Failure to Reach a Consensus in Polypharmacy Definition: An Obstacle to Measuring Risks and Impacts-Results of a Literature Review

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Therapeutics and Clinical Risk Management

Dovepress
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REVIEW

Failure to Reach a Consensus in Polypharmacy Definition: An Obstacle to Measuring Risks and Impacts—Results of a Literature Review

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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Introduction: The risk of polypharmacy is on the rise in most industrialized countries, threatening to burden their health systems. Although many definitions exist and numerous concepts are found in literature as synonyms, the phenomenon of polypharmacy remains poorly defined. The aim of this literature review is to provide an overview of available definitions of polypharmacy, to analyse their convergences and divergences and to discuss the consequences on the assessment of the problem.

Methods: A literature review was conducted to identify all published systematic reviews on definitions of polypharmacy available via Scopus and Pubmed databases. The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to appraise the methodological quality of the selected reviews. Available definitions and other characteristics were extracted; summarised in a table and analysed.

Results: Six systematic reviews were identified. They were published between 2000 and 2018. Three focussed on definitions of polypharmacy in the elderly; two in the general population and one in children. The strategy adopted in reviews is more rigorous in the most recent ones. However, they remain, at best, partially exhaustive. The definitions found in the literature used two main approaches, either (i) quantitative, applying varying thresholds and types of polypharmacy based on the number of medications being taken by the patient (ii) qualitative, based on the clinical indications and effects of a given drug regimen, with a growing number of characteristics to describe polypharmacy. The term "inappropriate" is increasingly associated with polypharmacy especially in studies that aimed to use this definition to identify possible solutions for healthcare providers in the field related to aging.

Conclusion: This review confirms a high variability and an evolution in the approaches defining "polypharmacy" in the absence of a consensus following standardized criteria. That makes it very difficult to estimate and measure the outcomes associated with this phenomenon.

Keywords: polypharmacy, definition, literature review

Introduction

The increasing life expectancy, the rising prevalence of chronic diseases and multimorbidity and the growing range of therapies are currently challenging public health in most industrialized countries and leading to increased risk of polypharmacy. This phenomenon, which is on the rise today, affects the elderly and could seriously threaten health systems. Despite this, there is no consensus definition for polypharmacy. The World Health Organization (WHO) defines polypharmacy as "the administration of many drugs at the same time or the administration of an

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DovePress
http://doi.org/10.2147/TCRM.S214187

excessive number of drugs".[1] Whether in practice or in research, this term has numerous meanings and many terms and concepts are used in the literature interchangeably as synonyms for "polypharmacy". This vagueness in polypharmacy definition creates confusion and makes it difficult to assess the extent of the problem, to measure its consequences and to search for solutions. In order to identify and apply relevant knowledge and effective interventions on polypharmacy, it is necessary to assess existing discrepancies in the literature. Given that systematic reviews are recognized as very useful in identifying evidence and basing health care on it,[2] we conducted an extensive search of systematic reviews to answer the following question: how is the term "polypharmacy" defined and how it is used in the literature?

The results of a very recent review were published at the end of 2017 and provide a very precise quantitative summary of the existing definitions for polypharmacy.[3] By using the results of this work and all other systematic reviews found, our literature review aims to provide an overview of the different approaches adopted, their evolution over time, the convergences and divergences of their results and to discuss their consequences on the evaluation of the problem.

Methods

A literature review was conducted to find all published systematic reviews on polypharmacy definitions. Scopus and Pubmed databases were searched from inception to December 2018 using keywords: "polypharmacy" and "definition".

Selection of Articles

Inclusion criteria were as followed: (a) systematic reviews focusing on polypharmacy definition; (b) systematic reviews addressing polypharmacy issues and including also polypharmacy definitions allowing for relevant data extraction; (c) publications in English or French.

A first selection was conducted based on titles and abstracts followed by a second selection on full text. The Assessment of Multiple Systematic Reviews (AMSTAR) tool was used to appraise the methodological quality of the selected reviews.[4] The 16 elements leading to its assessment criteria provide a reliable basis for evaluating systematic reviews of randomized and non-randomized controlled studies.[2] Some criteria were not relevant for our study, particularly those related to meta-analyses and risks of bias (on the table = NA for Not Applicable). Possible answers were "Yes" "partial Yes" "No" or "NP" when the information was not provided.

Data Analysis

The selected articles were analysed through a full-text reading and the following characteristics were extracted: author, author's country, year of publication, title, aim and purpose, review method (consulted databases, keywords, period), number of studies analysed, concerned population. Finally, all elements related to polypharmacy definition were also extracted in order to analyse convergences and divergences.

Results

Analyses and results are presented below in four main sections:

Selection of Articles

Ninety-nine articles were initially identified; among which 79 were considered irrelevant after titles and abstract reading (not systematic review, lack of a focus on polypharmacy definition; no other relevant definition elements; research protocol). Twenty were selected for full-text reading. Finally, only five reviews were selected after full-text reading and one paper mentioned in the selected reviews was manually retrieved. Figure 1 illustrates the review flow chart (see Figure 1)

Description of Included Reviews

Five reviews were in English and one in French. They were published between June 2000 and November 2018. Of the six reviews selected, three focussed on the elderly (one on elderly,[5] one on people aged 65 and over[6] and one people aged 60 and over[7]). Two others defined polypharmacy in the general population[3,8] and 1 review, the most recent, focused on paediatric polypharmacy.[9] The studies included in these included reviews were published between 1985 and July 2017.

Quality Assessment

The methodology used in reviews was analysed using the AMSTAR grid. However, the score provided by the AMSTAR tool was not calculated. Instead, available information was summarised in a table providing some indications on the quality of the methodology used in each review (Table 1). The strategy adopted in these reviews has evolved and is more rigorous in the most recent reviews. However, they remain, at best, partially exhaustive.

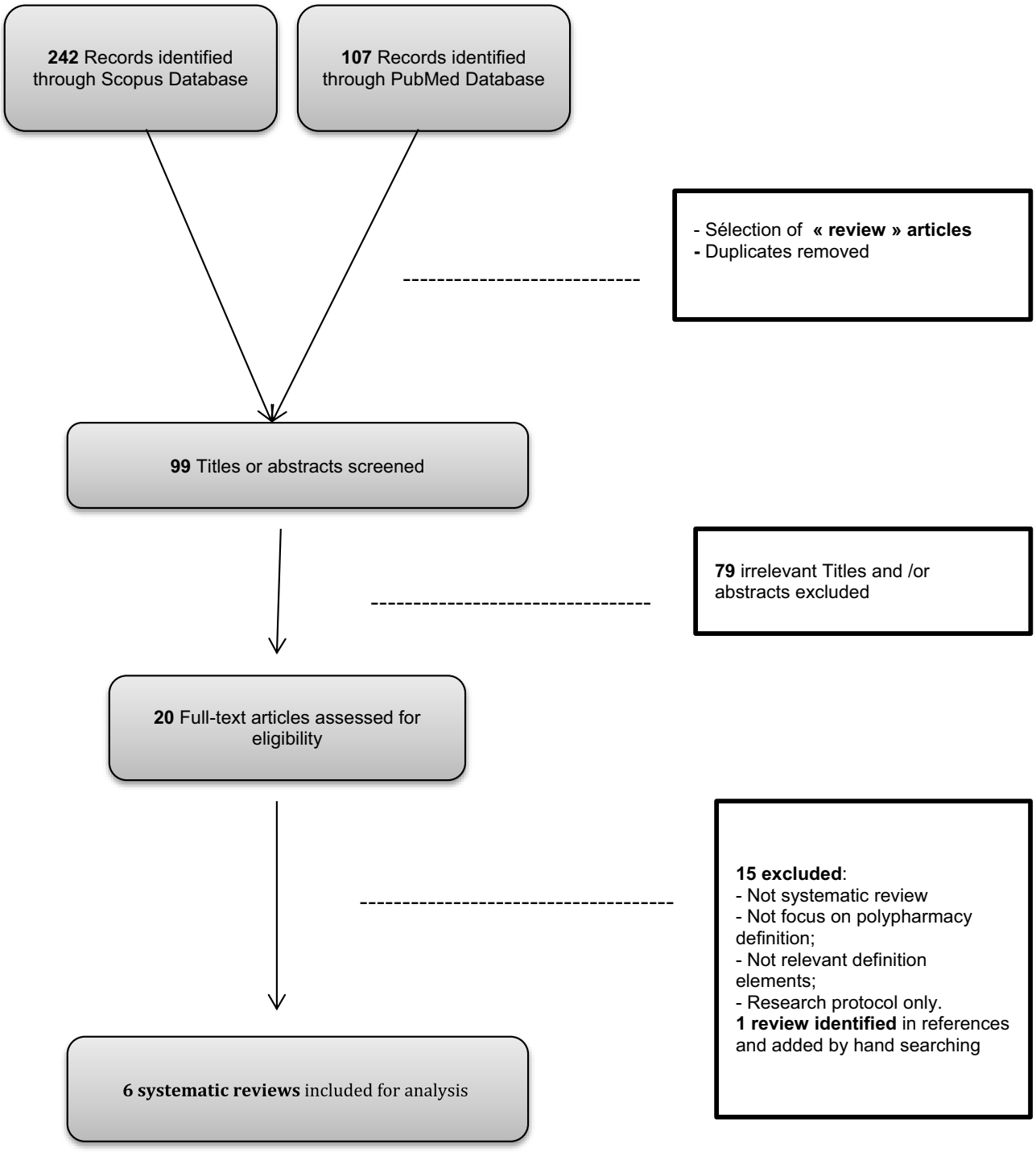

Figure 1 Flow chart for review of systematic reviews of polypharmacy definition.

Definition of Polypharmacy

The analysis of the selected reviews provided data on different ways in which polypharmacy was defined in the literature. As the content varied from one review to another (quantitative and/or descriptive synthesis, table or narrative text), th e extracted definition elements have been summarised in a table (See Table 2).

Towards Two Approaches to Define Polypharmacy

Among the reviews that we excluded because they were not systematic, some presented nevertheless interesting summaries of existing polypharmacy definitions.[10–13] The first of these, which is important to mention because it is cited as a reference in most of the works studied, was

Table 1 Quality Assessment Using the AMSTAR Tool

	Bakaki et al 2018[9]	Masnoon et al 2017[3]	Monégat et al 2014[8]	Bushardt et al 2008[5]	Fulton et al 2003[7]	Veehof et al 2000[6]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	NA					
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review	Yes	Yes	Partial Yes	Partial Yes	Yes	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes	Yes	No	No	No
4. Did the review authors use a comprehensive literature search strategy?	Partial Yes	Partial Yes	Partial Yes	No	Partial Yes	Partial Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes	Yes	NP	NP	NP
6. Did the review authors perform data extraction in duplicate?	Yes	Yes	NP	NP	NP	NP
7. Did the review authors provide a list of excluded studies and justify the exclusions?	Yes	Yes	No	No	Partial Yes	Partial Yes
8. Did the review authors describe the included studies in adequate detail?	Yes (n=363)	Yes (n=110)	No (n=34)	No (n=11)	Yes (n=16)	Yes (n=143)
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	NA					
10. Did the review authors report on the sources of funding for the studies included in the review?						
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?						
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?						
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?						
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes	Yes	Yes	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA					
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes	No	No	No	No

Table 2 Definitions of Polypharmacy

Author/ Year/ Country/	Title /Aim/Purpose	Sources/Method/ Period/ Number of Studies	Population	Polypharmacy Definitions
Bakaki et al[9] 2018 *(USA)* *PLoS ONE*	Defining pediatric polypharmacy: A scoping review. To describe definitions and terminology of pediatric polypharmacy.	(Conforms to the PRISMA checklist.) MEDLINE, PubMed, EMBASE, CINAHL, PsycINFO, Cochrane CENTRAL, and the Web of Science Core Collection databases were searched for English language articles with the concepts of "polypharmacy" and "children". Data were extracted about study characteristics, polypharmacy terms and definitions from qualifying studies, and were synthesized by disease conditions. From inception to October 2016 and was updated on July 11, 2017 (n= 363 studies included)	Children	324 studies provided numeric definitions, 131 specified duration of polypharmacy, and 162 explicitly defined it. Over 81% (n = 295) of the studies defined polypharmacy as two or more medications or therapeutic classes. The most common comprehensive definitions of pediatric polypharmacy included: two or more concurrent medications for 1 day (n = 41), two or more concurrent medications for 31 days (n = 15), and two or more sequential medications over one year (n = 12). Commonly used terms included polypharmacy, polytherapy, combination pharmacotherapy, average number, and concomitant medications. The term polypharmacy was more common in psychiatry literature while epilepsy literature favored the term polytherapy. This review found 162 studies that offered 203 distinct definitions of polypharmacy in the text: Only 19% (n = 35 outpatient, 3 inpatient) of the text definitions provided both a medication threshold number and a period A list of all 203 text definitions is available at the journal website

(*Continued*)

Table 2 (Continued).

Author/ Year/ Country/	Title /Aim/Purpose	Sources/Method/ Period/ Number of Studies	Population	Polypharmacy Definitions
Masnoon et al[3] 2017 *(Australia)* *BMC Geriatrics*	What is polypharmacy? A systematic review of definitions. To explore the definitions in existing literature. Additionally, to explore whether articles differentiated between appropriate and inappropriate polypharmacy and how this distinction was made.	(Conforms to the PRISMA checklist).MEDLINE (Ovid), EMBASE and Cochrane. Grey literature. Between 1st January 2000 and 30th May 2016 Published in English, (n=110 studies included)	All	A total of 138 definitions and associated terms. Definitions were categorised as: 111 Numerical only (using the number of medications to define polypharmacy): a wide range of variability in the definitions as well as associated terms (minor, moderate, major), the most commonly used term was "polypharmacy" but there was variation with regard to the actual definition of polypharmacy, which ranged from 2 or more medications to 11 or more medications. The most commonly used definition was 5 or more medication daily (51 studies). The second most common definition was 6 or more medications (10 studies). Only one study defined polypharmacy as the number of drug classes used by patient. 15 Numerical with an associated: Duration of therapy (11 studies): ranged from use of two or more medications for more than 240 days ("long term use") to five to nine medications used for 90 days or more. or healthcare setting (4 studies): included the use of five or more medications at hospital discharge, and the use of 10 or more medications during hospital stay. 12 Descriptive (using a brief description to define polypharmacy) as: Patients visiting multiple pharmacies to obtain medications; Co-prescribing multiple medications; Simultaneous and long term use of different drugs by the same individual; Polypharmacy definition ranges from the use of a large number of medications, to the use of potentially inappropriate medications, medication underuse and medication duplication; Potentially inappropriate medications; Use of multiple medications concurrently and the use of additional medications to correct adverse effects; Use of medications which are not clinically indicated. More drugs being prescribed or taken than are clinically appropriate in the context of a patient's comorbidities. (Some studies used different wording but conveyed the same definition ex: Coprescribing multiple medications and Simultaneous and long term use of different drugs by the same individual).

				7 studies defined appropriate or rational polypharmacy, or recognised the distinction between appropriate and inappropriate medications: defined polypharmacy using a brief description only (3 studies) or used a brief description and polypharmacy tools such as the Beers criteria and the Medication Appropriateness Index (MAI) (4 studies). (None of the studies explicitly identified the need to distinguish between appropriate and inappropriate polypharmacy based on the pharmacology of medications involved, how they interact with each other and comorbidities for a specific patient). Only one of the 110 studies included in the review highlighted the inconsistencies in the definitions of polypharmacy in the literature and suggested that polypharmacy be defined as "patients visiting multiple pharmacies which may be associated with safety concerns relating to potential outcomes such as medication duplication, drug-drug interactions and adverse effects".
Monégat et al[8] 2014 *(France)* *Questions d'économie de la Santé*	Polypharmacy: Definitions, Measurement and Stakes Involved Review of the Literature and Measurement Tests Based on a review of the literature, different definitions of polypharmacy were identified and the measurement of polypharmacy was examined according to different thresholds.	The review of the literature was carried out using the Medline and Gediweb databases. Completed with research based on references included in selected articles. The following key words were used to designate polypharmacy: "polypharmacy", "polymedication", "polyprescription", "multimedication", "multiprescription". Inclusion criteria were: articles or literature reviews on the definition and measurement of polypharmacy, studies on the prevalence of polypharmacy (excluding polypharmacy centered on a single therapeutic class or pathology) and articles in French or in English. Between 2000 and 2013 (n= 34 studies included)	All	Defined by the World Health Organisation as "the administration of many drugs at the same time or the administration of an excessive number of drugs" Notion of drug misuse: Polypharmacy refers to the administration of more drugs than clinically necessary. By extension, polypharmacy is said to be "appropriate" when the prescription of numerous medications is justified, and "inappropriate" when wrongly or indiscriminately prescribed. According to the time slots used to measure polypharmacy: Simultaneous polypharmacy: Corresponds to the number of drugs concurrently taken by a patient on a given day. A variant of this definition imposes that the simultaneous use of numerous medications should be prolonged through time; at least 60 consecutive days quarterly, for example.

(*Continued*)

Table 2 (Continued).

Author/ Year/ Country/	Title /Aim/Purpose	Sources/Method/ Period/ Number of Studies	Population	Polypharmacy Definitions
				Cumulative polypharmacy (also known as multiple medication): is defined by the sum of different medications administered over a given period of time. Numerous studies use a three-month period, the time necessary to take into account 95% of prescriptions based on the standard prescription renewal time (three months). Other periods (six months, twelve months) have also been used. Continuous polypharmacy: it is similar to cumulative polypharmacy but limited to medications taken for prolonged and regular periods. It only takes into account medications present in two given time periods spaced by an interval of six months, for example. Or by taking into account only medications present in the preceding quarter and the following quarter. According to a defined thresholds: Numerous thresholds have been identified - Essentially 5 or more medications - 10 medications or over - Other thresholds: "5 to 7"; "8 and over"; Threshold of 8 medications; "6 medications and over" According to the number of medications administered: Minor polypharmacy: the administration of 2 to 4 medications – Major polypharmacy: the use of 5 medications and over. hyperpolypharmacy or excessive multi-medication: the consumption of 10 or more medications. In an article published in 2014: The consumption of over 10 medications is now considered as major 20 medications or over is considered excessive. The consumption of 5 medications or under is now considered as "non-polypharmacy" or "oligopharmacy"

Bushardt et al[5] 2008 *(USA)* *Clinical Interventions in Aging*	Polypharmacy: Misleading, but manageable To identify a consensus definition for polypharmacy and evaluate its prevalence among elderly outpatients.	A review conducted within OVID for original articles. Using the following search terms and phrases: "polypharmacy," "elderly," "geriatrics," "inappropriate medication," and "multiple medication use." English language articles available in local holding, which described "polypharmacy" or the issue of the simultaneous use of multiple medications in elderly patients, were evaluated. Discrete definitions of polypharmacy were identified and recorded. Between January 1997 and May 2007 (n=11 studies included)	Elderly	Several different definitions involved one of the following concepts (24 définitions): Medication does not match the diagnostic (the most commonly cited, in 4 articles); Many medications; Duplication of medication; Drug/drug interactions; Inappropriate dosing frequency (excessive, too low, too long); Medication prescribed to treat the side effect of another medication (except for case where there is no other option); Two or more agents with the same chemical class; Two or more meds to treat the same condition; Two or more agents with the same or similar pharmacologic actions to treat different conditions; Minor polypharmacy = 2–4 meds/Major polypharmacy ≥5 meds; 3, 5 or 6 different medications; Two or more medications; Greater than 5 medications; Excessive use of medication; Unnecessary use of medication; Medications prescribed greater than twice per day; Complicated drug regimen effecting compliance; Contraindicated in the elderly; Taking an OTC medication, an herbal product or another person's medication; Availability of an equally effective, lower-cost alternative; Patient misunderstanding of the use of the medication (purpose, how to take it, side effects possible, toxicity signs, etc.); Dosage does not reflect age/renal/liver status; Improvement after discontinuation of medication; Diagnosis no longer present. The term "inappropriate" was part of definitions used in six articles. Some definitions for polypharmacy place a value on the number of concurrent medications; the most commonly referenced number was 6 medications or more.

(*Continued*)

Table 2 (Continued).

Author/ Year/ Country/	Title /Aim/Purpose	Sources/Method/ Period/ Number of Studies	Population	Polypharmacy Definitions
Fulton et al[7] 2003 *(USA)* *Journal of the American Academy of Nurse Practitioners*	Polypharmacy in the elderly: a literature review. To review the body of literature addressing polypharmacy in individuals aged 60 years and older to (a) determine primary care providers' definition of polypharmacy, (b) explore how polypharmacy was assessed in primary care, and (c) seek tested interventions that address polypharmacy.	A systematic review; Bibliographic databases: EBSCOHost, InfoTrac, OVID, FirstSearch, and FirstSearch Deluxe. The search terms "polypharmacy," "polypharmacy and elderly," "polypharmacy and research," and "multiple medications". Between January 1991 and October 2003 (n=16 studies included)	Elderly (≥60 years)	• Multiple definition are utilized: - Two or more drugs for 240 days or more - Concurrent use of two or more drugs - Use of for or more medications -Use of five or more different prescription medications • Additional definitions include regular daily consumption of multiple medication as well as the use of high-risk medications and questionable dosing • "Untoward iatrogenic sequel of the use of multiple, interacting medications" • European studies defined polypharmacy according to the number of medications taken, whereas the studies conducted in the United states defined polypharmacy according to whether a medication was clinically indicated

Veehof et al[6] 2000 *(Netherlands)* *European Journal of General Practice*	Polypharmacy in the elderly – A literature review. To define polypharmacy; to determine the extent and nature of polypharmacy in the elderly; and to discover the problems which may result from polypharmacy in general practice.	A Medline search from 1985 to 1998 yielded. Entries: polypharmacy and aged (=65 years and older) in combination with: adverse drug reactions, drug interactions, drug combinations. (n= 143 articles included)	Elderly (≥65 years)	Defined in two ways in the literature: Quantitative vs Qualitative. In quantitative descriptions the emphasis lies mainly on the amount of drugs, and qualitative descriptions focus on polypharmacy as a problem. For instance, polypharmacy defined as the prescription, administering or use of more drugs than is clinically indicated for a certain patient. The term polypharmacy was also applied when several drugs are used with one of the following characteristics: • Drug use with no apparent indication; • Use of two identical drugs; • Concurrent use of interacting drugs; • Use of contraindicated drugs; • Use of drugs to treat adverse drug reactions; • Improvement after stopping or interrupting medication. When mentioning polypharmacy some authors describe a regime in which there is at least one drug that is superfluous or the use of any drug that is not essential to the management of a medical problem. When approaching polypharmacy quantitatively, the criterion often used is the simultaneous use of more than five drugs (But it must be remembered that situations exist where the simultaneous prescription of several drugs is necessary and has to be considered effective pharmacotherapy). For the purpose of this study: polypharmacy means simply the simultaneous use of two or more drugs; the use of more than five drugs is defined as major polypharmacy.

Abbreviations: OTC, over the counter; PIM, potentially inappropriate medication; WHO, World Health Organization.

published back in 1998 by a general practitioner (R. David Lee) in the *Journal of the American Board of Family Practice*.[10] This article already identified polypharmacy as a serious problem because of the lack of relevant research data on its prevalence, complications and management solutions. According to the author, the definition of polypharmacy varies from one study to another, making it difficult to translate research results into useful information for primary care. Lee defines polypharmacy in its strictest sense as the concomitant use of many drugs and describes it as a practice that implies the prescribing of excessive medication. He also introduces two main approaches that we found in all selected reviews. The first approach focuses on the number of medications the patient is taking. The authors disagree, however, on the number of medications and on whether or not to consider medications over-the-counter drugs or herbal and alternative medications. The second approach which allows for an individualized approach to a patient's drug regimen focus on the clinical indications and effects of a given drug regimen, regardless of the number of medications used. Polypharmacy would therefore imply that more medications are used or prescribed than those that are clinically indicated.

From the first review we selected in 2000 to the last one published in 2018, we find this notion of "qualitative approach *vs*. quantitative approach" in the definition of polypharmacy. What changes are the nuances found in the results of each review; nuances that are a consequence of approaches and methods that have evolved and that are different from on review to another according to the purpose of each (for example: specific population, more or less in-depth analysis of the original articles). The progressive gain of ground in the definition by increasingly precise concepts (qualitative approach) as well as the progressive emergence of notion of inappropriate polypharmacy are also reflected in the comparison of the results of the different reviews.

An interesting approach to definition by attempting to measure polypharmacy is found in the French Institute for Research and Information in Health Economics (IRDES) systematic review from 2014.[8] Their results include all the aforementioned varieties of definitions (based on thresholds, on the number of medications or on other related characteristics) and focus specifically on time slots to measure polypharmacy. This approach distinguishes several types of polypharmacy: simultaneous, cumulative (or multiple medication) and continuous (see Table 2).

As mentioned above, in 2017, an Australian team published in the BMC Geriatric the results of a systematic literature review including 110 articles defining polypharmacy.[3] This review describes and quantifies available definitions by categories (numerical only; numerical with an associated duration of therapy or healthcare setting; descriptive). The vast majority of existing definitions (80.4%) are only quantitative; the most commonly used threshold is five or more daily medications (51 studies). Only one study, published in 2011 in the British Medical Journal defined polypharmacy as the number of drug classes used by patient.[14] Nearly eleven percent of studies added the criterion of duration of therapy or healthcare setting to the numerical definition. In addition, 8.9% of revised studies had a descriptive approach to define polypharmacy while some of them used different terms when referring to the same definition. Finally, this review identifies studies that define appropriate or rational polypharmacy as opposed to potentially inappropriate medication. Of the 110 studies included, it highlights a recent article (2015) that highlights the inconsistency in the definitions of polypharmacy and refers to situations where "patients visiting multiple pharmacies which may be associated with safety concerns relating to potential outcomes such as medication duplication, drug–drug interactions and adverse effects".[15]

The last selected review is a scoping review published by an American team in November 2018, including 363 articles.[9] It describes definitions and terminology of paediatric polypharmacy and provides an overview of the wide range of definitions associated to the term "polypharmacy" in paediatric studies. This review's results are similar to those found in other reviews concerning the general population: the vast majority of definitions are quantitative; the difference is the number of medications. In over 80% of the reviewed studies, polypharmacy among children was defined on the basis of two or more medications or two or more therapeutic classes. Commonly used terms included "polypharmacy", "polytherapy", "combination pharmacotherapy", "average number", and "concomitant medications". The term "polypharmacy" was more common in the psychiatric literature, while the term "polytherapy" was more frequently found in epilepsy literature.

A Need for a Consensus Definition to Enable Action: A Field of Application Related to Ageing

Between 2000 and 2008, we found three reviews with the same objective: to identify a consensus definition for

polypharmacy in the literature.[5–7] All of them focused on the elderly. This is quite logical as the elderly are affected by polypharmacy. The definitions found in the literature concern the two approaches described above: (i) quantitative, with varying thresholds and types of polypharmacy determined by the number of medications (e.g., minor, major, excessive); (ii) qualitative, with a growing number of concepts and characteristics to describe polypharmacy, including treatment duration and many other contextual elements and concepts (example: Bushardt in 2008 identified 24 different definitions,[5] the most cited being "Medication does not match the diagnosis").

The term "inappropriate" is increasingly associated with polypharmacy, particularly in reviews that aimed to use this definition to identify possible solutions for healthcare providers. Several evaluation tools and various methods have been developed for this purpose: The most well known are the Beers' criteria developed in 1997.[16] Beers' criteria help clinicians identify adverse reactions and medications to be avoided or used with caution among the elderly. These criteria were included in several research studies on inappropriate prescriptions in the late 1990s.[17–20] Other interventions for assess and control polypharmacy include "brown bag" approach[21], using mnemonics such as SAIL or TIDE,[22] or the "10-step approach".[23]

The three reviews conducted between 2000 and 2008 identify many variations in definitions from one school to another. Some authors note that European studies often defined polypharmacy according to the number of medications taken, while studies conducted in the United States tend to define polypharmacy according to the clinical indication of medication.[7] This qualitative approach is essential to studies focused on onco-geriatrics for example. In this multi-morbidity context, beyond the number of medications prescribed and used, polypharmacy is defined more broadly than potentially inappropriate medication (PIM) use "Medications of a specific drug type or class that may not be appropriate for a given patient because of age or a concurrent illness/condition", Medication underuse "Medications with a clear benefit for a given illness/condition that a patient is not taking", and Medication duplication "Medications of the same or a similar drug class or therapeutic effect concurrently being used that may not be beneficial".[11]

Discussion

A Lack of Consensus on Polypharmacy Definition

This literature review further confirms the lack of standardization in the use of the term "polypharmacy" both, in research and practice. The WHO definition ("the administration of many drugs at the same time or the administration of an excessive number of drugs") is broad enough so as to allow for the emergence of different definitions[1]. The first part suggests an administration of "many" drugs without specifying to which number this excessive nature corresponds. Moreover, the notion of "same time" raises the issue of the temporal dimension according to which polypharmacy is considered and measured. The other part of the definition refers to an "excessive number of drugs" introducing, thus, another notion; that of drug misuse.[8] A literature review conducted by a Canadian team, published in 1981, seeking to define "polypsychopharmacy" (polypharmacy in the field of psychiatry), had already revealed a large variability in definitions in the medical literature.[24] While being used for more than a century and a half,[25] this term has not reached a consensus yet in its definition. Instead, the most recent publications reveal a great heterogeneity in approaches and the impossibility of establishing a standard definition for polypharmacy.

Moreover, although not standardised, these definitions have been enriched and refined over time to include new characteristics and concepts linked to the quality of prescription (appropriate, rational vs. inappropriate), duration or context of therapy …, etc. This qualitative approach moves away from stricter definitions that are limited to the number of drugs consumed. Nevertheless, the most recent review shows that more than 80% of the definitions used in the literature are quantitative.[3]

Definition by Measurement: Different Approaches

Several research studies have focused on the study and development of indicators and potential tools to reliably measure polypharmacy. We mentioned the work of IRDES researchers, which defines indicators and assesses the technical feasibility of their calculation.[8] They compare five of the most frequently used measurement tools and test them on the basis of IMS-Health data to assess the ability of these indicators to identify polypharmacy. From this review of the literature, they retained four polypharmacy

indicators. Three indicators represent simultaneous polypharmacy and one, cumulative polypharmacy. To these, they added a continuous polypharmacy indicator, also found in the literature and retained within the PAERPA program framework.[26] A table summarizes the name, calculation and sources of each indicator (8, table T).

Two additional publications deal with the same issue. The first one[27] refers to explicit and implicit instruments, such as the Beers Criteria, STOPP/START criteria, and Medication Appropriateness Index, which are common criteria that can be used to identify high-risk medications that suggest reconsideration.[28] It also discusses the relevance of other ways to assess the medication burden in older adults using tools that consider pharmacological principles (i.e. dose–response and cumulative effects) and target-specific medications such as those with clinically significant anticholinergic effects and sedative effects (i.e. Anticholinergic Drug Score, Anticholinergic Risk Scale, Anticholinergic Cognitive Burden Scale, Sedative Load, and Drug Burden Index). The authors emphasize the importance of establishing clinically relevant cutoffs for polypharmacy, meaning that they must be measured and interpreted according to the clinical context, multimorbidity, patient preferences and goals of care.

The most recent paper in this field is a systematic review and expert consensus study that identifies what they consider to be the key elements of a measure of prescribing appropriateness in the context of polypharmacy.[29] Panel members particularly valued indicators concerned with adverse drug reactions, contraindications, drug–drug interactions, and the conduct of medication reviews. A set of 12 indicators of clinical importance considered relevant to polypharmacy appropriateness has been identified (29, Table 2). This review concludes by recalling that the use of these indicators in clinical practice and informatics systems is dependent on their operationalization and their utility (e.g. risk stratification, targeting and monitoring polypharmacy interventions) requires subsequent evaluation.

No Standard Definition: An Obstacle to Measuring Outcomes

This lack of consensus makes it very difficult to estimate and measure the outcomes associated with polypharmacy. Several of these reviews aimed at defining polypharmacy in order to study its prevalence in a given population (geriatric, onco-geriatric, paediatric or psychiatric) or to prove and quantify the association between polypharmacy and its associated consequences (falls, hospitalization, non-compliance with treatment, increased expenses …, etc.). The definition of these parameters is a fundamental step and a real challenge for researchers interested in developing adequate solutions based on evidence and proven methods including recommendations to guide practice and interventions targeting patients or healthcare providers. All reviews that attempted to conduct meta-analyses or to compare the results of previous work share a common limitation related to the use of different methodologies from one study/school to another. Several elements may vary: population profile, threshold definition (duration, number), healthcare environment (home, hospital, institution …), and specificities of contexts and health systems from one country to another.

Results show that the prevalence of polypharmacy in the elderly can vary from 13% to 92% depending on the definition used and the characteristics of the population studied.[11] A recent study exploring the correlation between polypharmacy and falls in a cohort of people over 60 years old in the United Kingdom, illustrated this variation: using the threshold of 4 or more drugs (adjusting for socio-demographic, medical and other lifestyle factors), the rate of falls is 18% higher among polymedicated people than among others (IRR 1.18, 95% CI 1.08 to 1.28), while the use of the threshold of 10 or more drugs was 50% higher (IRR 1.50, 95% CI 1.34 to 1.67).[30] The results of another systematic review that assessed prevalence and associated clinical signs through variations in polypharmacy definition and mood variation in adults with bipolar disorder showed a prevalence that varied between 85% and 36% depending on whether the study used a "permissive" (2 drugs simultaneously) or more "conservative" (4 and more) definition.[31]

It is also difficult to estimate the cost of polypharmacy and its burden on health systems. For instance, in Great Britain, we can have the total number of drugs dispensed and its evolution (1.08 billion ≈ 19.9 drugs/person in 2015 *Vs*. 962 million ≈183 drugs/per cent in 2011[32]); in USA the cost associated with the management of falls among people over 65 years old (£6million/day or £2.3 billion/year for the NHS in 2010[33] has been estimated in $20 billion in 2006[34]). However, even if we accept the proven link between polypharmacy and falls,[35–41] again, the absence of a standard definition makes it difficult to precisely quantify this cost.

Limitation

The fact that we have limited ourselves to systematic reviews without studying all the original articles could be considered as a limitation to this work. But this option was chosen in order to get an overview of the existing literature and to be able to assess whether there was a consensus definition of polypharmacy.

Conclusion

Published literature reports a high variability in the use of the term "polypharmacy" in the absence of a consensus following standardized criteria. In all reviews, we find this notion of "qualitative approach vs quantitative approach" in the definition of polypharmacy. The results (existing definitions of polypharmacy) were different from one review to another depending on the purpose and method of each and have, a fortiori, evolved over time.

Some researchers make trade-offs by choosing a definition for the purposes of their research. Others are trying to define relevant indicators to move towards a precise measurement of polypharmacy whether comparing the ability of indicators to identify polypharmacy and evaluating the technical feasibility of their calculations,[8] proposing alternative terminologies[15] or, much more recently, establishing a standard definition of the term "polypharmacy" based on an index including the many parameters associated with comorbidity and multi-morbidity.[42]

Research on polypharmacy is moving towards an increasingly holistic approach. Polypharmacy could be defined, therefore, within the intersection between its many etiological or risk factors (health status, general frailty, comorbid conditions, certain diagnoses, prescribing cascades, self-medication, inappropriate prescription, etc.); significant demographic factors (age, sex, level of education); healthcare environment; and the other factors influencing the number of doctor visits prescribers and hospital admissions. Paradoxically, this approach brings us further away from a standard definition because it defines several situations or types of polypharmacy. By combining all these considerations, some definitions qualify polypharmacy as "appropriate" when "the prescription of numerous medications is justified", and as "inappropriate" when "wrongly or indiscriminately prescribed".[25,43] In the same vein, we can define "inappropriate polypharmacy" as opposed to situations where the use of several medications would be desirable, justified and even necessary. This practice corresponds to the simultaneous administration of several medications, at least one of which would be inappropriate regarding its indications and/or the iatrogenic risks potentially implied by its administration.

Abbreviations

AMSTAR, Assessment of Multiple Systematic Reviews; IRDES, Institute for Research and Information in Health Economics; IRR, Incident Rate Ratio; MAI, Medication Appropriateness Index; NA, Not applicable; NHS, National Health Service; NP, Not provided; OTC, Over the counter; PIM, Potentially inappropriate medication; WHO, World Health Organization.

Disclosure

The authors report no conflicts of interest in this work.

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