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Defining polypharmacy in the elderly: a systematic review protocol

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ABSTRACT

Introduction: Ageing—along with its associated physiological and pathological changes—places individuals at a higher risk of multimorbidity and treatment-related complications. Today, polypharmacy, a common and important problem related to drug use, occurs subsequent to this multimorbidity in the elderly in all populations. In recent decades, several scientific investigations have studied polypharmacy and its correlates, using different approaches and definitions, and their results have been inconclusive. Differences in definitions and approaches in these studies form a barrier against reaching a conclusion regarding the risk factors and consequences of polypharmacy. It is therefore imperative to establish an appropriate definition of polypharmacy.

Methods and analysis: A systematic review will be conducted using PubMed, Scopus, Web of Science, EMBASE, PsycINFO and AgeLine bibliographic databases, as well as the grey literature on polypharmacy in older adults to answer these two questions: What definitions in the literature are being used for polypharmacy in older people?, and Which definitions are more comprehensive and applicable? 2 independent reviewers will conduct the primary screening of the articles and data extraction, and eligible sources will be selected after discussing non-conformities. All extracted data from selected articles will be categorised based on the type of study participants, study design and setting, the methodological quality of primary studies and any other potential source of heterogeneity, and results will be summarised in a table, which will contain the levels of evidence and methodological quality of the included studies. The most comprehensive definition of polypharmacy will be selected from the final list of definitions through an international expert webinar.

Ethics and Dissemination: This research is exempt from ethics approval because the work is carried out on published documents. We will disseminate this protocol in a related peer-reviewed journal.

Strengths and limitations of this study

- This systematic review develops a consensus on the definition of polypharmacy, a controversial term in medical articles.
- Primary screening of the articles, data extraction and quality assessment will be performed independently by two persons with extensive experience in systematic review methodology, to minimise the probability of personal biases.
- In this study, databases in languages other than English (French, German, Chinese, etc) will not be searched or included. This limitation may cause language bias.

drug-related harms because of age-related changes and pathologies; comorbidity of chronic conditions, such as cardiovascular diseases and psychological disorders; and different pharmacokinetics and pharmacodynamics. Consequently, older adults are more susceptible to adverse drug reactions (ADR).[2–7]

The term polypharmacy, which first appeared in the medical literature more than one and half centuries ago,[8] was originally coined to refer to certain issues related to multiple drug consumption and excessive drug use.[9] Since then, it has been used in different papers and reports, and with different meanings and definitions including but not limited to 'unnecessary drug use' and 'medication use without indication'.[10–12]

Problems associated with medication use in general, and polypharmacy in particular (with either of the above definitions), are more prevalent in the aged population because of numerous contributing factors. Lower compliance and adherence due to multiple and complex drug regimens are some of the issues among the elderly that can interfere with the treatment process, exacerbate disease and eventually increase the need for medication.[13 14]

As aforementioned, multimorbidity is one of the major problems that arise as populations age. In addition to issues in taking their

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INTRODUCTION

Drug-related harm among the elderly is one of the most challenging public health issues globally.[1] Older people are more vulnerable to morbidity and mortality secondary to

medication themselves, multimorbid senior patients are more vulnerable to prescription problems. Even in the best case scenarios, using good clinical practice and accepted guidelines for prescribing medication, the physician is obliged to use multiple guidelines for the treatment of various conditions within the same patient. On the other hand, available guidelines are usually devised with focus on a single disease, and overlook the possibility of comorbidities and the consumption of other medications by the patient. This increases the chances of ADR, drug–drug interaction and drug–disease interaction, and eventually poses greater risks to the patient as a result of a prescription cascade and already deteriorating health. This is a condition described as problematic or inappropriate polypharmacy, as opposed to appropriate polypharmacy, where the use of a combination of medicines has been optimised.[1 8 15 16]

Self-medication is a potential cause of polypharmacy and the availability of diverse over-the-counter drugs, especially potentially inappropriate medications for older people, exacerbate this problem. Other issues related to drug use include low literacy in general or low health literacy in particular. Additional contributing factors include miscommunication or misunderstanding physician orders as a result of cognitive dysfunction, and mistaking drugs because of similarity in shape or colour, both of which can arise more often in older age groups.[7 13 14 17 18]

Although the concept of 'polypharmacy' is used interchangeably to describe multiple, excessive, unnecessary, or unindicated drug consumption, each type of polypharmacy has specific consequences on both the patient and the health system. Each definition of polypharmacy implies that the patient has been exposed to a different risk, and is therefore subject to a variety of different consequences, including higher costs, higher prevalence of ADR, reduced compliance and adherence, lower quality of life, higher risk of hospitalisation and even death.[6 11 19 20]

Regardless of its definition, polypharmacy is a multifactorial problem that occurs in a variety of settings and conditions.[11 21–24] Previous studies have used different diagnostic criteria and indicators for the assessment of this problem,[8] and consequently reported various types of medication use and prescription problems as polypharmacy, and introduced a wide range of its aetiological patterns and outcomes with a wider range of effects and associations.[23 25–28] A clear unique definition is required to make these heterogeneous results comparable and to explain existing differences feasibly, because it seems that many of these differences are rooted in the different definitions that have been used (regardless of their level of accuracy). This review will be conducted to fill this important gap and to reach a consensus on the definition of polypharmacy, to make future studies more valid and reliable.

This study will be performed with the following two questions in mind:

- ▶ What definitions are being used in the literature for polypharmacy in the elderly?
- ▶ Which definitions are more comprehensive and applicable?

OBJECTIVES
The objectives of this study are as follows:
1. To identify polypharmacy definitions among older age populations;
2. To assess the heterogeneity of these definitions;
3. To find potential sources of heterogeneity in primary studies;
4. To reach a consensus about the definition of polypharmacy in the elderly within an expert group.

METHODS AND ANALYSIS
Eligibility criteria
Study characteristics
This systematic review will include observational (case report, case series, cross-sectional, case–control, cohort, etc) and interventional (quasi-experimental studies, randomised controlled trials, community trials, field trials, etc) studies in which polypharmacy is considered one of the main dependent or independent variables, and where a clear and practical definition is given. Animal studies will not be considered.

Types of participants
This systematic review will target studies in which groups or subgroups of participants are comprised of males or females aged 60 years and older.[29]

Setting and time frame
In this systematic review, no limit will be set for the study setting or time frame. All studies, including those conducted in clinical settings (hospital or nursing centres) as well as those conducted in community settings, will be considered. Also, articles will enter the initial screening stage without a time limit for execution or publication, to allow for observation of changing trends in the definition since the term entered the literature.

Report characteristics
Only articles that have their abstract in English will be chosen. No limitation will be considered for date of acceptance or publication. As for publication status, we will consider only articles that are published or in press.

Information sources
Our sources of information will include electronic databases, trial registries, different types of grey literature, and researches and authors themselves. An electronic search will be performed through PubMed, Scopus, Web of Science, EMBASE, PsycINFO and AgeLine bibliographic databases. To identify appropriate key words, in addition to Medical Subject Headings (MeSH) terms, popular and commonly used phrases stated in related

literature will be utilised. First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to the other databases. Other sources will be searched to identify related grey literature. ProQuest will be searched for dissertations. Meeting abstracts will be searched through Scopus, Web of Science and pertinent websites. Reference lists of relevant articles and systematic reviews, and tables of contents of key journals in this field, will be searched as well.

Search strategy

Our initial search syntax for PubMed will be:

1. polypharm*[tiab]
2. 'Later life'[tiab] OR Senior[tiab] OR Nonagenarian [tiab] OR Octogenarian[tiab] OR Centenarian[tiab] OR 'oldest old'[tiab] OR 'older old'[tiab] OR geriatric*[tiab]
3. Elder*[tiab] OR 'old age'[tiab] OR aging[tiab] OR veteran*[tiab] OR ageing[tiab]
4. 'Older people'[tiab] OR 'old people'[tiab] OR 'oldest people'[tiab]
5. 'Older adult'[tiab] OR 'older adults'[tiab] OR 'old adult'[tiab] OR 'old adults'[tiab] OR 'oldest adult'[tiab] OR 'oldest adults'[tiab]
6. 'Older person'[tiab] OR 'older persons'[tiab] OR 'old person'[tiab] OR 'old persons'[tiab] OR 'oldest person'[tiab] OR 'oldest persons'[tiab]
7. 'Older population'[tiab] OR 'old population'[tiab] OR 'oldest population'[tiab]
8. 'Older individual'[tiab] OR 'Older individuals'[tiab] OR 'old individual'[tiab] OR 'old individuals'[tiab] OR 'oldest individual'[tiab]' OR oldest individuals'[tiab]
9. 'Older patient'[tiab] OR 'older patients'[tiab] OR 'old patient'[tiab] OR 'old patients'[tiab] OR 'oldest patient'[tiab] OR 'oldest patients'[tiab]
10. 'Aged people'[tiab] OR 'aged adult'[tiab] OR 'aged adults'[tiab] OR 'aged patient'[tiab] OR 'aged patients'[tiab] OR 'aged person'[tiab] OR 'aged persons'[tiab] OR 'aged population' [tiab] OR 'aged individual'[tiab] OR 'aged individuals'[tiab]
11. OR #2 /#10
12. #1 AND #11

The search syntax for other databases are presented in online supplementary appendix 1.

Study records

Selection process: Two authors will independently perform the primary article screening. First they will review the title and abstract of the articles independently, and then their selected articles will be categorised into three groups: relevant, irrelevant and unsure. Articles categorised as irrelevant by both reviewers will be eliminated from the study. Then, each reviewer will review the full text of the remaining articles and make a list of articles to be included. The two lists will then be compared and

non-conformities will be discussed. When an agreement is not reached, the whole team will make the final decision.

Data management: Data will be extracted from papers and entered into data sheets (see online supplementary appendix 2) independently by two reviewers. These two sheets and their differences will be checked by a third reviewer. Any potential difference among reviewers will be discussed with the team and, if not resolved, the manuscript authors will be contacted. Also, if the required data are missing from the article or are incomplete or unclear, enquiries will be sent to the authors.

Data items

From each article, the following information will be extracted: author, publication year, journal title, format (summary, journal article), study design, study setting, definitions for polypharmacy, risk factors and consequences of polypharmacy, tools, sample demographics (age, sex, etc), type of participants, sample size, and geographical and time range of data collection.

Risk of bias in individual studies

Critical appraisal of articles will be performed using the checklist developed by the authors (shown in online supplementary appendix 3) to assess the methodological quality of each article based on its proposed definition. Moreover, the full texts will be appraised by two researchers separately, as aforementioned.

Data synthesis

In the final report, we will present a range of different definitions in a list based on different subgroups. Manuscripts will first be grouped by medical specialty field of medicine (psychology, cardiology, neurology, etc). Then, subgroups will be formed by level of evidence, type of study participants (inpatient, outpatient, general population, etc) and study setting (eg, hospital, clinics, community, etc). Studies will also be assigned to subgroups by their stated types of risk factors and consequences of polypharmacy. Eventually, stated definitions of polypharmacy will be recorded in results tables for each specialty field in order of importance and desirability, which will be based on the quality of their methodology, robustness of results and level of evidence. These definitions will then be compared with discuss similarities and differences. Collected information will also be used to illustrate the temporal changes in the definition of polypharmacy.

After performing data synthesis and categorising studies as described above, the final report will be prepared following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. In this step, the list of definitions will be shared with an international group of experts in the field of geriatric medicine via a webinar. Their feedback about the best definition of polypharmacy in elderly people

will be collected, and the final consensus will be built using Delphi techniques.

DISCUSSION

Although polypharmacy has been studied in numerous observational and interventional primary studies in the past two decades,[22 26 27 30] this important health problem still lacks a unique and precise definition.[1 7] As a consequence, all reviews performed on this subject are at risk of different types of heterogeneity due to various populations, research designs and study settings, as well as of unavoidable bias due to non-homogeneous definitions. The results of this systematic review can help clarify the exact meaning of polypharmacy for researchers who wish to design new primary or secondary studies concerning this issue. Moreover, it can play an important role in improving the internal validity of future evidence.

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