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REVIEW OF THERAPEUTICS

Prescribing cascades in ambulatory care: A structured synthesis of evidence

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Abstract

The strength of evidence for specific ambulatory care prescribing cascades, in which a marker drug is used to treat an adverse event caused by an index drug, has not been well characterized. To perform a structured, systematic, and transparent review of the evidence supporting ambulatory care prescribing cascades. Ninety-four potential prescribing cascades identified through a previously published systematic review. Systematic search of the literature to further characterize prescribing cascades. (1) Grading of evidence based on observational studies investigating associations between index and marker drugs, including: Level I—strong evidence [i.e. multiple high-quality studies]; Level II—moderate evidence [i.e. single high-quality study]; Level III—fair evidence [no high-quality studies but one or more moderate-quality studies]; and Level IV—poor evidence [other]. (2) Listing of the adverse event associated with the index drug in the product's United States Food and Drug Administration (FDA) label. (3) Synthesis of the evidence supporting mechanisms linking index drugs and associated adverse events. Of 99 potential cascades, 94 were supported by one or more confirmatory observational studies and were therefore included in this review. The 94 cascades related to 30 types of adverse drug reactions affecting 10 different anatomic/physiologic systems and were investigated by a total of 88 confirmatory studies, including prescription sequential symmetry analysis ($n=51$), cohort ($n=30$), and case–control ($n=7$) studies. Overall, the evidence from observational studies was strong for 18 (19.1%) prescribing cascades, moderate for 61 (64.9%), fair for 13 (13.8%), and poor for 2 (2.1%). Although the evidence supporting mechanisms that link index drugs and associated adverse events was variable, FDA labels included information about the adverse event associated with the index drug for most ($n=86$) but not all of the 94 prescribing cascades. Although we identified 18 of 94 prescribing cascades supported by strong clinical evidence and most adverse events associated with index drugs are included in FDA label, the evidentiary basis for prescribing cascades varies, with many requiring further evidence of clinical relevance.

KEYWORDS
adverse drug events, prescribing cascades, prescription drugs

1 | BACKGROUND

Due to aging societies the prevalence of multimorbidity and polypharmacy has risen over time.[1,2] Although there are many causes of polypharmacy, one important contributor is prescribing cascades, in which one drug (the "marker" drug) is used to treat an adverse event caused by another drug (the "index" drug).[3]

Dozens of specific prescribing cascades have been characterized using observational evidence, ranging from the initiation of loop diuretics to treat edema caused by calcium channel blockers (CCB)[4–10] to the initiation of thyroxine to manage hypothyroidism caused by amiodarone[11–14] to the use of topical antifungals to treat fungal infections triggered by inhaled corticosteroids.[13,15–17] Previously, we performed a systematic review of published prescribing cascades in community-dwelling adults.[18] We identified 103 publications examining potential prescribing cascades across a broad range of pharmacological drug groups. The review suggested prescribing cascades occur for a broad range of medications and concluded that adverse drug reactions should be included in the differential diagnosis for patients presenting with new symptoms, particularly older adults and those who started a new medication in the preceding 12 months.

Despite the insights from this prior work,[18] our previous goal was primarily to enumerate potential prescribing cascades rather than to systematically assess the evidence supporting them. Here, we grade the strength of evidence from observational studies supporting each cascade and examine whether the adverse event associated with the index drug is described in the product's United States Food and Drug Administration (FDA) label. In addition, we synthesized information on the mechanisms linking index drugs and associated adverse events. Assembling such otherwise disparate information is important not only to guide further scientific investigation, but also to inform educational efforts aiming to enhance the consideration of prescribing cascades in clinical practice (e.g., via drug compendia, clinical practice guidelines, and decision support software).

2 | METHODS

2.1 | Study design and selection of prescribing cascades

We performed an analysis of all prescribing cascades identified by our previous systematic review as relevant to ambulatory care,[18] for which one or more confirmatory studies had found a statistically significant association between an index and a marker drug. We limited our analyses to cohort, case–control, or prescription sequence symmetry analyses (PSSA)[19] with pre-specified hypotheses, and thus excluded both cross-sectional as well as exploratory studies aiming to identify new signals of prescribing cascades (as opposed to confirming pre-specified ones).[20] For each prescribing cascade, we first graded the strength of evidence supporting each prescribing cascade based on observational studies identified by our previous systematic review. Second, we examined FDA drug labeling information for each index drug to ascertain whether the adverse event of interest was provided within the labeling. Third, we synthesized evidence on the mechanism of action linking index drugs and associated adverse events.

2.2 | Evaluation of evidence from observational studies

We limited our analysis to empirical studies with predefined hypotheses, including cohort, sequential symmetry analysis, and case–control studies. Using these studies, we characterized levels of observational study evidence and agreed on the following domains: (i) the methodological quality of each study (risk of bias assessment using standardized tool); (ii) the number of studies reporting a given cascade; and (iii) the consistency of evidence across studies. Considering these domains, we differentiated between four levels of evidence (from I = strong to IV = poor) as shown in Table 1.Methodological quality (risk of bias) was assessed for each study using the appropriate *Joanna Briggs Institute*

TABLE 1 Criteria for the grading of clinical evidence supporting prescribing cascades.

Level	Criteria
I (Strong)	Two or more high-quality observational studies[a] with significant positive findings (i.e. showing a significantly increased likelihood of marker drug use associated with index drug use), AND no high-quality observational study with significant inverse findings (i.e. showing a significantly reduced likelihood of marker drug use associated with index drug use)
II (Moderate)	Single high-quality observational study[a] with significant positive findings, AND no high-quality observational study with significant inverse findings
III (Fair)	One or more observational studies[a] with significant positive findings, of which none with high quality but at least one with moderate quality AND no observational study with significant inverse findings
IV (Poor)	One or more observational studies[a] with significant positive findings but not meeting the criteria for levels I to III

[a]Cohort, Case–control, or Prescription Sequence Symmetry Analysis.

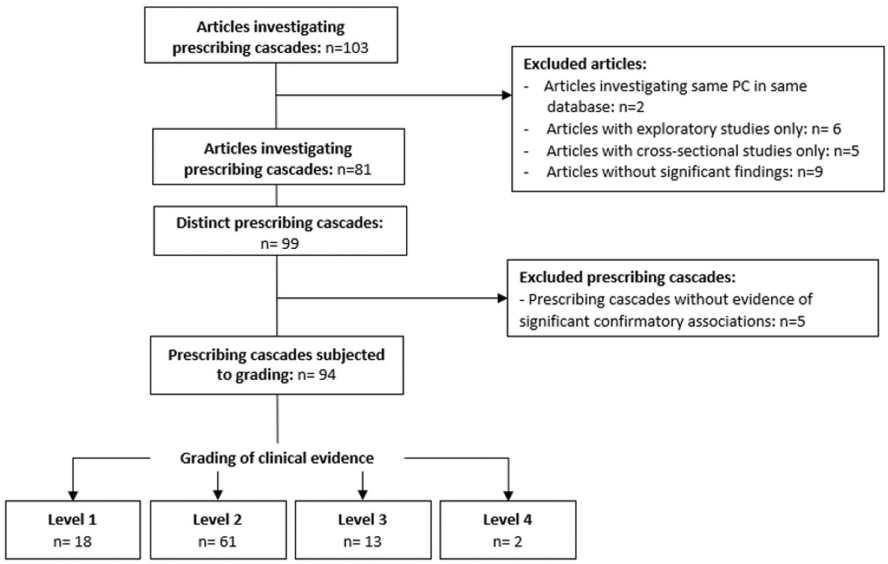

FIGURE 1 Flow chart describing the identification and grading of 94 prescribing cascades by observational study evidence.

(JBI)—Critical Appraisal checklist[21] (Box S1). Assessments were conducted by at least two reviewers independently, with disagreements resolved by discussion or consultation of a third reviewer where necessary, as detailed in our previously published systematic review.[18] The quality score of each individual study was calculated, where the cut-off score for high-quality study (low risk of bias) was ≥70%, for moderate-quality study design 50%–69%, and for low-quality (high risk of bias) study design <50% (Table S1 and S2).[22,23]

2.3 | Examination of labeling information

We used information from FDA.gov to evaluate whether, for each index drug, the adverse drug event of interest was included in the FDA label. When the index drug referred to a drug class, we consulted the labels of different class representatives examined in the included observational studies until we found one that listed the relevant adverse effect (regardless of frequency). We therefore only concluded that the relevant adverse event was absent from FDA labels after all available labeling information had been examined. The assessment served the purpose of eliciting whether the potential triggers for prescribing cascades were commonly known as adverse effects of index drugs, thereby highlighting any gaps within labels or need for further research (see full search strategies in Box S2).

2.4 | Examination of mechanisms of action

We also conducted systematic literature searches to identify mechanisms of action providing a causal link between the respective index drugs and the adverse events that the respective marker drugs would be used to treat. We considered that such information would be particularly valuable for educational purposes aiming to enhance consideration of prescribing cascades in clinical practice. First, we identified relevant articles from the reference lists of articles included in this review. Second, we searched for subsequently published articles, which cited the included articles. Third, we conducted searches in PubMed/Medline and EMBASE (from inception of each database to October 2022), and Google Scholar, using the particular index drug or drug class and the specific adverse event as search terms (see full search strategies in Boxes S3 and S4). We included and assembled data on mechanisms of action from primary literature sources (e.g., case reports, case-series, in-vitro studies, and in vivo studies), as well as secondary (e.g., systematic and narrative review articles) and tertiary literature (e.g., textbooks).

3 | RESULTS

Figure 1 shows that of 103 articles included in our previous systematic review,[18] three used the same database to investigate a single prescribing cascade at different points in time,[24–26] of which we only selected the most recent.[26] Six further studies only reported exploratory studies,[27–32] five only reported cross-sectional studies,[5,33–36] and nine articles did not find any significant positive associations between index and marker drugs.[37–45] The remaining 81 articles reported 99 prescribing cascades (i.e., distinct combinations of index and marker drugs). Of these, five potential cascades were not supported by any studies with significant positive associations and were therefore excluded. Thus, we characterized the evidence supporting 94 prescribing cascades.

Table 2 provides a summary of the 94 prescribing cascades, which relate to 30 types of adverse drug reactions (e.g., constipation, edema, hyperglycemia, etc.) affecting 10 different anatomical/physiological systems. The most commonly implicated adverse drug reactions were "nausea/dyspepsia/peptic ulcer," "lower urinary tract symptoms (including urinary incontinence)," "dizziness," and "depression." Further details of each prescribing cascade (i.e., the references of supporting studies, their design, and the mechanisms of action) are provided in Tables 3 and S3.

3.1 | Evidence from observational studies

The 94 prescribing cascades subjected to grading were investigated by a total of 88 studies (PSSA: $n = 51$; cohort: $n = 30$; case control: $n = 7$), of which many investigated two or more prescribing cascades. Some articles reported more than one study and employed different study designs.[12,46] The majority of studies were of high-quality (PSSA: $n = 46$ (90.2%); cohort: $n = 20$ (66.6%); case control: $n = 7$ (100.0%)) as shown in Tables S1 and S2. Figure 1 shows that of the 94 prescribing cascades subjected to grading, 18 (19.1%) were supported by multiple high-quality studies and were therefore classified as level I, while 61 (64.9%) were only supported by a single high-quality study and were classified as level II. There were 13 (13.8%) prescribing cascades that were only supported by moderate-quality studies (level III), and two (2.1%) were assigned level IV because there were studies with significant inverse findings ($n = 1$) or only low-quality studies with significant positive findings ($n = 1$). The prescribing cascades supported by the highest number of high-quality studies were CCBs → edema → diuretics ($n = 7$), gastroprokinetic/antipsychotics → extrapyramidal symptoms → antiparkinsons drugs ($n = 9$), and cholinesterase inhibitors → urinary incontinence → anticholinergic drugs ($n = 5$) (Table 3). Further details of the clinical evidence supporting prescribing cascades are provided in the Table S4.

3.2 | Information within FDA labels

Out of 94 prescribing cascades, FDA labels included information on relevant adverse events associated with index drugs of 86 cascades, whereas for 8 (8.5%) cascades no evidence was found, namely: flunarizine (not approved by FDA) → depression; flunarizine → parkinsonism; cibenzoline (not approved by FDA) → lower urinary tract symptoms (LUTS); amezinium metilsulfate (not approved by FDA) → LUTS; warfarin → osteoporosis; oral anticoagulants → constipation; and varenicline → neuropsychiatric symptoms (sleep disorder). In the case of oral anticoagulants → depression, we found depression only listed for direct oral anticoagulants but not vitamin K antagonists.

3.3 | Mechanisms of action supporting prescribing cascades

Examples of mechanisms of action that could be considered well established are those for CCB-induced edema (i.e. an increase in capillary hydrostatic pressure causing fluid leakage into perivascular tissues[47–49]) and antiepileptic-induced hypothyroidism (i.e. competition with thyroxin at protein binding sites and increased thyroxin metabolism through induction of hepatic enzymes).[50] The former was supported by an in vivo study showing significant increase in the dilation of arteriolar diameter of precapillary vessels under CCB exposure,[49] whereas the latter was supported by an in vitro study showing lower serum concentrations of free T3 and free T4 in patients taking antiepileptic drugs versus unexposed controls.[50]

In comparison, other mechanisms of actions appeared less well understood or supported by empirical data. Examples include statin-induced sleep disturbances (i.e., production of certain metabolites like prostaglandins by muscle cell damage that act as sleep disruptants[51]) and benzodiazepine (BZD)-induced dementia [i.e., via decreasing cognitive reserves in chronic usage, via chronic consumption causing downregulation of BZD (GABAergic) receptors, or both].[52,53] These latter mechanisms were postulated, but we found no empirical data supporting them.

4 | DISCUSSION

4.1 | Summary of findings

Building on our prior work to systematically identify prescribing cascades, we have graded the evidence from observational studies supporting 94 ambulatory care prescribing cascades in a structured, systematic, and transparent way. Only a minority of 18 prescribing cascades (19.1%) were supported by strong evidence (multiple high-quality observational studies), whereas the remaining 76 prescribing cascades were found to be supported either by moderate (61 cascades), fair (13 cascades), or poor (2 cascades) observational study evidence.

Examination of FDA labels found that relevant adverse events linked to the index drugs were listed for 86 cascades, but for four cascades, the respective index drugs were not approved by FDA and for a further four cascades, the existing FDA label did not include the relevant adverse event. Synthesizing information on mechanisms of action linking index drugs and adverse events revealed variability in the strength of supporting empirical evidence.

4.2 | Comparison to literature

Our previous systematic review identified a total of 99 ambulatory prescribing cascades, of which 94 cascades with observational study evidence were graded and further characterized here. In comparison, the recently published "ThinkCascades" instrument identifies a list of nine potentially inappropriate prescribing cascades as "important" to older people.[54] Of the nine prescribing cascades, five overlap with the prescribing cascades included in this review, all of which were found to be supported by strong observational study evidence, and had index drug-associated adverse effects listed in FDA labels (i.e., calcium channel blockers → peripheral edema → diuretics; antipsychotics → extrapyramidal symptoms → antiparkinsonian drugs; benzodiazepine → cognitive impairment → cholinesterase inhibitor; benzodiazepine → paradoxical agitation → antipsychotics; nonsteroidal anti-inflammatory drugs (NSAIDs) → hypertension → antihypertension drugs).

TABLE 2 Summary of the 94 prescribing cascades subjected to grading with adverse drug reaction, marker drugs, and index drugs.

Adverse drug reactions—Marker drugs	**Index drugs—Overall supporting evidence level**
A. Gastrointestinal	
Nausea/dyspepsia/peptic ulcer—H2RAs/PPIs, metoclopramide, peptic ulcer drugs, antiemetics	Level I: low-dose aspirin (tab. 3 #5); Level II: apixaban (S3 #33), cholinesterase inhibitors (S3 #35) Level II: OAC (DOACs and VKAs) (S3 #77); Level III: digoxin (S3 #81), loop diuretics (S3 #82), methylxanthines (S3 #83); NSAIDs (S3 #84); Level III: asthma drugs (S3 #88), potassium (S3 #89), insulin (S3 #90), nitrates (S3 #91), ACEi (S3 #92); Level IV: antidepressants (SSRI) (S3 #93)
Constipation—Anti-constipation drugs	Level II: oral anticoagulants (DOACs and VKAs) (S3 #78)
Hepatotoxicity—Hepatoprotective drugs	Level II: statins (S3 #38)
B. Cardiovascular	
Edema—Diuretics	Level I: CCBs (tab. 3 #1), thiazolidinediones (tab. 3 #2); Level II: gabapentinoids (S3 #36); Level II: beta blockers (S3 #54)
Hypertension—Antihypertensive	Level II: NSAIDs (S3 #65)
Arrhythmia—Antiarrhythmics	Level II: certain antibacterials (macrolides and ffluoroquinolones) (S3 #37); Level II: antipsychotics (haloperidol) (S3 #67)
C. Metabolic	
Hyperglycemia—Insulin, oral antidiabetics	Level II: antipsychotics (olanzapine and risperidone) (S3 #63), statins (S3 #64)
Hyperlipidemia—Anti-hyperlipidemic drug	Level II: atypical antipsychotics (olanzapine) (S3 #66)
D. Endocrine	
Hyperprolactinemia—Prolactin inhibitors	Level II: sulpiride antipsychotics (S3 #29)
Menopausal symptoms—Menopausal drugs	Level II: aromatase inhibitors (S3 #30)
Hypothyroidism—Thyroxin	Level I: antiepileptic (phenytoin, valproate, phenobarbital, carbamazepine, and oxcarbazepine) (tab. 3 #9); amiodarone (tab. 3 #10)
Hyperthyroidism—Carbimazole	Level II: amiodarone (S3 #62)
E. Urogenital	
Urinary incontinence—Anticholinergic drugs	Level I: cholinesterase inhibitors (tab. 3 #3)
Lower urinary tract symptoms—Urinary spasmolytics, drugs use for LUTS	Level I: statins (14); Level II: SSRI (S3 #19), cyclophosphamide (S3 #20) antiparkinson drugs (amantidine and levodopa/benserazide) (S3 #21), certain antidepressants (paroxetine and milnacipran) (S3 #22), diazepam (S3 #23), cibenzoline (S3 #24), amezinium (S3 #25), drugs for peptic ulcer (cimetidine, scopolamine) (S3 #26), anticholinergic bronchodilators (S3 #27), donepezil (S3 #43)
Erectile dysfunction—5 PDE inhibitors	Level II: antihypertensive drugs (thiazide, ACEi, and CCBs) (S3 #31)
F. Renal	
Hypokalemia—Potassium supplements	Level II: furosemide (S3 #32)
G. Nervous system	
EPS/Parkinsonism—Anti-Parkinson drugs	Level I: gastroprokinetics/antipsychotics (tab. 3 #6), antidepressants (tab. 3 #7); lithium (tab. 3 #13); Level II: benzodiazapines (S3 # 28); Level II: flunarizine (S3 #76)
Dizziness—Prochlorperazine	Level II: vasodilators (S3 #41), diuretic (S3 #42), BBs (S3 #43), CCBs (S3 #44), ACEi (S3 #45), ARB (S3 #46), NSAIDs (S3 #47), opioids (S3 # 48), antipsychotics (S3 #49), sedatives (S3 #50), cardiac therapy (cardiac glycosides, antiarrhythmic drugs, cardiac stimulants, vasodilators, and other cardiac preparations) (S3 #51); Level II: statins (S3 #61)
Depression—Antidepressants	Level I: flunarizine (tab. 3 #14); Level II: BBs (S3 #52), statins (S3 #53), OAC (DOACs and VKAs) (S3 #57), timolol (S3 #58), brimonidine (S3 #59), isotretinoin (S3 #75); Level III: antiparkinson (S3 #85), montelukast (S3 #88)
Seizures—Anticonvulsants	Level II: cholinesterase inhibitors (S3 #60)
Insomnia—Hypnotics	Level I: statins (tab. 3 #17); Level II: varenicline (S3 #79)
Dementia—Dementia drugs	Level I: benzodiazepines (tab. 3 #18), Level II: PPI (S3 #39)
Psychological symptoms: Antipsychotics	Level III: antiparkinson (S3 #86)
H. Musculoskeletal	
Muscle pain/cramps—Quinine/NSAIDs	Level I: statins (tab. 3 #11); Level II: diuretic (S3 #73), inhaled LABA (S3 #74)
Osteoporosis—Bisphosphonate	Level II: warfarin (S3 #34)

(Continues)

TABLE 2 (Continued)

Adverse drug reactions—Marker drugs	Index drugs—Overall supporting evidence level
Gout—Uric acid lowering therapy	Level III: thiazide diuretic (S3 #80)
I. Infection	
Infection, mycotic—Antifungals	Level I: SGLT2-I (tab. 3 #4), ICS (tab. 3 #8); Level II: acitretin (S3 #56)
Infection, bacterial—Antibiotics	Level I: ACEi (tab. 3 #16); Level II: PPI (S3 #40); Level IV: statins (S3 #94)
J. Respiratory	
Cough—Antitussives	Level I: ACEi (tab. 3 #12)
COPD—Inhaled beta-agonists, Inhaled/oral corticosteroids, Antibacterial, Long-acting bronchodilators, LABA- agonist	Level II: timolol (S3 #68, #69), latanoprost (S3 #70), cholinesterase inhibitors (S3 #71), PPI (S3 #72)

Note: For each prescribing cascade, further details on supporting evidence is provided in Table 3 (for Level I prescribing cascades) and Table S3 (for Level II, Level III, and Level IV prescribing cascades).

Abbreviations: 5-HT2, serotonin type 2 receptor; ACEi, Angiotensin-converting-enzyme inhibitors; ADR, Adverse drug reaction; ATC code R03, Anatomical Therapeutic Chemical Classification System code for Drugs for obstructive airway diseases; BBs, beta blockers; CCBs, calcium channel blockers; COPD, chronic obstructive pulmonary disease; DOACs, direct oral anticoagulants; EPS, extrapyramidal symptoms; H2RAs, H2 receptor antagonists blockers; ICS, inhaled corticosteroids; LABA, long acting beta-agonists; LUTS, lower urinary tract storage symptoms; NSAIDs, nonsteroidal anti-inflammatory drugs; OAC, oral anticoagulants; PDE, Phosphodiesterase; PPI, proton pump inhibitors; *SGLT2i*, Sodium/glucose cotransporter-2 inhibitors; SSRI, selective serotonin reuptake inhibitor; UTI, urinary tract infection; VKAs, Vitamin K antagonists.

4.3 | Strengths and limitations

To our knowledge this is the first study to grade and synthetize contemporary evidence on ambulatory care prescribing cascades using a highly structured, systematic, and transparent approach. The information assembled here is likely to be of interest to clinicians and researchers alike. Although our previous systematic review has identified prescribing cascades that may be incorporated into decision support software (or other instruments) which alert prescribers to potential prescribing cascades, alerting clinicians may be insufficient to alter their decision making. The information assembled here may support such implementation efforts, since clinicians may be more motivated to act on prescribing cascades, which are supported by strong observational study evidence and FDA labeling and where mechanisms of action are well understood. At the same time, the evidence gaps highlighted in this review may inform further research.

Nevertheless, this study also has some limitations. First, we excluded prescribing cascades, which had not previously been investigated by empirical studies. This explains why some prescribing cascades, which are frequently mentioned in clinical reviews (e.g., diuretics → urinary incontinence → over reactive bladder medications; antipsychotics → arthritis → anti-inflammatory drugs; and urinary anticholinergics → cognitive impairment → cholinesterase inhibitor) were not considered here.[54,55] Second, despite our use of several methods to enhance the rigor and comprehensiveness of our report, it is nevertheless possible that some studies, particularly regarding the mechanisms of action supporting prescribing cascades, may have been inadvertently excluded. As a consequence, the supporting evidence may be underestimated for some prescribing cascades. It is also possible that some important prescribing cascades were missed by our pragmatic exclusion of those that are not supported by at least one study with significant positive findings (e.g. because such studies were underpowered to detect significant differences).

4.4 | Implications for clinical practice and research

The multitude of studies that have been conducted to confirm hypothesized prescribing cascades as well as the recent development of a consensus-based instrument (Think Cascades)[54] demonstrates a growing clinical interest in prescribing cascades as a contributor to problematic polypharmacy. So far, the discussion has predominantly focused on prescribing cascades that are unrecognized and are therefore potentially inappropriate and avoidable.

However, not all the prescribing cascades characterized in this study fall within that category. For example, the use of proton pump inhibitors to manage symptoms of dyspepsia or to prevent gastrointestinal complications associated with aspirin may be appropriate in high-risk patients who require antiplatelet treatment. Similarly, the use of thyroxine to manage amiodarone-induced hypothyroidism will often be necessary since there are limited alternatives to amiodarone in the management of ventricular tachyarrhythmias.[56] Prescribing cascades are therefore not inappropriate per se but may be appropriate or even necessary when the index drug is indispensable and the adverse reaction caused by it requires treatment or prevention.[57,58] In addition to potentially inappropriate prescribing cascades, further research should aim to systematically identify and build consensus around necessary prescribing cascades.

Preventing avoidable prescribing cascades, nevertheless, remains an important goal in clinical practice. As in other areas of potentially inappropriate prescribing, explicit lists of (the most important) prescribing cascades can play a role in educational efforts to raise awareness and support clinicians in recognizing unintentional and inappropriate prescribing cascades.[54,59] Such lists may either be integrated into prescribing support software or be paper based. However, a vast number of potentially inappropriate prescribing cascades has been identified in this study and some

TABLE 3 Prescribing cascades classified as level I.

	Prescribing cascade (Index drug → *ADR* → marker drug)	Clinical evidence (No. of studies) PSSA (*n*)	Co-S (*n*)	CaCo-S (*n*)	Mechanism of action
1	CCBs → *Edema* → Diuretic	4	3		Dihydropyridine CCBs induce vasodilation of arterioles causing intracapillary hypertension and fluid extravasation
2	Thiazolidinediones → *Edema* → Diuretic	2			Thiazolidinediones cause sodium retention leading to edema
3	Cholinesterase inhibitors → *Urinary incontinence* → Urinary anticholinergics	1	4		Cholinesterase inhibitors increase acetylcholine levels leading to increased stimulation of smooth muscle muscarinic receptors in the urinary tract
4	SGLT2-I → *Genital mycotic infection* → Antifungal	1	1		SGLT2-I inhibitors cause glucose reabsorption in the renal tubules resulting in glycosuria, which provides a medium for fungal growth
5	Low dose aspirin → *Dyspepsia* → H2RAs, PPIs	2			Acetylsalicylic acid causes altered gastric emptying and functional dyspepsia as well as gastrointestinal injuries by inhibiting prostaglandin mediated mucosal protection
6	Gastroprokinetics/antipsychotics → *EPS/Parkinsonism* → Anti-Parkinson drugs	2	4	3	Many antipsychotics and related gastroprokinetic drugs (e.g., metoclopramide) block central dopamine receptors within the extrapyramidal motoric system
7	Antidepressants → *EPS/Parkinsonism* → Anti-Parkinson drugs	1	2		Antidepressants increase the availability of serotonin that in turn increases stimulation of 5-HT2 receptors (e.g., γ-GABA-ergic interneurons), which in turn leads to inhibition of dopamine release in the striatum to produce EPS
8	ICS → Oral candidiasis → Antifungal	4			ICS cause local immunosuppression or rise in salivary glucose levels, which facilitates candidiasis
9	Certain antiepileptic[a] drugs → *Hypothyroidism* → Hypothyroidism treatment drugs	1		1	Certain antiepileptic drugs increase metabolism of thyroxin hormones by increasing the free fraction not bound to proteins (via competition at thyroxin-binding globulin sites) and by induction of hepatic enzymes
10	Amiodarone → *Hypothyroidism* → Thyroxin	4	1		Amiodarone increases iodine levels leading to a compensatory inhibition of thyroid hormone production rate (Wolff-Chaikoff effect)
11	Statins → *Muscle pain* → Quinine, NSAID	4			Statins affect cholesterol, fatty acid, and mitochondrial metabolism and eicosanoid synthesis in muscle cells which cause cell damage and pain
12	ACEi → *Cough* → Antitussives	1	1		• ACEi induce concentration dependent acetylcholine induce contraction of bronchial smooth muscles • Bradykinin II (B2) receptor polymorphism increases cough reflex sensitivity to ACEi • ACEi reduce the breakdown of bradykinins, prostaglandins and substance P, which may cause cough
13	Lithium → *EPS* → Antiparkinson drugs		2		Lithium may diminish the number of dopamine receptors in the brain, which may result in relatively increased cholinergic activity
14	Flunarizine[b] → *Depression* → Antidepressants		2		Flunarizine acts on gamma-Aminobutyric acid (GABA)-ergic neurotransmitter and the serotonergic pathways which may reduce dopamine and serotonin release in brain which may cause depression

(Continues)

TABLE 3 (Continued)

	Prescribing cascade (Index drug → *ADR* → marker drug)	Clinical evidence (No. of studies)			Mechanism of action
		PSSA (*n*)	Co-S (*n*)	CaCo-S (*n*)	
15	Statins → *LUTS* → Urinary spasmolytics	3			Statins lower serum cholesterol, which may lead to demyelination of nerve fibers, which may alter aldosterone release and result in frequent urination
16	ACEi → *UTI* → Nitrofurantoin	2			ACEi may reduce GFR and urine output and consequently compromise bacterial clearance from the renal system
17	Statins → *Sleep disorder* → Hypnotics	2			Statins may lead to damage of muscle cells that could contribute to discharge of certain metabolites of muscles, like prostaglandins. These prostaglandins acting as sleep disrupting factor in the brain
18	Benzodiazepines → *Dementia* → Anti-dementia drugs	2			Benzodiazepines may decrease cognitive reserves in chronic usage—dementia exacerbation by chronic consumption may cause downregulation of BZD (GABAergic) receptors

Abbreviations: 5-HT2, serotonin type 2 receptor; ACEi, Angiotensin-converting-enzyme inhibitors; BZD, benzodiazepine; CaCo-S, case–control study; CCBs, calcium channel blockers; Co-S, cohort study; EPS, extrapyramidal symptoms; GFR, glomerular filtration rate; GI, gastrointestinal; H2RAs, H2 receptor antagonists; ICS, inhaled corticosteroids; LUTS, lower urinary tract storage symptoms; PPI, proton pump inhibitors; PSSA, prescription sequence symmetry analysis; *SGLT2i*, Sodium/glucose cotransporter-2 inhibitors; UTI, urinary tract infection.

[a]Includes phenytoin, valproate, phenobarbital, carbamazepine, and oxcarbazepine.

[b]Not approved by U.S. Food and Drug Administration.

previous literature.[18,54,60] Conversely, a much smaller number of cascades achieved expert consensus of clinical importance in a recent study[54] which highlights the need for further research to improve the evidence base of most such cascades. This study highlights knowledge gaps with respect to observational study evidence, FDA labeling of adverse events associated with index drugs, and mechanisms of action. However, to inform clinical relevance of potentially inappropriate prescribing cascades, further research should also investigate their prevalence, preventability, and reversibility as well as quantify the associated risk of patient harm.

5 | CONCLUSION

We identified and summarized contemporary evidence regarding nearly 100 prescribing cascades supported, many regarding therapies that are commonly used in ambulatory care. Although some prescribing cascades are supported by substantial, high-quality evidence, many others are not. Our identification of prescribing cascades supported by strong evidence may support their consideration in clinical practice, while identified knowledge gaps may inform further research.

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CONFLICT OF INTEREST STATEMENT

Dr. Alexander is past Chair and a current member of FDA's Peripheral and Central Nervous System Advisory Committee; is a co-founding Principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation, for whom he has served as a paid expert witness; and is a past member of OptumRx's National P&T Committee. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies. Prof. Dreischulte receives royalties as author of the book "Praxishandbuch Mutlimorbidität." He received funds from the Techniker Krankenkasse for the preparation of information materials on drug therapy. He received research funds from the German Research Foundation, the Federal Ministry for Education and Research, and the Innovation Fund of the Gemeinsamer Bundesausschuss. He received reimbursement for research grant review from the Innovation Fund. Prof. Schmiedl received consultancy fees from Biocon Limited, Bangalore, India and from pharma4u GmbH, Eschborn, Germany. He received funding for the preparation of medical education events from Daiichi Sankyo Deutschland GmbH. Faiza Shahid, Emma Wallace, and Ann Doherty have no conflict of interest to declare.

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SUPPORTING INFORMATION

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

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