

What Is Known About Preventing, Detecting, and Reversing Prescribing Cascades: A Scoping Review

Hana Brath,^{*‡} Nishila Mehta, BA,^{†‡} Rachel D. Savage, PHD,[‡] Sudeep S. Gill, MD MSC,^{§¶} Wei Wu, MSC,[‡] Susan E. Bronskill, PHD,^{‡¶||} Lynn Zhu, PHD,[‡] Jerry H. Gurwitz, MD,^{**} and Paula A. Rochon, MD MPH^{‡||††}

OBJECTIVES: To systematically describe the resources available on preventing, detecting, and reversing prescribing cascades using a scoping review methodology.

MEASUREMENTS: We searched Medline, EMBASE, PsycINFO, CINAHL, Cochrane Library, and Sociological Abstracts from inception until July 2017. Other searches (Google Scholar, hand searches) and expert consultations were performed for resources examining how to prevent, detect, or reverse prescribing cascades. We used these three categories along the prescribing continuum as an organizing framework to categorize and synthesize resources.

RESULTS: Of 369 resources identified, 58 met inclusion criteria; 29 of these were categorized as preventing, 20 as detecting, and 9 as reversing prescribing cascades. Resources originated from 14 countries and mostly focused on older adults. The goal of preventing resources was to educate and increase general awareness of the concept of prescribing cascades as a way to prevent inappropriate prescribing and to illustrate application of the concept to specific drugs (e.g., anticholinergics) and conditions (e.g., inflammatory bowel disease). Detecting resources included original investigations or case reports that identified prescribing cascades using health administrative data, patient cohorts, and novel sources such as social media. Reversing prescribing cascade resources focused on the medication review process and deprescribing initiatives.

CONCLUSION: Prescribing cascades are a recognized problem internationally. By learning from the range of resources to prevent, detect, and reverse prescribing cascades, this review contributes to improving drug prescribing, especially in older adults. © 2018 American Geriatrics Society and Wiley Periodicals, Inc. *J Am Geriatr Soc* 00:1–7, 2018.

Key words: scoping review; prescribing cascade; older adult; medication safety

Prescribing cascades occur when an adverse drug effect is misinterpreted as a new medical condition, resulting in the prescription of a potentially unnecessary drug to treat this new condition^{1–3}. First observed in clinical practice and described in the *Lancet*² and *British Medical Journal*¹ 20 years ago, the concept has been recently expanded to include drug prescribing that leads to potentially unnecessary over-the-counter medications and medical devices³. Since that first report, many prescribing cascade examples have been documented worldwide, with lists identifying more than 20 common prescribing cascades^{3–5} (e.g., antipsychotic→parkinsonism→antiparkinsonian drug therapy).

Prescribing cascades are an important public health problem because they lead to adverse outcomes and unnecessary costs for the individuals and the healthcare system that can be avoided. Contributing factors include advanced age and the associated increase in use of drug therapy. For example, a well-known prescribing cascade identified in the 1990s links the initiation of a nonsteroidal antiinflammatory drug to development of hypertension and subsequent initiation of antihypertensive therapy^{1–3}. This prescribing cascade involves multiple agents from two drug classes. The ability to recognize this association and where possible prevent cascades from occurring or detect them promptly to

From the *McMaster University, Hamilton, Ontario, Canada; †Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; ‡Women's College Research Institute, Women's College Hospital, Toronto, Ontario, Canada; §Department of Medicine, Queen's University, Kingston, Ontario, Canada; ¶Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada; ||Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada; **Division of Geriatric Medicine, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts; and the ††Department of Medicine, University of Toronto, Toronto, Ontario, Canada.

Corresponding Author: Paula A. Rochon, MD, MPH, Women's College Research Institute, Women's College Hospital, 76 Grenville Street, Toronto, Ontario, Canada. E-mail: paula.rochon@wchospital.ca

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mitigate or reverse their effects is not only critical for preventing unrecognized adverse events and thus improving medication safety, but also for improving the health and quality of life of individuals who they affect.

Prescribing occurs along a continuum: from the initial decision to prescribe to the decision to stop a medication. This process occurs within the context of medical care. Along the way, there are opportunities to review drug therapy. To take advantage of these opportunities, prescribers must be aware of what prescribing cascades are, which ones commonly occur, their clinical presentation, and interventions available to reduce their prevalence. Despite the value of this information to prescribers and patients, no such review exists. The purpose of this scoping review was to explore what is known about how to prevent, detect, and reverse prescribing cascades in order to improve medication safety.

METHODS

A scoping review was conducted following the Arksey and O'Malley⁶ framework enhanced by Levac and colleagues⁷ and the Joanna Briggs Institute⁸. A scoping review was selected over a systematic review given the breadth of our topic and our interest in identifying resources available within and outside of the peer-reviewed literature. Consistent with the methodology and goals of a scoping review⁸ and to identify all prescribing cascade resources, no exclusions were made based on quality, and risk of bias was not assessed. Resources included a range of materials, from original investigations to webpages.

A search of published and grey literature resources was performed to identify English-language resources discussing prescribing cascades. Grey literature is defined as documentary material that is not commercially published or publicly available, such as technical reports and internal business documents⁹. No exclusions were placed according to type of evidence, source, study design, setting, or study population. The search strategy was developed with the guidance of a librarian, and individuals with expertise in prescribing cascades reviewed it to ensure that search terms captured different permutations of the prescribing cascade concept. The full search strategy (databases and grey literature) is listed in Supplementary Appendix S1, which also describes the screening and data extraction processes.

Analysis

We developed a narrative summary of the included resources, using 3 categories that fall along the prescribing continuum as an organizing framework. Each resource was classified into one of the “preventing,” “detecting,” and “reversing” categories in a mutually exclusive manner. Resources to prevent prescribing cascades were defined as those that aimed to prevent potentially inappropriate prescribing by increasing prescribers' or patients' general awareness about prescribing cascades (e.g., commentaries or book chapters describing the concept). Resources to detect prescribing cascades were defined as those used at the time of deciding on a prescription to identify the presence of prescribing cascades (e.g., case study or original investigation identifying new prescribing cascade using

population-level data). Resources to guide clinical decision making at the time of prescribing (e.g., prescribing algorithm) would also be included. Resources to reverse prescribing cascades were those that described steps taken after identifying a prescribing cascade (e.g., medication reviews, deprescribing (e.g., dose tapering, drug discontinuation)). Critical resources from each of these categories were described to illustrate their unique contributions to our understanding of the prescribing cascade.

Descriptive statistics were used to describe the distribution of studies according to publication year, country of origin, and resource type.

RESULTS

Fifty-eight resources were included in the scoping review. Figure 1 describes our Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram and the selection process.

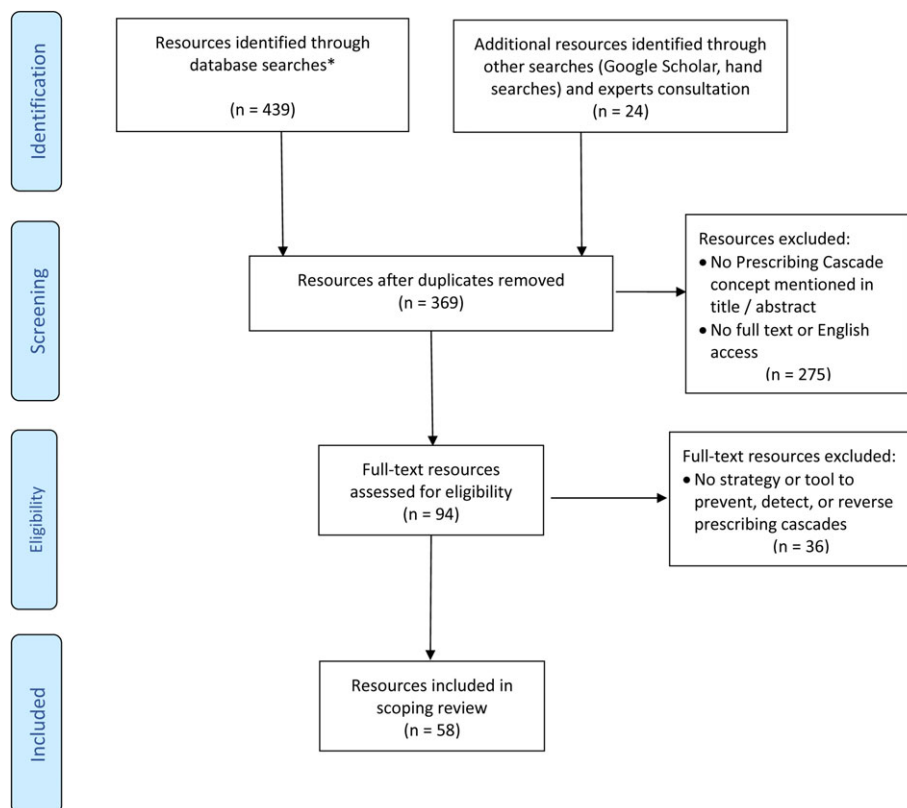
Table 1 provides a summary of the included resources; a full description is provided in Supplementary Appendix S2. Of the 58 resources, 29 were categorized as “preventing,” 20 as “detecting,” and 9 as “reversing” prescribing cascades (Table 1). Figure 2 illustrates two resources from each of these categories. Authors from 14 different countries, the majority based in Canada (n=18, 31%), the United States (n=16, 28%) and the United Kingdom (n=8, 14%) wrote the resources. Forty-six (79%) were published in 2011 or later, and 28 (48%) were published in 2015 or later. The resources included 40 journal articles (16 original investigations, 4 commentaries, 7 case reports, 13 reviews), 6 book chapters, 5 bulletins or reports, and 7 other resources (e.g., webpages, educational modules).

Prevent Prescribing Cascades

Eighteen of the 29 resources (62%) that were focused on preventing prescribing cascades were review articles or book chapters, 4 were original investigations, 3 were commentaries, and 4 were other types of resources.

The resources provided examples and lists of common prescribing cascades to help improve prescribers' awareness of drugs that commonly lead to prescribing cascades and thus were targeting prescribers (physicians, pharmacists, other healthcare providers)^{3–5}. Strategies to prevent initiation of the prescribing cascade were often incorporated into reviews and guidelines for prescribers. Suggested prescribing strategies to prevent prescribing cascades included starting drug therapies at lower initial doses^{1,10,11} and considering alternative drug therapies or nonpharmacological treatments¹ (Figure 2). One resource suggested better communication between individuals and their caregivers and healthcare providers as a strategy to prevent prescribing cascades (e.g., promoting self-reports of medication side effects)¹².

Some resources suggested things for providers to consider before prescribing a medication, including determining whether the medication to be prescribed would initiate a drug sequence that was a prescribing cascade. One study⁴ described a 4-step process, targeted to pharmacists, to reduce polypharmacy (Figure 2). Authors ask their audience first to consider whether the drug therapy in question is



* Databases included Medline, EMBASE, PsychINFO, CINAHL, Cochrane Library, Sociological Abstracts, Journal Abstracts, Canadian Agency for Drugs and Technologies in Health grey matters tool, the Turning Research Into Practice database, Proquest, and University of Toronto’s T Space

Figure 1. Flow diagram of included and excluded resources.

Table 1. Summary of Resources Describing Preventing, Detecting, and Reversing Prescribing Cascades

Resource Characteristics	Overall, N=58	Prevent, n=29	Detect, n=20	Reverse, n=9
Type of resource				
Original investigation	16	4	10	2
Commentary	4	3	0	1
Review	13	12	0	1
Case study	7	0	7	0
Book chapter	6	6	0	0
Bulletin or report	5	2	0	3
Other	7	2	3	2
Country of origin				
United States	16	11	5	0
Canada	18	8	6	4
Other	24	10 (Saudi Arabia, Indonesia, India, United Arab Emirates, Italy, Australia, United Kingdom, Spain)	9 (Argentina, Australia, Belgium, Italy, India, Portugal, United Kingdom)	5 (all United Kingdom)
Target audience¹				
Prescribers	51	29	14	8
Researchers	6	2	4	0
Policy makers	5	2	1	2
Public	3	1	2	0
Trainees	3	0	2	1

A full description of resources is provided in Supplementary Appendix S1.

¹Categories were not mutually exclusive.

part of a prescribing cascade and provide lists of common geriatric signs or symptoms that medications can cause and common prescribing cascades. By asking this, the resource builds awareness of the potential of a drug therapy to cause a prescribing cascade.

Detect Prescribing Cascades

Twenty resources described strategies and tools to detect prescribing cascades; 10 were original investigations, 7 were case reports, and 3 were other types of resources.

Original investigations to identify prescribing cascades included 3 retrospective cohort studies that used health administrative data^{13–15}, all of which focused on older adults. Two of these studies were conducted using Canadian data from the Institute of Clinical Evaluative Sciences¹⁶, Canada's largest holder of health administrative data, including all drugs prescribed to an estimated 1.8 million older adults¹⁶. Using these data, prescribing cascades were identified that linked use of cholinesterase inhibitor therapy to initiation of urinary anticholinergics¹⁴ and lithium to treatment for parkinsonism¹³. The former was one of the first published studies to use administrative health data to describe a prescribing cascade at a population level and illustrates important methodological considerations for researchers. In the United States, a study used Medicare data¹⁵ to explore the association between initiation of anti-psychotics and use of antiparkinson agents. One study used sequence symmetry analysis—a statistical signal detection

method¹⁷—to identify prescribing cascades in administrative health data by examining concomitant drug use or drug prescribing sequences that reflected prescribing cascades¹⁷.

One novel study used Twitter and online health forums to detect signals of prescribing cascades from user-generated data (Figure 2)¹⁸. Tweets could be from older adults and their families and caregivers. The extensive data available on individuals' drug use and experiences through social media provided an opportunity to detect new prescribing cascades before they could be recognized using administrative health data. In addition, social media data provided an opportunity to explore prescribing cascades involving over-the-counter self-medication after an adverse drug event¹⁸. Over-the-counter medications are not reimbursed, and their associations with prescribing cascades cannot be explored using administrative data.

Case studies were also an important resource to help prescribers learn to detect prescribing cascades. Case studies described prescribing cascades associated with a variety of drug therapies, including angiotensin-converting enzyme inhibitor-induced rhinorrhea¹⁹ and dexamethasone-induced psychosis²⁰. Case studies also illustrated the expanded prescribing cascade concept, which is when the prescribing cascade is extended beyond initiation of a new prescribed drug to consider other potentially unnecessary interventions, such as new use of over-the-counter self-medication or medical devices²¹.

Several resources (e.g., algorithms, case studies) were identified that aimed to assist prescribers in identifying

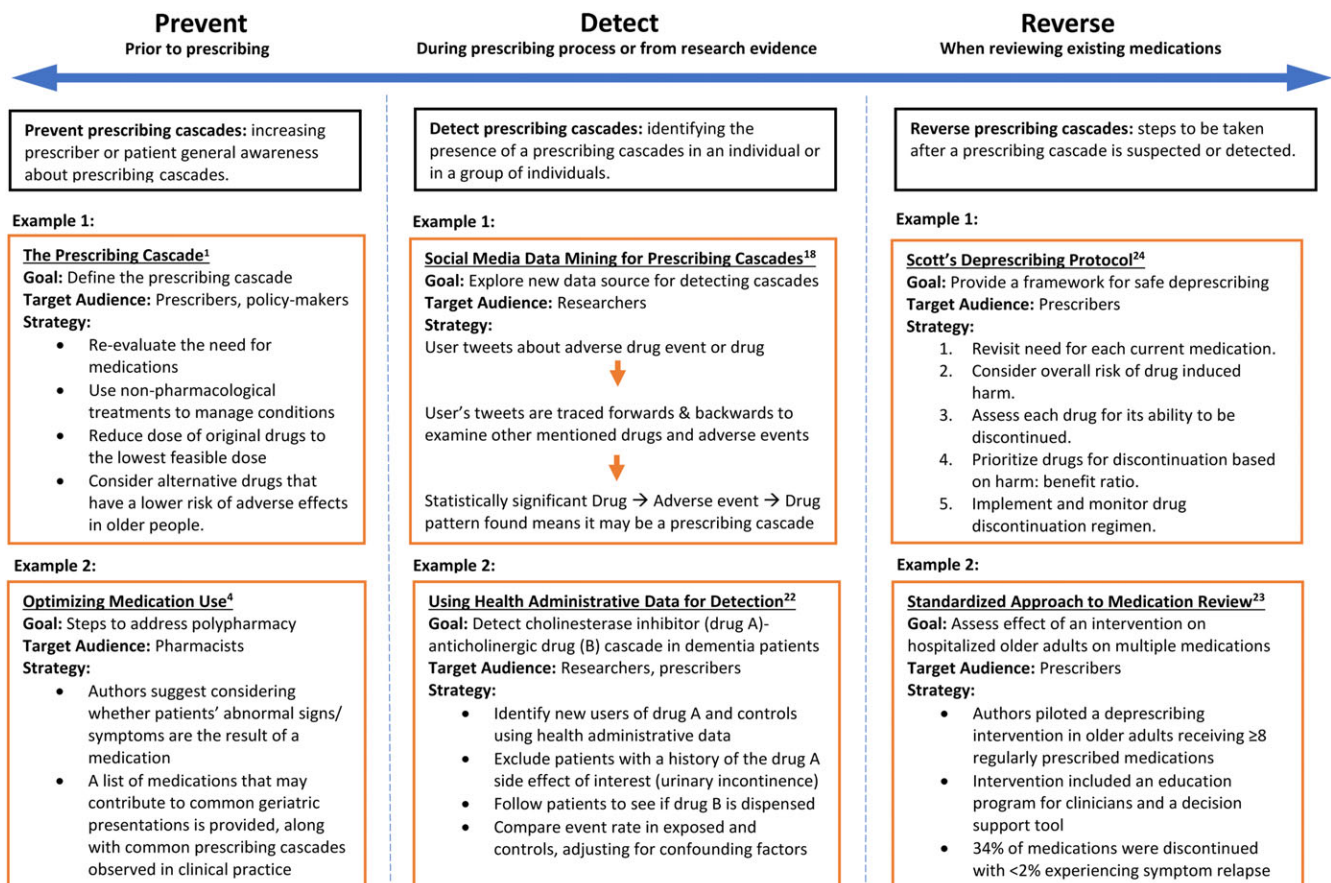


Figure 2. Selected strategies to prevent, detect, or reverse prescribing cascades.

prescribing cascades promptly. One simple tool²² was designed to determine whether an adverse drug event could be the result of a prescribing cascade. This tool consists of 4 questions, each with a series of answers that are assigned points. A total score of 4 or higher suggested that a prescribing cascade was responsible for the adverse event (Figure 2).

Reverse Prescribing Cascades

Nine resources described reversing prescribing cascades: 2 original investigations, 1 commentary, 1 review article, and 5 other resources.

An original investigation²³ explored whether a structured approach to deprescribing could identify and inform discontinuation of unnecessary medications. This study piloted a decision support tool based on a 5-step deprescribing protocol (Figure 2)²⁴ and accompanying educational seminar in an acute care setting. The 5-step deprescribing protocol was developed based on a review of evidence of the efficacy and safety of deprescribing. The protocol has been tested in a cohort of prescribers and pharmacists, and its face validity has been demonstrated. One of the steps was to identify drug therapies without valid indication for their use, including situations in which drugs were part of a prescribing cascade. This intervention significantly reduced the median number of medications prescribed per person in older adults²⁴, highlighting the potential benefits of such protocols and need for rigorous evaluation through controlled trials. A multifaceted intervention for primary care has been proposed²⁵ that includes an adapted version of the deprescribing protocol²⁴ and will be evaluated using a mixed-methods approach.

Many of the deprescribing initiatives provided education on how to deprescribe safely that targeted prescribers (e.g., pharmacists, physicians) or trainees (e.g., geriatric medicine residents, pharmacy students)^{26–28}. These resources offered methods to detect and reverse prescribing cascades in clinical situations, such as during medication review. They also provided questions about the medication regime for prescribers to explore to identify prescribing cascades (e.g., What is the indication for this drug?)²⁶. Some resources encouraged patient education by presenting questions that older adults or caregivers could ask during medication review to improve prescribing cascade detection and reversal. One resource suggested that older adults routinely assess and monitor their symptoms for improvement and resolution while discontinuing medications. Authors also suggested different standards when conducting medication reviews, including engaging with patients in person, as opposed to only using health records, to ensure successful medication regime improvement²⁷. Engaging patients in the deprescribing process was also suggested to improve their awareness and compliance, which can reverse prescribing cascades^{27,28}.

A successful dose-tapering strategy used during drug discontinuation at a geriatric day hospital to reverse prescribing cascades was described.²⁹ This illustrated that successful deprescribing initiatives for frail older adults can be a time-consuming process occurring over weeks that relies on input from an interprofessional team. Online education

modules have also been created for prescribers to learn more about successful deprescribing³⁰.

DISCUSSION

Our scoping review identified almost 60 resources designed to prevent, detect, or reverse the prescribing cascade. Authors from 14 countries published these resources. The majority were recently published, indicating the international relevance of the prescribing cascade concept and growing awareness of and concern about prescribing cascades as we strive to improve medication safety.

Most original investigations focused on older adults. Although prescribing cascades can occur in anyone receiving more than 1 drug therapy, regardless of age, prescribing cascades in older adults have received the most attention because they are more likely to have chronic conditions that require a number of drug therapies, and prescribing cascades are most common when multiple drug therapies are prescribed. Furthermore, general aging processes can mask drug-related adverse events, and causes of new symptoms (e.g., delirium) become increasingly difficult to attribute to medication.

The organizing framework used to guide our synthesis of preventing, detecting, and reversing prescribing cascades was useful to categorize the numerous heterogeneous strategies we found according to their relevance at different time points along the prescribing continuum. Prevention of the prescribing cascade begins before or during prescribing. Detection of prescribing cascades can take place during prescribing, when reviewing medications, or from population-level research. Reversal of prescribing cascades is a shared effort between clinicians and patients to reverse a prescribing cascade after detection. We identified resources with important practical strategies to assist at all stages, including prescribing cascade detection algorithms²², protocols²⁴, games¹⁷, and checklists⁴. Evaluations of these strategies found that their target groups received them favorably and showed efficacy in changing prescriber behavior by reducing medication burden in individuals²³. The novelty of these strategies is that they offer practical steps to implement in clinical practice to reduce prescribing cascades and problematic polypharmacy. Crucial points for prescribers are highlighted in Figure 3.

Of the resources included, those identifying reversal strategies were the most recently published. This can probably be attributed to recent interest in deprescribing. There are global deprescribing initiatives, an increase in research in the area, and widespread resource stewardship campaigns such as Choosing Wisely³¹. These efforts often identify prescribing cascades as major contributors to problematic polypharmacy and suggest deprescribing strategies to reverse them safely^{24,26,32}. As deprescribing initiatives gain traction, it is anticipated that incorporating of the prescribing cascade concept in resources designed to optimize prescribing, particularly for older adults, will grow.

Our scoping review of prescribing cascade resources provides a foundation from which this information can be further developed for widespread use in the healthcare system. The prescribing cascade concept is now more than 20 years old. Despite this, we found only 16 original investigations, with the majority published in the last 2 years of

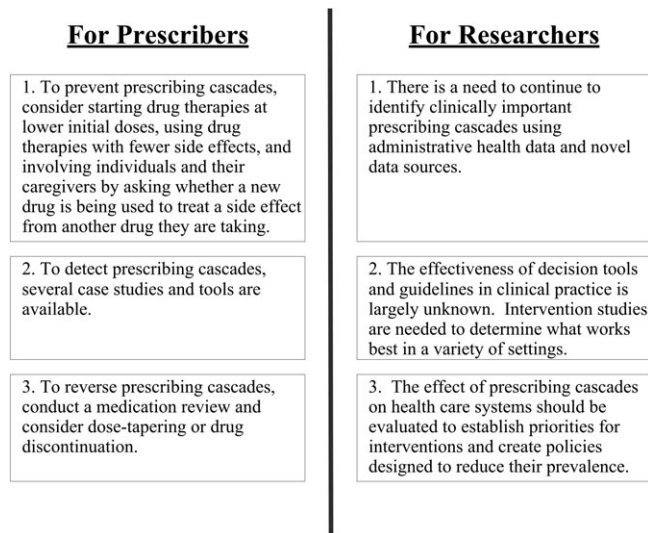


Figure 3. Crucial points for prescribers and researchers to prevent, detect, or reverse prescribing cascades.

our search. This suggests that there are clinically important prescribing cascades that have yet to be detected or characterized. As new drugs are developed, it will be important to continue this work to identify whether they trigger prescribing cascades. Particular emphasis should be placed on prevention to avoid initiation of prescribing cascades. Initiating a new drug therapy at a lower starting dose, considering drug therapies with fewer side effects, and involving individuals and their caregivers in asking whether a new drug is being used to treat a side effect from another drug they are taking are important strategies (Figure 3). The recent extension of the prescribing cascade concept to over-the-counter medications and medical devices provides opportunities to improve the accuracy with which the effect and cost of prescribing cascades are measured using innovative data sources^{3,18}.

Strategies to prevent, detect, and reverse prescribing cascades should be tested and evaluated for their effectiveness in clinical practice, particularly in the context of medically complex older adults with multimorbidity and associated polypharmacy. Three phases of moving information into clinical practice have been identified: innovation, testing, and expansion and spread³³. The innovation phase is the process of creating the new model or theory; in the testing phase, the effect of the model or theory is evaluated in a target setting; and the expansion and spread phase addresses how to expand the initiative beyond the initial setting and incorporate it broadly into clinical practice. It is likely that the majority of the resources included in this scoping review were in the innovation phase. As such, these strategies should continue to undergo rigorous testing, which could include large-scale initiatives to prevent and reduce prescribing cascades. These strategies may include developing ways to reduce prescribing cascades using electronic health records with clinical decision support and developing pragmatic trials targeting prescribers and their patients to evaluate the benefit of these initiatives in reducing prescribing cascades.

Finally, research is needed on the effects on health and health systems of these cascades to establish priorities for

interventions and policies designed to reduce the prevalence of prescribing cascades. Monitoring the prevalence and effects on health systems over time can help us evaluate the effectiveness of any widespread policies or guidelines designed to mitigate polypharmacy. A list of recommendations for researchers is provided in Figure 3.

There are several limitations to this study. First, our search strategy may not have captured all the resources describing prescribing cascades. We reviewed the resources identified with experts, and therefore it is unlikely that major resources were missed. We did not include studies describing prescribing cascades that did not provide a strategy to prevent, detect, or reverse a prescribing cascade. As such, we captured only part of the prescribing cascade literature. Furthermore, we predefined mutually exclusive categories of preventing, detecting, and reversing to organize and synthesize the resources retrieved in our scoping review. There is overlap between these categories, and we may therefore have underestimated the number of resources in each category. Finally, we wanted to capture all relevant resources and not exclude based on quality. As such, the quality of the resources was not evaluated.

Conclusion

Prescribing cascades are a recognized problem internationally. By learning from the range of resources to prevent, detect, and reverse prescribing cascades, this review contributes to improving drug prescribing, especially for older adults. As deprescribing initiatives gain traction, it is anticipated that raising awareness about the prescribing cascade concept in resources designed to optimize prescribing, particularly for older adults, will grow.

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Author Contributions: PAR conceived the idea and supervised the study. PAR designed the study. HB did the literature search. HB, NM, WW acquired the data. HB, NM, WW, LZ, PAR, RDS analyzed and interpreted data. HB, NM, RDS and PAR drafted the manuscript, with critical revisions for important intellectual content from all authors. All authors approved the final version of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplemental Appendix S1. Search Strategy, Resource Screening, and Data Extraction

Supplemental Appendix S2. Resources Describing Strategies to Prevent, Detect, or Reverse Prescribing Cascades According to Resource Type

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