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# Potentially Inappropriate Drug Duplication in a Cohort of Older Adults with Dementia

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## ABSTRACT

**Background:** Concurrent use of 2 nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, loop diuretics, angiotensin-converting enzyme inhibitors, or anticoagulants is considered potentially inappropriate by Screening Tool of Older Persons' Prescriptions and Screening Tool to Alert to Right Treatment criteria.

**Objective:** The objective was to examine drug duplication in a cohort of older adults with dementia.

**Methods:** Cohort entry for Nova Scotia Seniors' Pharmacare Program beneficiaries was the date an International Classification of Diseases ninth edition or 10th edition code for dementia was recorded in accessed databases between March 1, 2005, and March 31, 2015. Medication dispensation and sociodemographic data were captured from the Nova Scotia Seniors' Pharmacare Program database between April 1, 2010, and March 31, 2015. Duplication was considered when 2 drugs from the same class were dispensed such that the supply in the patient's possession could overlap for more than 30 days. We reported number of cases of duplication and duration of overlap. Sex differences in drug duplication were assessed with bivariate logistic regression.

**Results:** In the cohort of 28,953 Nova Scotia Seniors' Pharmacare Program beneficiaries with dementia, we documented concurrent use in 101 (1.7%) nonsteroidal anti-inflammatory drugs users (mean duration = 75.6 days), 95 (1.0%) selective serotonin reuptake inhibitors users (mean duration = 146.6 days), 5 (0.07%) loop diuretic users (mean duration = 530.6 days), 183 (2.0%) angiotensin-converting enzyme inhibitor users (mean duration = 123.9 days), and 160 (3.5%) anticoagulant users (mean duration = 63.6 days). Nonsteroidal anti-inflammatory drug pairs were most commonly celecoxib with naproxen or diclofenac. Selective serotonin reuptake inhibitors duplication was most commonly sertraline with citalopram. No sex differences in risk for drug duplication were identified.

**Conclusions:** Drug duplication was identified in a cohort of older adults with dementia and is a feasible target for intervention. (*Curr Ther Res Clin Exp.* 2021; 82:XXX–XXX)

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## Introduction

Many older adults living with dementia also live with multimorbidity,<sup>1</sup> frailty,<sup>2</sup> polypharmacy,<sup>3,4</sup> and risk of drug interactions.<sup>5</sup> Prescribing guidelines focusing on the care of older adults aim to reduce potentially inappropriate medication use, manage

polypharmacy, and reduce the risks of drug–drug interactions.<sup>6–9</sup> To support clinicians the Screening Tool of Older Persons' Prescriptions (STOPP) and Screening Tool to Alert to Right Treatment criteria (START)<sup>9,10</sup> provide specific guidance for prescribing to older adults with dementia. One STOPP criterion recommends optimization of monotherapy by achieving a target dose before adding a second agent.<sup>9,10</sup> In particular, the STOPP criteria specify avoiding concurrent use of 2 drugs from the same class and specifically avoiding use of 2 nonsteroidal anti-inflammatory drugs (NSAIDs),<sup>7–10</sup> selective serotonin reuptake inhibitors (SSRIs), loop diuretics, angiotensin-converting enzyme (ACE) inhibitors, or an-

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ticoagulants. These classes of medications are all considered safe for older adults with dementia when indicated,<sup>11–14</sup> but concurrent use of 2 medications from any of these classes is to be avoided due to the increased risk of adverse drug events without additional benefit.<sup>15,16</sup> Overall, polypharmacy and potentially inappropriate medication use in persons with dementia is an under-researched problem.<sup>17,18</sup> Moreover, the role of drug duplication as a contributor to inappropriate prescribing is poorly understood.<sup>17,18</sup> A survey of drug duplication in a population of older adults with dementia provides a quality indicator of medication use that can be used to focus professional education.<sup>19,20</sup> The objective of this retrospective cohort study was to examine the occurrence of duplicate drug prescriptions from the classes of NSAIDs, SSRIs, loop diuretics, ACE inhibitors, and anticoagulant agents in a population of older adults with dementia in Nova Scotia, Canada.

**Materials and Methods**

Administrative claims data were extracted and linked by Health Data Nova Scotia from Medical Services Insurance Physician's Billings (MSI) which provides eligible residents with coverage for medically required hospital, medical, dental, and optometric services with some restrictions), Nova Scotia Seniors' Pharmacare (PHARM) (a voluntary prescription medication program for adults aged 65 years and older), Vital Statistics (which includes information on births, marriages, domestic partnerships, deaths and causes of deaths, and population growth), and the Canadian Institute for Health Information–Discharge Abstract Database (that captures administrative, clinical, and demographic information on hospital discharges). Cohort entry was the date a Seniors' Pharmacare beneficiary had a first occurrence of an International Classification of Diseases ninth or 10th edition<sup>21</sup> (ICD 9/10) code corresponding to a dementia diagnosis. We selected ICD 9/10 codes based on the Nova Scotia Dementia Strategy,<sup>22</sup> which provided recommendations for identifying cases of dementia using locally available administrative datasets (see the **Appendix** in the online version). ICD-9/10 codes were examined from March 1, 2005, to March 31, 2015, allowing up to 10 years to build the cohort. Drug dispensations in the PHARM database for requested drug classes (**Table 1**) were abstracted for the 5 years from April 1, 2010, to March 31, 2015, including Anatomical Therapeutic Chemical code, prescription fill date, and days supplied. PHARM medication dispensation data were linked to sociodemographic characteristic, including age at dementia diagnosis, date of dementia diagnosis, sex, and date of death (if death occurred during the period of observation) from the Canadian Institute for Health Information–Discharge Abstract Database and Vital Statistics datasets. Exposure to a medication was defined as dispensation according to the PHARM record, with the required assumption that dispensation was equivalent to medication use. Cohort exit was at the date of death or March 31, 2015.

For each patient, the prescription claim dates and days supplied for drugs of interest were captured and compared to identify overlapping drug use from the same class. Reporting included the number of individuals receiving at least 1 relevant medication class prescription, drugs identified in cases of duplication, mean duration of overlap, and mean age at dementia diagnosis for those receiving duplicate drug class prescriptions. Previous research suggests that women more frequently experience polypharmacy than men and may experience greater polypharmacy with higher medication use counts.<sup>23–25</sup> We therefore stratified all reporting by sex and we conducted bivariate logistic regression to assess whether sex was associated with drug class duplication for each class. Data analysis was completed using STATA version 15.1 (StataCorp, College Station, Texas). This study received ethics approval from the Nova Scotia Health Research and Ethics Board (approval file No. 1023625).

**Table 1**  
Drug classes and drugs studied.

NSAID		SSRI		Loop diuretic		ACE inhibitor		Anticoagulant	
Generic name	ATC code	Generic name	ATC code	Generic name	ATC code	Generic name	ATC code	Generic name	ATC code
Indomethacin	M01AB01	Fluoxetine	N06AB03	Furosemide	C03CA01	Captopril	C09AA01	Warfarin	B01AA03
Sulindac	M01AB02	Citalopram	N06AB04	Bumetamide	C03CA02	Enalapril	C09AA02	Acenocou-marol	B01AA07
Diclofenac	M01AB05	Paroxetine	N06AB05	Ethacrynic acid	C03CC01	Lisinopril	C09AA03	Heparin	B01AB01
Etodolac	M01AB08	Sertraline	N06AB06			Perindopril	C09AA04	Dalteparin	B01AB04
Ketorolac	M01AB15	Fluvoxamine	N06AB08			Ramipril	C09AA05	Enoxaparin	B01AB05
Diclofenac, combinations	M01AB55	Escitalopram	N06AB10			Quinapril	C09AA06	Dabigatran etexilate	B01AE07
Piroxicam	M01AC01					Benazepril	C09AA07	Rivarox-aban	B01AF01
Tenoxicam	M01AC02					Cilazapril	C09AA08	Apixaban	B01AF02
Meloxicam	M01AC06					Fosinopril	C09AA09		
Ibuprofen	M01AE01					Trandolapril	C09AA10		
Naproxen	M01AE02					Enalapril + diuretic	C09BA02		
Ketoprofen	M01AE03					Lisinopril + diuretic	C09BA03		
Flurbiprofen	M01AE09					Perindopril + diuretic	C09BA04		
Tiaprofenic acid	M01AE11					Ramipril + diuretic	C09BA05		
Celecoxib	M01AH01					Quinapril + diuretic	C09BA06		
Nabumetone	M01AX01					Cilazapril + diuretic	C09BA08		

ATC = Anatomical Therapeutic Chemical.

**Table 2**

Detailed description of drug duplication in a cohort of Nova Scotia Seniors' Pharmacare Beneficiaries with Dementia (NSSPBD) participants over the period from April 1, 2010, to March 31, 2015.

Drug	NSAID	SSRI	Loop diuretic	ACE inhibitor	Anticoagulant
NSSPBD receiving at least 1 Rx*	6,119 (21.1)	9,091 (31.4)	7,022 (24.2)	9,083 (31.3)	4,511 (15.5)
Age at dementia diagnosis, y <sup>†</sup>	79.4 (7.7)	82.1 (7.9)	84.3 (7.7)	81.7 (7.7)	82.9 (7.2)
Mean duration of Rx, d <sup>†</sup>	207.7 (360.4)	760.4 (617.3)	687.6 (601.8)	860.0 (615.5)	683.7 (735.7)
Total cases of duplication*	317 (1.1)	357 (1.2)	9 (0.03)	555 (1.9)	461 (1.6)
Cases exceeding 30-d duplication*	101 (0.3)	95 (0.3)	5 (0.02)	183 (0.6)	160 (0.6)
Cases exceeding 90-d duplication*	23 (0.1)	24 (0.1)	<5 (<0.02)	46 (0.2)	29 (0.1)

ACE = angiotensin-converting enzyme; NSAID = nonsteroidal anti-inflammatory drug; Rx = prescription; SSRI = selective serotonin reuptake inhibitor.

\* Values are presented as n (%).

<sup>†</sup> Values are presented as mean ± SD.

## Results

During 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. The average age at dementia diagnosis was 81.1 years (95% CI, 81.0–81.2 years) with the mean age of women being 2.5 years (95% CI, 2.9–3.6 years) older than men at dementia diagnosis ( $P < 0.0001$ ).

### NSAIDs

Six thousand one hundred ninety-nine NSSPBD (20.2% of the cohort) participants received at least 1 prescription for an NSAID and mean duration of use was 207.7 days. In general, NSAIDs were used for longer durations in women than in men (mean = 220.0 vs 186.7 days;  $P = 0.0006$ ). Prescribing guidelines recommend <90 days of NSAID use, which was exceeded by 35.5% of NSAID users. There was concurrent use of 2 prescription NSAIDs in 317 NSSPBD participants of any duration. Given that short periods of overlap may represent drug switching, limiting overlap to periods exceeding 30 days identified 101 cases of NSAID duplication with an average period of duplication of 75.6 days (Table 2). Limiting NSAID duplication to periods of overlap exceeding 90 days left 23 cases. Common drug duplicate pairs included celecoxib with naproxen, celecoxib with diclofenac, or diclofenac with naproxen. Duplicate NSAID use showed no sex difference (odds ratio [OR] = 1.01; 95% CI, 0.66–1.55).

### SSRIs

SSRI use was common with 22.1% of the cohort (n = 8305) receiving at least 1 prescription for an SSRI. Mean duration of SSRI use was 760.4 days or 2.1 years. Duration of SSRI use was longer in women than men (784.5 days vs 700.3 days;  $P < 0.0001$ ). There was concurrent use of 2 SSRIs in 357 NSSPBD. The overlap varied from 1 day to 1908 days with an average of 48.6 days. Limiting overlap to cases exceeding 30 days identified 95 cases of SSRI duplication with an average period of duplication lasting 146.6 days (Table 2). There were 24 cases of SSRI duplication that exceeded 90 days. The most common SSRI duplicate pair was sertraline with citalopram. Duplicate SSRI use showed no sex difference (OR = 0.67; 95% CI, 0.42–1.07).

### Loop diuretics

Loop diuretic use was common with 24.3% of NSSPBD receiving at least 1 prescription for a loop diuretic. Furosemide accounted for 99.9% of loop diuretic prescriptions. Concurrent loop diuretic use was rare and limited to 9 NSSPBD (Table 2). Removing cases of overlap <30 days in duration to account for drug switching reduced loop diuretic overlap to 5 instances with a mean duration of overlap of 530.6 days or 1.5 years.

### ACE inhibitors

Nine thousand eighty-three (31.4%) NSSPBD participants received at least 1 prescription for an ACE inhibitor with a mean duration of use of 860 days or 2.4 years. Duration of use was similar in men and women (835.6 days vs 846.3 days;  $P = 0.22$ ). ACE inhibitor duplication is reported in Table 2. Limiting overlap to more than 30 days identified 183 cases of ACE inhibitor duplication with an average period of duplication of 123.9 days. Common pairs included an ACE inhibitor with combination products that included a diuretic with the original parent ACE inhibitor rather than duplication of 2 different ACE inhibitors. This was done presumably to increase ACE inhibitor dose without increasing diuretic exposure and represented 115 of the 183 cases (62.8%). Duplicate ACE inhibitor use showed no sex difference (OR = 1.19; 95% CI, 0.86–1.63).

### Anticoagulant agents

There were 4511 NSSPBD who received at least 1 prescription for an anticoagulant with a mean duration of use of 683.7 days or 1.9 years. Duration of use was longer in men than women (706.3 days vs 659.6 days;  $P = .02$ ). There were 461 instances of duplication of anticoagulant agents among NSSPBD participants. The overlap varied from 1 to 233 days with an average of 30.53 days. Limiting overlap to more than 30 days identified 160 cases of anticoagulant duplication with an average period of duplication of 63.6 days (Table 2). Limiting anticoagulant duplication to periods of overlap exceeding 90 days left 29 cases. Duplicate anticoagulant use showed no sex difference (OR = 1.17; 95% CI, 0.84–1.62).

## Discussion

We report concurrent use of NSAIDs, SSRIs, loop diuretics, ACE inhibitors, and anticoagulant agents in a cohort of older adults with dementia in Nova Scotia, Canada. NSAID and SSRI duplication exceeding 30 days was present in 101 (1.7% of NSAID users) and 95 (1.0% of SSRI users) cases, respectively. Loop diuretic duplication was rare. Of the 183 cases of ACE inhibitor duplication exceeding 30 days 62.8% were ACE inhibitor–diuretic combination products duplicated with the parent ACE inhibitor to increase ACE inhibitor dose. Anticoagulant duplication likely reflected duplication for bridging because it was most commonly oral and parenteral therapies combined. None of the examined drug classes demonstrated a sex difference in risk for drug duplication.

NSAID duplication was previously investigated in Korea due to concerns of high rates of NSAID duplication.<sup>26,27</sup> In 21 million patient visits by individuals of all ages, Kang and colleagues<sup>26</sup> identified 59,636,222 NSAID prescriptions with 13.3% involving therapeutic duplication over the first 3 months of 2011. Follow-up study in Korea by Jung and colleagues<sup>27</sup> showed NSAID duplication fell to 5.6% after implementation of a nationwide drug utilization monitoring program. In our carefully selected population of NSSPBD,

over the 5 years of study, we identified 37,916 NSAID prescriptions written to 6199 NSSPBD. Only 5.2% of these NSSPBD were identified to have NSAID duplication. In the Korean studies, women made up 59.3%<sup>26</sup> and 75.3%<sup>27</sup> of NSAID prescriptions, comparable to 66.6% of NSSPBD. In our population, women were older than men receiving NSAID prescriptions but received prescriptions for similar durations. Like in Jung and colleagues,<sup>27</sup> celecoxib was commonly implicated in NSAID duplication (43% of cases). This may relate to expectations of additional benefit from COX-2 inhibition, which is unlikely to help with pain, and likely to increase cardiovascular risk. Prescribing by different providers was believed to have contributed to NSAID duplication in the Korean studies. We did not collect information on prescriber so we cannot comment on this but consider it as a possibility. We were also unable to report on nonprescription NSAID or aspirin use, so we are likely underreporting therapeutic NSAID duplication in NSSPBD participants.

Canadian researchers Sanyal and colleagues<sup>28</sup> looked at the cost-effectiveness of a community pharmacist-led education program for community dwelling older adults to support NSAID discontinuation. They considered a population of older adults in the province of Québec and used decision tree and Markov state transition modeling to analyze the cost of such a program. The researchers found that an educational intervention by community pharmacists to encourage NSAID discontinuation was less costly and more effective than standard care when considering adverse events prevented.

In rural Sri Lanka, NSAIDs were the most common medication duplicated, with 2 different agents dispensed from the same class on the same prescription representing 43% or 56 of 130 duplication events.<sup>29</sup> We cannot compare our NSAID duplication due to different survey methods, but note that this identifies that many jurisdictions likely should pay attention to NSAID duplication as a potential target for intervention.

Short periods of SSRI duplication were expected to account for drug switching within the class. However, the 95 cases of SSRI duplication identified with a mean period of duplication lasting 146.6 days exceeds the duration needed for a typical taper and switch and is more likely to represent long-term concurrent use of 2 SSRIs. Martinot and colleagues<sup>30</sup> previously looked for duplicate antidepressant use in a French population and found duplication in 0.4% of the cohort.

We found that duplication of loop diuretics was not common, with only 9 cases identified over the 5 years of study of NSSPBD participants. This is reassuring, but the limited occurrences of long duration of overlap does suggest that concomitant loop diuretics may be considered a viable method for managing fluid overload by a small number of clinicians. No reports on concurrent loop diuretics were identified for comparison to other jurisdictions.

There were very few cases of ACE inhibitor duplication ( $n = 183$ ) in our cohort of NSSPBD participants. Additionally, 62.8% of the ACE inhibitor duplicate pairs included combination products with a diuretic with the parent ACE inhibitor presumably to increase ACE inhibitor dose without increasing diuretic exposure. This is reassuring and suggests that remaining ACE inhibitor overlap may represent drug switching due to intolerance more than intentional cotherapy.

Anticoagulant duplication in NSSPBD participants can likely be explained by bridging with parenteral anticoagulants or switching of warfarin to dabigatran. These findings were expected because novel oral anticoagulants are easier to manage for older adults who meet the criteria for their use,<sup>31-33</sup> and bridging is expected for procedures.

Our results should be interpreted with caution. The PHARM database includes only those adults aged 65 years or older who subscribe to the public medication insurance program, so older

people with dementia who have private insurance were not included. Due to underdiagnosis, dementia is difficult to identify in administrative databases, although we mitigated this as much as possible by using previously validated case definitions and allowing a long duration of time to build the cohort we may have missed some cases. Additionally, we could only identify prescription drugs that were dispensed, which means that nonprescription NSAID and aspirin use are unable to be included in the analysis. Because we only could access dispensed prescription not what was actually taken by the patient, this introduces some uncertainty in the rate of duplication. We could not ascertain adherence, dosing, or details of medical conditions.

## Conclusions

This study examined a cohort of older adults with dementia who likely included the most vulnerable and frail older adults in the province. We anticipated low levels of drug duplication because this population would be recognized as being at risk for adverse reactions due to drug duplication. Instead, there was potentially inappropriate prescribing in each of the categories investigated. There were cases of overlapping NSAID, SSRI, loop diuretics, and ACE inhibitors identified. This is concerning because duplication of these classes of medications does not increase therapeutic effect but most likely increases risk of adverse drug events. Because multiple prescribers or multiple pharmacies may increase risk of drug duplication, a collaborative team approach headed by a single prescriber with ready access to pharmacist medication review and consultation is likely the best option to protect older adults with dementia from potential harms of drug duplication.<sup>34,35</sup>

## Declaration of Competing Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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The data used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

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S. Trenaman completed proposal writing, data analysis, and manuscript writing. S. Kirkland, S. Bowles, and M. Andrew all provided support, advice, and editing during all stages of research and writing.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.curtheres.2021.100644](https://doi.org/10.1016/j.curtheres.2021.100644).



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