Title: Prescribing Cascades: An Umbrella Review and Updated Systematic Review

Authors:

Massimo Carollo, MD[1,2], Salvatore Crisafulli, PhD[1], Marta Zerio, MSc[1], Francesco Maccarrone, MSc[1], Anna Paladin, MSc[1], Margherita Selleri, MSc[1], Anna Forti, MD[1], Francesco U. S. Mattace-Raso, PhD[2], Gianluca Trifirò, PhD[1]*

Affiliations:

1. Department of Diagnostics and Public Health, Clinical Pharmacology Unit, University of Verona, Verona, Italy
2. Section of Geriatric Medicine, Department of Internal Medicine, Erasmus MC University Medical Center, Rotterdam, The Netherlands

***Corresponding author**

Prof. Gianluca Trifirò

gianluca.trifiro@univr.it

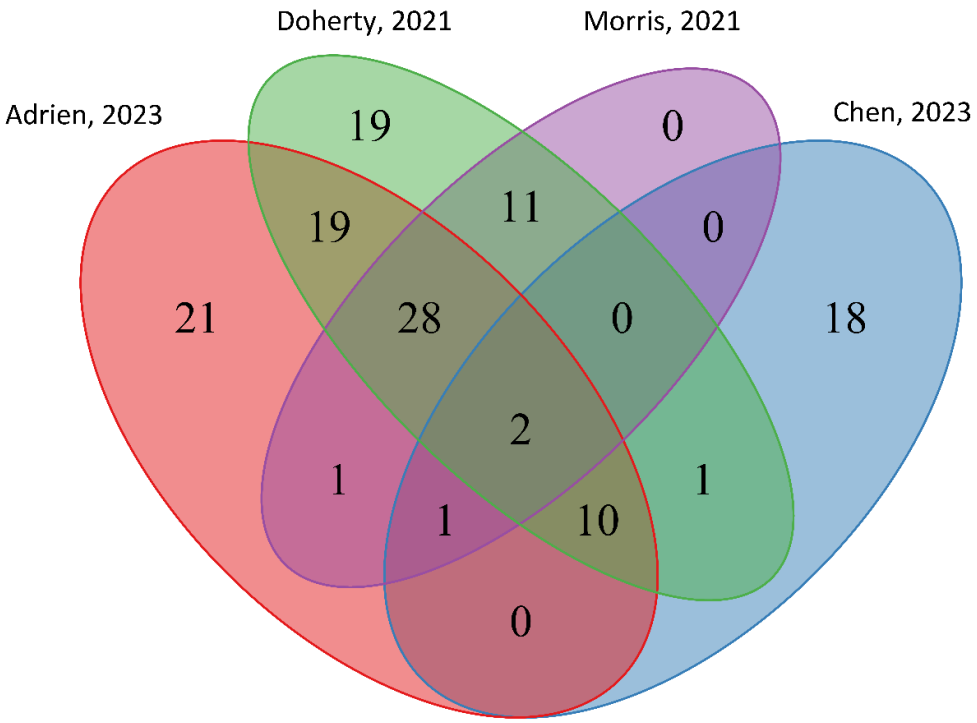
Department of Diagnostics and Public Health, University of Verona, Italy

P.le L.A. Scuro 10, 37124, Verona

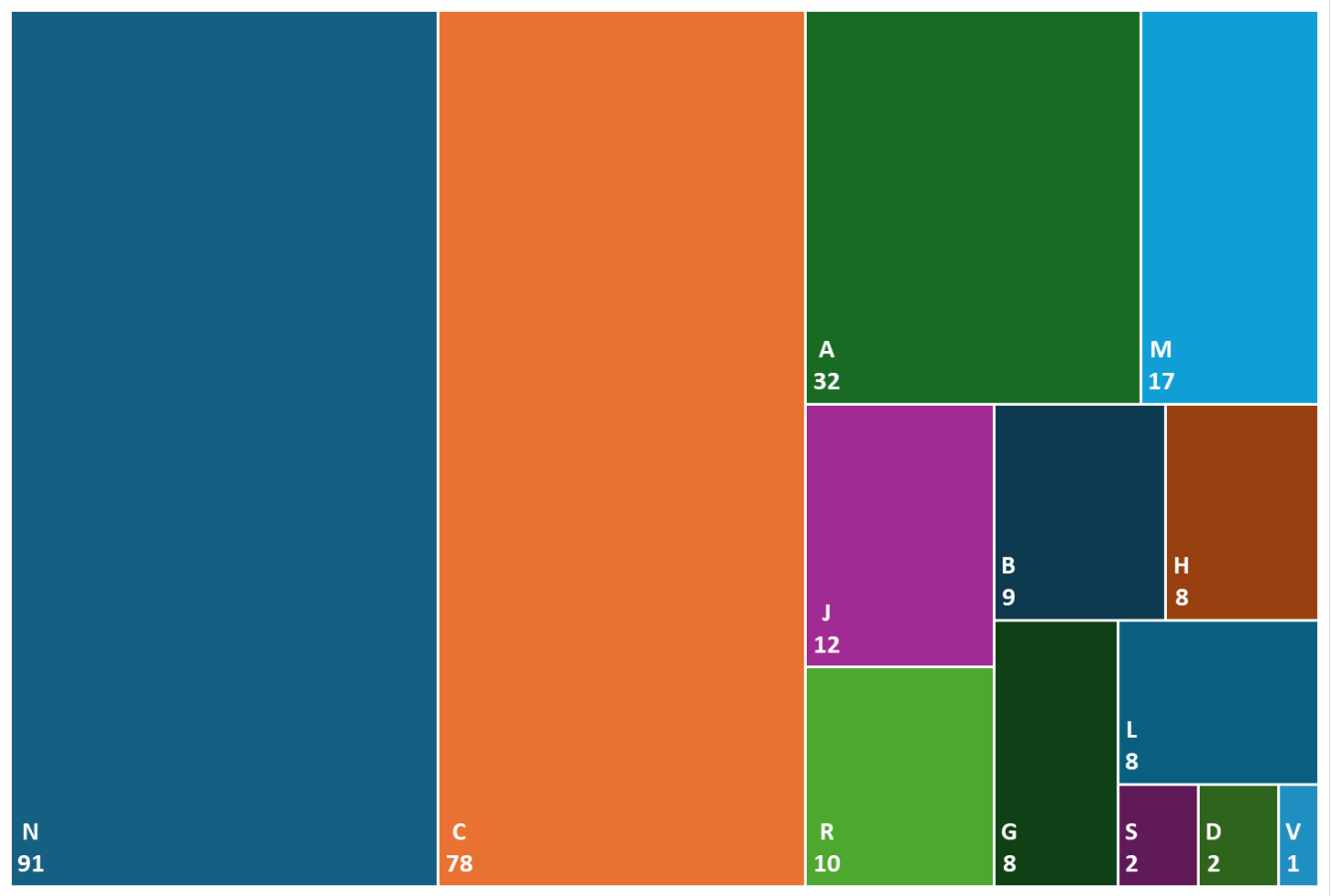
+39 045 812 4706

Table of contents

Supplementary Figure 1. Overlap of primary studies identified in the systematic and scoping reviews.



Supplementary Figure 2. Drug classes potentially inducing adverse drug reactions leading to prescribing cascades, grouped by first-level ATC classification system.



Abbreviations: A = Alimentary tract and metabolism; B = Blood and blood forming organs; C = Cardiovascular system; D = Dermatologicals; G = Genito urinary system and sex hormones; H = Systemic hormonal preparations, excl. sex hormones and insulins; J = Antiinfectives for systemic use; L = Antineoplastic and immunomodulating agents; M = Musculo-skeletal system; N = Nervous system; R = Respiratory system; S = Sensory organs; V = Various.

Supplementary Table 1. Search strategy overview for the umbrella review, by bibliographic database.

Search number	Query	Results
PubMed		
#1	"prescri* cascade*"[All Fields] OR "medication cascade*"[All Fields] OR "therapeutic cascade*"[All Fields] OR "drug cascade*"[All Fields] OR "prescri* sequen*"[All Fields] OR "sequen* prescri*"[All Fields] OR "sequence of prescription*"[All Fields] OR "precipitating drug*"[All Fields] OR "precipitating medication*"[All Fields]	340
#2	"adverse event*"[All Fields] OR "adverse drug event*"[All Fields] OR "adverse reaction*"[All Fields] OR "adverse drug reaction*"[All Fields] OR "ADR"[All Fields] OR "side effect*"[All Fields] OR "adverse drug effect*"[All Fields] OR "drug-induced"[All Fields] OR "Drug-Related Side Effects and Adverse Reactions"[MeSH Terms]	833,031
#3	"symmetry-analys*"[All Fields] OR "sequence-ratio*"[All Fields] OR "symmetry-ratio*"[All Fields] OR "prescription sequence symmetry analysis"[All Fields] OR "PSSA"[All Fields] OR "prescription pattern analysis"[All Fields]	1,086
#4	#2 AND #3	91
#5	#1 OR #4	393
#6	"systematic review*"[All Fields] OR "systematic overview*"[All Fields] OR "Systematic Reviews as Topic"[MeSH Terms] OR "Systematic Review"[Publication Type] OR "Systematic Review"[MeSH Terms] OR "meta analys*"[All Fields] OR "meta-analys*"[All Fields] OR "metaanalys*"[All Fields] OR "metanalys*"[All Fields] OR "Meta-Analysis as Topic"[MeSH Terms] OR "Meta-Analysis"[Publication Type] OR "Meta-Analysis"[MeSH Terms] OR "scoping review*"[All Fields]	615,849
#7	#5 AND #6	18
Scopus		
#1	ALL("prescri* cascade*") OR ALL("medication cascade*") OR ALL("therapeutic cascade*") OR ALL("drug cascade*") OR TITLE-ABS-KEY("prescri* sequen*") OR TITLE-ABS-KEY("sequen* prescri*") OR TITLE-ABS-KEY("sequence of prescription*") OR TITLE-ABS-KEY("precipitating drug*") OR TITLE-ABS-KEY("precipitating medication*")	1,840
#2	TITLE-ABS-KEY("adverse drug reaction*") OR TITLE-ABS-KEY("adverse event*") OR TITLE-ABS-KEY("adverse drug event*") OR TITLE-ABS-KEY("adverse reaction*") OR TITLE("ADR") OR TITLE-ABS-KEY("side effect*") OR TITLE-ABS-KEY("adverse drug effect*") OR TITLE-ABS-KEY("drug-induced")	1,485,443
#3	TITLE-ABS-KEY("symmetry-analys*") OR TITLE-ABS-KEY("sequence-ratio*") OR TITLE-ABS-KEY("symmetry-ratio*") OR TITLE-ABS-KEY("prescription sequence symmetry analysis") OR TITLE-ABS-KEY("PSSA") OR TITLE-ABS-KEY("prescription pattern analysis")	5,755
#4	#2 AND #3	99
#5	#1 OR #4	1,893
#6	TITLE("systematic review*") OR TITLE("systematic overview*") OR DOCTYPE(re) OR TITLE("meta analys*") OR TITLE("meta-analys*") OR TITLE("metaanalys*") OR TITLE("metanalys*") OR TITLE("scoping review*")	5,281,722
#7	#5 AND #6	375
Embase		
#1	'prescri* cascade*' OR 'medication cascade*' OR 'therapeutic cascade*' OR 'drug cascade*' OR 'prescri* sequen*' OR 'sequen* prescri*' OR 'sequence of prescription*' OR 'precipitating drug*' OR 'precipitating medication*'	711

#2	'adverse event*' OR 'adverse drug event*' OR 'adverse reaction*' OR 'adverse drug reaction*' OR 'adr' OR 'side effect*' OR 'adverse drug effect*' OR 'drug-induced' OR 'drug-related side effects' AND 'adverse reactions'/exp	69,671
#3	'symmetry-analys*' OR 'sequence-ratio*' OR 'symmetry-ratio*' OR 'prescription sequence symmetry analysis' OR 'pssa' OR 'prescription pattern analysis'	1,358
#4	#2 AND #3	15
#5	#1 OR #4	719
#6	systematic review*' OR 'systematic overview*' OR 'systematic review (topic)'/exp OR 'systematic review':it OR 'systematic review'/exp OR 'meta analys*' OR 'meta-analys*' OR 'metaanalys*' OR 'metanalys*' OR 'meta analysis (topic)'/exp OR 'meta-analysis':it OR 'meta analysis'/exp OR 'scoping review*' OR 'scoping review':it OR 'scoping review (topic)'/exp OR 'scoping review'/exp	920,204
#7	#5 AND #6	35
Web of Science (All Databases)		
#1	TS="prescri* cascade*" OR TS="medication cascade*" OR TS="therapeutic cascade*" OR TS="drug Cascade*" OR TS="prescri* sequen*" OR TS="sequen* prescri*" OR TS="sequence of prescription*" OR TS="precipitating drug*" OR TS="precipitating medication*"	878
#2	TS="adverse drug reaction*" OR TS="adverse event*" OR TS="adverse drug event*" OR TS="adverse reaction*" OR TI="ADR" OR TI="side effect*" OR TI="adverse drug effect*" OR TI="drug-induced"	645,733
#3	TS="symmetry-analys*" OR TS="sequence-ratio*" OR TS="symmetry-ratio*" OR TS="prescription sequence symmetry analysis" OR TS="PSSA" OR TS="prescription pattern analysis"	7,496
#4	#2 AND #3	127
#5	#1 OR #4	944
#6	TS="systematic review*" OR KP="systematic review*" OR TS="systematic overview*" OR KP="systematic overview*" OR TS="meta analys*" OR TS="meta-analys*" OR TS="metaanalys*" OR TS="metanalys*" OR KP="meta-analys*" OR KP="meta analys*" OR KP="metanalys*" OR KP="metaanalys*" OR TS="scoping review*" OR KP="scoping review*"	1,135,804
#7	#5 AND #6	41
Cochrane Library		
#1	prescri* NEXT cascade	4
#2	medication NEXT cascade*	0
#3	therapeutic NEXT cascade*	4
#4	drug NEXT cascade	0
#5	prescri* NEXT sequen*	13
#6	sequen* NEXT prescri*	5
#7	sequence NEXT of NEXT prescription	0
#8	precipitating NEXT drug*	1
#9	precipitating NEXT medication*	0
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	27
#11	adverse NEXT drug NEXT reaction*	64,176
#12	adverse NEXT event*	169,964
#13	adverse NEXT drug NEXT event*	907
#14	adverse NEXT reaction*	22,509
#15	ADR	1,686
#16	side NEXT effect*	179,783

#17	adverse NEXT drug NEXT effect*	380
#18	drug-induced	7,110
#19	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	5,142
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	328,368
#21	symmetry-analysis*	19
#22	sequence-ratio*	5
#23	symmetry-ratio*	36
#24	prescription* NEXT sequence* NEXT symmetry NEXT analysis	3
#25	PSSA	9
#26	prescription* NEXT pattern* NEXT analysis	0
#27	#21 OR #22 OR #23 OR #24 OR #25 OR #26	65
#28	#20 AND #27	11
#29	#10 OR #28	37
#30	systematic NEXT review*	24,972
#31	systematic NEXT overview*	161
#32	MeSH descriptor: [Systematic Review] explode all trees	1
#33	MeSH descriptor: [Systematic Reviews as Topic] explode all trees	123
#34	meta NEXT analys*	30,585
#35	meta-analys*	30,585
#36	metaanalys*	24,914
#37	metanalys*	153
#38	MeSH descriptor: [Meta-Analysis] explode all trees	82
#39	MeSH descriptor: [Meta-Analysis as Topic] explode all trees	1,472
#40	scoping NEXT review*	375
#41	#30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	41,133
#42	#29 AND #41	6

Supplementary Table 2. Search strategy overview for the systematic review update, by bibliographic database.

Search number	Query	Results
PubMed		
#1	"prescri* cascade*"[All Fields] OR "medication cascade*"[All Fields] OR "therapeutic cascade*"[All Fields] OR "drug cascade*"[All Fields] OR "prescri* sequen*"[All Fields] OR "sequen* prescri*"[All Fields] OR "sequence of prescription*"[All Fields] OR "precipitating drug*"[All Fields] OR "precipitating medication*"[All Fields]	340
#2	"adverse event*"[All Fields] OR "adverse drug event*"[All Fields] OR "adverse reaction*"[All Fields] OR "adverse drug reaction*"[All Fields] OR "ADR"[All Fields] OR "side effect*"[All Fields] OR "adverse drug effect*"[All Fields] OR "drug-induced"[All Fields] OR "Drug-Related Side Effects and Adverse Reactions"[MeSH Terms]	833,031
#3	"symmetry-analys*"[All Fields] OR "sequence-ratio*"[All Fields] OR "symmetry-ratio*"[All Fields] OR "prescription sequence symmetry analysis"[All Fields] OR "PSSA"[All Fields] OR "prescription pattern analysis"[All Fields]	1,086
#4	#2 AND #3	91
#5	#1 OR #4	393
#6	#5 AND (2022:2025[pdat])	135
Scopus		
#1	ALL("prescri* cascade*") OR ALL("medication cascade*") OR ALL("therapeutic cascade*") OR ALL("drug cascade*") OR TITLE-ABS-KEY("prescri* sequen*") OR TITLE-ABS-KEY("sequen* prescri*") OR TITLE-ABS-KEY("sequence of prescription*") OR TITLE-ABS-KEY("precipitating drug*") OR TITLE-ABS-KEY("precipitating medication*")	1,840
#2	TITLE-ABS-KEY("adverse drug reaction*") OR TITLE-ABS-KEY("adverse event*") OR TITLE-ABS-KEY("adverse drug event*") OR TITLE-ABS-KEY("adverse reaction*") OR TITLE("ADR") OR TITLE-ABS-KEY("side effect*") OR TITLE-ABS-KEY("adverse drug effect*") OR TITLE-ABS-KEY("drug-induced")	1,485,443
#3	TITLE-ABS-KEY("symmetry-analys*") OR TITLE-ABS-KEY("sequence-ratio*") OR TITLE-ABS-KEY("symmetry-ratio*") OR TITLE-ABS-KEY("prescription sequence symmetry analysis") OR TITLE-ABS-KEY("PSSA") OR TITLE-ABS-KEY("prescription pattern analysis")	5,755
#4	#2 AND #3	99
#5	#1 OR #4	1,893
#6	#5 AND PUBYEAR AFT 2021	601
Embase		
#1	'prescri* cascade*' OR 'medication cascade*' OR 'therapeutic cascade*' OR 'drug cascade*' OR 'prescri* sequen*' OR 'sequen* prescri*' OR 'sequence of prescription*' OR 'precipitating drug*' OR 'precipitating medication*'	711
#2	'adverse event*' OR 'adverse drug event*' OR 'adverse reaction*' OR 'adverse drug reaction*' OR 'adr' OR 'side effect*' OR 'adverse drug effect*' OR 'drug-induced' OR 'drug-related side effects' AND 'adverse reactions'/exp	69,671
#3	'symmetry-analys*' OR 'sequence-ratio*' OR 'symmetry-ratio*' OR 'prescription sequence symmetry analysis' OR 'pssa' OR 'prescription pattern analysis'	1,358
#4	#2 AND #3	15
#5	#1 OR #4	719
#6	#5 AND #6	290

Web of Science (All Databases)		
#1	TS="prescri* cascade*" OR TS="medication cascade*" OR TS="therapeutic cascade*" OR TS="drug Cascade*" OR TS="prescri* sequen*" OR TS="sequen* prescri*" OR TS="sequence of prescription*" OR TS="precipitating drug*" OR TS="precipitating medication*"	878
#2	TS="adverse drug reaction*" OR TS="adverse event*" OR TS="adverse drug event*" OR TS="adverse reaction*" OR TI="ADR" OR TI="side effect*" OR TI="adverse drug effect*" OR TI="drug-induced"	645,733
#3	TS="symmetry-analys*" OR TS="sequence-ratio*" OR TS="symmetry-ratio*" OR TS="prescription sequence symmetry analysis" OR TS="PSSA" OR TS="prescription pattern analysis"	7,496
#4	#2 AND #3	127
#5	#1 OR #4	944
#6	#5 Timespan: 2022-01-01 to 2025-08-01 (Publication Date)	282

Cochrane Library		
#1	prescri* NEXT cascade	4
#2	medication NEXT cascade*	0
#3	therapeutic NEXT cascade*	4
#4	drug NEXT cascade	0
#5	prescri* NEXT sequen*	13
#6	sequen* NEXT prescri*	5
#7	sequence NEXT of NEXT prescription	0
#8	precipitating NEXT drug*	1
#9	precipitating NEXT medication*	0
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	27
#11	adverse NEXT drug NEXT reaction*	64,176
#12	adverse NEXT event*	169,964
#13	adverse NEXT drug NEXT event*	907
#14	adverse NEXT reaction*	22,509
#15	ADR	1,686
#16	side NEXT effect*	179,783
#17	adverse NEXT drug NEXT effect*	380
#18	drug-induced	7,110
#19	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	5,142
#20	#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19	328,368
#21	symmetry-analysis*	19
#22	sequence-ratio*	5
#23	symmetry-ratio*	36
#24	prescription* NEXT sequence* NEXT symmetry NEXT analysis	3
#25	PSSA	9
#26	prescription* NEXT pattern* NEXT analysis	0
#27	#21 OR #22 OR #23 OR #24 OR #25 OR #26	65
#28	#20 AND #27	11
#29	#10 OR #28	37
#30	#29 AND Date (Custom Range: 01/01/2022 to 16/07/2025)	9

Supplementary Table 3. Reasons for exclusions of the studies from the umbrella review after full-text screening.

First author, publication year	DOI	Reason(s) for exclusion
Brath et al., 2018	10.1111/jgs.15543	Focus on information resources. The aim of the review was to systematically describe the resources available on preventing, detecting, and reversing prescribing cascades using a scoping review methodology
He et al., 2021	10.3760/cma.j.cn112338-20201208-01386	Language criterion: non-English publication (i.e., Chinese)
Randles et al., 2022	10.1093/ageing/afac218.210	Conference abstract
Randles et al., 2022	10.1007/s41999-022-00711-8	Conference abstract

Supplementary Table 4. Risk of bias of the reviews included in the umbrella review.

Author, year	1	2	3	4	5	6	7	8	9	10	11	Overall
Adrien, 2023	Y	Y	Y	Y	N	N	Y	Y	N/A	Y	Y	Low
Chen, 2023	Y	Y	Y	Y	N	N	Y	Y	N/A	Y	Y	Low
Doherty, 2022	Y	Y	Y	Y	Y	Y	Y	Y	N/A	Y	Y	Low
Morris, 2021	Y	Y	Y	Y	N	N	Y	Y	N/A	Y	Y	Low

Supplementary Table 5. Prescribing cascades identified by the studies included in the updated systematic literature search.

First author, year	DOI	Study design	Prescribing cascades identified
Abdelaziz, 2025 [1]	10.1111/bcpt.70038	PSSA	• Roflumilast → ADR → Antithyroid agents (i.e., methimazole, propylthiouracil) • Roflumilast → ADR → Parathyroid hormones (i.e., calcitonin) • Roflumilast → ADR → Hematopoietic agents (i.e., filgrastim, epoetin α, pegfilgrastim, darbepoetin α, eltrombopag olamine, sargramostim) • Roflumilast → ADR → Meglitinides (i.e., repaglinide, nateglinide) • Roflumilast → ADR → Antituberculosis agents (i.e., ethambutol hydrochloride, rifampin, isoniazid, pyrazinamide, rifapentine) • Roflumilast → ADR → Sodium chloride preparations • Roflumilast → ADR → Chemotherapy (i.e., methotrexate, mercaptopurine, temozolomide, hydroxyurea, cyclophosphamide, etoposide, capecitabine, oxaliplatin, fluorouracil, fludarabine phosphate, docetaxel, tretinoin, chlorambucil, procarbazine hydrochloride, cedazuridine/decitabine, mechlorethamine hydrochloride, melphalan) • Roflumilast → ADR → Digoxin • Roflumilast → ADR → Hormone-modifying therapy (i.e., megestrol acetate, tamoxifen citrate, abiraterone acetate, anastrozole, letrozole, leuprolide acetate, bicalutamide, exemestane, enzalutamide, apalutamide, triptorelin pamoate, nilutamide) • Roflumilast → ADR → Folic acid and derivatives (i.e., acetylcysteine/folic acid/levomefolate calcium/methylcobalamin, folic acid/L. casei, cyanocobalamin/folic acid/pyridoxine, levomefolate calcium, calcium ascorbate/calcium threonate/cobamamide/docosahe, leucovorin calcium, boron/calcium/cholecalciferol/vitamin B12/folic acid/magnesium/vitamines, cholecalciferol/folic acid, levoleucovorin calcium, folic acid/methylcobalamin/turmeric root extract, acetylcysteine/folic acid/methylcobalamin) • Roflumilast → ADR → Miscellaneous anti-infective agents (i.e., metronidazole, nitazoxanide, bismuth subcitrate potassium/metronidazole/tetracycline HCl, trimethoprim, rifabutin, atovaquone, tinidazole, bismuth subsalicylate/metronidazole/tetracycline HCl, atovaquone/proguanil hydrochloride) • Roflumilast → ADR → Lactulose

			• Roflumilast → ADR → Emollients, moisturizers and protectants (i.e., ammonium lactate, urea, aloe vera/glycerin, multi-ingredient foam, cream and lotion, lactic acid, lactic acid/vitamin E, barrier skin protectant, menthol/zinc oxide) • Roflumilast → ADR → Miscellaneous urinary anti-infective agents (i.e., antibacterial/analgesic combination, nitrofurantoin monohydrate, nitrofurantoin macrocrystals, belladonna alkaloids and analgesics, methenamine hippurate, fosfomycin tromethamine, nitrofurantoin, methenamine mandelate) • Roflumilast → ADR → Miscellaneous skin and mucous membrane agents (i.e., estradiol, diclofenac epolamine, tacrolimus, multi-ingredient gel and spray, calcipotriene, pimecrolimus, imiquimod, aminolevulinic acid hydrochloride, eflornithine hydrochloride, diclofenac sodium, estradiol acetate, becaplermin, lidocaine/prilocaine/cream base, oxymetazoline hydrochloride, acetic acid glacial/oxyquinoline sulfate, nitroglycerin, castor oil/Peru balsam/trypsin, sinecatechins, formaldehyde, castor oil/Peru balsam, glycopyrronium tosylate, bexarotene, camphor/menthol, acetic acid/oxyquinoline sulfate/ricinoleic acid) • Roflumilast → ADR → Miscellaneous antiemetics (i.e., ondansetron hydrochloride, prochlorperazine maleate, meclizine hydrochloride, ondansetron, metoclopramide hydrochloride, dronabinol, prochlorperazine, trimethobenzamide hydrochloride, aprepitant, dimenhydrinate, fosaprepitant dimeglumine, granisetron, prochlorperazine edisylate, granisetron hydrochloride, palonosetron hydrochloride, rolapitant, netupitant/palonosetron, dolasetron mesylate) • Roflumilast → ADR → Miscellaneous antigout agents (i.e., allopurinol, probenecid, colchicine/probenecid, colchicine, febuxostat, lesinurad) • Roflumilast → ADR → Anti-infective and anti-inflammatory (eye, ear, nose, throat) (i.e., dexamethasone/neomycin sulfate/polymyxin b sulfate, hydrocortisone/neomycin sulfate/polymyxin b sulfate, dexamethasone/tobramycin, loteprednol etabonate/tobramycin, colistin sulfate/hydrocortisone acetate/neomycin sulfate/thonzonium bromide, prednisolone sodium phosphate/sulfacetamide sodium, prednisolone acetate/sulfacetamide sodium, bacitracin zinc/hydrocortisone/neomycin sulfate/polymyxin b sulfate) • Roflumilast → ADR → Miscellaneous central nervous system agents (i.e., ropinirole hydrochloride, pramipexole dihydrochloride, pregabalin, milnacipran hydrochloride, bromocriptine mesylate, memantine hydrochloride, carbidopa/levodopa, fluoxetine hydrochloride/olanzapine, dextromethorphan hydrobromide/quinidine sulfate, riluzole, sodium oxybate, carbidopa/entacapone/levodopa, atomoxetine

			hydrochloride, rasagiline, dalfampridine, ubrogepant, erenumab-aooe, galcanezumab-gnlm, valbenazine, deutetrabenazine, rimegepant, rotigotine, fremanezumab-vfrm, flumazenil, cabergoline, carbidopa) • Roflumilast → ADR → Antidiarrheal agents (i.e., atropine sulfate/diphenoxylate hydrochloride, loperamide hydrochloride, bifidobacterium lactis/lactobacillus acidophilus, paregoric, bifidobacterium bifidum/lactobacillus acidophilus, crofelemer, bismuth subsalicylate, lactobacillus acidophilus, bifidobacterium/lactobacillus acidophilus) • Roflumilast → ADR → Antiarrhythmic agents (i.e., dronedarone hydrochloride, flecainide acetate, propafenone hydrochloride, amiodarone hydrochloride, mexiletine hydrochloride, dofetilide, disopyramide phosphate, quinidine sulfate, quinidine gluconate, lidocaine hydrochloride) • Roflumilast → ADR → Anticholinergic/antimuscarinic/antispasmodic (i.e., chlordiazepoxide hydrochloride/clidinium bromide, hyoscyamine sulfate, methscopolamine bromide, dicyclomine hydrochloride, scopolamine, glycopyrrolate, atropine sulfate/hyoscyamine sulfate/phenobarbital/scopolamine hydrobromide, propantheline bromide, umeclidinium, formoterol fumarate/glycopyrrolate, atropine sulfate/ethanol/hyoscyamine sulfate/phenobarbital/scopolamine hydrobromide, atropine sulfate, hyoscyamine sulfate/phenyltoloxamine citrate, scopolamine hydrobromide) • Roflumilast → ADR → Antipruritic agents and local anesthetics (i.e., lidocaine, lidocaine/prilocaine, lidocaine hydrochloride, ethyl chloride, doxepin hydrochloride, lidocaine/tetracaine, lidocaine/menthol, hydrocortisone acetate/lidocaine hydrochloride, aloe/collagen/lidocaine hydrochloride, lidocaine hydrochloride/menthol, benzocaine/butamben/tetracaine, pramoxine hydrochloride, pramoxine hydrochloride/zinc acetate, mineral oil/pramoxine hydrochloride/zinc oxide, aluminum hydroxide/magnesium hydroxide/simethicone/diphenhydramine) • Roflumilast → ADR → Eye, ear, nose, and throat miscellaneous agents (i.e., olopatadine hydrochloride, bimatoprost, timolol maleate, travoprost, dorzolamide hydrochloride/timolol maleate, latanoprost, brimonidine tartrate, cromolyn sodium, brimonidine tartrate/timolol maleate, brinzolamide, timolol, tafluprost, brimonidine tartrate/brinzolamide, dorzolamide hydrochloride, naloxone hydrochloride, latanoprost/netarsudil, betaxolol hydrochloride, nedocromil sodium, esketamine, saliva substitutes, unoprostone isopropyl, hypochlorous acid, bicarbonates/calcium/chloride/phosphate/sodium, latanoprostene bunod, meta

			cresyl acetate, netarsudil, carbamide peroxide, ranibizumab, levobunolol hydrochloride) • Roflumilast → ADR → Smooth-respiratory muscle relaxants (i.e., theophylline, dyphylline/guaifenesin, dyphylline, aminophylline) • Roflumilast → ADR → Eye, ear, nose, and throat antibiotics (i.e., ofloxacin, erythromycin, ciprofloxacin hydrochloride/dexamethasone, moxifloxacin hydrochloride, besifloxacin hydrochloride, tobramycin, gentamicin sulfate, polymyxin b sulfate/trimethoprim sulfate, bacitracin, ciprofloxacin hydrochloride, gatifloxacin, ciprofloxacin hydrochloride/hydrocortisone, bacitracin zinc/polymyxin b sulfate, gramicidin/neomycin sulfate/polymyxin b sulfate, bacitracin zinc/neomycin/polymyxin b sulfate, levofloxacin, gentamicin sulfate/prednisolone acetate, ciprofloxacin hydrochloride/fluocinolone acetonide) • Roflumilast → ADR → Miscellaneous anticonvulsants (i.e., topiramate, gabapentin, lamotrigine, divalproex sodium, levetiracetam, lacosamide, primidone, zonisamide, carbamazepine, oxcarbazepine, gabapentin enacarbil, valproic acid, magnesium sulfate, tiagabine hydrochloride, eslicarbazepine acetate) • Roflumilast → ADR → Antivirals (i.e., oseltamivir phosphate, acyclovir, valacyclovir hydrochloride, famciclovir, amantadine hydrochloride, raltegravir potassium, emtricitabine/tenofovir disoproxil fumarate, atazanavir sulfate, ritonavir, efavirenz/emtricitabine/tenofovir disoproxil fumarate, valganciclovir hydrochloride, maraviroc, nevirapine, abacavir sulfate/lamivudine, darunavir ethanolate, dolutegravir sodium, etravirine, ribavirin, sofosbuvir, ganciclovir, rimantadine hydrochloride, lamivudine, tenofovir disoproxil fumarate, stavudine, tipranavir, emtricitabine/tenofovir alafenamide, sofosbuvir/velpatasvir, baloxavir marboxil, bictegravir/emtricitabine/tenofovir alafenamide, tenofovir alafenamide, glecaprevir/pibrentasvir, ibalizumab-uiyk, entecavir, letermovir, cobicistat/darunavir/emtricitabine/tenofovir alafenamide, lamivudine/zidovudine, lopinavir/ritonavir, telaprevir, rilpivirine hydrochloride, cobicistat/elvitegravir/emtricitabine/tenofovir disoproxil fumarate, fosamprenavir calcium, abacavir sulfate, nelfinavir mesylate, simeprevir, zanamivir, enfuvirtide, saquinavir mesylate, ledipasvir/sofosbuvir, atazanavir/cobicistat, cobicistat/darunavir, cobicistat/elvitegravir/emtricitabine/tenofovir alafenamide, abacavir/dolutegravir/lamivudine, dasabuvir/ombitasvir/paritaprevir/ritonavir, acyclovir sodium, efavirenz)

			• Roflumilast → ADR → Skin and mucous membrane antibiotics and combinations (i.e., mupirocin, clindamycin phosphate, mupirocin calcium, erythromycin, gentamicin sulfate, benzoyl peroxide/clindamycin phosphate, sulfacetamide sodium/sulfur, clindamycin phosphate/tretinoin, benzoyl peroxide/erythromycin, sulfacetamide sodium, ozenoxacin, bacitracin, hydrocortisone acetate/neomycin sulfate/polymyxin b sulfate) • Roflumilast → ADR → Miscellaneous antibiotics (i.e., clindamycin hydrochloride, linezolid, rifaximin, vancomycin hydrochloride, clindamycin phosphate, amoxicillin/clarithromycin/omeprazole, colistimethate sodium, tedizolid phosphate, retapamulin, dextrose/vancomycin hydrochloride, clindamycin palmitate hydrochloride, daptomycin, dalbavancin, vancomycin hcl/solution multi ingredient, polymyxin b sulfate) • Roflumilast → ADR → Analgesics/antipyretics (i.e., tramadol hydrochloride, acetaminophen/butalbital/caffeine, acetaminophen/butalbital, acetaminophen/tramadol hydrochloride, acetaminophen, clonidine hydrochloride, acetaminophen/phenyltoloxamine citrate, paracetamol/chlorpheniramine maleate/phenylephrine hcl/phenyltoloxamine citrate, cough/cold combination, paracetamol/caffeine/phenyltoloxamine citrate/salicylamide, paracetamol/caffeine/magnesium salicylate/phenyltoloxamine citrate, acetaminophen/aspirin/caffeine/salicylamide, tramadol hydrochloride/cream multi ingredient) • Roflumilast → ADR → Benzodiazepines (i.e., temazepam, alprazolam, diazepam, lorazepam, oxazepam, triazolam, chlordiazepoxide hydrochloride, clorazepate dipotassium, flurazepam hydrochloride, estazolam, quazepam, midazolam hydrochloride)
Alghamdi, 2023 [2]	10.3390/ph16121694	PSSA	• Alzheimer's disease medications (i.e., rivastigmine, galantamine, memantine, donepezil) → Hypertension → β-blockers (i.e., metoprolol, bisoprolol, propranolol, sotalol, atenolol, nebivolol, carvedilol, celiprolol)
Chikermane, 2024 [3]	10.1016/j.archger.2024.105629	Nested case-control study	• Cholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine) → Urinary incontinence → Oxybutynin, darifenacin, solifenacin, trospium, tolterodine, fesoterodine

Chikermane, 2025 [4]	10.2147/DHPS.S506523	Retrospective cohort study	• Rivastigmine → Behavioral and psychological symptoms of dementia → Atypical antipsychotics (i.e., olanzapine, quetiapine, clozapine, risperidone, aripiprazole, ziprasidone, asenapine, paliperidone, iloperidone, lurasidone, brexpiprazole) or typical antipsychotics (i.e., perphenazine, fluphenazine, thioridazine, thiothixene, perphenazine/amitriptyline, trifluoperazine, chlorpromazine, loxapine, pimozide)
Dehade, 2025 [5]	10.2174/0115748863288106240313042127	Case report	• Levosulpiride → Tremors, rigidity → Levodopa/carbidopa+pramipexole
Elli, 2022 [6]	10.1007/s41999-022-00636-2	Cross-sectional study	• Proton pump inhibitors → Anemia → Antianemic drugs (i.e., iron supplements, folate, vitamin B12, erythropoietin)
Farrell, 2022 [7]	10.1371/journal.pone.0272418	Descriptive qualitative study	• Fentanyl → Sweating → Oxybutynin • Fentanyl → Nausea → Dimenhydrinate • Fentanyl → Tremors, anxiety → Lorazepam • Trazodone, dimenhydrinate, baclofen, cetirizine → Urinary retention → Furosemide • Pantoprazole → Low magnesium → Magnesium supplement • Rosuvastatin → Muscle pain → Diclofenac, amitriptyline, hydromorphone, ibuprofen, tramadol • Diclofenac, ibuprofen → Gastrointestinal symptoms → Pantoprazole, ranitidine • Pantoprazole → Low B12 → B12 supplement • Venlafaxine → Hypertension → Amlodipine • Metformin, domperidone → Diarrhea → Loperamide • Amlodipine, pregabalin → Edema → Furosemide • Methylphenidate → High heart rate and blood pressure → Metoprolol, irbesartan • Hydromorphone → Constipation → Polyethylene glycol • Candesartan/hydrochlorothiazide → Increased blood glucose → Metformin • Rheumatoid arthritis medications (i.e., celecoxib, methotrexate, hydroxychloroquine) → Stomach upset → Pantoprazole • Sitagliptin → Diarrhea → Loperamide
Funabashi, 2025 [8]	10.1038/s41598-025-96103-6	PSSA	• Dipeptidyl peptidase 4 (DPP-4) inhibitors (i.e., sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, saxagliptin, trelagliptin, omarigliptin) → Nausea, vomiting, gastric discomfort → Prokinetic agents (including dopamine D2 receptor

			blockers, i.e., domperidone, domperidone suppositories, and metoclopramide, and serotonin 5-HT4 receptor agonists, i.e., mosapride and itopride) • Dipeptidyl peptidase 4 (DPP-4) inhibitors (i.e., sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, saxagliptin, trelagliptin, omarigliptin) → Constipation → Laxatives (i.e., magnesium oxide, senna extract, sennoside A B calcium, magnesium sulfate hydrate, castor oil, aromatic castor oil, glycerin, glycerin enema solution, carmellose sodium, sodium picosulfate hydrate, lubiprostone, naldemedine tosilate, elobixibat hydrate, sennoside A B, powdered coptis rhizome/powdered senna leaf/powdered rhubarb, powdered glycyrrhiza/powdered senna leaf/powdered fennel/sulfur/white soft sugar, dioctyl sodium sulfosuccinate/casanthranol, carlsbad salt, macrogol 4000, bisacodyl, sodium bicarbonate/sodium dihydrogen phosphate anhydrous/sodium dihydrogen phosphate anhydrous)
Growdon, 2024 [9]	10.1111/jgs.18892	PSSA	• Gabapentinoids (i.e., gabapentin, pregabalin) → Peripheral oedema → Loop diuretics (i.e., furosemide, bumetanide, torsemide, ethacrynic acid)
Growdon, 2025 [10]	10.1093/gerona/glaf150	PSSA	• Loop diuretics (i.e., furosemide, torsemide, bumetanide, ethacrynic acid) → Urinary symptoms - Urinary symptom medications (i.e., antimuscarinics including solifenacin, oxybutynin, fesoterodine, darifenacin, trospium, tolterodine, flavoxate; β-3 adrenergic agonists including mirabegron, vibegron; peripheral α-1 blockers including alfuzosin, doxazosin, terazosin, tamsulosin, silodosin; 5-α reductase inhibitors including finasteride, dutasteride)
Hasegawa, 2023 [11]	10.1111/ggi.14755	Retrospective cohort study	• NSAIDs, acetylsalicylic acid, laxatives, anti-anxiety medications, antipsychotics, anti-Parkinson medications (anticholinergic medications), selective serotonin reuptake inhibitor (SSRI), cholinesterase inhibitors, bisphosphonate, biguanide → Impaired appetite → Drugs not reported • Hypnotics, anti-anxiety medications (benzodiazepines), tricyclic antidepressants, overactive bladder medications (muscarine receptor antagonists), intestinal tract anticonvulsants (atropine, butylscopolamine), antihistamines (including H2 receptor antagonists), α-glucosidase inhibitors, antipsychotics (phenothiazine), anti-Parkinson medications (anticholinergic medications) → Constipation → Drugs not reported • Anti-hypertensives (central anti-hypertensives, α blockers, β blockers), hypnotics, anti-anxiety medications (benzodiazepines), antidepressants (tricyclic), antiepileptics, antipsychotics (phenothiazine), anti-Parkinson medications (anticholinergic

			medications), antihistamines (including H2 receptor antagonists) → Cognitive dysfunction → Drugs not reported
Hsieh, 2024 [12]	10.1097/MJT.0000000000001685	Case report	• Naltrexone+quetiapine+paroxetine → Depressed mood, delusional jealousy, and auditory hallucinations → Risperidone • Quetiapine+risperidone → Extrapyramidal symptoms (i.e., rigidity, unsteady gait, unstable posture) → Biperiden • Quetiapine+paroxetine+risperidone → Unstable physical status (i.e., altered mental status, with disorientation, agitation, reversed circadian rhythm), suspected serotonin syndrome/neuroleptic malignant syndrome → Amantadine
Ito, 2025 [13]	10.1093/ijpp/riaf012	PSSA	• Pregabalin → Oedema (MedDRA/J preferred terms "face oedema", "generalised oedema", "oedema", "oedema peripheral", "localised oedema") → Loop diuretics (i.e., furosemide, azosemide, torsemide, bumetanide)
Janetzki, 2024 [14]	10.1007/s40264-023-01374-5	PSSA	• Atenolol → COPD development → Tiotropium, aclidinium, indacaterol, glycopyrronium • Cefuroxime → COPD development → Tiotropium, indacaterol, glycopyrronium • Naproxen → COPD development → Tiotropium, indacaterol • Nicotine → COPD development → Indacaterol, umeclidinium • Ibuprofen → COPD development → Tiotropium, glycopyrronium • Acamprosate → COPD development → Tiotropium, aclidinium • Mycophenolate → COPD development → Tiotropium, glycopyrronium • Rizatriptan, gemfibrozil, methyldopa → COPD development → Tiotropium • Mesalazine, dantrolene → COPD development → Indacaterol • Valproic acid → COPD development → Aclidinium • Gabapentin → COPD development → Umeclidinium • Tranexamic acid → COPD development → Glycopyrronium • Atenolol → COPD progression → Fluticasone propionate/salmeterol, glycopyrronium/indacaterol • Cefuroxime, baclofen → COPD progression → Glycopyrronium/indacaterol • Naproxen → COPD progression → Aclidinium/formoterol, fluticasone propionate/salmeterol, budesonide/formoterol • Nicotine → COPD progression → Fluticasone furoate/umeclidinium/vilanterol, glycopyrronium/indacaterol, tiotropium/olodaterol

			• Ibuprofen → COPD progression → Fluticasone propionate/salmeterol, budesonide/formoterol • Acamprosate, mesalazine, valproic acid, labetalol → COPD progression → Fluticasone propionate/salmeterol • Rizatriptan → COPD progression → Aclidinium/formoterol, budesonide/formoterol • Acetazolamide → COPD progression → Tiotropium/olodaterol • Captopril → COPD progression → Aclidinium/formoterol • Furosemide → COPD progression → Fluticasone furoate/vilanterol • Mefenamic acid → COPD progression → Budesonide/formoterol
Lai, 2024 [15]	10.1007/s10067-024-06891-x	PSSA	• Acetylsalicylic acid (low-dose), thiazide diuretics, loop diuretics, ethambutol, pyrazinamide, metformin → Gout flares → Urate→lowering drugs (i.e., allopurinol, benzbromarone, probenecid, sulfinpyrazone), colchicine
Lan, 2025 [16]	10.1111/ggi.70118	Case report	• Quetiapine+tiapride → Dizziness and behavioral worsening → Hydroxyzine • Hydroxyzine → Increased dry mouth, constipation, and cognitive decline → Lactulose • Quetiapine+tiapride → Vertigo → Betahistine
Lu, 2024 [17]	10.1038/s41598-024-58153-0	Retrospective cohort study	• Thiazides (C03A) → Hyperuricemia → Antigout medications (i.e., benzbromarone, febuxostat, allopurinol, colchicine)
Lund, 2023 [18]	10.1111/dom.14982	PSSA	• Digitalis glycosides, macrolides, inhaled β2-agonists/glucocorticoids → Diabetes → Antidiabetic medications
McCarthy, 2022 [19]	10.1007/s40266-022-00964-9	Descriptive qualitative study/consensus study	• Calcium channel blocker → Peripheral edema → Diuretic • Diuretic → Urinary incontinence → Overactive bladder medication • Antipsychotic → Extrapyramidal symptoms → Antiparkinsonian agent • Benzodiazepine → Cognitive impairment → Cholinesterase inhibitor, memantine • Benzodiazepine → Paradoxical agitation or agitation secondary to withdrawal → Antipsychotic • SSRI, SNRI → Insomnia → Sleep agent (e.g., benzodiazepines, benzodiazepine receptor agonists, sedating antidepressant, melatonin) • NSAID → Hypertension → Antihypertensive • Urinary Anticholinergics → Cognitive impairment → Cholinesterase inhibitor, memantine • α-1 receptor blocker → Orthostatic hypotension, dizziness → Vestibular sedative (e.g., betahistine, antihistamines, benzodiazepines)

Mohammad, 2024 [20]	10.1111/jgs.19191	Mixed-methods study (literature review + PSSA)	• Amiodarone → Hypothyroidism → Thyroid hormones • Lithium → Tremor → Propranolol • ACE inhibitors → Cough → Cough and cold preparations • Statins → Cognitive impairment → Antidementia medications • PPIs → C. difficile infection → Intestinal antiinfectives • Lithium → Parkinsonism → Tertiary amines, dopaminergics • Lithium → Hypothyroidism → Thyroid hormones • Antipsychotics → Hyperprolactinemia, oligomenorrhea → Prolactin inhibitors • Antipsychotics → Parkinsonism → Tertiary amines, dopaminergics • ACE inhibitors → Cough → Antibacterials (systemic use) • ACE inhibitors → Urinary tract infection → Antibacterials (systemic use) • ACE inhibitors → Erectile dysfunction → Medications used in erectile dysfunction • Statins → Erectile dysfunction → Medications used in erectile dysfunction • Dihydropyridines → Peripheral oedema → High-ceiling diuretics • ARBs → Erectile dysfunction → Medications used in erectile dysfunction • Dihydropyridines → Erectile dysfunction → Medications used in erectile dysfunction • ACE inhibitors → Cough → Antihistamines (systemic use) • B-blockers → Erectile dysfunction → Medications used in erectile dysfunction • Low-ceiling diuretics → Erectile dysfunction → Medications used in erectile dysfunction • Non-dihydropyridines → Erectile dysfunction → Medications used in erectile dysfunction • Statins → Arrhythmia → Antithrombotics • Statins → Sleeplessness → Hypnotics, sedatives • Statins → Urinary incontinence → Medications for urinary frequency and incontinence • Low-ceiling diuretics → Gout → Anti-gout medication • High-ceiling diuretics → Erectile dysfunction → Medications used in erectile dysfunction • Antiepileptics → Urinary tract infection → Antibacterials (systemic use) • ACE inhibitors → Arthritis → Anti-inflammatories, antirheumatic medications • Statins → Agitation → Antipsychotics, benzodiazepines • Antidepressants → Migraine → Analgesics, antipyretics

			• Statins → Confusion state → Antipsychotics • ACE inhibitors → Cough → Adrenergics, inhalants • Statins → Depression → NS-MRI, SSRI, other antidepressants • Non-dihydropyridines → Peripheral oedema → High-ceiling diuretics • Antidepressants → Parkinsonism → Tertiary amines, dopaminergics • β-blockers → Depression → NS-MRI, SSRI, other antidepressants • Antiepileptics → Peripheral oedema → High-ceiling diuretics • Diuretics → Diuresis excessive → Urologicals • ACE inhibitors → Depression → NS-MRI, SSRI, other antidepressants • Anti-inflammatories, antirheumatic medications → Peripheral oedema → High-ceiling diuretics • Dihydropyridines → Depression → NS-MRI, SSRI, other antidepressants • Antidepressants → Urinary incontinence → Medications for urinary frequency and incontinence
Ndai, 2025 (1) [21]	10.1002/pds.70132	PSSA	• ACE inhibitors → ADR → Other nasal preparations (R01AX) • ACE inhibitors → ADR → Other antianemic preparations (B03XA) • ACE inhibitors → ADR → Antiallergic agents, excl. corticosteroids (R01AC) • ACE inhibitors → ADR → Electrolyte solutions (B05XA) • ACE inhibitors → ADR → Selective β-2-adrenoreceptor agonists (R03AC) • ACE inhibitors → ADR → Pregnadien derivatives (G03DB) • ACE inhibitors → ADR → Leukotriene receptor antagonists (R03DC) • ACE inhibitors → ADR → Antipropulsives (A07DA) • ACE inhibitors → ADR → Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids (R03AL) • ACE inhibitors → ADR → Drugs for treatment of hyperkalemia and hyperphosphatemia (V03AE) • ACE inhibitors → ADR → Bile acid sequestrants (C10AC) • ACE inhibitors → ADR → Carbohydrates (V06DC) • ACE inhibitors → ADR → Butyrophenone derivatives (N05AD) • ACE inhibitors → ADR → Phenylpiperidine derivatives (N02AB) • ACE inhibitors → ADR → Other antiallergics (S01GX) • ACE inhibitors → ADR → Corticosteroids (R01AD) • ACE inhibitors → ADR → Propulsives (A03FA) • ACE inhibitors → ADR → Imidazole derivatives (J01XD)

			• ACE inhibitors → ADR → Osmotically acting laxatives (A06AD) • ACE inhibitors → ADR → Serotonin (5-HT3) antagonists (A04AA) • ACE inhibitors → ADR → Sympathomimetics (R01BA) • ACE inhibitors → ADR → Other antiemetics (A04AD) • ACE inhibitors → ADR → Other systemic drugs for obstructive airway diseases (R03DX) • ACE inhibitors → ADR → Anticholinergics (S01FA) • ACE inhibitors → ADR → Other antispasmodics in combination with analgesics (A03DC) • ACE inhibitors → ADR → Adrenergic and dopaminergic agents (C01CA) • ACE inhibitors → ADR → Glucocorticoids (R03BA) • ACE inhibitors → ADR → Diazepines, oxazepines, thiazepines, and oxepines (N05AH) • ACE inhibitors → ADR → Sulfonamides (D06BA) • ACE inhibitors → ADR → Benzodiazepine derivatives (N03AE) • ACE inhibitors → ADR → Sympathomimetics in glaucoma therapy (S01EA) • ACE inhibitors → ADR → Benzodiazepine derivatives (N05BA) • ACE inhibitors → ADR → Other aminoglycosides (J01GB) • ACE inhibitors → ADR → Dopa and dopa derivatives (N04BA) • ACE inhibitors → ADR → Other drugs for constipation (A06AX) • ACE inhibitors → ADR → Benzodiazepine derivatives (N05CD) • ACE inhibitors → ADR → Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) (A02BX) • ACE inhibitors → ADR → Selective serotonin reuptake inhibitors (N06AB) • ACE inhibitors → ADR → Amides (N01BB) • ACE inhibitors → ADR → Anticholinergics (R03BB) • ACE inhibitors → ADR → Phenothiazine derivatives (R06AD) • ACE inhibitors → ADR → Nitrofuran derivatives (J01XE) • ACE inhibitors → ADR → H2-receptor antagonists (A02BA)
Ndai, 2025 (2) [22]	10.1101/2025.03.10.25323711	PSSA	• ARBs → Suppression of erythropoiesis → Other antianemic preparations (B03XA) • ARBs → Depression/anxiety/mood disorders → Benzodiazepine derivatives (N03AE) • ARBs → Angioedema → Adrenergics in combination with anticholinergics, including triple combinations with corticosteroids (R03AL)
Ochi, 2024 [23]	10.1002/npr2.12499	Cross-sectional study	• Benzodiazepines → Constipation → Laxatives

Omata, 2024 [24]	10.1007/s40801-024-00446-x	PSSA	• Gabapentinoids (i.e., mirogabalin and pregabalin), benzodiazepines → Peripheral oedema → Loop diuretics (i.e., furosemide, azosemide, bumetanide, torsemide, piretamide)
Rahbek, 2022 [25]	10.1001/jamanetworkopen.2022.11883	Cross-sectional study	• Hormone therapy (G03CA, G03F) → Nausea → Antiemetics (sedating antihistamines including cyclizine (R06AE03), meclizine (R06AE05), promethazine (R06AD02), propulsives including metoclopramide (A03FA01), domperidone (A03FA03), antiemetics including scopolamine (A04AD01), ondansetron (A04AA01))
Ravinandan, 2025 [26]	10.22159/ajpcr.2025v18i5.54320	Case report	• Dapagliflozin → Upper respiratory tract infection → Ciprofloxacin+tinidazole+pantoprazole
Rochon, 2025 [27]	10.1007/s41999-025-01215-x	Descriptive qualitative study/consensus study	• ACE inhibitor → Cough → Cough remedy • Antihypertensive → Orthostatic hypotension/dizziness → Antiemetic • β-blocker (lipophilic, e.g., propranolol) → Depression → Antidepressant • β-blocker (lipophilic, e.g., propranolol) → Erectile dysfunction → PDE-5 inhibitor, alprostadil • Calcium channel blocker → Peripheral edema → Diuretic • Calcium channel blocker → Constipation → Laxative • Diuretic → Gout / Hyperuricemia → Anti-gout agent • Diuretic → Urinary incontinence → Overactive bladder medication • Statin (HMG Co-A reductase inhibitor) → Myalgia, myositis → Pain reliever • Statin (HMG Co-A reductase inhibitor) → Myalgia, myositis → Mineral supplement • Statin (HMG Co-A reductase inhibitor) → Myalgia, myositis → Quinine sulfate • Statin (HMG Co-A reductase inhibitor) → Insomnia → Sleep agent • Digoxin → Nausea → Antiemetic • Midodrine → Hypertension → Antihypertensive • Anticonvulsant → Rash → Topical corticosteroid • Anticonvulsant → Nausea → Antiemetic • Antipsychotic → Extrapyramidal symptoms → β-blocker • Antipsychotic → Extrapyramidal symptoms → Antiparkinsonian agent • Antipsychotic → Extrapyramidal symptoms → Anticholinergic, antimuscarinic • Antipsychotic → Akathisia or tardive movements → Sedative • Antipsychotic → Arrhythmia → Antiarrhythmic • Antipsychotic → Hyperglycemia → Antihyperglycemic • Benzodiazepine → Cognitive impairment → Cholinesterase inhibitor • Cholinesterase inhibitor → Urinary incontinence → Overactive bladder medication

			• Cholinesterase inhibitor → Insomnia → Sleep agent • Cholinesterase inhibitor → Gastrointestinal upset → Antiemetic • Cholinesterase inhibitor → Gastrointestinal upset → Bismuth subsalicylate • Cholinesterase inhibitor → Diarrhea → Antidiarrheal • Cholinesterase inhibitor → Rhinorrhea → Antihistamine • Dopaminergic antiparkinsonian agent → Psychotic symptoms, hallucinations → Antipsychotic • Gabapentinoid → Peripheral edema → Diuretic • SSRI, SNRI → Urinary incontinence → Overactive bladder medication • Tricyclic antidepressant → Cognitive impairment → Cholinesterase inhibitor • Tricyclic antidepressant → Constipation → Laxative • Tricyclic antidepressant → Urinary incontinence → Overactive bladder medication • Flunarizine → Depression → Antidepressant • Lithium → Extrapyramidal symptoms → Antiparkinsonian agent • Venlafaxine → Hypertension (dose-related) → Antihypertensive • Venlafaxine → Tremor → Benzodiazepine • DPP-4 inhibitor (e.g., sitagliptin, saxagliptin) → Joint pain → NSAID • SGLT-2 inhibitor → Mycotic genital infections → Antifungal • Metformin → Diarrhea → Antidiarrheal • Pioglitazone or Rosiglitazone → Edema → Diuretic • Rosiglitazone → Heart failure → Diuretic • Anticholinergic antiemetic → Urinary retention → α-1 receptor blocker • Antidopaminergic antiemetic → Extrapyramidal symptoms → Antiparkinsonian agent • Laxative → Diarrhea → Antidiarrheal agent • Proton pump inhibitor → Osteoporosis, fractures → Vitamin supplement • Proton pump inhibitor → Vitamin or Mineral deficiency → Vitamin or Mineral • Bisphosphonate → Gastritis → Gastroprotective agent • NSAID → Gastritis, gastric ulcer, gastrointestinal bleed → Gastroprotective agent • NSAID → Nausea → Antiemetic • NSAID → Hypertension → Antihypertensive • NSAID → Worsening of heart failure → Heart failure agent • Opioid → Depression → Antidepressant • α-1 receptor blocker → Orthostatic hypotension, dizziness → Vestibular suppressant

			• Urinary anticholinergic → Dry mouth → Saliva substitute • Carbapenem (e.g., imipenem, meropenem, ertapenem) → Seizures → Anticonvulsant • Corticosteroid → Insomnia → Sleep agent • Corticosteroid → Psychosis → Antipsychotic • Corticosteroid → Hypertension → Antihypertensive • Acitretin → Vulvo-vaginal candidiasis → Antifungal • Erythromycin → Arrhythmia → Antiarrhythmic • Fludrocortisone → Hypertension → Antihypertensive • Iron supplement → Constipation → Laxative
Russell, 2023 [28]	10.3390/medicina59010118	Case report	• Fluoxetine+bupropion+doxepin → Interaction with hydrocodone leading to reduced analgesic effectiveness → Upward dose titration of hydrocodone → Excessive sedation and fall
Saito, 2023 [29]	10.1159/000531240	Cross-sectional study	• Antidementia drugs, including cholinesterase inhibitors (i.e., donepezil, galantamine, rivastigmine) and NMDA receptor antagonist (i.e., memantine) → Excitement, insomnia, hallucinations, confusion (only for memantine), delusions → Antipsychotics • Benzodiazepines, Z-drugs → Delirium, dementia, cognitive impairment → Antipsychotics
Trenaman, 2022 [30]	10.3389/fphar.2022.878092	Retrospective cohort study	• Anticholinergic medications (all the Anticholinergic Cognitive Burden Scale medications) → Gastrointestinal disorders → PPIs (i.e., rabeprazole, omeprazole, pantoprazole, lansoprazole, esomeprazole)
Vouri, 2023 [31]	10.1002/pds.5607	PSSA	• Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Polymyxins (J01XB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Zinc (A12CB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Magnesium compounds (A02AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Magnesium (A12CC) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Dantrolene and derivatives (M03CA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Estrogens, combinations with other drugs (G03CC) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)

			• Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → 3-oxoandrosten (4) derivatives (G03BA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Proteolytic enzymes (D03BA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Phenothiazines with aliphatic side→chain (N05AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Electrolyte solutions (B05XA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other drugs affecting bone structure and mineralization (M05BX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Ovulation stimulants, synthetic (G03GB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Anticholinesterases (N07AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Glucagon-like peptide-1 (GLP-1) analogues (A10BJ) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Choline esters (N07AB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Phenothiazines with piperazine structure (N05AB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other aminoglycosides (J01GB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Osmotically acting laxatives (A06AD) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Mineralocorticoids (H02AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → α-glucosidase inhibitors (A10BF) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Glycopeptide antibacterials (J01XA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Salt solutions (B05CB)

			• Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Trimethoprim and derivatives (J01EA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Enemas (A06AB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Butyrophenone derivatives (N05AD) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Combinations of oral blood glucose-lowering drugs (A10BD) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Fatty acid derivatives (N03AG) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other anti-dementia drugs (N06DX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Propulsives (A04AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other blood glucose-lowering drugs, excl. insulins (A10BX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Barbiturates and derivatives (N03AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Preparations with no effect on uric acid metabolism (M04AC) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Anticholinesterases (N06DA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other antibacterials (J01XX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other diagnostic agents (V04CX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Bisphosphonates (M05BA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Calcitonin preparations (H05BA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Biguanides (P01BB)

			• Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Antibiotics (A07AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Phenothiazine derivatives (R06AD) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Antipropulsives (A07DA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other antispasmodics in combination with analgesics (A03DC) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Sulfonamides (D06BA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Aminosalicylic acid and similar agents (A07EC) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Sympathomimetics used as decongestants (S01GA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Benzodiazepine derivatives (N05CD) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Opioids in combination with non-opioid analgesics (N02AJ) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Prostaglandin analogues (S01EE) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → First-generation cephalosporins (J01DB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Nitroimidazole derivatives (P01AB) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Anti-inflammatory preparations, non-steroids for topical use (M02AA) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Other opioids (N02AX) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Lincosamides (J01FF) • Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Antiinfectives and antiseptics for local oral treatment (A01AB)

			• Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin) → ADR → Antiinfectives (S03AA)
Vouri, 2022 [32]	10.1111/bcp.15447	PSSA	• Gabapentinoids (i.e., gabapentin, pregabalin) → Peripheral oedema → Loop diuretics (i.e., furosemide, bumetanide, torsemide, ethacrynic acid)
Wang, 2022 [33]	10.1111/jgs.18103	PSSA	• Loop diuretic (i.e., furosemide, bumetanide, torsemide) → Hypokalemia → Potassium supplementation
Zagozdzon, 2022 [34]	10.1016/j.ejpsy.2022.06.002	Retrospective cohort study	• Clozapine, first-generation antipsychotics (multi-drug sequences) → ADR → Cardiometabolic drugs (antihypertensive drugs, antiarrhythmic agents, lipid-lowering drugs, antidiabetic agents)

Abbreviations: ACE inhibitors = Angiotensin-converting-enzyme inhibitors; ADR = Adverse drug reaction; ARB = Angiotensin II receptor blockers; COPD = Chronic obstructive pulmonary disease; NMDA receptor antagonist = N-methyl-D-aspartate receptor antagonist; NS-MRI = Non-selective monoamine reuptake inhibitor; NSAIDs = Nonsteroidal anti-inflammatory drugs; PSSA = Prescription sequence symmetry analysis; SNRI = Serotonin-norepinephrine reuptake inhibitors; SSRI = Selective serotonin reuptake inhibitor.

Supplementary Table 6. Reasons for exclusions of the studies from the updated systematic review after full-text screening.

First author, publication year	DOI	Reason(s) for exclusion
Ahmed, 2024	10.3389/fpsyt.2024.1394813	Escitalopram prescription resulted in peripheral edema, but did not trigger a prescribing cascade
Asad, 2024	10.3855/jidc.19554	Qualitative study on hospital pharmacists' perceptions in preventing and minimizing prescribing cascades
Bordy, 2022	10.1016/j.acvdsp.2022.04.152	Conference abstract
Chikermane, 2022	10.1016/j.jval.2022.04.027	Conference abstract (of an included study)
Dalton, 2024	10.1016/j.sapharm.2024.02.013	Survey on community pharmacists' awareness, identification, and management of prescribing cascades
Daunt, 2022	10.1007/s41999-022-00711-8	Conference abstract
Daunt, 2024	10.1093/ageing/afae178.013	Conference abstract, authors did not identify new cascades, but relied on a systematic review (Doherty, 2022)
Doherty, 2025	10.1370/afm.240383	Authors did not identify new cascades, but relied on ThinkCascades, a published list of 9 clinically important prescribing cascades
Gromek, 2022	10.1111/jgs.18066	Retrospective analysis of a previously described prescribing cascade
Gupta, 2024	10.1210/jendso/bvae163.640	Conference abstract
Jambon-Barbara, 2024	10.1016/j.sleep.2024.09.045	Sequence symmetry analysis analyzing medical device-based therapies for sleep apnoea (e.g., positive airway pressure)
Kim, 2024	DOI not available. Available at: https://meeting.americangeriatrics.org/sites/default/files/media/files/2024%20Abstract%20Supplement.pdf	Conference abstract from the American Geriatric Society 2024 virtual annual scientific meeting
Kulkarni, 2023	10.1016/j.jval.2023.03.885	Conference abstract
Kulkarni, 2024	10.1161/circ.150.suppl_1.4142268	Conference abstract
Largeau, 2022	10.1111/fcp.12788	Conference abstract
Mccabe, 2022	10.1007/s11606-022-07653-8	Conference abstract
Morris, 2022	10.1111/jgs.v70.S1	Conference abstract
Ndai, 2023	10.1111/jgs.18681	Authors did not identify new cascades, but relied on a systematic review (Morris, 2021)
Nguyen, 2022	10.1016/j.eururo.2022.01.009	Opinion paper
Noorani, 2022	10.1007/s41999-022-00711-8	Conference abstract
Panagiotou, 2022	10.1111/jgs.17755	Conference abstract
Patel, 2023	10.1111/jgs.18336	Conference abstract
Rochon, 2024	10.1111/jgs.19282	Cross-sectional study analyzing a previously described prescribing cascade
Valle, 2022	10.1192/j.eurpsy.2022.1671	Conference abstract
Vouri, 2022	10.1002/pds.5518	Conference abstract (of an included study)
Wang, 2022	10.1002/pds.5518	Conference abstract (of an included study)
Wang, 2023	10.1002/phar.2883	Secondary analysis of an included study
Yilmaz, 2025	10.1136/ejhpharm-2025-eahp.227	Conference abstract

Supplementary Table 7. Risk of bias of the studies included in the updated systematic review.

Author, year	1	2	3	4	5	6	7	8	9	10	11	Overall
Case-control study												
Chikermane, 2024	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Low
Case reports												
Dehade, 2025	Y	U	U	U	Y	U	Y	Y				Moderate
Hsieh, 2024	Y	Y	Y	Y	Y	Y	Y	Y				Low
Lan, 2025	Y	Y	Y	Y	Y	Y	Y	Y				Low
Ravinandan, 2025	Y	Y	Y	Y	Y	Y	Y	Y				Low
Russell, 2023	Y	Y	Y	Y	Y	Y	Y	Y				Low
Cross-sectional studies												
Elli, 2022	Y	Y	Y	Y	Y	Y	Y	Y	N/A			Low
Ochi, 2024	Y	Y	U	Y	Y	Y	Y	Y	N/A			Low
Rahbek, 2022	Y	Y	Y	Y	Y	Y	Y	Y	N/A			Low
Saito, 2023	Y	Y	Y	Y	Y	Y	Y	Y	N/A			Low
Descriptive qualitative study												
Farrell, 2022	U	Y	Y	Y	Y	U	Y	Y	Y	Y		Low
McCarthy, 2022	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Low
Rochon, 2025	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Low
PSSA												
Abdelaziz, 2025	N/A	N/A	Y	N	Y	N/A	Y	Y	N	N	Y	Moderate
Alghamdi, 2023	N/A	N/A	Y	N	Y	N/A	Y	U	N	N	Y	Moderate
Funabashi, 2025	N/A	N/A	Y	Y	U	N/A	Y	Y	N	N	Y	Moderate
Growdon, 2024	N/A	N/A	Y	N	Y	N/A	Y	Y	N	U	Y	Moderate
Growdon, 2025	N/A	N/A	Y	N	Y	N/A	Y	Y	N	U	Y	Moderate
Ito, 2025	N/A	N/A	Y	N	Y	N/A	Y	U	N	U	Y	Moderate
Janetzki, 2024	N/A	N/A	Y	Y	Y	N/A	Y	Y	U	U	Y	Low
Lai, 2024	N/A	N/A	Y	N	Y	N/A	Y	U	N	N	Y	Moderate
Lund, 2023	N/A	N/A	Y	Y	Y	N/A	Y	Y	U	U	Y	Low
Mohammad, 2024	N/A	N/A	Y	Y	Y	N/A	Y	Y	U	U	Y	Low
Ndai, 2025 (1)	N/A	N/A	Y	Y	U	N/A	Y	Y	N	N	Y	Moderate
Ndai, 2025 (2)	N/A	N/A	Y	N	U	N/A	Y	U	N	N	Y	High
Omata, 2024	N/A	N/A	Y	Y	Y	N/A	Y	Y	Y	N	Y	Low
Vouri, 2022	N/A	N/A	Y	N	Y	N/A	Y	Y	U	N	Y	Moderate
Vouri, 2023	N/A	N/A	Y	N	Y	N/A	Y	Y	U	U	Y	Moderate
Wang, 2022	N/A	N/A	Y	N	Y	N/A	Y	Y	U	U	Y	Moderate
Retrospective cohort studies												
Chikermane, 2025	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Low
Hasegawa, 2023	N	Y	Y	N	N	U	Y	U	U	N	N	High
Lu, 2024	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Low
Trenaman, 2022	U	Y	Y	Y	Y	Y	Y	Y	U	Y	Y	Low
Zagozdzon, 2022	U	Y	Y	U	N	Y	Y	U	U	U	U	High

Abbreviations: PSSA = Prescription sequence symmetry analysis.

Supplementary Table 8. Prescribing cascades retrieved from case reports, case series, or descriptive studies only.

ADR leading to prescribing cascade	Drug/drug class inducing ADR	Drugs for ADR treatment	Source study: First author, year of publication
Blood and lymphatic system disorders			
Febrile neutropenia	Antineoplastic agents	Imipenem	Ponte et al., 2017 (CSe) [35]
Cardiac disorders			
Cardiac failure	NSAIDs	Heart failure agents	Rochon et al., 2025 (D) ^ [27]
Tachycardia	Methylphenidate	Metoprolol, irbesartan	Farrell et al., 2022 (D) ^ [7]
Gastrointestinal disorders			
Constipation	Solifenacin	Laxatives (e.g., magnesium oxide, lactulose, polyethylene glycol)	Yan et al., 2020 (CR) [36]
	Hydroxyzine		Lan et al., 2025 (CR) ^ [16]
	Hydromorphone		Farrell et al., 2022 (D) ^ [7]
	Iron supplements		Rochon et al., 2025 (D) ^ [27]
Diarrhea	Metformin	Antidiarrheals (e.g., loperamide)	Farrell et al., 2013 (CR) [37] Farrell et al., 2022 (D) ^ [7] Rochon et al., 2025 (D) ^ [27]
	Laxatives, i.e., prokinetics (e.g., metoclopramide, domperidone)		Ponte et al., 2017 (CSe) [35] Farrell et al., 2022 (D) ^ [37] Rochon et al., 2005 (RC) [38]
	Sitagliptin		Farrell et al., 2022 (D) ^ [7]
	AChEIs		Rochon et al., 2025 (D) ^ [27]
	Xinbao pills, baoxinning, ningxinbao capsules, shexiang baoxin pills, compound cerebroprotein hydrolysate tablets, xuesaitong dispersible tablets	Compound digestive enzyme capsules, lacidophilin tablets, live combined bacillus subtilis and enterococcus faecium enteric-coated capsules, trihexyphenidyl	Kang et al., 2013 (CR) [39]
Dry mouth	Fesoterodine	Anetholtrithione	Nguyen & Spinelli, 2016 (CR)
	Hydroxyzine	Lactulose	Lan et al., 2025 (CR) ^ [16]
	Urinary anticholinergics	Saliva substitute	Rochon et al., 2025 (D) ^ [27]
Epigastric discomfort	Rheumatoid arthritis medications (i.e., celecoxib, methotrexate, hydroxychloroquine)	Pantoprazole	Farrell et al., 2022 (D) ^ [7]
Gastritis	Bisphosphonates	Gastroprotective agents	Rochon et al., 2025 (D) ^ [27]
	NSAIDs		
Gastrointestinal disorder	NSAIDs (e.g., diclofenac, ibuprofen)	Pantoprazole, ranitidine	Farrell et al., 2022 (D) ^ [7]
Gastrointestinal haemorrhage	NSAIDs	Gastroprotective agents	Rochon et al., 2025 (D) ^ [27]
Nausea	Lipid-lowering agents	Metoclopramide	Ponte et al., 2017 (CSe) [35]
	Fentanyl	Dimenhydrinate	Farrell et al., 2022 (D) ^ [7]
	Anticovulsants	Antiemetics	Rochon et al., 2025 (D) ^ [27]
	AchEIs	Bismuth subsalicylate	Rochon et al., 2025 (D) ^ [27]
Peptic ulcer	NSAIDs	Gastroprotective agents	Rochon et al., 2025 (D) ^ [27]
Vomit	Lipid-lowering agents	Metoclopramide	Ponte et al., 2017 (CSe) [35]
General disorders and administration site conditions			
Oedema	Acetylsalicylic acid	Diuretics (e.g., amiloride, chlorthalidone, eplerenone, furosemide, torsemide, bumetanide, hydrochlorothiazide, indapamide, spironolactone, triamterene, ethacrynic acid, metolazone, chlorothiazide, eplerenone)	Farrell et al., 2013 (CR) [37]
	Metformin		
	Amitriptyline		
	Rosuvastatin		
Pyrexia	Imipenem	NSAIDs	Ponte et al., 2017 (CSe) [35]
Infections and infestations			
Upper respiratory tract infection	Dapagliflozin	Ciprofloxacin+tinidazole+pantoprazole	Ravinandan et al., 2025 (CR) ^ [26]
Injury, poisoning and procedural complications			
Fall	Ropinirole	Midodrine	Becerra et al., 2021 (CR) [40]
	Furosemide		Farrell et al., 2013 (CR) [37]
	Benzodiazepines		Hofmann et al., 2020 (CR) [41]
	Fluoxetine+bupropion+doxepin	Interaction with hydrocodone leading to reduced analgesic effectiveness → Upward dose titration of hydrocodone	Russell et al., 2023 (CR) ^ [28]
Metabolism and nutrition disorders			
Hyperglycaemia/diabetes mellitus	Chlorthalidone	Antidiabetic drugs (e.g., metformin, glyburide, insulin)	Farrell et al., 2020 (D) [42]
	Candesartan/hydrochlorothiazide	Metformin	Farrell et al., 2022 (D) ^ [7]
Hyperlipidaemia	Lapatinib	Lipid-lowering agents	Ponte et al., 2017 (CSe) [35]

Hypokalaemia	Fludrocortisone	Potassium chloride	Pepa et al., 2018 (CR) [43]
Hypomagnesaemia	Pantoprazole	Magnesium supplement	Farrell et al., 2022 (D) ^ [7]
Hypovitaminosis	PPIs	Vitamin supplements	Rochon et al., 2025 (D) ^ [27]
Mineral deficiency	PPIs	Vitamin supplements	Rochon et al., 2025 (D) ^ [27]
Vitamin B12 deficiency	PPIs (e.g., pantoprazole, rabeprazole)	Vitamin B12	Farrell et al., 2013 (CR) [37] Farrell et al., 2022 (D) ^ [7]
Musculoskeletal and connective tissue disorders			
Arthralgia	DPP-4 inhibitors (e.g., sitagliptin, saxagliptin)	NSAIDs	Rochon et al., 2025 (D) ^ [27]
Myalgia	Rosuvastatin	Diclofenac, amitriptyline, hydromorphone, ibuprofen, tramadol	Farrell et al., 2022 (D) ^ [7]
Myositis	Statins	Analgesics	Rochon et al., 2025 (D) ^ [27]
		Mineral supplements	
		Quinine sulfate	
Osteoporosis	PPIs	Vitamin supplements	Rochon et al., 2025 (D) ^ [27]
Nervous system disorders			
Akathisia	Antipsychotics	Sedatives	Rochon et al., 2025 (D) ^ [27]
Dementia/Cognitive disorder	Risperidone	Memantine	Pepa et al., 2018 (CR) [43]
	Hydroxyzine	Lactulose	Lan et al., 2025 (CR) ^ [16]
	Antidepressants (tricyclic)	AChEIs	Rochon et al., 2025 (D) ^ [27]
	Tolterodine	Memantine, donepezil	Chi et al., 2019 (CR) [44]
Dizziness	Quetiapine+tiapride	Hydroxyzine	Lan et al., 2025 (CR) ^ [16]
	α-1 receptor blocker	Vestibular sedative (e.g., betahistine, antihistamines, benzodiazepines)	McCarthy et al. , 2022 (D) ^ [19]
Dystonia	Metoclopramide	Lorazepam	Ponte et al., 2017 (CSe) [35]
		Biperiden	Veloso & Cambao, 2015 (CR) [45]
	Paracetamol		
Extrapyramidal syndromes	Levosulpiride	Levodopa/carbidopa+pramipexole	Dehade, 2025 (CR) ^ [5]
	Quetiapine+risperidone	Biperiden	Hsieh et al., 2024 (CR) ^ [12]
	Antipsychotics	β blockers	Rochon et al., 2025 (D) ^ [27]
Headache	Allopurinol+tamsulosin+duloxetine	Topiramate	Farrell et al., 2020 (D) [42]
Seizures	Metoclopramide	Anticonvulsants (e.g., valproic acid, lorazepam+phenytoin)	Ponte et al., 2017 (CSe) [35]
	Carbapenems (i.e., imipenem, meropenem, ertapenem)		Ponte et al., 2017 (CSe) [35] Rochon et al., 2025 (D) ^ [27]
Serotonin syndrome	Quetiapine+paroxetine+risperidone	Amantadine	Hsieh et al., 2024 (CR) ^ [12]
Tremor	Quetiapine	Anti-Parkinson drugs (e.g., levodopa)	Farrell et al., 2020 (D) [42]
	Paroxetine		
	Fentanyl	Benzodiazepines (e.g., lorazepam)	Farrell et al., 2022 (D) ^ [7]
	Venlafaxine		Rochon et al., 2025 (D) ^ [27]
	Xinbao pills, baoxinning, ningxinbao capsules, shexiang baoxin pills, compound cerebroprotein hydrolysate tablets, xuesaitong dispersible tablets	Compound digestive enzyme capsules, lacidophilin tablets, live combined bacillus subtilis and enterococcus faecium enteric-coated capsules, trihexyphenidyl	Kang et al., 2013 (CR) [39]
Vertigo	Quetiapine+tiapride	Betahistine	Lan et al., 2025 (CR) ^ [16]
Psychiatric disorders			
Agitation	Benzodiazepine	Antipsychotic	McCarthy et al., 2022 (D) ^ [19]
	Ertapenem	Quetiapine, valproic acid, donepezil, alprazolam	Ribo & Ribo, 2014 (CR) [46]
	Quetiapine+paroxetine+risperidone	Amantadine	Hsieh et al., 2024 (CR) ^ [12]
Anxiety	Fentanyl	Lorazepam	Farrell et al., 2022 (D) ^ [7]
Behaviour disorder	Quetiapine+tiapride	Hydroxyzine	Lan et al., 2025 (CR) ^ [16]
Confusional state	Carbamazepine	Rivastigmine	Farrell et al., 2020 (D) [42]
	Pregabalin		
	Codeine		
	Quetiapine+paroxetine+risperidone	Amantadine	Hsieh et al., 2024 (CR) ^ [12]
Delusional disorder, jealous type	Naltrexone+quetiapine+paroxetine	Risperidone	Hsieh et al., 2024 (CR) ^ [12]
Depression	Naltrexone+quetiapine+paroxetine	Risperidone	Hsieh et al., 2024 (CR) ^ [12]
	Opioids	Antidepressants	Rochon et al., 2025 (D) ^ [27]
Disorientation	Ertapenem	Quetiapine, valproic acid, donepezil	Ribo & Ribo, 2014 (CR) [46]
	Quetiapine+paroxetine+risperidone	Amantadine	Hsieh et al., 2024 (CR) ^ [12]
Hallucination	Ertapenem	Quetiapine, valproic acid, donepezil	Ribo & Ribo, 2014 (CR) [46]

	Naltrexone+quetiapine+paroxetine	Risperidone	Hsieh et al., 2024 (CR) ^ [12]
	Dopaminergic anti-Parkinson drugs	Antipsychotics	Rochon et al., 2025 (D) ^ [27]
Insomnia	Ertapenem	Quetiapine, valproic acid, donepezil	Ribo & Ribo, 2014 (CR) [46]
	SSRI, SNRI	Sleep agent (e.g., benzodiazepines, benzodiazepine receptor agonists, sedating antidepressant, melatonin)	McCarthy et al., 2022 (D) ^ [19]
	Corticosteroids	Sleep agents	Rochon et al., 2025 (D) ^ [27]
Oppositional defiant disorder	Memantine	Dextromethorphan+quinidine	Pepa et al., 2018 (CR) [43]
Psychotic disorder	Dopaminergic anti-Parkinson drugs	Antipsychotics	Rochon et al., 2025 (D) ^ [27]
	Corticosteroids		
Renal and urinary disorders			
Urinary incontinence	Furosemide	Drugs for urinary frequency and incontinence (e.g., oxybutynin, tolterodine, solifenacin, trospium, darifenacin, fesoterodine, tamsulosin, dutasteride, flavoxate)	Farrell et al., 2020 (D) [42] Nguyen & Spinelli, 2016 (CR) [47]
	Spironolactone		Nguyen & Spinelli, 2016 (CR) [47]
	Donepezil	Tolterodine	Chi et al., 2019 (CR) [44]
Urinary retention	Antihistamines (e.g., dimenhydrinate, cetirizine)	Furosemide	Farrell et al., 2022 (D) ^ [7]
	Baclofen		
	Trazodone		
Skin and subcutaneous tissue disorders			
Hyperhidrosis	Fentanyl	Oxybutynin	Farrell et al., 2022 (D) ^ [7]
Rash	Anticonvulsants	Topical corticosteroids	Rochon et al., 2025 (D) ^ [27]
Vascular disorders			
Hypertension	Paroxetine	Lisinopril	Farrell et al., 2020 (D) [42]
	Venlafaxine	Antihypertensives (e.g., amlodipine)	Farrell et al., 2022 (D) ^ [7] Rochon et al., 2025 (D) ^ [27]
	Methylphenidate	Metoprolol, irbesartan	Farrell et al., 2022 (D) ^ [7]
	Midodrine	Antihypertensive	Rochon et al., 2025 (D) ^ [27]
	Corticosteroids (e.g., fludrocortisone)		
Orthostatic hypotension	Ropinirole	Midodrine	Becerra et al., 2021 (CR) [40]
	Antihypertensive (e.g., α-1 receptor blocker)	Vestibular sedative (e.g., betahistine, antihistamines, benzodiazepines)	McCarthy et al., 2022 (D) ^ [19] Rochon et al., 2025 (D) ^ [27]

Abbreviations: AChEIs = Acetylcholinesterase inhibitors; ADR = Adverse drug reaction; DPP-4 inhibitors = Inhibitors of dipeptidyl peptidase 4; NSAIDs = Non-steroidal anti-inflammatory drugs; PPIs = Proton pump inhibitors.

Legend:
^ Study retrieved from the updated systematic review
Computational: Computational study
CR: Case report
CSe: Case series
D: Qualitative descriptive study/consensus study

Supplementary Table 9. Prescribing cascades in which adverse drug reactions or drugs involved were not reported.

ADR not reported			
Not reported	Roflumilast	Antithyroid agents Parathyroid hormones Hematopoietic agents Meglitinides Antituberculosis agents Sodium chloride preparations Chemotherapy Digoxin Hormone-modifying therapy Folic acid and derivatives Miscellaneous anti-infective agents Lactulose Emollients, moisturizers and protectants Miscellaneous urinary anti-infective agents Miscellaneous skin and mucous membrane agents Miscellaneous antiemetics Miscellaneous antigout agents Anti-infective and anti-inflammatory (eye, ear, nose, throat) Miscellaneous central nervous system agents Antidiarrheal agents Antiarrhythmic agents Anticholinergic/antimuscarinic/antispasmodic Antipruritic agents and local anesthetics Eye, ear, nose, and throat miscellaneous agents Smooth-respiratory muscle relaxants Eye, ear, nose, and throat antibiotics Miscellaneous anticonvulsants Antivirals Skin and mucous membrane antibiotics and combinations Miscellaneous antibiotics Analgesics/antipyretics Benzodiazepines	Abdelaziz et al., 2025 (PSSA) ^ [48]
Not reported	NSAIDs (M01A)	Opioids (N02A) Other analgesics (= Paracetamol) (N02B) Corticosteroids for systemic use, plain (H02A) Anti-ulcer drugs (A02B) Drugs for constipation (A06A) Propulsives (A03F) Cough suppressants (R05D)	Hallas et al., 2018 (PSSA) [49]
	Opioids (N02A)	Drugs for constipation (A06A) Propulsives (A03F) Drugs affecting bone structure and mineralization (M05B) Antacids (A02A)	
	Antithrombotic agents (B01A)	Cholesterol lowering drugs (C10A) Drugs for constipation (A06A) Other analgesics (= Paracetamol) (N02B) Antidepressants (N06A) Anti-ulcer drugs (A02B) Calcium channel blockers (C08C)	
	High-ceiling diuretics (C03C)	Potassium (A12B)	
	Thiazides (C03A)		
	Other analgesics (= Paracetamol) (N02B)	Drugs for constipation (A06A) Antacids (A02A) Propulsives (A03F)	
	Potassium (A12B)	Potassium-sparing agents (C03D)	

	Inhaled beta-agonists (R03A)	Drugs affecting bone structure and mineralization (M05B)	
	Cough suppressants (R05D)	Drugs for constipation (A06A)	
	Beta blockers (C07A)	Other analgesics (= Paracetamol) (N02B) Antidepressants (N06A)	
	Beta-lactam antibacterials, penicillins (J01C)	Agents against amoebiasis and other protozoal diseases (P01A)	
	Macrolides, lincosamides and streptogramins (J01F)	Inhaled anticholinergics and steroids (R03B)	
	Corticosteroids for systemic use, plain (H02A)	Drugs affecting bone structure and mineralization (M05B)	
Not reported	Non-vitamin K oral anticoagulants	Antiarrhythmics, class III (C01BD) Aldosterone antagonists (C03DA) Antiarrhythmics, class Ic (C01BC) Osmotically acting laxatives (A06AD) Benzodiazepines, sedatives (N05BA) Topical corticosteroids for treatment of hemorrhoids/anal fissures (C05AA) Verapamil (C08DA) ACE inhibitors (C09AA) Benzodiazepines, hypnotics (N05CD) Angiotensin II antagonists (C09CA) Selective serotonin reuptake inhibitors (N06AB) Other antidepressants (N06AX) Proton pump inhibitors (A02BC) Phenylpiperidine opioids (N02AB) Propulsives (A03FA) Potassium (A12BA) Iron bivalent, oral (B03AA) Loop diuretics (C03CA) Digitalis glycosides (C01AA) Contact laxatives (A06AB)	Hellfritzsch et al., 2018 (PSSA) [50]
Not reported	AChEIs (i.e., donepezil, rivastigmine, galantamine) Memantine	Anticholinergics	Narayan et al., 2019 [51]
Not reported	ACE inhibitors	Other nasal preparations (R01AX) Other antianemic preparations (B03XA) Antiallergic agents, excl. corticosteroids (R01AC) Electrolyte solutions (B05XA) Selective β-2-adrenoreceptor agonists (R03AC) Pregnadien derivatives (G03DB) Leukotriene receptor antagonists (R03DC) Antipropulsives (A07DA) Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids (R03AL) Drugs for treatment of hyperkalemia and hyperphosphatemia (V03AE) Bile acid sequestrants (C10AC) Carbohydrates (V06DC) Butyrophenone derivatives (N05AD) Phenylpiperidine derivatives (N02AB) Other antiallergics (S01GX) Corticosteroids (R01AD) Propulsives (A03FA) Imidazole derivatives (J01XD) Osmotically acting laxatives (A06AD) Serotonin (5-HT3) antagonists (A04AA) Sympathomimetics (R01BA) Other antiemetics (A04AD) Other systemic drugs for obstructive airway diseases (R03DX) Anticholinergics (S01FA) Other antispasmodics in combination with analgesics (A03DC) Adrenergic and dopaminergic agents (C01CA)	Ndai et al., 2025 (1) (PSSA) ^ [52]

		Glucocorticoids (R03BA) Diazepines, oxazepines, thiazepines, and oxepines (N05AH) Sulfonamides (D06BA) Benzodiazepine derivatives (N03AE) Sympathomimetics in glaucoma therapy (S01EA) Benzodiazepine derivatives (N05BA) Other aminoglycosides (J01GB) Dopa and dopa derivatives (N04BA) Other drugs for constipation (A06AX) Benzodiazepine derivatives (N05CD) Other drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD) (A02BX) SSRIs (N06AB) Amides (N01BB) Anticholinergics (R03BB) Phenothiazine derivatives (R06AD) Nitrofuran derivatives (J01XE) H2-receptor antagonists (A02BA)	
Not reported	Polypharmacy + anticholinergic drugs	Proton pump inhibitors H_2 receptor blockers	Rababa et al., 2016 (RC) [53]
Not reported	Antiepileptics	Propulsives, laxatives, intestinal antiinfectives, potassium, diuretics, antifungals, chemotherapeutics, corticosteroids, anti-acne medications, pituitary hormones, antibiotics, non-steroidal and anti-rheumatic medications, bone disease medications, opioids, dopaminergic medications, anxiolytics, addiction medications, expectorants, antiinfectives, decongestants, and antiallergics	Tsiropoulos et al., 2009 (PSSA) [54]
Not reported	Statins (i.e., simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin)	Polymyxins (J01XB) Zinc (A12CB) Magnesium compounds (A02AA) Magnesium (A12CC) Dantrolene and derivatives (M03CA) Estrogens, combinations with other drugs (G03CC) SGLT-2i (A10BK) 3-oxoandrosten (4) derivatives (G03BA) Proteolytic enzymes (D03BA) Phenothiazines with aliphatic side–chain (N05AA) Electrolyte solutions (B05XA) Other drugs affecting bone structure and mineralization (M05BX) Ovulation stimulants, synthetic (G03GB) Anticholinesterases (N07AA) Glucagon-like peptide-1 (GLP-1) analogues (A10BJ) Choline esters (N07AB) Phenothiazines with piperazine structure (N05AB) Other aminoglycosides (J01GB) Osmotically acting laxatives (A06AD) Mineralocorticoids (H02AA) α-glucosidase inhibitors (A10BF) Glycopeptide antibacterials (J01XA) Salt solutions (B05CB) Trimethoprim and derivatives (J01EA) Dipeptidyl peptidase 4 (DPP-4) inhibitors (A10BH) Enemas (A06AB) Butyrophenone derivatives (N05AD) Combinations of oral blood glucose-lowering drugs (A10BD) Fatty acid derivatives (N03AG)	Vouri et al., 2023 (PSSA) ^ [55]

		Other anti-dementia drugs (N06DX) Propulsives (A04AA) Other blood glucose-lowering drugs, excl. insulins (A10BX) Barbiturates and derivatives (N03AA) Preparations with no effect on uric acid metabolism (M04AC) Anticholinesterases (N06DA) Other antibacterials (J01XX) Other diagnostic agents (V04CX) Bisphosphonates (M05BA) Calcitonin preparations (H05BA) Biguanides (P01BB) Antibiotics (A07AA) Phenothiazine derivatives (R06AD) Antipropulsives (A07DA) Other antispasmodics in combination with analgesics (A03DC) Sulfonamides (D06BA) Aminosalicylic acid and similar agents (A07EC) Sympathomimetics used as decongestants (S01GA) Benzodiazepine derivatives (N05CD) Opioids in combination with non-opioid analgesics (N02AJ) Prostaglandin analogues (S01EE) First-generation cephalosporins (J01DB) Nitroimidazole derivatives (P01AB) Anti-inflammatory preparations, non-steroids for topical use (M02AA) Other opioids (N02AX) Lincosamides (J01FF) Antiinfectives and antiseptics for local oral treatment (A01AB) Antiinfectives (S03AA)	
Not reported	Clozapine First-generation antipsychotics (multi-drug sequences)	Cardiometabolic drugs (antihypertensive drugs, antiarrhythmic agents, lipid-lowering drugs, antidiabetic agents)	Zagozdzon et al., 2022 (RC) ^ [34]
Drugs for ADR treatment not reported			
Dementia/Cognitive disorder	Anti-hypertensives (central anti-hypertensives, α blockers, β blockers), hypnotics, anti-anxiety medications (benzodiazepines), antidepressants (tricyclic), antiepileptics, antipsychotics (phenothiazine), anti-Parkinson medications (anticholinergic medications), antihistamines (including H2 receptor antagonists)	Not reported	Hasegawa et al., 2023 (RC) ^ [56]
Constipation	Hypnotics, anti-anxiety medications (benzodiazepines), tricyclic antidepressants, overactive bladder medications (muscarine receptor antagonists), intestinal tract anticonvulsants (atropine, butylscopolamine), antihistamines (including H2 receptor antagonists), α-glucosidase inhibitors, antipsychotics (phenothiazine), anti-Parkinson medications (anticholinergic medications)	Not reported	
Impaired appetite	NSAIDs, acetylsalicylic acid, laxatives, anti-anxiety medications, antipsychotics, anti-Parkinson medications (anticholinergic medications), selective serotonin reuptake inhibitor (SSRI), cholinesterase inhibitors, bisphosphonate, biguanide	Not reported	

Abbreviations: ACE inhibitors = Angiotensin-converting-enzyme inhibitors; AChEIs = Acetylcholinesterase inhibitors; ADR = Adverse drug reaction; NSAIDs = Non-steroidal anti-inflammatory drugs; PSSA = Prescription sequence symmetry analysis.

Legend:
^ Study retrieved from the updated systematic review
PSSA: Retrospective study with PSSA analysis
RC: Retrospective cohort study

Supplementary Table 10. Drug classes potentially inducing adverse drug reactions leading to prescribing cascades, grouped by second-level ATC classification system.

Therapeutic class description	Second-level ATC	N *
Psychoanaleptics	N06	26
Psycholeptics	N05	23
Lipid modifying agents	C10	19
Agents acting on the renin–angiotensin system	C09	15
Analgesics	N02	14
Diuretics	C03	13
Drugs used in diabetes	A10	12
Antiepileptics	N03	11
Anti-inflammatory and antirheumatic products	M01	11
Antibacterials for systemic use	J01	11
Calcium channel blockers	C08	10
Drugs for acid related disorders	A02	10
Anti-Parkinson drugs	N04	9
Other nervous system drugs	N07	8
Cardiac therapy	C01	7
Corticosteroids for systemic use	H02	7
Antithrombotic agents	B01	7
Beta blocking agents	C07	7
Antihypertensives	C02	7
Drugs for obstructive airway diseases	R03	7
Drugs for functional gastrointestinal disorders	A03	5
Sex hormones and modulators of the genital system	G03	4
Urologicals	G04	4
Antineoplastic agents	L01	4
Antihistamines for systemic use	R06	3
Muscle relaxants	M03	3
Drugs for treatment of bone diseases	M05	2
Endocrine therapy	L02	2
Mineral supplements	A12	2
Antidiarrheals, intestinal anti-inflammatory/anti-infective agents	A07	2
Immunosuppressants	L04	2
Ophthalmologicals	S01	2
Other #		9

Abbreviations: ATC = Anatomic Therapeutic Chemical.

* Each ATC category was counted only once per Preferred Term, regardless of the number of drugs associated with the same PT.

Includes (N= 1 each): Antimycobacterials (J04), Anti-acne preparations (D10), Antigout preparations (M04), Antiemetics and antinauseants (A04), Antipsoriatics (D05), Calcium homeostasis regulators (H05), Antianemic preparations (B03), All other therapeutic products (V03), Antihemorrhagics (B02).

References

1. Abdelaziz A, Gaber CE, Gupta P, Lee TA. High Throughput Pharmacovigilance Screening for Roflumilast Adverse Effects in Real-World Settings: A Sequence Symmetry Analysis. *Basic Clin Pharmacol Toxicol*. 2025;136(5):e70038. doi:10.1111/bcpt.70038

2. Alghamdi A, Bijlsma MJ, de Vos S, Schuiling-Veninga CCM, Bos JHJ, Hak E. Association between Incidence of Prescriptions for Alzheimer's Disease and Beta-Adrenoceptor Antagonists: A Prescription Sequence Symmetry Analysis. *Pharmaceuticals*. 2023;16(12). doi:10.3390/ph16121694

3. Chikermane SG, Li J, Aparasu RR. Risk of antimuscarinic initiation with cholinesterase inhibitor use in Alzheimer's disease. *Arch Gerontol Geriatr*. 2025;128. doi:10.1016/j.archger.2024.105629

4. Chikermane SG, Li J, Aparasu RR. Risk of Antipsychotic Initiation Among Older Dementia Patients Initiating Cholinesterase Inhibitors. *Drug Healthc Patient Saf*. 2025;17:75-85. doi:10.2147/DHPS.S506523

5. Dehade A, Chakrabarti SS, Reddy NTS, Kaur U. Dopaminergic Drugs and Valproate-associated Refractory Hyponatremia Over Levosulpiride-induced Parkinsonism in an Elderly Female Patient When Deprescribing was the Only Therapy. *Curr Drug Saf*. 2025;20(2):232-236. doi:10.2174/0115748863288106240313042127

6. Elli C, Novella A, Nobili A, Ianes A, Pasina L. Anemia in nursing homes, proton pump inhibitors and prescribing cascade of antianemic drugs. *Eur Geriatr Med*. 2022;13(3):553-558. doi:10.1007/s41999-022-00636-2

7. Farrell B, Galley E, Jeffs L, Howell P, McCarthy LM. "Kind of blurry": Deciphering clues to prevent, investigate and manage prescribing cascades. *PLoS ONE*. 2022;17(8 August). doi:10.1371/journal.pone.0272418

8. Funabashi A, Ito H, Maeda M, Hasegawa Y, Tsukioka R, Onda M. Evaluation of dipeptidyl peptidase-4 inhibitor-associated gastrointestinal symptoms using the prescription claims database. *Sci Rep*. 2025;15(1):11494. doi:10.1038/s41598-025-96103-6

9. Growdon ME, Jing B, Morris EJ, et al. Which older adults are at highest risk of prescribing cascades? A national study of the gabapentinoid–loop diuretic cascade. *J Am Geriatr Soc*. 2024;72(6):1728-1740. doi:10.1111/jgs.18892

10. Growdon ME, Jing B, Deardorff WJ, et al. Loop diuretics and subsequent use of urinary symptom medications in older adults: evaluation of a possible prescribing cascade. *J Gerontol Ser A*. 2025;80(8):glaf150. doi:10.1093/gerona/glaf150

11. Hasegawa S, Mizokami F, Mizuno T, et al. Investigation of geriatric syndromes associated with medication in Japan using insurance claims data. *Geriatr Gerontol Int*. 2024;24(1):61-67. doi:10.1111/ggi.14755

12. Hsieh YY, Lin CM, Chen CY. Serotonin Syndrome from the Complex Drug Interactions of Second-Generation Antipsychotics in Older Patients: Case Report and Literature Review. *Am J Ther*. 2024;31(3):E300-E303. doi:10.1097/MJT.0000000000001685

13. Ito H, Hasegawa Y, Maeda M, et al. Evaluation of pregabalin-induced oedema using the adverse event spontaneous reporting database and the prescription claims database. *Int J Pharm Pract*. 2025;33(3):340-346. doi:10.1093/ijpp/riaf012

14. Janetzki JL, Sykes MJ, Ward MB, Pratt NL. Chronic Obstructive Pulmonary Disease Adverse Event Signals Associated with Potential Inhibitors of Glutathione Peroxidase 1: A Sequence Symmetry Analysis. *Drug Saf*. 2024;47(1):59-70.

15. Lai SW, Hwang BF, Kuo YH, Liu CS, Liao KF. Risk of gout flare after medication: prescription symmetry sequence analysis. *Clin Rheumatol*. 2024;43(3):1183-1188.

16. Lan YY, Kovinthapillai R, Szostakiewicz J, Neumann-Podczaska A, Wieczorowska-Tobis K. Less is more: A case of interdisciplinary deprescribing of multiple neuroleptics and polypharmacy in a geriatric patient with neurodegenerative diseases in long-term care. *Geriatr Gerontol Int*. Published online 2025. doi:10.1111/ggi.70118

17. Lu SY, Hsu HY, Hsieh YW, Lu CR, Huang HY, Chang SS. Prescribing cascades of antigout medications from thiazide diuretics in gout-naïve hypertensive adults receiving first-line pharmacological management. *Sci Rep*. 2024;14(1):7402. doi:10.1038/s41598-024-58153-0

18. Lund LC, Jensen PH, Pottegård A, Andersen M, Pratt N, Hallas J. Identifying diabetogenic drugs using real world health care databases: A Danish and Australian symmetry analysis. *Diabetes Obes Metab*. 2023;25(5):1311-1320. doi:10.1111/dom.14982

19. McCarthy LM, Savage R, Dalton K, et al. ThinkCascades: A Tool for Identifying Clinically Important Prescribing Cascades Affecting Older People. *Drugs Aging*. 2022;39(10):829-840. doi:10.1007/s40266-022-00964-9

20. Mohammad AK, Hugtenburg JG, Vanhommerig JW, van den Bemt PMLA, Denig P, Karapinar-Carkıt F. Identifying and quantifying potentially problematic prescribing cascades in clinical practice: A mixed-methods study. *J Am Geriatr Soc*. 2024;72(12):3681-3694. doi:10.1111/jgs.19191

21. Ndai AM, Smith K, Keshwani S, et al. High-Throughput Screening for Prescribing Cascades Among Real-World Angiotensin-Converting Enzyme Inhibitor Initiators. *Pharmacoepidemiol Drug Saf*. 2025;34(3). doi:10.1002/pds.70132

22. Ndai AM, Smith K, Keshwani S, et al. High-Throughput Screening for Prescribing Cascades Among Real-World Angiotensin-II Receptor Blockers (ARBs) Initiators. *medRxiv*. Published online 2025. doi:10.1101/2025.03.10.25323711

23. Ochi S, Tsuboi T, Hasegawa N, et al. The association between benzodiazepine prescriptions and the risk of laxative use in schizophrenia treatment. *Neuropsychopharmacol Rep*. 2025;45(1). doi:10.1002/npr2.12499

24. Omata R, Asami A, Hara A, Urushihara H. Prescribing Cascades of Loop Diuretics and Anti-vertigo Drugs Following Treatment with Gabapentinoids and Benzodiazepines: Prescription Sequence Symmetry Analysis of a Large-Scale Claims Database Including Japanese Older Adults. *Drugs - Real World Outcomes*. 2024;11(3):529-540. doi:10.1007/s40801-024-00446-x

25. Rahbek MT, Gram EAB, Hallas J, Christensen MMH, Lund LC. Analysis of Antiemetic Use after Initiation of Hormone Therapy. *JAMA Netw Open*. 2022;5(5):E2211883. doi:10.1001/jamanetworkopen.2022.11883

26. Ravinandan AP, Maheswari E, Vishwas HN. RETHINKING PRESCRIPTIONS: DESIGNING A CLINICAL PROCESS MAP TO MITIGATE DAPAGLIFLOZIN-INDUCED PRESCRIBING CASCADES. *Asian J Pharm Clin Res*. 2025;18(5):1-4. doi:10.22159/ajpcr.2025v18i5.54320

27. Rochon PA, O'Mahony D, Cherubini A, et al. International expert panel's potentially inappropriate prescribing cascades (PIPC) list. *Eur Geriatr Med*. Published online July 31, 2025. doi:10.1007/s41999-025-01215-x

28. Russell J, Arwood MJ, Toro-Pagán NMD, et al. Case Report: Performing a Medication Safety Review Assisted by Pharmacogenomics to Explain a Prescribing Cascade Resulting in a Patient Fall. *Med Kaunas Lith*. 2023;59(1). doi:10.3390/medicina59010118

29. Saito Y, Oishi S, Takizawa T, et al. Analysis of Concomitant Medications Prescribed with Antipsychotics to Patients with Dementia. *Dement Geriatr Cogn Disord*. 2023;52(4):222-231. doi:10.1159/000531240

30. Trenaman SC, Harding A, Bowles SK, Kirkland SA, Andrew MK. A Prescribing Cascade of Proton Pump Inhibitors Following Anticholinergic Medications in Older Adults With Dementia. *Front Pharmacol*. 2022;13. doi:10.3389/fphar.2022.878092

31. Vouri SM, Morris EJ, Walsh M, et al. High-throughput screening for prescribing cascades among real world statin initiators. *Pharmacoepidemiol Drug Saf*. 2023;32(7):773-782. doi:10.1002/pds.5607

32. Vouri SM, Morris EJ, Wang GHM, Hashim Jaber Bilal A, Hallas J, Henriksen DP. Association between gabapentinoids and oedema treated with loop diuretics: A pooled sequence symmetry analysis from the USA and Denmark. *Br J Clin Pharmacol*. 2022;88(12):5269-5294. doi:10.1111/bcp.15447

33. Wang GHM, Morris EJ, Smith SM, Hallas J, Vouri SM. Continued potassium supplementation use following loop diuretic discontinuation in older adults: An evaluation of a prescribing cascade relic. *J Am Geriatr Soc*. 2023;71(2):505-515. doi:10.1111/jgs.18103

34. Zagozdzon P, Dorozynski P, Waszak P, Harasimowicz A, Dziubich T. Antipsychotic drug prescription sequence analysis in relation to death occurrence and cardiometabolic drug usage: A retrospective longitudinal study. *Eur J Psychiatry*. 2023;37(1):1-7. doi:10.1016/j.ejpsy.2022.06.002

35. Ponte ML, Wachs L, Wachs A, Serra HA. Prescribing cascade. A proposed new way to evaluate it. *Medicina (Mex)*. 2017;77(1):13-16.

36. Yan X, Chen W, Wang L. Elevated sera creatinine levels in elderly patients caused by prescribing cascade. *Clin Medicat J*. 2020;18:87-89. doi:10.3969/j.issn.1672-3384.2020.05.018

37. Farrell B, Shamji S, Ingar N. Reducing fall risk while managing pain and insomnia. *Can Pharm J CPJ*. 2013;146(6):335-341. doi:10.1177/1715163513504529

38. Rochon PA, Stukel TA, Sykora K, et al. Atypical antipsychotics and parkinsonism. *Arch Intern Med*. 2005;165(16):1882-1888. doi:10.1001/archinte.165.16.1882

39. Kang J, Liu X, Zhang B. An Older Patient with Diarrhea and Tremor Induced by Polypharmacy. *Clin Medicat J*. 11:30-31+59. doi:10.3969/j.issn.1672-3384.2013.02.009

40. Becerra AF, Boch M, Al-Mezrakchi YA. Ropinirole-Associated Orthostatic Hypotension as Cause of a Prescribing Cascade in an Elderly Man. *Cureus*. 2021;13(6):e15506. doi:10.7759/cureus.15506

41. Hofmann A, Khalid A, Mao YH, et al. Prescribing cascade in mental health: the older person at risk. *Prog Neurol Psychiatry*. 2020;24(2):17-20. doi:10.1002/pnp.665

42. Farrell BJ, Jeffs L, Irving H, McCarthy LM. Patient and provider perspectives on the development and resolution of prescribing cascades: a qualitative study. *BMC Geriatr*. 2020;20(1):368. doi:10.1186/s12877-020-01774-7

43. Pepa PA, Langley-DeGroot MH, Rule OS. Prescribing cascade in a geropsychiatric patient: A slippery slope. *J Geriatr Ment Health*. 2018;5(1):62. doi:10.4103/jgmh.jgmh_17_17

44. Chi DY. The prescribing cascade and medication therapy management between cholinesterase inhibitors and anticholinergic drugs. *Chin Pharm J*. Published online 2019:411-414.

45. Veloso TS, Cambão MS. Migraine treatment: a chain of adverse effects. *SpringerPlus*. 2015;4(1):409. doi:10.1186/s40064-015-1206-1

46. Ribo FZ, Ribo A. Ertapenem-induced Neuropsychiatric Symptoms in an Elderly Patient with Chronic Kidney Disease Resulting to a Prescribing Cascade. *J Pharmacovigil*. 2014;2(6):1-3. doi:10.4172/2329-6887.1000152

47. Nguyen PVQ, Spinelli C. Prescribing cascade in an elderly woman. *Can Pharm J CPJ*. 2016;149(3):122-124. doi:10.1177/1715163516640811

48. Abdelaziz A, Gaber CE, Gupta P, Lee TA. High Throughput Pharmacovigilance Screening for Roflumilast Adverse Effects in Real-World Settings: A Sequence Symmetry Analysis. *Basic Clin Pharmacol Toxicol*. 2025;136(5):e70038. doi:10.1111/bcpt.70038

49. Hallas J, Wang SV, Gagne JJ, Schneeweiss S, Pratt N, Pottegård A. Hypothesis-free screening of large administrative databases for unsuspected drug-outcome associations. *Eur J Epidemiol*. 2018;33(6):545-555. doi:10.1007/s10654-018-0386-8

50. Hellfritzsch M, Rasmussen L, Hallas J, Pottegård A. Using the Symmetry Analysis Design to Screen for Adverse Effects of Non-vitamin K Antagonist Oral Anticoagulants. *Drug Saf*. 2018;41(7):685-695. doi:10.1007/s40264-018-0650-6

51. Narayan SW, Pearson SA, Litchfield M, et al. Anticholinergic medicines use among older adults before and after initiating dementia medicines. *Br J Clin Pharmacol*. 2019;85(9):1957-1963. doi:10.1111/bcp.13976

52. Ndai AM, Smith K, Keshwani S, et al. High-Throughput Screening for Prescribing Cascades Among Real-World Angiotensin-Converting Enzyme Inhibitor Initiators. *Pharmacoepidemiol Drug Saf*. 2025;34(3):e70132. doi:10.1002/pds.70132

53. Rababa M, Al-Ghassani AA, Kovach CR, Dyer EM. Proton Pump Inhibitors and the Prescribing Cascade. *J Gerontol Nurs*. 2016;42(4):23-31; quiz 32-33. doi:10.3928/00989134-20151218-04

54. Tsiropoulos 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. doi:10.1002/pds.1736

55. Vouri SM, Morris EJ, Walsh M, et al. High-throughput screening for prescribing cascades among real world statin initiators. *Pharmacoepidemiol Drug Saf*. 2023;32(7):773-782. doi:10.1002/pds.5607

56. Hasegawa S, Mizokami F, Mizuno T, et al. Investigation of geriatric syndromes associated with medication in Japan using insurance claims data. *Geriatr Gerontol Int*. 2024;24(1):61-67. doi:10.1111/ggi.14755