Prescribing Cascades Among Older Community-Dwelling Adults: Application of Prescription Sequence Symmetry Analysis to a National Database in Ireland

Ann Sinéad Doherty, PhD
Lars Christian Lund, PhD
Frank Moriarty, PhD
Fiona Boland, PhD
Barbara Clyne, PhD
Tom Fahey, MD
Seán P. Kennelly, PhD
Denis O'Mahony, DSc
Emma Wallace, PhD

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CORRESPONDING AUTHOR

Ann Doherty
Department of General Practice, School of Medicine
Western Gateway Building
University College Cork
Cork T12 XF62 Ireland
adoherty@ucc.ie

ABSTRACT

PURPOSE Prescribing cascades occur when one medication is used to treat adverse effects of another medication. Older adults with polypharmacy are at higher risk for this phenomenon. We examined the prevalence, magnitude, and effect modification of 9 prescribing cascades (ThinkCascades) among older community-dwelling adults in a national prescription database.

METHODS We used prescription sequence symmetry analysis to examine prescriptions for ThinkCascades medications dispensed in primary care under the General Medical Services scheme in Ireland. Analyses were based on prescriptions dispensed between 2017 and 2020 among 533,464 adults aged 65 years or older. Incident users of both medications in each ThinkCascades dyad were included. We used an observation window of 365 days and examined other windows in sensitivity analyses. Adjusted sequence ratios (aSRs) took into account secular prescribing trends. We also conducted analyses stratified by sex, age, and individual index medication.

RESULTS Five prescribing cascades had significant positive aSRs, indicating that the patient was more likely to receive the index medication before the marker medication. The largest signal was identified for the calcium channel blocker to diuretic cascade (prevalence, 2.6%; aSR = 1.93; 95% CI, 1.79-2.09). Positive signals were also identified for the α_1-receptor blocker to vestibular sedative cascade (prevalence, 3.0%; aSR = 1.63; 95% CI, 1.46-1.81); the selective serotonin reuptake inhibitor/selective norepinephrine reuptake inhibitor to sleep medication cascade (prevalence, 2.5%; aSR = 1.54; 95% CI, 1.40-1.69); the antipsychotic to antiparkinsonian cascade (prevalence, 0.4%; aSR = 1.20; 95% CI, 1.00-1.43); and the benzodiazepine to antipsychotic cascade (prevalence, 3.2%; aSR = 1.15; 95% CI, 1.08-1.21).

CONCLUSIONS To our knowledge, this study is the first to describe the prevalence of an expert consensus–based list of prescribing cascades, ThinkCascades, in a national population of older adults, and it identified 5 clinically relevant prescribing cascades. These findings highlight prescribing cascades as an important underresearched area contributing to complex polypharmacy among older people living with multimorbidity.

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INTRODUCTION

Prescribing cascades occur when one medication is used to treat or prevent an adverse drug reaction (ADR) to another medication, either intentionally or unintentionally.[1-4] Unintentional prescribing cascades arise when the prescriber misinterprets the patient's symptoms as a new emergent illness and constitutes an aspect of potentially inappropriate prescribing.[4] With unintentional prescribing cascades, the medication-related harm attributed to the culprit medication is compounded by additional risk introduced by the second medication. Commonly identified prescribing cascades include calcium channel blockers (CCBs) leading to pedal edema and resultant diuretic prescribing,[5-9] and antipsychotics causing extrapyramidal symptoms leading to antiparkinsonian medication prescribing.[10-13]

Failure to recognize an ADR may be more common in older adults for several reasons. Older adults are more likely to experience polypharmacy (≥5 prescribed medications),[14] a known risk factor for potentially inappropriate prescribing[15,16] and ADR occurrence.[17-21] ADRs may manifest nonspecifically in older adults as signs and symptoms with multiple possible etiologies (eg, constipation, dizziness), possibly

even overlapping with preexisting morbidities or conditions more likely to develop in older populations.[22] Many older adults have multimorbidity, which may influence the differential diagnosis.[23,24] For example, pedal edema as an ADR arising from CCB therapy in an older person with hypertension, obesity, and diabetes could reasonably be misinterpreted as heart failure, if a clinician gives greater consideration to existing cardiometabolic morbidities than to the prescription record.

An international multidisciplinary expert panel recently achieved consensus on a list of 9 clinically important prescribing cascades specifically relevant to older adults, called ThinkCascades.[25,26] These 9 prescribing cascades were selected from an inventory of possible cascades identified by a literature review and group discussion. To our knowledge, no studies thus far have validated this explicit list in a national sample of older adults. We sought to assess the prevalence of ThinkCascades among community-dwelling adults aged 65 years or older living in Ireland and to explore potential effect modifiers through stratified analyses.

METHODS

Reporting in this study has been guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Supplemental Table 1).[27] Ethical approval for the study was obtained from the Clinical Research Ethics Committee of University College Cork (ECM 4 (u) 06/20/2023).

Study Design

We conducted a retrospective observational cohort study with a case-only design, with separate analyses examining additional negative control populations. Prescription sequence symmetry analysis (PSSA) was performed. This analysis includes incident users of both medications of interest, namely, the medication hypothesized to cause the ADR (index medication) and the medication used to treat the ADR (marker medication). By examining only those individuals who receive both the index and marker drugs, time-invariant characteristics (eg, age and sex) are controlled for.

PSSA compares the ratio of those who experience the sequence of index medication being prescribed followed by the marker medication, with those who experience the opposite sequence. Risk is estimated by first calculating a crude sequence ratio, by dividing the number of individuals who receive the index to marker medication sequence (numerator) by the number of individuals who receive the marker to index medication sequence (denominator), which is then adjusted for secular prescribing trends. This adjusted sequence ratio (aSR) is calculated by dividing the crude sequence ratio by the null-effect sequence ratio (SR_0), which represents the background trend of prescribing of the outcome medication. Further detail on the calculation of this ratio is provided in Supplemental Appendix 1. A symmetry plot—a histogram depicting the number of individuals who initiate the marker medication either before or after the index medication, where the histogram is centered on the date of index medication initiation—gives an indication of any observed association. Table 1 provides information on interpreting PSSA results.

Data Source

We used data from an Irish national database of prescriptions dispensed in primary care. Ireland has a mixed public-private primary care system, with many medications reimbursed under several community drug schemes operated by the Health Service Executive Primary Care Reimbursement Service. We analyzed data from the General Medical Services (GMS) scheme, which covers more than 60% of adults aged 65 years or older and approximately 80% of those aged 75 years or older in Ireland.[28] This scheme provides access to covered prescriptions via a low copay (varying by age, capped monthly per household). Eligibility for the GMS scheme uses income-related means testing, with a higher threshold for those aged 70 years or older. The data contain an individual identifier, participant sex and age group, and information about each medication including its name, World Health Organization Anatomic Therapeutic Chemical (ATC) code, strength, date of dispensing, and quantity dispensed.

Study Population

We included in our study adult patients aged 65 years or older defined as incident users of both medications in each ThinkCascades dyad during the period January 1, 2018 to December 31, 2020. To exclude prevalent users, we applied a 1-year run-in period (January 1, 2017 to December 31, 2017). Any patient who had a prescription dispensed for the first time from January 1, 2018 was thus considered an incident user. Patients whose first dispensing of both the index and marker medication occurred on the same day were excluded from analysis as it was not possible to determine the sequence of initiation for this group.

We examined 9 ThinkCascades dyads (index and marker medication pairs) representing 9 unique populations. For each dyad, levothyroxine (ATC code H03AA1) was examined as a negative control marker medication in separate analyses. Negative controls represent index and marker medication pairs for which no association is expected; analyzing these controls helps identify potential sources of bias. Levothyroxine was selected based on the assumption that health care attendances prior to initiation would be broadly similar to those for each ADR of interest. With this approach, an additional 9 control populations were generated for each negative control dyad examined.

Exposure and Outcomes of Interest

Exposure was defined as the first dispensing of the index medication within each ThinkCascades dyad (Supplemental Table 2). The primary outcome was defined as the first dispensing of the marker medication in each dyad. For some dyads, more

than one drug class was examined as the exposure and for others, more than one drug class was examined as the outcome. The primary exposure window was set at 365 days to allow sufficient time for the ADR to occur while minimizing time-varying confounding due to disease progression or temporal prescribing trends, in line with previous literature.[29]

Analytic Plan

Primary Analysis

PSSA was conducted to calculate a crude SR for each ThinkCascades dyad. We calculated the null-effect sequence ratio (SR_0) based on the method described by Tsiropoulos et al (Supplemental Appendix 1).[30] This ratio represents the background rate of prescribing of the outcome medication.

The prevalence of each dyad was estimated by dividing the number of patients who received the sequence of index to marker medication (numerator) by the total number of index medication initiators (denominator) during the study period.

We calculated a trend-adjusted sequence difference (Δ_0), an estimate of the number of attributable cases in the population, in accordance with literature recommendations.[31] The sequence difference represents the difference between the number of index-marker sequences and the number of marker-index sequences. This sequence difference can be biased if not adjusted for the SR_0, the background rate of prescribing of the outcome medication. Further detail on the calculation of Δ_0 is provided in Supplemental Appendix 1.

The relative incidence of each ThinkCascades was estimated by comparing the excess of patients who received the index medication before the marker medication to the total number of incident index medication users within the study period. We adjusted the relative incidence to obtain an estimate of the proportion of patients with the index medication who received the prescribing cascade, as recommended in the literature.[29]

The number needed to harm until time *t* was calculated as the reciprocal of the excess risk of the prescribing cascade among those exposed to the index medication. This number represents the number of index medication initiators who need to be treated for 1 additional individual to initiate the marker medication and thus be harmed.[29]

We conducted analysis was using R version 4.4.0 (R Foundation for Statistical Computing).[32]

Stratified and Sensitivity Analyses

We examined several explanatory variables—sex, age group (65-69 years, 70-74 years, and ≥75 years), and individual index medication—as potential effect modifiers in stratified analyses. Sensitivity analyses examined multiple shorter exposure windows (180, 90, 60, and 30 days) to reduce within-person time-varying confounding. Additionally, we repeated the primary analysis with a shorter run-in period, guided by the waiting time distribution plots for each dyad (Supplemental Figures 1-9). Analyses were repeated with a 6-month run-in period (from January 1, 2017 to June 30, 2017) for all, except the nonsteroidal anti-inflammatory drug (NSAID) to antihypertensive cascade, for which we used a 9-month run-in period (January 1, 2017 to September 30, 2017).

RESULTS

Population Characteristics

A total of 46,678,010 index and marker medication prescriptions were dispensed among 533,464 older adults from 2017 to 2020, of which 35,273,662 prescriptions were dispensed among 498,937 older adults during the observation period of 2018 to 2020. The number of incident users of ThinkCascades index medications ranged from 17,078 (α_1-receptor blockers) to 137,280 (NSAIDs).

Table 2 summarizes the characteristics of each of the 9 dyad populations. Most dyad populations had a higher proportion of females except for the α_1-receptor blocker to vestibular sedative dyad, which was predominantly male, as expected, because of the clinical indication for the former drug class. The population was oldest for antidementia medication dyads and youngest for the NSAID to antihypertensive dyad.

Primary Analysis

Numerical results of the PSSA for the 9 ThinkCascades dyads are shown in Table 3, with the corresponding forest plot shown in Figure 1. The PSSA symmetry plots for the dyads are shown in Figure 2.

Significant positive associations were identified for 5 ThinkCascades dyads when examined at a medication class level, indicating an increased likelihood of marker medication initiation following index medication initiation (Table 3 and Figure 1). The 5 dyads were (1) CCB leading to diuretic prescribing; (2) antipsychotic leading to antiparkinsonian agent prescribing; (3) benzodiazepine leading to antipsychotic

Table 1. Interpretation of PSSA Symmetry Plots and aSR Values

Symmetry observed[a]	Likelihood	aSR value	Interpretation
Positive asymmetry	Patient is more likely to receive the index medication before the marker medication	> 1	Potential prescribing cascade
Symmetric	Patient is equally likely to receive the index medication before vs after the marker medication	CI crosses 1	No association
Negative asymmetry	Patient is more likely to receive the marker medication before the index medication	< 1	Potential prescribing cascade avoidance

aSR = adjusted sequence ratio; PSSA = prescription sequence symmetry analysis.

[a] Data plotted as a histogram of the number of users who initiate the marker medication either before or after the index medication during the observation window, with the histogram centered on the date of index medication initiation.

prescribing; (4) selective serotonin reuptake inhibitor (SSRI) or selective norepinephrine reuptake inhibitor (SNRI) leading to sleep agent prescribing; and (5) α_1-receptor blocker leading to vestibular sedative prescribing.

Significant negative associations were identified for 3 ThinkCascades dyads, indicating a decreased likelihood of marker medication initiation following index medication initiation (Table 3 and Figure 1). These dyads were (1) diuretic to overactive bladder medication; (2) benzodiazepine to antidementia agent; and (3) NSAID to antihypertensive.

There was no significant association for the remaining ThinkCascades dyad—urinary anticholinergic to antidementia agent—indicating neither an increased nor a decreased likelihood of marker medication initiation following index medication initiation, with the confidence interval for the aSR crossing 1 (Table 3 and Figure 1).

The prevalence of each ThinkCascades dyad, expressed as the proportion of incident index medication users who experienced the index to marker medication sequence order, ranged from 0.4% to 3.2% across the 5 significant positive signals identified (Table 3).

The adjusted sequence difference (Δ_0)—the difference between the number of index-marker sequences and the number of marker-index sequences—ranged from 46 for the antipsychotic to antiparkinsonian agent dyad to 884 for the CCB to diuretic dyad (Table 3).

The number needed to harm until time *t*—the number of index medication initiators who need to be treated for 1 additional individual to initiate the marker medication and thus be harmed—ranged from 78 for the CCB to diuretic dyad to 1,644 for the antipsychotic to antiparkinsonian agent dyad (Table 3).

Stratified and Sensitivity Analyses

The magnitude of the aSR varied by sex, age, and individual index medication (Supplemental Tables 3-12). For example,

Table 2. Descriptive Statistics for ThinkCascades Dyads for Incident Users of the Index Medication and Incident Users of Both Index and Marker Medications

		Sex		Age group		
Dyad and incident user group	Sample size, n	Male, No. (%)	Female, No. (%)	65-69 years, No. (%)	70-74 years, No. (%)	≥75 years, No. (%)
CCB to diuretic						
CCB only	66,903	28,351 (42.4)	38,552 (57.6)	19,415 (29.0)	30,556 (45.7)	16,932 (25.3)
CCB and diuretic	2,784	1,113 (40.0)	1,671 (60.0)	611 (21.9)	633 (22.7)	1,540 (55.3)
Diuretic to overactive bladder agent						
Diuretic only	66,198	29,174 (44.1)	37,024 (55.9)	12,803 (19.3)	40,129 (60.6)	13,266 (20.0)
Diuretic and overactive bladder agent	1,012	394 (38.9)	618 (61.1)	194 (19.2)	153 (15.1)	665 (65.7)
Antipsychotic to antiparkinsonian agent						
Antipsychotic only	70,976	27,133 (38.2)	43,843 (61.8)	13,918 (19.6)	13,336 (18.8)	43,722 (61.6)
Antipsychotic and antiparkinsonian agent	502	225 (44.8)	277 (55.2)	113 (22.5)	96 (19.1)	293 (58.4)
Benzodiazepine to antidementia agent						
Benzodiazepine only	82,874	32,690 (39.4)	50,184 (60.6)	21,976 (26.5)	17,698 (21.4)	43,200 (52.1)
Benzodiazepine and antidementia agent	948	418 (44.1)	530 (55.9)	59 (6.2)	119 (12.6)	770 (81.2)
Benzodiazepine to antipsychotic						
Benzodiazepine only	82,874	32,690 (39.4)	50,184 (60.6)	21,976 (26.5)	17,698 (21.4)	43,200 (52.1)
Benzodiazepine and antipsychotic	5,038	2,056 (40.8)	2,982 (59.2)	1,017 (20.2)	855 (17.0)	3,166 (62.8)
SSRI/SNRI to sleep agent						
SSRI/SNRI only	45,859	16,541 (36.1)	29,318 (63.9)	16,558 (36.1)	9,276 (20.2)	20,025 (43.7)
SSRI/SNRI and sleep agent	1,867	689 (36.9)	1,178 (63.1)	531 (28.4)	382 (20.5)	954 (51.1)
NSAID to antihypertensive						
NSAID only	137,280	57,620 (42.0)	79,660 (58.0)	42,873 (31.2)	35,546 (25.9)	58,861 (42.9)
NSAID and antihypertensive	8,127	3,440 (42.3)	4,687 (57.7)	3,956 (48.7)	1,989 (24.5)	2,182 (26.8)
Urinary anticholinergic to antidementia agent						
Urinary anticholinergic only	17,078	6,163 (36.1)	10,915 (63.9)	4,190 (24.5)	3,706 (21.7)	9,182 (53.8)
Urinary anticholinergic and antidementia agent	161	63 (39.1)	98 (60.9)	8 (5.0)	31 (19.3)	122 (75.8)
α_1-Receptor blocker to vestibular sedative						
α_1-Receptor blocker	25,980	25,310 (97.4)	670 (2.6)	6,053 (23.3)	6,779 (26.1)	13,148 (50.6)
α_1-Receptor blocker and vestibular sedative	1,333	1,282 (96.2)	51 (3.8)	333 (25.0)	318 (23.9)	682 (51.2)

CCB = calcium channel blocker; NSAID = nonsteroidal anti-inflammatory drug; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

the association for the antipsychotic to antiparkinsonian dyad was not consistent across all antipsychotics and was seen only for olanzapine (aSR = 2.90; 95% CI, 1.38-6.47) and risperidone (aSR = 3.95; 95% CI, 1.68-10.33) (Supplemental Table 6). For individual CCBs, amlodipine, lercanidipine, and diltiazem showed positive prescribing cascade signals, whereas nifedipine, felodipine, and verapamil did not (Table 4).

The strength of identified associations varied as the observation window was reduced (Supplemental Table 13). Four of the 5 significant associations in the primary analysis using a 1-year run-in period persisted in analyses using shorter run-in periods (Supplemental Table 14).

The negative control analyses for each dyad using levothyroxine resulted in either a significant negative association or no association (Supplemental Tables 3-12).

DISCUSSION

Principal Findings

To our knowledge, this study is the first describing the prevalence of ThinkCascades in a national sample of older adults. At a medication class level, we identified 4 potential prescribing cascades. A fifth potential cascade, antipsychotics leading to antiparkinsonian agent use, was significant in the primary analysis but not in the sensitivity analyses; however, analyses stratified by individual medications did identify significant positive associations for 2 drugs in the antipsychotic class (olanzapine and risperidone). Overall, these 5 potential prescribing cascades were relatively uncommon, but nonetheless, the numbers needed to harm merit clinical consideration and suggest that these cascades are important sources of avoidable potential medication-related harm.

Comparison With Other Studies

Here we report that the CCB to diuretic cascade previously identified in the United States, Canada, and Taiwan[5-8,33-35] also occurs within the European context. The magnitude of the association corresponds with that in prior US studies focused solely on dihydropyridine CCBs.[6,7,9,35] Our analyses expand on information for this cascade, additionally exploring the associations for nondihydropyridine CCBs. In contrast to prior studies that used a dichotomous age cut point of

Table 3. Numerical Results of PSSA for ThinkCascades Dyads

Dyad	Prevalence, %	cSR (95% CI)	SR_0	aSR (95% CI)	Δ_0	Excess Risk (95% CI)[a]	$NNTH_t$ (95% CI)
CCB to diuretic	2.6	**1.74 (1.61-1.88)**	0.90	**1.93 (1.79-2.09)**	884	0.013 (0.012 to 0.014)	78 (73 to 86)
Diuretic to overactive bladder agent	0.6	0.70 (0.62-0.79)	0.86	0.81 (0.72-0.92)	−106	−0.001 (−0.002 to −0.001)	−677 (−1,826 to −408)
Antipsychotic to antiparkinsonian agent	0.4	1.07 (0.90-1.27)	0.89	**1.20 (1.00-1.43)**	46	<0.001 (0 to 0.001)	1,644 (911 to ∞)
Benzodiazepine to antidementia agent	0.4	0.59 (0.52-0.67)	0.89	0.66 (0.58-0.75)	−194	−0.002 (−0.003 to −0.001)	−458 (−708 to −326)
Benzodiazepine to antipsychotic	3.2	**1.09 (1.03-1.15)**	0.95	**1.15 (1.08-1.21)**	351	0.004 (0.002 to 0.006)	242 (182 to 426)
SSRI/SNRI to sleep agent[b]	2.5	**1.57 (1.43-1.72)**	1.02	**1.54 (1.40-1.69)**	397	0.009 (0.007 to 0.010)	115 (99 to 141)
NSAID to antihypertensive	1.6	0.39 (0.37-0.40)	0.92	0.42 (0.40- 0.44)	−3,319	−0.023 (−0.025 to −0.021)	−44 (−48 to −41)
Urinary anticholinergic to antidementia agent	0.5	1.15 (0.84-1.56)	0.89	1.29 (0.94-1.76)	20	0.001 (<−0.001 to 0.002)	883 (Not estimable[c])
α_1-Receptor blocker to vestibular sedative[d]	3.0	**1.45 (1.30-1.62)**	0.89	**1.63 (1.46-1.81)**	319	0.012 (0.010 to 0.014)	85 (74 to 105)

aSR = adjusted sequence ratio; CCB = calcium channel blocker; cSR = crude sequence ratio; $NNTH_t$ = number needed to harm until time *t*; NSAID = nonsteroidal anti-inflammatory drug; PSSA = prescription sequence symmetry analysis; SNRI = selective norepinephrine reuptake inhibitor; SR = sequence ratio; SR_0 = null effect sequence ratio; SSRI = selective serotonin reuptake inhibitor; Δ_0 = trend-adjusted sequence difference.

Notes: Analysis used prescriptions dispensed during 2018-2020, a 365-day observation window, and 1-year run-in period (2017). Bold denotes significant positive SRs. Raw numbers of incident users are given in Supplemental Table 3 and Supplemental Tables 5 through 12. See Table 1 for information on interpreting aSR values.

[a] Adjusted excess risk of marker medication initiation among those who initiated the index medication.
[b] Sleep agents: benzodiazepines, benzodiazepine receptor antagonists, sedating antidepressants, promethazine, clonazepam.
[c] The 95% CI was not estimable because the CI for the aSR crosses 1 and consequently for excess risk crosses 0.
[d] Vestibular sedatives: betahistine, promethazine, benzodiazepines.

65 years, we provide a more granular assessment of age as a potential effect modifier through stratified analyses using 3 age groups.

For the potential prescribing cascade of antipsychotic to antiparkinsonian, the identified prevalence (0.4%) corresponds with prior estimates of concomitant use reported in Australia, Italy, and the United States (0.2% to 0.8%).[36-38] Asian PSSA studies have reported conflicting results on whether the risk of incident antiparkinsonian medication use was greater with typical or atypical antipsychotics.[10-13,39]

Importantly, we report on potential prescribing cascades not previously quantified within the literature, such as SSRI- or SNRI-induced insomnia leading to sleep agent initiation. To date, only a small number of case reports have documented benzodiazepine-induced agitation being treated with antipsychotics.[40,41] Similarly, our findings indicate that a potential prescribing cascade signal does occur for α_1-receptor blocker–induced dizziness, in contrast to findings of a prior study.[42]

Three ThinkCascades dyads displayed significant negative associations, possibly suggesting that prescribers are aware of and intentionally avoid these potential prescribing cascades. Qualitative studies of general practitioners acknowledge the hypertensive and nephrotoxic risks associated with NSAIDs, particularly in older adults, and the need for cautious prescribing.[43-45] Alternatively, these significant negative associations may indicate a potential prescribing cascade is operating in the opposite direction. For example, antidementia medication initiators may be more likely to initiate benzodiazepines, perhaps to address behavioral and psychological symptoms of dementia.

Implications for Clinical Practice, Research, and Policy

Prescribing cascades are difficult for patients and prescribers to identify,[46,47] and identification may be compounded in older adults, among whom ADR symptoms often manifest nonspecifically and with multiple potential etiologies.[22] Efforts to increase awareness of prescribing cascades may therefore support clinical decision making. Further studies are warranted to identify whether effect modification by age, sex, and individual medication can be replicated. Nevertheless, prescribing cascades are challenging to identify and confirm, and may require clinical process mapping to untangle the medication initiation sequence.[46,47]

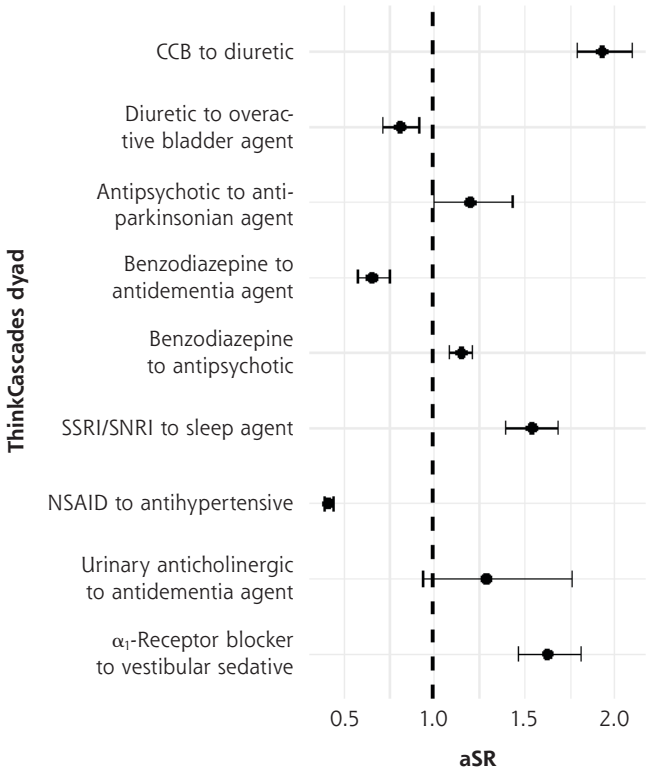
Further real-world studies of ThinkCascades are required to ascertain the generalizability of each dyad internationally. We found signals for only 5 ThinkCascades, with 4 supported by sensitivity analyses. Evidence to date suggests both within- and between-country variation in the detection of significant associations for several drug pairs.[48-50] Challenges persist in identification of prescribing cascades using routine administrative data. There is a paucity of research, however, confirming true prescribing cascades through data linkage or patient medical record review. In a US study of 5,312 patients who initiated a CCB, 64 patients were identified as having a potential prescribing cascade over 360 days of follow-up.[35] Following corresponding medical record review, only 35 (54.7%) of that group were determined to represent true prescribing cascades. Future research efforts should focus on ascertaining the prevalence of true prescribing cascades across different dyads.

An increasing number of medications in older people is strongly associated with an increased risk of medication-related harm and serious ADRs.[20,51] For clinicians, considering ADRs as part of the differential in patients presenting with new symptoms in primary care is an important step in identifying and mitigating the risk of medication-related harm.[19] Furthermore, identifying prescribing cascades and deprescribing when appropriate offers potential to reduce pill counts and associated treatment burden for patients.

Strengths and Limitations

The PSSA methodology we used is a powerful tool to detect potential prescribing cascade signals recommended by ThinkCascades. This study is the first to our knowledge describing the prevalence of ThinkCascades in a national sample of older adults, thereby providing a baseline for comparison with other countries. Including negative controls, exploring

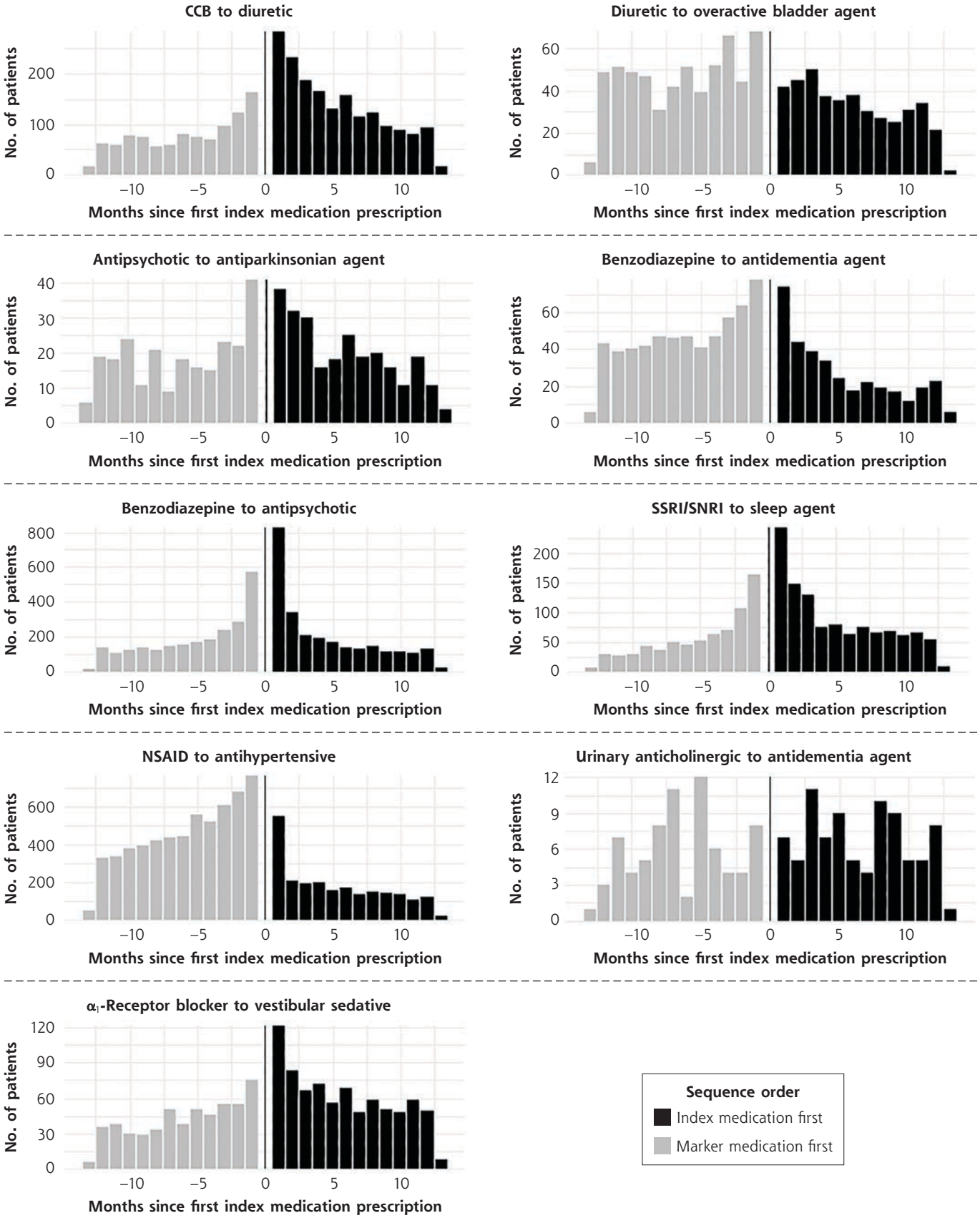
Figure 1. Forest Plot of ThinkCascades Dyads



aSR = adjusted sequence ratio; CCB = calcium channel blocker; NSAID = nonsteroidal anti-inflammatory drug; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Notes: Analysis used prescriptions dispensed during 2018-2020, a 365-day observation window, and a 1-year run-in period (2017). Bars indicate 95% CIs.

Figure 2. PSSA Symmetry Plots for ThinkCascades Dyads



CCB = calcium channel blocker; NSAID = nonsteroidal anti-inflammatory drug; PSSA = prescription sequence symmetry analysis; SNRI = selective norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

Notes: Analysis used prescriptions dispensed during 2018-2020, a 365-day observation window, and a 1-year run-in period (2017). See Table 1 for information on interpreting the plots.

Table 4. Stratified PSSA for the Calcium Channel Blocker to Diuretic Prescribing Cascade

Calcium channel blocker	cSR (95% CI)	SR_0	aSR (95% CI)	Δ_0	Excess risk (95% CI)[a]	$NNTH_t$ (95% CI)
Overall[b]	**1.74 (1.61-1.88)**	0.90	**1.93 (1.79-2.09)**	884	0.013 (0.012 to 0.014)	78 (73 to 86)
Amlodipine	**2.02 (1.82-2.24)**	0.90	**2.23 (2.01-2.48)**	600	0.015 (0.013 to 0.016)	69 (63 to 75)
Felodipine	1.24 (0.73-2.11)	0.91	1.36 (0.81-2.32)	9	0.010 (−0.008 to 0.021)	104 (Not estimable[c])
Nifedipine	1.22 (0.51-2.98)	0.90	1.35 (0.56-3.30)	3	0.004 (−0.013 to 0.012)	226 (Not estimable[c])
Lercanidipine	**1.47 (1.30-1.67)**	0.90	**1.63 (1.44-1.85)**	246	0.010 (0.008 to 0.012)	99 (83 to 125)
Verapamil	1.12 (0.65-1.96)	0.90	1.25 (0.73-2.18)	6	0.006 (−0.011 to 0.015)	176 (Not estimable[c])
Diltiazem	**1.84 (1.06-3.26)**	0.91	**2.04 (1.18-3.60)**	18	0.014 (0.004 to 0.020)	69 (49 to 232)
Negative control[d]	0.59 (0.50-0.70)	0.95	0.62 (0.52-0.73)	−136	−0.003 (−0.005 to −0.002)	−301 (−498 to −200)

aSR = adjusted sequence ratio; ATC = Anatomic Therapeutic Chemical; cSR = crude sequence ratio; $NNTH_t$ = number needed to harm until time *t*; PSSA = prescription sequence symmetry analysis; SR = sequence ratio; SR_0 = null effect sequence ratio; Δ_0 = trend-adjusted sequence difference.

Note: Analysis used prescriptions dispensed during 2018-2020, a 365-day observation window, and a 1-year run-in period (2017). Bold denotes significant positive SRs. Raw numbers of incident users are given in Supplemental Table 3.

[a] Adjusted excess risk of marker medication initiation among those who initiated the index medication.
[b] Exposure was initiation of any calcium channel blocker (ATC code C08: amlodipine, felodipine, nifedipine, lercanidipine, verapamil, or diltiazem, excluding combinations); outcome was initiation of any diuretic (ATC code C03).
[c] The 95% CI was not estimable because the CI for the aSR crosses 1 and consequently for excess risk crosses 0.
[d] Exposure was initiation of any calcium channel blocker (as above); outcome was initiation of levothyroxine (ATC code H03AA1).

multiple observation windows, and reducing the run-in period supports the robustness of our study findings, and stratification by sex, age, and individual index medication provides further clinical context.

There are several limitations. PSSA is observational in nature and cannot definitively determine whether the marker medication was prescribed to treat the adverse effects of the index medication. Significant positive associations may have alternative explanations such as protopathic bias or disease progression.

The data examined do not include medications dispensed on private/non-GMS prescriptions or over-the-counter medications. Additionally, prevalent users who obtained GMS eligibility after the run-in period could be misclassified as incident users. GMS data overrepresent older adults and those more socioeconomically deprived compared with the general population. Nevertheless, more than 60% of adults aged 65 years or older and approximately 80% of those aged 75 years or older have GMS coverage.[28] Finally, a lack of diagnosis or morbidity codes prevented the exclusion of patients having diagnoses with a clinical indication for the marker medication before index medication initiation.

Conclusions

Prescribing cascades are an underresearched area of potentially inappropriate prescribing. Our study details the prevalence of 9 clinically relevant potential prescribing cascades, ThinkCascades, in a national prescription database. Potential prescribing cascades were relatively uncommon among older Irish adults but may represent important sources of avoidable potential medication-related harm. Several cascades were less likely to occur in our population and may suggest heightened awareness among prescribers of these potential cascades.

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Author information: Department of General Practice, School of Medicine, University College Cork, Cork, Ireland (Doherty, Wallace); Clinical Pharmacology, Pharmacy and Environmental Medicine, Department of Public Health, University of Southern Denmark, Odense, Denmark (Lund); School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, Dublin, Ireland (Moriarty); Data Science Centre, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, Dublin, Ireland (Boland); Department of Public Health and Epidemiology, School of Population Health, Royal College of Surgeons (RCSI) University of Medicine and Health Sciences, Dublin, Ireland (Clyne); Department of General Practice, Royal College of Surgeons in Ireland (RCSI) University of Medicine and Health Sciences, Dublin, Ireland (Fahey); Department of Age-related Healthcare, Tallaght University Hospital, Dublin, Ireland (Kennelly); Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland (Kennelly); Department of Medicine (Geriatrics), School of Medicine, University College Cork, Cork, Ireland (O'Mahony); Geriatric Medicine, Cork University Hospital, Cork, Ireland (O'Mahony)

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Supplemental materials

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