


Assessing the Scope and Appropriateness of Prescribing Cascades

Lisa M. McCarthy, PharmD, MSc,^{*†‡}  Jessica D. Visentin, PharmD,^{*} and Paula A. Rochon, MD, MPH^{*‡§}

As originally defined, the term “prescribing cascade” describes a sequence of events that begins when an adverse drug event (ADE) occurs, is misinterpreted as a new medical condition, and a subsequent drug is then inadvertently prescribed to treat the new condition. We refine the definition to encompass both recognized and unrecognized ADEs because they can both contribute to problematic prescribing practices. In addition, we discuss that although prescribing cascades are most commonly viewed as problematic, they may be appropriate and therapeutically beneficial in certain clinical situations. We differentiate between appropriate and problematic prescribing cascades by adopting a similar approach to the framework proposed in the highly acclaimed King’s Fund report *Polypharmacy and Medicines Optimization*. Practical considerations are also presented to aid clinicians in preventing the propagation of problematic prescribing cascades within their clinical practice. Providing new perspectives on the scope and appropriateness of the prescribing cascade concept is an important step in describing clinically relevant cascades and in encouraging safe prescribing practices. *J Am Geriatr Soc* 00:1–4, 2019.

Key words: polypharmacy; prescribing cascade; medication safety; older adults

From the ^{*}Women’s College Research Institute, Women’s College Hospital, Toronto, Ontario, Canada; [†]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada; [‡]Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada; and the [§]Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Ontario, Canada.

Address correspondence to Lisa M. McCarthy, PharmD, MSc, Women’s College Research Institute at Women’s College Hospital, 76 Grenville Street, Toronto, Ontario, Canada, M5S 1B2; E-mail: lisa.mccarthy@utoronto.ca

Drs. McCarthy and Visentin contributed equally to this publication.

DOI: 10.1111/jgs.15800

In recent years, polypharmacy, known as the concurrent use of multiple medications by one individual, has become a well-recognized clinical phenomenon garnering the attention of clinicians and researchers internationally.¹ Global recognition of the importance of addressing polypharmacy is demonstrated by the widespread uptake of deprescribing protocols² and recent initiatives led by the World Health Organization to reduce severe, avoidable medication-related harm.³

Prescribing cascades are an important, yet underrecognized, contributor to polypharmacy.⁴ The term refers to a sequence of events that begins when an adverse drug event (ADE) is misinterpreted as a new medical condition, and a subsequent drug is then inadvertently prescribed to treat this ADE.^{5,6} As the term has gained increasing recognition, questions have arisen regarding nuances of the definition. We aim to (1) refine the prescribing cascade concept to include both unrecognized and recognized ADEs, and (2) differentiate between appropriate and problematic prescribing cascades by adopting a similar approach to the framework proposed in the King’s Fund report *Polypharmacy and Medicines Optimization*.¹

To address these objectives, we have systematically dissected the elements involved in the propagation of a prescribing cascade (Figure 1). A drug (drug A) is initially prescribed, leading to an ADE. This ADE is then assessed by the clinician and either recognized and correctly attributed to the offending drug (drug A) or not recognized and misinterpreted as a new medical condition or exacerbation of an underlying one. The clinician’s interpretation of the ADE directly informs his or her course of action. In the case of recognized ADEs, the offending drug (drug A) may be discontinued or dose reduced, or a subsequent drug (drug B) may be knowingly prescribed to combat a side effect (resulting in an intentional prescribing cascade). In the case of unrecognized ADEs, a subsequent drug (drug B) is unknowingly prescribed to treat what is thought to be new or worsening disease (resulting in an unintentional prescribing cascade). Table 1 summarizes the key definitions.

Although prescribing cascades that stem from the management of recognized ADEs were not included in the original definition, they are arguably equally important contributors to problematic prescribing. In situations where an

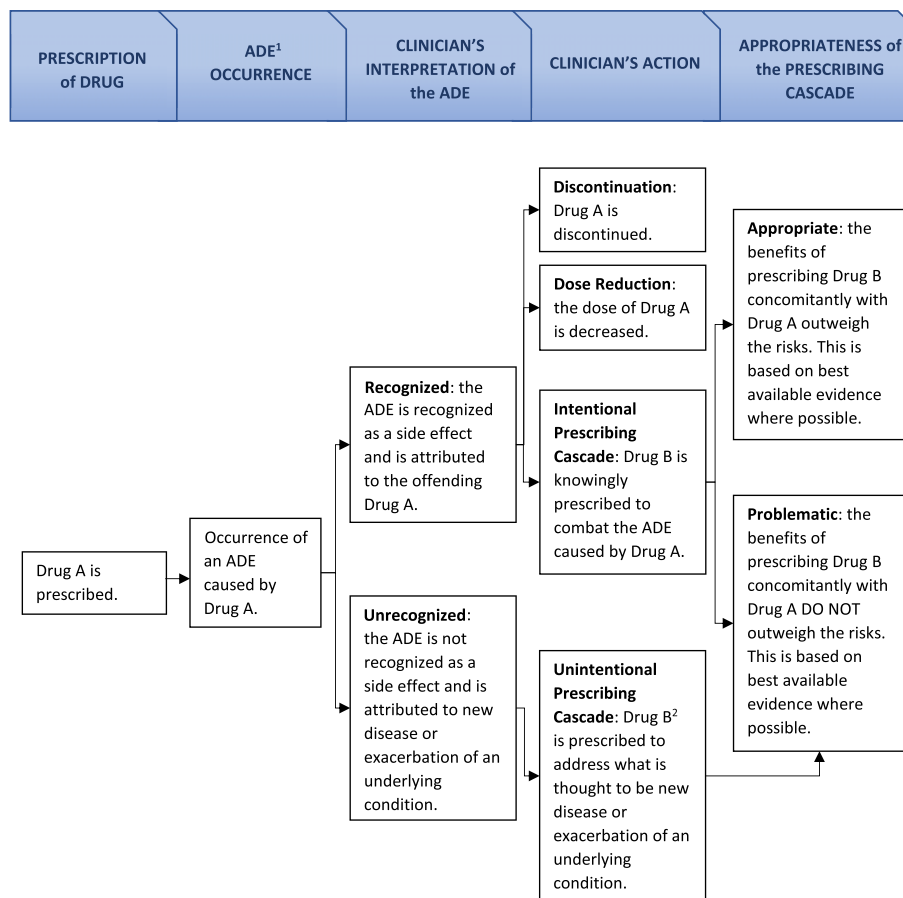


Figure 1. Propagation of appropriate and problematic prescribing cascades. ¹ADE, adverse drug event. ²Drug B could belong to a variety of different drug classes depending on how the presenting signs or symptoms of an unrecognized ADE are interpreted (ie, new disease vs exacerbation of an underlying condition). For example, a patient with dementia and benign prostatic hyperplasia (BPH) is prescribed a cholinesterase inhibitor (ChEI). The ChEI causes urinary frequency; however, the prescriber does not recognize it as an ADE. If the prescriber interprets urinary frequency as a new medical condition, an anticholinergic medication may be initiated for presumed overactive bladder. However, if the prescriber interprets these symptoms as an exacerbation of the patient's preexisting BPH, an α -blocker may instead be added to the patient's medication regimen.

ADE is recognized, there is an added layer of complexity. Once the ADE has been identified, clinicians are then required to assess the appropriateness of each therapy before deciding whether the benefits of propagating a prescribing cascade outweigh the risks. cursory risk-benefit assessments and inadequate documentation can promote problematic prescribing cascades.

To date, multiple reports of prescribing cascades have been published. Although these reports effectively highlight the harmful consequences of prescribing cascades, it is important to acknowledge that appropriate and therapeutically beneficial prescribing cascades also exist. This approach mirrors the framework proposed by the King's Fund report.¹ The 2013 report differentiates "appropriate polypharmacy" from "problematic polypharmacy" to dispel the common misconception that patient harm always ensues. The authors argue that the use of multiple medications can be beneficial in individuals with multimorbidity when medications have been optimized according to the best available evidence. Similarly, prescribing cascades can be either "appropriate" or "problematic" depending on the circumstances at hand.

This situation is illustrated in the following clinical vignette. A man in his 70s was diagnosed with early-stage

Alzheimer's disease and subsequently started on a cholinesterase inhibitor (ChEI). The patient had been tolerating ChEI therapy quite well; however, as the dose was titrated upward, he began to experience increased urinary frequency and urgency. The patient also reported several recent episodes of urinary incontinence. In this case, the clinicians recognized that the ChEI was likely a contributor to the urinary incontinence. Both the patient and his family were advised of the potential ADE and offered several management options including discontinuing or reducing the dose of the ChEI. However, the patient and his family were reluctant to alter the ChEI because they felt there had been some appreciable benefits in cognition and functional status. Nonpharmacologic strategies were initially implemented to try and combat his urinary symptoms; however, these interventions were largely ineffective. Given the patient's goals of care, he was started on a course of mirabegron because the benefits were considered to outweigh the risks at that point in time.

This case emphasizes that there is no one-size-fits-all approach to assessing the appropriateness of a prescribing cascade. Several overarching principles, discussed in detail elsewhere,^{6,7} are available to guide the assessment of appropriateness. In essence, these principles suggest that thorough

Table 1. Key definitions

Term	Definition
Intentional prescribing cascade	A sequence of events that begins when an ADE occurs, is recognized and attributed to the offending drug, and a subsequent drug is then intentionally prescribed to combat the ADE.
Unintentional prescribing cascade ¹	A sequence of events that begins when an ADE occurs and is unrecognized as related to the offending drug. Instead the sign or symptom is misinterpreted as a new medical condition (or exacerbation of an underlying one), and a subsequent drug is then inadvertently prescribed to treat the condition.
Appropriate polypharmacy	The concurrent use of multiple medications by one individual, when medication use has been optimized and when the medications are prescribed according to best evidence.
Problematic polypharmacy	The concurrent use of multiple medications by one individual, when medications are prescribed inappropriately or when the intended benefit of the medication is not realized.
Appropriate prescribing cascade	The benefits of propagating a prescribing cascade outweigh the risks. This is based on best available evidence where possible. Appropriate prescribing cascades are always intentional (see above definition).
Problematic prescribing cascade	The benefits of propagating a prescribing cascade do not outweigh the risks. This is based on best available evidence where possible. Problematic prescribing cascades may be intentional or unintentional (see above definition).

¹Consistent with the original prescribing cascade definition.
Abbreviation: ADE, adverse drug event.

examination of the risks and benefits of each medication involved in the cascade be completed before the patient's receipt of a subsequent drug. Even with this guidance, interpretations of prescribing cascades remain variable and depend on the clinical context. This is an important consideration when interpreting data from healthcare administrative repositories. Although population-level research is helpful in estimating the magnitude of a prescribing cascade, it can also obscure patient-specific circumstances and individual clinicians' thoughtful considerations. These thoughtful considerations do not always guarantee avoidance of harm to the patient, but in many circumstances they can differentiate an appropriate cascade from a problematic one.

As in the scenario just described, the use of an additional medication to combat ChEI-induced urinary incontinence is habitually discouraged. However, given the patient's goals of care and his promising response to the ChEI, the initiation of mirabegron was considered appropriate by the patient, his family, and all clinicians involved in his care. An anticholinergic medication was purposefully not prescribed to treat the urinary incontinence in this scenario, so as to avoid prescribing two medications with opposing mechanisms of action. In this case, the decision to propagate a prescribing cascade importantly focused on quality-of-life outcomes that were central to the patient's desires and consistent with his goals of care.

Table 2. Key considerations for clinicians in preventing problematic prescribing cascades

Category	Considerations
Management of the adverse drug event (ADE)	<ul style="list-style-type: none"> • Have the options of discontinuing, dose-reducing or switching the inciting drug (drug A) been thoroughly explored? Have nonpharmacologic strategies to address the ADE been reviewed? <ul style="list-style-type: none"> ◦ Consider documenting why these approaches are not viable options given the patient's current clinical situation.
Appropriateness of the intentional prescribing cascade	<ul style="list-style-type: none"> • Have the risks and benefits of adding a subsequent drug (drug B) to combat the ADE been assessed and reviewed with the patient? The risks associated with prescribing cascades are more often indolent and progressive, rather than imminent, observable consequences. Has the patient been informed of the potential long-term risks? • Does initiation of an intentional prescribing cascade align with the patient's goals of care? Is the intent of the prescribing cascade to improve quality of life or an outcome that is of importance to the patient? How does the patient feel about adding an additional medication to their existing regimen?
Ongoing assessment of the intentional prescribing cascade	<ul style="list-style-type: none"> • Is improvement in the ADE objectively measurable? If not, can the patient quantify their experience with the ADE (ie, rating on a scale of 0-10) or describe its impact on their function? <ul style="list-style-type: none"> ◦ Oftentimes assessment of benefit of the drug (drug B) is lost in translation between initial follow-up and ongoing assessment several weeks or months later. Documenting objective findings or concrete elements of the patient report can help determine if the intentional prescribing cascade is still appropriate. • Has the patient been informed that periodic follow-up will be required to assess the ongoing appropriateness of the subsequent drug (drug B)? Is the patient willing and able to attend follow-up appointments? <ul style="list-style-type: none"> ◦ When the subsequent drug (drug B) is initially prescribed, a follow-up visit should be booked with the patient to reassess appropriateness of the cascade.

This scenario also calls into question the importance of follow-up in assessing the ongoing appropriateness of a prescribing cascade. Although a cascade may be appropriate at one time in a patient's journey, the same medication may no longer be appropriate if therapy is not reassessed within a reasonable time frame. As in the illustrative case, the benefits of mirabegron may no longer outweigh the risks of therapy as the patient's social circumstances, ChEI therapy, concurrent medications, or comorbid conditions change. Regular follow-up and thorough documentation completed by a mutually agreed upon member of the healthcare team (eg, physician, pharmacist, nurse, etc) are required every time a prescribing cascade is initiated to review the ongoing appropriateness of therapy. A summary of key considerations for clinicians in preventing problematic prescribing cascades is presented in Table 2.

Expanding the scope of the prescribing cascade concept and acknowledging that prescribing cascades may be therapeutically beneficial in certain clinical situations can have direct implications on research and clinical practice. Exploring nuances of the prescribing cascade concept is an important step in describing clinically relevant cascades and in encouraging appropriate prescribing practices.

ACKNOWLEDGMENTS

The authors would like to thank Drs. Jerry H. Gurwitz, Nathan M. Stall, and Miles J. Luke for their critical review of this commentary. Dr. Rochon holds the Retired Teachers of Ontario (RTO/ERO) Chair in Geriatric Medicine at the University of Toronto.

Conflict of Interest: The authors have declared no conflicts of interest for this article.

Author Contributions: Drs. McCarthy and Visentin contributed equally to this publication. Drs. McCarthy, Visentin, and Rochon conceptualized the commentary. Drs. McCarthy and Visentin wrote the first draft, and Dr. Rochon provided iterative critical reviews. All authors read and approved the final manuscript.

Sponsor's Role: There was no sponsor for this article, and as such, no sponsor had a role in the creation of this submission or in the decision to submit the manuscript for publication.

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