered control subjects during this period might in fact be receiving donepezil. If anything, this misclassification would bias our findings toward a more conservative result (ie, false-negative findings). Indeed, in our subgroup analysis of patients newly dispensed cholinesterase inhibitors in 2002, the hazard for receipt of an anticholinergic was again higher for the drug cohort (HR, 1.69; 95% CI, 1.07-2.67). This HR was similar in magnitude to the one for the main cohort, supporting the contention that the main cohort finding is valid.

Baseline use of anticholinergic medications (such as tricyclic antidepressants, low-potency neuroleptics, and antiparkinsonian drugs) was more common in the control cohort than in the drug cohort (Table 1). Thus, we were concerned that the association between cholinesterase inhibitors and anticholinergic medications for incontinence might result from a "protective" effect of higher baseline anticholinergic drug use among control cohort subjects. To assess this possibility, a fifth analysis involved restricting the cohorts to subjects who had not received other anticholinergic medications at baseline. These "anticholinergic naïve" subjects were patients who

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had not received tricyclic antidepressants, low-potency neuroleptics, antiparkinsonian drugs, or other medications with moderate or strong anticholinergic activity.[23,24] In this subgroup analysis, the HR for receipt of an anticholinergic drug was again higher for the drug cohort (HR 1.47; 95% CI, 1.30-1.65). This HR was similar in magnitude to the HR for the main cohort, thereby countering the argument of a "protective" effect of other anticholinergic medications on the outcome.

The control cohort had evidence of a higher comorbid disease burden compared with the drug cohort, as measured using both the Charlson comorbidity scores and the total number of medications (Table 1). Redelmeier and colleagues[25] have suggested that physicians may undertreat patients with multiple chronic medical conditions. There are several possible explanations for this finding. For example, physicians may be more reluctant to add medications to an already complex list of drugs for fear of drug interactions or skepticism about incremental benefits. Alternatively, the physician may fail to recognize the opportunity to provide drug therapy for every comorbidity in a patient with multiple chronic diseases. Given these concerns, we performed a sixth subgroup analysis to assess the possibility that our main results were biased by differences in baseline comorbidity between the cohorts (in effect, that the higher burden of comorbidity among control subjects led to the lower prescribing of anticholinergic medications for incontinence). We performed a matched-pair analysis with 1:1 matching of drug and control cohort subjects. Subjects were matched on the following 4 variables: Charlson comorbidity scores (within 1 point), number of medications (within 1), age (within 1 year), and sex. The analysis involved a Cox proportional hazards model with a matched-pair design. The HR for a receipt of an anticholinergic was again higher for the drug cohort (HR, 1.83; 95% CI, 1.62-2.07). With the consistent results of these 6 sensitivity analyses, we had more confidence in the general validity of our findings.

COMMENT

We found that cholinesterase inhibitor use was associated with an increased risk of receiving anticholinergic medications to manage urinary incontinence in a population-based cohort. This result persisted when we adjusted for other risk factors for urinary incontinence and when we examined subgroups of the main cohort. These findings are of concern for 2 reasons. First, cholinesterase inhibitors and anticholinergic drugs have opposing actions, and concomitant use of anticholinergic drugs may therefore dilute the benefits of cholinesterase inhibitors. This line of reasoning has been used by the Saskatchewan Formulary Committee to exclude the reimbursement of cholinesterase inhibitors to patients who are coadministered anticholinergic drugs.[26] Second, the use of anticholinergics in these patients may represent an unrecognized adverse drug event related to cholinesterase inhibitor use. The argument could be made that it would be more appropriate to reduce the dose of the cholinesterase inhibitor rather than add an anticholinergic drug to the treatment of patients who develop incontinence.

Several case series have found an association between the use of cholinesterase inhibitors and new-onset or worsening urinary incontinence.[9,10] Interestingly, this association was generally not described in the clinical trials that evaluated the cholinesterase inhibitors for dementia. There may be several reasons for this. First, these trials were generally of short duration. Second, the trials enrolled a relatively young and healthy group; patients with significant comorbidity were excluded from participation. Third, it has been found that the reporting of safety information in clinical trials is often neglected and receives less attention compared with efficacy outcomes.[27]

Other authors have also found that patients receiving cholinesterase inhibitors are more likely to receive a variety of anticholinergic medications.[23] In the present study, we focused on the use of anticholinergic medications for urinary incontinence because clinicians might misattribute the incontinence to the inevitable progression of the underlying dementia. If incontinence is drug related, on the other hand, there is the potential for reversibility.

The prescribing pattern we have documented represents a prescribing cascade, in which an adverse drug reaction involving a cholinesterase inhibitor (ie, urinary incontinence) is misinterpreted as a new medical condition, thereby leading to another drug being prescribed.[8] Other authors have used the related concept of "prescription sequence analysis" in pharmacoepidemiology research.[28] We focused on the outcome of a new anticholinergic prescription rather than a new diagnosis of urinary incontinence for several reasons. First, we had less confidence in the diagnostic coding of incontinence in administrative data than we did in the recording of drug dispensations in the ODB database.[29] Second, the prescribing cascade we describe represents more than just an adverse drug event; it represents the possible misattribution of an adverse drug event and subsequent inappropriate prescribing (specifically, the addition of an anticholinergic drug to combat the adverse effects of the initial drug therapy). The opposing effects of cholinesterase inhibitors and anticholinergic drugs for incontinence may lead to additional adverse drug reactions. Furthermore, anticholinergic medications can reduce or eliminate any cognitive benefits produced by the cholinesterase inhibitors. A recent cohort study has demonstrated the adverse effects of anticholinergic drugs in patients with dementia treated with cholinesterase inhibitors.[24] In this cohort study, patients using a combination of donepezil and a drug with anticholinergic effects had significant worsening in serial cognitive assessments over 2 years relative to patients using donepezil alone. Most clinical trials of cholinesterase inhibitors excluded patients using anticholinergic drugs.

Our study has several potential limitations. First, it is possible that the baseline differences in our drug and control cohorts could have led to different risks of experiencing the outcome. However, the control cohort was in fact somewhat older and had more comorbid conditions compared with the drug cohort. These factors would likely bias our findings toward being underestimates. This supposition is further supported by the fact that similar proportions of subjects were excluded from the control and drug cohorts because of prior incontinence (11.6%

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vs 10.9%, respectively). Another limitation is that we were not able to directly measure dementia severity in the 2 cohorts. Despite this limitation, our results were consistent in a series of subgroup analyses including one for residents of long-term care for which dementia severity should be more evenly matched between cohorts.

What do these results mean for clinical practice? Physicians may judge the combination of cholinesterase inhibitors to manage dementia and anticholinergic drugs to manage incontinence to be justified in selected cases. For example, there may be cases in which the cholinesterase inhibitor has clearly benefited the patient but incontinence develops as well. In cases such as this, clinicians should at least be conscious of the opposing effects of cholinesterase inhibitors and anticholinergic drugs. Oxybutynin is considered by some authorities to be a potentially inappropriate medication because it is often poorly tolerated by older adults owing to its anticholinergic effects.[2,3,13] Although extended-release oxybutynin and tolterodine have been cited as being better tolerated, their use in patients with baseline cognitive dysfunction must still be carefully monitored.[30]

In conclusion, clinicians should consider the prescribing cascade model when evaluating elderly patients. In particular, they should consider the possible contributing role of cholinesterase inhibitors in new-onset or worsening urinary incontinence. Clinicians should carefully assess the potential risks of coprescribing cholinesterase inhibitors and anticholinergic drugs to patients with dementia.

Accepted for Publication: October 26, 2004.
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Funding/Support: Dr Gill was supported by a Canadian Institutes of Health Research (CIHR), Postdoctoral Fellowship and the Annie Kirshenblatt Memorial Scholarship. Dr Naglie is supported by the Mary Trimmer Chair in Geriatric Medicine Research from the University of Toronto. Dr Rochon is supported by a CIHR Investigator Award. Dr Lee's Behavioural Neurology Fellowship was supported in part by Eli Lilly Canada. This work was supported by a CIHR Chronic Disease New Emerging Team (NET) program grant (NET 54010). The NET program receives joint sponsorship from the Canadian Diabetes Association, the Kidney Foundation of Canada, the Heart and Stroke Foundation of Canada, and the CIHR Institutes of Nutrition, Metabolism and Diabetes, and Circulatory and Respiratory Health. Drs Mamdani and Bronskill were supported in part by New Investigator Awards through the NET program.
Acknowledgment: In addition to the listed authors, we acknowledge the input of the following NET members: A. Laupacis, MD, MSc; K. Sykora, MSc; M. P. Hillmer, MSc; W. P. Wodchis, PhD; C. Marras, MD; and S. Garfinkel, MSc.

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