

Title: Prescribing cascades with recommendations to prevent or reverse them: a systematic review

Running head: Prevent and reverse prescribing cascades

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Supplementary table 1: PRISMA-checklist

Abstract

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No, study aims to identify which prescribing cascades could possibly occur
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes

Section and Topic	Item #	Checklist item	Reported (Yes/No)
Registration	12	Provide the register name and registration number.	CRD42021253004

Manuscript

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			Page number
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Supplementary table 1: abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1. introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1. introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	2.2 Inclusion and exclusion of publications
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	2.1 Search strategy and data sources
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary table 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	2.2 Inclusion and exclusion of publications
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	2.4 Data extraction
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in	2.4 Data extraction and Supplementary

Section and Topic	Item #	Checklist item	Location where item is reported
		each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	table 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Supplementary table 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Not applicable, study aims to identify which prescribing cascades could possibly occur
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Effect measures of the original publications were extracted (Supplementary table 8 and 9)
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	2.4 Data extraction
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Supplementary table 4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Supplementary table 4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	2.4 Data extraction
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Not applicable. (not the main aim of this study)
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Not applicable
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Not applicable
Certainty	15	Describe any methods used to assess certainty (or confidence) in the body of	7

Section and Topic	Item #	Checklist item	Location where item is reported
assessment		evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	3. Results and Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Supplementary table 5
Study characteristics	17	Cite each included study and present its characteristics.	3. Results and Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Not applicable
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Supplementary table 7 and 8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Table 1
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	3.1 Prescribing cascades, 3.2 Dose dependency and recommended actions and Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Not applicable
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Not applicable
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Not applicable
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Table 2
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	4. Discussion and 4.1 Comparison with previous studies
	23b	Discuss any limitations of the evidence included in the review.	4.4 Limitations

Section and Topic	Item #	Checklist item	Location where item is reported
	23c	Discuss any limitations of the review processes used.	4.4 Limitations
	23d	Discuss implications of the results for practice, policy, and future research.	4.2 Implications for policy, practice and research
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Tite page
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Tite page
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Tite page
Competing interests	26	Declare any competing interests of review authors.	Tite page
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary documents

Supplementary table 2: Search strategy

All database searches were conducted on January 19th 2021. No filters or limitations were used in any of the databases.

OVID Medline

1	((prescri* adj6 cascade*) or (prescri* adj6 sequence*) or (prescri* adj6 symmetry*)).mp.	327
2	("Drug-Related Side Effects and Adverse Reactions"/ or ae.fs. or ci.fs. or adverse*.mp. or side-effect*.mp. or drug-induced*.mp.) and (symmetry-analys* or sequence-ratio* or symmetry-ratio*).mp.	78
3	(Drug Prescriptions/ or prescri*.mp.) and ci.fs. and adverse*.mp. and (event* or side-effect* or drug-induced* or reaction*).mp. and case*.mp.	2360
4	1 or 2 or 3	2719

OVID Embase

1	((prescri* adj6 cascade*) or (prescri* adj6 sequence*) or (prescri* adj6 symmetry*)).mp.	516
2	(exp side effect/ or exp drug safety/ or exp chemically induced disorder/ or ae.fs. or si.fs. or adverse*.mp. or side-effect*.mp. or drug-induced*.mp.) and (symmetry-analys* or sequence-ratio* or symmetry-ratio*).mp.	115
3	(exp prescription/ or prescri*.mp.) and exp chemically induced disorder/ and adverse*.mp. and (event* or side-effect* or drug-induced* or reaction*).mp. and case*.mp.	520
4	1 or 2 or 3	1094

Cochrane Database of Systematic Reviews & Cochrane CENTRAL Register of Controlled Trials

#1	((prescri* NEAR/6 cascade*) or (prescri* NEAR/6 sequence*) or (prescri* NEAR/6 symmetry*))	35
#2	MeSH descriptor: [Drug-Related Side Effects and Adverse Reactions] explode all trees	3620
#3	ae.fs or ci.fs or adverse* or side-effect* or drug-induced*	360639
#4	(#2 or #3) and (symmetry-analys* or sequence-ratio* or symmetry-ratio*)	11
#5	MeSH descriptor: [Drug Prescriptions] explode all trees	923
#6	prescri*	38005
#7	(#5 or #6) AND ci.fs. AND adverse* AND (event* or side-effect* OR drug-induced* OR reaction*) AND case*	0
#8	#1 OR #4 OR #7	45
	<i>#8 in Cochrane Database of Systematic Reviews</i>	7
	<i>#8 in Cochrane CENTRAL Register of Controlled Trials</i>	38

CINAHL

S1	((prescri* N6 cascade*) or (prescri* N6 sequence*) or (prescri* N6 symmetry*))	116
S2	(MH "Adverse Drug Event+")	29,869
S3	MW ae OR MW ci OR adverse* OR side-effect* OR drug-induced*	624,530
S4	S2 OR S3	636,998
S5	(symmetry-analys* or sequence-ratio* or symmetry-ratio*)	122
S6	S4 AND S5	28
S7	(MH "Prescriptions, Drug+")	12,841
S8	prescri*	121,572
S9	S7 OR S8	121,733

S10	MW ci AND adverse AND (event* OR side-effect* OR drug-induced* OR reaction*) AND case*	4,395
S11	S9 AND S10	478
S12	S1 OR S6 OR S11	608

ci.fs.: chemically induced floating subheading; ae.fs: adverse effects floating subheading; si.fs, side effects floating subheading; ADJ6: either the word are next to each other or can have up to five word in between, in any order; .MP: multi-purpose, a .MP search looks in the Title, Original Title, Abstract, Subject Heading, Name of Substance, and Registry Word fields; MW ci: chemically induced floating subheading; MW ae: adverse effects floating subheading; N6: either the word are next to each other or can have up to six word in between, in any order; NEAR/6: either the word are next to each other or can have up to five word in between, in any order

Supplementary table 3: Data extraction form

	Data	Description of data	Classification/As described in text
Study characteristics (methods)			
Reference	Author	First author of publication	As described in text
	Year	Year of publication	As described in text
	Title	Title of publication	As described in text
	Country	Country where the study was performed. If that information is not available; country of origin of the first author	As described in text
	Objective	Extracted from the introduction or when absent in introduction, extracted from the abstract of the article	As described in text
	Definition prescribing cascade	The definition of a prescribing cascade described or used for the study. Could be found under PSSA definition	Term used for prescribing cascades (e.g., problematic, unintentional) + definition
	Design	Design of the study	Classify into: Cohort study or case-control study
	Setting	The database or records used to collect the data needed for the research on prescribing cascades	Classify into: Primary care, secondary care, nursing home, or NR. If a combination of databases/records were used, select Other: [databases/records]
	Run-in period	The baseline period that was imposed in the study to ensure that an index or marker medication was indeed the first dispensing and it could be defined as incidence	In months
	Interval limit	The (maximum) timespan examined between the prescribing of index medication and marker medication	
	Inclusion criteria	All inclusion criteria as reported in the study	
	Exclusion criteria	All exclusion criteria as reported in the study	As described in text
	Continued exposure	The way continued medication exposure of index medication and marker medication was determined	
	Age category	Age distribution of the cohort/population	Classify into >18; >65; >80; Other: [age category used]

Primary outcome	As mentioned in section outcomes (or in the objective)	As described in text	
Comments	Other relevant information regarding the study characteristics		
Patient characteristics (results)			
Number, total	Total number of patients analyzed in the study after all selection/inclusion criteria	As described in text, or calculate it	
Age, mean	Mean age of the analyzed patients		
Female (%)	Percentage of the analyzed female population		
Gender	Gender of the analyzed patients		
Number of Medication, mean	The mean number of medication patients have in use		
Comments	Other relevant information regarding the patient characteristics		
Analysis (methods/results)			
Type analysis	The type of analysis that is used	Classify into: PSSA, logistic regression, other: [analysis used]	
Overall analysis	Overall result of the analysis	Classify into NS, S or IS	
Comments	Other relevant information regarding the analysis	As described in text	
Risk factors	Age	Classify into NS, S or IS + conclusion of the analysis	
	Sex		Whether sex has been analyzed as a risk factor
	Gender		Whether gender has been analyzed as a risk factor (gender refers to the socially constructed roles, behaviours, expressions and identities of female, male and gender diverse people)
	Other		Whether other factors have been analyzed
	Comments	Other relevant information regarding factors that the study has controlled for	As described in text
Subgroup analysis	Description of which subgroup analyses were performed (e.g., additional PSSA analysis, sensitivity analysis and stratification)	Classify into: sex, age, dose and other: [subgroup analysis + the explanation on the analysis]	
Results subgroup analysis	Results of the subgroup analysis	Classify into: Yes (result subgroup analysis coincides with result main analysis) or No (result subgroup	

			analysis does not coincide with result main analysis) + actual result
Prescribing cascade			
Index medication	Group	The pharmacological subgroup of the index medication	As described in text. If necessary, classify it in the right subgroup using WHO ATC system
	Individual	Name of the index medication within the group, if reported	
	ATC code	The ATC code used in the study for the index medication.	
	ADR	ADR stated in the study (caused by the index medication)	
Marker medication	Group	The pharmacological subgroup of the marker medication	
	Individual	Name of the marker medication within the group, if reported	
	ATC code	The ATC code used in the study for the marker medication	
	Micromedex	If the ADR be found for the index medication in Micromedex	Classify into: Yes + percentage (if available) or No
	SmPC	If the ADR be found for the index medication in the SmPC	Classify into: Yes + percentage (if available) or No
	Comments	Other relevant information regarding the prescribing cascade	As described in text.
Additional information			
	Dose dependent	Information on whether the ADR is dose dependent	As described in text, NR if nothing is reported
	Frequency	Information on the prevalence of the ADR	
	Time span ADR	Information on when the ADR usually occurs after start of the index medication	
	Sex dependent	Information on whether the ADR is sex-dependent	
	Actions to take	Information on which actions can be taken to prevent or reverse the ADR (e.g. dose reduction)	
	Mechanism ADR	Information on the mechanism of the ADR	
	Comments	Other relevant information reported	
Conclusions and Limitations			
	Conclusion	Conclusion of the study including the conclusions of the subgroup analysis	As described in text
	Limitations	The limitations as reported	
	Comments	Other relevant information which could not be assigned to the other columns	

ADR: adverse drug reaction; ATC: Anatomical Therapeutic Chemical; WHO: World Health Organization; SmPC: Summary of Product Characteristics; NS: not significant; S: significant; IS: inverse significant; NR: not reported

Supplementary table 4: Grouping of similar prescribing cascades

Four rules were applied to group prescribing cascades according to index medication (rule 1 and 2), marker medication (rule 3) and adverse drug reaction (ADR, rule 4). The anatomical therapeutic chemical (ATC) classification was used for medication, where the third level is the pharmacological subgroup and the fourth level is the chemical subgroup. The Medical Dictionary for Regulatory Activities (MedDRA) was used to classify ADRs.

1. Index medication is reported at pharmacological subgroup (ATC 3rd level) or chemical subgroup (ATC 4th level) if multiple index medications were reported belonging to the same subgroup AND the ADR was confirmed in the Summary of Product Characteristics (SmPC) for ≥50% of the medication within this group

	Index medication (ATC code)	ADR (MedDRA notation)	Marker medication (ATC code)
Prescribing cascade 1	Lisinopril (C09AA03)	Cough (10011224)	Cough suppressants (R05D)
Prescribing cascade 2	ACE-inhibitors (C09AA)	Cough (10011224)	Cough suppressants (R05D)
<i>Distinct prescribing cascade</i>	<i>ACE-inhibitors (C09AA)</i>	<i>Cough (10011224)</i>	<i>Cough suppressants (R05D)</i>

2. Individual index medication is reported if:
 - a. the index medication was reported in the publication as medication group but the ADR was confirmed for <50% of the individual substances in the pharmacological subgroup (ATC 3rd level) or chemical subgroup (ATC 4th level)
 - b. the index medication was only reported at individual substance level and no other index medication was reported belonging to the same subgroup

<u>Example 2a</u>	Index medication (ATC code)	ADR (MedDRA notation)	Marker medication (ATC code)
Prescribing cascade 1	Benzodiazepine (N05BA)	Dementia (20000073)	Anti-dementia drugs (N06D)
<i>Distinct prescribing cascade</i>	<i>Alprazolam, Clonazepam, Lorazepam (ADR only confirmed for these medications, being <50% within N05BA group)</i>	<i>Dementia (20000073)</i>	<i>Anti-dementia drugs (N06D)</i>

<u>Example 2b</u>	Index medication (ATC code)	ADR (MedDRA notation)	Marker medication (ATC code)
Prescribing cascade 1	Amiodarone (C01BD01)	Hyperthyroidism (10020850)	Antithyroid preparations (H03B)
<i>Distinct prescribing cascade</i>	<i>Amiodarone (C01BD01)</i>	<i>Hyperthyroidism (10020850)</i>	<i>Antithyroid preparations (H03B)</i>

3. The marker medication is reported at pharmacological subgroup (ATC 3rd level) or chemical subgroup (ATC 4th level) if multiple marker medications were reported in the publication(s) belonging to the same subgroup

	Index medication (ATC code)	ADR (MedDRA notation)	Marker medication (ATC code)
Prescribing cascade 1	ACE-inhibitors (C09AA)	Cough (10011224)	Cough suppressants (R05D)
Prescribing cascade 2	ACE-inhibitors (C09AA)	Cough (10011224)	Dextromethorphan (R05DA09)
<i>Distinct prescribing cascade</i>	<i>ACE-inhibitors (C09AA)</i>	<i>Cough (10011224)</i>	<i>Cough suppressants (R05D)</i>

4. The ADRs are grouped using the MedDRA classification system when multiple terms were used fitting the same ADR class.

	Index medication (ATC code)	ADR (MedDRA notation)	Marker medication (ATC code)
Prescribing cascade 1	Donepezil (N06DA02)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)
Prescribing cascade 2	Donepezil (N06DA02)	Dribbling of urine (10013639)	Oxybutynin (G04BD04)
<i>Distinct prescribing cascade</i>	<i>Donepezil (N06DA02)</i>	<i>Urinary incontinence (10046543)</i>	<i>Oxybutynin (G04BD04)</i>

Supplementary table 5: Excluded full-text publications

Reference	Exclusion reason summarized
1. Abou Aitah A, Ang S. Hyperpolypharmacy and prescribing cascade recipe for delirium and increasing the length of hospital stay. <i>Journal of the American Geriatrics Society</i> . 2019;67:S19.	Congress/abstract only
2. Abudalou M, Mohamed AS, Vega EA, Al Sbihi A. Colchicine-induced rhabdomyolysis: a review of 83 cases. <i>BMJ Case Reports CP</i> . 2021;14(7):e241977.	No prescribing cascade described
3. Adimadhyam S, Lee TA, Calip GS, Marsh DES, Layden BT, Schumock GT. SGLT2 inhibitors and mycotic infections: A prescription sequence symmetry analysis. <i>Pharmacoepidemiology and Drug Safety</i> . 2018;27:54.	Publication duplicate
4. Aggarwal A, Khandelwal A, Garg A, Jiloha RC. Akathisia associated with mianserin. <i>Journal of Clinical Psychopharmacology</i> . 2010;30(3):338-9.	Case-report
5. Ahc M. The Cascade Effect: Calcium Channel Blockers and High Blood Pressure. <i>Internal Medicine Alert</i> . 2020;42(9):1-2.	Congress/abstract only
6. Anderson TS, Steinman MA. Antihypertensive Prescribing Cascades as High-Priority Targets for Deprescribing. <i>JAMA internal medicine</i> . 2020;180(5):651-2.	Publication on background information/Review
7. Anonymous. Prescribing cascade: calcium-channel blockers and diuretics. <i>Drug and therapeutics bulletin</i> . 2020.	Publication on background information/Review
8. Anonymous. New evidence for a prescribing cascade in older adults with dementia. <i>Geriatrics and Aging</i> . 2005;8(6):11.	Congress/abstract only
9. Argento VS, Skudlarska BA, Blagodatny M, Kwon S. A case of failing dominos: Prescribing cascade in a geriatric patient. <i>JOURNAL OF THE AMERICAN GERIATRICS SOCIETY</i> . 2008;56(4):S122-S3.	Congress/abstract only
10. Bailey L, Varma S, Ahmad N, Gee S, Taylor DM. Factors predicting use of laxatives in outpatients stabilized on clozapine. <i>Therapeutic advances in psychopharmacology</i> . 2015;5(5):256-62.	No prescribing cascade described
11. Baileys K. The Case of the Checkpoint Inhibitor Side Effects. <i>Oncology Nursing Society</i> ; 2018 2018.	Case-report
12. Baker EL, Loewenthal T, Salerno E, Baker WL. Probable enoxaparin-induced hepatotoxicity. <i>American Journal of Health-System Pharmacy</i> . 2009;66(7):638-41.	No prescribing cascade described
13. Baker FM, Cook P. Compazine complications: a review. <i>Journal of the National Medical Association</i> . 1981;73(5):409-12.	No prescribing cascade described
14. Balducci L, Goetz-Parten D, Steinman M. Polypharmacy and the management of the older cancer patient. <i>Annals of oncology</i> . 2013;24:vii36-vii40.	Publication on background information/Review
15. Baloch N. 'Steroid psychosis': a case report. <i>The British Journal of Psychiatry</i> . 1974;124(583):545-6.	No prescribing cascade described
16. Barclay ML, Brownlie BE, Turner JG, Wells JE. Lithium associated thyrotoxicosis: a report of 14 cases, with statistical analysis of incidence. <i>Clinical Endocrinology</i> . 1994;40(6):759-64.	No prescribing cascade described
17. Batanero-Hernan MC, Guinea-Lopez MC, Garcia-Jimenez E, Rodriguez-Chamorro MA. Identification of prescription cascades in the pharmacological treatment of population over 65 years in the province of Guadalajara (Spain). <i>Pharmaceutical Care Espana</i> . 2018;20(3):201-17.	Foreign language

18.	Baumgartner G, Zieglmeier M, Hermann R, Derendorf H. A female patient with itching and edemas: How medication management uncovers prescription cascades. <i>Deutsche Apotheker Zeitung</i> . 2013;153(11):48-56.	Foreign language
19.	Becerra AF, Boch M, Al-Mezrakchi YA. Ropinirole-Associated Orthostatic Hypotension as Cause of a Prescribing Cascade in an Elderly Man. <i>CUREUS</i> . 2021;13(6).	Case-report
20.	Becerra-Fernández A. Autoimmune thyrotoxicosis during lithium therapy in a patient with manic-depressive illness. <i>The American journal of medicine</i> . 1995;99(5):575.	No prescribing cascade described
21.	Beck RW, Moke P, Blair RC, Nissenbaum R. Uveitis associated with topical beta-blockers. <i>Archives of ophthalmology (Chicago, Ill : 1960)</i> . 1996;114(10):1181-2.	No prescribing cascade described
22.	Beddoe R, Jureidini J. Dangers of unrecognized psychiatric adverse events from psychotropic drugs: First person account, review and suggested response. <i>Australian and New Zealand Journal of Psychiatry</i> . 2017;51(1):99.	Congress/abstract only
23.	Ben-Noun L. Acute asthma associated with sustained-release verapamil. <i>The Annals of pharmacotherapy</i> . 1997;31(5):593-5.	Case-report
24.	Bilen S, Saka M, Ak F, Oztekin N. Persistent dystonia induced by fluoxetine. <i>Internal medicine journal</i> . 2008;38(8):672-4.	No prescribing cascade described
25.	Blaauwhof AMA, Hak E, Bos JHJ, Schuiling-Veninga CCM. Psychotropic co-medication in Dutch children and adolescents using psychostimulants; a prescription sequence symmetry analysis. <i>Pharmacoepidemiology and Drug Safety</i> . 2019;28:166.	Congress/abstract only
26.	Blazer DG, Petrie WM, Wilson WP. Affective psychoses following renal transplant. <i>Diseases of the Nervous System</i> . 1976.	No prescribing cascade described
27.	Bocchetta A, Cabras F, Pinna M, Poddighe A, Sardau C, Arda R, et al. An observational study of 110 elderly lithium-treated patients followed up for 6 years with particular reference to renal function. <i>International Journal of Bipolar Disorders</i> . 2017;5(1):1-7.	No prescribing cascade described
28.	Bogazzi F, Tomisti L, Bartalena L, Aghini-Lombardi F, Martino E. Amiodarone and the thyroid: A 2012 update. <i>JOURNAL OF ENDOCRINOLOGICAL INVESTIGATION</i> . 2012;35(3):340-8.	Publication on background information/Review
29.	Brown DV, Heller F, Barkin R. Anticholinergic syndrome after anesthesia: a case report and review. <i>American journal of therapeutics</i> . 2004;11(2):144-53.	No prescribing cascade described
30.	Brown ES, Hong SC. Antidepressant-induced bruxism successfully treated with gabapentin. <i>Journal of the American Dental Association (1939)</i> . 1999;130(10):1467-9.	Case-report
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Aging and Geriatric Research, University of Florida College of Medicine, Gainesville Florida North Florida/South Georgia Veterans Health System, Malcom Randall VAMC, GRECC, Gainesville Florida Malden, Massachusetts: Wiley-Blackwell; 2020 2020. 440-1 p.		
260.	Waal HJ. Propranolol-induced Depression. British Medical Journal. 1967;2(5543):50.	No prescribing cascade described
261.	Wahab IA, Pratt NL, Kalisch LM, Roughead EE. Comparing time to adverse drug reaction signals in a spontaneous reporting database and a claims database: a case study of rofecoxib-induced myocardial infarction and rosiglitazone-induced heart failure signals in Australia. Drug safety. 2014;37:53-64.	Publication on background information/Review
262.	Wahab IA, Pratt N, Kalisch L, Roughead E. Sequence symmetry analysis and disproportionality analyses: what percentage of adverse drug reaction do they signal? : OMICS Publishing Group; 2013.	Publication on background information/Review
263.	Wahab IA, Pratt NL, Ellett LK, Roughead EE. Sequence Symmetry Analysis as a Signal Detection Tool for Potential Heart Failure Adverse Events in an Administrative Claims Database. Drug safety. 2016;39(4):347-54.	Hypothesis-free
264.	Wang M-T, Wang Y-H, Chang H-A, Tsai C-L, Yang Y-S, Lin CW, et al. Benzodiazepine and Z-drug use and risk of pneumonia in patients with chronic kidney disease: A population-based nested case-control study. PloS one. 2017;12(7):e0179472.	No prescribing cascade described
265.	Wang TT, Pratt N, Killer G, Roughead EE, Griffiths J. Proton pump inhibitors and clostridium difficile-associated disease in Canadian and Australian community settings-a prescription sequence symmetry analysis. Pharmacoepidemiology and Drug Safety. 2013;22:187-8.	Congress/abstract only
266.	Weinberger MH. Estrogens and hypertension. Comprehensive therapy. 1982;8(6):71-5.	No prescribing cascade described
267.	Wilson WH, Claussen AM. Seizures associated with clozapine treatment in a state hospital. The Journal of clinical psychiatry. 1994.	No prescribing cascade described
268.	Winterstein AG, Kubilis P, Bird S, Cooper-Dehoff RM, Nichols GA, Delaney JA. Misclassification in assessment of diabetogenic risk using electronic health records. Pharmacoepidemiology and Drug Safety. 2014;23(8):875-81.	No prescribing cascade described
269.	Wong S-M, Tse H-F, Siu C-W. Pulmonary hypertension and isolated right heart failure complicating amiodarone induced hyperthyroidism. Heart, lung & circulation. 2012;21(3):163-5.	No prescribing cascade described
270.	Woodford HJ. Calcium Channel Blockers Co-prescribed with Loop Diuretics: A Potential Marker of Poor Prescribing? Drugs & aging. 2020;37(2):77-81.	Publication on background information/Review
271.	Yamauchi K, Ohmori T. [Two cases of tardive Tourette syndrome]. Seishin shinkeigaku zasshi = Psychiatria et neurologia Japonica. 2006;108(5):459-65.	No prescribing cascade described
272.	Yang SY, Kao Yang YH, Chong MY, Yang YH, Chang WH, Lai CS. Risk of extrapyramidal syndrome in schizophrenic patients treated with antipsychotics: A population-based study. Clinical Pharmacology and Therapeutics. 2007;81(4):586-94.	No prescribing cascade described
273.	Ye C, Ninneman M, Christian JS, Zhang F, Musselman D. Seizure Induced by a Therapeutic Dose of Venlafaxine ER: A Case Report. Journal of psychiatric practice. 2018;24(2):117-20.	Case-report
274.	Zandifar A, Mohammadi MR, Badrfam R. Low-dose quetiapine in the treatment of SSRI-induced bruxism and mandibular dystonia: Case series. Iranian journal of psychiatry. 2018;13(3):227.	No prescribing cascade described

275.	Zanoletti E, Bertino G, Malvezzi L, Benazzo M, Mira E. Angioneurotic edema of the upper airways and antihypertensive therapy. <i>Acta otolaryngologica</i> . 2003;123(8):960-4.	Case-report
276.	Zhan C, Roughead E, Liu L, Pratt N, Li J. A data-driven method to detect adverse drug events from prescription data. <i>Journal of biomedical informatics</i> . 2018;85:10-20.	Hypothesis-free
277.	Zhou Z, Li Q, Zheng J. Hypertrophic cranial pachymeningitis induced by long-term administration of nonsteroidal antiinflammatory drugs. <i>The Annals of pharmacotherapy</i> . 2010;44(4):755-9.	No prescribing cascade described
278.	Zieglmeier M. Detecting adverse effects - Preventing prescription cascades? The backgrounds of the calcium channel blockers survey - An opinion piece. <i>Deutsche Apotheker Zeitung</i> . 2017;157(20):430-4.	Publication on background information/Review
279.	Zieglmeier M. The prescription cascade as part of the system. <i>Deutsche Apotheker Zeitung</i> . 2020;160(25):A21.	No prescribing cascade described
280.	Zribi A, Nasr SB, Hamdi S, Ayari J, Fendri S, Balti M, et al. Oxaliplatin-induced peripheral neuropathy risk factors and management in Tunisian population. <i>The Pan African Medical Journal</i> . 2020;35.	Case-report

Supplementary table 6: Excluded distinct prescribing cascades

Prescribing cascade			
<i>Index medication (ATC code)</i>	<i>ADR (MedDRA notation)</i>	<i>Marker medication (ATC code)</i>	<i>Exclusion reason^a</i>
Alimentary tract and metabolism (A)			
1. H2-receptor antagonists (A02BA)	Dementia (20000073)	Tacrine, donepezil, rivastigmine, glantamine (within N06DA) and memantine (N06DX01) ^b	No analysis was performed [1]
2. Metoclopramide (A03FA01)	Parkinson's Disease (10034010)	Levodopa-carbidopa, levodopa-carbidopa-entacapone, amantadine, ropinirole, pramipexole, selegiline, entacapone (within N04B) ^b	No analysis was performed [2]
Blood and blood forming organs (B)			
3. Warfarin (B01AA03)	Osteoporosis (10031282)	Minodronate, etidronate, alendronate, ibandronate, risedronate (within M05BA) ^b	ADR not found in SmPC [3]
4. Direct thrombin inhibitors (B01AE)	Osteoporosis (10031282)	Minodronate, etidronate, alendronate, ibandronate, risedronate (within M05BA) ^b	ADR not found in SmPC [3]
5. Direct factor Xa inhibitors, dabigatran, rivaroxaban, apixaban, edoxaban (within B01AF) ^c	Osteoporosis (10031282)	Minodronate, etidronate, alendronate, ibandronate, risedronate (within M05BA) ^b	ADR not found in SmPC [3]
Cardiovascular system (C)			
6. Cibenzoline (C01BG07)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	ADR not found in SmPC [4]
7. Miscellaneous antihypertensives (C)	Depression (10012378)	Antidepressants (N06A)	Unspecific index medication [5, 6]
8. Low-ceiling diuretics, excluding thiazides (C03B)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	ADR not found in SmPC [7]
9. Vasodilators (C04)	Hyperglycemia (10020639)	Insulin (A10AD01)	ADR not found in SmPC [8]

10.	Angiotensin 2 receptor blocker (C09CA)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	ADR not found in SmPC [7]
11.	Angiotensin 2 receptor blocker & diuretic (C09DA)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	ADR not found in SmPC [7]

Genito urinary system and sex hormones (G)

12.	Estradiol, estriol, conjugated estrogen (within G03CA) ^c	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	ADR not found in SmPC [7]
13.	Hormone replacement therapy (within G03C, G03DA) ^b	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	ADR not found in SmPC [7]

Nervous system (N)

14.	Morphine, nicomorphine, pethidine, dextropropoxyphene (within N02A) ^b	Constipation (10010774)	Drugs for constipation (A06A)	Intentional prescribing cascade [9]
15.	Antipsychotic (N05A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	No analysis was performed [10]
16.	Amisulpride (N05AL05)	Cardiac arrhythmias (10007518)	Class 1 B antiarrhythmic agents (C01BB)	No analysis was performed [11]
17.	Flunarizine (N07CA03)	Depression (10012378)	Antidepressant (N06A)	No analysis was performed [12]

Respiratory system (R)

18.	Diphenhydramine (R06AA02)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	No analysis was performed [4]
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Sensory organs (S)

19.	Pilocarpine (S01EB01)	Conduction disorder (10010276)	Inserting pace maker	Medical device or medical product [13]
20.	Levobunolol (S01ED03)	Conduction disorder (10010276)	Inserting pace maker	Medical device or medical product [13]
21.	Ketotifen (S01GX08)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	No analysis was performed [4]

Multiple ATC groups

22.	Anticholinergic agents Biperiden, orphenadrine, trihexyphenidyl (within N04A), atropine, oxyphenyclimine (within A03), oxybutynin (G04BD04),	Constipation (10010774)	Lactitol, lactulose, bisacodyl, magnesium oxide, docusate sodium, triticum, ispaghula (within A06A) ^b	Unspecific index medication [9]
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thiazinamium (R06AD06) ^b				
23.	Amitriptyline, clomipramine, doxepine, imipramine, maprotiline, nortriptyline (within N06AA), disopyramide (C01BA03), chlorpromazine, chlorprotixene, clozapine, thioridazine (within N05A), flavoxate (G04BD02) ^b	Constipation (10010774)	Lactitol, lactulose, bisacodyl, magnesium oxide, docusate sodium, triticum, ispaghula (within A06A) ^b	Unspecific index medication [9]
No ATC codes index medication				
24.	Blonanserine	Osteoporosis (10031282)	Minodronate, etidronate, alendronate, ibandronate, risedronate (within M05BA) ^b	Index medication unfound in EMA and FDA [14]
25.	Intestinal Lavage Solution	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	Unspecific index medication [4]
26.	Multiple-agent regimen without a thiazide diuretic	Hyperglycemia (10020639)	Insulin (A10AD01)	Unspecific index medication [8]
27.	Multiple-agent regimen with a thiazide diuretic	Hyperglycemia (10020639)	Insulin (A10AD01)	Unspecific index medication [8]
28.	Perospirone	Osteoporosis (10031282)	Minodronate, etidronate, alendronate, ibandronate, risedronate (within M05BA) ^b	Index medication unfound in EMA and FDA [14]
29.	Tranilast	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	No analysis was performed [4]

ATC: Anatomical Therapeutic Chemical; ADR: adverse drug reaction; MedDRA: Medical Dictionary for Regulatory Activities; SmpC: Summary of Product Characteristics; EMA: European Medicines Agency; FDA: Food and Drug Administration.

^a An explanation for the exclusion categories is given:

- No analysis was performed: Prescribing cascades were excluded if the study did not perform a statistical analysis on the prescribing cascade (for example due to lack of patients for the specific prescribing cascade).
- Unspecific index medication: Prescribing cascades were excluded if the index medication was described at multiple ATC levels.
- ADR not found in SmpC: Prescribing cascades were also excluded if the ADR was not confirmed in the Summary of Product Characteristics (SmpC) of the index medication.
- Intentional prescribing cascade: A prescribing cascade was excluded if the treatment with the marker medication was intentional. Intentional treatment was either as stated in the publication itself or derived from guidelines (prescribing a laxative to prevent ADRs when prescribing opiates)

- Medical device or medical product: Prescribing cascades were excluded if a medical device or a medical product (e.g. urinary incontinence products) was (also) used to treat the ADR.
Index medication unfound in EMA and FDA: at the time of the research the index medication could not be found in the EMA or in the FDA.

^b The medication was analyzed as a group.

^c No analysis was performed for the whole index medication ATC group.

Supplementary table 7: Distinct potential prescribing cascades identified in publications with only non-significant or inverse associations

Prescribing cascade			
<i>Index medication (ATC code)</i>	<i>Adverse drug reaction (MedDRA notation)</i>	<i>Marker medication (ATC code)</i>	<i>References</i>
Alimentary tract and metabolism (A)			
1. Insulins and analogues (A10A), blood glucose lowering drugs (A10B), other drugs used in diabetes (A10X)	Depression (10012378)	Antidepressants (N06A)	[5]
2. Insulins and analogues (A10A), blood glucose lowering drugs (A10B), other drugs used in diabetes (A10X)	Parkinsonism (10034010)	Anti-parkinson drugs (N04)	[15]
3. Biguanides (A10BA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
4. Sodium-glucose co-transporter 2 inhibitors (A10BK)	Urinary tract infection (10046571)	Miscellaneous antibiotics (within J01) ^b	[16]
Blood and blood forming organs (B)			
5. Antithrombotic agents, dabigatran, rivaroxaban, apixaban (within B01A) ^a	Gastrointestinal disorders (10017947)	Drugs for acid related disorders (A02), drugs for functional gastrointestinal disorders and other antiemetics (A03A, A03E, A03F, A04AD), bile therapy (A05AX), drugs for constipation (A06A, A07)	[17]
6. Antithrombotic agents (B01A)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04B)	[18]
Cardiovascular system (C)			
7. Digitalis glycosides (C01AA)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	[18]
8. Digitalis glycosides (C01AA)	Depression (10012378)	Antidepressants (N06A)	[19, 20]
9. Antiarrhythmics, class I and III (C01B)	Depression (10012378)	Antidepressants (N06A)	[19]
10. Organic nitrates (C01DA)	Depression (10012378)	Antidepressants (N06A)	[19]
11. Methylodopa (C02AB)	Depression (10012378)	Antidepressants (N06A)	[19]
12. Antihypertensives (C02)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
13. Diuretics (C03)	Depression (10012378)	Antidepressants (N06A)	[5]

14.	Low-ceiling diuretics, thiazides (C03A)	Depression (10012378)	Antidepressants (N06A)	[19, 20]
15.	Low-ceiling diuretics, thiazides (C03A)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
16.	High-ceiling diuretics (C03C)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
17.	High-ceiling diuretics (C03C)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	[18]
18.	Aldosterone antagonists and other potassium-sparing agents (C03D)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
19.	Aldosterone antagonists and other potassium-sparing agents (C03D)	Depression (10012378)	Antidepressants (N06A)	[19, 20]
20.	Peripheral vasodilators (C04A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
21.	HMG CoA reductase inhibitors (C10AA)	Myopathy, unspecified (10028649)	Antiinflammatory and antirheumatic products, non-steroids (M01A)	[21]
22.	Angiotensin II receptor blockers (C09C)	Depression (10012378)	Antidepressants (N06A)	[20]
23.	Lipid modifying agents, plan & combinations (C10A, C10B)	Depression (10012378)	Antidepressants (N06A)	[20, 22]
24.	HMG CoA reductase inhibitors (C10AA)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	[18]
Genito urinary system and sex hormones (G)				
25.	Drugs for urinary frequency and incontinence (G04BD)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
26.	Alpha-adrenoreceptor antagonists (G04CA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
27.	Finasteride (G04CB01), dutasteride (G04CB02)	Depression (10012378)	Antidepressants (N06A)	[6, 23, 24]
Antiinfectives for systemic use (J)				
28.	Tetracyclines (J01A)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
29.	Penicillins (J01C)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
30.	Other beta-lactam antibacterials (J01D)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
31.	Sulfonamides and trimethoprim (J01E)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
32.	Macrolides, lincosamides and streptogramins (J01F)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
33.	Aminoglycoside antibacterials (J01G)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
34.	Quinolone antibacterials (J01M)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	[25]
Musculo-skeletal system (M)				

35. Muscle relaxants, centrally acting agents (M03B)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
36. Allopurinol (M04AA01)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
Nervous system (N)			
37. Opioid analgesics (N02A)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
38. Acetylsalicylic acid (N02BA01)	Gastrointestinal disorders (10017947)	H2-receptor antagonists (A02BA), proton pump inhibitors (A02BC)	[26]
39. Antiepileptics (N03A)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
40. Antiepileptics (N03A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
41. Dopaminergic agents (N04B)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
42. Levodopa (N04BA)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
43. Dopamine agonists (N04BC)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
44. Antipsychotics (N05A)	Dyslipidemia (10058110)	Lipid modifying agents (C10)	[27]
45. Antipsychotics (N05A)	Osteoporosis (10031282)	Bisphosphonates (M05BA)	[14]
46. Antipsychotics (N05A)	Hyperlipidaemia (10062060)	Lipid modifying agents (C10)	[28]
47. Antipsychotics (N05A)	Hypertension (10020772)	Antihypertensives (C02)	[27]
48. Antipsychotics (N05A)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
49. Miscellaneous antipsychotics (within N05A) ^b	Metabolic events	Drugs for hypertension (C03A, C03C, C09, C07, C08CA), oral blood glucose-lowering drugs (A10B), lipid-modifying agents (C10), excluding propranolol (C07AA05)	[27]
50. Haloperidol (N05AD01)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
51. Risperidon (N05AX08)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
52. Anxiolytics (N05B)	Diabetes mellitus (10012601)	Drugs used in diabetes (A10)	[29]
53. Anxiolytics (N05B)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
54. Anxiolytics (N05B)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
55. Benzodiazepine derivatives (N05BA)	Constipation (10010774)	Drugs for constipation (A06A)	[30]

56. Antidepressants (N06A)	Diabetes mellitus (10012601)	Drugs used in diabetes (A10)	[29]
57. Selective serotonin reuptake inhibitors (N06AB)	Restless leg syndrome (10038741)	Quinine (P01BC01), ropinirole (N04BC04), pramipexole (N04BC05), rotigotine (N04BC10)	[31]
58. Selective serotonin reuptake inhibitors (N06AB)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
59. Venlafaxine (N06AX16)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	[7]
60. Anticholinesterases (N06DA)	Depression (10012378)	Antidepressants (N06A)	[32]
61. Anticholinesterases (N06DA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
62. Donepezil, rivastigmine, galantamine (within N06DA) ^b	Dyspepsia (10013946)	Proton pump inhibitors (A02BC)	[32]
63. Varenicline (N07BA03)	Anxiety (10002855)	Anxiolytics (N05BA)	[33, 34]
64. Varenicline (N07BA03)	Depression (10012378)	Antidepressants (N06A)	[33, 34]
65. Varenicline (N07BA03)	Insomnia (10022437)	Hypnotics and sedatives (N05C)	[33]
66. Flunarizine (N07CA03)	Parkinsonism (10034010)	Anti-parkinson drugs (N04)	[35]
67. Flunarizine (N07CA03)	Depression (10012378)	Antidepressants (N06A)	[35]
Respiratory system (R)			
68. Antihistamines for systemic use (R06A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	[10]
69. Chlorpheniramine (R06AB02)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	[4]
Sensory organs (S)			
70. Antiglaucoma preparations and miotics (S01E)	Congestive heart failure (10010684)	High-ceiling diuretics (C03C)	[13]

ATC: anatomical therapeutic chemical; MedDRA: Medical Dictionary for Regulatory Activities; HMG CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A.

^a No analysis was performed for the whole index medication ATC group.

^b The medication was analyzed as a group.

Supplementary table 8: Distinct potential prescribing cascades with at least one positive significant result, confirmed ADR in the SmPC and a dose dependency analysis and/or recommendations to prevent or reverse the prescribing cascade

Prescribing cascade			Prescribing cascade analyses ^a	Dose dependency analysis ^b
<i>Index medication (ATC code)</i>	<i>Adverse drug reaction (MedDRA notation)</i>	<i>Marker medication (ATC code)</i>	<i>aSR, cSR, OR, aOR, RaRa, ReRi, HR, aHR, χ^2^c</i>	<i>aSR, cSR, OR, aOR, ReRi, HR, aH, χ^2^c</i>
Alimentary tract and metabolism (A)				
1. Metoclopramide (A03FA01)	Extrapyramidal syndrome (10015836)	Anti-parkinson drugs (N04)	aOR 3.04 [2.22-4.17] [36] aOR 2.94 [2.35-3.67] [37]	aOR 5.46 [3.45-8.64] [36]
2. Omeprazole, pantoprazole, rabeprazole, esomeprazole (within A02BC) ^{d*}	Chronic obstructive pulmonary disease (10009033)	Long-acting muscarinic antagonist or long-acting beta2-agonist (within R03BB)**	Index medication: all 4 significant. Example omeprazole: aSR 1.29 [1.22-1.36] [38] Lansoprazole aSR 1.08 [0.96-1.22] [38]	
3. Cimetidine (A02BA01)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.99 [1.24-3.20] [4]	
4. Scopolamine butylbromide (A03BB01)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.72 [1.55-1.92] [4]	
Cardiovascular system (C)				
5. Cardiac therapy (C01)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.14 [1.06–1.22] [10]	
6. Amezinium metilsulfate (within C01CA) ^{e*}	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.89 [1.10-3.26] [4]	
Droxidopa, midodrine ^{e*}			Index medication: all 2 non-significant. Example Midodrine: aSR 1.21 [0.67–2.20] [4]	

7.	ACE-inhibitors, including combinations (C09A, C09B)	Cough (10011224)	Cough suppressants (R05D)	aSR 2.2 [1.9-2.4] [39]	
	ACE-inhibitors (C09AA)			aSR 1.33 [1.31-1.34] [26] aSR 2.0 [1.8-2.2] [40] OR 1.58 [1.21-2.07] [41]	
8.	Low-ceiling diuretics, thiazides (C03A)	Gout (10018627)	Antigout preparations (M04A)	aReRi 1.99 [1.21-3.26] [42]	aReRi 2.41 [1.39-4.19] [42]
9.	HMG CoA reductase inhibitors (C10AA)	Hepatotoxicity (10019851)	Ursodeoxycholic acid (A05AA02)	aSR 1.26 [1.21-1.31] [26]	
	Atorvastatin		Miscellaneous hepatoprotective medication	aSR 1.27 [1.23–1.32] [43]	
10.	Amiodarone (C01BD01)	Hyperthyroidism (10020850)	Antithyroid preparations (H03B)	aSR 11.14 [7.12-18.34] [44] aOR 6.3 [3.4–8.4] [45]	aOR 12.9 [6.10–27.30] [45]
11.	Amiodarone (C01BD01)	Hypothyroidism (10021114)	Thyroid hormones (H03AA)	aSR 3.77 [3.43-4.14] [26] aSR 3.57 [3.18-4.02] [44] aSR 2.63 [1.47–4.72] [46] aSR 12.8 [8.44-20.28] [47] aOR 6.60 [3.90–11.10] [45]	aOR 4.8 [1.9–12.5] [45]
12.	Miscellaneous diuretics (within C03) ^f	Leg cramps (10024125)	Quinine (P01BC01)	aSR 1.47 [1.33-1.63] [48]	
13.	HMG CoA reductase inhibitors (C10AA)	Leg cramps (10024125)	Quinine (P01BC01)	aSR 1.16 [1.04-1.29] [48]	
	Simvastatin			aSR 2.28 [2.17-2.40] [44]	
14.	Calcium channel blocker (C08)	Oedema peripheral (10030124)	Diuretics (C03)	aHR 3.89 [3.11-4.87] [49] Incidence 4.9% [4.2–5.7%] [50]	aHR 4.26 [2.82-6.43] [49]
	Dihydropyridines (C08CA)			aSR 1.46 [1.45-1.48] [26] Patients aged 65–84 years: OR 2.56 [1.20–5.43] and Patients aged	

				≥85 years: OR 3.89 [1.76–8.61] [51]	
Nifedipine, felodipine, isradipine**				aSR 1.67 [1.59-1.76] [52]	
Amlodipine				aSR 1.89 [1.86-1.93] [52]	aSR 2.20 [2.13-2.27] [52]
Amlodipine, nifedipine, felodipine**				aOR 1.04 [0.98–1.10] [2]	
15.	Prazosin (C02CA01) [#]	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	aSR 1.84 [1.29–2.63] [7]	
16.	Diuretics (C03)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.07 [1.01–1.14] [10]	
17.	Beta blocking agents (C07)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.13 [1.05–1.21] [10]	
18.	Beta blocking agents (C07A)	Depression (10012378)	Antidepressants (N06A)	ReRi 2.60 [2.30-3.0] [5] RaRa 1.5 [1.4-1.7] [53] RaRa 1.09 [0.95-1.26] [19] aOR 0.69 [0.68–0.70] [20]	
19.	Calcium channel blocker (C08)	Constipation (10010774)	Drugs for constipation (A06A), magnesium oxide (A02AA02)	ReRi 1.92 [1.02–3.62] [9]	
20.	Calcium channel blocker (C08)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.22 [1.16–1.36] [10]	
21.	Miscellaneous calcium channel blockers (C08) ^g	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	aSR 1.45 [1.33-1.57] [7]	
22.	Miscellaneous ACE-inhibitors (C09AA) ^h	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	aSR 1.28 [1.19-1.39] [7]	
23.	Miscellaneous ACE-inhibitors & diuretics (C09BA)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	aSR 1.35 [1.15-1.58] [7]	
24.	ACE-inhibitors (C09AA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.22 [1.14–1.31] [10]	
25.	Miscellaneous ACE-inhibitors (C09AA) ⁱ	Urinary tract infection (10046571)	Nitrofurantoin derivatives (J01XE)	aSR 1.68 [1.21–2.36] [54] aSR 1.24 [0.84-1.84] [26]	

26.	Angiotensin II receptor blockers (C09C)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.20 [1.11–1.30] [10]	
27.	HMG CoA reductase inhibitors (C10AA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.50 [1.40–1.61] [10]	
Dermatologicals (D)					
28.	Acitretin (D05BB02)	Vulvo-vaginal candidiasis (10047784)	Antiinfectives and antiseptics (G01A)	OR 6.50 [2.30-8.20] [55]	RaRa <100 DDD vs. >100 DDD 3.3 [1.1-9.6] [55]
29.	Diphenhydramine (D04AA32)	Constipation (10010774)	Drugs for constipation (A06A)	OR 2.18 [1.01- 4.71] [30]	
Systemic hormonal preparations, excl. Sex hormones and insulins (H)					
30.	Glucocorticoids (H02AB)	Hyperglycaemia (10020639)	Drugs used in diabetes (A10)	OR 1.93 [1.72-2.17] [56]	OR 10.34 [3.16-33.90] [56]
Antineoplastic and immunomodulating agents (L)					
31.	Cyclophosphamide (L01AA01)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.52 [1.14–2.04] [4]	
Musculo-skeletal system (M)					
32.	Miscellaneous NSAIDs (within M01A)	Hypertension (10020772)	Antihypertensives (C02)	aOR 1.66 [1.54-1.80] [57]	aOR 1.82 [1.62-2.05] [57] (as group, including diflunisal)
33.	Antiinflammatory and antirheumatic products, non-steroids (M01A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.37 [1.27–1.47] [10]	
Nervous system (N)					
34.	Opioids (N02A)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.24 [1.17–1.31] [10]	
35.	Morphine, oxycodone (within N02AA)*	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	Index medication: all 2 significant. Example morphine: aSR 1.29 [1.14–1.45] [4]	
	Codeine phosphate			aSR 1.04 [0.86-1.25] [4]	

36.	Levodopa/Benserazide, Amantadine (within N04B)*	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	Index medication: all 2 significant. Example Amantadine: aSR 1.53 [1.12–2.09] [4]	
	Biperiden, trihexyphenidyl*			Index medication: all 2 non-significant. Example biperiden: aSR 1.39 [0.93–2.07] [4]	
37.	Antipsychotics (N05A)	Constipation (10010774)	Drugs for constipation (A06A)	OR 2.91 [1.09–3.71][30]	
38.	Antipsychotics (N05A)	Extrapyramidal syndrome (10015836)	Anti-parkinson drugs (N04)	aSR 9.24 [7.35-11.8] [58] aOR 5.4 [4.8-6.1] [59][59][59] OR 10.1 [4.6–22.3] [60] $\chi^2 = 124.4$, df=3, Pb0.0005) [61] ReRi 0.26 [0.10-0.64] [62] aSR 1.30 [1.00-1.69] [63]	aOR 2.5 [1.8-3.2] [59] aOR 9.9 [3.5–27.5] [60]
	Miscellaneous				
	First & second generation**			Nursing homes: incidence in 1997, 20.7% [20.6-20.8]; 1998, 14.2% [14.1-14.3]; 1999, 7.8% [7.6-7.9]; 2000, 9.0% [8.9-9.1] (all, P < 0.005) and Assisted living facilities: incidence 1997, 24.5% [24.2-24.6]; 1998, 17.1% [16.9-17.3]; 1999, 22.3% [22.1-22.5]; 2000, 21.1% [20.9-21.3] (all, P < 0.005) (as index group)[64]	
	Haloperidol, sulpiride, risperidon*			Index medication: all 3 significant. Example	

				Risperidone: aSR 1.21 [1.04–1.41] [11]	
	Quetiapine			aSR 0.83 [0.66–1.04] [11]	
	Olanzapine, amisulpride*			Index medication: all 2 inverse significant. Example amisulpride: aSR 0.54 [0.40–0.73] [11]	
39.	Diflunisal (N02BA11)	Hypertension (10020772)	Antihypertensives (C02)	OR 1.94 [1.34–2.80] [57]	aOR 1.82 [1.62–2.05][57] (as group including NSAIDs, see cascade 32)
40.	Pregabalin (N03AX16), gabapentin (N03AX12)**	Oedema peripheral (10030124)	Miscellaneous diuretics (within C03)	aHR 1.44 [1.23–1.70] [65]	aHR 2.34 [1.17–4.67] [65]
41.	Chlorpromazine, Risperidone, Levomopromazine, Sulpiride (within N05A)*	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	Index medication: all 4 significant. Example Risperidone: aSR 1.55 [1.34–1.79] [4]	
42.	Lithium (N05AN01)	Tremor (10044565)	Anti-parkinson drugs (N04)	aHR 1.87 [1.06–3.30] [66]	
43.	Diazepam (N05BA01)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.44 [1.28–1.63] [4]	
44.	Hypnotics and sedatives (N05C)	Dizziness (10013573)	Prochlorperazine (N05AB04)	aSR 1.18 [1.11–1.26] [10]	
45.	Benzodiazepine derivatives (N05CD)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	aSR 1.10 [1.03–1.18] [7]	
46.	Antidepressants (N06A)	Constipation (10010774)	Drugs for constipation (A06A)	OR 3.12 [1.21 - 8.03] [30]	
47.	Anticholinesterases (N06DA)	Urinary incontinence (10046543)	Urologicals (G04)	aHR 1.55 [1.39–1.72] [67] aSR 1.08 [0.93–1.26] [7] aHR 1.41 [1.17–1.69] [68]	
	Donepezil, galantamine, rivastigmine, memantine**			aSR 1.04 [0.81–1.34] [32]	
	Donepezil, rivastigmine, galantamine**			aHR 1.13 [0.97–1.32] [69]	
	Rivastigmine,				

	galantamine**				
	Donepezil, rivastigmine, galantamine**			aHR 0.7 [0.68–0.92] [2]	
48.	Donepezil (N06DA02)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.98 [1.57–2.50] [4]	
Respiratory system (R)					
49.	Adrenergics, inhalants (R03A)	Leg cramps (10024125)	Quinine (P01BC01)	aSR 2.42 [2.02–2.89] [48]	
50.	Tiotropium bromide (R03BB04)	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	aSR 1.75 [1.42–2.16] [4]	
51.	Inhaled glucocorticosteroids (R03BA), and in combinations with adrenergics (R03AK)	Oral Candidiasis (10030963)	Intestinal antiinfectives (A07A), antimycotics for systemic use (J02A)	cSR 1.50 [1.46–1.54] [70]	cSR 3.10 [3.01–3.19] [70]
	Inhaled glucocorticosteroids (R03BA)		Intestinal antiinfectives (A07A)	aSR 1.94 [1.71–2.21] [71] aOR 2.11 [1.62, 2.75] [72] OR 1.43 (P=0.22 one sided) [73]	aOR 1.61 [1.3–1.96] [72] OR 1.36 [0.93–1.98] [71]
	Fluticasone			aSR 2.34 [2.19–2.5] [44]	
Sensory organs (S)					
52.	Antiglaucoma preparations and miotics (S01E)	Obstructive airways disorder (10061877)	Drugs for obstructive airway diseases (R03)	OR 0.92 [0.54 - 1.60] [74]	
	Beta blocking agents (S01ED)			aHR 3.06 [1.67–5.54] [75] aHR 2.79 [1.88–4.15] [76]	
	Timolol		Adrenergics, inhalants (R03A) or Other drugs for obstructive airway diseases, inhalants (R03B)	Marker medication: all 2 significant. Example R03A: aSR 1.48 [1.22– 1.78] [77]	

Latanoprost	Adrenergics for systemic use (R03C)	aSR 1.14 [0.97–1.35] [77]
	Adrenergics, inhalants (R03A)	aSR 1.24 [1.11–1.38] [77]
	Other drugs for obstructive airway diseases, inhalants (R03B) or Adrenergics for systemic use (R03C)	Marker medication: all 2 non-significant. Example R03C: aSR 1.14 [1.00–1.29] [77]
Pilocarpine	Adrenergics, inhalants (R03A) or Other drugs for obstructive airway diseases, inhalants (R03B) or Adrenergics for systemic use (R03C)	Marker medication: all 3 non-significant. Example R03C: aSR 1.10 [0.82–1.48] [77]
	Adrenergics, inhalants (R03A) or Other drugs for obstructive airway diseases, inhalants (R03B) or Adrenergics for systemic use (R03C)	Marker medication: all 3 non-significant. Example R03C: aSR 1.11 [0.89–1.37] [77]
Bimatoprost	Adrenergics, inhalants (R03A) or Other drugs for obstructive airway diseases, inhalants (R03B) or Adrenergics for systemic use (R03C)	Marker medication: all 3 non-significant. Example R03C: aSR 1.11 [0.89–1.37] [77]

ATC: anatomical therapeutic chemical; MedDRA: Medical Dictionary for Regulatory Activities; PSSA: prescription sequence symmetry analysis; ACE-inhibitor: Angiotensin-converting enzyme inhibitor; HMG CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A; NSAID, non-steroidal anti-inflammatory drugs.

^a Prescribing cascades with a significant positive association between the index and marker medication are indicated as (+); non-significant association indicated as (-); inverse association as (~).

^b Prescribing cascades with a significant or increasing positive association for high(er) dose(s) in comparison to low(er) dose indicated as (+); a non-significant association as (-); an inverse association as (~).

^c aSR: adjusted sequence ratio; cSR: crude sequence ratio; OR: Odds ratio; aOR: adjusted Odds ratio; RaRa: rate ratio; HR: hazard ratio; aHR: adjusted hazard ratio.

^d In the Summary of Product Characteristics (SmPC) the ADR was only found for rabeprazole

^e In the SmPC the ADR was only found for phenylephrine, dobutamine, midodrine, ephedrine

^f In the SmPC the ADR was only found for furosemide, bumetanide, hydrochlorothiazide, methyclothiazide, spirinolactone, amiloride, finerenone, triamterene

^g In the SmPC the ADR was only found for amlodipine, nifedipine

^h In the SmPC the ADR was only found for captopril, ramipril, moexipril

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ⁱ In the SmPC the ADR was only found for benazepril, quinapril

[#] Analysis was performed for women only.

^{*} No analysis was performed for the whole index medication ATC group.

^{**} The medication was analyzed as a group.

Supplementary table 9: Distinct potential prescribing cascades with at least one positive significant result, confirmed ADR but NO dose dependency analysis and/or recommendations to prevent or reverse the prescribing cascade

Prescribing cascade			Analyses
<i>Index medication (ATC code)</i>	<i>ADR (MedDRA notation)</i>	<i>Marker medication (ATC code)</i>	<i>aSR, cSR, OR, aOR, RaRa, RiRa, aRiRa, ReRi, HR, aHR, χ^2^a</i>
Alimentary tract and metabolism (A)			
1. Proton pump inhibitors (A02BC)	Dementia (20000073)	Anti-dementia drugs (N06D)	aSR 1.29 [1.12–1.48] [1]
2. Drugs used in diabetes (A10)	Soft tissue infection (10062255)	dicloxacillin and flucloxacillin (within J01CF) ^b	aSR 1.24 [1.15–1.33] [78]
3. Proton pump inhibitors (A02BC)	Clostridium difficile infection (10054236)	Vancomycine (A07AA09)	RiRa 2.40 [1.88, 3.05] [79] OR 3.5 [2.3–5.2] [80]
4. Sodium-glucose co-transporter 2 (SGLT2) inhibitors (A10BK)	Genital infection fungal (10061180)	Antifungals for topical use (D01A)	aHR 2.18 [1.99–2.40] [16] HR 4.25 [3.5–5.15] [81] ASR 1.24 [1.20–1.28] [82]
5. Rosiglitazone (A10BG02)	Oedema peripheral (10030124)	Furosemide (C03CA01)	Caucasian population: RiRa 1.65 [1.58–1.72] [83]
6. Pioglitazone (A10BG03)	Oedema peripheral (10030124)	Furosemide (C03CA01)	Caucasian population: RiRa 1.47 [1.14–1.91] [83]
Blood and blood forming organs (B)			
7. Antithrombotic agents, dabigatran, rivaroxaban, apixaban (within B01A) ^c	Gastrointestinal disorders (10017947)	Metoclopramide (A03FA01), domperidone (A03FA03), metopimazine (A04AD05)	Index medication: all 4 significant. Example rivaroxaban: aSR 1.23 [1.20–1.27] [17]
8. Antithrombotic agents, dabigatran, rivaroxaban, apixaban (within B01A) ^c	Gastrointestinal disorders (10017947)	Drugs for constipation (A06A)	Index medication: all 4 significant. Example dabigatran:

				aSR 1.13 [1.08–1.19] [17]
9.	Antithrombotic agents, dabigatran, rivaroxaban, apixaban (within B01A) ^c	Gastrointestinal disorders (10017947)	Drugs for functional gastrointestinal disorders and other antiemetics (A03A, A03E, A03F), Bile therapy (A04AD, A05AX), drugs for constipation (A06A, A07)	Index medication: all 4 significant. Example apixaban: 1.47 [1.39–1.55] [17]
10.	Solutions for parenteral nutrition (B05BA)	Liver injury (10067125)	Magnesium isoglycyrrhizinate, Diammonium glycyrrhizinate, Bicyclol, Silybin, Reduced glutathione, Ademetionine (A16AA02), Ursodeoxycholic acid (A05AA02), Polyene, phosphatidylcholine Bifendate	aSR 3.60 [3.26–3.97] [84]

Cardiovascular system (C)

11.	Antiadrenergic agents (C02A, C02B)	Hyperglycemia (10020639)	Insulins and analogues (A10A)	aOR 1.51 [1.29–1.75] [8]
12.	Low-ceiling diuretics, thiazides (C03A)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	aSR 1.28 [1.20–1.38] [18]
13.	Low-ceiling diuretics, thiazides (C03A)	Hyperglycemia (10020639)	Insulins and analogues (A10A)	cOR 1.28 [1.16–1.40] [8]
14.	Furosemide (C03CA01)	Hypokalaemia (10021015)	Potassium chloride (A12BA01)	aSR 2.94 [2.83–3.05][44]
15.	Beta blocking agents (C07)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	aSR 1.18 [1.09–1.28] [18]
16.	Beta blocking agents (C07)	Hyperglycemia (10020639)	Insulins and analogues (A10A)	aOR 1.29 [1.14–1.46] [8]
17.	Calcium channel blocker (C08)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	aSR 1.29 (1.21–1.38) [18]
18.	Calcium channel blocker (C08)	Depression (10012378)	Antidepressants (N06A)	RaRa 1.31 [1.14–1.51] [19] OR 0.75 [0.74–0.76] [20]
19.	Calcium channel blocker (C08)	Hyperglycemia (10020639)	Insulins and analogues (A10A)	aOR 1.50 [1.28–1.76] [8]
20.	Agents acting on the renin-angiotensin system (C09)	Hyperglycemia (10020639)	Insulins and analogues (A10A)	aOR 1.64 [1.28–2.09] [8]
21.	ACE-inhibitors (C09AA)	Depression (10012378)	Antidepressants (N06A)	RaRa 1.29 [1.08–1.56] [19]

				OR 0.75 [0.73–0.76] [20]
22.	ACE-inhibitors (C09AA)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	aSR 1.29 [1.21–1.37] [18]
23.	Angiotensin II receptor blockers (C09C)	Erectile dysfunction (10061461)	Drugs used in erectile dysfunction (G04BE)	aSR 1.16 [1.06–1.26] [18]
24.	HMG CoA reductase inhibitors (C10AA)	Dementia (20000073)	Tacrin, donepezil, rivastigmine, galantamine hydrobromide, memantine (within N06D) ^b	aSR 1.71 [1.55–1.89] [85]
25.	HMG CoA reductase inhibitors (C10AA)	Diabetes mellitus (10012601)	Drugs used in diabetes (A10)	aSR 1.09 [1.04–1.15] [78]
26.	HMG CoA reductase inhibitors (C10AA)	Soft tissue infection (10062255)	Dicloxacillin (J01CF01), flucloxacillin (J01CF05)	aSR 1.40 [1.34–1.47] [78] aSR 1.18 [1.15–1.22] [26]
27.	HMG CoA reductase inhibitors (C10AA)	Depression (10012378)	Antidepressants (N06A)	aSR 1.19 [1.18–1.21] [26] aRaRa 1.06 [0.79–1.45] [22]
28.	HMG CoA reductase inhibitors (C10AA)	Lower urinary tract symptoms (10071289)	Drugs for urinary frequency and incontinence (G04BD)	aSR 1.17 [1.16–1.19] [26]
29.	HMG CoA reductase inhibitors (C10AA)	Sleep disorder (10040984)	Hypnotics and sedatives (N05C)	aSR 1.10 [1.09–1.12] [26]
30.	HMG CoA reductase inhibitors (C10AA)	Muscle pain (10028322)	Antiinflammatory and antirheumatic products, non-steroids (M01A)	aSR 1.02 [1.02–1.03] [26]
31.	HMG CoA reductase inhibitors (C10AA)	Infection (10021789)	Antibiotics (A07AA)	aSR 3.1 [1.2–5.0] [26]
32.	HMG CoA reductase inhibitors (C10AA)	Insomnia (10022437)	Psycholeptics (N05)	OR 1.15 [1.12–1.18] [86]
Antiinfectives for systemic use (J)				
33.	Antibacterials for systemic use (J01)	Vulvo-vaginal candidiasis (10047784)	Antifungals for topical use (D01A)	aSR 5.9 [4.4–7.4] [87]
34.	First (J01DB), second (J01DC), third (J01DD), fourth (J01DE) generation cephalosporins	Sleep disorder (10040984)	Hypnotics and sedatives (N05C)	aSR 12.8 [9.1–16.5] [34]
35.	Ciprofloxacin (J01MA02)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	aSR 1.17 [1.02–1.33] [25]
36.	Erythromycin (J01FA01)	Arrhythmia (10003119)	Antiarrhythmic (C01B)	aSR 1.78 [1.09–2.89] [25]

Nervous system (N)

37. Sumatriptan, ergotamine (Within N02C) ^b	Depression (10012378)	Antidepressants (N06A)	aReRi 1.4 [1.2–1.7] [88]
38. Opioid analgesics (N02A)	Dementia (20000073)	Tacrin, donepezil, rivastigmine, galantamine hydrobromide, memantine (within N06D) ^b	aSR 1.71 [1.49–1.96] [85]
39. Antiepileptics (N03A)	Hypothyroidism (10021114)	Thyroid hormones (H03AA)	aSR 1.13 [1.09–1.18] [89]
40. Antipsychotics (N05A)	Diabetes mellitus (10012601)	Drugs used in diabetes (A10)	HR 1.74 [1.10–2.76] [29] OR 1.63 [1.37–1.94] [28]
41. Antipsychotics (N05A)	Hyperglycaemia (10020639)	Drugs used in diabetes (A10)	Miscellaneous [11] aSR 1.53 [1.06–2.22] [27] miscellaneous in multiple countries [90]
42. Levosulpiride (N05AL07)	Parkinsonism (10034010)	Levodopa (N04BA01)	aOR 3.3 [2.52–4.32] [37]
43. Lithium (N05AN01)	Parkinsonism (10034010)	Dopaminergic agents (N04B)	RaRa 1.88 [1.60–2.20] [15]
44. Amisulpride, aripiprazole, olanzapine, quetiapine, risperidone, sulpiride (within N05A) ^c	Mouth ulceration (10028034)	Corticosteroids for local oral treatment (A01AC)	Index medication: 3 significant, 3 non-significant. Example Quetiapine: aHR 1.48 [1.30–1.69] [91]
45. Antipsychotics (N05A), Metoclopramide (A03FA01)	Extrapyramidal syndrome (10015836)	Anti-parkinson drugs (N04)	Incidence (0.8%) [92]
46. Lithium (N05AN)	Hypothyroidism (10021114)	Thyroid hormones (H03AA)	aSR 3.69 [2.72–5.08] [44]
47. sulpiride, haloperidol, risperidone, olanzapine, quetiapine, amisulpride (within N05A) ^c	Cardiac arrhythmias (10007521)	Antiarrhythmics, class Ib (C01BB)	Index medication: 1 significant, 5 non-significant. Example haloperidol: aSR 2.81 [1.03–7.66] [11]
48. Sulpiride, haloperidol, risperidone, olanzapine, quetiapine, amisulpride	Hyperprolactinaemia (10020737)	Prolactine inhibitors (G02CB)	Index medication: 1 significant, 5 non-significant. Example

(within N05A) ^c			sulpiride: aSR 12.0 [1.59- 91.2] [11]
49. Anxiolytics (N05B)	Extrapyramidal syndrome (10015836)	Anti-parkinson drugs (N04)	aSR 2.48 [2.16- 2.85] [58]
50. Benzodiazepenis derivates (N05B, N05CD)	Dementia (20000073)	Anti-dementia drugs (N06D)	aSR 1.77 [1.39- 2.27] [85] aSR 1.23 [1.11- 1.37] [93]
51. Hypnotics and sedatives (N05C)	Extrapyramidal syndrome (10015836)	Anti-parkinson drugs (N04)	aSR 2.28 [1.97- 2.64] [58]
52. Antidepressants (N06A)	Dementia (20000073)	Tacrin, donepezil, rivastigmine, galantamine hydrobromide, memantine (within N06D) ^b	aSR 1.43 [1.28- 1.61] [85]
53. Antidepressants (N06A)	Parkinsonism (10034010)/ Extrapyramidal syndrome (10015836)	Dopaminergic agents (N04B)	RaRa 1.79 [1.72-1.86] [15] aSR 2.26 [1.93- 2.66] [58]
54. Paroxetine, fluvoxamine, mianserin, milnacipran (within N06A) ^c	Lower urinary tract symptoms (10071289)	Oxybutynin (G04BD04)	Index medication: 2 significant, 2 non-significant. Example Paroxetine: aSR 1.77 [1.33- 2.36] [4]
55. Donepezil, rivastigmine, galantamine (within N06DA) ^b	Anxiety (10002855)	Anxiolytics (N05B)	aSR 1.16 [1.01- 1.34] [32]
56. Donepezil, rivastigmine, galantamine (within N06DA) ^b	Insomnia (10022437)	Hypnotics and sedatives (N05C)	aSR 1.19 [1.05- 1.36] [32]
57. Donepezil, rivastigmine, galantamine (within N06DA) ^b	Diarrhoea (10012735)	Antipropulsives (A07DA)	aSR 1.42 [1.14- 1.77] [32]
58. Donepezil, rivastigmine, galantamine (within N06DA) ^b	Nausea (10028813)	Antiemetics and antinauseants (A04A)	aSR 1.18 [1.05- 1.32] [32]
59. Donepezil, , galantamine (within N06DA) ^c	Overactive bladder (10059617)	Oxybutynin (G04BD04)	Donepezil: HR 1.55 [1.31- 1.83] Galantamine:

				HR 1.17 [0.87–1.58] [94]
60.	Donepezil, rivastigmine, galantamine (within N06DA) ^b	Seizure (10039906)	Antiepileptics (N03A)	aSR 1.26 [1.03–1.55] [32]
61.	Varenicline (N07BA03)	Neuropsychiatric adverse events	Psychostimulants (N06B), Antidepressants in combination with psycholeptics (N06CA), Anxiolytics (N05B), Hypnotics and sedatives (N05C)	aSR 7.0 [4.7–9.2] [34]
Respiratory system (R)				
62.	Montelukast (R03DC03)	Depression (10012378)	Antidepressants (N06A)	cSR 1.19 [1.11–1.28] [95]
Sensory organs (S)				
63.	Antiglaucoma preparations and miotics (S01E)	Depression (10012378)	Antidepressants (N06A)	Miscellaneous [77]

ATC: anatomical therapeutic chemical; ADR: adverse drug reaction; MedDRA: Medical Dictionary for Regulatory Activities; PSSA: prescription sequence symmetry analysis; ACE-inhibitor: Angiotensin-converting enzyme inhibitor; NSAID: non-steroidal anti-inflammatory drugs; SmpC: Summary of Product Characteristics. HMG CoA: 3-hydroxy-3-methyl-glutaryl-coenzyme A.

^a aSR: adjusted sequence ratio; cSR: crude sequence ratio; OR: Odds ratio; aOR: adjusted Odds ratio; RaRa: rate ratio; RiRa: risk ratio; aRiRa: adjusted risk ratio; ReRi: relative risk; HR: hazard ratio; aHR: adjusted hazard ratio.

^b The medication was analyzed as a group.

^c No analysis was performed for the whole index medication ATC group.

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