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ORIGINAL ARTICLE

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.

1 | BACKGROUND

A prescribing cascade occurs when a medication is used to treat or prevent the adverse effects of another medication.[1–3] 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.[4] 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.[5–7] 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.[4] Prescribing cascades can be further characterised as either appropriate (potential benefits>risks), or inappropriate (risks>potential benefits).[4] 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.[4]

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.[8] Multimorbidity, which is more common in older adults, may also make the identification of new onset ADRs more challenging.[9,10] 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.[11] 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[12] and pre-registered with PROSPERO [CRD42021243163].[13] This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[14,15] (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).[16–18] Thus, only the final study publication,[18] 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.[5,19–32] Thirteen studies reported analyses stratified by age.[7,33–44] Total study sample sizes ranged from 126[45] to 11 593 989[46] participants. (See eTable 3, Appendix S1).

3.3 | Methodological approach to analysis

Most studies (n = 88) were retrospective cohort studies,[5,7,18,21,23–27,29–34,36–44,47–113] three of which incorporated a case–control study within the study design[49,85,110] and one that conducted a preliminary cross-sectional study.[112] Five were case–control studies,[19,20] five cross-sectional studies,[6,46,114–116] and three case-crossover studies.[45,117,118] 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,[5,7,28,29,39] concomitant medication use or polypharmacy,[7,40,44,85,104] duration,[32,94] comorbidity,[36,38,40,44] race[34] and nursing home residence.[26] For other studies, analyses were adjusted by age,[20,22,24,30,52,71,89] sex,[20,22,24,30,52,71,73,82] race,[22,24] dose,[52,71] nursing home residence,[22] concomitant medication or polypharmacy,[22,52,71] comorbidity,[24] with some studies conducting adjusted analyses but not reporting the independent association of these covariates.[23,27,31,88,117,118]

Length of follow up ranged from one month[55,91,107,118] to seven years,[113] with the majority over one year (n = 33 studies).

3.4 | Initial medication(s) prescribed to patient

A 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 Fi

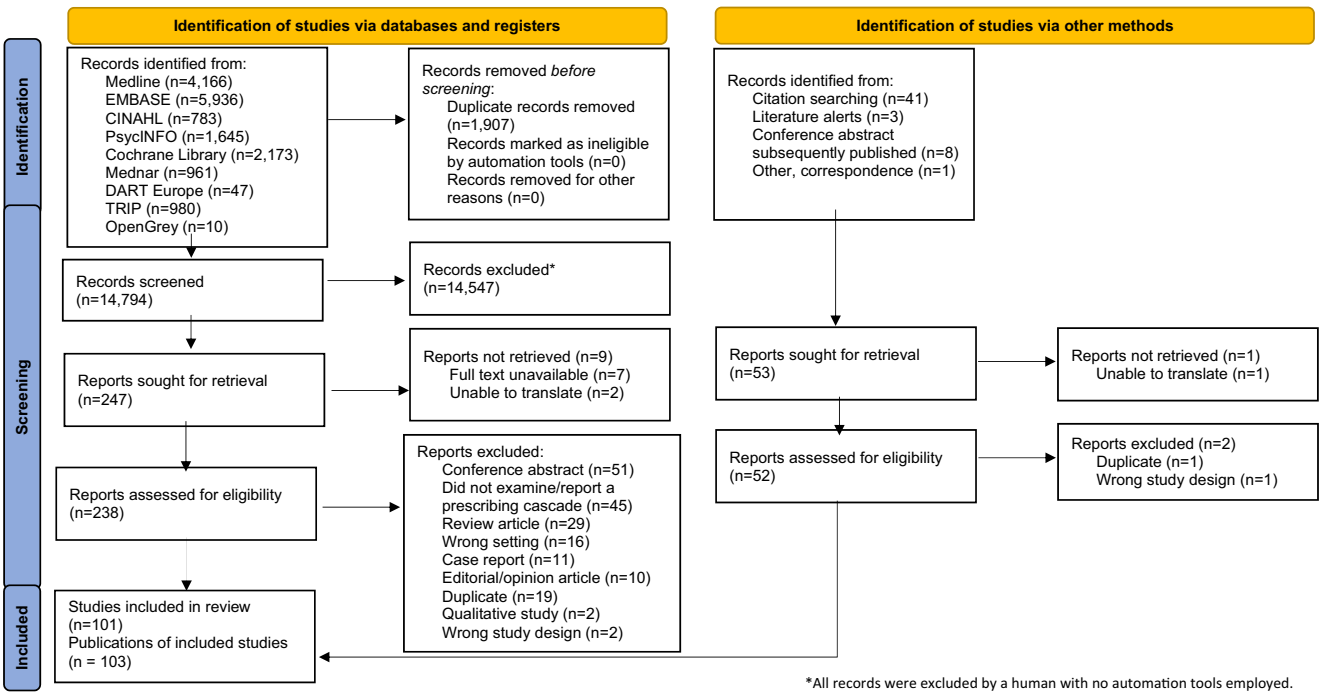


FIGURE 1 PRISMA flow diagram of included studies.

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)[a,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	*Risk of UTI (<6 months)* SGLT2-I users (3.6%) compared to DPP4-I users (4.9%), aHR 0.90 (95%CI 0.66–1.24) *Risk of genital infections (<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 1.65 (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)
Roughead (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)
Blood and blood forming organs				
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)
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* = 3440 *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* = 9473
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 0.350–1.21)
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)

TABLE 1 (Continued)

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 → Solifenacin: 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)[c,116]	Dihydropyridine calcium channel blockers (DH-CCBs)	Oedema	Loop diuretic	Among 5 458 467 DH CCB users (weighted), 185 130 individuals (3.4% weighted) were identified with new loop diuretic use.
Pouwels (2013)[128]	ACEI	Urinary tract infection (UTI)	Nitrofurantoin	*PSSA: ACEI → Nitrofurantoin ± 4 weeks* aSR 1.68 (95% CI 1.21–2.36); *n* = 161
Pouwels (2014)[b,118]	ACEI	UTI	Nitrofurantoin	*ACEI → Nitrofurantoin (<30 days vs <60–90 days)* Crude OR = 1.84 (95%CI 1.51–2.25)
Pouwels (2016)[69]	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)

TABLE 1 (Continued)

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 → Loop diuretic < 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)
Silwer (2006)[92]	Statin	Muscle pain	NSAID	*PSSA: Statin → NSAID ± 365 days* aSR 0.94 (95%CI 0.85–1.05)
Singh (2021)[64]	CCBs	Lower extremity oedema	Diuretics	*CCB → Diuretic day 8 → 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 36462 prevalent CCB users (1.3%, 95%CI 4.1–4.6). *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 → Hypnotic drugs ± 365 days* aSR 1.18 (95%CI 1.11–1.25)
Thiessen (1990)[e,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 → Cough medication ± 6 months* 2000–2012: SR 2.0 (95%CI 1.8–2.2)
Vouri (2018)[c,6]	DH-CCBs	Lower extremity oedema	Loop diuretic	*DH-CCB → 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 → Loop diuretic (2014) ± 360 days* aSR 1.87 (95%CI 1.84–1.90)
Vouri (2021)[105]	DH-CCBs	DH-CCB induced oedema	Loop diuretic	*PSSA: DH-CCB → Loop diuretic ± 360 days* aSR 2.27 (95% CI 1.44–3.58)

(Continues)

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Vouri (2021)[104]	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)[36]	Beta-blocker	Oedema	Loop diuretic	*PSSA: Beta-blocker → Loop diuretic ± 90 days* aSR 1.78 (99%CI 1.72–1.84)
Yokoyama (2021)[d,85]	Amiodarone	Hypothyroidism	Thyroid preparations	*PSSA: Amiodarone → Thyroid preparations ± 12 months* aSR 12.8 (95%CI 8.44–20.28)
Dermatologicals				
Azoulay (2007)[b,45]	Isotretinoin	Depression	Antidepressants	*Isotretinoin → Antidepressant (5 month risk and control windows)* aRR 2.68 (95%CI 1.10–6.48)
Hersom (2003)[72]	Isotretinoin Minocycline	Depression	Antidepressants (MAOIs excluded)	*Isotretinoin → Antidepressant (study period)* aRR 0.97 (95%CI 0.92–1.02) *Minocycline → Antidepressant (study period)* aRR 0.98 (95%CI 0.95–1.02)
Sturkenboom (1995)[65]	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				
Dyson (2020)[33]	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)[d,110]	5-ARI Alpha blocker (AB)	Depression	Antidepressant (<90 days of depression diagnosis)	*5ARI → Antidepressant (compared with AB only users)* 5-ARIs only: aIRR = 0.94 (95%CI 0.85–1.04) 5-ARIs + ABs: aIRR = 1.04 (94%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				

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Corrao (2005)[d,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 ratios)* Erythromycin: 1.96 (95%CI 1.45–2.59); *n* = 8956 Clarithromycin: 1.18 (95%CI 1.08–1.29); *n* = 97 900 Rokitamycin: 1.27 (95%CI 1.00–1.66); *n* = 15 247 Ciprofloxacin: 1.25 (95%CI 1.14–1.37); *n* = 58 070 Norfloxacin: 1.17 (95%CI 1.00–1.36); *n* = 22 421 Levofloxacin: 1.33 (95%CI 1.03–1.38); *n* = 14 159 *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) Levofloxacin: 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)[a,22]	NSAID	Hypertension	Antihypertensive	*NSAID → Antihypertensive (<365 days)* OR = 2.01 (95%CI 1.89–2.14)
Nervous system				
Avorn (1995)[a,19]	Neuroleptics	Extrapyramidal symptoms	APD (excluding 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)

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Dalgard Dunvald (2020)[38]	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)[a,130]	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)[26]	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)[100]	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 1.93–2.66); *n* = 728 Antipsychotic: aSR 9.24 (95%CI 7.35–11.8); *n* = 817
Kalisch Ellett (2018)[c,114]	Antipsychotics	EPS Hyperprolactinaemia Diabetes mellitus	Anticholinergic Hyperprolactinaemia medications Oral diabetes medications	*Concomitant medication use* Anticholinergic: *n* = 51 (0.7%) Hyperprolactinaemia medications: *n* = 8 (0.1%) Oral diabetes medicines: *n* = 874 (11.8%)
Kroger (2015)[b,117]	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)[79]	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)[44]	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)[27]	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 (95%CI 1.06–3.30) *Start of anti-Parkinson drug or PD diagnosis (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 <6 months* 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 <3 month* 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)[c,46]	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* = 25 949 (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 (2018)[94]	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)[55]	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)[60]	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 1.13–2.06) *Risperidone → Insulin ± 12 months* USA Public: aSR 1.09 (95%CI 1.07–1.12)
Read (2021)[28]	Gabapentinoid	Oedema	Diuretic	*Gabapentinoid → Diuretic < 90 days (versus non-users)* aHR 1.44 (95%CI 1.23–1.70).

(Continues)

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Rochon (2005)[29]	Antipsychotic	Parkinsonism	Anti-Parkinson drug or Parkinson diagnosis (composite)	*Antipsychotic → Anti-Parkinson drug/diagnosis <1 year (versus atypical 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)[66]	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)[43]	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)[107]	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)[70]	AChEI	Nausea Dyspepsia Diarrhoea Urinary incontinence Seizures Anxiety Insomnia Depression	Antiemetics PPIs/H2RAs Loperamide/Oral rehydration sachets Oxybutynin Anxiolytics Anticonvulsants Hypnotics and sedatives Antidepressants	*AChEI → Marker drug ± 1 year* Loperamide/Oral rehydration: aSR 1.42 (95%CI 1.14–1.77); $n = 348$ Anxiolytics: aSR 1.16 (95%CI 1.01–1.34); $n = 807$ Hypnotics and sedatives: aSR 1.19 (95%CI 1.05–1.36); $n = 963$ Antiemetics: aSR 1.18 (95%CI 1.05–1.32); $n = 1202$ Anticonvulsants: aSR 1.26 (95%CI 1.03–1.55); $n = 389$ PPI/H2RAs: aSR 0.87 (95%CI 0.77–0.98), $n = 1079$ 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)[c,131]	AChEI or Memantine	Rhinorrhea	Rhinorrhea medications (see Appendix S1)	*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)[80]	Varenicline	Neuropsychiatric adverse events: Depression Anxiety Sleep disorders	Antidepressant Anxiolytics Hypnotics and sedatives (composite outcome)	*PSSA: Varenicline → Any NPAE drug ± 365 days* aSR 1.00 (95%CI 0.89–1.13) *PSSA: Varenicline → Hypnotics and sedatives ± 365 days* Sleep disorder drug: aSR = 1.25 (95% CI 1.05–1.48)
Wang (2021)[42]	Varenicline (Nicotine replacement therapy [NRT] as comparator)	Neuropsychiatric adverse events: Depression Anxiety Insomnia	Antidepressants Antidepressants in combination with psycholeptics Anxiolytics 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)[86]	Antipsychotics	Osteoporosis	Bisphosphonate	*PSSA: Antipsychotic → Bisphosphonate* No association identified.

TABLE 1 (Continued)

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 ± 12 months* Crude SR 2.89 (95%CI 2.80–2.97) *PSSA: Inhaled corticosteroid → Systemic antifungal ± 12 months* 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 ± 12 months* Crude SR 1.94 (95%CI 1.71–2.21)
Winkel (2018)[40]	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)

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Bytzer & Hallas (2000)[81]	Predefined list of 32 index medications (see Appendix S1)	Dyspepsia or nausea	Cisapride or Metoclopramide	*PSSA: Index medication → Cisapride < 100 days* 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 → 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* = 676 Asthma drugs: 1.42 (95%CI 1.14–1.79); *n* = 307 Methylxanthines: 2.03 (95%CI 1.25–3.65); *n* = 63
Caughey (2010)[48]	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 AR2B: 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)[108]	Antidepressant with or without NSAID	GI adverse effects	H2RAs PPIs Prostaglandins	*Antidepressant → Ulcer drugs (compared with TCA only)* SSRI: IRR 1.2 (95%CI 0.5–2.8); *n* = 1181 SSRI + NSAID: IRR 12.4 (95%CI 3.2–48.0); *n* = 86

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Garrison (2012)[51]	Statin Diuretic Inhaled long-acting beta-agonists (LABA)	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
Hallas & Bytzer (1998)[89]	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) Methylxanthines: aSR 1.49 (1.05–2.19)
Hashimoto (2015)[53]	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) Cibenzoline: sSR 2.97 (95%CI 1.92–4.59) Amezinium metilsufate: 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)

(Continues)

TABLE 1 (Continued)

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 ARB+ 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 Hypnotic sedatives: aSR 1.10 (95%CI 1.03–1.18); *n* = 3326
Kim (2019)[a,119]	Propulsives Antipsychotics Antivertigo agent (see Appendix S1)	Drug induced Parkinsonism	APD or Parkinson diagnosis (composite) (see Appendix S1)	*Index medication → Anti-Parkinson drug/diagnosis <1 year* Levosulpiride: OR 4.3 (95%CI 3.5–5.3); *n* = 595 Mosapride: OR 2.1 (95%CI 1.7–2.6); *n* = 430 Domperidone: OR 2.1 (95%CI 1.6–2.8); *n* = 247 Metoclopramide: OR 2.7 (95%CI 1.8–4.1); *n* = 121 Itopride: OR 1.6 (95%CI 1.2–2.2); *n* = 232 Clebopride: OR 12.8 (95%CI 2.8–57.0); *n* = 19 Combined propulsive use: OR 3.9 (95%CI 2.8–5.5); *n* = 219 Typical antipsychotic: OR 6.4 (95%CI 1.4–28.2); *n* = 17 Atypical antipsychotic: OR 2.4 (95%CI 1.2–4.9); *n* = 56 Risperidone: OR 13.5 (95%CI 1.8–102.1); *n* = 23 Flunarizine: OR 5.0 (95%CI 2.7–9.0); *n* = 86
Ko (2019)[76]	Statins Statins	Skin and soft tissue infection New onset diabetes mellitus	Dicloxacillin/Flucloxacillin Antidiabetic	*PSSA: Statin → Antibiotic ± 365 days* aSR 1.40 (95%CI 1.34–1.47); *n* = 7726 *PSSA: Statin → Antidiabetic ± 365 days* aSR 1.09 (95%CI 1.04–1.15); *n* = 6794 *PSSA: Antidiabetic → Antibiotic ± 365 days* aSR 1.24 (95%CI 1.15–1.33); *n* = 2828

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)[54]	Amiodarone Lithium Frusemide Fluticasone Simvastatin	Hypothyroidism Hyperthyroidism Hypokalaemia Oral candidiasis Muscle cramps	Thyroxine Carbimazole Potassium Nystatin Quinine sulphate	*PSSA: Amiodarone → Thyroxine ± 360 days* aSR 3.57 (95% CI 3.17–4.02) *Lithium → Thyroxine ± 360 days* aSR 3.43 (95% CI 2.55–4.70) *Amiodarone → Carbimazole ± 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)[132]	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)[62]	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); $n = 3118$ ß-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)[63]	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)[30]	AChEIs Metoclopramide CCBs	Urinary incontinence Parkinsonism Pedal oedema	Urinary medications Anti-Parkinson drug Diuretic	*AChEI → Urinary medications < 6 months* 60 cases of prescribing cascade were identified. Extending to 365 days resulted in 52 additional cases. *Metoclopramide → Anti-Parkinson drug < 6 months* 11 cases of the prescribing cascade were identified. Extending to 365 days resulted in 5 additional cases. *CCB → Diuretic < 6 months* 289 cases of prescribing cascade were identified. Extending to 365 days resulted in 369 cases.

(Continues)

TABLE 1 (Continued)

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	*PSSA*: *Index drug → Furosemide ± 12 months* Fosaprepitant: aSR 2.60 (95%CI 2.42–2.81); *n* = 3394 Granisetron: aSR 2.24 (95%CI 2.42–2.81); *n* = 2299 Tropisetron: aSR 1.43 (95%CI 1.08–1.79); *n* = 340 Degarelix: aSR 1.66 (95%CI 1.29–2.06); *n* = 293 Brinzolamide: aSR 1.18 (95%CI 1.06–1.32); *n* = 1304 Travoprost: aSR 1.18 (95%CI 1.01–1.35); *n* = 788 Latanoprost: aSR 1.11 (95%CI 1.04–1.19); *n* = 3619 Brimonidine: aSR 1.10 (95%CI 1.00–1.20); *n* = 2012 Pizotifen: aSR 1.27 (95%CI 1.11–1.44); *n* = 978 Rizatriptan: aSR 1.16 (95%CI 1.03–1.31); *n* = 1036 Sumatriptan: aSR 1.16 (95%CI 1.03–1.29); *n* = 1250 Benzhexol: aSR 1.65 (95%CI 1.12–2.24); *n* = 142 Mesalazine: aSR 1.33 (95%CI 1.13–1.54); *n* = 646 Levetiracetam: aSR 1.13 (95%CI 1.03–1.23); *n* = 2005 Fluorometholone: aSR 1.11 (95%CI 1.07–1.15); *n* = 9410 Ranitidine: aSR 1.08 (95%CI 1.04–1.12); *n* = 10875 Denosumab: aSR 1.07 (95%CI 1.03–1.10); *n* = 16714

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% C; 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* = 24 210
Chen (2021)[87]	*Confirmatory analysis* Amiodarone *Exploratory analysis* ACEIs Statins Buffered LDA Enteric-coated LDA DH-CCBs	Hypothyroidism Gout Cough UTI Storage LUTS Depression Sleep disturbances Hepatotoxicity Muscle pain Skin and soft tissue infection Infection in those with type-2 diabetes GI complications Oedema	*Confirmatory analysis* Thyroxine Allopurinol *Exploratory analysis* (see Appendix S1)	*Confirmatory PSSA ± 1 year* Amiodarone → Thyroxine: aSR 3.77 (95%CI 3.43–4.14); *n* = 2667 Amiodarone → Allopurinol: aSR 0.83 (95%CI 0.76–0.90); *n* = 2071 *Exploratory PSSA ± 1 year* ACEIs → Antitussive: aSR 1.33 (95% CI 1.31–1.34); *n* = 141 924 Statins → Drugs for urinary frequency: aSR 1.17 (95% CI 1.16–1.19); *n* = 107 422 Statins → Antidepressants: aSR 1.19 (95% CI 1.18–1.21); *n* = 117 443 Statins → Hypnotics: aSR 1.10 (95% CI 1.09–1.12); *n* = 124 061 Statins → Ursodeoxycholic acid: aSR 1.26 (95% CI 1.21–1.31); *n* = 11 231 Statins → NSAIDs: aSR 1.02 (95% CI 1.02–1.03); *n* = 430 774 Statins → Dicloxacillin/Flucloxacillin: aSR 1.18 (95% CI 1.15–1.22); *n* = 23 068 Statins → Antibiotic treatment (those with type 2 diabetes): aSR 1.38 (95% CI 1.36–1.39); *n* = 150 016 DH-CCBs → Loop diuretic: aSR 1.46 (95% CI 1.45–1.48); *n* = 139 375

(Continues)

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Lai (2014)[78]	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

TABLE 1 (Continued)

Primary author (year)	Initial medication(s)	Suspected ADR	New medication(s)	Quantitative association (primary analysis or association at 1 year)
Hallas (2018)[101]	186 758 associations tested in the main analysis; 30 best signals reported	Exploratory analysis	30 strongest signals reported	*PSSA: Index → Marker medication ± 12 months* Opioids → Drugs for constipation (crude SR 2.34, 95%CI 2.31–2.38); *n* = 84 020 High ceiling diuretics → Potassium SR 3.31 (95%CI 3.24–3.38); *n* = 48 539 Thiazide → Potassium SR 3.46 (95%CI 3.39–3.54); *n* = 45 175 Opioids → Propulsives SR 2.14 (95%CI 2.10–2.17); *n* = 62 139 NSAIDS → Anti-ulcer drugs SR 1.71 (95%CI 1.67–1.74); *n* = 49 646 Antithrombotic → Anti-ulcer drugs SR 1.41 (95%CI 1.39–1.44); *n* = 54 841 Cough suppressants → Drugs for constipation SR 1.95 (95%CI 1.90–2.00); *n* = 260 015 Corticosteroids, systemic use → Drugs affecting bone structure and mineralisation SR 3.40 (95%CI 3.27–3.54); *n* = 13 023
Hellfritzsch (2018)[102]	Non-vitamin K oral anticoagulants (NOAC)	Exploratory analysis	20 strongest signals reported	*PSSA: NOAC → Marker drug ± 6 months* Benzodiazepines, hypnotic: cSR 8.28 (95%CI 6.01–12.05); NNTH 193 Osmotic laxatives: cSR 1.35 (95%CI 1.25–1.46); NNTH 133 Benzodiazpines, sedative: cSR 1.99 (95%CI 1.74–2.30); NNTH 174 Corticosteroids, anal use: cSR 2.03 (95%CI 1.76–2.35); NNTH 176 SSRI: cSR 1.57 (95%CI 1.37–1.77); NNTH 202 Other antidepressant: cSR 1.59 (95%CI 1.41–1.80); NNTH 207 PPI: cSR 1.19 (95%CI 1.11–1.28); NNTH 209 Phenylpiridine opioids: cSR 2.12 (95%CI 1.81–2.51); NNTH 215 Propulsives: cSR 1.51 (95%CI 1.35–1.71); NNTH 216 Iron bivalent, oral: cSR 1.62 (95%CI 1.42–1.86); NNTH 238 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.

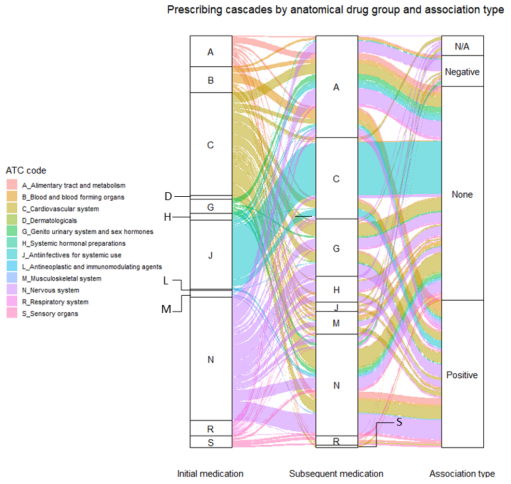
[a]Case–control study.

[b]Case-crossover study.

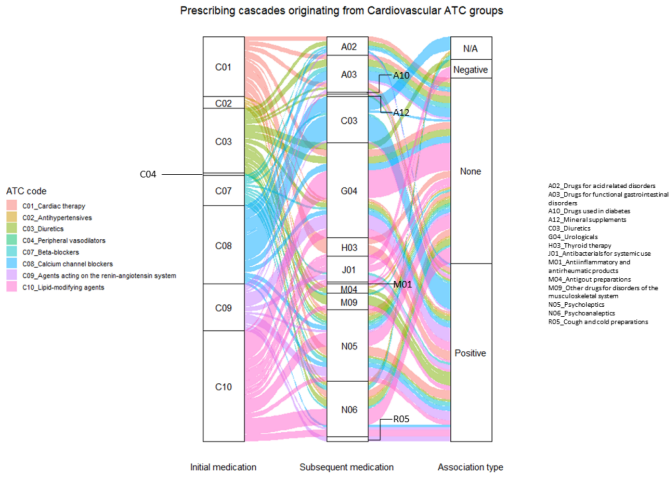
[c]Cross-sectional study.

[d]Includes case–control study.

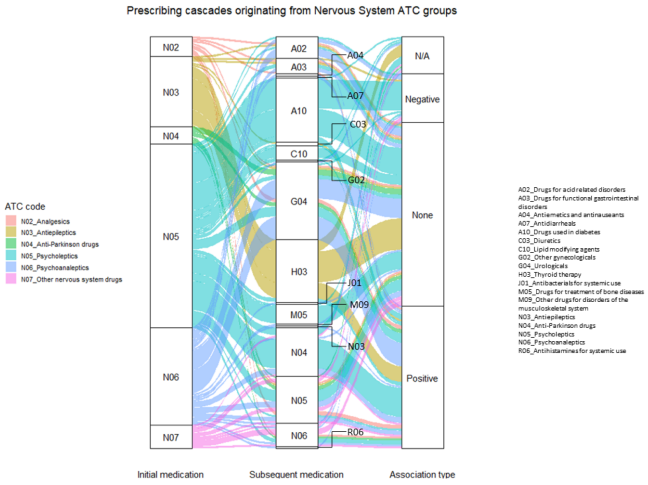
[e]Includes cross-sectional study.



(A) ATC1 level



(B) Cardiovascular medications (ATC3 level)



(C) Nervous system medications (ATC3 level).

FIGURE 2 Prescribing cascades examined in non-exploratory studies ($n = 94$) stratified by ATC classification. These alluvial plots represent initial (column 1) and subsequent (column 2) medication pairs examined and the primary quantitative association identified (column 3). The height of the strata in columns 1 and 2 is proportional to the number of instances that the relevant medication has been examined across included studies. The height of the strata in column 3 is proportional to the number of identified quantitative associations that belong to each association type. The width of the linkage between column 1 and column 2 is proportional to the number of instances that the unique medication pair has been examined across included studies. The width of the linkage between column 2 and column 3 is proportional to the number of tested medication pairs that result in a prescribing cascade (positive association), do not result in a prescribing cascade (none), indicate a lower likelihood of a prescribing cascade (negative association), or where no association could be examined due to study reporting (N/A: non-applicable); (A) ATC1 level; (B) Cardiovascular medications (ATC3 level); (C) Nervous system medications (ATC3 level).

gure 2.[68,75,78,87,101,102,106] 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 ($n = 13$)[33,37,40,45,52,55,57,72,93,97,98,110,112]; peripheral oedema ($n = 11$)[5–7,28,30,36,64,96,103–105,116]; 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]

TABLE 2 Summary of findings for the most commonly identified prescribing cascades

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* = 139375[87] <360 days: aSR 1.87 (95%CI 1.84–1.90); 55818[7] <360 days: aSR 2.27 (95% CI 1.44–3.58); *n* = 90[105] <360 days: aSR 1.72 (95%CI 1.66–1.78) relative to levothyroxine negative control; aSR 1.45 (1.41–1.49) relative to ACEI/ARB negative control[35] Rate of being dispensed a loop diuretic versus general comparator group[5] 1–30 days: aHR 2.51 (95%CI 2.13–2.96) 31–60 days: aHR 2.99 (95%CI 2.43–3.69) 61–90 days: aHR 3.89 (95%CI 3.11–4.87) 91–180 days: aHR 3.20 (95%CI 2.72–3.76) 181–365 days: aHR 2.22 (95%CI 1.90–2.60)
Amiodarone	Hypothyroidism	Thyroxine	<1 year: aSR 3.77 (95% 3.43–4.14); *n* = 2667[87] <360 days: aSR 3.57 (95%CI 3.17–4.02)[54] <1 year: aSR 2.14 (99%CI 1.92–2.39); *n* = 2613[79] <1 year Australia: aSR 5.30 (95%CI 4.69–5.96); *n* = 1979[61] < 1 year Hong Kong: aSR 2.33 (95%CI 1.99–2.72); *n* = 754 < 1 year Japan: aSR 1.77 (95%CI 0.61–5.08); *n* = 6 < 1 year Korea: aSR 1.52 (95%CI 1.29–1.80); *n* = 657 < 1 year Taiwan: aSR 3.26 (95%CI 2.26–4.70); *n* = 153 <1 year: Pooled aSR 2.63 (95%CI 1.47–4.72) <6 months: aSR 13.6 (95%CI 7.73–25.96)[85] <12 months: aSR 12.8 (95%CI 8.44–20.28) <18 months: aSR 11.4 (95%CI 7.98–16.80) <24 months: aSR 11.7 (95%CI 8.32–16.94) <30 months: aSR 10.8 (95%CI 7.86–15.29) <36 months: aSR 10.8 (95%CI 7.89–15.00)
Inhaled corticosteroids	Oral candidiasis	Topical antifungals	<90 days OR 1.66; *n* = 21[56] <1 year: SR 2.89 (95%CI 2.80–2.97)[39] <1 year: SR SR 1.94 (95%CI 1.71–2.21)[71] <360 days: aSR 2.34 (95% CI 2.19–2.50)[54]
Neuroleptics/ Antipsychotic	Parkinsonian symptoms/ extrapyramidal symptoms	Anti-parkinson medication or Parkinson diagnosis	<90 days: aOR 5.4 (95%CI 4.8–6.1)[19] <1 year (1 antipsychotic): aSR 9.24 (7.35–11.8); *n* = 817[100] <1 year (2 antipsychotics): aSR 22.2 (9.94–61.7); *n* = 137 <1 year (≥3 antipsychotics): aSR 34.8 (5.87–1413.8); *n* = 37 Never use: aOR 1.0 (referent); *n* = 10714[119] 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[29] 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)[26] Donepezil→Medication for managing Lower Urinary Tract Symptoms (LUTS)[53] <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[44] <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[24] Galantamine: aHR 1.17 (95%CI 0.87–1.58) versus rivastigmine use

(Continues)

TABLE 2 (Continued)

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)[31] 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[87]
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[89] <1 year: SR 1.71 (95%CI 1.67–1.74); *n* = 49646[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 (99%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) Genital 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 month: SR 1.57 (1.37–1.77); *n* = 1137; NNTH 202[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)[54] 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* = 446[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[87]
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[87] Simvastatin → Antidepressant (April 1991–December 1995): aSR 1.59 (1.08–2.45); *n* = 91[98]
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* = 1304[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)[130] <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	<3 months: aSR 1.24 (95%CI 1.05–1.45); $n = 625$[66] <6 months: aSR 1.20 (95%CI 1.06–1.37); $n = 973$ <12 months: aSR 1.23 (95%CI 1.11–1.37); $n = 1450$ <24 months: aSR 1.34 (95%CI 1.23–1.47); $n = 2049$ <36 months: aSR 1.41 (95%CI 1.29–1.53); $n = 2408$ <48 months: aSR 1.44 (95%CI 1.33–1.56); $n = 2653$ <3 years: aSR 2.19 (95%CI 1.92–2.49); $n = 1285$[94] <2 years: aSR 2.00 (95%CI 1.71–2.34); $n = 780$ <1 year: aSR 1.77 (95%CI 1.39–2.27); $n = 286$
SSRI	Urinary incontinence	Drugs for urinary frequency and incontinence (or incontinence products)[41]	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; NNTH, number needed to har; 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 ($n = 5$),[5,7,87,104,105] 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).[6,21,25,30,43,46,53,55,63,64,78,79,112,114,115] 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 inhibitor[24,30] and SSRI initiation,[41] 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

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.[120] 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%, $p < 0.001$).[5] 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).[20] Risk increased with increasing daily metoclopramide dose and the effect persisted after adjustment for demographic, health service utilization, and medication use variables.[20]

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.[9,10,121–123] 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.[1,8,124]

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[11] and the second that focused on the use of PSSA as a potential pharmacovigilance tool.[120] In 2018, Brath et al retrieved 10 original investigations and seven case reports pertaining to prescribing cascades.[11] A considerable number of studies have been published since, indicating that this is a rapidly developing field. Morris el 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.[120] 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,[60,95,96] 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.[125] 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.[8,124] The failure to recognise an ADR may result in a prescribing cascade, furthering the risk for additional medication-related harm.[1,2] 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.[1,8,124]

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.[126] 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.[127] 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.[127]

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.[48,62,102] One study examined the association between prescribing cascades that resulted in prochlorperazine initiation and reported a subsequent 49% increased risk of hip fracture.[48] 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[11,120] 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.[1,8,124] 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 CONTRIBTIONS

Conception and funding acquisition: EW. Study design EW, AD, FM, FB, BC, SK, and TF. Data acquisition: AD, FS, and EW. Data interpretation: AD, FS, TD, FM, FB, BC, TF, SK, and EW. Drafting of manuscript: AD, and EW. Revising of manuscript and agreement of final manuscript: AD, FS, FM, FB, BC, SK, TF, TD, and EW.

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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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SUPPORTING INFORMATION

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

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