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Exploring high priority potentially inappropriate prescribing cascades in older adults: population level retrospective cohort study

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ABSTRACT

OBJECTIVE

To identify and prioritise potentially inappropriate prescribing cascades based on population prevalence, incidence, and temporal association between the initial and subsequent drug.

DESIGN

Population level retrospective cohort study.

SETTING

Health administrative data from a source population of community dwelling older adults in Ontario, Canada.

PARTICIPANTS

2 297 942 community dwelling older adults alive on 1 January 2022.

MAIN OUTCOME MEASURES

65 potentially inappropriate prescribing cascades were identified through a 2025 international expert Delphi consensus. For each prescribing cascade, the analytic cohort comprised incident users of the initial and subsequent drug combination during the accrual period. The population prevalence of the drug starting the prescribing cascade and the incidence of the initial and subsequent drug combination were measured, and the strength of the temporal association between the initial and subsequent drug was evaluated using adjusted sequence ratios derived from prescription sequence symmetry analyses. Prioritised cascades were those with a population drug prevalence of the initial drug ≥5%, prescribing cascade incidence of ≥1%, and adjusted sequence ratio >1, with the lower limit of the 95% confidence interval (CI) above the corresponding threshold for each measure. Results were stratified by sex.

RESULTS

The cohort comprised 2 297 942 people (54.3% female) aged ≥66 years. Twenty four prescribing cascades (37%) met all three prioritisation criteria. From the prioritised list, cardiovascular drugs were the most prevalent drugs starting the prescribing cascade (drug class range 19.0-65.9%). The highest incidence cascades were iron supplement to laxative (11.9%, 95% CI 11.7% to 12.1%), hydroxymethylglutaryl coenzyme A reductase inhibitor to pain reliever (10.9%, 10.7% to 11%), and cholinesterase inhibitor to sleep agent (10.3%, 9.9% to 10.7%). Temporal association, reported as adjusted sequence ratios, was highest for corticosteroid to antipsychotic (2.55, 95% CI 2.47 to 2.64), laxative to antidiarrheal (2.53, 2.43 to 2.65), and cholinesterase inhibitor to antiemetic drug treatment (2.24, 1.90 to 2.65). The adjusted sequence ratios were consistent when stratified by sex except for the selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor to overactive bladder drug cascade, which was stronger for male older adults (1.21, 1.10 to 1.33) than for female older adults (1.02, 0.96 to 1.09).

CONCLUSIONS

This prioritised list of 24 potentially inappropriate prescribing cascades could inform prescribing and deprescribing initiatives and policy development to improve drug safety in older adults at individual patient and population levels.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Potentially inappropriate prescribing cascades (PIPCs) are common in older adults, are often unrecognised, and might contribute to inappropriate polypharmacy, which is costly to patients and healthcare systems

PIPCs can increase treatment burden, reduce adherence, and heighten the risk of hospital admission, underscoring the importance of prevention

In practice, systematically identifying this pattern of potentially inappropriate prescribing to inform drug reviews and deprescribing efforts may be challenging—prescribing cascades need to be understood at a population level

WHAT THIS STUDY ADDS

Sixty five PIPCs identified through a 2025 international expert Delphi consensus panel were examined to determine how common these prescribing cascades are in a large population of community dwelling older adults

Measures included the population prevalence of the initial drug, the incidence of the initial and subsequent drug combination, and the strength of the temporal association between this drug combination using adjusted sequence ratios to create a prioritised list

This prioritised list of 24 PIPCs could inform system level prescribing and deprescribing initiatives and be integrated into clinical decision support systems, providing new opportunities to enhance drug safety at patient and population levels

Introduction

Potentially inappropriate prescribing cascades (PIPCs) typically occur when a drug is prescribed (initial drug), a drug related adverse event develops that is misinterpreted as a new medical condition, and a second, potentially inappropriate drug (subsequent

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drug) is started to manage the adverse event.[1-3] Starting the subsequent drug may be unnecessary and potentially harmful[4] (eFigure 1). The prescribing cascade framework, which was originally described in *The BMJ*,[2] is a common and often unrecognised contributor to inappropriate polypharmacy and is costly to patients and healthcare systems.[5 6] Yet, in practice, systematically identifying this pattern of potentially inappropriate prescribing to inform drug reviews and deprescribing efforts may be challenging. In 2025, an international group of experts in drug prescribing and older adults from eight countries created the PIPC list composed of 65 PIPCs using a modified Delphi method.[7] Many of the drug treatments on this list are for the management of chronic conditions and require long term prescriptions.

Clinicians should be aware of drug treatments commonly prescribed to older adults in their community, anticipate prescribing cascades that may occur in their clinical practice, recognise the combinations of drug treatments that can lead to these prescribing cascades, and have a sense of how likely they are to occur. This information can inform prescribing and deprescribing decisions. Although prescribing cascades are described in many different clinical settings,[8-10] their population level impact on prescribing patterns in community dwelling older adults and sex specific differences have not been thoroughly evaluated. To address these practical needs, our study applied a population level analytic strategy to quantify how often the drugs starting the prescribing cascade are being used, how frequently the prescribing cascades occur, and the strength of temporal association supporting the prescribing cascade. Our objective was to examine the PIPCs identified from the Delphi consensus study in a large population of older adults to create a prioritised list based on population prevalence, prescribing cascade incidence, and strength of the temporal association between the initial and the subsequent drug, overall and separately for male older adults and female older adults. This prioritised PIPC list could inform the development and implementation of targeted interventions to alert healthcare providers to these potentially inappropriate, common, and often underappreciated sources of polypharmacy and possible drug related harm.

Methods

Study design and setting

We conducted a population based retrospective cohort study of community dwelling older adults receiving care in the universal and publicly funded health system of Ontario, Canada. We prioritised prescribing cascades at a population level, incorporating the full burden of drug treatments among older adults. eTable 1 describes the data sources used to create the cohort and captures demographic characteristics and the prescription drugs dispensed. Data were linked using unique encoded identifiers and analysed at ICES (formerly the Institute for Clinical Evaluative Sciences). ICES is an independent, not-for-profit research institute whose legal status under Ontario's health information privacy law allows the collection and analysis of healthcare and demographic data, without consent, for health system evaluation and improvement. Figure 1 shows the overall study design and flow.

Study cohort creation

Using these linked datasets, we constructed the study cohort as follows. We identified a source population of all community dwelling adults aged ≥66 years as of 1 January 2022 (the cohort entry date). People were excluded at the cohort entry date if they were aged ≥110 years or had incomplete data; were not an Ontario resident and not eligible for the Ontario Health Insurance Plan within the previous two years to ensure baseline data could be captured; had no Ontario Drug Benefit claims within the previous 12 months to ensure the study population used the benefit; were long term care home residents in the previous six months; or died on or before the cohort entry date (eFigure 2). We continued to follow older adults who were subsequently admitted to long term care homes.

Analytic cohort creation

We used the 65 PIPCs from our previously published Delphi consensus study.[7] The PIPC list was created by 12 panellists from eight countries who were experts in internal medicine, geriatric medicine, and clinical pharmacology. We followed a modified Delphi method using a structured and validated process to achieve consensus. The PIPC list was organised by physiological system to align with the STOPP/START criteria.[11] For each of the PIPCs, the initial drug was defined as the prescribed drug (or drug class) starting the cascade and the subsequent drug as the drug prescribed to manage a possible adverse effect. The initial drug and the subsequent drug were reported as an individual drug or a drug class depending on how they were described in the source publication. Over-the-counter drug treatments were not included. This list has been endorsed by the European Geriatric Medicine Society with representatives from more than 38 member countries.[12]

For each of the 65 PIPCs, we created separate analytic cohorts from the source population of all community dwelling older adults. Firstly, we identified people with incident use of the initial drug during the accrual period (from 1 January 2022 to 31 December 2023; ie, an incident user was not dispensed the initial drug in the previous year; eFigure 3). Secondly, we further restricted the analytic cohort to those also with incident use of the subsequent drug during the accrual period. Thirdly, people were excluded if the initial and subsequent drug start dates were the same (prescribing sequence could not be determined) or the interval between initial dispensing of the two drugs was greater than one year. The one year time window was selected to maximally capture potential prescribing cascade events while minimising events owing to unrelated prescribing. This time window

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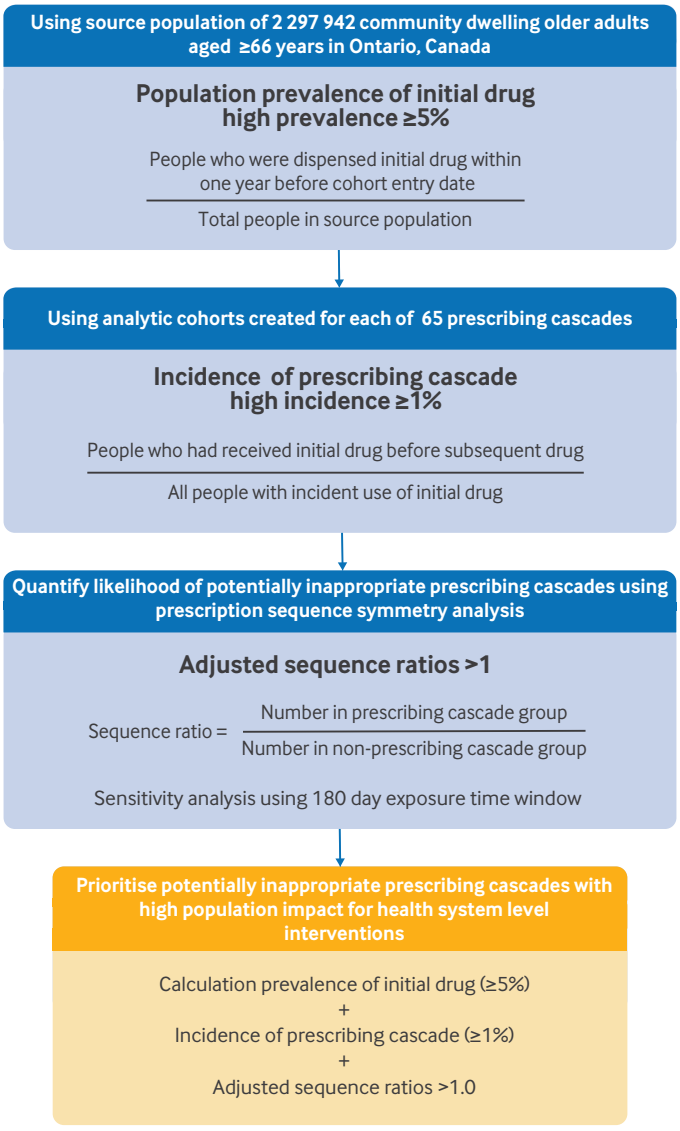


Fig 1 | Study flow diagram describing three steps followed to identify prioritised potentially inappropriate prescribing cascades. Firstly, population prevalence of the initial drug was determined. Secondly, incidence of the prescribing cascade was obtained. Thirdly, prescription sequence symmetry analysis was used to measure strength of temporal association between prescribing of initial and subsequent drug for each potentially inappropriate prescribing cascade specific analytic cohort. Adjusted sequence ratio >1.0 suggests evidence of a prescribing cascade. Finally, prioritised potentially inappropriate prescribing cascades were identified as those with high population prevalence of initial drug (≥5%), high incidence of a potentially inappropriate prescribing cascade (≥1%), and high likelihood of a potentially inappropriate prescribing cascade (adjusted sequence ratio >1), with lower limit of 95% confidence interval above corresponding threshold for each measure

was most frequently used for screening studies with prescription sequence symmetry analysis and shown to have good sensitivity.[13] Finally, if people started both drugs more than once in the accrual period, only the first combination was included. The index date was defined as the dispensing date of the initial drug. This approach was used to create separate analytic cohorts for each of the 65 PIPCs, which included incident users of initial and subsequent drugs during the study accrual period. When an older adult had more than one prescribing cascade, they were included in more than one analytic cohort.

For each of the 65 PIPCs, the initial and subsequent drugs were identified using the list of drug identification numbers available in Canada. This list was reviewed and refined by a clinical pharmacist (TZ) using standard references[14] in consultation with members of the research team to ensure the drugs or drug classes were relevant to the related PIPC while maintaining specificity (eAppendix 1). The classification of drugs was based on whether an individual drug or a drug class was described as part of one of the 65 prescribing cascades included on this PIPC list.[7] We acknowledge that an individual drug within a drug class may have a different mechanism of action and so different adverse effects. For example, for the calcium channel blocker to diuretic cascade, the risk of oedema is higher for a dihydropyridine calcium channel blocker (eg, amlodipine) than for a non-dihydropyridine calcium channel blocker.[15]

Cohort characteristics

Demographic data collected were age and sex. Race and gender data were unavailable, limiting assessment of intersectional differences.

Analyses

Separate analyses were conducted for each of the 65 PIPCs (fig 1). We calculated the population prevalence of the initial drugs. Population prevalence of the initial drug was defined as the proportion of people dispensed the initial drug within one year before the cohort entry date (from 1 January 2021 to 31 December 2021), divided by the total number of people in the source population of older adults (eFigure 2). Because the source population was more than 2 million, we prespecified that a population prevalence rate of ≥5% would be a high initial drug prevalence threshold and was the first criterion for the prioritisation. We are unaware of previously published recommendations for this threshold. After establishing the baseline burden of initial drug use, we quantified how often the subsequent drug followed the initial drug in people who were newly treated. The incidence of each PIPC was then calculated, which was the proportion of older adults who were dispensed the initial drug before the subsequent drug among all people with incident use of the initial drug over one year at any point during the accrual period. We calculated 95% confidence intervals (CIs) using the Wilson score method.[16] We prespecified that a prescribing cascade incidence of ≥1% over one year was high and had population level implications.

While incidence reflects how often these drug combinations occur, the sequence of the initial and subsequent drug use quantifies the strength of association of the prescribing cascade. Therefore, we applied prescription sequence symmetry analysis[17] to measure the strength of temporal association between prescribing of the initial and subsequent drug for each

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Table 1 | Population prevalence of initial drug dispensing for all 65 potentially inappropriate prescribing cascades in community dwelling older adults in Ontario within one year before 1 January 2022

System and drug class	Overall, % (95% CI)	Female older adults, % (95% CI)	Male older adults, % (95% CI)
Population	2 297 942	1 248 787	1 049 155
Cardiovascular system			
Drug class			
Antihypertensive	65.9 (65.8 to 66.0)	63.6 (63.5 to 63.7)	68.6 (68.5 to 68.7)
HMG Co-A reductase inhibitor (statin)	54.9 (54.9 to 55.0)	48.5 (48.4 to 48.6)	62.6 (62.5 to 62.7)
Angiotensin converting enzyme inhibitor	27.2 (27.1 to 27.2)	22.9 (22.8 to 23.0)	32.2 (32.2 to 32.3)
Beta blocker	26.1 (26.1 to 26.2)	23.7 (23.6 to 23.8)	29.0 (28.9 to 29.1)
Calcium channel blocker	23.6 (23.6 to 23.7)	23.5 (23.4 to 23.6)	23.8 (23.7 to 23.8)
Diuretic	19.0 (19.0 to 19.1)	20.1 (20.1 to 20.2)	17.7 (17.6 to 17.7)
Individual drug			
Digoxin	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)	1.0 (1.0 to 1.0)
Midodrine	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.2 (0.2 to 0.2)
Central nervous system			
Drug class			
SSRI or SNRI	13.5 (13.5 to 13.6)	17.1 (17.1 to 17.2)	9.3 (9.2 to 9.3)
Gabapentinoid	9.0 (8.9 to 9.0)	10.1 (10.0 to 10.1)	7.7 (7.6 to 7.7)
Benzodiazepine	8.9 (8.8 to 8.9)	11.0 (10.9 to 11.0)	6.3 (6.3 to 6.4)
Anticonvulsant	5.6 (5.5 to 5.6)	6.1 (6.1 to 6.2)	4.9 (4.9 to 4.9)
Antipsychotic	3.5 (3.5 to 3.5)	3.9 (3.9 to 4.0)	3.0 (2.9 to 3.0)
Tricyclic antidepressant	3.2 (3.2 to 3.2)	4.1 (4.0 to 4.1)	2.1 (2.1 to 2.2)
Dopaminergic antiparkinsonian agent	1.8 (1.8 to 1.8)	1.7 (1.7 to 1.7)	1.9 (1.9 to 1.9)
Cholinesterase inhibitor	1.8 (1.8 to 1.8)	1.9 (1.9 to 1.9)	1.6 (1.6 to 1.6)
Individual drug			
Venlafaxine	2.2 (2.2 to 2.2)	2.8 (2.8 to 2.9)	1.4 (1.4 to 1.4)
Lithium	0.2 (0.2 to 0.2)	0.2 (0.2 to 0.2)	0.2 (0.2 to 0.2)
Flunarizine	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)
Endocrine system			
Drug class			
Dipeptidyl peptidase-4 inhibitor	9.6 (9.6 to 9.7)	8.0 (8.0 to 8.1)	11.5 (11.4 to 11.5)
Sodium-glucose cotransporter-2 inhibitor	7.8 (7.8 to 7.9)	5.7 (5.6 to 5.7)	10.4 (10.4 to 10.5)
Individual drug			
Metformin	17.9 (17.8 to 17.9)	14.8 (14.7 to 14.9)	21.5 (21.4 to 21.6)
Pioglitazone or rosiglitazone	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)
Rosiglitazone	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)
Gastrointestinal system			
Drug class			
Proton pump inhibitor	30.5 (30.4 to 30.5)	32.4 (32.3 to 32.5)	28.2 (28.1 to 28.3)
Laxative	12.0 (12.0 to 12.0)	12.0 (12.0 to 12.1)	11.9 (11.9 to 12.0)
Antidopaminergic antiemetic	2.3 (2.3 to 2.3)	2.6 (2.6 to 2.7)	1.8 (1.8 to 1.8)
Anticholinergic antiemetic	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
Musculoskeletal system			
Drug class			
Opioid	15.2 (15.1 to 15.2)	15.3 (15.2 to 15.4)	14.9 (14.9 to 15.0)
Non-steroidal anti-inflammatory drug	13.5 (13.5 to 13.5)	14.1 (14.0 to 14.1)	12.8 (12.8 to 12.9)
Bisphosphonate	7.9 (7.9 to 7.9)	11.9 (11.9 to 12.0)	3.1 (3.0 to 3.1)
Urogenital system			
Drug class			
Alpha-1 receptor blocker	11.0 (10.9 to 11.0)	1.2 (1.2 to 1.2)	22.5 (22.5 to 22.6)
Urinary anticholinergic	2.3 (2.3 to 2.3)	2.8 (2.7 to 2.8)	1.6 (1.6 to 1.7)
Miscellaneous system			
Drug class			
Corticosteroid	22.8 (22.8 to 22.9)	23.9 (23.8 to 24.0)	21.6 (21.5 to 21.7)
Carbapenem	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)
Individual drug			
Iron supplement	6.0 (5.9 to 6.0)	6.2 (6.2 to 6.3)	5.7 (5.6 to 5.7)
Fludrocortisone	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)	0.1 (0.1 to 0.1)
Acitretin	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)
Erythromycin	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)	<0.1 (<0.1 to <0.1)

Some studies used terminology such as antihypertensives to describe a drug class. Other studies were more specific and used a term that was a recognised drug class such as calcium channel blockers. The terminology provided in the prescribing cascade study was used to define our drug classes (eAppendix 1).
CI=confidence interval; HMG Co-A=hydroxymethylglutaryl coenzyme A; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.

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Table 2 | Incidence of 65 potentially inappropriate prescribing cascades in community dwelling older adults in Ontario between 1 January 2022 and 31 December 2023

Potentially inappropriate prescribing cascade*	Number of incident users of initial drug	Number of people who had initial drug before subsequent drug	Incidence of prescribing cascade, % (95% CI)
Cardiovascular system			
Drug class			
Antihypertensive to antiemetic	152 254	3086	2.0 (2.0 to 2.1)
HMG Co-A reductase inhibitor to mineral supplement	177 825	219	0.1 (0.1 to 0.1)
HMG Co-A reductase inhibitor to sleep agent		7654	4.3 (4.2 to 4.4)
HMG Co-A reductase inhibitor to pain reliever		19 339	10.9 (10.7 to 11.0)
HMG Co-A reductase inhibitor to quinine sulfate		0	0
Angiotensin converting enzyme inhibitor to cough remedy	90 592	1877	2.1 (2.0 to 2.2)
Beta blocker to antidepressant	138 746	7221	5.2 (5.1 to 5.3)
Beta blocker to phosphodiesterase-5 inhibitor		8	<0.1 (<0.1 to <0.1)
Calcium channel blocker to diuretic	147 366	11 018	7.5 (7.3 to 7.6)
Calcium channel blocker to laxative		11 129	7.6 (7.4 to 7.7)
Diuretic to overactive bladder drug	171 937	4595	2.7 (2.6 to 2.8)
Diuretic to anti-gout agent		12 906	7.5 (7.4 to 7.6)
Individual drug			
Digoxin to antiemetic	9164	423	4.6 (4.2 to 5.1)
Midodrine to antihypertensive	5086	148	2.9 (2.5 to 3.4)
Central nervous system			
Drug class			
SSRI or SNRI to overactive bladder drug	102 746	3107	3.0 (2.9 to 3.1)
Gabapentinoid to diuretic	166 525	8162	4.9 (4.8 to 5.0)
Benzodiazepine to cholinesterase inhibitor	117 635	591	0.5 (0.5 to 0.5)
Anticonvulsant to antiemetic	84 200	2840	3.4 (3.3 to 3.5)
Anticonvulsant to topical corticosteroid		7539	9.0 (8.8 to 9.2)
Antipsychotic to anti-tremor antimuscarinic	82 417	91	0.1 (0.1 to 0.1)
Antipsychotic to sedative		7211	8.7 (8.6 to 8.9)
Antipsychotic to antiparkinsonian agent		472	0.6 (0.5 to 0.6)
Antipsychotic to antihyperglycaemic		1074	1.3 (1.2 to 1.4)
Antipsychotic to beta blocker		1765	2.1 (2.0 to 2.2)
Antipsychotic to antiarrhythmic		1636	2.0 (1.9 to 2.1)
Tricyclic antidepressant to cholinesterase inhibitor	35 808	156	0.4 (0.4 to 0.5)
Tricyclic antidepressant to laxative		3186	8.9 (8.6 to 9.2)
Tricyclic antidepressant to overactive bladder drug		2008	5.6 (5.4 to 5.9)
Cholinesterase inhibitor to antiemetic	24 035	437	1.8 (1.7 to 2.0)
Cholinesterase inhibitor to antidiarrheal		392	1.6 (1.5 to 1.8)
Cholinesterase inhibitor to sleep agent		2475	10.3 (9.9 to 10.7)
Cholinesterase inhibitor to overactive bladder drug		835	3.5 (3.3 to 3.7)
Cholinesterase inhibitor to bismuth subsalicylate		0	0
Cholinesterase inhibitor to antihistamine		≤5	—†
Dopaminergic antiparkinsonian agent to antipsychotic	16 303	614	3.8 (3.5 to 4.1)
Individual drug			
Venlafaxine to antihypertensive	11 720	421	3.6 (3.3 to 3.9)
Venlafaxine to benzodiazepine		530	4.5 (4.2 to 4.9)
Lithium to antiparkinsonian agent	532	9	1.7 (0.9 to 3.2)
Flunarizine to antidepressant	112	7	6.3 (3.1 to 12.3)
Endocrine system			
Drug class			
Dipeptidyl peptidase-4 inhibitor to NSAID	40 320	2173	5.4 (5.2 to 5.6)
Sodium-glucose cotransporter-2 inhibitor to antifungal	107 103	7129	6.7 (6.5 to 6.8)
Individual drug			
Metformin to antidiarrheal	60 490	734	1.2 (1.1 to 1.3)
Pioglitazone or rosiglitazone to diuretic	26	≤5	—†
Rosiglitazone to diuretic	≤5	≤5	—†
Gastrointestinal system			
Drug class			
Proton pump inhibitor to vitamin supplement	282 806	5084	1.8 (1.8 to 1.9)
Proton pump inhibitor to vitamin or mineral supplement		12 902	4.6 (4.5 to 4.6)
Laxative to antidiarrheal agent	337 509	7268	2.2 (2.1 to 2.2)
Antidopaminergic antiemetic to antiparkinsonian agent	72 975	282	0.4 (0.3 to 0.4)
Anticholinergic antiemetics to alpha-1 receptor blocker	20 694	112	0.5 (0.4 to 0.7)
Musculoskeletal system			
Drug class			
Opioid to antidepressant	421 230	25 737	6.1 (6.0 to 6.2)

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Table 2 | Continued

Potentially inappropriate prescribing cascade*	Number of incident users of initial drug	Number of people who had initial drug before subsequent drug	Incidence of prescribing cascade, % (95% CI)
NSAID to antiemetic	332 527	5627	1.7 (1.7 to 1.7)
NSAID to gastroprotective agent		22 273	6.7 (6.6 to 6.8)
NSAID to heart failure agent		11 908	3.6 (3.5 to 3.6)
NSAID to antihypertensive		10 000	3.0 (3.0 to 3.1)
Bisphosphonate to gastroprotective agent	73 922	4342	5.9 (5.7 to 6.1)
Urogenital system			
Drug class			
Alpha-1 receptor blocker to vestibular suppressant	106,620	904	0.8 (0.8 to 0.9)
Urinary anticholinergic to saliva substitute	29 104	0	0
Miscellaneous system			
Drug class			
Corticosteroid to antipsychotic	533 033	12 959	2.4 (2.4 to 2.5)
Corticosteroid to sleep agent		29 599	5.6 (5.5 to 5.6)
Corticosteroid to antihypertensive		14 867	2.8 (2.8 to 2.8)
Carbapenem to anticonvulsant	≤5	≤5	—†
Individual drug			
Iron supplement to laxative	108 383	12 908	11.9 (11.7 to 12.1)
Fludrocortisone to antihypertensive	2128	100	4.7 (3.9 to 5.7)
Acitretin to antifungal	936	41	4.4 (3.3 to 5.9)
Erythromycin to antiarrhythmic	407	13	3.2 (1.9 to 5.4)

CI=confidence interval; HMG Co-A=hydroxymethylglutaryl coenzyme A; NSAID=non-steroidal anti-inflammatory drug; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
*List of 65 potentially inappropriate prescribing cascades obtained from "International expert panel's potentially inappropriate prescribing cascades (PIPC) list."[7]
†Incidence of prescribing cascade could not be calculated owing to small number of people dispensed initial drug before subsequent drug.

PIPC specific analytic cohort. The crude sequence ratio was calculated by dividing the number of people who had the initial drug before the subsequent drug (patterns suggesting a PIPC) by the number who had the subsequent drug before the initial drug (pattern not consistent with a PIPC; fig 1). Given that prescribing trends over time may influence the sequences of drug initiation and bias the sequence ratio, a corrective measure called the null effect sequence ratio was calculated. The null effect sequence ratio quantifies the background rate for the sequence of two drugs over the observation period. The adjusted sequence ratio was calculated by dividing the crude sequence ratio by the null effect sequence ratio and providing 95% CIs, thereby giving a corrected estimate of the temporal association between drugs. An adjusted sequence ratio >1.0, with the lower limit of the 95% CI above 1, suggests evidence of a prescribing cascade with the population presenting an asymmetrical distribution of prescription sequence[13 17] (fig 1 and eAppendix 2).

We defined prioritised PIPCs as prescribing cascades that met all three criteria of high initial drug prevalence (≥5%), high incidence of the prescribing cascade (≥1%), and strength of temporal association measured using adjusted sequence ratios >1.0, with the lower limit of the 95% CI above the corresponding threshold for each measure (fig 1). For each prioritised PIPC, the population prevalence rate of the drug starting the prescribing cascade, the incidence of the prescribing cascade, and the adjusted sequence ratios were stratified by sex to identify potential sex differences in prescribing patterns. The widths of all confidence intervals were not adjusted for multiplicity and should not be used in place of hypothesis testing. Because the timing of subsequent drug prescribing suggesting a prescribing cascade may vary and to reduce within person time varying confounding, we conducted a sensitivity analysis using a time window of 180 days to assess the robustness of the primary analyses. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC).

Patient and public involvement

This study uses a retrospective cohort design. Although patients were not directly involved in the design of this retrospective study, input from clinicians and stakeholders informed the development and interpretation of the PIPC list. Throughout the study, we reached out to patients, providers, and the public through forums such as presentations at the local, national, and international level where we received input and feedback that helped shape our project. A knowledge user targeted dissemination strategy of our Delphi PIPC list included a peer reviewed publication, conference presentation, and profile on social media platforms. Patients, providers, and the public will also be involved in the next phase of this work focusing on designing tools and knowledge translation materials to educate them about drugs, potential adverse effects and risk of polypharmacy, and raising awareness about the clinical implications of the high priority prescribing cascades.

Results

The study source population included 2 297 942 community dwelling older adults (54.3% female, 12.8% aged ≥85 years).

Population prevalence of initial drug

Overall, 34 (52.3%) initial drugs had a high prevalence (5.6-65.9%; table 1). Cardiovascular drugs were most

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Table 3 | Prescription sequence symmetry analyses for all 65 potentially inappropriate prescribing cascades

Potentially inappropriate prescribing cascade*	Prescription sequence symmetry analyses				
	Number of people who had initial drug before subsequent drug	Number of people who had initial drug after subsequent drug	Crude sequence ratio	Null effect sequence ratio	Adjusted sequence ratio (95% CI)
Cardiovascular system					
Drug class					
Antihypertensive to antiemetic	3086	1917	1.61	0.97	1.65 (1.56 to 1.75)
HMG Co-A reductase inhibitor to mineral supplement	219	134	1.63	0.93	1.76 (1.42 to 2.19)
HMG Co-A reductase inhibitor to sleep agent	7654	6216	1.23	0.92	1.34 (1.29 to 1.38)
HMG Co-A reductase inhibitor to pain reliever	19 339	18 144	1.07	0.92	1.16 (1.14 to 1.19)
HMG Co-A reductase inhibitor to quinine sulfate	0	0	—†	—†	—†
Angiotensin converting enzyme inhibitor to cough remedy	1877	1197	1.57	1.07	1.47 (1.37 to 1.58)
Beta blocker to antidepressant	7221	5927	1.22	0.98	1.25 (1.21 to 1.29)
Beta blocker to phosphodiesterase-5 inhibitor	8	7	1.14	1.16	0.98 (0.36 to 2.71)
Calcium channel blocker to diuretic	11 018	6671	1.65	1.00	1.65 (1.60 to 1.70)
Calcium channel blocker to laxative	11 129	9111	1.22	0.98	1.24 (1.21 to 1.28)
Diuretic to overactive bladder drug	4595	4877	0.94	0.99	0.95 (0.91 to 0.99)
Diuretic to anti-gout agent	12 906	16 131	0.80	0.98	0.82 (0.80 to 0.84)
Individual drug					
Digoxin to antiemetic	423	264	1.60	0.95	1.68 (1.44 to 1.96)
Midodrine to antihypertensive	148	300	0.49	0.88	0.56 (0.46 to 0.68)
Central nervous system					
Drug class					
SSRI or SNRI to overactive bladder drug	3107	2808	1.11	1.03	1.07 (1.02 to 1.13)
Gabapentinoid to diuretic	8162	6809	1.20	0.99	1.21 (1.17 to 1.25)
Benzodiazepine to cholinesterase inhibitor	591	618	0.96	1.09	0.88 (0.79 to 0.99)
Anticonvulsant to antiemetic	2840	2343	1.21	0.95	1.27 (1.20 to 1.34)
Anticonvulsant to topical corticosteroid	7539	8363	0.90	0.92	0.98 (0.95 to 1.01)
Antipsychotic to anti-tremor antimuscarinic	91	26	3.50	0.95	3.69 (2.39 to 5.70)
Antipsychotic to sedative	7211	5912	1.22	0.92	1.32 (1.28 to 1.37)
Antipsychotic to antiparkinsonian agent	472	575	0.82	1.03	0.80 (0.71 to 0.90)
Antipsychotic to antihyperglycaemic	1074	1754	0.61	1.06	0.58 (0.53 to 0.62)
Antipsychotic to beta blocker	1765	3292	0.54	0.99	0.54 (0.51 to 0.57)
Antipsychotic to antiarrhythmic	1636	3083	0.53	0.99	0.54 (0.51 to 0.57)
Tricyclic antidepressant to cholinesterase inhibitor	156	120	1.30	1.06	1.22 (0.96 to 1.55)
Tricyclic antidepressant to laxative	3186	3163	1.01	1.05	0.96 (0.92 to 1.01)
Tricyclic antidepressant to overactive bladder drug	2008	2178	0.92	1.06	0.87 (0.82 to 0.93)
Cholinesterase inhibitor to antiemetic	437	206	2.12	0.95	2.24 (1.90 to 2.65)
Cholinesterase inhibitor to antidiarrheal	392	220	1.78	0.97	1.83 (1.55 to 2.16)
Cholinesterase inhibitor to sleep agent	2475	2044	1.21	0.92	1.31 (1.23 to 1.39)
Cholinesterase inhibitor to overactive bladder drug	835	745	1.12	0.99	1.13 (1.02 to 1.25)
Cholinesterase inhibitor to bismuth subsalicylate	0	0	—†	—†	—†
Cholinesterase inhibitor to antihistamine	≤5	≤5	—†	—†	—†
Dopaminergic antiparkinsonian agent to antipsychotic	614	351	1.75	0.97	1.80 (1.58 to 2.05)
Individual drug					
Venlafaxine to antihypertensive	421	431	0.98	1.02	0.96 (0.84 to 1.10)
Venlafaxine to benzodiazepine	530	945	0.56	0.96	0.59 (0.53 to 0.65)
Lithium to antiparkinsonian agent	9	9	1.00	1.13	0.89 (0.35 to 2.23)
Flunarizine to antidepressant	7	10	0.70	0.93	0.75 (0.29 to 1.98)
Endocrine system					
Drug class					
Dipeptidyl peptidase-4 inhibitor to NSAID	2173	2264	0.96	0.87	1.10 (1.04 to 1.17)
Sodium-glucose cotransporter-2 inhibitor to antifungal	7129	3431	2.08	0.98	2.12 (2.04 to 2.21)
Individual drug					
Metformin to antidiarrheal	734	465	1.58	1.03	1.54 (1.37 to 1.73)
Pioglitazone or rosiglitazone to diuretic	≤5	≤5	—†	—†	—†
Rosiglitazone to diuretic	≤5	≤5	—†	—†	—†
Gastrointestinal system					
Drug class					
Proton pump inhibitor to vitamin supplement	5084	4040	1.26	0.96	1.31 (1.26 to 1.36)
Proton pump inhibitor to vitamin or mineral supplement	12 902	10 161	1.27	1.01	1.25 (1.22 to 1.29)
Laxative to antidiarrheal agent	7268	2886	2.52	0.99	2.53 (2.43 to 2.65)
Antidopaminergic antiemetic to antiparkinsonian agent	282	522	0.54	1.08	0.50 (0.43 to 0.58)
Anticholinergic antiemetics to alpha-1 receptor blocker	112	733	0.15	1.06	0.14 (0.12 to 0.18)
Musculoskeletal system					
Drug class					
Opioid to antidepressant	25 737	19 731	1.30	1.01	1.29 (1.27 to 1.32)
NSAID to antiemetic	5627	3483	1.62	0.97	1.66 (1.59 to 1.73)

(Continued)

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Table 3 | Continued

Potentially inappropriate prescribing cascade*	Prescription sequence symmetry analyses				
	Number of people who had initial drug before subsequent drug	Number of people who had initial drug after subsequent drug	Crude sequence ratio	Null effect sequence ratio	Adjusted sequence ratio (95% CI)
NSAID to gastroprotective agent	22 273	18 530	1.20	0.97	1.24 (1.21 to 1.26)
NSAID to heart failure agent	11 908	10 129	1.18	1.01	1.17 (1.14 to 1.20)
NSAID to antihypertensive	10 000	9052	1.10	1.01	1.10 (1.07 to 1.13)
Bisphosphonate to gastroprotective agent	4342	5112	0.85	0.93	0.91 (0.88 to 0.95)
Urogenital system					
Drug class					
Alpha-1 receptor blocker to vestibular suppressant	904	110	8.22	0.94	8.70 (7.12 to 10.61)
Urinary anticholinergic to saliva substitute	0	0	—†	—†	—†
Miscellaneous system					
Drug class					
Corticosteroid to antipsychotic	12 959	5051	2.57	1.01	2.55 (2.47 to 2.64)
Corticosteroid to sleep agent	29 599	23 089	1.28	0.98	1.31 (1.29 to 1.34)
Corticosteroid to antihypertensive	14 867	15 997	0.93	1.02	0.91 (0.89 to 0.93)
Carbapenem to anticonvulsant	≤5	≤5	—†	—†	—†
Individual drug					
Iron supplement to laxative	12 908	11 233	1.15	0.98	1.17 (1.14 to 1.20)
Fludrocortisone to antihypertensive	100	93	1.08	0.94	1.15 (0.87 to 1.52)
Acitretin to antifungal	41	49	0.84	1.03	0.82 (0.54 to 1.24)
Erythromycin to antiarrhythmic	13	9	1.44	2.05	0.71 (0.30 to 1.65)

CI=confidence interval; HMG Co-A=hydroxymethylglutaryl coenzyme A; NSAID=non-steroidal anti-inflammatory drug; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
*List of 65 potentially inappropriate prescribing cascades obtained from "International expert panel's potentially inappropriate prescribing cascades (PIPC) list."[7]
†Sequence ratio could not be calculated owing to small number of people dispensed initial and subsequent drug.

common (19.0-65.9% for drug classes) and were dispensed less frequently to female older adults than male older adults (eg, statins in 48.5% of female older adults *v* 62.6% of male older adults), while central nervous system drugs (1.8-13.5% for drug classes) were dispensed more frequently to female older adults (eg, selective serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs) in 17.1% of female older adults *v* 9.3% of male older adults).

Incidence of potentially inappropriate prescribing cascades

The PIPCs with the highest incidence were iron supplement to laxative (11.9%, 95% CI 11.7% to 12.1%), hydroxymethylglutaryl coenzyme A reductase inhibitor to pain reliever (10.9%, 10.7% to 11%), and cholinesterase inhibitor to sleep agent (10.3%, 9.9% to 10.7%). Overall, 49 of 65 (75.3%) PIPCs had an incidence ≥1% over one year during the accrual period (table 2).

Strength of associations of PIPCs

Table 3 describes the prescription sequence symmetry analyses for the 65 PIPCs. Within the PIPC list, there were 12 drugs or drug classes that started more than one PIPC. For example, antipsychotics and cholinesterase inhibitors each started six PIPCs. The adjusted sequence ratio ranged from 0.14 (95% CI 0.12 to 0.18; anticholinergic anti-emetics to alpha-1 receptor blocker) to 8.70 (7.12 to 10.61; alpha-1 receptor blocker to vestibular suppressant). Overall, 34 (52.3%) of the 65 PIPCs had a high sequence ratio defined as an adjusted sequence ratio >1.0. The adjusted sequence ratios were consistent when stratified by sex except for SSRI or SNRI to overactive bladder drug cascade, which showed a statistically significant association for male older adults (1.21, 95% CI 1.10 to 1.33) but not for female older adults (1.02, 0.96 to 1.09).

Prioritised PIPCs

eFigure 4 provides a four quadrant scatter plot showing the prevalence rate of the initial drug, prescribing cascade incidence, and adjusted sequence ratio for all 65 PIPCs by seven physiological systems. Table 4 describes the 24 prioritised PIPCs that met all three criteria, suggesting the highest population level burden, stratified by sex. Examples include the calcium channel blocker to diuretic, sodium-glucose cotransporter-2 inhibitor to antifungal, and non-steroidal anti-inflammatory drug to antihypertensive prescribing cascade. One PIPC did not meet prioritisation criteria in female older adults (SSRI or SNRI to overactive bladder drug) and one did not meet prioritisation criteria in male older adults (anticonvulsant to antiemetic).

Discussion

Principal findings

PIPCs are a common but often unrecognised contributor to polypharmacy and drug related harm at the population level. Our study used a comprehensive Delphi consensus list of 65 PIPCs[7] to examine the extent of this form of potentially inappropriate prescribing in a large population. Using a source population of nearly 2.3 million older adults, we identified 24 drug combinations that met our three criteria—high prevalence of the initial drug (5% or more), high incidence of the prescribing cascade (1%

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Table 4 | Population prevalence of initial drug, incidence of prescribing cascade, and adjusted sequence ratios for 24 prioritised potentially inappropriate prescribing cascades by sex

	Overall			Female older adults			Male older adults		
Potentially inappropriate prescribing cascade	Prevalence rate of initial drug, %	Incidence of prescribing cascade, % (95% CI)	Adjusted sequence ratio (95% CI)	Prevalence rate of initial drug, %	Incidence of prescribing cascade, % (95% CI)	Adjusted sequence ratio (95% CI)	Prevalence rate of initial drug, %	Incidence of prescribing cascade, % (95% CI)	Adjusted sequence ratio (95% CI)
Cardiovascular system									
Drug class									
Antihypertensive to antiemetic	65.9	2.0 (2.0 to 2.1)	1.65 (1.56 to 1.75)	63.6	2.0 (2.0 to 2.2)	1.64 (1.52 to 1.77)	68.6	2.0 (1.9 to 2.1)	1.67 (1.53 to 1.82)
HMG Co-A reductase inhibitor to pain reliever	54.9	10.9 (10.7 to 11.0)	1.16 (1.14 to 1.19)	48.5	10.7 (10.5 to 10.9)	1.16 (1.13 to 1.19)	62.6	11.1 (10.9 to 11.3)	1.17 (1.13 to 1.20)
HMG Co-A reductase inhibitor to sleep agent		4.3 (4.2 to 4.4)	1.34 (1.29 to 1.38)		4.7 (4.5 to 4.8)	1.29 (1.24 to 1.35)		3.9 (3.7 to 4.0)	1.43 (1.35 to 1.51)
Angiotensin converting enzyme inhibitor to cough remedy	27.2	2.1 (2.0 to 2.2)	1.47 (1.37 to 1.58)	22.9	2.3 (2.1 to 2.4)	1.53 (1.39 to 1.69)	32.2	1.9 (1.7 to 2.0)	1.39 (1.25 to 1.55)
Beta blocker to antidepressant	26.1	5.2 (5.1 to 5.3)	1.25 (1.21 to 1.29)	23.7	5.6 (5.5 to 5.8)	1.20 (1.15 to 1.26)	29.0	4.8 (4.6 to 4.9)	1.30 (1.24 to 1.37)
Calcium channel blocker to diuretic	23.6	7.5 (7.3 to 7.6)	1.65 (1.60 to 1.70)	23.5	7.7 (7.5 to 7.8)	1.64 (1.58 to 1.71)	23.8	7.2 (7.0 to 7.4)	1.66 (1.58 to 1.74)
Calcium channel blocker to laxative		7.6 (7.4 to 7.7)	1.24 (1.21 to 1.28)		7.4 (7.3 to 7.6)	1.27 (1.22 to 1.32)		7.7 (7.5 to 7.9)	1.21 (1.16 to 1.26)
Central nervous system									
Drug class									
SSRI or SNRI to overactive bladder drug	13.5	3.0 (2.9 to 3.1)	1.07 (1.02 to 1.13)	17.1	3.3 (3.2 to 3.5)	1.02 (0.96 to 1.09)	9.3	2.5 (2.4 to 2.7)	1.21 (1.10 to 1.33)
Gabapentinoid to diuretic	9.0	4.9 (4.8 to 5.0)	1.21 (1.17 to 1.25)	10.1	4.9 (4.7 to 5.0)	1.22 (1.17 to 1.27)	7.7	5.0 (4.8 to 5.1)	1.19 (1.13 to 1.25)
Anticonvulsant to antiemetic	5.6	3.4 (3.3 to 3.5)	1.27 (1.20 to 1.34)	6.1	3.2 (3.1 to 3.4)	1.24 (1.15 to 1.33)	4.9	3.6 (3.4 to 3.8)	1.32 (1.21 to 1.44)
Endocrine system									
Drug class									
Dipeptidyl peptidase-4 inhibitor to NSAID	9.6	5.4 (5.2 to 5.6)	1.10 (1.04 to 1.17)	8.0	5.6 (5.3 to 6.0)	1.11 (1.02 to 1.21)	11.5	5.2 (4.9 to 5.5)	1.09 (1.01 to 1.19)
Sodium-glucose cotransporter-2 inhibitor to antifungal	7.8	6.7 (6.5 to 6.8)	2.12 (2.04 to 2.21)	5.7	8.9 (8.6 to 9.1)	2.20 (2.08 to 2.32)	10.4	4.9 (4.8 to 5.1)	2.05 (1.93 to 2.18)
Individual drug									
Metformin to antidiarrheal	17.9	1.2 (1.1 to 1.3)	1.54 (1.37 to 1.73)	14.8	1.4 (1.2 to 1.5)	1.48 (1.26 to 1.73)	21.5	1.1 (1.0 to 1.2)	1.62 (1.37 to 1.93)
Gastrointestinal system									
Drug class									
Proton pump inhibitor to vitamin supplement	30.5	1.8 (1.8 to 1.9)	1.31 (1.26 to 1.36)	32.4	1.8 (1.8 to 1.9)	1.29 (1.22 to 1.36)	28.2	1.8 (1.7 to 1.8)	1.33 (1.25 to 1.42)
Proton pump inhibitor to vitamin or mineral supplement		4.6 (4.5 to 4.6)	1.25 (1.22 to 1.29)		4.4 (4.3 to 4.5)	1.23 (1.19 to 1.28)		4.8 (4.7 to 4.9)	1.28 (1.23 to 1.33)
Laxative to antidiarrheal agent	12.0	2.2 (2.1 to 2.2)	2.53 (2.43 to 2.65)	12.0	2.2 (2.2 to 2.3)	2.43 (2.30 to 2.58)	11.9	2.1 (2.0 to 2.1)	2.67 (2.50 to 2.85)
Musculoskeletal system									
Drug class									
Opioid to antidepressant	15.2	6.1 (6.0 to 6.2)	1.29 (1.27 to 1.32)	15.3	6.4 (6.3 to 6.5)	1.26 (1.23 to 1.29)	14.9	5.8 (5.7 to 5.9)	1.34 (1.30 to 1.37)
NSAID to gastroprotective agent	13.5	6.7 (6.6 to 6.8)	1.24 (1.21 to 1.26)	14.1	7.0 (6.8 to 7.1)	1.20 (1.17 to 1.23)	12.8	6.4 (6.3 to 6.5)	1.28 (1.25 to 1.32)
NSAID to antiemetic		1.7 (1.7 to 1.7)	1.66 (1.59 to 1.73)		1.8 (1.8 to 1.9)	1.62 (1.53 to 1.71)		1.5 (1.5 to 1.6)	1.73 (1.61 to 1.85)
NSAID to antihypertensive		3.0 (3.0 to 3.1)	1.10 (1.07 to 1.13)		3.0 (2.9 to 3.1)	1.09 (1.05 to 1.13)		3.0 (2.9 to 3.1)	1.11 (1.06 to 1.16)
NSAID to heart failure agent		3.6 (3.5 to 3.6)	1.17 (1.14 to 1.20)		3.6 (3.6 to 3.7)	1.17 (1.13 to 1.21)		3.5 (3.4 to 3.6)	1.17 (1.12 to 1.21)
Miscellaneous system									
Drug class									
Corticosteroid to sleep agent	22.8	5.6 (5.5 to 5.6)	1.31 (1.29 to 1.34)	23.9	5.8 (5.7 to 5.9)	1.24 (1.21 to 1.27)	21.6	5.3 (5.2 to 5.4)	1.44 (1.40 to 1.48)
Corticosteroid to antipsychotic		2.4 (2.4 to 2.5)	2.55 (2.47 to 2.64)		2.3 (2.2 to 2.3)	2.29 (2.19 to 2.39)		2.6 (2.6 to 2.7)	2.92 (2.78 to 3.07)
Individual drug									
Iron supplement to laxative	6.0	11.9 (11.7 to 12.1)	1.17 (1.14 to 1.20)	6.2	11.5 (11.3 to 11.8)	1.22 (1.18 to 1.26)	5.7	12.4 (12.1 to 12.7)	1.10 (1.06 to 1.14)

CI=confidence interval; HMG Co-A=hydroxymethylglutaryl coenzyme A; NSAID=non-steroidal anti-inflammatory drug; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor.
eTable 3 describes the 24 prioritised PIPCs stratified by age groups; 21 of 24 continue to meet all the prioritisation criteria in the ≥85 year age group—SSRI or SNRI to overactive bladder drug (adjusted sequence ratio 0.93, 95% CI 0.82 to 1.05), dipeptidyl peptidase-4 inhibitor to non-steroidal anti-inflammatory drug (0.92, 0.74 to 1.14), and sodium-glucose cotransporter-2 inhibitor to antifungal (prevalence rate of initial drug 4.0) did not meet the criteria. The sensitivity analyses using 180 days of follow-up showed that the results were consistent with the one year follow-up period (eTable 4).

or more), and high strength of association suggesting a prescribing cascade (adjusted sequence ratio >1).

Comparison with other studies

This large scale study quantified the population prevalence of the initial drug and incidence of a comprehensive, Delphi derived list of PIPCs at the population level. This study builds on earlier studies that explored nine clinically important prescribing cascades in a national database of about half a million older adults in Ireland,[8] another study that explored these nine clinically important prescribing cascades in a family medicine database of about 4000 older adults in the Netherlands,[10] and a third study that explored potentially problematic prescribing cascades using Dutch community pharmacy data.[9]

Research implications

This study adds to the evolution of our research on prescribing cascades and to clinical practice. Our initial publications described the prescribing cascade framework[1 2 18] and the resources available to prevent, detect, and reverse them.[19] We showed that PIPCs occur using population based retrospective cohort studies exploring the calcium channel blocker to diuretic[20] and the gabapentinoid to diuretic[21] PIPCs. We also explored the negative consequences of prescribing cascades.[22 23]

Our current study broadens our perspective to explore prescribing cascades at a population level so we can prioritise interventions. We used a comprehensive list of 65 PIPCs created by an international group of experts in drug prescribing for older adults,[7] focusing only on drugs that are frequently prescribed to older adults and quantifying their relevance at a population level. Therefore, this study evaluates one of the largest lists of PIPCs in an extensive population.

While the prescribing cascades identified in this study are only potentially inappropriate, this prioritised PIPC list may help alert clinicians and health systems to possible problematic and unsafe prescribing situations. As with all prescribing decisions, the cascades identified need to be reviewed in the context of the individual patient because some PIPC drug combinations may be clinically appropriate while others should be revisited.[7 18] Beyond determining clinical appropriateness, additional factors should be taken into account by clinicians when considering the management of a PIPC. The degree of harm should also be considered because some drugs included in these prescribing cascades have important risks (eg, antipsychotics, gabapentinoids) and others may be less harmful over the short term (eg, proton pump inhibitors). Decisions to re-evaluate prescribing should also account for the financial cost to patients and to healthcare systems, especially when additional drugs are added to treat the adverse effects of a drug that could have been discontinued.

To support more targeted action, our prioritised list offers a structured way to focus attention on cascades with the greatest population impact. Although clinicians may be familiar with the concept of prescribing cascades,[2 18] the large number of potential prescribing cascades may be a barrier for targeted action. Our list of prioritised PIPCs, which is organised by physiological system to align with the STOPP/START criteria,[11] provides a foundation for drug optimisation and deprescribing initiatives. The opportunity to add clinical decision support tools to alert prescribers and pharmacists to the presence of PIPCs, especially when new drugs are added or existing drugs are being reviewed, makes the findings directly applicable to practice across the full range of clinical settings.[24 25]

Our final list of 24 PIPCs includes some where the suspected adverse effect may occur quite quickly and others where it may take months to become apparent. For example, when exploring the calcium channel blocker to diuretic prescribing cascade, loop diuretic dispensing occurred within the first 30 days.[20] For the gabapentinoid to diuretic prescribing cascade, increased loop diuretic dispensing occurred within 90 days.[21] In contrast, the beta blocker to antidepressant prescribing cascade may take months before it occurs. These timing patterns show why some cascades are more readily detectable than others.

Many of the drugs included on our PIPC list are prescribed on a chronic basis, meaning that people will be at risk from these PIPCs indefinitely, especially as new drugs are added over time. This list can provide focused guidance on identifying patients at high risk who need increased vigilance. Sex related differences in the prevalence of a broad range of prescribing cascades have been inadequately described. Older women may be at greater risk from the adverse health consequences of inappropriate prescribing because they live longer, experience more chronic conditions, and are more likely to experience polypharmacy[6 26] and adverse drug events[27 28] than men, making it important to explore these potential differences.

These observed patterns have clinical relevance and highlight opportunities for drug reviews. Identifying the downstream outcomes after a prescribing cascade is important because prescribing cascades can increase treatment burden, reduce adherence, and heighten the risk of hospital admission, underscoring the importance of prevention.[22 29 30] Identifying a PIPC provides an important opportunity to conduct a drug review and determine if changes are needed to the initial or subsequent drug. When assessing any PIPC, clinicians should ask three basic questions.[18 31] Firstly, is the new drug being prescribed to treat a possible adverse effect from another drug? Secondly, is a safer alternative or lower dose available for the initial drug? Thirdly, is the initial drug truly necessary or effective, or could it be stopped[6 18]? For example, for the non-steroidal anti-inflammatory to antihypertensive PIPC, the initial drug dose could be reduced, the initial drug substituted with an alternative treatment like acetaminophen, or in some patients, discontinued.[18 32]

We should also recognise that in certain circumstances a prescribing cascade may be appropriate—it could be an attempt to manage a known adverse effect

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to enable someone to remain on the initial treatment. For example, if an antipsychotic drug is required, prescribing a drug to manage extra-pyramidal adverse effects may be appropriate so that the person can remain on the antipsychotic drug. The risks and benefits of continuing the drug treatment that led to the prescribing cascade should also be considered as part of shared decision making with the patient.[18] To assist with future prescribing cascade identification, clinicians should record when a drug was prescribed and why it was prescribed at the time of prescribing so that the sequence of events leading to a prescribing cascade is more readily apparent.[33]

At a broader healthcare system level, these findings highlight additional opportunities for intervention. For example, at the time of prescribing, prescribers should be aware of PIPCs that could occur after starting a new drug. Additionally, at points of healthcare contact, opportunities exist to implement drug review policies designed to identify existing PIPCs and determine if changes can be made to drug treatments to reduce the risk and to monitor for the development of future PIPCs. The prioritised PIPC list could also be applied by organisations to identify areas of drug prescribing where special prescriber education may be warranted to highlight opportunities for deprescribing. Given how often these PIPCs occur, population level interventions may emerge to improve drug safety and provide guidance specifically for men and women.

Strengths and limitations

Our study incorporates a Delphi consensus list of PIPCs created by international experts in drug prescribing,[7] a large, population based cohort of older adults, and robust three part analytic methods. Together, these add to the PIPC list[7] by providing a comprehensive picture of common PIPCs at the population level. We focus on older adults who use the most drug treatments and are most at risk of adverse events but recognise that PIPCs can occur in all age groups. Because our data source includes only adults aged ≥66 years, the findings may not be generalisable to younger populations in whom prescribing patterns and prescribing cascade dynamics may differ.

Several limitations should be considered when interpreting our findings. We recognise that it is not possible to know the exact circumstances that led to the prescription of the second drug. Point estimates were generated using a fixed one year observation window after drug initiation, which may have overestimated person time at risk in patients who died or left the province during this period. This approach is consistent with the methods used in previous studies.[8 13] We also recognise that we may have underestimated the extent of prescribing cascades at the population level. We did not account for over-the-counter drugs and potential adverse drug events occurring over longer periods of time. Additionally, we did not evaluate prescribing cascades involving more than two drugs, all of which may underestimate the complexity and cumulative burden of prescribing cascades.

We acknowledge that combining population prevalence, incidence, and strength of temporal association of prescribing represents just one way to prioritise PIPCs at a population level. This list may also differ depending on the healthcare system, the underlying population, and prescribing practices.[34] Our study was conducted in Canada's largest province where drug treatment is publicly funded for older adults. We also focus on frequently prescribed common drugs readily available in most developed countries in generic forms.

The prescription sequence symmetry analysis may be sensitive to temporal prescribing trends and may be influenced by channelling bias, although adjustment for null effect ratios was applied to mitigate this concern. This method does not fully account for confounding by indication or time varying confounding that could occur during the observation period. For example, people with the calcium channel blocker to diuretic prescribing cascade may have existing cardiovascular disease that warrants the use of a diuretic.[22] Given this approach, the use of the subsequent drug may misattribute the need for the drug to manage cardiovascular disease to the prescribing cascade. Although the purpose of this self-controlled design is to avoid confounding by indication, we recognise it could still occur.

Our analyses are intended as signalled detection rather than confirmation of causal prescribing cascades, which is the main reason why the prescribing cascades were defined as potentially inappropriate. Prescription sequence symmetry analysis is a relatively crude but efficient screening method to evaluate temporal association using large databases and does not imply causation. For example, the results suggest that when a patient is taking a calcium channel blocker and a diuretic, this may be an opportunity for a review to determine if the diuretic was prescribed as part of a prescribing cascade and whether it is appropriate based on a patient's specific circumstances. Additionally, identifying these PIPCs requires further evaluation because they may be appropriate drug combinations under certain circumstances.

Our study is important because it assesses the population level impact of PIPCs, focusing on the incidence, prevalence, and strength of association. Estimating their impact on patient outcomes such as morbidity or mortality is beyond the scope of this paper. The current study proposes a list that may be used to examine patient outcomes in the future. Our findings offer clear implications for practice and policy and frame how our results can guide the next steps.

Conclusions

Important prescribing cascades that affect older adults often go unnoticed. By combining population prevalence, incidence, and temporal prescription sequence symmetry analyses, our study highlighted 24 common prescribing cascades and their sex specific differences. This prioritised list could inform system level prescribing and deprescribing initiatives and

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be integrated into clinical decision support systems, providing new opportunities to enhance drug safety at the patient and population levels.

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Ethical approval: Data use was authorised under section 45 of Ontario's Personal Health Information Protection Act and does not require research ethics board review. Results were reported using the strengthening the reporting of observational studies (STROBE) guidelines for cohort studies.

Data sharing: The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (eg, healthcare organisations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supplementary file: Supplementary appendix

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