Prescribing cascades in community-dwelling adults: A systematic review

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Abstract
The misattribution of an adverse drug reaction (ADR) as a symptom or illness can lead to the prescribing of additional medication, referred to as a prescribing cascade. The aim of this systematic review is to identify published prescribing cascades in community-dwelling adults. A systematic review was reported in line with the PRISMA guidelines and pre-registered with PROSPERO. Electronic databases (Medline [Ovid], EMBASE, PsycINFO, CINAHL, Cochrane Library) and grey literature sources were searched. Inclusion criteria: community-dwelling adults; risk-prescription medication; outcomes-initiation of new medicine to “treat” or reduce ADR risk; study type-cohort, cross-sectional, case-control, and case-series studies. Title/abstract screening, full-text screening, data extraction, and methodological quality assessment were conducted independently in duplicate. A narrative synthesis was conducted. A total of 101 studies (reported in 103 publications) were included. Study sample sizes ranged from 126 to 11,593,989 participants and 15 studies examined older adults specifically (≥60 years). Seventy-eight of 101 studies reported a potential prescribing cascade including calcium channel blockers to loop diuretic (n = 5), amiodarone to levothyroxine (n = 5), inhaled corticosteroid to topical antifungal (n = 4), antipsychotic to anti-Parkinson drug (n = 4), and acetylcholinesterase inhibitor to urinary incontinence drugs (n = 4). Identified prescribing cascades occurred within three months to one year following initial medication. Methodological quality varied across included studies. Prescribing cascades occur for a broad range of medications. ADRs should be included in the differential diagnosis for patients presenting with new symptoms, particularly older adults and those who started a new medication in the preceding 12 months.

KEYWORDS
appropriate prescribing, community-dwelling adults, prescribing cascades, systematic review

Abbreviations: ADR, adverse drug reaction; ATC, Anatomical Therapeutic Classification; CCB, calcium channel blocker; ED, Emergency Departments; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis; TRIP, Turning Research Into Practice.

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1 | BACKGROUND

A prescribing cascade occurs when a medication is used to treat or prevent the adverse effects of another medication. An unintentional prescribing cascade occurs when the adverse drug reaction (ADR) is misinterpreted as a new medical condition, leading to the prescription of new medication to treat the emerging symptoms. For example, calcium channel blocker (CCB) induced lower extremity oedema may be misinterpreted as a sign of congestive heart failure and result in the inappropriate prescribing of a loop diuretic to alleviate the oedema instead of simply switching the CCB to an alternative class antihypertensive agent. Intentional prescribing cascades occur when the ADR is recognised and a subsequent medication is prescribed to combat this ADR either via treatment of the ADR or prevention of it in the first instance. Prescribing cascades can be further characterised as either appropriate (potential benefits > risks), or inappropriate (risks > potential benefits). Furthermore, this characterisation of appropriateness is a dynamic entity; an appropriate prescribing cascade can become inappropriate over time, particularly should the clinical circumstances of the patient change.

It is not clear what drives prescribing cascades. Older adults may be more vulnerable due to the nonspecific nature of ADR symptoms in older adults, e.g. falls, fatigue or constipation, all of which have multiple potential causes. Multimorbidity, which is more common in older adults, may also make the identification of new onset ADRs more challenging. However, the failure to correctly identify an ADR and the resultant prescribing cascade compounds the risk for medication-related harm.

To date prescribing cascades have remained under-researched. A previous scoping review identified only 10 original investigations and seven case reports that examined prescribing cascades. In order to optimise prescribing, it is vital that clinically relevant prescribing cascades that commonly occur in practice are identified. The objective of this systematic review was to identify published prescribing cascades in community-dwelling adults.

2 | MATERIALS AND METHODS

2.1 | Search protocol

The study protocol was previously published and pre-registered with PROSPERO [CRD42021243163]. This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. (eTable 1 and eTable 2 in Appendix S1).

2.2 | Search strategy

Searches were conducted in the following databases: Medline (Ovid), EMBASE, PsycInfo, CINAHL and the Cochrane Library. Searches were initially conducted from inception to March 2021 and updated in February 2022. The search strategy (eBox 1 in Appendix S1) was developed in consultation with an experienced librarian. No restrictions were placed on language or publication year. Grey literature database searches were conducted in MedNar, Dart Europe, Open Grey, and the Turning Research Into Practice (TRIP) databases using keyword searches. Forwards and backwards citation searching of articles selected for full text review was also conducted. Retrieved results were exported to EndNote X9 prior to screening and study selection using Covidence® systematic review management system. Following duplicates removal, titles and abstracts were independently screened by two reviewers (AD and EW, OC or FS) according to inclusion criteria. Disagreements were managed by consensus. Additional information was sought from study authors where necessary.

Studies were included if they met the following criteria:

1. Population: community-dwelling adults (≥18 years).
2. Risk: prescription of medication that had the potential to cause an ADR that resulted in the prescription of further medication.
3. Outcome: prescribing cascade defined as the initiation of a new medication to ‘treat’ an ADR (unintentional cascade) or to reduce the risk of an ADR (intentional cascade).
4. Study type: prospective or retrospective cohort, cross-sectional, case-crossover, case-control or case-series studies.
5. Setting: primary care and community settings, including ambulatory care.

2.2.1 | Exclusion criteria

The following studies were excluded:

1. Population of interest <18 years;
2. Studies conducted solely in nursing homes, residential care, inpatient settings or Emergency Departments (ED);
3. Case reports

2.3 | Data extraction and quality assessment

Data extraction was conducted by two independent reviewers (AD and EW, OC or FS) using a standardised Microsoft Excel proforma. (see eBox 2, Appendix S1). The methodological quality of included publications was independently performed in duplicate (AD and EW, OC or FS) using the appropriate JBI- Critical Appraisal checklist (eBox 3, Appendix S1). Data synthesis was conducted using a narrative synthesis. Alluvial plots of drug pair combinations were created, using R-Studio 2021.09.2 statistical software using the ggalluvial package, to identify the drug-pair combinations examined and to summarise the overall quantitative association reported.
3 | RESULTS

3.1 | Study identification

The study identification flow diagram is presented in Figure 1. A total of 103 publications relating to 101 studies met the inclusion criteria. Three publications included data from the same study relating to updated data collection time periods (2000–2006; 2000–2010; and 2000–2012). Thus, only the final study publication, which contained the entire data collection period, was included in the narrative synthesis.

3.2 | Study population demographics

Seventy-nine studies presented study participants demographics, of which 15 specifically examined older adults (≥60 years), with different age-related thresholds (e.g., ≥60; ≥65; ≥66 years) used across studies. Thirteen studies reported analyses stratified by age, with most studies (n = 88) being retrospective cohort studies, of which 5 specifically incorporated a case–control study within the study design. Five were case–control studies, and one that conducted a preliminary cross-sectional study. Two broad range of medication types were examined as potentially precipitating a prescribing cascade (see Table 1 and column 1, Figure 2A). Ninety-four studies were hypothesis-driven or examined a predefined list of medications (Table 2 and Figure 2A). Seven studies conducting exploratory analyses to identify new signals of potential prescribing cascades are not represented in

3.4 | Initial medication(s) prescribed to patient

All studies used routine data (health insurance claims, prescription dispensing, clinical databases, national health surveys and pharmacovigilance data). In total, 83 studies examined dispensed prescriptions whereas 18 studies examined prescribed medications (see eTable 3, Appendix S1).

Of 101 studies, 62 used prescription sequence symmetry analysis (PSSA) to determine the ratio of participants who initiated two medications in both possible sequences (i.e., Drug A → Drug B vs. Drug B → Drug A), with the majority (n = 52) adjusting for prescribing trends. Several studies reported stratified results by dosage, concomitant medication use or polypharmacy, duration, comorbidity, race and nursing home residence. For other studies, analyses were adjusted by age, sex, dose, nursing home residence, concomitant medication or polypharmacy, with some studies conducting adjusted analyses but not reporting the independent association of these covariates.

Length of follow up ranged from one month to seven years, with the majority over one year (n = 33 studies).
TABLE 1 Primary results of included studies by ATC pharmacological classification (n = 101)

| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|---------------|-------------------|---------------------------------------------------------------|
| **Alimentary tract and metabolism** | | | | |
| Adimadhyam (2019)47 | Sodium/Glucose cotransporter-2 inhibitors (SGLT2-I) | Genital mycotic infections | Antifungal | PSSA SGLT2-I → Antifungal ± 365 days aSR 1.24 (95%CI 1.20–1.28) |
| Avorn (1995)20 | Metoclopramide | Extrapyramidal symptoms (EPS) | Anti-Parkinson drug (APD) | Metoclopramide → APD (<90 days) aOR 3.04 (95%CI 2.22–4.17) |
| Gadzhanova (2017)88 | SGLT2-I Dipeptidyl peptidase 4 inhibitor (DPP4-I) | Urinary or genital infections | Trimethoprim Nitrofurantoin Norfloxacin | SGLT2-I users (3.6%) compared to DPP4-I users (4.9%), aHR 0.90 (95%CI 0.66–1.24) Risk of UTI (<6 months) SGLT2-I users (2.9%) compared with DPP4-I users (0.9%), aHR 3.50 (95%CI 1.95–5.89) |
| Janetzki (2021)99 | PPI | Development or exacerbation of chronic obstructive pulmonary disease (COPD) | Long-acting muscarinic antagonist (LAMA) or long-acting beta-2 agonist (LABA) listed for the treatment of COPD | PSSA: PPI → LAMA/LABA ± 1 year  Omeprazole: aSR = 1.29 (95%CI 1.22–1.36)  Esomperazole: aSR = 1.25 (95%CI 1.22–1.29)  Rabeprazole: aSR = 1.15 (95%CI 1.08–1.21)  Pantoprazole: aSR = 1.08 (95%CI 1.05–1.12)  Lansoprazole: aSR = 1.08 (95%CI 0.96–1.22) |
| Lund (2021)111 | SGLT2-I Glucagon-like peptide-1 receptor agonists (GLP1-RA) | Gout | Any uric acid lowering therapy, colchicine or first hospital diagnosis of gout (composite) | Risk of gout (<3 years): intention to treat analysis HR: 0.58 (0.44 to 0.75) [GLP1-RA as referent] Risk of gout (<3 years): per-protocol analysis HR: 0.48 (0.33 to 0.70) [GLP1-RA as referent] PSSA: SGLT2-I → Gout ± 365 days aSR 0.63 (95%CI 0.47–0.84) PSSA: GLP1-RA → Outcome ± 365 days aSR 0.94 (95%CI 0.78–1.13) |
| Park (2018)32 | PPI Histamine 2 receptor antagonist (H2RA) | Dementia | Anti-dementia medication (secondary outcome) | PSSA: PPI → Anti-dementia medication ± 3 years aSR 1.38 (95%CI 1.28–1.48); n = 3025 PSSA: H2RA → Anti-dementia medication ± 3 years aSR 2.35 (2.13–2.59); n = 2308 |
| Roughead (2015)96 | Pioglitazone Rosiglitazone | Oedema | Furosemide | PSSA: Rosiglitazone → Furosemide ± 1 year Pooled (Australia and Canada): aSR 1.15 (95%CI 1.58–1.72) Pooled (Asia): aSR 1.21 (95%CI 1.01–1.45) PSSA: Pioglitazone → Furosemide ± 1 year Pooled (Australia and Canada): aSR 1.47 (95%CI 1.41–1.91) Pooled (Asia): aSR 1.11 (95%CI 0.86–1.32) |
TABLE 1 (Continued)

| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|---------------|-------------------|---------------------------------------------------------------|
| **Blood and blood forming organs** | | | | |
| Roughhead (2016)⁹⁵ | PPI | Clostridium difficile infection | Oral vancomycin | PSSA: PPI → Oral vancomycin ± 1 year  
Pooled estimate: aSR 2.40 (95% CI 1.88–3.05)  
Pooled estimate (Asia only): aSR 3.16 (95% CI 1.95–5.10) |
| Wahab (2014)¹¹³ | Rosiglitazone | Heart failure | Furosemide | PSSA: Rosiglitazone → Furosemide (Jul 2000 to Dec 2007)  
aSR = 1.73 (99% CI 1.34–2.24) |
| Hachiken (2013)¹⁰⁹ | Low dose aspirin (LDA) | Gastrointestinal (GI) complications | H2RAs  
PPIs | PSSA: LDA → PPIs ± 365 days  
Enteric coated LDA: aSR 1.87 (95% CI 1.26–2.83)  
Buffered LDA: aSR 0.95 (95% CI 0.75–1.20)  
Buffered LDA: aSR 1.25 (95% CI 1.22–1.28) |
| Maura (2018)⁹³ | Direct oral anticoagulants (DOACs; excluding edoxaban) | GI events (composite)  
Nausea  
Constipation  
Depression  
Glaucoma | Gastrointestinal medications (composite)  
Gastrointestinal medications without acid disorder drugs  
Antiemetics  
Drugs for constipation | PSSA: DOAC → Gastrointestinal medications (composite) ± 360 days  
aSR 0.95 (95% CI 0.92–0.97); n = 24 916  
Apixaban → Gastrointestinal medications ± 360 days  
aSR 1.18 (95% CI 1.10–1.26); n = 34 440  
PSSA: DOAC → Gastrointestinal medications (without acid disorder drugs ± 360 days)  
aSR 1.26 (95% CI 1.24–1.29); n = 37 764  
PSSA: DOAC → Antiemetic ± 360 days  
aSR 1.25 (95% CI 1.22–1.28); n = 27 080  
PSSA: DOAC → Drugs for constipation ± 360 days  
aSR 1.25 (95% CI 1.22–1.27); n = 43 112  
DOAC → Antidepressant medication ± 360 days  
aSR 1.26 (95% CI 1.23–1.30); n = 20 613  
DOAC → Glaucoma medication ± 360 days  
aSR 1.01 (95% CI 0.97–1.05); n = 9 473 |
| Takada (2014)⁶⁷ | Low dose aspirin (LDA)  
Enteric coated  
Buffered | GI complications | H2RAs  
PPIs | PSSA: LDA → PPIs ± 12 months  
Enteric coated LDA: aSR 1.20 (95% CI 0.97–1.49)  
Buffered LDA: aSR 0.59 (95% CI 0.33–1.05)  
PSSA: LDA → H2RAs ± 12 months  
Enteric coated LDA: aSR 0.83 (95% CI 0.67–1.02)  
Buffered LDA: aSR 0.78 (95% CI 0.50–1.21) |
| Yokoyama (2020)⁸⁴ | Oral anticoagulants | Osteoporosis | Bisphosphonate | PSSA: Warfarin → Bisphosphonate ± 12 months  
aSR 1.43 (95% CI 1.02–2.03); n = 148 |
| **Cardiovascular system** | | | | |
| Bowman (1995)⁷³ | Angiotensin converting enzyme inhibitor (ACEI) | Cough | Antitussive | ACEI → Antitussive (<1 year; adjusted)  
aOR 1.53 (95% CI 1.17–2.01) |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|---------------|-------------------|----------------------------------------------------------------|
| Fujimoto (2014) 50    | Statins               | Lower urinary tract symptoms (LUTS) | Drugs for storage LUTS | PSSA: Statins → Drugs for storage LUTS ±365 days  
All statins: aSR 1.17 (95% CI 1.05–1.30)  
Pravastatin: aSR 1.27 (95% CI 1.05–1.54)  
Statins → Solfenacin: aSR 1.47 (95% CI 1.25–1.73)  
Statins → Oxybutynin: aSR 1.71 (95% CI 1.09–2.72) |
| Gurwitz (1997) 23     | Antihypertensive medication (see Appendix S1) | Gout | Anti-gout medication (see Appendix S1) | Antihypertensive → Anti-gout medication <365 days  
Non-thiazide antihypertensive alone: aRR 1.00 (95% CI 0.65–1.53)  
Thiazide diuretic alone: aRR 1.99 (95% CI 1.21–3.26)  
Thiazide diuretic plus non-thiazide antihypertensive: aRR 2.29 (95% CI 1.55–3.37) |
| Hallas (1996) 52      | Beta blockers Cardiovascular drugs (see Appendix S1) | Depression | Antidepressants | Beta-blocker → Antidepressant (study period)  
aRR 1.09 (95% CI 0.95, 1.26)  
ACEIs → Antidepressant  
aRR 1.29 (95% CI 1.08, 1.56)  
Calcium channel blockers → Antidepressant  
aRR 1.31 (95% CI 1.14, 1.51) |
| Lindberg & Hallas (1998) 98 | Cholesterol-lowering medication | Depression | Antidepressants | PSSA: Cholesterol-lowering drug → Antidepressant (study period)  
All drugs: aSR 0.90 (95% CI 0.68–1.22); n = 184  
Simvastatin: aSR 1.59 (1.08–2.45); n = 91 |
| Morris (2021) 116     | Dihydropyridine calcium channel blockers (DH-CCBs) | Oedema | Loop diuretic | Among 5458467 DH CCB users (weighted), 185130 individuals (3.4% weighted) were identified with new loop diuretic use. |
| Pouwels (2013) 128    | ACEI                  | Urinary tract infection (UTI) | Nitrofurantoin | PSSA: ACEI → Nitrofurantoin ±4weeks  
aSR 1.68 (95% CI 1.21–2.36); n = 161 |
| Pouwels (2014) 118    | ACEI                  | UTI | Nitrofurantoin | ACEI → Nitrofurantoin (<30 days vs <60–90 days)  
Crude OR = 1.84 (95% CI 1.51–2.25) |
| Pouwels (2016) 29     | Statin                | Infection | Antibiotic | PSSA: Statin → Antibiotic ±13 months  
Any antibiotic: aSR 0.86 (95% CI 0.81–0.91) |
| Pratt (2015) 61       | Amiodarone            | Hypothyroidism | Thyroxine | PSSA: Amiodarone → Thyroxine ±12 months  
Pooled aSR 2.63 (95% CI 1.47–4.72) |
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Savage (2020)⁵        | Calcium channel blockers (CCBs) ACEIs or Angiotensin receptor blockers (ARBs) (comparator) | Oedema       | Loop diuretic   | CCB $\rightarrow$ Loop diuretic $\leq$90 days  
Incident CCB users had a higher cumulative incidence of loop diuretic than the comparators (1.4% vs. 0.7% [other antihypertensive comparator] and 0.5% [general comparator], $p < .001$).  
CCB versus other antihypertensive (ACEI or ARB)  
1–30 days: aHR 1.68 (95%CI 1.38–2.05)  
31–60 days: aHR 2.26 (95%CI 1.76–2.92)  
61–90 days: aHR 2.40 (95%CI 1.84–3.13)  
91–180 days: aHR 2.24 (95%CI 1.86–2.71)  
181–365 days: aHR 1.64 (95%CI 1.38–1.94) |
| Silver (2006)⁹²       | Statin                | Muscle pain   | NSAID            | PSSA: Statin $\rightarrow$ NSAID $\pm$ 365 days  
aSR 0.94 (95%CI 0.85–1.05) |
| Singh (2021)⁵⁴        | CCBs                  | Lower extremity oedema | Diuretics | CCB $\rightarrow$ Diuretic day 8 $\rightarrow$ day 365  
Cohort 1: 161 incident diuretic users among 3304 incident CCB users (4.9%, 95%CI 4.2–5.7).  
Cohort 2: 1586 incident diuretic users among 36 462 prevalent CCB users (1.3%, 95%CI 1.4–4.6).  
Cohort 3: 130 incident diuretic use among 2525 participants with polypharmacy at the day of incident CCB dispensing (5.1, 95%CI 4.3–6.0). |
| Takada (2014)¹²⁹      | Statins               | Sleep disturbance | Hypnotic drugs | PSS: Statin $\rightarrow$ Hypnotic drugs $\pm$ 365 days  
aSR 1.18 (95%CI 1.11–1.25) |
| Thiessen (1990)¹¹²     | Beta-blocker          | Depression    | Antidepressants  | Beta-blocker: Antidepressant $<34$ days (concurrent use)  
Beta-blocker: RR 2.6 (95%CI 2.3–3.0) |
| Vegter (2013)¹⁸        | ACEI                  | Cough         | Cough medication | PSSA: ACEI $\rightarrow$ Cough medication $\pm$ 6months  
2000–2012: SR 2.0 (95%CI 1.8–2.2) |
| Vouri (2018)⁷–⁶        | DH-CCBs               | Lower extremity oedema | Loop diuretic | DH-CCB $\rightarrow$ Loop diuretic (2014)  
The potential prescribing cascade was identified in 2.2 million visits (4.6%) using the primary definition of prescribing cascade. |
| Vouri (2019)⁷          | DH-CCBs               | Lower extremity oedema | Loop diuretic | PSSA: DH-CCB $\rightarrow$ Loop diuretic (2014) $\pm$ 360 days  
aSR 1.87 (95%CI 1.84–1.90) |
| Vouri (2021)³⁰⁵         | DH-CCBs               | DH-CCB induced oedema | Loop diuretic | PSSA: DH-CCB $\rightarrow$ Loop diuretic $\pm$ 360 days  
aSR 2.27 (95% CI 1.44–3.58) |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|------------------------|---------------|------------------|---------------------------------------------------------------|
| Vouri (2021)         | DH-CCB                 | DH-CCB induced oedema | Loop diuretic | PSSA: DH-CCB → Loop diuretic ±360 days Relative to levothyroxine initiators: aSR 1.72 (95%CI 1.66–1.78) Relative to ACEI/ARBs initiators: aSR 1.45 (1.41–1.49) |
| Vouri (2022)         | Beta-blocker           | Oedema         | Loop diuretic    | PSSA: Beta-blocker → Loop diuretic ±90 days aSR 1.78 (99%CI 1.72–1.84) |
| Yokoyama (2021)      | Amiodarone             | Hypothyroidism | Thyroid preparations | PSSA: Amiodarone → Thyroid preparations ±12 months aSR 12.8 (95%CI 8.44–20.28) |

**Dermatologicals**

| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|------------------------|---------------|------------------|---------------------------------------------------------------|
| Azoulay (2007)       | Isotretinoin           | Depression    | Antidepressants   | Isotretinoin → Antidepressant (5 month risk and control windows) aRR 2.68 (95%CI 1.10–6.48) |
| Hersom (2003)        | Isotretinoin Minocycline | Depression    | Antidepressants (MAOIs excluded) | Isotretinoin → Antidepressant (study period) aRR 0.97 (95%CI 0.92–1.02) Minocycline → Antidepressant (study period) aRR 0.90 (95%CI 0.95–1.02) |
| Sturkenboom (1995)   | Acitretin              | Vulvo-vaginal infection | Vulvo-vaginal anti-infective drug | Acitretin → Vulvo-vaginal anti-infective (study period) Pooled Mantel–Haenszel IRR: 3.3 (95%CI 1.1–9.6) |

**Genito urinary system and sex hormones**

| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|------------------------|---------------|------------------|---------------------------------------------------------------|
| Dyson (2020)         | 5-α reductase inhibitors (5-ARI) | Depression    | Antidepressant   | PSSA: 5-ARI → Antidepressant ±365 days Crude SR 0.84 (95% CI 0.80–0.89) |
| Hagberg (2017)       | 5-ARI Alpha blocker (AB) | Depression    | Antidepressant (<90 days of depression diagnosis) | SARI → Antidepressant (compared with AB only users) 5-ARIs only: aIRR = 0.94 (95%CI 0.85–1.04) 5-ARIs + ABs: aIRR = 1.04 (95%CI 0.89–1.21) Nested case–control analysis (compared with AB only users) 5-ARIs only: aOR 0.88 (95%CI 0.78–1.01) 5-ARIs+ABs: aOR 0.90 (95%CI 0.73–1.10). |

**Anti-infectives for systemic use**
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Corrao (2005)49       | Antibacterial drugs for systemic use | Arrhythmia triggered by prolonged QT interval | Antiarrhythmic | PSSA: Antibacterial → Antiarrhythmic (study period)  
Erythromycin: aSR 1.78 (95% CI 1.09–2.89); n = 73  
Ciprofloxacin: aSR 1.17 (95% CI 1.02–1.33); n = 870  
Cohort analysis (standardised incidence ratio)  
Erythromycin: 1.96 (95% CI 1.45–2.59; n = 8956  
Clarithromycin: 1.18 (95% CI 1.08–1.29); n = 97900  
Rokitamycin: 1.27 (95% CI 1.00–1.66; n = 15247  
Ciprofloxacin: 1.25 (95% CI 1.14–1.37; n = 58070  
Norfloxacain: 1.17 (95% CI 1.00–1.36; n = 22421  
Levofoxicin: 1.33 (95% CI 1.03–1.38; n = 14159  
Case-control analysis  
Erythromycin: OR 1.89 (95% CI 1.33–2.68)  
Clarithromycin: OR 1.18 (95% CI 1.04–1.34)  
Ciprofloxacin: OR 1.21 (95% CI 1.05–1.39)  
Levofoxicin: OR 1.33 (95% CI 1.04–1.70) |

**Antineoplastic and immunomodulating agents**

| Farkas (2021)21 | Aromatase inhibitors (AI) | For the treatment of menopausal symptoms  
Vasomotor symptoms, vaginal dryness, arthralgias, pain | See Appendix S1 | Medication use in 12 months before AI:  
Any new side effect medication: 7436 (40.2%)  
Opiates 31.5%; SSRIs 16.1%; Gabapentin 7.0%  
Medication use in the 24 months after AI:  
Any new side effect medication: 13179 (71.2%)  
Opiates 55.1%; SSRIs 22.6%; Benzodiazepines 18.4%; Tramadol 17.7%; Gabapentin 14.6% |

**Musculo-skeletal system**

| Gurwitz (1994)22 | NSAID | Hypertension | Antihypertensive | NSAI → Antihypertensive (<365 days)  
OR = 2.01 (95% CI 1.89–2.14) |

| Avorn (1995)19 | Neuroleptics | Extrapyramidal symptoms | APD (excluding a amantadine monotherapy) | Any Anti-Parkinson drug (<90 days)  
Any neuroleptic: aOR 5.4 (95% CI 4.8–6.1)  
Anticholinergic Anti-Parkinson drug (<90 days)  
Any neuroleptic: aOR 8.5 (95% CI 4.8–6.1)  
Dopaminergic agent (<90 days)  
Any neuroleptic: aOR 2.2 (95% CI 1.9–2.7) |

| Brandt-Christensen (2007)37 | APD  
Control 1: Antidiabetics  
Control 2: unexposed | Depression | Antidepressants | Anti-Parkinson drug → Antidepressant (versus unexposed)  
APD cohort: RR 2.10 (95% CI 2.04–2.16)  
Antidiabetic cohort: RR 1.34 (95% CI 1.32–1.36) |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|---------------|-------------------|---------------------------------------------------------------|
| DoHerT et al. (2020)   | Selective serotonin reuptake inhibitors (SSRI) | Restless leg syndrome (RLS) | Dopamine agonist Quinine | PSSA: SSRI → RLS drug ± 365 days
Any drug: aSR 0.99 (95% CI 0.95–1.02)
Dopamine agonist only: aSR 1.21 (95% CI 1.12–1.32); n = 2267 |
| Gau (2010)            | Lithium Carbamazepine Valproate | Hypothyroidism | Thyroxine, liothyronine or thyroid hormone and hypothyroidism diagnosis (composite) | Likelihood for incident hypothyroidism (study period)
Lithium: OR 1.41 (95% CI 1.14–1.74)
Carbamazepine: OR 1.37 (95% CI 1.13–1.65)
Valproate: OR 1.72 (95% CI 1.40–2.11) |
| Gill (2005)           | Acetylcholinesterase inhibitors (AChEI) | Urge urinary incontinence | Urinary anticholinergics | AChEI → Anticholinergic
Patients dispensed cholinesterase inhibitors were more likely to receive an anticholinergic medication in follow-up (4.5% vs. 3.1%; p < .001). |
| Hirano (2020)         | Anxiolytic Hypnotic Antidepressants Antipsychotics | EPS | Diagnosis of EPS and APD prescription in same month (composite) | PSSA: Psychotropic medication → EPS and APD ± 12 months
Anxiolytic: aSR 2.48 (95% CI 2.16–2.85); n = 992
Hypnotic: aSR 2.28 (95% CI 1.97–2.64); n = 872
Antidepressant: aSR 2.26 (95% CI 1.93–2.64); n = 728
Antipsychotic: aSR 9.24 (95% CI 7.35–11.8); n = 817 |
| Kalisch Ellett (2018)  | Antipsychotics | EPS | Anticholinergic Hyperprolactinaemia Diabetes mellitus | Concomitant medication use
Anticholinergic: n = 51 (0.7%)
Hyperprolactinaemia medications: n = 8 (0.1%)
Oral diabetes medicines: n = 874 (11.8%) |
| Kroger (2015)         | AChEI | Urinary incontinence | Drugs for urinary frequency and incontinence | AChEI → Drugs for urinary frequency < 90 days
All patients (n = 2700): aHR 1.13 (95% CI 0.97–1.32)
Rivastigmine patients (n = 1853): aHR 1.13 (95% CI 0.95–1.34)
Galantamine patients (n = 1043): aHR 1.10 (95% CI 0.81–1.50) |
| Lai (2013)            | Antiepileptic drugs (AEDs) | Hypothyroidism | Levothyroxine | PSSA: AEDs → Levothyroxine ± 12 months
Any AED: aSR 1.13 (99% CI 1.09–1.18)
Carbamazepine: aSR 1.21 (99% CI 1.08–1.34)
Phenobarbital: aSR 1.25 (99% CI 1.15–1.36)
Phenytoin: aSR 1.75 (99% CI 1.58–1.94)
Valproate: aSR 1.34 (99% CI 1.20–1.49)
Oxcarbazepine: aSR 1.22 (99% CI 1.03–1.46) |
| Lampela (2016)        | AChEI or Memantine | Urinary incontinence | Urinary anticholinergics | AChEI → Urinary anticholinergics (versus memantine users)
<6 months: aHR 1.47 (95% CI 1.17–1.86)
<12 months: aHR 1.41 (95% CI 1.17–1.69) |
| Marras (2016)         | Lithium Valproic acid Antidepressant | Drug induced tremor diagnosed as Parkinson’s Disease (PD) | Anti-Parkinson drug or PD diagnosis (see Appendix S1) | Start of dopaminergic drug (no previous antipsychotic use)
Lithium (versus antidepressant): aHR 1.68 (95% CI 1.13–2.48) |

**TABLE 1 (Continued)**
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Masurkar (2021)²⁴     | AChEI                 | Overactive bladder | Urinary anticholinergic | AChEI → Anticholinergic cascade <6months                     |
|                       |                       |                |                   | Rivastigmine: aHR = 1.0                                       |
|                       |                       |                |                   | Donepezil: aHR = 1.55 (95%CI 1.31–1.83)                       |
|                       |                       |                |                   | Galantamine: aHR = 1.17 (95%CI 0.87–1.58)                      |
| Movig (2002)⁴¹        | SSRI                  | Urinary incontinence | Spasmolytic agent or 30 or more units of incontinence wear | SSRI → Spasmolytic agent/incontinence wear <3month|
|                       |                       |                |                   | During SSRI (versus before SSRI): IDR 1.57 (95%CI 1.38–1.79) |
|                       |                       |                |                   | During SSRI (versus after SSRI): IDR 2.03 (95%CI 1.76–2.34)    |
|                       |                       |                |                   | During SSRI (versus before and after SSRI): IDR 1.75 (95%CI 1.56–1.97) |
|                       |                       |                |                   | Risk for incontinence during exposed period (versus non-exposed) aRR 1.61, 95%CI 1.42–1.82 |
| Narayan (2019)²⁵      | AChEI or Memantine    | Several ADRs examined relating to anticholinergic medication use | Anticholinergics (see Appendix S1) | Anti-dementia drug → Marker medication ± 180 days |
|                       |                       |                |                   | Exposed to at least one anticholinergic ±180 days: n = 1439 |
|                       |                       |                |                   | Exposed to at least one anticholinergic after anti-dementia drug: n = 416 |
| Onder (2014)c⁴⁶        | Anti-Parkinson drugs and antipsychotics (concomitant use) | Parkinsonism (side effect of antipsychotics); Behavioural disorders (side effect of anti-Parkinson drugs) | Anti-Parkinson drugs and antipsychotics (concomitant use) | Prevalence of concomitant use of anti-Parkinson and antipsychotic medication (2011) |
|                       |                       |                |                   | Total population: n = 25949 (0.2%)                           |
|                       |                       |                |                   | 65–74 years: n = 10 200 (0.2%)                               |
|                       |                       |                |                   | 75–84 years: n = 10 625 (0.2%)                               |
|                       |                       |                |                   | ≥85 years: n = 5124 (0.3%)                                    |
| Park (2016)⁶⁴         | Benzodiazepines       | Dementia       | Anti-dementia drugs | PSSA: Benzodiazepines → Anti-dementia drugs ± 3 years          |
|                       |                       |                |                   | aSR 2.19 (95%CI 1.92–2.49); n = 1285                          |
| Petri (1988)⁵⁶         | Flunarizine           | Depression     | Antidepressant     | Flunarizine → Antidepressant <30 days                         |
|                       |                       |                |                   | Number of antidepressant starts during or within 30 days after flunarizine use was 5 out of a total of 34 histories |
| Petri (1990)⁵⁷         | Flunarizine           | Depression or Parkinsonism | Antidepressant or Anti-Parkinson drug | Flunarizine → Antidepressant (study period) Incidence Rate = 1.342 (95%CI 1.00–1.80) |
|                       |                       |                |                   | Flunarizine → Anti-Parkinson drug                              |
|                       |                       |                |                   | In a subset of 777 flunarizine recipients there were 10 participants who received anti-Parkinson drugs |
| Pratt (2013)⁹⁰        | Antipsychotics        | Acute hyperglycaemia | Insulin | PSSA: Olanzapine → Insulin ± 12 months                        |
|                       |                       |                |                   | USA Public: aSR 1.14 (95%CI 1.1–1.17)                          |
|                       |                       |                |                   | Sweden: aSR 1.53 (95%CI 1.33–2.06)                            |
|                       |                       |                |                   | Risperidone → Insulin ± 12 months                             |
|                       |                       |                |                   | USA Public: aSR 1.09 (95%CI 1.07–1.12)                         |
| Read (2021)³⁸         | Gabapentinoid         | Oedema         | Diuretic          | Gabapentinoid → Diuretic <90 days (versus non-users)          |
|                       |                       |                |                   | aHR 1.44 (95%CI 1.23–1.70).                                   |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|--------------|------------------|----------------------------------------------------------|
| Rochon (2005)         | Antipsychotic         | Parkinsonism | Anti-Parkinson drug or Parkinson diagnosis (composite) | Antipsychotic → Anti-Parkinson drug/diagnosis <1 year (versus typical antipsychotic); Typical antipsychotics: adjusted HR 1.30 (95%CI 1.04–1.58); No therapy: aHR 0.40 (95%CI 0.29–0.43) |
| Takada (2016)         | Benzodiazepine        | Dementia     | Anti-dementia drug | PSSA: Benzodiazepine → Anti-dementia drug ± 12 months 12 months: aSR 1.23 (95%CI 1.11–1.37) |
| Takeuchi (2015)       | Atypical antipsychotics | Hyperlipidemia | Anti-hyperlipidemic drugs | PSSA: Atypical antipsychotics → Anti-hyperlipidemic drugs Olanzapine ±360 days: aSR 2.19 (95%CI 1.55–3.12) |
| Thacker (2006)        | AChEI                 | Drug-induced airways complications | Antibacterial and oral corticosteroid | AChEI → Antibacterial and oral corticosteroid <1 month Fully-adjusted RR = 1.19 (95%CI 0.52–2.74) |
| Venalainen (2017)     | AChEI                 | Nausea       | Antiemetics       | AChEI → Marker drug ± 1 year Loperamide/Oral rehydration: aSR 1.42 (95%CI 1.14–1.77); n = 348 |
|                       |                       | Diarrhoea    | Loperamide/H2RAs  | Anxiolytics: aSR 1.16 (95%CI 1.01–1.34); n = 807 |
|                       |                       | Urinary incontinence | Loperamide/Oral rehydration sachets Oxybutynin | Hypnotics and sedatives: aSR 1.19 (95%CI 1.05–1.36); n = 963 |
|                       |                       | Seizures     | Anxiolytics       | Antipsychotics: aSR 1.18 (95%CI 1.05–1.32); n = 1202 |
|                       |                       | Anxiety      | Anticonvulsants   | Anticonvulsants: aSR 1.26 (95%CI 1.03–1.55); n = 389 |
|                       |                       | Insomnia     | Hypnotics and sedatives | PPI/H2RAs: aSR 0.87 (95%CI 0.77–0.98); n = 1079 |
|                       |                       | Depression   | Antidepressants   | Antidepressant: aSR 0.77 (95%CI 0.70–0.85); n = 1698 |
|                       |                       |              | Oxybutynin: aSR 1.04 (95%CI 0.81–1.34); n = 261 | |
| Vouri (2020)          | AChEI or Memantine    | Rhinorrhea   | Rhinorrhea medications | AChEI/Memantine → Rhinorrhea medications (concomitant use) AChEI users were more likely to use a rhinorrhea medication compared to non-AChEI users, OR 7.16 (95%CI 2.25–22.73); adjusted OR = 4.7 (95%CI 1.53–14.43) |
| Wang (2021)           | Varenicline           | Neuropsychiatric adverse events: Depression | Antidepressant | PSSA: Varenicline → Any NPAE drug ±365 days aSR 1.00 (95%CI 0.89–1.13) |
|                       |                       | Anxiety      | Anxiolytics       | PSSA: Varenicline → Hypnotics and sedatives ± 365 days Sleep disorder drug: aSR = 1.25 (95%CI 1.05–1.48) |
|                       |                       | Sleep disorders | Hypnotics and sedatives (composite outcome) | General population with psychiatric disorders <24 weeks Any NPAE medication: adjusted OR 0.82 (95% CI 0.68 to 0.99) General population without psychiatric disorders <24 weeks Any NPAE medication: adjusted OR 0.85, (95% CI 0.72 to 1.00) COPD population with psychiatric disorders <24 weeks Any NPAE medication: adjusted OR 0.97 (95% CI 0.66 to 1.44) COPD population without psychiatric disorders <24 weeks Any NPAE medication: adjusted OR 0.81 (95% CI 0.54 to 1.20) |
| Yokoyama (2020)       | Antipsychotics        | Osteoporosis | Bisphosphonate   | PSSA: Antipsychotic → Bisphosphonate No association identified. |
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|---------------|-------------------|-------------------------------------------------------------------|
| **Respiratory system** |                        |               |                   |                                                                   |
| Fox (2022)34          | Montelukast            | Neuropsychiatric adverse events (NPAE) | Antidepressants Benzodiazepines Hypnotics Antipsychotics Mood stabilisers Buspirone (composite outcome) | PSSA: Montelukast → Any NPAE medication ± 14–365 days SR 0.84 (95%CI 0.80–0.89) |
| Henriksen (2017)39    | Inhaled corticosteroids | Oral candidiasis | Systemic or topical antifungal | PSSA: Inhaled corticosteroid → Topical antifungal ± 12months Crude SR 2.89 (95%CI 2.80–2.97) PSSA: Inhaled corticosteroid → Systemic antifungal ± 12months Crude SR 1.50 (95%CI 1.46–1.54) |
| Petri (1991)56        | Inhaled corticosteroids | Oral candidiasis | Topical antifungal | Inhaled corticosteroids → Topical antifungal ± 90 days Crude OR = 1.66 (n = 21) |
| Van Boven (2013)71    | Inhaled corticosteroids | Oral candidiasis | Topical antifungal | PSSA: Inhaled corticosteroids → Topical antifungal ± 12months Crude SR 1.94 (95%CI 1.71–2.21) |
| Winkel (2018)60       | Montelukast            | Depression     | Antidepressant (excluding bupropion) | PSSA: Montelukast → Antidepressant ± 1 year Crude SR 1.19 (95%CI 1.11–1.28) |
| **Sensory organs**    |                        |               |                   |                                                                   |
| Roughead (2012)97     | Timolol Latanoprost Bimatoprost Pilocarpine Brimonidine | Exacerbation of airways disease Exacerbation of depression | Inhaled beta-agonists Inhaled corticosteroids Oral corticosteroids SSRI | PSSA: Glaucoma → marker medications ± 1 year Timolol → Inhaled beta agonist: aSR 1.48 (95%CI 1.22–1.78); n = 786 Timolol → Inhaled corticosteroid: aSR 1.43 (95%CI 1.13–1.81); n = 494 Latanoprost → Inhaled beta agonist: aSR 1.24 (95%CI 1.11–1.38); n = 2251 Latanoprost → Oral corticosteroid: aSR 1.14 (95%CI 1.00–1.29); n = 1671 Timolol → Antidepressant: aSR 1.24 (95%CI 1.07-1.43); n = 1253 Timolol → SSRI: aSR 1.30 (95%CI 1.08–1.56); n = 791 Latanoprost → Antidepressant: aSR 1.16 (95%CI 1.03–1.31); n = 1871 Latanoprost → SSRI: aSR 1.20 (95%CI 1.03–1.39); n = 1155 |
| **Multiple medication groups examined** |                        |               |                   |                                                                   |
| Brandt-Christensen (2006)82 | Antidepressant Lithium Antidiabetic Parkinsonism APD | (see Appendix S1 for exclusions) |                      | Index drug → Anti-Parkinson drug (versus unexposed) Antidepressant: RR 1.79 (95%CI 1.72-1.86) Lithium: RR 1.88 (95%CI 1.60–2.20) Antidiabetic: RR 0.80 (95%CI 0.74–0.86) |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Bytzer & Hallas (2000) | Predefined list of 32 index medications (see Appendix S1) | Dyspepsia or nausea | Cisapride or Metoclopramide | NSAIDS: aSR = 1.33 (95%CI 1.02–1.77); n = 211  
Methylxanthines: aSR = 2.36 (1.00–8.44); n = 18  
PSSA: Index medication → Cisapride < 100 days  
Dyspepsia or nausea  
Cisapride or Metoclopramide  
PSSA: Index medication → Metoclopramide < 100 days  
Insulin: aSR = 2.91 (95%CI 1.40–8.11); n = 28  
Opioids: aSR = 2.84 (95%CI 2.48–3.28); n = 1017  
Potassium supplement: 1.42 (95%CI 1.15–1.79); n = 324  
Digoxin: 2.87 (95%CI 2.01–4.35); n = 138  
Nitrates: 1.74 (95%CI 1.16–2.77); n = 88  
Loop diuretics: 1.50 (95%CI 1.23–1.85); n = 383  
ACEIs: 2.27 (95%CI 1.46–3.85); n = 77  
Oral corticosteroids: 1.33 (95%CI 1.11–1.60); n = 458  
Antibiotics: 1.40 (95%CI 1.24–1.60); n = 974  
Penicillins: 1.38 (95%CI 1.21–1.59); n = 868  
Macrolides: 1.58 (95%CI 1.31–1.94); n = 414  
NSAIDs: 1.48 (95%CI 1.28–1.74); n = 307  
Methylxanthines: 2.03 (95%CI 1.25–3.65); n = 63 |
| Caughey (2010) | Medicines commonly associated with dizziness identified (see Appendix S1) | Dizziness | Prochlorperazine | PSSA: Index medication → Prochlorperazine ± 12 months  
Cardiac therapy: aSR = 1.14 (95%CI 1.06–1.22); n = 3017  
Nitrates: aSR = 1.11 (95%CI 1.03–1.21); n = 2224  
Isosorbide mononitrate: aSR = 1.21 (95%CI 1.07–1.38); n = 918  
Diuretic: aSR = 1.07 (95%CI 1.01–1.14); n = 3845  
Beta-blocker: aSR = 1.13 (95%CI 1.05–1.21); n = 3156  
CCBs: aSR = 1.22 (95%CI 1.16–1.36); n = 2696  
ACE inhibitors: aSR = 1.22 (95%CI 1.14–1.31); n = 3162  
ARB: aSR = 1.20 (95%CI 1.11–1.30); n = 2577  
Statins: aSR = 1.50 (95%CI 1.40–1.61); n = 3411  
NSAIDs: aSR = 1.37 (95%CI 1.27–1.47); n = 3079  
Opioids: aSR = 1.24 (95%CI 1.17–1.31); n = 5266  
Sedatives: aSR = 1.18 (95%CI 1.11–1.26); n = 3470 |
| de Jong (2003) | Antidepressant with or without NSAID | GI adverse effects | H2RAs | Antidepressant → Ulcer drugs (compared with TCA only)  
SSRI: IRR 1.2 (95%CI 0.5–2.8); n = 1181  
PPIs  
Prostaglandins  
SSRI + NSAID: IRR 12.4 (95%CI 3.2–48.0); n = 86 |
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|-----------------------|--------------|-------------------|--------------------------------------------------|
| Garrison (2012)³³     | Statin, Diuretic      | Nocturnal leg cramps | Quinine           | PSSA: Index drug → Quinine ± 1 year  
All statins: aSR 1.16 (95%CI 1.04–1.29); n = 1326  
All LABAs: aSR 2.42 (95%CI 2.02–2.89); n = 576  
LABA alone: aSR 2.17 (95%CI 1.56–3.02); n = 137  
LABA-corticosteroid: aSR 2.55 (95%CI 2.06–3.12); n = 439  
All diuretics: aSR 1.47 (95%CI 1.33–1.63); n = 1590  
Loop diuretic: aSR 1.20 (95%CI 1.00–1.44); n = 447  
Thiazide diuretic: aSR 1.48 (95%CI 1.29–1.68); n = 977  
Potassium-sparing diuretic: aSR 2.12 (95%CI 1.61–2.78); n = 206 |
| Halas & Bytzer (1998)³⁹ | Predefined list of 33 medications (see Appendix S1) | Dyspepsia | Ulcer drug prescription | PSSA: Index drug → Ulcer drug prescription ± 100 days  
NSAIDs: aSR 1.80 (95%CI 1.64–1.99)  
CCBs: aSR 1.40 (95%CI 1.18–1.67)  
Oral corticosteroids: aSR 1.15 (95%CI 1.02–1.30)  
ACEIs: aSR 1.38 (1.12–1.73)  
Methyloxanthines: aSR 1.49 (1.05–2.19) |
| Hashimoto (2015)³³     | Medicines that cause storage symptoms; Medicines that cause voiding symptoms | LUTS | Medications for (LUTS) | PSSA: Index drug → Medications for LUTs ± 12 months  
Oxycodone: aSR 1.20 (95%CI 1.03–1.41)  
Morphine: aSR 1.29 (95%CI 1.14–1.45)  
Donepezil: aSR 1.98 (95%CI 1.57–2.50)  
Intestinal lavage solution: aSR 1.86 (95%CI 1.65–2.10)  
Cyclophosphamide: aSR 1.52 (95%CI 1.14–2.04)  
Levodopa/benserazide: aSR 1.82 (95%CI 1.18–2.81)  
Amantadine: aSR 1.53 (95%CI 1.12–2.09)  
Paroxetine: aSR 1.77 (95%CI 1.33–2.36)  
Milnacipran: aSR 2.10 (95%CI 1.28–3.45)  
Diazepam: aSR 1.73 (95%CI 1.46–2.06)  
Risperidone: aSR 1.55 (95%CI 1.34–1.79)  
Levomepromazine: aSR 2.20 (95%CI 1.34–1.79)  
Sulpiride: aSR 1.32 (95%CI 1.01–1.72)  
Cimetidine: aSR 1.99 (95%CI 1.24–3.20)  
Scopolamine butylbromide: aSR 1.72 (95%CI 1.55–1.92)  
Tiotropium bromide: aSR 1.75 (95%CI 1.42–2.16)  
Ciclosporine: sSR 2.97 (95%CI 1.92–4.59)  
Amezinium metilsulfate: aSR 1.89 (95%CI 1.10–3.26) |
| Huh (2019)³¹          | Metoclopramide or levosulpiride | Drug induced Parkinsonism | Levodopa | PSSA: Metoclopramide → Levodopa < 90 days  
aOR 2.94 (95%CI 2.35, 3.67)  
PSSA: Levosulpiride → Levodopa < 90 days  
aOR 3.30 (95%CI 2.52, 4.32) |
| Primary author (year)       | Initial medication(s)                  | Suspected ADR               | New medication(s)                  | Quantitative association (primary analysis or association at 1 year) |
|---------------------------|----------------------------------------|-----------------------------|------------------------------------|--------------------------------------------------------------------|
| Kalisch Ellett (2014)⁷⁴  | See Appendix S1                        | Urinary incontinence        | Oxybutynin                         | PSSA: Index medication → Oxybutynin ±12 months                       |
|                           |                                        |                             |                                    | Prazosin (women only): aSR 1.84 (95% CI 1.29–2.63); n = 135        |
|                           |                                        |                             |                                    | Low-ceiling diuretics, excluding thiazides: aSR 1.22 (95% CI 1.06–1.41); n = 750 |
|                           |                                        |                             |                                    | CCBs: aSR 1.45 (95% CI 1.33–1.57); n = 2230                        |
|                           |                                        |                             |                                    | ACEIs: aSR 1.28 (95% CI 1.19–1.39); n = 2616                      |
|                           |                                        |                             |                                    | ACEIs + diuretic: aSR 1.35 (1.15–1.58); n = 620                   |
|                           |                                        |                             |                                    | ARBs: aSR 1.42 (1.30–1.55); n = 2040                             |
|                           |                                        |                             |                                    | ARBs + diuretic: aSR 1.32 (1.16–1.49); n = 999                    |
|                           |                                        |                             |                                    | HRT: aSR 1.54 (95% CI 1.42–1.67); n = 2446                       |
|                           |                                        |                             |                                    | Antipsychotics: aSR 0.83 (95% CI 0.78–0.89); n = 2121             |
|                           |                                        |                             |                                    | Low-ceiling diuretics, excluding thiazides: aSR 1.22 (95% CI 1.06–1.41); n = 750 |
|                           |                                        |                             |                                    | CCBs: aSR 1.45 (95% CI 1.33–1.57); n = 2230                        |
|                           |                                        |                             |                                    | ACEIs: aSR 1.28 (95% CI 1.19–1.39); n = 2616                      |
|                           |                                        |                             |                                    | ACEIs + diuretic: aSR 1.35 (1.15–1.58); n = 620                   |
|                           |                                        |                             |                                    | ARBs: aSR 1.42 (1.30–1.55); n = 2040                             |
|                           |                                        |                             |                                    | ARBs + diuretic: aSR 1.32 (1.16–1.49); n = 999                    |
|                           |                                        |                             |                                    | HRT: aSR 1.54 (95% CI 1.42–1.67); n = 2446                       |
|                           |                                        |                             |                                    | Antipsychotics: aSR 0.83 (95% CI 0.78–0.89); n = 2121             |
|                           |                                        |                             |                                    | Low-ceiling diuretics, excluding thiazides: aSR 1.22 (95% CI 1.06–1.41); n = 750 |
|                           |                                        |                             |                                    | CCBs: aSR 1.45 (95% CI 1.33–1.57); n = 2230                        |
|                           |                                        |                             |                                    | ACEIs: aSR 1.28 (95% CI 1.19–1.39); n = 2616                      |
|                           |                                        |                             |                                    | ACEIs + diuretic: aSR 1.35 (1.15–1.58); n = 620                   |
|                           |                                        |                             |                                    | ARBs: aSR 1.42 (1.30–1.55); n = 2040                             |
|                           |                                        |                             |                                    | ARBs + diuretic: aSR 1.32 (1.16–1.49); n = 999                    |
|                           |                                        |                             |                                    | HRT: aSR 1.54 (95% CI 1.42–1.67); n = 2446                       |
|                           |                                        |                             |                                    | Antipsychotics: aSR 0.83 (95% CI 0.78–0.89); n = 2121             |
|                           |                                        |                             |                                    | Statistical significance was observed at α < 0.05                 |

**Table 1 (Continued)**
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|---------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Nishtala & Chyou (2017) | Amiodarone, Lithium, Frusemide, Fluticasone, Simvastatin | Hypothyroidism, Hyperthyroidism, Hypokalaemia, Oral candidiasis, Muscle cramps | Thyroxine, Carbidzole, Potassium, Nystatin, Quinine sulphate | PSSA: Amiodarone → Thyroxine ± 360 days  
aSR 3.37 (95% CI 3.17–4.02)  
Lithium → Thyroxine ± 360 days  
aSR 3.43 (95% CI 2.55–4.70)  
Amiodarone → Carbidzole ± 360 days  
aSR 8.81 (95% CI 5.86–13.77)  
Simvastatin → Quinine sulphate ± 360 days  
aSR 1.69 (95% CI 1.61–1.77)  
Fluticasone → Nystatin ± 360 days  
aSR 2.34 (95% CI 2.19–2.50)  
Frusemide → Potassium ± 360 days  
aSR 2.94 (95% CI 2.83–3.05) |
| Pouwels (2013) | SSRI with or without NSAID | Peptic ulcer | Peptic ulcer drug treatment | PSSA: SSRI +/- NSAID → Peptic ulcer treatment ± 4 weeks  
SSRI: aSR 0.83 (95%CI 0.65–1.06)  
NSAID: aSR 2.50 (95%CI 2.27–2.76)  
SSRI + NSAID: aSR 1.48 (95%CI 0.90–2.49) |
| Rasmussen (2015) | Antithrombotic drugs, Cardiovascular drugs (see Appendix S1) | Erectile dysfunction | 5-phosphodiesterase inhibitor | PSSA: Cardiovascular drugs → 5-phosphodiesterase inhibitor ± 6 months  
Thiazides: aSR 1.28 (95%CI 1.20, 1.38); NNTH 370 (95%CI 300, 500); n = 3118  
β-blockers: aSR 1.18 (95%CI 1.09, 1.28); NNTH 680 (95%CI 480, 1200); n = 2511  
CCBs: aSR 1.29 (95%CI 1.21, 1.38); NNTH 330 (95%CI 270, 440); n = 3379  
ACEIs: aSR 1.29 (95%CI 1.21, 1.37); NNTH 350 (95%CI 290, 440); n = 4182  
ARBs: aSR 1.16 (95%CI 1.06, 1.26); NNTH 540 (95%CI 360, 1200); n = 2082 |
| Singh (2021) | Antipsychotic or Metoclopramide | Parkinsonism | Anti-Parkinson drug | Antipsychotic/metoclopramide → Anti-Parkinson drug < day 8–365  
Cohort 1: 36 (0.8%) incident anti-Parkinson drug users among 4534 incident antipsychotic/metoclopramide users  
Cohort 2: 20 (0.5%) incident users of anti-Parkinsonian drugs among 3485 antipsychotic/metoclopramide users |
| Trenaman (2021) | AChEs, Metoclopramide, CCBs | Urinary incontinence, Parkinsonism, Pedal oedema | Urinary medications, Anti-Parkinson drug, Diuretic | AChEI → Urinary medications <6months  
60 cases of prescribing cascade were identified. Extending to 365 days resulted in 52 additional cases.  
Metoclopramide → Anti-Parkinson drug <6months  
11 cases of the prescribing cascade were identified. Extending to 365 days resulted in 5 additional cases.  
CCB → Diuretic <6months  
289 cases of prescribing cascade were identified. Extending to 365 days resulted in 369 cases. |
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|--------------|-------------------|-------------------------------------------------------------------|
| **Exploratory studies** |                        |              |                   |                                                                 |
| Tsiropoulos (2009)68   | AEDs                   | Exploratory analysis | Any other medication presented in the same period | PSSA: All AEDs → Marker medication  
Propulsives ±183 days: aSR 1.31 (95%CI 1.11–1.56); n = 571  
Laxatives ±183 days: aSR 1.57 (95%CI 1.29–1.92); n = 432  
Topical corticosteroids ±183 days: aSR 1.32 (95%CI 1.16–1.52); n = 900 |
|                       |                        |              |                   | PSSA: Carbamazepine → Marker medication  
Propulsives ±183 days: aSR 1.57 (95%CI 1.14–2.19); n = 163  
Laxatives ±183 days: aSR 1.61 (95%CI 1.01–2.59); n = 82  
Topical corticosteroids ±183 days: aSR 1.48 (95%CI 1.17–1.87); n = 305 |
|                       |                        |              |                   | Anti-acne preparations ±183 days: aSR 3.66 (95%CI 1.31–2.62); n = 23 |
|                       |                        |              |                   | Bone disease treatment ±548 days: aSR 1.98 (95%CI 1.03–3.92); n = 43 |
|                       |                        |              |                   | PSSA: Oxcarbazepine → Marker medication  
Propulsives ±183 days: aSR 2.54 (95%CI 1.71–3.85); n = 119  
Laxatives ±183 days: aSR 3.74 (95%CI 2.31–6.29); n = 103  
Topical corticosteroids ±183 days: aSR 1.40 (95%CI 1.08–1.83); n = 245 |
|                       |                        |              |                   | Phenobarbital → Marker medication  
Bone disease treatment ±548 days: aSR 4.51 (95%CI 1.42–8.82); n = 18 |

**King (2020)75**  
654 different medications examined  
New onset heart failure  
Furosemide  

**TABLE 1** (Continued)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|------------------------|--------------|-------------------|------------------------------------------------------------------|
| Wahab (2016) 106     | 691 different medications examined | Heart failure | Furosemide        | PSSA: Index medication → Furosemide ± 1 year                       |
|                      |                        |              |                   | Teriparatide: aSR 5.02 (95% CI 1.07–23.7); n = 10                  |
|                      |                        |              |                   | Lodoxamide: aSR 2.50 (95% CI 1.06–5.91); n = 27                   |
|                      |                        |              |                   | Famotidine: aSR 1.69 (95% CI 1.38–2.08); n = 423                  |
|                      |                        |              |                   | Latanoprost: aSR 1.48 (95% CI 1.38–1.59); n = 3107                |
|                      |                        |              |                   | Pilocarpine: aSR 1.43 (95% CI 1.16–1.77); n = 632                 |
|                      |                        |              |                   | Brinzolamide: aSR 1.37 (95% CI 1.16–1.62); n = 564               |
|                      |                        |              |                   | Betahistine: aSR 1.31 (95% CI 1.07–1.62); n = 359                 |
|                      |                        |              |                   | Ranitidine: aSR 1.24 (95% CI 1.17–1.31); n = 5554                |
|                      |                        |              |                   | Paracetamol: aSR 1.06 (95% CI 1.04–1.09); n = 24210              |
| Chen (2021) 87       | Confirmatory analysis  | Hypothyroidism | Thyroxine         | Confirmatory PSSA ± 1 year                                       |
|                      | Amiodarone             | Gout         | Allopurinol       | Amiodarone → Thyroxine: aSR 3.77 (95% CI 3.43–4.14); n = 2667    |
|                      | Exploratory analysis   | Cough        | Exploratory PSSA ± 1 year | Amiodarone → Allopurinol: aSR 0.83 (95% CI 0.76–0.90); n = 2071 |
|                      | ACEIs                  | UTH          | ACEIs → Antitussive: aSR 1.33 (95% CI 1.31–1.34); n = 141924     |
|                      | Statins                | Storage LUTS | Statins → Drugs for urinary frequency: aSR 1.17 (95% CI 1.16–1.19); n = 107422 |
|                      | Buffered LDA           | Depression   | Statins → Antidepressants: aSR 1.19 (95% CI 1.18–1.21); n = 117443 |
|                      | Enteric-coated LDA     | Sleep disturbances |                   | Statins → Hypnotics: aSR 1.10 (95% CI 1.09–1.12); n = 124061   |
|                      | DH-CCBs                | Hepatotoxicity |                   | Statins → Ursoodeoxycholic acid: aSR 1.26 (95% CI 1.21–1.31); n = 11231 |
|                      |                        | Muscle pain  |                   | Statins → NSAIDs: aSR 1.02 (95% CI 1.02–1.03); n = 430774        |
|                      |                        | Skin and soft tissue infection |                   | Statins → Dicloxacillin/Flucloxacinil: aSR 1.18 (95% CI 1.15–1.22); n = 23068 |
|                      |                        | Infection in those with type-2 diabetes |                   | Statins → Antibiotic treatment (those with type 2 diabetes): aSR 1.38 (95% CI 1.36–1.39); n = 150016 |
|                      |                        | GI complications |                   | DH-CCBs → Loop diuretic: aSR 1.46 (95% CI 1.45–1.48); n = 139375  |

(Continues)
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|-----------------------|------------------------|---------------|-------------------|---------------------------------------------------------------|
| Lai (2014)            | Sulpiride Non-sulpiride antipsychotics | EPS Diabetes Hyperprolactinaemia Cardiac arrhythmias | Confirmatory analyses: Anticholinergics Oral hyperglycaemics Prolactine inhibitors Class 1B antiarrhythmics Exploratory analyses: all medications prescribed after the index date | Confirmatory PSSA analyses ± 12 months Sulpiride → Anticholinergics: aSR 1.73 (95% CI 1.46–2.06); n = 568 Haloperidol → Anticholinergics: aSR 1.99 (95% CI 1.68–2.35); n = 611 Risperidone → Anticholinergics: aSR 1.21 (95% CI 1.04–1.41); n = 702 Olanzapine → Anticholinergics: aSR 0.73 (95% CI 0.58–0.93); n = 281 Amisulpiride → Anticholinergics: aSR 0.54 (95% CI 0.40–0.73); n = 188 Sulpiride → Prolactine inhibitors: aSR 12.0 (95% CI 1.59–91.2); n = 16 Amisulpiride → Prolactine inhibitors: aSR 8.05 (95% CI 1.00–65.4); n = 8 Haloperidol → Class 1b antiarrhythmics: sSR 2.81 (95% CI 1.03–7.66); n = 21 Exploratory PSSA analyses: Sulpiride → Marker medication ± 12 months Stomatological preparations: aSR 1.86 (95% CI 1.13–3.07); n = 71 Corticosteroids for local oral treatment: aSR 1.71 (95% CI 1.00–2.91); n = 59 Beta blockers, any: aSR 1.42 (95% CI 1.12–1.71); n = 371 Beta blockers, non-selective: aSR 1.61 (95% CI 1.28–2.03); n = 304 Dermatological preparations, corticosteroids: aSR 2.18 (95% CI 1.21–3.92); n = 57 Corticosteroids weak, other combinations: aSR 2.15 (95% CI 1.08–4.28); n = 42 Quinolones: aSR 1.50 (95% CI 1.00–2.24); n = 101 Fluroquinolones: aSR 1.81 (95% CI 1.03–3.17); n = 55 Anti-inflammatory preparations, non-steroidal for topical use: aSR 1.36 (95% CI 1.01–1.84); n = 173 |
| Primary author (year) | Initial medication(s) | Suspected ADR | New medication(s) | Quantitative association (primary analysis or association at 1 year) |
|----------------------|-----------------------|---------------|-------------------|---------------------------------------------------------------|
| Hallas (2018)        | 186 758 associations tested in the main analysis; 30 best signals reported | Exploratory analysis | 30 strongest signals reported | PSSA: Index → Marker medication ± 12 months<br>Opoids → Drugs for constipation (crude SR 2.34, 95%CI 2.31–2.38; n = 84020<br>High ceiling diuretics → Potassium SR 3.31 (95%CI 3.24–3.38); n = 48 539<br>Thiazide → Potassium SR 3.46 (95%CI 3.39–3.54); n = 45 175<br>Opioids → Propulsives SR 2.14 (95%CI 2.10–2.17); n = 62 139<br>NSAIDS → Anti-ulcer drugs SR 1.71 (95%CI 1.67–1.74); n = 49 646<br>Antithrombotic → Anti-ulcer drugs SR 1.41 (95%CI 1.39–1.44); n = 54 841<br>Cough suppressants → Drugs for constipation SR 1.95 (95%CI 1.90–2.00); n = 260 015<br>Corticosteroids, systemic use → Drugs affecting bone structure and mineralisation SR 3.40 (95%CI 3.27–3.54); n = 13 023 |
| Hellfritzsch (2018)  | Non-vitamin K oral anticoagulants (NOAC) | Exploratory analysis | 20 strongest signals reported | PSSA: NOAC → Marker drug ± 6 months<br>Benzodiazepines, hypnotic: cSR 8.28 (95%CI 6.01–12.05); NNTH 193<br>Osmotic laxatives: cSR 1.35 (95%CI 1.25–1.46); NNTH 133<br>Benzodiazepines, sedative: cSR 1.99 (95%CI 1.74–2.30); NNTH 174<br>Corticosteroids, anal use: cSR 2.03 (95%CI 1.76–2.35); NNTH 176<br>SSRI: cSR 1.57 (95%CI 1.37–1.77); NNTH 202<br>Other antidepressant: cSR 1.59 (95%CI 1.41–1.80); NNTH 207<br>PPi: cSR 1.39 (95%CI 1.11–1.28); NNTH 209<br>Phenylpiridine opioids: cSR 2.12 (95%CI 1.81–2.51); NNTH 215<br>Propulsives: cSR 1.51 (95%CI 1.35–1.71); NNTH 216<br>Iron bivalent, oral: cSR 1.62 (95%CI 1.42–1.86); NNTH 238<br>Contact laxatives: cSR 1.29 (95%CI 1.17–1.43); NNTH 253 |

Abbreviations: aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; aOR, adjusted odds ratio; aSR, adjusted sequence ratio; cSR, crude sequence ratio; HR, hazard ratio; IDR, incidence density ratio; IRR, incidence rate ratio; NNTH, number needed to harm; PSSA, prescription sequence symmetry analysis.

*aCase–control study.
*bCase-crossover study.
*cCross-sectional study.
*dIncludes case–control study.
*eIncludes cross-sectional study.
Initial medication Anatomical Therapeutic Classification (ATC) codes were not reported for 66 studies and were assigned by our research team.

3.5 | Suspected adverse reaction(s)

Throughout the included studies, suspected ADRs were presumed to have occurred based on the initiation of the second medication as a treatment. In one study examining the CCB→loop diuretic prescribing cascade, an additional medical chart review was also conducted.\(^{105}\)

The suspected ADRs, symptoms or new diagnoses explored were broad-ranging (see Table 2) most commonly depression (\(n = 13\))\(^{33,37,40,45,52,55,77,72,93,97,98,110,112}\); peripheral oedema (\(n = 11\))\(^{5,7,28,30,36,44,96,103-105,116}\); urinary incontinence (\(n = 9\))\(^{24,26,30,41,44,50,53,74,117}\) and parkinsonism (\(n = 9\))\(^{27,29,31,46,57,63,82,119}\).
| Initial medication | Suspected ADR | Second medication | Main findings |
|-------------------|--------------|------------------|---------------|
| DH-CCB            | Oedema       | Loop diuretic    | <1 year: aSR 1.46 (95% CI 1.45–1.48); n = 13937587<sup>87</sup>  
<360 days: aSR 1.87 (95% CI 1.84–1.90); 558187<sup>7</sup>  
<360 days: aSR 2.27 (95% CI 1.44–3.58); n = 90<sup>105</sup>  
<360 days: aSR 1.72 (95% CI 1.66–1.79) relative to levethyroxine negative control; aSR 1.45 (1.41–1.49) relative to ACEI/ARB negative control<sup>35</sup> |
| Amiodarone        | Hypothyroidism| Thyroxine        | <1 year: aSR 3.77 (95% CI 3.43–4.14); n = 266787<sup>5</sup>  
<360 days: aSR 3.57 (95% CI 3.17–4.02) |
| Inhaled corticosteroids | Oral candidiasis | Topical antifungals | <90 days OR 1.66; n = 21<sup>56</sup>  
<1 year: SR 2.89 (95% CI 2.80–2.97)  
<1 year: SR 1.94 (95% CI 1.71–2.21)  
<360 days: aSR 2.34 (95% CI 2.19–2.50)<sup>54</sup> |
| Neuroleptics/ Antipsychotic | Parkinsonian symptoms/ extrapyramidal symptoms | Anti-parkinson medication or Parkinson diagnosis | <90 days: aOR 5.4 (95% CI 4.8–6.1)<sup>19</sup>  
<1 year (1 antipsychotic): aSR 9.24 (7.35–11.8); n = 817<sup>100</sup>  
<1 year (2 antipsychotics): aSR 22.2 (9.94–61.7); n = 137  
<1 year (≥3 antipsychotics): aSR 34.8 (5.87–141.8); n = 37  
Never use: aOR 1.0 (referent); n = 10714<sup>119</sup>  
Very-late use (≥181 days): aOR 1.1 (95% CI 0.6–1.8); n = 61  
Late use (31–180 days): aOR 2.0 (95% CI 1.2–3.3); n = 94  
Early use (8–30 days): aOR 6.0 (95% CI 2.3–15.9); n = 43  
Current use (≤7 days): aOR 3.0 (95% CI 1.7–5.4); n = 80  
Typical: aOR 6.4 (95% CI 1.4–28.2); n = 17  
Haloperidol: aOR 4.3 (95% CI 0.9–20.1); n = 12  
Atypical: aOR 2.4 (95% CI 1.2–4.9); n = 56  
Quetiapine: aOR 0.9 (95% CI 0.4–2.2); n = 26  
Risperidone: aOR 13.5 (95% CI 1.8–102.1); n = 23  
Combined use: aOR 3.2 (95% CI 0.6–17.9); n = 7  
Typical antipsychotics: aHR 1.30 (95% CI 1.04–1.58) versus atypical antipsychotic use<sup>29</sup>  
No therapy: aHR 0.40 (95% CI 0.29–0.43) |
| Acetylcholinesterase inhibitors | Urinary incontinence | Drugs for urinary frequency and incontinence | During follow-up (1st June 1999–31st March 2003): older adults dispensed acetylcholinesterase inhibitors had a higher risk of subsequently receiving an anticholinergic medication to treat urge urinary incontinence (aHR, 1.55; 95% CI, 1.39–1.72)<sup>26</sup>  
Donepezil—Medication for managing Lower Urinary Tract Symptoms (LUTS)<sup>53</sup>  
<3 months: 1.32 (95% CI 1.00–3.50); n = 243  
<12 months: aSR: 1.98 (95% CI 1.57–2.50); n = 319  
<6 months: aHR 1.47 (95% CI 1.17–1.86) versus memantine users<sup>64</sup>  
<12 months: aHR 1.41 (95% CI 1.17–1.69) versus memantine users  
Donepezil: aHR 1.55 (95% CI 1.31–1.83) versus rivastigmine use<sup>24</sup>  
Galantamine: aHR 1.17 (95% CI 0.87–1.58) versus rivastigmine use |

(Continues)
| Initial medication | Suspected ADR | Second medication | Main findings |
|--------------------|---------------|-------------------|---------------|
| Metoclopramide     | Parkinsonian symptoms | Levodopa          | <90 days: aOR 3.04 (95% CI 2.22–4.17)\(^{20}\) <90 days: aOR 2.94 (95% CI 2.35–3.67)\(^{21}\) Anti-Parkinson medication or diagnosis <1 year: aOR 2.7 (95% CI 1.8–4.1); n = 121\(^{119}\) |
| ACE inhibitors     | Cough          | Antitussive       | <1 year OR = 1.58 (95% CI 1.21–2.07)\(^{73}\) <6 months: SR 2.0 (95% CI 1.8–2.2); n = 1898; estimated 13.4% mistreated cough\(^{18}\) <1 year: aSR 1.33 (95% CI 1.31–1.34); n = 141924\(^{37}\) |
| NSAID              | GI symptoms    | Anti-ulcer medication | <4 weeks: aSR 2.50 (95% CI 2.27–2.76); n = 2016\(^{132}\) <100 days: aSR 1.80 (95% CI 1.64–1.99); n = 1814\(^{39}\) <1 year: SR 1.71 (95% CI 1.67–1.74); n = 4964\(^{101}\) |
| Ranitidine         | Heart failure  | Furosemide        | <1 year: aSR 1.08 (95% CI 1.04–1.12); n = 10875\(^{75}\) <1 year: aSR 1.24 (95% CI 1.17–1.31); n = 5554\(^{106}\) |
| Rosiglitazone      | failure        | Furosemide        | <1 year Australia-1: aSR 1.70 (95% CI 1.34–2.15)\(^{96}\) <1 year Australia-2: aSR 1.63 (95% CI 1.51–1.76) <1 year Canada: aSR 1.65 (95% CI 1.57–1.73) <1 year Pooled estimate (Australia & Canada): aSR 1.65 (95% CI 1.58–1.72) <1 year Hong Kong: aSR 3.37 (95% CI 1.69–6.72) <1 year Korea: aSR 1.14 (95% CI 1.08–1.21) <1 year Taiwan: aSR 1.12 (95% CI 0.99–1.25) <1 year Pooled estimate (Asia): aSR 1.21 (95% CI 1.01–1.45) July 2000–December 2007: aSR 1.73 (95% CI 1.34–2.24)\(^{113}\) |
| SGLT2-I            | Genital infections | Antifungal | <30 days: aSR 1.35 (95% CI 1.26–1.44)\(^{47}\) <60 days: aSR 1.48 (95% CI 1.40–1.56) <90 days: aSR 1.53 (95% CI 1.43–1.60) <180 days: aSR 1.42 (95% CI 1.37–1.47) <365 days: aSR 1.24 (95% CI 1.20–1.28) Genetic infection occurred more frequently among SGLT2-I users than DPP-4 users (2.9% vs. 0.9%, aHR 3.50, 95% CI 1.95–5.89)\(^{88}\) |
| DOAC               | Depression     | Antidepressant    | <3 months: aSR 1.29 (95% CI 1.23–1.35); n = 7253\(^{93}\) <6 months: aSR 1.28 (95% CI 1.24–1.33); n = 12530 <12 months: aSR 1.26 (95% CI 1.23–1.30); n = 20613 SSRI <6 months: SR 1.57 (1.37–1.77); n = 1137; NNTH 207\(^{102}\) Other antidepressant <6 month: SR 1.59; 1076; (1.41–1.80); NNTH 207 |
| High ceiling diuretics | Hypokalaemia | Potassium         | Furosemide <360 days: aSR 2.94 (95% CI 2.83–3.05)\(^{34}\) High ceiling diuretic <1 year: SR 3.31 (95% CI 3.24–3.38); n = 48539\(^{101}\) |
| Statins            | Lower urinary tract symptoms (LUTS) | Drugs for urinary frequency and incontinence | <91 days: aSR 1.21 (95% CI 1.00, 1.46); n = 445\(^{50}\) <182 days: aSR 1.19 (95% CI 1.04, 1.38); n = 785 <365 days: aSR 1.17 (95% CI 1.05, 1.30); n = 1373 <1 year: aSR 1.17 (95% CI 1.16–1.19); n = 107422\(^{37}\) |
| Statins            | Skin soft tissue infection | Antibiotic (Dicloxacillin or Flucloxacillin) | <1 year: aSR 1.18 (95% CI 1.15–1.22); n = 23068\(^{87}\) <91 days: aSR 1.40 (95% CI 1.29–1.52); n = 2498\(^{76}\) <182 days: aSR 1.41 (95% CI 1.33–1.50); n = 4277 <365 days: aSR 1.40 (95% CI 1.34–1.47); n = 7726 |
| Statins            | Depression     | Antidepressant    | <1 year: aSR 1.19 (95% CI 1.18–1.21); n = 117443\(^{37}\) Simvastatin → Antidepressant (April 1991–December 1995): aSR 1.59 (1.08–2.45); n = 91\(^{88}\) |
| Statins            | Muscle cramps  | Quinine           | <360 days: aSR 1.69 (95% CI 1.61–1.77)\(^{70}\) <1 year: aSR 1.16 (95% CI 1.04–1.29); n = 1326\(^{51}\) |
| Brinzolamide       | Heart failure  | Furosemide        | <1 year Brinzolamide: aSR 1.18 (95% CI 1.06–1.32); n = 130\(^{75}\) <1 year Brinzolamide: aSR 1.37 (95% CI 1.16–1.62); n = 564\(^{106}\) |
| Latanoprost        | Heart failure  | Furosemide        | <1 year Latanoprost: aSR 1.11 (95% CI 1.04–1.19); n = 3619\(^{75}\) <1 year Latanoprost: aSR 1.48 (95% CI 1.38–1.59); n = 3107\(^{106}\) |
| Carbamazepine      | Hypothyroidism | Levothyroxine     | 1998–2004: aOR 1.37 (95% CI 1.13–1.65)\(^{330}\) <1 year: aSR 1.21 (99% CI 1.08–1.34)\(^{79}\) |
### TABLE 2 (Continued)

| Initial medication | Suspected ADR                  | Second medication | Main findings                                                                 |
|--------------------|--------------------------------|-------------------|--------------------------------------------------------------------------------|
| Valproate          | Hypothyroidism                 | Levothyroxine     | 1998–2004: aOR 1.72 (95%CI 1.40–2.11)\(^{130}\)  
<1 year: aSR 1.34 (99% CI 1.20–1.49)\(^{79}\) |
| Lithium            | Drug induced tremor Parkinson  | Anti-parkinson drug | Jan 1995–December 1999: RR 1.88 (95%CI 1.60–2.20)\(^{82}\)  
Up to 2 year follow-up (referent valproic acid): aHR 1.50 (95%CI 0.68–3.36)\(^{27}\)  
Up to 2 year follow-up (referent antidepressant): aHR 1.56 (95%CI 0.98–2.48) |
| Lithium            | Hypothyroidism                 | Thyroxine         | 1998–2004: aOR 1.41 (95%CI 1.14–1.74)\(^{130}\)  
<360 days: aSR 3.43 (95% CI 2.55–4.70)\(^{54}\) |
| Benzodiazepine     | Dementia                       | Anti-dementia drug | <3months: aSR 1.24 (95%CI 1.05–1.45); n = 625\(^{46}\)  
<6months: aSR 1.20 (95%CI 1.06–1.37); n = 973  
<12months: aSR 1.23 (95%CI 1.11–1.37); n = 1450  
<24months: aSR 1.34 (95%CI 1.23–1.47); n = 2049  
<36months: aSR 1.41 (95%CI 1.29–1.53); n = 2408  
<48months: aSR 1.44 (95%CI 1.33–1.56); n = 2653  
<3years: aSR 2.19 (95%CI 1.92–2.49); n = 1285\(^{94}\)  
<2years: aSR 2.00 (95%CI 1.71–2.34); n = 780  
<1year: aSR 1.77 (95%CI 1.39–2.27); n = 286 |
| SSRI               | Urinary incontinence           | Drugs for urinary frequency and incontinence (or incontinence products)\(^{91}\) | Paroxetine <1 year: aSR 1.77 (95%CI 1.33–2.36)\(^{53}\)  
During SSRI (before SSRI as referent): IDR 1.57 (95%CI 1.38–1.79)\(^{41}\)  
During SSRI (after SSRI as referent): IDR 2.03 (95%CI 1.76–2.34)  
During SSRI (before and after SSRI as referent): IDR 1.75 (95%CI 1.56–1.97)  
Patients had a 61% higher risk for incontinence (aRR 1.61, 95%CI 1.42–1.82) |

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aSR, adjusted sequence ratio; IDR, incidence density ratio; NTH, number needed to harm; SR, crude sequence ratio.

### 3.6 | New medication(s) prescribed

The medication sub-classifications most frequently initiated as a new medication in the 94 studies are summarised in Figure 2A. Seventy-eight studies reported at least one significant positive association, indicating a potential prescribing cascade (Table 1 and Figure 2A–C).

The most commonly identified prescribing cascades are summarised in Table 2. These include; amiodarone associated with subsequent thyroid hormone prescriptions for hypothyroidism (n = 5),\(^{54,61,79,85,87}\) CCBs associated with diuretic prescriptions to treat peripheral oedema (n = 5),\(^{5,7,8,7,104}\) topical antifungals to treat oral candidiasis following inhaled corticosteroids (n = 4),\(^{39,54,56,71}\) anti-Parkinson medication to treat Parkinsonian symptoms following antipsychotic initiation (n = 4),\(^{19,29,100,119}\) urinary anticholinergics to treat urinary incontinence following acetylcholinesterase inhibitors (n = 4),\(^{24,26,44,53}\) and antitussives to treat cough following angiotensin-converting enzyme inhibitors (ACEIs) (n = 3).\(^{18,73,87}\) Additional prescribing cascades identified included metoclopramide to anti-Parkinson medication (n = 3).\(^{20,31,119}\) and NSAID to anti-ulcer medication.\(^{89,91,101}\)

No association between drug pairs could be determined for several studies, largely due to either a cross-sectional study design examining concurrent drug use, insufficient drug-pair sample size to determine a sequence ratio or reporting of incidence rates with no incidence rate ratio (labelled N/A in Figure 2).\(^{5,21,25,30,43,46,53,55,63,64,78,79,112,114,115}\) Several studies reported at least one negative association between drug pairs, indicating a reduced likelihood of the second medication being initiated (see eTable 3 Appendix S1).\(^{33,60,68–70,74,81,87,89,93,111}\)

### 3.7 | Modifiers of identified associations

Older people (aged ≥65 years) were more likely to receive; (i) anticholinergics for urinary incontinence following SSRI initiation,\(^{41}\) (ii) ulcer drug therapy within 100 days of NSAID initiation,\(^{89}\) (iii) diuretic to treat beta-blocker induced oedema,\(^{36}\) and, (iv) thyroxine for hypothyroidism following amiodarone initiation.\(^{85}\) Females were more likely to receive an antitussive for cough following ACEI initiation,\(^{73}\) anticholinergic medication for urinary incontinence following acetylcholinesterase inhibitors,\(^{24,30}\) and SSRI initiation,\(^{45}\) and levothyroxine following amiodarone initiation.\(^{85}\)

Differential associations were identified for initial medication dosage in nine studies. Those who received higher doses of CCBs,\(^{5,7}\) and gabapentinoids were more likely to receive a diuretic for oedema,\(^{28}\) higher doses of inhaled corticosteroids were associated with a greater likelihood of treatment for oral candidiasis,\(^{39}\); and higher metoclopramide dosage was found to increase the likelihood for dopaminergic treatment initiation.\(^{20}\)
Polypharmacy (≥5 drugs) was associated with a greater likelihood of receiving thyroid hormones for amiodarone induced hypothyroidism.85

3.8 | Intentional and unintentional cascades

The intentionality of potential prescribing cascades was not reported in any study nor was the intended duration (if any) of the prescription of the second medication. One study provided a breakdown of prescriptions for the initial drug by prescriber type: 23% private cardiologist, 35.5% hospital practitioner, 30.3% General Practitioner, and 11.3% other private specialist, but did not provide details of the prescriber of the second drug.93 Another study reported that of the sample who initiated the second drug (irrespective of initiating the first drug), 87.1% of prescriptions were started by family physicians.51

3.9 | Clinical importance of prescribing cascade

Two studies reported a number needed to harm (NNTH) for investigated cascades.62,102 (See Table 1). One study (n = 90) conducted a medical chart validation study of those initiated a loop diuretic after initiating a dihydropyridine CCB (n = 64) and determined that 54.7% (n = 35) experienced a prescribing cascade.105

3.10 | Quality assessment

Overall, the methodological quality varied across included studies (Figure 3 and eTables 4–6, Appendix S1). Among the retrospective cohort studies (eTable 4, Appendix S1) there was a lack of clarity surrounding the similarity of exposed and unexposed groups at baseline and the presence of the outcome at the start of the study. For case–control studies (eTable 5, Appendix S1), reporting of baseline

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**FIGURE 3** Quality appraisal summary of included studies (n = 98): (A) cohort studies; (B) case–control studies; (C) cross-sectional studies.
comparison of cases and controls was inadequate as well as the appropriateness of matching cases with controls.

4 | CONCLUSION AND IMPLICATIONS

4.1 | Principal findings

This systematic review identified 101 studies across 103 publications that examined potential prescribing cascades across a broad range of pharmacological drug groups. All studies used routine administrative data that included either medication prescribing or dispensed medications data. Of the 101 included studies, 78 (77%) reported at least one significant positive quantitative association that indicates a potential prescribing cascade. The most commonly identified prescribing cascades include: (i) CCBs → loop diuretics to treat peripheral oedema (n = 5); (ii) amiodarone → thyroxine to treat hypothyroidism (n = 5); inhaled corticosteroids → topical antifungal to treat candidiasis (n = 4); (iii) antipsychotics → anti-Parkinson medication to treat Parkinsonism (n = 4); and (iv) acetylcholinesterase inhibitors → drugs for urinary frequency (n = 4).

Study methodological quality was variable with a considerable proportion of studies not reporting participant demographics. Almost two-thirds of included studies used PSSA methodology in which all included participants have experienced the outcome at the start of the study. A recent scoping review reported that whilst the PSSA method is a useful tool in detecting prescribing cascades, such cascades need careful clinical review as there is a risk of both false positive and false negative findings. This is particularly problematic when screening for cascades without predefined hypotheses. In our systematic review, the vast majority of included studies (n = 94, 93%) examined predefined medications as potentially contributing to a prescribing cascade. However, PSSA analyses cannot determine causality and should be interpreted with caution.

Several well-designed cohort and case–control studies examining prescribing cascades were identified. For example, a Canadian population-based study reported that incident CCB users had a higher cumulative incidence of loop diuretic use at one year follow up compared to patients dispensed ACEIs or angiotensin-II-receptor blocker antihypertensives (adjusted hazards ratio 1.4% vs. 0.7%, p < 0.001). In a US case–control study, metoclopramide users were three times more likely to begin use of a levodopa-containing medication compared with nonusers (OR = 3.09; 95% CI 2.25 to 4.26). Risk increased with increasing daily metoclopramide dose and the effect persisted after adjustment for demographic, health service utilization, and medication use variables.

Fifteen of 101 studies focused specifically on older populations, with 11 reporting a significant association between increasing age and prescribing cascade occurrence. Older adults are more likely to experience medication-related harm due to increasing prevalence of multimorbidity, polypharmacy and age-related physiological changes that affect drug metabolism. Furthermore, ADRs are more difficult to diagnose in older adults due to their often non-specific presentation and overlap with pre-existing conditions or conditions likely to develop among older adults.

4.2 | Comparison with existing literature

Two scoping reviews of prescribing cascades have been conducted to date, one that focused on literature surrounding the prevention, detection and reversal of prescribing cascades and the second that focused on the use of PSSA as a potential pharmacovigilance tool. In 2018, Brath et al retrieved 10 original investigations and seven case reports pertaining to prescribing cascades. A considerable number of studies have been published since, indicating that this is a rapidly developing field. Morris et al. concluded that PSSA methodology demonstrated only moderate sensitivity and specificity in identifying prescribing cascades and more consistency was required in how these studies were reported. As described previously, similar issues with methodological quality were identified in this systematic review.

4.3 | Clinical and research implications

Multi-country studies have shown variation in prescribing cascade likelihood both within and across countries, underscoring the need to consider the local prescribing context. Differences in sample demographics, medication availability, approved clinical indications, help-seeking behaviour and prescribing cultures or genetic polymorphisms may influence the incidence of prescribing cascades.

The complexity of optimising prescribing for patients with multimorbidity presents challenges for the prescriber due to the preponderance of single-disease guidelines, resultant polypharmacy, fragmentation and lack of continuity of care and resourcing constraints. Identification of ADRs remains a clinically challenging area, particularly in relation to older adults. Non-specific presentation of ADR symptoms in older adults, such as delirium, falls, fatigue and constipation, can be challenging to identify as being medication-related as such symptoms have several causes and may overlap with existing multimorbidity. The failure to recognise an ADR may result in a prescribing cascade, furthering the risk for additional medication-related harm. The potential for ADRs should be considered as part of the differential diagnosis for all patients reporting new symptoms, particularly among those who have started a new medication within the previous year.

Developing an explicit list of evidence-based prescribing cascades is one way of supporting clinicians’ awareness and detection of this issue. The iKASCADE international consortium are currently developing an inventory of prescribing cascades affecting older adults, through a modified Delphi procedure where international experts in medicines management for older adults will rank a list of prescribing cascades as to their clinical importance. The development of an explicit list of clinically important and common prescribing cascades is an important step in raising awareness of this
issue and in supporting clinicians to detect cascades. To maximise use in clinical practice will require explicit criteria of prescribing cascades be incorporated into existing electronic health record and prescribing support systems. Such systems will need to be able to detect the sequential prescription of drugs known to represent potentially inappropriate prescribing cascades.

The use of routine administrative data in included studies means that information on the broader clinical context and the rationale for medication prescribing is lacking. The identification of significant negative associations between drug pairs may indicate that prescribers are aware of certain prescribing cascades and proactively avoid their development or that therapeutic alternatives were prescribed. However, no exploration of intentionality of identified cascades could be made based on the data used in included studies.

Overall, it is difficult to determine the clinical importance of prescribing cascades identified as few studies examined clinical endpoints. One study examined the association between prescribing cascades that resulted in prochlorperazine initiation and reported a subsequent 49% increased risk of hip fracture. Future research is required to determine the relative clinical impact of increased medication exposure and the clinical appropriateness of prescribing cascades.

4.4 | Strengths and limitations

This systematic review extends the work of previously published scoping reviews by conducting a comprehensive literature search using several databases, including several grey literature searches.

This study also has some limitations. The lack of a MeSH term for prescribing cascades meant broad search terms were used, which led to a high yield of citations to be searched. Additional information was sought from study authors but a small number of studies (n = 10) could not be retrieved for eligibility assessment due to the lack of access to the full text or a translated version. The information collated is somewhat limited by the methodological and reporting quality of included studies.

5 | CONCLUSION

Prescribing cascades are of increasing interest to the research and clinical communities, with a broad range of medications involved. The identification of the most common prescribing cascades can support optimising prescribing as one part of identifying potentially inappropriate prescribing. Few studies have examined the clinical importance or the broader clinical context, including intentionality of prescribing cascades, thereby limiting the inferences that can be drawn about the implications for clinical practice. Challenges remain in differentiating ADR symptoms from that of new onset disease and advancing age and frailty. ADRs should be considered as part of the differential diagnosis in patients presenting with new symptoms, particularly for those who have started a new medication in the preceding 12 months.

AUTHOR CONTRIBUTIONS
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CONFLICT OF INTEREST
The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT
Additional systematic review data is available from the authors on request.

ETHICS STATEMENT
Ethical approval was not required for this systematic review.

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REFERENCES
1. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. Br Med J. 1997;315(7115):1096-1099.
2. Rochon PA, Gurwitz JH. The prescribing cascade revisited. Lancet. 2017;389(10081):1778-1780.
3. Rochon PA, Gurwitz JH. Drug therapy. Lancet. 1995;346(8966):32-36.
4. McCarthy LM, Visentin JD, Rochon PA. Assessing the scope and appropriateness of prescribing cascades. J Am Geriatr Soc. 2019;67(5):1023-1026.
5. Savage RD, Visentin JD, Bronskill SE, et al. Evaluation of a common prescribing cascade of calcium channel blockers and diuretics in older adults with hypertension. JAMA Intern Med. 2020;180(5):643-651.
edema-loop diuretic prescribing cascade. *J Am Pharm Assoc.* 2018;58(5):534-539.

7. Vourri SM, Jiang X, Manini TM, et al. Magnitude of and characteristics associated with the treatment of calcium channel blocker-induced lower-extremity edema with loop diuretics. *JAMA Netw Open.* 2019;2(12):e1918425.

8. Lavan AH, Gallagher P. Predicting risk of adverse drug reactions in older adults. *Ther Adv Drug Saf.* 2016;7(1):11-22.

9. Palladino R, Taysu Lee J, Ashworth M, Triassi M, Millett C. Associations between multimorbidity, healthcare utilisation and health status: evidence from 16 European countries. *Age Ageing.* 2016;45(3):431-435.

10. Salisbury C, Johnson L, Purdy S, Valderas JM, Montgomery AA. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract.* 2011;61(582):e12-e21.

11. Brath H, Mehta N, Savage RD, et al. What is known about preventing, detecting, and reversing prescribing cascades: a scoping review. *J Am Geriatr Soc.* 2018;66(11):2079-2085.

12. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analyses (PRISMA-P) statement. *Syst Rev.* 2015;2015:4.

13. Doherty A, Moriarty F, Boland F. et al. Prescribing cascades in community-dwelling adults: protocol for a systematic review. *HRB Open Res.* 2021;4:72.

14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.

15. Vegter S, De Jong-Van Den Berg LTW. Misdiagnosis and mistreatment of a common side-effect—Anticholinesterase-inhibiting enzyme inhibitor-induced cough. *Br J Clin Pharmacol.* 2010;69(2):200-203.

16. Vegter S, De Boer P, Van Dijk KW, Visser S, De Jong-Van Den Berg LTW. Misdiagnosis and mistreatment of ACE-inhibitor-induced cough occurs frequently and decreases therapy compliance. *Pharm Weekbl.* 2012;147(42):177-180.

17. Vegter S, De Boer P, van Dijk KW, Visser S, de Jong-van den Berg LTW. The effects of antitussive treatment of ACE-inhibitor-induced cough on therapy compliance: a prescription sequence symmetry analysis. *Drug Saf.* 2013;36(6):435-439.

18. Avorn J, Bohn RL, Mogun H, et al. Neuroleptic drug exposure and treatment of parkinsonism in the elderly: a case-control study. *Am J Med.* 1995;99(1):48-54.

19. Avorn J, Gurwitz JH, Bohn RL, Mogun H, Monane M, Walker A. Increased incidence of levodopa therapy following metoclopramide use. *JAMA.* 1995;274(22):1780-1782.

20. Farkas AH, Winn A, Pezzin LE, Fergestrom N, Laud P, Neuner JM. The use and concurrent use of side effect controlling medications among women on oral contraceptive use. *J Women’s Health.* 2021;30(1):131-136.

21. Gurwitz JH, Avorn J, Bohn RL, Glynn RJ, Monane M, Mogun H. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA.* 1994;272(10):781-786.

22. Gurwitz JH, Kalish SC, Bohn RL, et al. Thiazide diuretics and the initiation of anti-gout therapy. *J Clin Epidemiol.* 1997;50(8):953-959.

23. Masurkar PP, Chatterjee S, Sherrer JT, Aparasu RR. Antimuscarinic cascade across individual cholinesterase inhibitors in older adults with dementia. *Drugs Aging.* 2021;38(7):593-602.

24. Narayan SW, Pearson SA, Litchfield M, et al. Anticholinergic medications use among older adults before and after initiating dementia medicines. *Br J Clin Pharmacol.* 2019;85(9):1957-1963.

25. Gill SS, Mandani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med.* 2005;165(7):808-813.

26. Gill SS, Mandani M, Naglie G, et al. A prescribing cascade involving cholinesterase inhibitors and anticholinergic drugs. *Arch Intern Med.* 2005;165(7):808-813.

27. Marras C, Herrmann N, Fischer HD, et al. Lithium use in older adults is associated with increased prescribing of Parkinson medications. *Am J Geriatr Psychiatry.* 2016;24(4):301-309.

28. Read SH, Giannakaeas V, Pop P, et al. Evidence of a gabapentinoid and diuretic prescribing cascade among older adults with lower back pain. *J Am Geriatr Soc.* 2021;69(10):2842-2850.

29. Rochon PA, Stukel TA, Sykora K, et al. Atypical antipsychotics and Parkinsonism. *Arch Intern Med.* 2005;165(16):1882-1888.

30. Trenaman SC, Bowles SK, Kirkland S, Andrew MK. An examination of three prescribing cascades in a cohort of older adults with dementia. *BMC Geriatr.* 2021;21(1):1-11.

31. Huh Y, Kim DH, Choi M, et al. Metoclopramide and levosulpiride use and subsequent levodopa prescription in the Korean elderly: the prescribing cascade. *J Clin Med.* 2019;8(9):1496.

32. Park SK, Baek YH, Pratt N, Kalisch Ellett L, Shin YJ. The uncertainty of the association between proton pump inhibitor use and the risk of dementia: prescription sequence symmetry analysis using a Korean healthcare database between 2002 and 2013. *Drug Saf.* 2018;41(6):615-624.

33. Dyson TE, Cantrell MA, Lund BC. Lack of association between 5x-reductase inhibitors and depression. *J Urol.* 2020;204(4):793-798.

34. Fox CW, Khaw CL, Gerke AK, Lund BC. Montelukast and neuropsychiatric events—a sequence symmetry analysis. *J Asthma.* 2022:1-7.

35. Vouri SM, Jiang X, Brumback B, Winterstein AG. Use of negative controls in a prescription sequence symmetry analysis used to mitigate time-varying bias. *Pharmacoepidemiol Drug Saf.* 2020;29(suppl 3):390-391.

36. Vouri SM, Morris EJ, Jiang X, et al. Evaluation of a beta-blocker–edema-loop diuretic prescribing cascade: a prescription sequence symmetry analysis. *Am J Hypertens.* 2022;35:601-609.

37. Brandt-Christensen M, Kvist K, Nilsson FM, Andersen PK, Kessing LV. Treatment with antiparkinson and antidepressant drugs: a register-based, pharma-epidemiological study. *Mov Disord.* 2007;22(14):2037-2042.

38. Dunvald ACD, Henriksen DP, Hallas J, Christensen MMH, Lund LC. Selective serotonin reuptake inhibitors and the risk of restless legs syndrome: a symmetry analysis. *Eur J Clin Pharmacol.* 2020;76(5):719-722.

39. Henriksen DP, Davidsen JR, Christiansen A, Laursen CB, Damkier P, Hallas J. Inhaled corticosteroids and systemic or topical antifungal therapy: a symmetry analysis. *Ann Am Thorac Soc.* 2017;14(6):1045-1047.

40. Winkel JS, Damkier P, Hallas J, Henriksen DP. Treatment with montelukast and antidepressive medication—a symmetry analysis. *Pharmacoepidemiol Drug Saf.* 2018;27(12):1409-1415.

41. Movig KLL, Leufkens HGM, Belitser SV, Lenderink AW, Egberts ACG. Selective serotonin reuptake inhibitor-induced urinary incontinence. *Pharmacoepidemiol Drug Saf.* 2002;11(4):271-279.

42. Wang Y, Bos JH, Schuiling-Veninga CCM, et al. Neuropsychiatric safety of varenicline in the general and COPD population with and without psychiatric disorders: a retrospective cohort study in a real-world setting. *BMJ Open.* 2021;11(5):e042417.

43. Takeuchi Y, Kajiyama K, Ishiguro C, Uyama Y. Atypical antipsychotics and the risk of hyperlipidemia: a sequence symmetry analysis. *Drug Saf.* 2015;38(7):641-650.

44. Lampela P, Taipale H, Hartikainen S. Use of cholinesterase inhibitors increases initiation of urinary anticholinergics in persons with Alzheimer’s disease. *J Am Geriatr Soc.* 2016;64(7):1510-1512.

45. Azoulay L, Blais L, Koren G, Le Lorier J, Béard A. Isotretinoin and the risk of depression in patients with acne vulgaris: a case-crossover study. *J Clin Psychiatry.* 2008;69(4):526-532.

46. Onder G, Bonnassi S, Abbatecola AM, et al. High prevalence of poor quality drug prescribing in older individuals: a nationwide report from the Italian Medicines Agency (AIFA). *J Gerontol Series A: Biol Sci Med Sci.* 2014;69(4):430-437.
47. Adimadhyam S, Schumock GT, Calip GS, Smith Marsh DE, Layden BT, Lee TA. Increased risk of mycotic infections associated with sodium-glucose co-transporter 2 inhibitors: a prescription sequence symmetry analysis. Br J Clin Pharmacol. 2019;85(1):160-168.

48. Caughey GE, Roughhead EE, Pratt N, Shakib S, Vitry AI, Gilbert AL. Increased risk of hip fracture in the elderly associated with prochlorperazine: is a prescribing cascade contributing? Pharmacoepidemiol Drug Saf. 2010;19(9):977-982.

49. Corraro G, Botteri E, Bagnardi V, et al. Generating signals of drug-adverse effects from prescription databases and application to the risk of arrhythmia associated with antibacterials. Pharmacoepidemiol Drug Saf. 2005;14(1):31-40.

50. Fujimoto M, Higuchi T, Hosomi K, Takada M. Association of statin use with storage lower urinary tract symptoms (LUTS): data mining of prescription database. Int J Clin Pharmacol Ther. 2014;52(9):762-769.

51. Garrison SR, Dormuth CR, Morrow RL, Carney GA, Khan KM. Nocturnal leg cramps and prescription use that precedes them: a sequence symmetry analysis. Arch Intern Med. 2012;172(2):120-126.

52. Hallas J. Evidence of depression provoked by cardiovascular medication: a prescription sequence symmetry analysis. Epidemiology. 1996;7(5):478-484.

53. Hashimoto M, Hashimoto K, Ando F, Kimura Y, Nagase K, Arai K. Prescription rate of medications potentially contributing to lower urinary tract symptoms and detection of adverse reactions by prescription sequence symmetry analysis. J Pharm Health Care Sci. 2015;1(1):7.

54. Nishtala PS, Chyou TY. Exploring New Zealand prescription data using sequence symmetry analyses for predicting adverse drug reactions. J Clin Pharm Ther. 2017;42(2):189-194.

55. Petri H, de Vet HC, Naus J, Urquhart J. Prescription sequence analysis: a new and fast method for assessing certain adverse reactions of prescription drugs in large populations. Stat Med. 1988;7(11):1171-1175.

56. Petri H, Kessels F, Kamakura T. Markers of adverse drug reactions in medication histories. An analysis of inhaled steroid utilization. Pharmaceutisch Weekbl. 1991;13(2):97-106.

57. Petri H, Leufkens H, Naus J, Silken R, Van Hessen P, Urquhart J. Rapid method for estimating the risk of acutely controversial side effects of prescription drugs. J Clin Epidemiol. 1990;43(5):433-439.

58. Pouwels K, Visser S, Bos J, Hak E. Angiotensin-converting enzyme inhibitor treatment and the development of urinary tract infection. Pharmacoepidemiol Drug Saf. 2013;22:127-128.

59. Adrian Kym P, Elizabeth Ellen R, Nicole LP. Sequence symmetry analysis graphic adjustment for prescribing trends. BMC Med Res Methodol. 2019;19(1):143.

60. Pratt N, Andersen M, Bergman U, et al. Multi-country rapid adverse drug event assessment: the Asian Pharmacoepidemiology Network (AsPEN) antipsychotic and acute hyperglycaemia study. Pharmacoepidemiol Drug Saf. 2013;22(9):915-924.

61. Pratt N, Chan EW, Choi NK, et al. Prescription sequence symmetry analysis: assessing risk, temporality, and consistency for adverse drug reactions across datasets in five countries. Pharmacoepidemiol Drug Saf. 2015;24(8):858-864.

62. Rasmussen L, Hallas J, Madsen KG. Cardiovascular drugs and erectile dysfunction—a symmetry analysis. Br J Clin Pharmacol. 2015;80(5):1219-1223.

63. Singh S, Cocoros NM, Haynes K, et al. Antidopaminergic-Antiparkinsonian medication prescribing cascade in persons with Alzheimer's disease. J Am Geriatr Soc. 2021;69:1328-1333.

64. Singh S, Cocoros NM, Haynes K, et al. Identifying prescribing cascades in Alzheimer's disease and related dementias: the calcium channel blocker-diuretic prescribing cascade. Pharmacoepidemiol Drug Saf. 2021;30:1066-1073.

65. Sturkenboom MC, Middelbeek A, de Jong van den Berg LT, van den Berg PB, Stricker BH, Wesseling H. Vulvo-vaginal candidiasis associated with acitretin. J Clin Epidemiol. 1995;48(8):991-997.

66. Takada M, Fujimoto M, Hosomi K. Association between benzodiazepine use and dementia: data mining of different medical databases. Int J Med Sci. 2016;13(11):825-834.

67. Takada M, Fujimoto M, Hosomi K. Difference in risk of gastrointestinal complications between users of enteric-coated and buffered low-dose aspirin. Int J Clin Pharmacol Ther. 2014;52(3):181-191.

68. Tsiroupolos I, Andersen M, Hallas J. Adverse events with use of antiepileptic drugs: a prescription and event symmetry analysis. Pharmacoepidemiol Drug Saf. 2009;18(6):483-491.

69. Pouwels KB, Widyakusuma NN, Bos JHJ, Hak E. Association between statins and infections among patients with diabetes: a cohort and prescription sequence symmetry analysis. Pharmacoepidemiol Drug Saf. 2016;25(10):1124-1130.

70. Venalainen O, Bell JS, Kirkpatrick CM, Nishtala PS, Liew D, Ilomaki J. Adverse drug reactions associated with cholinesterase inhibitors-sequence symmetry analyses using prescription claims data. J Am Med Dir Assoc. 2017;18(2):186-189.

71. van Boven JFM, de Jong-van den Berg LTW, Veget S. Inhaled corticosteroids and the occurrence of oral candidiasis: a prescription sequence symmetry analysis. Drug Saf. 2013;36(4):231-236.

72. Hersom K, Neary MP, Levaux HP, Klaskala W, Strauss JS. Isotretinoin and antidepressant pharmacotherapy: a prescription sequence symmetry analysis. J Am Acad Dermatol. 2003;49(3):424-432.

73. Bowman L, Carlstedt BC, Miller ME, McDonald CJ. Evaluation of ACE-inhibitor (ACE-I) associated cough using modified prescription sequence analysis (PSA). Pharmacoepidemiol Drug Saf. 1995;4(1):17-22.

74. Kalisch Ellett LM, Pratt NL, Barratt JD, Rowett D, Roughhead EE. Risk of medication-associated initiation of oxybutynin in elderly men and women. J Am Geriatr Soc. 2014;62(4):690-695.

75. King CE, Pratt NL, Craig N, et al. Detecting medicine safety signals using prescription sequence symmetry analysis of a national prescribing data set. Drug Saf. 2020;43(8):787-795.

76. Ko HHT, Lareu RR, Dix BR, Hughes JD, Parsons RW. A sequence symmetry analysis of the interrelationships between statins, diabetes and skin infections. Br J Clin Pharmacol. 2019;85:2559-2567.

77. Knowledge and confidence in medication management. Nurs Manag. 2017;24(5):14.

78. Lai EC-C, Hsieh C-Y, Yang Y-HK, Lin S-J. Detecting potential adverse reactions of sulpiride in schizophrenic patients by prescription sequence symmetry analysis. PLoS One. 2014;9(2):e89795.

79. Lai EC-C, Yang Y-HK, Lin S-J, Hsieh C-Y. Use of antiepileptic drugs and risk of hypothyroidism. Pharmacoepidemiol Drug Saf. 2013;22(10):1071-1079.

80. Wang Y, van Boven JFM, Bos JHJ, et al. Risk of neuropsychiatric adverse events associated with varenicline treatment for smoking cessation among Dutch population: a sequence symmetry analysis. Pharmacoepidemiol Drug Saf. 2022;31(2):158-166.

81. Bytzer P, Hallas J. Drug-induced symptoms of functional dyspepsia and nausea. A symmetry analysis of one million prescriptions. Aliment Pharmacol Ther. 2000;14(11):1479-1484.

82. Brandt-Christensen M, Kvist K, Nilsson FM, Andersen PK, Kessing LV. Treatment with antidepressants and lithium is associated with increased risk of treatment with antiparkinson drugs: a pharmacoepidemiological study. J Neurol Neurosurg Psychiatry. 2006;77(6):781-783.

83. Iwasawa M, Sagami K, Yokoyama S, Hosomi K, Takada M. Adherence to guidelines for antilucre drug prescription in patients receiving low-dose aspirin therapy in Japan. Int J Clin Pharmacol Ther. 2019;57(4):197-206.
123. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995–2010. BMC Med. 2015;13:74.

124. Petrovic M, van der Cammen T, Onder G. Adverse drug reactions in older people. Drugs Aging. 2012;29(6):453-462.

125. Wallace E, Salisbury C, Guthrie B, Lewis C, Fahey T, Smith SM. Managing patients with multimorbidity in primary care. Br Med J. 2015;350:h176.

126. Sternberg SA, Petrovic M, Onder G, Cherubini A, O’Mahony D, Gurwitz JH, Pegreffi F, Mason R, Akerman J, McCarthy L, Lawson A, Li J, Wu W, Rochon PA. Identifying key prescribing cascades in older people (iKASCADE): a transnational initiative on drug safety through a sex and gender lens-rationale and design. Eur Geriatr Med 2021 Jun;12(3):475–483. doi: 10.1007/s41999-021-00480-w. Epub 2021 Apr 9. PMID: 33835427.

127. O’Mahony D, Rochon PA. Prescribing cascades: we see only what we look for, we look for only what we know. Age Ageing. 2022;51(7):afac138. doi:10.1093/ageing/afac138

128. Pouwels KB, Visser ST, Bos HJ, Hak E. Angiotensin-converting enzyme inhibitor treatment and the development of urinary tract infections: a prescription sequence symmetry analysis. Drug Saf. 2013;36(11):1079-1086.

129. Takada M, Fujimoto M, Yamazaki K, Takamoto M, Hosomi K. Association of statin use with sleep disturbances: data mining of a spontaneous reporting database and a prescription database. Drug Saf. 2014;37(6):421-431.

130. Gau CS, Chang CJ, Tsai FJ, Chao PF, Gau SS. Association between mood stabilizers and hypothyroidism in patients with bipolar disorders: a nested, matched case-control study. Bipolar Disord. 2010;12(3):253-263.

131. Vouri SM, Possinger MC, Usmani S, Solberg LM, Manini T. Evaluation of the potential acetylcholinesterase inhibitor-induced rhinorrhea prescribing cascade. J Am Geriatr Soc. 2020;68(2):440-441.

132. Bouwens KB, Kalkman GA, Schagen D, Visser ST, Hak E. Is combined use of SSRIs and NSAIDs associated with an increased risk of starting peptic ulcer treatment? Br J Clin Pharmacol. 2014;78(1):192-193.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.