



Original Research Paper

Informing a medical subject heading (MeSH) request: The ‘Prescribing cascades’ case study

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ABSTRACT

Background: ‘Prescribing cascades’ describes initiation of new treatments in response to adverse drug effects, often misinterpreted as new conditions. Although Medical Subject Headings (MeSH) enable accurate indexing and retrieval, no MeSH term exists for this concept. This study assessed the need for a dedicated MeSH term and its potential impact on indexing consistency.

Methods: A cross-sectional analysis was conducted using 139 articles from a published scoping review. PubMed metadata provided publication details and indexing status. MEDLINE-indexed articles were analyzed for MeSH attribution. Associations between the presence of keywords (“inapprop-”, “adverse”, “cascade”) in titles/abstracts and specific MeSH terms were quantified using odds ratios (OR) with 95% confidence intervals (CI) (R/RStudio).

Results: Of 139 articles included in the scoping review, 119 were indexed in PubMed and 106 in MEDLINE, with 1055 MeSH terms covering 313 unique terms. The most prevalent were “Drug-Related Side Effects and Adverse Reactions” (32.1%), “Polypharmacy” (30.2%), and “Inappropriate Prescribing” (26.4%). Indexing was manual in 47 cases, automated in 45, and curated in 14. After 2022, automated indexing reduced use of “Drug Interactions” and “Medication Errors.” Only three associations demonstrated predictive values: the root “inapprop-” in abstracts predicted the MeSH “Inappropriate Prescribing” (OR = 5.1 [95% CI 1.9–13.7]); “inapprop-” in titles for “Potentially Inappropriate Medication List” (OR = 204 [95% CI 9.1–4551.3]); and “adverse” in abstracts for “Drug-Related Side Effects and Adverse Reactions” (OR = 2.8 [95% CI 1.2–6.7]). The word “cascade” in titles was associated with “Drug-Related Side Effects and Adverse Reactions” (OR = 3.6 [95% CI 1.4–9.2]).

Conclusion: Current evidence does not support a dedicated MeSH for ‘prescribing cascades’ as existing descriptors are sufficient to capture its main dimensions. Further research should prioritize definitional consensus and compositional indexing strategies to enhance retrieval accuracy.

1. Introduction

The systematic organization of biomedical literature in PubMed relies on the Medical Subject Headings (MeSH), a controlled vocabulary developed by the U.S. National Library of Medicine (NLM) to ensure consistent indexing and accurate retrieval of biomedical knowledge, thereby supporting evidence synthesis and clinical decision-making.^{1,2} Initially created in the 1960s with around 4000 terms derived from library catalog headings, MeSH had grown by 2025 to include 30,000 descriptors used to index articles in MEDLINE. The vocabulary is updated annually by the NLM to reflect evolving scientific terminology,

synonyms, and linguistic variations, with new descriptors also open to suggestions from researchers, publishers, and users.¹ However, MeSH suggestions undergo a rigorous analysis by the MeSH staff. Previous studies reported three reasons why suggestions can be disregarded: the proposed pharmacy-specific MeSH could be created using a combination of already existing MeSH (cluster coding); the concept underlying the proposed MeSH was covered by an existing MeSH; and the proposed MeSH would cover a small number of articles, with no specific number of articles required to consider a new MeSH.³ To keep up with the rapidly increasing volume of literature worldwide, human indexing in MEDLINE was gradually replaced by a hybrid approach in 2011, combining human

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curation with the algorithmic Medical Text Indexer (MTI). In 2019, the NLM began large-scale experiments with fully automated indexing using MTIA, followed in 2024 by the deployment of MTIX, a neural network–based system designed to enhance performance. Since April 2022, all journals indexed in MEDLINE have been processed primarily through automated systems, with selective human curation.^{4,5} Subsequently, the NLM classifies the articles according to the three indexing methods: Manual (articles that had their MeSH selected by humans), Automated (articles with their MeSH entirely selected by a computer algorithm), and Curated (articles originally automatically indexed but then reviewed by humans). This shift toward automation further increases the importance of consistent and standardized terminology in titles and abstracts, as indexing outcomes are now more directly driven by textual signals.

Despite the potential benefits of automated indexing (i.e., efficiency and speed), different analyses reported poor results and negative effects on literature retrieval.^{6,7} Concepts without dedicated MeSH terms are vulnerable to incomplete or irregular retrieval. In the absence of a standardized MeSH term, researchers and clinicians may face difficulties in accessing the complete body of evidence, which can compromise both the integrity of systematic reviews and the translation of knowledge into healthcare practice^{8–13}. This gap is concerning especially for emerging clinical constructs such as ‘prescribing cascades’, where definitional ambiguity complicates recognition and management.¹⁴

‘Prescribing cascades’ were first conceptualized by Rochon and Gurwitz as sequences in which adverse drug effects are misinterpreted as new medical conditions, leading to the initiation of additional therapies.¹⁵ Since then, this definition has evolved to include both unintentional and intentional cascades, reflecting the complexity of pharmacotherapy in multimorbid, older populations.^{16,17} Despite this conceptual expansion, no dedicated MeSH term exists, meaning that the literature remains indexed under broad descriptors (e.g., ‘Drug-Related Side Effects and Adverse Reactions’, ‘Inappropriate Prescribing’). Dalton et al.’s recent scoping review 2025¹⁴ highlighted that this terminological heterogeneity is mirrored by substantial variation in published definitions, with less than half of the included studies adhering to the original concept of misinterpreted adverse effects. These authors also claim for the creation of a ‘Prescribing Cascades’ MeSH as a potential solution.

In this context, this study aims to assess the need for a dedicated ‘Prescribing Cascades’ MeSH term by analyzing how the articles included in Dalton et al.’s scoping review 2025¹⁴ are currently indexed and whether existing terms adequately capture this concept.

2. Methods

This is a cross-sectional study of the MeSH terms used to index the articles evaluated by Dalton et al., 2025¹⁴ aimed at describing how ‘prescribing cascades’ had been defined or conceptualized in the published literature. Dalton et al. conducted a robust scoping review based on a publicly available protocol (<https://osf.io/ysqbt/>) complying rigorous standards,¹⁸ which included a comprehensive (highly sensitive) search strategy using seven bibliographic databases. This scoping review screened 651 articles to find the 139 that describe “how the term ‘prescribing cascade’ has been defined or conceptualized in the published literature”. This dataset was considered sufficient for the present analysis because it represents the most updated and comprehensive synthesis of how prescribing cascades have been defined and discussed in the literature.

2.1. Data collection

A database containing the 139 articles cited in Table S1 of Appendix C of Dalton et al.¹⁴ was created. Articles were searched in PubMed and the metadata of those included in this bibliographic resource were extracted using the “Save citations to file” feature, both in PubMed and in PMID formats.

Metadata from the PubMed format file were used to populate the articles database. These data comprised publication year (from the DP field), article’s title (from the TI field), abstract (from the AB field), and all the MeSH terms attributed to each article (from MH field). Author names, Dalton et al.’s reference numbers, and the country of the lead author were extracted from Table S1 of Appendix C.

Using the PMID format file exported from PubMed, the XML files of these articles were extracted using the PubData2XML webpage (<https://pubmed2xl.com/xml/>). Using the package xml2 for R/RStudio, the information contained in the element “MedlineCitation” was extracted to obtain the indexing method from the information in the attribute “IndexingMethod” and the record status from the attribute “Status”. Two possible statuses indicating MEDLINE inclusion were recorded: MEDLINE and PubMed-not-MEDLINE. Three different indexing methods could exist for the records indexed in MEDLINE: Manual (indexed by humans), Automated (indexed by NLM MTIA algorithm) and Curated (human curated after automated indexing).

2.2. Data analysis

Descriptive analyses were conducted to describe the characteristics of the articles and their indexing characteristics, including the MeSH attributed to the articles by the NLM. Among the list of MeSH used to index included articles, the presence of those more related to the concept of ‘prescribing cascades’ considering the two characteristics of Rochon and Gurwitz concept (i.e., side effect and inappropriateness) was investigated. To evaluate the strength of the association between having one of those MeSH terms attributed and using the root “inapprop-” or the word “adverse” in titles or abstracts of the included articles, odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated.

Also, the association between the appearance of the MeSH terms and the root “inapprop-” or the word “adverse” contained in the definitions compiled by Dalton et al., 2025¹⁴ was investigated through OR and 95% CI. Finally, the association between the presence of the word “cascade” in titles or abstracts with the MeSH terms was explored. When a positive association between any MeSH and the word “cascade” was coincident with an association with “inapprop-” or adverse” words, a binary logistic regression was conducted.

3. Results

Among the 139 articles included in Dalton et al.’s study,¹⁴ 119 were indexed in PubMed, but only 106 indexed in MEDLINE and subsequently had MeSH attributed. These articles were published between 1997 and 2025, with leading authors from 18 different countries, being the U.S. (n = 42) and Canada (n = 22) the two most frequent.

The 106 articles were indexed with 1055 MeSH terms in total,

Table 1
Frequency of Medical Subject Headings related to ‘prescribing cascades’ used in the 106 articles included in Dalton et al.’s and indexed in MEDLINE.

MeSH	Created	Freq (%)	Manual	Automated	Curated
Drug-Related Side Effects and Adverse Reactions	2014	34 (32.1%)	14	14	6
Polypharmacy	1997	32 (30.2%)	21	8	3
Inappropriate Prescribing	2011	28 (26.4%)	11	12	5
Practice Patterns, Physicians'	1987	19 (17.9%)	12	5	2
Drug Interactions	1972	7 (6.6%)	5	0	2
Medication Errors	1967	6 (5.7%)	5	0	1
Deprescriptions	2016	5 (4.7%)	0	2	3
Potentially Inappropriate Medication List	2016	3 (2.8%)	1	2	0

corresponding to 313 different MeSH terms. The four more prevalent MeSH terms were generic terms (i.e., Humans, Aged, Female, and Male). Table 1 presents the prevalence of the 8 MeSH terms used to index the articles and related to the topic of ‘prescribing cascades’. Only three of these terms appeared in more than 20% of the articles, namely “Drug-Related Side Effects and Adverse Reactions”, “Polypharmacy”, and “Inappropriate Prescribing”.

Of the 106 Dalton et al.’s articles, 47 were manually indexed (by humans), 45 automatically (by computerized algorithms), and 14 were humanly curated after automatically indexed. The indexing method was associated with differences in MeSH attribution patterns. After the full implementation of the automated indexing process (2022), two MeSH terms decreased their appearance rate, namely “Drug Interactions” and “Medication Errors” that were only used in articles humanly curated after computerized automated indexing (Supplementary material).

Among the definitions of ‘prescribing cascades’ compiled from the 106 articles, 16 (21.7%) contained the root “inapprop-” and 83 (78.3%) contained the word “adverse”. Also, these articles, 22 (20.8%) contained “inapprop-” in the abstract and 3 (2.8%) in the title, while 50 (47.2%) contained the word “adverse” in the abstract and 4 (2.9%) in the title. The word “cascade” appeared in 79 abstracts (74.5%) and 58 titles (54.7%).

Table 2 presents the prevalence of MeSH attributed to the Dalton et al.’s selected articles when they have the root “inapprop-” or the word “adverse” in their titles and abstracts. Three MeSH terms closely related to Rochon and Gurwitz definition of prescribing cascades showed the highest prevalences. Having these terms in the titles resulted in higher prevalences of MeSH attribution than having them in the abstracts. The strength of these associations was summarized using ORs and 95% CI – see Fig. 1. Only three associations showed any significant predictive power: the root “inapprop-” in abstract for the MeSH “Inappropriate Prescribing” (OR = 5.1; 95%CI 1.9:13.7); the root “inapprop-” in title for the MeSH “Potentially Inappropriate Medication List” (OR = 204; 95% CI 9.1:4551.3); and the word “adverse” in the abstract for the MeSH “Drug-Related Side Effects and Adverse Reactions” (OR = 2.8; 95%CI 1.2:6.7).

Table 3 presents the prevalence of the eight MeSH terms related to the concept of ‘prescribing cascades’ among the MEDLINE records corresponding to Dalton et al.’s selected articles. Only the MeSH term “Drug-Related Side Effects and Adverse Reactions” was associated with the existence of the word “cascade” in the title of the articles (OR = 3.3; 95%CI 1.3:8.7). To identify the potential confounder of the word “adverse”, a logistic regression showed that both words have independent association with the attribution of the MeSH “Drug-Related Side Effects and Adverse Reactions”: “cascade” in title and OR = 3.626 (95%

CI 1.431:9.186) and “adverse” in abstract OR = 3.200 (95%CI 1.313:7.799).

4. Discussion

The findings of this cross-sectional study assessing the articles included by Dalton et al., 2025¹⁴ highlight an important challenge in biomedical indexing: the need to capture emerging clinical concepts while preserving the coherence of the MeSH thesaurus as a controlled vocabulary. Although the concept of ‘prescribing cascades’ has gained recognition in clinical practice and research,^{19,20} the current evidence does not support its inclusion as a standalone MeSH term.

The expansion of MeSH terms should remain judicious. With more than 30,000 descriptors already included,¹ the vocabulary must balance specificity with usability. An indiscriminate addition of new terms may result in a controlled indexing tool becoming a complete language system, complicating both indexer decision-making and literature retrieval. This has been observed in other cases where researchers have advocated for new MeSH terms, including in oncology,²¹ molecular biology²² and pharmacy^{23,24} fields. These examples highlight the importance of establishing definitional clarity and widespread adoption prior to a request for MeSH inclusion. As highlighted by Chute et al., 1998²⁵, terminologies must avoid redundancy, maintain non-overlapping representations, and support compositional use. If every nuanced concept were granted a unique descriptor, the system would lose the efficiency and standardization that underpin its value. Additionally, one should consider that modern approaches to biomedical terminology increasingly rely on compositional models,²⁶ in which existing atomic terms can be combined to create more precise meanings. In the case of prescribing cascades, existing MeSH descriptors such as “Inappropriate Prescribing” and “Drug-Related Side Effects and Adverse Reactions” already provide sufficient indexing foundations, a conclusion supported by the present study showing that the presence of these terms in titles and abstracts strongly influenced indexing outcomes. Moreover, when used in combination with “Polypharmacy,” these terms can successfully capture the dimensions of ‘prescribing cascades’ without requiring the creation of a new heading.

Compositional indexing not only reduces the number of potential MeSH terms required but also facilitates the retrieval of literature on closely related concepts and facilitates the automatic exploding feature of PubMed.¹³ Creating a Prescribing Cascades MeSH term could identify articles about prescribing cascades and prevent indexing these articles with other MeSH terms that identify related topics. Therefore, searching for articles about inappropriate prescribing, which should include articles about prescribing cascades, would require using both MeSH terms. However, indexing articles about prescribing cascades with the two MeSH terms (“Inappropriate Prescribing” and “Drug-Related Side Effects and Adverse Reactions”) allows these articles to be retrieved when either of these two MeSH terms is used in the search.

Also, he literature itself lacks definitional consensus of ‘prescribing cascades’. Dalton et al.’s scoping review of 139 publications demonstrated substantial heterogeneity in how ‘prescribing cascades’ is defined, with fewer than half of studies adhering to the original definition centered on misinterpretation of adverse drug effects. Variations include distinctions between intentional and unintentional cascades, appropriate versus inappropriate cascades, and even extensions to over-the-counter products and diagnostic testing^{15–17}. This definitional variability challenges the rationale for introducing a new dedicated MeSH term, since robust and uniform use of a term is a prerequisite for any addition to a controlled vocabulary. In fact, we found a dispersion in the MeSH attributed to these articles (no MeSH was used in more than one third of the articles), reinforcing that without consensus, indexing would remain inconsistent, and retrieval fragmented.

An additional concern is that the current inconsistency in how ‘prescribing cascades’ is used in the literature directly contributes to poor indexing performance. Examining the articles included in Dalton

Table 2
Prevalence of Medical Subject Headings related to ‘prescribing cascades’ concept when inapprop- or adverse appeared in titles or abstracts of included articles.

MeSH terms N (%)	Title		Abstract	
	Inapprop- N = 3	Adverse N = 4	Inapprop-N = 22	Adverse N = 50
Drug-Related Side Effects and Adverse Reactions	1 (33.3%)	3 (75.0%)	5 (22.7%)	22 (44.0%)
Polypharmacy	1 (33.3%)	1 (25.0%)	10 (45.5%)	17 (34.0%)
Inappropriate Prescribing	2 (66.7%)	0	12 (54.5%)	14 (28.0%)
Practice Patterns, Physicians'	0	2 (50.0%)	4 (18.2%)	11 (22.0%)
Drug Interactions	0	0	3 (13.6%)	7 (14.0%)
Medication Errors	0	0	1 (4.5%)	3 (6.0%)
Deprescriptions	0	0	2 (9.1%)	4 (8.0%)
Potentially Inappropriate Medication List	2 (66.7%)	0	1 (4.5%)	1 (2.0%)

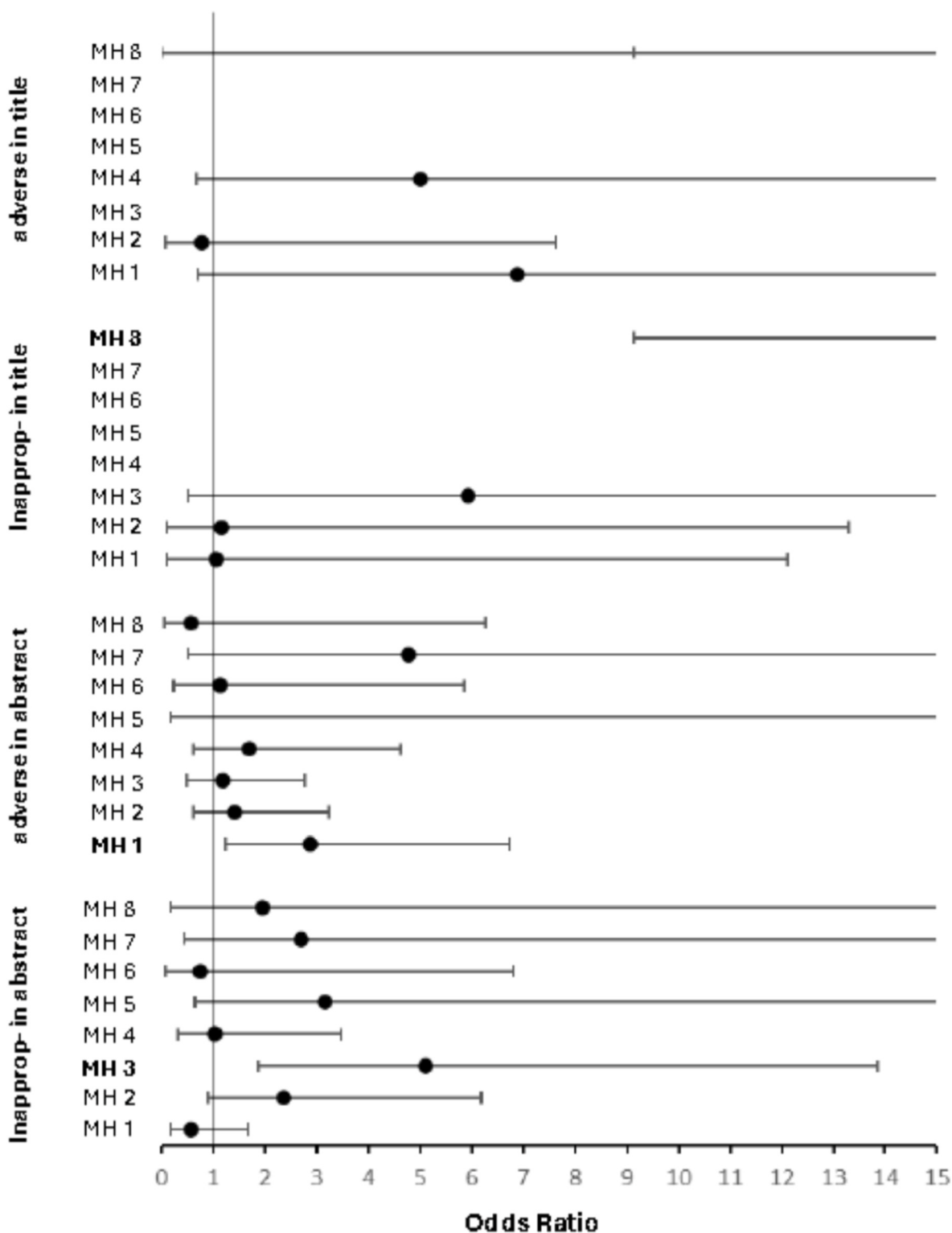


Fig. 1. Predictive power of “inapprop-” and “adverse” in title and abstract for MeSH attribution. MH01: Drug-Related Side Effects and Adverse Reactions; MH02: Polypharmacy; MH03: Inappropriate Prescribing; MH04: Practice Patterns, Physicians; MH05: Drug Interactions; MH06: Medication Errors; MH07: Deprescriptions; MH08: Potentially Inappropriate Medication List.

et al., 2025¹⁴, no single MeSH term was consistently applied, and more than one third of publications were not indexed with any directly relevant term. While observational studies cannot usually establish causality using ORs, in the MeSH attribution process there is a direct, deterministic relationship between terms in titles and abstracts and indexing outcomes. This applies both to previous manual indexing and to the

current automated systems. Therefore, the observed dispersion in MeSH assignment is not a failure of the indexing process itself, but rather a reflection of inconsistent terminology used by authors. This reinforces the guidance of the Granada Statements²⁷ created by the International Collaboration of Pharmacy Journal Editors (ICPJE),²⁸ which explicitly recommend the appropriate use of standardized terminology in titles

Table 3
Prevalence Medical Subject Headings related to ‘prescribing cascades’ when “cascade” appeared in titles or abstracts of the included articles.

MeSH terms	“cascade” in title (n = 58)		“cascade” in abstract (n = 79)	
	N (%)	OR (95% CI)	N (%)	OR (95%CI)
Drug-Related Side Effects and Adverse Reactions	25 (43.1%)	3.3 (1.3:8.0)	26 (32.9%)	1.2 (0.5:3.1)
Polypharmacy	14 (24.1%)	0.5 (0.2:1.2)	25 (31.6%)	1.3 (0.5:3.5)
Inappropriate Prescribing	18 (31.0%)	1.7 (0.7:4.2)	21 (26.6%)	1.0 (0.4:2.8)
Practice Patterns, Physicians'	10 (17.2%)	0.9 (0.3:2.4)	16 (20.3%)	2.0 (0.5:7.6)
Drug Interactions	0	–	7 (8.9%)	26.3 (0.1:13703.5)
Medication Errors	4 (6.9%)	1.7 (0.3:9.7)	4 (5.1%)	0.7 (0.1:3.9)
Deprescriptions	2 (3.4%)	0.5 (0.1:3.3)	4 (5.1%)	1.4 (0.1:13.0)
Potentially Inappropriate Medication List	1 (1.7%)	0.4 (0.0:4.6)	1 (1.3%)	0.2 (0.0:1.8)

and abstracts to improve indexing and retrieval (see section “The appropriate use of terminology in publishing”, recommendations number 3 and 4).²⁷

Studies have reported a poor standardization in pharmacy-related terminology. Drug safety terminology,²⁹ but especially the term drug-related problems, central in the initial stages of pharmaceutical care, are examples of conceptual confusion,³⁰ which led to an inconsistent use.³¹ Even more importantly, terms that describe pharmacist services and their integration into healthcare teams are used inconsistently^{32–34}. The immediate consequence of this lack of definitional clarity is a weak set of pharmacy-specific MeSH,²³ together with poor indexing.^{35,36} Another consequence of the inconsistent use of terms in pharmacy is the creation of ambiguous and redundant MeSH terms. This occurred with the concept of medication review and the two different MeSH terms that have unclear differences: “Drug Utilization Review” and “Medication Review”. The definitions of these two MeSH provided by the NLM are confusing, which led to an inaccurate attribution of the two MeSH terms. Despite its definition mentioning Medicaid’s drug utilization review programs, the MeSH Drug Utilization Review is commonly used for pharmacoepidemiologic studies that are not related to the prospective (ProDUR) or retrospective (RetroDUR) drug utilization reviews that Medicaid mandated in 1993. This MeSH term has been used for articles with “medication review” in the title or abstract.

Since 2022, PubMed automated indexing has been a reality that editors, authors, and researchers must accept. Understanding and assessing how to obtain the greatest benefit from the system and getting the most appropriate MeSH terms attributed should be a priority among all the actors. Studies demonstrated that pharmacy practice is underconsidered in MEDLINE,³⁷ which reflects in the poor MeSH indexing. However, learning how the algorithms select MeSH terms, and writing titles and abstracts wisely may increase the visibility of the field. Importantly, our findings show that the dispersion in MeSH attribution observed across the analyzed articles is not primarily attributable to the transition toward automated indexing. Instead, it reflects persistent inconsistency in the terminology used by authors in titles and abstracts, which affects both manual and automated indexing processes.

To increase the accuracy of automated indexing systems and to ensure a more consistent MeSH attribution, MeSH thesaurus use Concepts (the bearers of linguistic meaning in MeSH as defined by a <ScopeNote>), being the MeSH Descriptor identified as Preferred Concept.³⁸ For instance, after the request of the “Pharmacist–Patient Relations” MeSH²³ the NLM decided to include this term as a Concept of the MeSH “Professional–Patient Relations”.³ So, as a note to NLM MeSH

staff, ‘prescribing cascades’ could be included as an additional Concept (i.e., Narrower) under the Descriptor [i.e., Preferred concept] Inappropriate Prescribing, using the original Rochon and Gurwitz’s definition as <ScopeNote> (i.e., Initiation of additional therapies after misinterpreting adverse drug effects are as new medical conditions).¹⁵ This concept would prompt automated indexing systems to assign the MeSH term Inappropriate Prescribing to papers that use the term ‘prescribing cascades’ in their titles or abstracts.

Several actions could be taken to improve the consistent use of terminology. Pharmacists undergraduate, but more important, postgraduate training should include semiotics courses. Journal editors could include in the instructions for authors the preferred terms for concepts related to the area of journal’s scope and reviewers should enforce their consistent use. And researchers, although tempted to create new and more specific terms, should balance the benefits of the increased specificity with the inconveniences of the inconsistency.

This study has some limitations. Its cross-sectional design prevents assessment of temporal trends in MeSH use and indexing practices. The analysis relied on published articles included in Dalton et al. (2025) and, although this was the most comprehensive scoping review about the concept of prescribing cascades, it may not capture all relevant literature. The analysis relied exclusively on PubMed metadata, which may restrict the extrapolation of results to other bibliographic databases or indexing contexts. Therefore, the conclusions of this study are specific to the concept of prescribing cascades and should not be extrapolated to other emerging clinical constructs.

5. Conclusion

Overall, this study suggests that proposing a dedicated MeSH term for ‘prescribing cascades’ is not the best option. Rather than expanding the thesaurus, efforts should focus on consolidating a shared definition of the concept, and encouraging the consistent use of existing MeSH terms in titles and abstracts and, thus, leveraging compositional indexing strategies to ensure accurate retrieval. This could be achieved by increasing the use of terms like inappropriate prescribing, adverse effects, or polypharmacy in titles and abstracts, which lead automated indexing systems to select existing MeSH terms like “Inappropriate Prescribing”, “Drug-Related Side Effects and Adverse Reactions”, and “Polypharmacy”. Also, the inclusion by the NLM of ‘Prescribing Cascades’ as a Concept of the Descriptor “Inappropriate Prescribing” would increase the accuracy of NLM’s automated indexing systems.

CRediT authorship contribution statement

Fernando Fernandez-Llimos: Writing – review & editing, Writing – original draft, Validation, Methodology, Formal analysis, Data curation, Conceptualization. **Fernanda S. Tonin:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization.

Ethical approval statement

This study did not involve human participants or animals and therefore did not require institutional ethics approval.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Fernando Fernandez-Llimos reports was provided by University of Porto. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sapharm.2026.02.009>.

Data availability

The data underlying this article are available in the article and in its online supplementary material. Further information can be shared at reasonable request to the corresponding author.

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