Prescribing Cascades: Identifying, Managing, and Preventing the Domino Effect
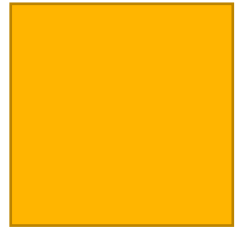
Dr Kieran Dalton

Lecturer in Clinical Pharmacy,
University College Cork,
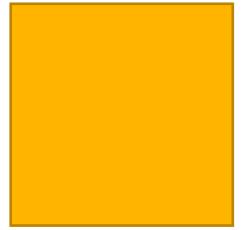Ireland

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University of Toronto,
Canada

Disclosures

- No relevant conflicts of interest to disclose.

- Both presenters are investigators on the iKASCADE project (*Identifying Key Prescribing CASCADes in the Elderly: A Transnational Initiative on Drug Safety*).

- Dr Lisa McCarthy is a Co-Lead at deprescribing.org and Research Committee Co-Chair for the Canadian Medication Appropriateness and Deprescribing Network.

Overview

- What prescribing cascades are: how and why they occur

- Tools to address prescribing cascades

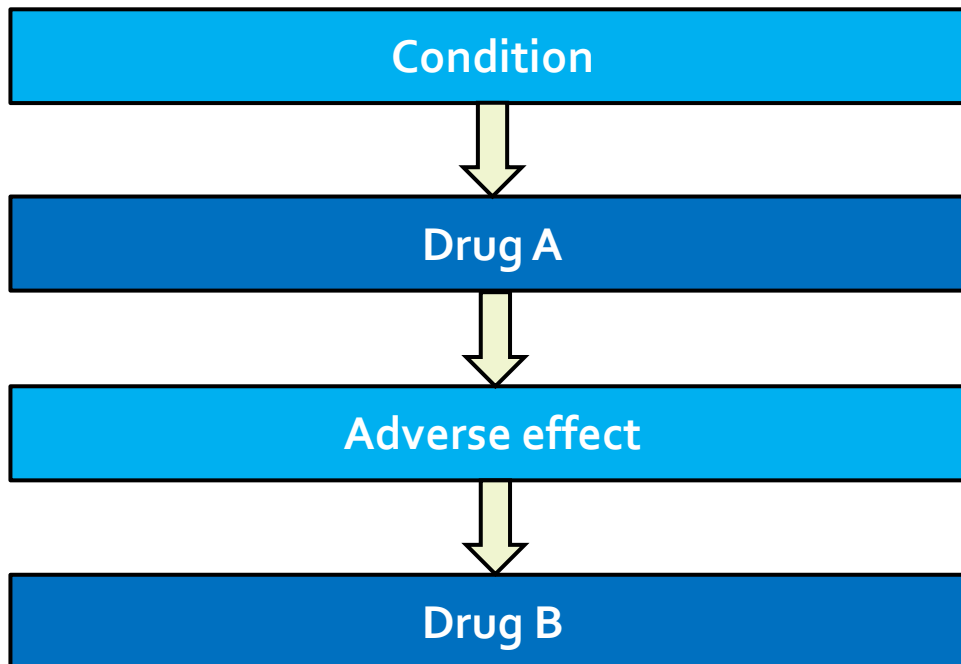- Journal Club Paper Focus

REVIEW ARTICLE

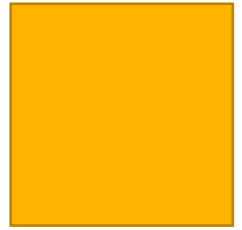## Prescribing Cascades with Recommendations to Prevent or Reverse Them: A Systematic Review

Oriane Adrien[1] · Atiya K. Mohammad[1,2] · Jacqueline G. Hugtenburg[3] · Lisa M. McCarthy[4,5] · Simone Priester-Vink[6] · Robbert Visscher[1] · Patricia M. L. A. van den Bemt[2] · Petra Denig[2] · Fatma Karapinar-Carkıt[1,7,8]

- Discussion / Questions

What is a prescribing cascade?

```
┌─────────────────────────────────────┐
│             Condition               │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│              Drug A                  │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│           Adverse effect            │
└─────────────────────────────────────┘
                  ↓
┌─────────────────────────────────────┐
│              Drug B                  │
└─────────────────────────────────────┘
```
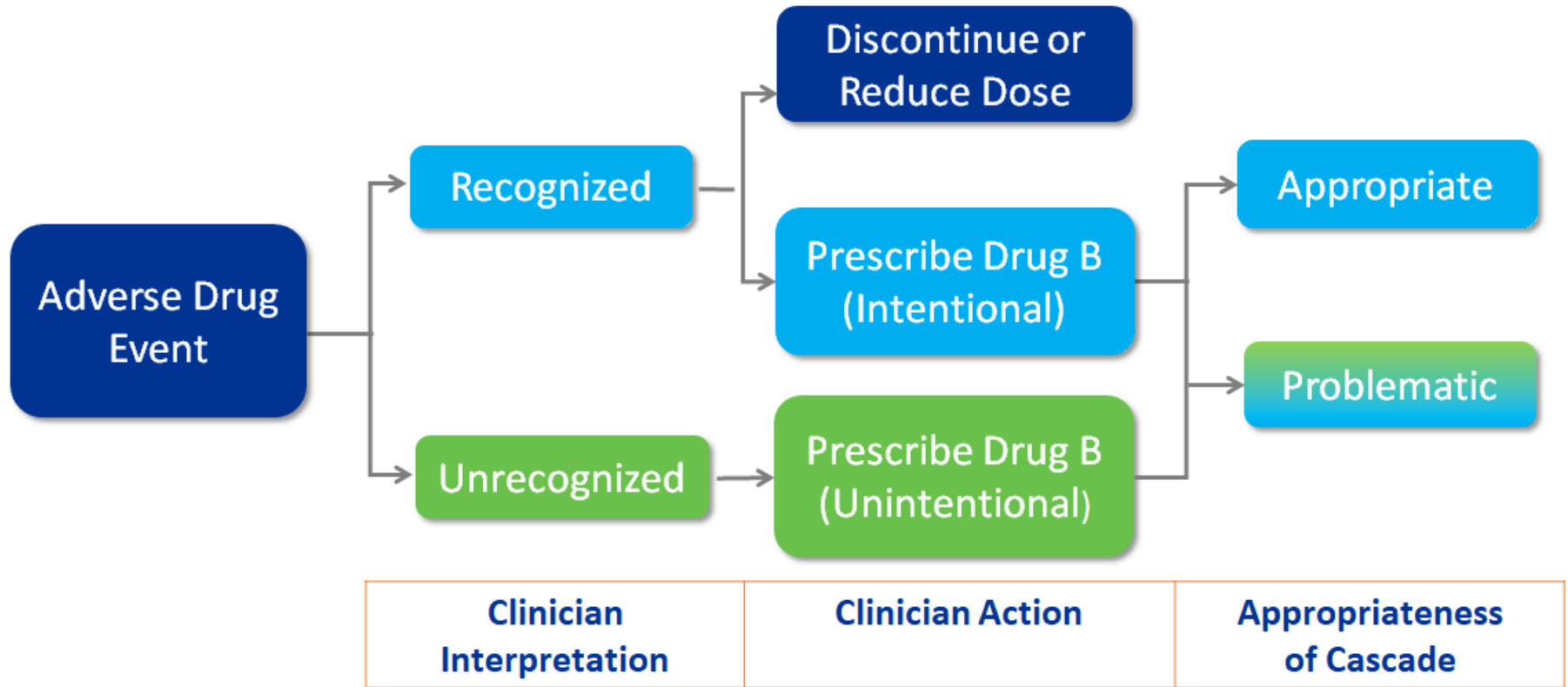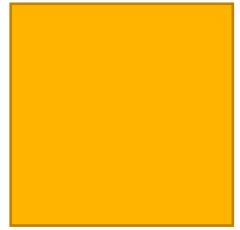
What is a prescribing cascade?

First framed in 1995:

• A phenomenon where the:

"*misinterpretation of an adverse reaction as another medical condition may lead to the prescription of additional medications with their own potential to cause side effects*"

Rochon PA, Gurwitz JH. Lancet 1995; 346: 32-6.
Rochon PA, Gurwitz JH. BMJ 1997; 315:1096-9.

Recognized vs. Unrecognized Appropriate vs. Problematic

Adapted from Figure 1. McCarthy et al. J Am Geriatr Soc 2019;67:1023-26
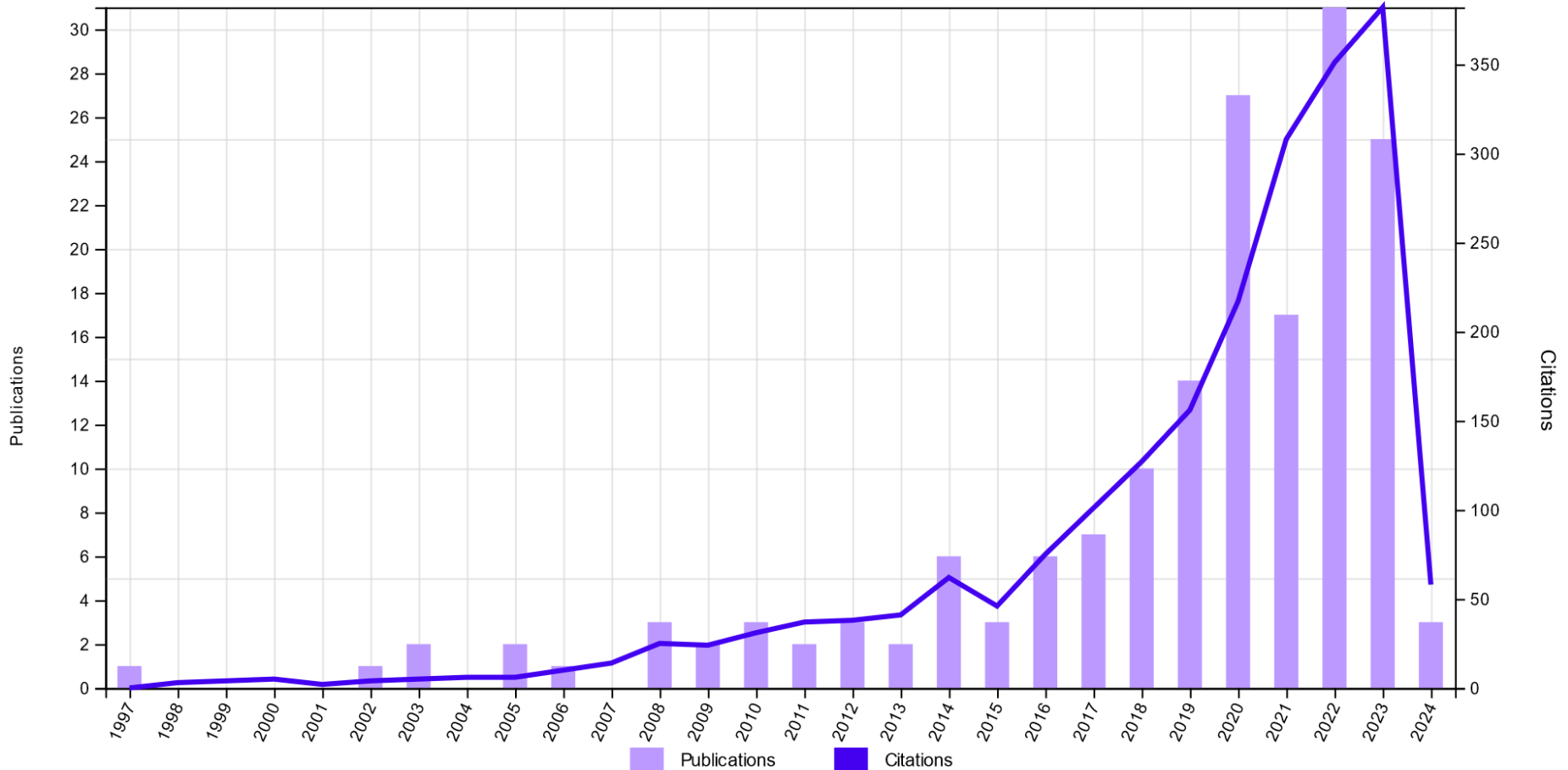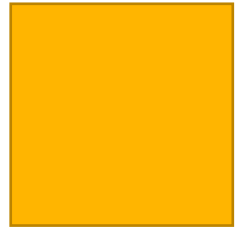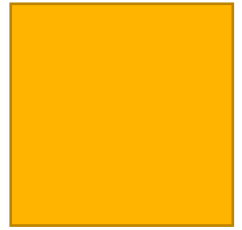
Publications re: Prescribing Cascades

Figure from Web of Science |Topic: "Prescribing Cascade" | 2024-02-27

Scoping review of prescribing cascade definitions

- 1/2 included a definition stating the side effect was **misinterpreted** (50%).

  ➢ 1/8 indicated a **possible misinterpretation** (12.5%).

- Nearly 1/4 mentioned the side effect could be **(un)recognised** (22.9%).

- Around 1/5 addressed **appropriateness/inappropriateness** (20.8%).

- Around 1/20 referenced their **intentional/unintentional** nature (5.2%).

➢ **Considerable heterogeneity in prescribing cascade descriptions**
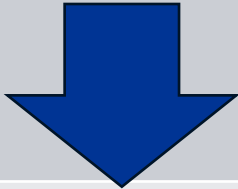
Qualitative Interviews: How and Why Cascades Occur

Long-Term Care Homes

Geriatric Day Hospital

Self-referral (across Ontario, Canada)

Caregiver(s)

Primary Care Providers

Specialist Care Providers

Patients
> 65 years + may have $\geq$ 1 cascade
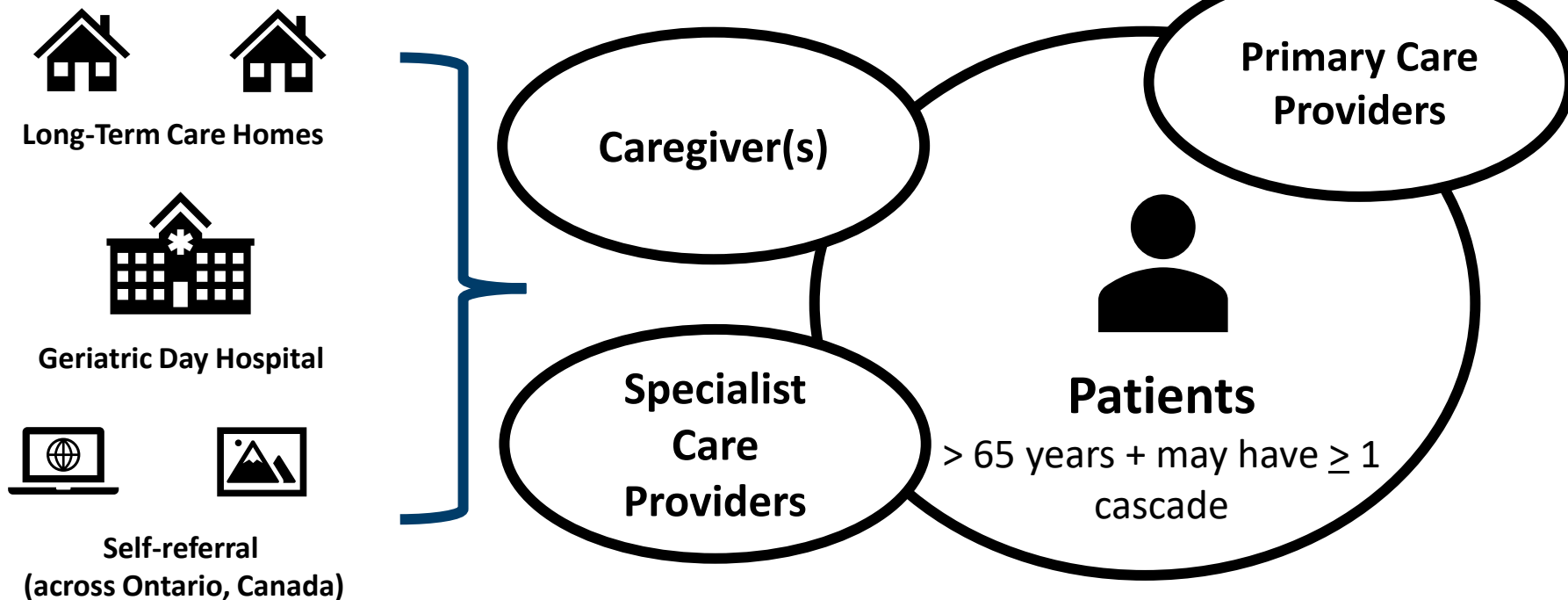
- Addressing cascades is complex and contextually situated.
- Investigation and management of prescribing cascades is simultaneous and iterative (rather than linear and sequential).
- Tools (implicit and explicit) to help prevent, identify, and investigate/manage cascades may help.

Existing Tools

Action*	Tools
Recognize/ Prevent	• Explicit lists • Prescribing Cascades scale modeled on Naranjo scale (Ponte *et al.* Medicina (Buenos Aires) 2017;77:13-16)
Investigate / Manage	• Process Map • Deprescribing Frameworks, • Deprescribing Guides, Guidelines (for individual medications)

*Farrell BJ, Galley E, Jeffs L, Howell P, McCarthy L. PLOS One 2022
Toenjes S et al. MSc Thesis, University of Toronto. Pending publication.

Process Map

- Use a clinical process map to recognize and investigate prescribing cascades in your patients.

- Establish the timeline of:
  - ➢ Medication changes
  - ➢ Side effects/ADRs
  - ➢ Related events

PIggott K et al. BMJ 2020;368:bmj.m261
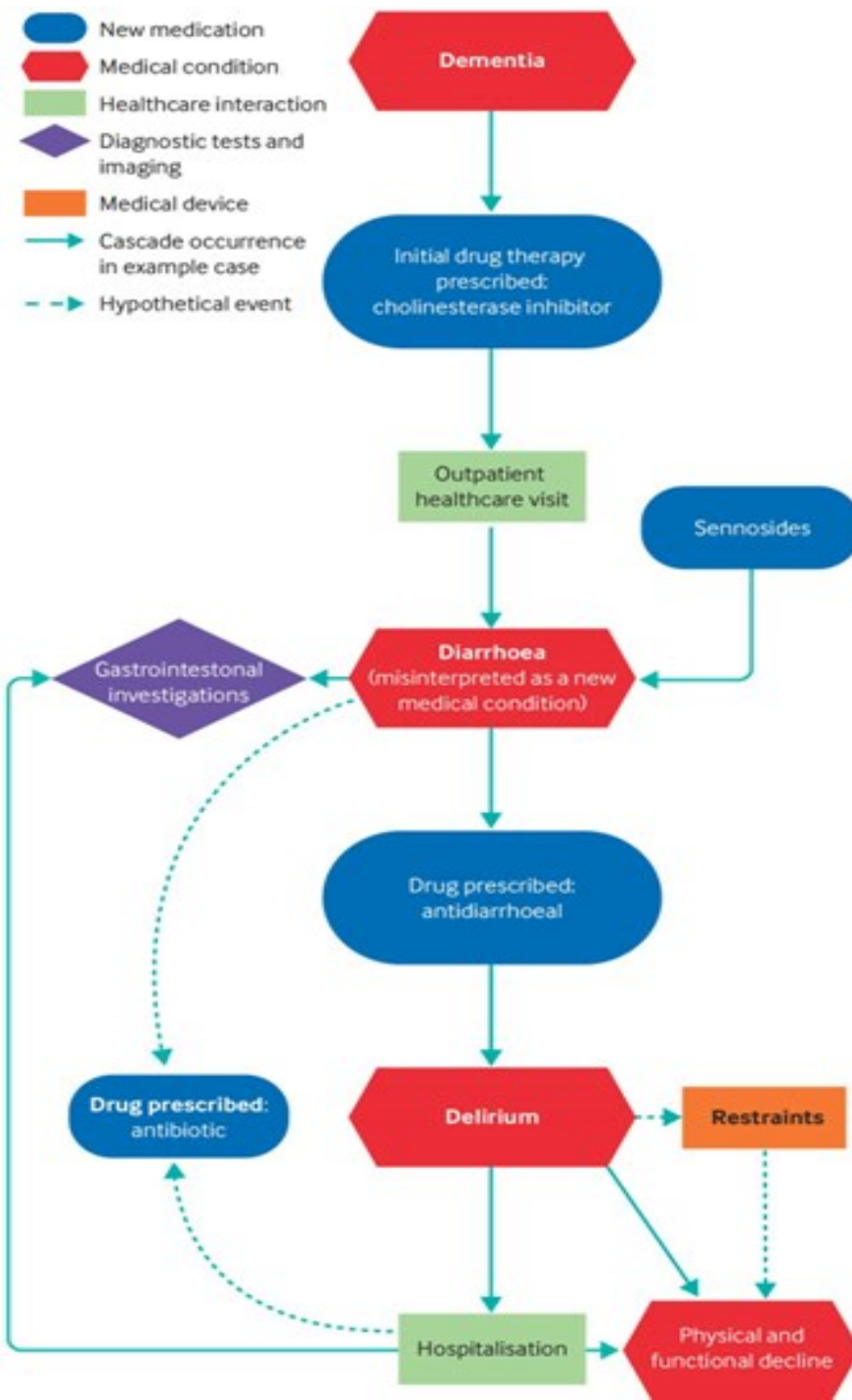
Explicit Lists as Tools
for Recognizing/Preventing Cascades
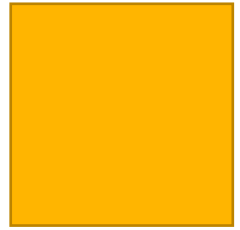
ThinkCascades (2022)

Doherty et al.

Systematic Review (2022)

Adrien and Mohammad et al.

Systematic Review (2023)

Towards an Explicit List of Cascades (1) - ThinkCascades

- Led by the iKASCADE team

- GOAL: **Short** list of clinically important cascades affecting older adults

- Inventory of prescribing cascades + 3 rounds of Delphi with international interprofessional panel

| Belgium | Canada | Ireland | Israel | Italy | USA |

McCarthy LM, Savage R, Dalton K *et al.* Drugs Aging 2022;39:829. doi: 10.1007/s40266-022-00964-9

ThinkCascades

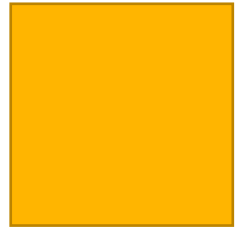| Drug A	Side Effect	Drug B
Cardiovascular System (n=2)		
Calcium Channel Blocker	Peripheral edema	Diuretic
Diuretic	Urinary incontinence	Overactive bladder medication
Central Nervous System (n=4)		
Antipsychotic	Extrapyramidal symptoms	Antiparkinsonian agent
Benzodiazepine	Cognitive impairment	Cholinesterase inhibitor or memantine
Benzodiazepine	Paradoxical agitation or agitation secondary to withdrawal	Antipsychotic
Selective serotonin reuptake inhibitor/SNRI	Insomnia	Sleep agent (e.g., benzodiazepine, benzodiazepine receptor agonist, sedating antidepressant, melatonin)
Musculoskeletal System (n=1)		
NSAID	Hypertension	Antihypertensive
Urogenital System (n=2)		
Urinary anticholinergics for overactive bladder	Cognitive impairment	Cholinesterase inhibitor or memantine
Alpha-1 receptor blocker	Orthostatic hypotension, dizziness	Vestibular sedatives (e.g. betahistine, antihistamines, benzodiazepines)

Towards an Explicit List of Cascades (2) - *Doherty et al.*

ORIGINAL ARTICLE

PRP ASPET BRITISH PHARMACOLOGICAL SOCIETY

Prescribing cascades in community-dwelling adults: A systematic review

Ann S. Doherty[1] | Faiza Shahid[2] | Frank Moriarty[3] | Fiona Boland[1,4] |
Barbara Clyne[1] | Tobias Dreischulte[2] | Tom Fahey[1] | Seán P. Kennelly[5,6] |
Emma Wallace[7]

Databases: 5 databases + grey literature (up to Feb 2022)

Eligibility criteria:
- Community dwelling adults (≥18)
- Rx of medication with potential to cause ADR resulted in Rx of 2nd medication
- Unintentional or intentional cascade
- Prospective or retrospective cohort, cross-sectional, case-crossover, case-control, or case-series
- Primary and community settings including ambulatory care

Doherty *et al.* - Results
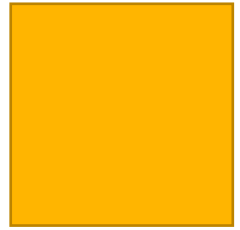
- *n*=101 included studies
  - 78/101 reported ≥ 1 potential prescribing cascade with significant positive quantitative association
- Most were retrospective cohort studies (*n*=88)
- *n*=62/101 used prescription sequence symmetry analysis

Prescribing Cascade	Number of Studies
calcium channel blocker --> loop diuretic	5
amiodarone --> levothyroxine	5
inhaled corticosteroid --> topical antifungal	4
antipsychotic --> anti-Parkinson drug	4
acetylcholinesterase inhibitor --> urinary incontinence medication	4

Towards an Explicit List of Cascades (3) - Adrien & Mohammad
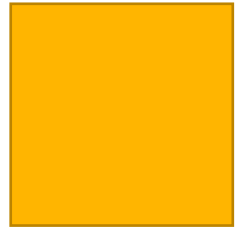
REVIEW ARTICLE

Check for updates

Prescribing Cascades with Recommendations to Prevent or Reverse Them: A Systematic Review

Oriane Adrien[1] · Atiya K. Mohammad[1,2] · Jacqueline G. Hugtenburg[3] · Lisa M. McCarthy[4,5] · Simone Priester-Vink[6] · Robbert Visscher[1] · Patricia M. L. A. van den Bemt[2] · Petra Denig[2] · Fatma Karapinar-Carkit[1,7,8]

Aim: to provide an overview of prescribing cascades including dose-dependency information and recommendations that HCPs can use to prevent or reverse prescribing cascades.

➢ prescribing cascades related to confirmed ADRs

Prescribing cascade – Definition and Eligibility
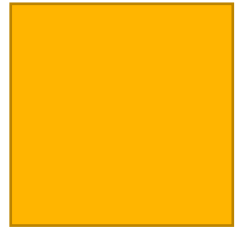
- Where describing a first medication (index medication), an **ADR that could be confirmed in its SPC**, and the initiation of a second medication that could 'treat' the ADR (marker medication), for which an **association between index and marker medication was confirmed in ≥1 study**.

  ➢ Prescribing cascades used as positive controls were included

Index medication
↓
ADR (from SPC)
↓
Marker medication
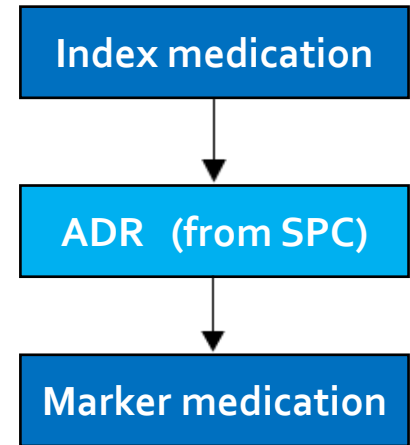
- **<u>Excluded if:</u>**
  ➢ treatment with the marker medication was **intentional**
  ➢ a **medical device/product used** to treat ADR (e.g. for urinary incontinence)
  ➢ index medication was described at an unspecific level (e.g. highest ATC level)
  ➢ if the medication could not be found in the EMA/FDA

Searching & Publication Eligibility

- Five databases searched (to Sept 2021).
- Backward and forward citation searching.

- **Publications included:** in English and reporting a statistical analysis to identify or confirm prescribing cascades in adults.
  - ➢ e.g. prescription sequence symmetry analysis, regression

- **Publications excluded:** case reports, case series, reviews, and those with hypothesis-free or discovery-driven analyses.
  - ➢ e.g. pharmacovigilance studies using data-mining techniques to detect unconfirmed potential ADRs.

Results – Adrien & Mohammad

- 95 publications included

Publication year	
1986–1999	21 (22.1)
2000–2010	18 (18.9)
2011–2021	56 (58.9)
Study design	
Cohort study	80 (84.2)
Case control	15 (15.8)
Type of analysis	
PSSA	45 (47.4)
Regression techniques[a]	36 (37.9)
Chi-square test	8 (8.4)
Descriptive analysis	3 (3.2)
Prevalence rate ratios Mantel–Haenszel	2 (2.1)
Bivariate analysis	1 (1.1)
Setting	
Primary care	34 (35.8)
Secondary care	6 (6.3)
Nursing home	3 (3.2)
Combination	27 (28.4)
Nationwide databases	9 (9.5)
Veterans	4 (4.2)
Other[b]	12 (12.6)

Flowchart:

Non-distinct prescribing cascades ($n = 571$) → **Grouped** → Distinct prescribing cascades ($n = 214$) → Excluded for various reasons, e.g. no ADR in SPC ($n = 29$)

Distinct prescribing cascades minus exclusions ($n = 185$) → Showed no significant positive association ($n = 70$)

Prescribing cascades with ≥1 significant positive association ($n = 115$) → No dose dependency occurrence or no recommendation to prevent or reverse the cascade ($n = 63$)

Prescribing cascades with dose dependency occurrence or a recommendation to prevent or reverse the cascade ($n = 52$)

	Prescribing cascade			Prescribing cascade analyses[a]	Dose-dependency analysis[b]	Recommendations
	Index medication (ATC code)	*Adverse drug reaction (MedDRA notation)*	*Marker medication (ATC code)*	*P = PSSA* *R = Regression* *O = Other[c]*	*P = PSSA* *R = Regression* *O = Other[c]*	*DIS = Discontinuation* *DL = Dosage lowering* *SW = Switch (to)*
13.	HMG CoA reductase inhibitors (C10AA)	Leg cramps (10024125)	Quinine (P01BC01)	+P [36]		DIS, SW [36]
	Simvastatin			+P [32]		
14.	Calcium channel blocker (C08)	Oedema peripheral (10030124)	Diuretics (C03)	+R [37] +O [38]	+R [37]	DIS, DL, SW [37]
	Dihydropyridines (C08CA)			+P [27] +R [39]		
	Nifedipine, felodipine, isradipine**			+P [40]		DIS, DL, SW [40]
	Amlodipine			+P [40]	+P [40]	DIS, DL, SW [40]
	Amlodipine, nifedipine, felodipine**			-R [41]		
15.	Prazosin (C02CA01)[#]	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	+P [42]		DL, SW [42]
16.	Diuretics (C03)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]
17.	Beta blocking agents (C07)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]
18.	Beta blocking agents (C07A)	Depression (10012378)	Antidepressants (N06A)	+O [43, 44] −O [45] ~R [46]		SW [43]
19.	Calcium channel blocker (C08)	Constipation (10010774)	Drugs for constipation (A06A), magnesium oxide (A02AA02)	+O [47]		SW [47]
20.	Calcium channel blocker (C08)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]
21.	Miscellaneous calcium channel blockers (C08)[g]	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	+P [42]		DL, SW [42]
22.	Miscellaneous ACE-inhibitors (C09AA)[h]	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	+P [42]		DL, SW [42]
23.	Miscellaneous ACE-inhibitors & diuretics (C09BA)	Urinary incontinence (10046543)	Oxybutynin (G04BD04)	+P [42]		DL, SW [42]
24.	ACE-inhibitors (C09AA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]
25.	Miscellaneous ACE-inhibitors (C09AA)[i]	Urinary tract infection (10046571)	Nitrofuran derivatives (J01XE)	+P [48] -P [27]		DL, SW [48]
26.	Angiotensin II receptor blockers (C09C)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]
27.	HMG CoA reductase inhibitors (C10AA)	Dizziness (10013573)	Prochlorperazine (N05AB04)	+P [25]		DIS, DL [25]

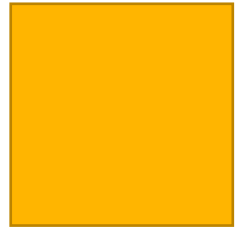# Dose Dependency and Recommendations to Switch

- Dose dependency analysis for 12 distinct prescribing cascades (23.1%)

Index Drug(s)	ADR
Inhaled glucocorticocoids	Oral candidiasis*
Metoclopramide, antipsychotics	Extrapyramidal syndrome
Thiazides	Gout
Amiodarone	Hypo- and hyperthyroidism
Acitretin	Candidiasis
Glucocorticoids	Hyperglycemia
NSAIDs/diflunisal	Hypertension
Calcium channel blockers, pregabalin/gabapentin	Peripheral oedema

- Recommendations to switch index medication for 22 prescribing cascades (42.3%)
- Three mentioned which medication to switch to:
  - ➢ ACE-I $\rightarrow$ cough: switch to ARB
  - ➢ Metoclopramide $\rightarrow$ extrapyramidal syndrome: switch to ondansetron/granisetron
  - ➢ Antiglaucoma preparation (AP) $\rightarrow$ obstructive airways disorder: switch to other AP
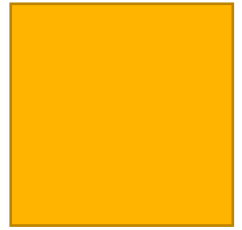
Limitations/Strengths

Limitations

- Some cascades assessed in many studies, others in one.

- Cascade occurrence may vary by country/culture/setting

Strengths

- Explored dose-relationships

- Highlights specific examples from literature about HOW to manage cascades

- ADR confirmation against existing source
  - ➢ missed signals?

Discussion Points from Adrien & Mohammad Paper

- This review is an **important starting point** for specific interventions on HOW to minimise prescribing cascades
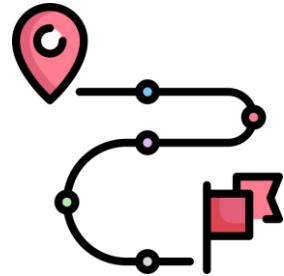
- **More evidence needed**:

  ➤ whether using low(er) dosages can prevent/reverse prescribing cascades

 ➤ knowledge synthesis of possible alternatives to switch to

- Creating **electronic decision support** tools to help identify/manage
  - ➤ 84.1% of community pharmacists in Ireland agreed that electronic alerts in pharmacy dispensing software that flag potential prescribing cascades would be useful.

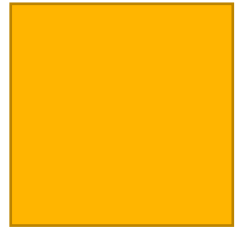Dalton *et al.* 2024. (Awaiting publication in RSAP)

Discussion: Questions/Comments
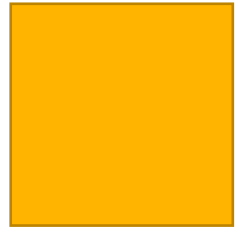
- What are your thoughts stemming from this?
  - Does this align with your experience of cascades in practice?
  - What questions or observations do you have about the papers we discussed (e.g., strengths, limitations)?

- What gaps do you see in existing tools?

- What suggestions do you have for us to move forward from this point?

Future Directions

- Greater consistency in defining prescribing cascades.

- Greater awareness about the phenomenon.
  - For healthcare professionals and patients.

- Tools/resources to help recognize, manage, and prevent.

Get In Touch

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