An examination of three prescribing cascades in a cohort of older adults with dementia

Shanna Claire Trenaman (shanna.trenaman@dal.ca)
Dalhousie University https://orcid.org/0000-0002-7982-4437
Susan K Bowles
NSHealth
Susan Kirkland
Dalhousie Medical School: Dalhousie University Faculty of Medicine
Melissa K Andrew
Dalhousie Medical School: Dalhousie University Faculty of Medicine

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Abstract

Background

Prescribing cascades are a source of inappropriate prescribing for older adults with dementia. We aimed to study three prescribing cascades in older Nova Scotians with dementia using administrative databases.

Methods

Cohort entry for Nova Scotia Seniors' Pharmacare Program beneficiaries was at the date of dementia diagnosis. Prescription drug dispensation data was extracted for inciting medication and second treatment (cholinesterase inhibitor and bladder anticholinergic, metoclopramide and Parkinson's disease medication, or calcium channel blocker (CCB) and diuretic) over the six-year period from April 1, 2009 to March 31, 2015. In three separate analyses, dispensation of an inciting medication signaled a look back of 365 days from the date of first dispensation to confirm that the second treatment was started after the inciting medication. The prescribing cascade was considered when second treatment was started within 180 days of the inciting treatment. Sex differences in the prescribing cascade were tested using t-tests or chi square tests as appropriate. Both univariate (unadjusted) and multivariate (adjusted) logistic regression (adjusted for age, rurality, and sex) and Cox proportional hazards regression was used to identify risk factors for the prescribing cascade.

Results

In the period from March 1, 2005 to March 31, 2018 28,953 Nova Scotia Seniors Pharmacare beneficiaries with dementia (NSSPBD) were identified. There were 60 cases of bladder anticholinergics following cholinesterase inhibitors, 11 cases of Parkinson's disease medication following metoclopramide, and 289 cases of a diuretic following CCB. Regression analysis demonstrated that risk of bladder anticholinergics following cholinesterase inhibitors and diuretics following CCBs were associated with female sex. Cox regression analyses suggested that bladder anticholinergics were less often used by those on cholinesterase inhibitors but did not identify CCB use as leading more frequently to diuretic use.

Conclusions

Of the three prescribing cascades investigated, diuretics following CCB was the most common and bladder anticholinergics following cholinesterase inhibitors the second most common. Both these prescribing cascades were more common for women suggesting clinicians need increased attention to monitor for prescribing cascades among women.

Background

The concept of the prescribing cascade was first reported by Rochon and Gurwitz in 1995 (1). It is defined as an adverse drug event misinterpreted as a new medical condition resulting in a new medication being

prescribed to treat the adverse drug event (1–3). Prescribing cascades affect people of any age (4–7) but most commonly occur in older adults (6,8,9). This is related to the high level of medication use in older adults (10,11). Polypharmacy (12) is associated with increased incidence of adverse drug events (13,14) which may provide opportunities for prescribing cascades to occur. Older adults with dementia are more susceptible to adverse drug events than similarly aged controls without dementia due to their higher level of medication use (15–19).

Cholinesterase inhibitors, used to manage symptoms of dementia, exert their therapeutic activity by binding and inhibiting the cholinesterase enzyme (20,21), increasing the concentration of available acetylcholine (22–24). As cholinesterase inhibitors are not selective for the brain, acetylcholine concentrations are increased systemically. Activation of muscarinic receptors (25,26) in the urinary tract causes forceful contraction of the detrusor muscle which may result in urge type urinary incontinence. Treating this iatrogenic urinary incontinence with a bladder anticholinergic is thus a prescribing cascade.

Metoclopramide is used to treat nausea, vomiting, diabetic gastroparesis, or loss of appetite; all of which can occur in older adults. Metoclopramide's mechanism of action is to antagonize the activity of dopamine at receptors in the chemoreceptor trigger zone, located outside the blood-brain barrier, and in the gut (27). Metoclopramide is non-selective and notably, crosses the blood brain barrier allowing for inhibition of dopamine receptors within the brain. This inhibition can induce Parkinsonian type movement changes. These symptoms can be mistaken for development of Parkinson's Disease or vascular pseudoparkinsonism and if this leads to treatment with dopaminergic medications it represents a prescribing cascade.

Calcium channel blockers (CCB) are recommended as initial therapy as monotherapy or combination therapy for adults with either diastolic or systolic hypertension (28,29). CCBs are associated with the adverse event of pedal edema (prevalence 2–25%) which is likely due to vasodilation of peripheral arterioles and depends on drug, dose, duration and sex (30–33). As CCB-induced edema is dose dependent (30,34,35), and older adults who experience alteration in drug pharmacokinetics may experience increased CCB drug exposure, they may also be at a greater risk of this adverse event (36). Treating primary care providers may mistake CCB-induced pedal edema for symptoms of heart failure or peripheral vascular disease and initiate a prescribing cascade by prescribing diuretics to treat the CCB-induced edema (37,38).

Identifying the presence of prescribing cascades is an important component of addressing inappropriate medication by older adults which helps avoid both increased cost of medications, and sequelae of avoidable adverse drug events (2,3,39). We aimed to determine the incidence of and risk factors of these three prescribing cascades in a population of older adults with dementia in Nova Scotia, Canada.

Methods

Data Sources

Administrative claims data were made available through Health Data Nova Scotia (HDNS) following REB approval (File #: 1023625). Data were extracted from Medical Services Insurance (MSI) Physician's Billings (MED), Seniors Pharmacare (PHARM), Vital Statistics (VITAL), and the Canadian Institute for Health Information – Discharge Abstract Database (DAD). The data set included administrative data from March 1,

2005 to March 31, 2018. Databases used were housed by HDNS and data linkage was done by a third party using MSI health card number, which was not available to the research team but instead was replaced with a study identification number.

Cohort Definition

Cohort entry was from the date that the Nova Scotia Seniors' Pharmacare Beneficiary had at least one occurrence of any one of the International Classification of Diseases Clinical Modification (ICD) 9/10 codes that identify dementia from the MED or DAD databases (Table 1). The ICD codes chosen were identified in the Nova Scotia Dementia Strategy (40) as the most complete method to identify cases of dementia using locally available administrative data.

Individuals were enrolled in the cohort upon identification of appropriate dementia definition codes in the entry event window between March 1, 2005 to March 31, 2015. Cohort exit was at the date of death or March 31, 2015. The MED database provided date of dementia diagnosis, and age at first appearance of a dementia diagnosis, and the VITAL database provided the date of death. The cohort excluded adults less than 65 years of age with a dementia diagnosis and any adults over 65 years of age with dementia who did not participate in the Nova Scotia Seniors' Pharmacare Program (approximately 63% of adults over 65 years of age participate in the Nova Scotia Seniors' Pharmacare Program (41)).

Once meeting cohort entry criteria, prescription drug dispensation data was extracted for requested drug classes (Table 2) over the six-year period from April 1, 2009 to March 31, 2015. Medication use and other descriptors were abstracted from the PHARM database, including medication (ATC code), quantity dispensed, prescription fill date, sex, and geographic location specified as urban or rural based on the second digit of the postal code (42).

Analytic Procedures

In three separate analyses, individuals were followed from April 1, 2010 until they had a dispensation of any one of the three inciting medications (Table 2), died or the follow-up period ended. Once dispensation of an inciting medication (cholinesterase inhibitor, metoclopramide or CCB) was identified there was a look back of 365 days from the date of first dispensation to confirm that the second treatment (bladder anticholinergic, Parkinson's disease medication or diuretic) was started after the inciting medication. The first year of data collection provided this look-back period. If the second treatment was started up to 180 days after the inciting medication this was identified as an instance of the prescribing cascade. Robustness of the prescribing cascade definition was tested by altering the window from 180 days to 90, 60 and 30 days. This allowed us to assess the lag between inciting medication and implicated medication to consider whether there was biologic plausibility of a prescribing cascade. Sex differences in the prescribing cascade were tested using t-tests or chi square tests as appropriate. Both univariate (unadjusted) and multivariate (adjusted) logistic regression (adjusted for age, rurality, and sex) was used to identify risk factors for the prescribing cascade.

In a secondary analysis we considered the dispensation of the prescribing cascade implicated drug (second treatment) as an outcome of interest in a survival analysis using Cox proportional hazard models to examine hazard ratios. Time to event was considered from date of the inciting medication prescription to dispensation

of the prescribing cascade-implicated drug, with comparisons made for those dispensed and not dispensed an inciting medication within the time frame. Missing data were handled using case-wise deletion.

Statistical Software

All data analysis was completed on STATA version 15.1, StataCorp, Lakeway Drive, College Station, Texas, USA.

Results

In the period from April 1, 2010 to March 31, 2015, a total of 28,953 Nova Scotia Seniors Pharmacare Beneficiaries with dementia (NSSPBD) (62% women) were identified as receiving a dementia diagnosis. The average age at dementia diagnosis was 81.1 years (95% confidence interval (CI): [81.0-81.2]) with the mean age of women being 2.5 years (95% CI: [2.9-3.6]) older than men at dementia diagnosis ($p<0.0001$). Details on cohort sex, age and geographic location are provided in Table 3.

Cascade 1: Cholinesterase inhibitor & bladder anticholinergic

A total of 117,416 cholinesterase inhibitor (ATC N06DA) prescriptions were dispensed to 5,772 NSSPBD (68.7% women and 19.9% of NSSPBD) over the period of investigation. Cholinesterase inhibitors used were donepezil (57.0%), galantamine (36.0%), and rivastigmine (7.0%). For all cholinesterase inhibitor users in the cohort the time between dementia diagnosis (occurring between 2005 and 2015) and first dispensation for a cholinesterase inhibitor in the study period (occurring between 2010 and 2015) was on average 2.5 years (95% CI: [2.5-2.6]) with women having a longer time between diagnosis and cholinesterase inhibitor treatment (2.6 vs. 2.3 years, $p<0.0001$) than men. NSSPBD receiving cholinesterase inhibitor treatment used these agents on average 1.9 (95% CI [1.8-1.9]) years with women using cholinesterase inhibitors for longer durations (1.9 vs. 1.8 years, $p=0.0012$) (Table 4).

There were 17,806 prescriptions for bladder anticholinergics (ATC G04BD) dispensed to 1,263 NSSPBD (73.0% women and 4.4% of NSSPBD). NSSPBD who received at least one prescription for a bladder anticholinergic were on average 79.5 years of age at the time of their dementia diagnosis and 81.9 years at the time of their first bladder anticholinergic prescription. Bladder anticholinergics used were oxybutynin (73.2%), tolterodine (14.5%), solifenacin (8.2%), trospium, darifenacin, and fesoterodine (combined 4.1%). For all bladder anticholinergic users in the cohort the time between dementia diagnosis (occurring between 2005 and 2015) and first dispensation of a bladder anticholinergic (occurring between 2010 and 2015) was on average 2.3 years (95% CI [2.2-2.4]) which was similar for men and women ($p=0.45$). Those NSSPBD receiving a bladder anticholinergic used the treatment on average 1.3 years (95% CI [1.2-1.4). Duration of bladder anticholinergic use was similar for men and women (1.3 years, $p=0.4$) (Table 4).

The accepted definition of the prescribing cascade, where cholinesterase inhibitor preceded the bladder anticholinergic by up to six months (180 days), was identified in 60 cases (41 women and 19 men, 0.2% of NSSPBD) (Table 4). Shortening the window for the prescribing cascade to 90 days reduced the number of identified cases to 36 (25 women, 11 men, 0.1%), a window of 60 days reduced the number of identified cases

to 32 (21 women, 11 men, 0.1%) and limiting the window for the prescribing cascade to 30 days reduced the number of identified cases to 16 (10 women, 6 men).

Cross sectional analysis with logistic regression (Table 5) suggested that age and sex were statistically significant risk factors for occurrence of the prescribing cascade with younger age and female sex being associated with the increased use of bladder anticholinergics following cholinesterase inhibitors. In unadjusted and multivariate Cox regression, those dispensed cholinesterase inhibitors were found to have a lower risk of subsequently receiving a bladder anticholinergic medication (unadjusted hazard ratio [HR], 0.77; 95% CI, 0.68-0.87; adjusted

HR, 0.79; 95% CI, 0.68-0.92) (Table 6).

Cascade 2: Metoclopramide & antiparkinsonian agents

In total 3,760 prescriptions for metoclopramide (ATC A03FA01) were dispensed to 1,038 NSSPBD (76.7% women and 3.6% of NSSPBD). NSSPBD who received at least one dispensation for metoclopramide were on average 81.6 years of age at the time of their dementia diagnosis and 84.9 years of age at the time of their first metoclopramide prescription. For all metoclopramide users in the cohort the time between dementia diagnosis (occurring between 2005 and 2015) and first dispensation for metoclopramide was on average 3.3 years (95% CI: [3.1-3.4]) and longer for women than men (3.4 versus 2.9 years, p=0.0075). Those NSSPBD receiving metoclopramide used it for an average 0.2 years or 2.4 months. Duration of use did not differ between men and women (0.2 versus 0.2 years, p=0.29) (Table 4).

25,984 prescriptions for Parkinson's Disease medications (ATC N03) were dispensed to 997 NSSPBD (53.8% women and 3.4% of NSSPBD). NSSPBD who received at least one prescription for a Parkinson's Disease medication were on average 78.6 years of age at the time of their dementia diagnosis and 81.0 years at the time of their first Parkinson's Disease medication prescription. Parkinson's Disease medications used included levodopa and decarboxylase inhibitor (74%), pramipexole (12.2%), ropinirole (3.8%), entacapone (3.3%), amantadine (2.8%), selegiline (2.0%), and levodopa, decarboxylase inhibitor and COMT inhibitor (1.1%). For all Parkinson's Disease medication users in the cohort the time between dementia diagnosis (occurring between 2005 and 2015) and first dispensation of a Parkinson's Disease medication was on average 2.4 years (95% CI: [2.3-2.6]) with no difference between men and women (2.4 versus 2.5, p=0.33). Those NSSPBD receiving Parkinson's Disease treatment used it for on average 2.3 years (95% CI: [2.1-2.5]) with no statistically significant difference in duration between men and women (2.4 versus 2.2, p=0.059) (Table 4).

The accepted definition of the prescribing cascade, where metoclopramide preceded the Parkinson's Disease medication by less than six months (180 days), was identified in only 11 cases (table 4). Due to the very low number of cases of the prescribing cascade it was not possible to perform a logistic or cox regression analysis to identify risk factors or a sex-difference for this prescribing cascade.

Cascade 3: Calcium Chanel Blocker - diuretic

In total 93,688 prescriptions for a CCB (ATC C08CA) were dispensed to 4,639 NSSPBD (71.4% women and 16.0% of NSSPBD). NSSPBD who received at least one dispensation for a CCB were on average 81.3 years of age at the time of their dementia diagnosis. Women who received at least one prescription for a CCB were on

average 4.8 years older than men at their dementia diagnosis (82.6 versus 77.8 years, p<0.0001). The average age NSSPBD initiated CCB at 83.5 years but women were also older than men at the time of their first CCB prescription by a mean 5.1 years (85.0 versus 79.9, p<0.0001)). The time between dementia diagnosis and first dispensation for a CCB was on average 2.3 years with women having a mean 0.3 years longer lag between dementia diagnosis and initiation of a CCB (2.4 versus 2.1 years, p=0.0002). Those NSSPBD receiving CCB treatment used these agents for on average 1.9 years. Women used CCB longer than men (1.9 versus 1.8 years, p=0.0004). CCB prescriptions were most commonly for amlodipine (67.4%), followed by felodipine (3.9%), and nifedipine (31.3%) (Table 4).

There were 117,692 prescriptions for diuretic medications dispensed to 6,389 NSSPBD (70.6% women and 22.1% of NSSPBD). NSSPBD who received at least one prescription for a diuretic were on average 82.4 years of age at the time of their dementia diagnosis. At their first diuretic prescription NSSPBD were on average 84.8 years and women were older than men (86.1 versus 81.8 years (p<0.0001)). The time between dementia diagnosis and first dispensation for a diuretic was on average 2.5 years. Women had a mean of 0.3 years longer lag between dementia diagnosis and diuretic treatment (2.6 versus 2.3 years, p<0.0001)). Those NSSPBD receiving a diuretic used these agents for on average 1.6 years with women having a longer duration than men (1.6 versus 1.5 years, p=0.0012). Diuretics used by NSSPBD included furosemide (86.0%), spironolactone (5.2%), hydrochlorothiazide (6.5%), amiloride, ethacrynic acid and bumetanide (0.4%) (Table 4).

The accepted definition of the prescribing cascade, where CCB prescription preceded the diuretic medication prescription by less than six months (180 days), was identified in 289 cases. This represents 1.0% of all NSSPBD and 6.0% of NSSPBD who used CCB (Table 4). Shortening the window for the prescribing cascade to 90, 60 or 30 days reduced the number of cases of the prescribing cascade to 238, 202, and 130 respectively.

Logistic regression (Table 5) showed that in unadjusted analysis those of older age and women were at an increased risk of the prescribing cascade. In adjusted analysis (female) sex was the only covariate that was statistically significantly associated with increased for risk of the prescribing cascade. In unadjusted and multivariate Cox regression, those dispensed CCB were not found to have a different risk of subsequently receiving a diuretic (unadjusted hazard ratio [HR], 1.00; 95% CI, 0.94-1.05; adjusted HR, 1.04; 95% CI, 0.98-1.10) (Table 6).

Discussion

We investigated the incidence and risk factors for three prescribing cascades in an administrative data cohort of older adults with dementia. None of the three prescribing cascades investigated were common: bladder anticholinergics following cholinesterase inhibitors with 60 cases (0.2% of cohort), Parkinson's disease medication following metoclopramide with 11 cases (0.04% of cohort), and any diuretic following CCB with 289 cases (1.0% of cohort) over the five years of study. Regression analysis demonstrated that risk of both bladder anticholinergics following cholinesterase inhibitors and diuretics following CCBs was associated with female sex. The risk of bladder anticholinergics following cholinesterase inhibitors was more common among those with a younger age at dementia diagnosis. In unadjusted regression analyses, diuretics following CCBs were more common in those whose dementia was diagnosed at an older age. Compared with people not taking

the inciting medication, Cox regression suggested that bladder anticholinergics were less often used by those on cholinesterase inhibitors and did not identify CCB use as leading more frequently to diuretic prescription.

The cohort of NSSPBD approaches 12% of the population of Nova Scotians over 65 years of age. This exceeds published estimates that 7–10% of older adults over age 65 live with dementia (43). Nova Scotia has one of the oldest populations in Canada which may contribute to the higher prevalence of dementia in NSSPBD. There is also a sex imbalance in NSSPBD with an increased proportion of women (62.0% women), which is consistent with women being more likely to experience dementia than men (44). The sex distribution varied by age. There were more women than men with dementia at all age groups, skewing to greater proportions of women as age category increased which likely reflects women's longer life expectancy.

An Ontario study by Gill *et al.* also investigated bladder anticholinergics prescribed to adults with dementia (9). They found that older adults dispensed cholinesterase inhibitors were at a higher risk of being prescribed a bladder anticholinergic than those who were not, and found 916 prescribing cascade events over the 4 year period (HR 1.55; 95% CI (1.39 to 1.72)) (9). The study authors did not comment on sex differences in use of bladder anticholinergics or in users of cholinesterase inhibitors. We had contrary findings in that bladder anticholinergic use was less common in users of cholinesterase inhibitors (HR 0.77; 95% CI (0.68–0.87)). This is promising that in the years since Gill's study (which was run from 1999 to 2003) clinicians are more focused on avoiding this drug combination.

An Australian investigation into this same prescribing cascade found 36 cases over 4 years of study in a population of 4,393 older adults with dementia (0.8% of their cohort compared to our finding of 0.2%). In the Australian study nearly half of the cases of the prescribing cascade had each medication prescribed by a different prescriber (45). This highlights the importance of encouraging a single prescriber, ideally each person's primary care provider, to oversee treatment choices.

It is important that we avoid bladder anticholinergics regardless of cholinesterase inhibitor use in older adults with dementia. Bladder anticholinergics can lead to worsening cognitive and functional outcomes in older adults with dementia (46,47), are included on Beers' list and the STOPP criteria (48,49) as not appropriate for older adults with dementia so should be avoided. That bladder anticholinergics inhibit the desired effect of the cholinesterase inhibitor treatment (50) is only part of the reason they are considered inappropriate for older adults with dementia. Younger women may be those at greatest risk of bladder anticholinergics following cholinesterase as they may be; at greatest risk of the adverse effect of urinary incontinence from cholinesterase inhibitors, those least likely to accept this adverse effect, or those most likely to request treatment for incontinence. This provides a starting point for interventions that can be used to reduce this prescribing cascade and identifies the population that needs consideration for management of urinary incontinence.

The prescribing cascade of Parkinson's Disease medication being initiated after metoclopramide was rare in our study population. A low use of metoclopramide was identified, only 1,038 individuals (3.6%) and duration of use was short (mean of 73 days), so only a small portion of the cohort would have been at risk of developing movement-related adverse effects. The low incidence of this prescribing cascade in NSSPBD compares favourably with other jurisdictions. In a Korean population of adults over 60 years of age, those prescribed metoclopramide were about three times more likely to be prescribed levodopa than those who were

not (OR 3.04; 95% CI (2.46–3.77) (4). They also demonstrated that the odds of levodopa prescription increased with increasing duration of metoclopramide treatment (2.82 times for days 1–19 and 4.14 times for > 20 days; both odds ratios were adjusted for age, sex and exposure to antipsychotic medications) (4). In a case-control study of New Jersey Medicaid program patients aged 65 years or older, those taking metoclopramide were also three times more likely to begin using a drug containing levodopa than patients not taking metoclopramide (OR 3.09; 95% CI (2.25 to 4.26)) (51). It is reassuring that this prescribing cascade is not common in our cohort. It is also reassuring that metoclopramide was not commonly used and only for short durations. This may reflect use of metoclopramide for palliation or oncology purposes rather than chronic use for gastrointestinal syndromes.

In our cohort, 289 individuals (1.0%) met the criteria for the prescribing cascade where diuretics were used to treat CCB-induced pedal edema. This level of the prescribing cascade is consistent with population based estimates of 2–25% of CCB users experiencing the adverse drug effect of pedal edema (30) and Canadian studies of adults initiating CCB therapy demonstrating that between 4.6 and 9.5% initiate diuretic therapy shortly thereafter (38,52,53). CCB-induced pedal edema may result in a prescribing cascade rather than drug discontinuation as the drug-induced pedal edema may be mistaken for a symptom of heart failure or peripheral vascular disease which are both common in older adults. Unfortunately, the primary mechanism of edema formation secondary to CCB use is arteriolar dilatation, not fluid overload, so a loop diuretic is not likely to resolve the problem (37). More concerning is the potential complications from initiation of an unneeded loop diuretic including electrolyte monitoring, urinary incontinence, falls, and acute kidney injury. Diuresing euvolemic older adults experiencing CCB-induced edema places them at risk of dehydration, falls, urinary incontinence, acute kidney injury, electrolyte imbalance and many other consequences of overdiuresis (32,54–56) which may be more serious for older adults with dementia who may be unable to manage their medications, hydration, or continence independently. The requirement of careful attention to hydration and possibly supplemental potassium may be far more challenging for older adults with dementia to manage than those with intact cognition and may increase caregiver burden for those reliant for support in medication management.

Women have been shown to be more likely to experience peripheral edema after treatment with CCB (30). This was also identified in our population with women being at increased risk of the prescribing cascade in both adjusted and unadjusted analysis. In considering the reason women may be more sensitive to the adverse event of pedal edema, it may be due to the nature of feminine footwear which makes pedal edema easier for women to detect or more challenging for them to manage. Controlling for other factors age was not statistically significant while female sex remained so suggesting that female sex is what is driving the risk for diuretics after CCB given the cohort was predominantly women and the women were of older age.

Research using administrative data has several inherent limitations. The identification of individuals with dementia presents its own challenges, though these were mitigated by leveraging previous work of the Nova Scotia Dementia Strategy (40). Dementia likely remains underdiagnosed in Nova Scotia, so despite having access to a validated method of identifying those with dementia through administrative data we were unable to capture older women and men who have dementia but have not had a diagnosis recorded in the medical administrative record. We did not capture any adults with dementia under the age of 65 as we were unable to examine drug use in these cases. We must also consider that not everyone participates in the Nova Scotia

Seniors' Pharmacare Program which limits generalizability of results as those not participating in provincial seniors' drug plan are not captured. The majority of older adults (approximately 63%) (41) in Nova Scotia subscribe to Senior's Pharmacare, though Seniors Pharmacare subscribers and non-subscribers may differ in important ways such as prior employment history (leading to use of private drug insurance rather than the public Pharmacare system) and hence socioeconomic status. We also were unable to identify which NSSPBD resided in a long-term care facility because this data was not captured in medical data until after the period of observation. We were however able to ascertain if they resided in an urban or rural location. We had limited ability to describe the clinical picture of the individual patients and we did not have data on medication indication, dose or directions. This includes not knowing if the patient had an indication that would make the second treatment appropriate. We assumed dispensation was equivalent to use which is not necessarily true. This is particularly meaningful for metoclopramide which can be used on an as needed basis. When examining the prescribing cascade, we did not have access to use of doctor-provided samples, medications purchased outside of the Pharmacare drug insurance program, or those purchased without a prescription. We were only able to examine dates representing fill dates by the pharmacy and recognize this does not necessarily represent when the prescriptions were actually used by the patients. There were also limitations with respect to missing data, most importantly that a small percentage (0.8%) were missing data on sex. There are also possibly errors in the entered data as with any administrative dataset. Despite these limitations, the NSSPP data provided a unique and powerful opportunity to evaluate prescribing in a substantial portion of the older adults living with dementia in Nova Scotia.

Conclusions

The prescribing cascade of bladder anticholinergics being used to treat cholinesterase inhibitor induced urinary incontinence occurred in 0.2% of our study population over a five-year period. Though rare overall, this prescribing cascade occurred more often for women, suggesting that sex-specific monitoring and management for cholinesterase inhibitor-induced urinary incontinence may be warranted. The incidence of the prescribing cascade of Parkinson's Disease medications following metoclopramide-induced movement adverse events was rare. This is a positive finding for prescribing in Nova Scotia and suggests that prescribers are aware of and avoiding this prescribing cascade. Of people on a CCB, 6% initiate a diuretic within six months of the CCB therapy. This is a common prescribing cascade (1.7%) and older adults with dementia would benefit from identification of this potential prescribing complication and CCB dose reduction or discontinuation by preventing unneeded diuretic use and potential complications such as falls, dehydration and urinary incontinence. This investigation only examines three of the many prescribing cascades that may affect older adults with dementia. Maintaining one prescriber is likely helpful in preventing occurrence of the prescribing cascade as there is consistent oversight for prescribing for each patient. Continued attention to prescribing cascades and their sex-specific incidence will be important to improve health care and outcomes for older adults with dementia.

Abbreviations

ATC - Anatomical Therapeutic Chemical

CCB - Calcium Channel Blocker

DAD - Canadian Institute for Health Information – Discharge Abstract Database

HDNS - Health Data Nova Scotia

ICD - International Classification of Diseases Clinical Modification

MED - Physician's Billings

MSI - Medical Services Insurance

NSSPBD - Nova Scotia Seniors Pharmacare Beneficiary with dementia

PHARM - Seniors Pharmacare

VITAL - Vital Statistics

Declarations

Ethics approval and consent to participate: Ethics approval was provided by the Nova Scotia Health Research Ethics Board (NSHA REB ROMEO FILE #: 1023625). The data used in this study was anonymised before its use.

Consent for publication: Not Applicable.

Availability of data and materials: Data is held by Health Data Nova Scotia, an agent of the custodian (Department of Health and Wellness), and access requests can be handled by the corresponding author in consultation with the data custodian and agent.

Competing interests: The authors declare no competing interests.

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Authors' contributions: SCT completed proposal writing, data analysis and manuscript writing. SK, SKB and MKA all provided support, advice and editing during all stages of research and writing.

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References

1. Rochon PA, Gurwitz JH. Drug therapy. Lancet Lond Engl. 1995 Jul 1;346(8966):32–6.
2. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet Lond Engl. 2017 06;389(10081):1778–80.

3. McCarthy LM, Visentin JD, Rochon PA. Assessing the Scope and Appropriateness of Prescribing Cascades. J Am Geriatr Soc. 2019 May;67(5):1023–6.
4. Huh Y, Kim D-H, Choi M, Park J-H, Kwon D-Y, Jung J-H, et al. Metoclopramide and Levosulpiride Use and Subsequent Levodopa Prescription in the Korean Elderly: The Prescribing Cascade. J Clin Med [Internet]. 2019 Sep 19 [cited 2019 Dec 19];8(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6780178/
5. Nguyen PV, Spinelli C. Prescribing cascade in an elderly woman. Can Pharm J CPJ Rev Pharm Can RPC. 2016;149(3):122–4.
6. Vouri SM, Van Tuyl JS, Olsen MA, Xian H, Schootman M. An Evaluation of a Potential Calcium Channel Blocker – Lower Extremity Edema – Loop Diuretic Prescribing Cascade. J Am Pharm Assoc JAPhA. 2018;58(5):534-539.e4.
7. Le Noury J, Nardo JM, Healy D, Jureidini J, Raven M, Tufanaru C, et al. Study 329 continuation phase: Safety and efficacy of paroxetine and imipramine in extended treatment of adolescent major depression. Int J Risk Saf Med. 2016 Sep 17;28(3):143–61.
8. Vouri SM. Rhinorrhea as a Result of Alzheimer's Disease Treatment. Sr Care Pharm. 2020 Apr 1;35(4):148–9.
9. Gill SS, Mamdani M, Naglie G, Streiner DL, Bronskill SE, Kopp A, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. Arch Intern Med. 2005 Apr 11;165(7):808–13.
10. Rotermann M, Sanmartin C, Hennessy D, Arthur M. Prescription medication use by Canadians aged 6 to 79. Health Rep. 2014;25(6):3–9.
11. Canadian Institute of Health Information. Drug Use Among Seniors in Canada, 2016 [Internet]. 2016. Available from: www.cihi.ca
12. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr [Internet]. 2017 Oct 10 [cited 2019 Dec 14];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5635569/
13. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. Ann Pharmacother. 2010;44(6):957–63.
14. Zhan C, Sangl J, Bierman AS, Miller MR, Friedman B, Wickizer SW, et al. Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. Jama. 2001;286(22):2823–9.
15. Mullan J, Burns P, Mohanan L, Lago L, Jordan M, Potter J. Hospitalisation for medication misadventures among older adults with and without dementia: A 5-year retrospective study. Australas J Ageing. 2019 Dec;38(4):e135–41.
16. Eshetie TC, Nguyen TA, Gillam MH, Kalisch Ellett LM. A narrative review of problems with medicines use in people with dementia. Expert Opin Drug Saf. 2018;17(8):825–36.
17. Parameswaran Nair N, Chalmers L, Connolly M, Bereznicki BJ, Peterson GM, Curtain C, et al. Prediction of Hospitalization due to Adverse Drug Reactions in Elderly Community-Dwelling Patients (The PADR-EC Score). PloS One. 2016;11(10):e0165757.
18. Kanagaratnam L, Drame M, Novella JL, Trenque T, Joachim C, Nazeyrollas P, et al. Risk Factors for Adverse Drug Reactions in Older Subjects Hospitalized in a Dedicated Dementia Unit. Am J Geriatr Psychiatry Off J

Am Assoc Geriatr Psychiatry. 2016;(Journal Article).

19. Kanagaratnam L, Mahmoudi R, Novella J-L, Jolly D, Dramé M, Trenque T. Adverse drug reactions in elderly subjects hospitalized in a specialized dementia management unit. Drugs Aging. 2014 Oct;31(10):769–76.
20. Saxena M, Dubey R. Target Enzyme in Alzheimer's Disease: Acetylcholinesterase Inhibitors. Curr Top Med Chem. 2019;19(4):264–75.
21. Hampel H, Mesulam M-M, Cuello AC, Farlow MR, Giacobini E, Grossberg GT, et al. The cholinergic system in the pathophysiology and treatment of Alzheimer's disease. Brain J Neurol. 2018 01;141(7):1917–33.
22. Krall WJ, Sramek JJ, Cutler NR. Cholinesterase inhibitors: a therapeutic strategy for Alzheimer disease. Ann Pharmacother. 1999 Apr;33(4):441–50.
23. Kumar A, Singh A, Ekavali. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol Rep. 2015 Apr;67(2):195–203.
24. Håkansson L. Mechanism of action of cholinesterase inhibitors in Alzheimer's disease. Acta Neurol Scand Suppl. 1993;149:7–9.
25. Mansfield KJ, Liu L, Mitchelson FJ, Moore KH, Millard RJ, Burcher E. Muscarinic receptor subtypes in human bladder detrusor and mucosa, studied by radioligand binding and quantitative competitive RT-PCR: changes in ageing. Br J Pharmacol. 2005 Apr;144(8):1089–99.
26. Sjögren C. The Effects of Anticholinergics on the Urinary Bladder Mechanism. Acta Pharmacol Toxicol (Copenh). 1978;43(s1):69–73.
27. Isola S, Adams N. Metoclopramide. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2020 Sep 18]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK519517/
28. Leung AA, Daskalopoulou SS, Dasgupta K, McBrien K, Butalia S, Zarnke KB, et al. Hypertension Canada's 2017 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults. Can J Cardiol. 2017;33(5):557–76.
29. Nerenberg KA, Zarnke KB, Leung AA, Dasgupta K, Butalia S, McBrien K, et al. Hypertension Canada's 2018 Guidelines for Diagnosis, Risk Assessment, Prevention, and Treatment of Hypertension in Adults and Children. Can J Cardiol. 2018;34(5):506–25.
30. Makani H, Bangalore S, Romero J, Htyte N, Berrios RS, Makwana H, et al. Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate–a meta-analysis of randomized trials. J Hypertens. 2011 Jul;29(7):1270–80.
31. Norvasc Monograph [Internet]. Norvasc Monograph. 2017 [cited 2019 Dec 17]. Available from: https://www.pfizermedicalinformation.ca/en-ca/norvasc#
32. Sica DA. Calcium channel blocker-related periperal edema: can it be resolved? J Clin Hypertens Greenwich Conn. 2003 Aug;5(4):291–4, 297.
33. Leonetti G, Magnani B, Pessina AC, Rappelli A, Trimarco B, Zanchetti A, et al. Tolerability of long-term treatment with lercanidipine versus amlodipine and lacidipine in elderly hypertensives. Am J Hypertens. 2002 Nov;15(11):932–40.
34. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Am J Hypertens. 2001 Sep;14(9 Pt 1):978–9.

35. Messerli FH. Vasodilatory edema: a common side effect of antihypertensive therapy. Curr Cardiol Rep. 2002 Nov;4(6):479–82.
36. Reeve E, Trenaman SC, Rockwood K, Hilmer SN. Pharmacokinetic and pharmacodynamic alterations in older people with dementia. Expert Opin Drug Metab Toxicol. 2017;13(6):651–68.
37. Woodford HJ. Calcium Channel Blockers Co-prescribed with Loop Diuretics: A Potential Marker of Poor Prescribing? Drugs Aging. 2019 Dec 4;
38. Vouri SM, van Tuyl JS, Olsen MA, Xian H, Schootman M. An evaluation of a potential calcium channel blocker-lower-extremity edema-loop diuretic prescribing cascade. J Am Pharm Assoc JAPhA. 2018 Oct;58(5):534-539.e4.
39. Brath H, Mehta N, Savage RD, Gill SS, Wu W, Bronskill SE, et al. What Is Known About Preventing, Detecting, and Reversing Prescribing Cascades: A Scoping Review. J Am Geriatr Soc. 2018;66(11):2079–85.
40. Dementia Strategy [Internet]. 2015 [cited 2020 Jan 28]. Available from: https://novascotia.ca/dhw/dementia/
41. personal communication. Ingrid Sketris. 2018; Halifax, NS, Canada.
42. Nova Scotia Postal Codes [Internet]. 2001 [cited 2019 Dec 18]. Available from: https://www.businesssellcanada.com/sale/cpc/pc_b.htm
43. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. Alzheimers Dement J Alzheimers Assoc. 2013 Jan;9(1):63-75.e2.
44. Andrew MK, Tierney MC. The puzzle of sex, gender and Alzheimer's disease: Why are women more often affected than men? Womens Health [Internet]. 2018 Dec 26 [cited 2020 Sep 17];14. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6311541/
45. Narayan SW, Pearson S, Litchfield M, Le Couteur DG, Buckley N, McLachlan AJ, et al. Anticholinergic medicines use among older adults before and after initiating dementia medicines. Br J Clin Pharmacol. 2019 Sep;85(9):1957–63.
46. Triantafylidis LK, Clemons JS, Peron EP, Roefaro J, Zimmerman KM. Brain Over Bladder: A Systematic Review of Dual Cholinesterase Inhibitor and Urinary Anticholinergic Use. Drugs Aging. 2018;35(1):27–41.
47. Sink KM, Thomas J, Xu H, Craig B, Kritchevsky S, Sands LP. Dual use of bladder anticholinergics and cholinesterase inhibitors: long-term functional and cognitive outcomes. J Am Geriatr Soc. 2008 May;56(5):847–53.
48. By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. J Am Geriatr Soc. 2019 Apr;67(4):674–94.
49. O'Mahony D, O'Sullivan D, Byrne S, O'Connor MN, Ryan C, Gallagher P. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2015;44(2):213–8.
50. Carnahan RM, Lund BC, Perry PJ, Chrischilles EA. The concurrent use of anticholinergics and cholinesterase inhibitors: rare event or common practice? J Am Geriatr Soc. 2004 Dec;52(12):2082–7.
51. Avorn J, Gurwitz JH, Bohn RL, Mogun H, Monane M, Walker A. Increased incidence of levodopa therapy following metoclopramide use. JAMA. 1995 Dec 13;274(22):1780–2.

52. Savage RD, Visentin JD, Bronskill SE, Wang X, Gruneir A, Giannakeas V, et al. Evaluation of a Common Prescribing Cascade of Calcium Channel Blockers and Diuretics in Older Adults With Hypertension. JAMA Intern Med. 2020 May 1;180(5):643–51.
53. Nguyen PV-Q, Spinelli C. Prescribing cascade in an elderly woman. Can Pharm J CPJ Rev Pharm Can RPC. 2016 May;149(3):122–4.
54. Sica DA. Diuretic-related side effects: development and treatment. J Clin Hypertens Greenwich Conn. 2004 Sep;6(9):532–40.
55. Berry SD, Mittleman MA, Zhang Y, Solomon DH, Lipsitz LA, Mostofsky E, et al. New loop diuretic prescriptions may be an acute risk factor for falls in the nursing home. Pharmacoepidemiol Drug Saf. 2012 May;21(5):560–3.
56. Kelly J, Chamber J. Inappropriate use of loop diuretics in elderly patients. Age Ageing. 2000 Nov;29(6):489–93.
57. Robertson DR, Waller DG, Renwick AG, George CF. Age-related changes in the pharmacokinetics and pharmacodynamics of nifedipine. Br J Clin Pharmacol. 1988 Mar;25(3):297–305.

Tables

Table 1: ICD9/10 diagnosis codes that were identified by the Nova Scotia Dementia Strategy as most likely to identify an individual with a diagnosis of dementia

Description	ICD-9	ICD-10
Alcohol-induced persisting amnestic disorder	290.x	F01.x, F05.1
Alcohol-induced persisting dementia	291.1	F10.6
Amnestic disorder in conditions classified elsewhere	291.2	F10.7
Dementia in conditions classified elsewhere	294.0	F04.x
Other cerebral degenerations ***Includes****: Alzheimer's disease; Frontotemporal dementia; Senile degeneration of the brain; Communicating hydrocephalus; Idiopathic normal pressure hydrocephalus; Cerebral degeneration in diseases classified elsewhere; dementia with Lewy's bodies; Dementia with Parkinsonism; Cerebral degeneration, unspecified.* ***Excludes****: Obstructive hydrocephalus; Reye's syndrome*	331.0-331.3, 331.5-331.7, 331.82, 331.83, 331.89, 331.9	G30.x, G31.0, G31.1, G31.8, G31.9, G32.8, G91.0, G91.2-G91.3, G91.8, G91.9, G94.x
Senility without mention of psychosis	797	R54.x

Table 2: Prescribing Cascade Medications

Prescribing Cascade	Inciting Medication	Second Treatment
1	donepezil (N06DA02) rivastigmine (N06DA03) galantamine (N06DA04)	oxybutynin (G04BD04) tolterodine (G04BD07) solifenacin (G04BD08) trospium (G04BD09) darifenacin (G04BD10) fesoterodine (G04BD11)
2	metoclopramide (A03FA01)	levodopa-carbidopa (N04BA02) levodopa-carbidopa-entacapone (N04BA03) amantadine (N04BB01) ropinirole (N04BC04) pramipexole (N04BC05) selegiline (N04BD01) entacapone (N04BX02)
3	amlodipine (C08CA01) nifedipine (C08CA05) felodipine (C08CA02	furosemide (C03CA01) spironolactone (C03DA01) hydrochlorothiazide (C03EA01) amiloride (C03DB01) ethacrynic acid (C03CC01) bumetanide (C03CA02)

Table 3: Details of the cohort of Nova Scotia Seniors' Pharmacare Beneficiaries with Dementia

	Total	Women	Men
Number NSSPBD	28,953	17,946 (62.0%)	10,529 (36.4%)
Mean age at diagnosis in years (95% CI)	81.1 (81.0-81.2)	82.1 (82.0-82.2)	79.6 (79.4-79.7)
Age 65.0-74.9 (% cohort)	6,355 (21.9%)	3,266 (11.2%)	2,922 (10.0%)
Age 75.0-84.9 (% cohort)	12,222 (42.2%)	7,412 (25.6%)	4,637 (16.0%)
Age 85.0-94.9 (% cohort)	8,254 (28.5%)	5,764 (19.9%)	2,385 (8.2%)
Age 95+ (% cohort)	808 (2.8%)	637 (2.2%)	159 (0.5%)
Urban dwelling (%)	18,485 (63.8%)	11,812 (40.8%)	6,673 (23.0%)
Rural dwelling (%)	9,342 (32.3%)	5,806 (20.1%)	3,536 (12.2%)

Table 4: Detailed drug utilization: Details of cohort for those who experienced a prescribing cascade

Medication class	Cholinesterase inhibitor (N06DA)	Bladder Anticholinergic (G04BD)	Metoclopramide (*A03FA01*)	Parkinson's Disease medication (*N04B*)	CCB (*C08CA*)	Diuretic (*C03*)
Total prescriptions	117,416	17,806	3,760	25,984	93,688	117,692
NSSPBD receiving at least one prescription	5,772	1,263	1,038	997	4,639	6,389
Mean age at dementia diagnosis, years (SD)	79.8 (6.8)	79.5 (7.6)	81.6 (7.8)	78.6 (7.2)	81.3 (7.7)	82.4 (7.7)
Mean age at first prescription, years (SD)	82.4 (6.9)	81.9 (7.5)	84.9 (7.8)	81.0 (7.1)	83.5 (7.6)	84.9 (7.6)
Mean duration, years (SD)	1.9 (1.5)	1.3 (1.3)	0.2 (0.5)	2.3 (2.6)	1.9 (1.5)	1.6 (1.6)

SD = standard deviation

Table 5: Cross-sectional analysis Logistic Regression (unadjusted and adjusted) for risk factors for prescribing cascades

	Covariates	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (95% CI)
Bladder anticholinergics following cholinesterase inhibitors	Age at diagnosis (years)	**0.94 (0.91 - 0.97)**	**0.93 (0.90 - 0.97)**
	Rurality (Urban)	0.88 (0.51 - 1.5)	0.92 (0.53 - 1.58)
	Sex (Male)	**0.54 (0.30 - 0.99)**	**0.46 (0.25 - 0.85)**
Diuretic following CCB	Age at diagnosis (years)	**1.01 (1.00 – 1.02)**	1.01 (0.99 – 1.03)
	Rurality (Urban)	1.17 (0.91 – 1.5)	1.14 (0.88 – 1.48)
	Sex (Male)	**0.67 (0.51 – 0.88)**	**0.0033 (0.00090 – 0.012)**

Table 6: Hazard Event Rates Ratios for prescribing cascades

Main Analysis (Full Cohorts)	**Cholinesterase Inhibitor User (n=5772)**	**No Cholinesterase Inhibitor (n=13770)**
Total Number (%) of events (newly dispensed bladder anticholinergic)	366 (6.3%)	868 (6.3%)
Duration of Follow-up, mean ± SD, days	525 ± 75.3	332 ± 27.7
Unadjusted HR (95% CI)	0.77 (0.68-0.87)	1.00 (Referent)
Adjusted HR (95% CI) (age, sex, rural/urban)	0.79 (0.68-0.92)	1.00 (Referent)
Main Analysis (Full Cohorts)	**CCB User (n=4639)**	**No CCB (n=14903)**
Total Number (%) of events (newly dispensed diuretic)	1708 (36.8%)	4536 (30.4%)
Duration of Follow-up, mean ± SD, days	653.1±24.6	651.3±17.4
Unadjusted HR (95% CI)	1.00 (0.94-1.05)	1.00 (Referent)
Adjusted HR (95% CI) (age, sex, rural/urban)	1.04 (0.98-1.10)	1.00 (Referent)