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Title Page

Title: Incidence, prevalence, risk factors and health consequences of polypharmacy among adults in South Asia: a systematic review protocol

Authors:

Nusrat Khan[1,2]

Kaushik Chattapadhay[1,2]

Jo Leonardi Bee[1,2]

1.Division of Epidemiology & Public Health, School of Medicine, University of Nottingham, Nottingham, United Kingdom

2.The Nottingham Centre for Evidence-Based Healthcare: A Joanna Briggs Institute Centre of Excellence,

Corresponding Author: Nusrat Khan

Nusrat.khan@brac.net

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Title

Incidence, prevalence, risk factors and health consequences of polypharmacy among adults in South Asia: a systematic review protocol

Review objectives and questions

The objectives of this systematic review are to summarize the incidence, prevalence, risk factors and health consequences of polypharmacy among adults in South Asia (i.e., Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka).

1) What is the incidence and prevalence of polypharmacy among adults in South Asia?

2) What are the risk factors of polypharmacy among adults in South Asia?

3) What are the health consequences of polypharmacy among adults in South Asia?

Introduction

The dual burden of diseases and multimorbidity

The burden of infectious diseases and non-communicable diseases (NCDs) is known as the dual burden of diseases.[1] The associated morbidity and mortality have a huge negative impact on the patient, their family/carer, the health system, and the economy. In developed countries, the burden of NCDs is high, which has been the case for the last few decades.[2] In many developing countries, the burden has already shifted from infectious diseases to NCDs.[1] According to the World Health Organization, in 2015, NCDs accounted for 70% of the total of 56.4 million deaths worldwide, and infectious diseases and other health conditions accounted for the rest.[2-4]

Multimorbidity is defined as the coexistence of two or more chronic diseases in an individual. Similar to the dual burden of diseases, multimorbidity places a huge burden on the patient, their family/carer, the health system and the economy.[5] Globally, the prevalence of multimorbidity is nearly eight percent.[6] The prevalence is also increasing in low and middle-income countries (LMICs).[3]

Polypharmacy

The concurrent use of multiple drugs is known as polypharmacy.[7] A standardized universally accepted definition of polypharmacy is not available. A recently published systematic review reported that approximately half of the published studies defined polypharmacy as administering five or more medicines to an individual. They found a huge variation in the definition of polypharmacy used, which ranged from two or more medications to eleven or more medications.[8] Globally, the prevalence of polypharmacy has almost doubled in the last twenty years and currently varies widely at country-level (7-90%),[7-19] however, due to under-reporting, the true prevalence could be much higher. The number of drugs prescribed to an individual depends on a number of factors, such as their disease diagnosis, their functional status and life expectancy, their preferences and the healthcare infrastructure including the availability of medicines. With the rise in multimorbidity and aging population, the trend of prescribing multiple drugs is increasing.[18-21]

Medicine can be provided by different healthcare providers - trained or untrained. In some cases, self-medication is also practiced, which can be either appropriate or problematic. When the usage of multiple drugs is evidence-based and optimized, it improves patient's health outcomes including life expectancy and quality of life (QoL). This is considered as appropriate polypharmacy. In many cases, polypharmacy is the most obvious therapeutic option. However, on many occasions, especially when the use of multiple drugs is not based on evidence, it can lead to interactions between drugs and results in adverse drug events (ADEs).[6,22] This is known as problematic polypharmacy. According to a recently published study, 1% of all hospital admissions are caused by drug-drug interactions, and appropriate medication can prevent such interactions.[23] The risk of ADEs is 13% when two drugs are used; and increases to 58% and 82% when five drugs and seven or more drugs are used, respectively.[24] ADEs are mainly of

two types: adverse drug reactions and adverse drug effects. These two types are inter-related. Adverse drug reactions are detected by their clinical manifestations (symptoms and/or signs). Adverse drug effects are usually detected by laboratory tests (e.g. biochemical) or by clinical investigations (e.g. endoscopy).[14] Problematic polypharmacy can have a negative effect on the patient, their family/carer, the health system, and the economy. In patients, it can adversely affect their health outcomes (including life expectancy and QoL) and their compliance with medicines.[25-27] Many high-income countries have published guidance and other tools on polypharmacy (and on deprescribing). For example, the UK's National Institute for Health and Care Excellence (NICE) has published a document summarizing the evidence-base on this key therapeutic topic, which has been identified to support medicines optimization.[28]

The scenario in South Asia

The current territories of eight countries namely, Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka from South Asia.[29] Despite various diversities, these countries are grouped together due to their common geographical location, socio-cultural and ethical traits.[30] One-third of the world's total population lives in South Asia.[29] Like the rest of the world, the dual burden of diseases is high in this region.[2] A recently published systematic review reported that the prevalence of multimorbidity (of chronic diseases) in South Asia ranged widely from around 5% to 83%, with the most common chronic diseases being hypertension, arthritis, diabetes, cardiac problems and skin diseases.[29]

In South Asia, a diverse range of healthcare providers works in rural and urban areas. Generally, modern medicine (allopathy), as well as traditional medicine practitioners, are considered as medical professionals in South Asia. A registered traditional medicine practitioner undergoes the formal training programme, similar to modern medicine practitioners. There are unqualified practitioners as well. All these practitioners prescribe different types of medicines, and many times without any scientific evidence base.[30] In South Asia, modern and traditional medicines are used simultaneously by many people. In addition, self-medication is widely practiced for preventing and managing illnesses.[31] Some of the reasons behind self-medication are poor accessibility, availability, and affordability of quality healthcare as well as easy availability of many drugs over-the-counter.[32] Thus, the usage of multiple drugs, many times without any evidence, leads to inappropriate polypharmacy in South Asia.[31,33-37]

The rationale for the systematic review

Several studies have been conducted in South Asia on incidence, prevalence, risk factors and health consequences of polypharmacy among adults.[30,33-46] A preliminary search was conducted in MEDLINE, EMBASE, CINAHL, PsycINFO, BNI, Web of Science, Scopus and AMED and until now, no systematic review has been conducted on this topic. This summarized information will help to inform local, national, regional and international health experts to fully understand the issue and draw attention to further plans for necessary action, such as developing and implementing guidelines and tools to support medicines optimization (and deprescribing).

Keywords

Polypharmacy, incidence, prevalence, risk factors, health consequences, South Asia

Inclusion criteria

Population

The review will include studies conducted among adults (aged ≥18 years) in the general population or in any disease-specific group and residing in any country within South Asia (i.e., Afghanistan, Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka). Any setting will be eligible, including community, residential care, primary care, secondary care, and tertiary care.

Condition

We will include any health condition. In research studies on polypharmacy, authors will exclude complex and severe conditions where management requires multiple medicines (thus, we will follow the authors' reported opinion in this regard).

The review will include studies on polypharmacy, where polypharmacy is defined as simultaneous usage of multiple regular medicines (as defined by the respective authors of the included studies). This will include, but not limited to, prescribed medicines and over-the-counter medicines, both western and traditional medicines (we will follow the authors' reported opinion in this regard). We anticipate that data on polypharmacy will be reported via participant-reported methods or case/medical notes and prescriptions.

Outcome/exposure

Question 1: Incidence/prevalence of polypharmacy

This review question will include studies reporting the incidence/prevalence of polypharmacy.

Question 2: Risk factors of polypharmacy

This review question will include studies that report the risk factors of polypharmacy as the exposure and the incidence/prevalence of polypharmacy as the outcome. Risk factors of polypharmacy will include, but not limited to, non-modifiable factors (e.g., age, sex, ethnicity), lifestyle factors (e.g., smoking, alcohol intake, diet, physical activity, weight), environmental factors (e.g., occupation, housing, water and sanitation), and health conditions (e.g., cardiovascular diseases, mental health disorders, cancer, endocrine disorders).

Question 3: Health consequences of polypharmacy

The review question will include studies that report the incidence/prevalence of polypharmacy as the exposure and the health consequences of polypharmacy as the outcome. Health consequences as an outcome of polypharmacy will include, but not limited to, hospital related outcomes (e.g., admissions, readmissions, length of stay assessed at short (<30 days), medium (30-90 days) or long term (>90days) time points) and any negative clinical outcomes (e.g., drug effects - immediate and delayed, mortality and morbidity).

Study design

The incidence/prevalence of polypharmacy review question will include the following epidemiological study designs: cross-sectional, prospective cohort and longitudinal. The risk factors and health consequences of polypharmacy review questions will include the following epidemiological study designs: comparative case-control, cross-sectional, cohort and longitudinal.

Methods

The systematic review process will follow the preferred reporting items for systematic reviews and meta-analyses (PRISMA) and Joanna Briggs Institute (JBI) systematic review methodology guidelines.[47-52]

Search strategy

An initial limited search was carried out in MEDLINE and EMBASE databases using the initial keywords, and these keywords were polypharmacy and South Asia. The titles and abstracts of the studies were screened for keywords, and the index terms used to describe the article were also identified. The search results were inspected to ensure that the relevant articles were identified.

We aim to search for a wide range of sources, to find both published and unpublished studies. The following**,** databases will be searched from their dates of inception: MEDLINE, EMBASE, CINAHL, PsycINFO, BNI, Web of Science, Scopus and AMED. No date or language restrictions will be applied, and translations will be sought where necessary. The search strategy, to be used in MEDLINE, is detailed in Appendix I. This search strategy will be adopted for other databases, in consultation with an information specialist/librarian. The search for unpublished studies will include EthOS, OpenGrey, ProQuest Dissertations, and Theses. The reference list of all the identified reviews and studies selected for inclusion in the review will be screened for additional studies.

Study selection

Following the search, all identified citations will be collated and uploaded into Endnote 8.2 (Clarivate Analytics, PA, USA), a reference management software, and duplicates will be removed.[53] Titles and abstracts will be screened for eligibility using the inclusion criteria by two reviewers independently (NK and KC/JLB). Studies identified as potentially eligible or those without an abstract will have their full-text retrieved and their details will be imported into the JBI's premier software for systematic review of the literature, a system for the unified management, assessment, and review of information (JBI SUMARI).[52] Full-text of the studies will be assessed against the inclusion criteria by two reviewers independently (NK and KC/JLB). Full-text studies that do not meet the inclusion criteria will be excluded, and the reasons for exclusion will be reported. Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer (KC/JLB) will be involved. Although one search strategy will be used to answer three separate research questions posed, it should be noted that studies will be selected for each of these questions and three separate PRISMA flowcharts will be used for reporting purpose.

Assessment of methodological quality

Included studies will be critically assessed, independently, by two reviewers (NK and KC/JLB) using the standardized critical appraisal tools incorporated within JBI SUMARI, as appropriate to the study design.[47-55] All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis, where possible. As recommended by JBI, a cut-off score will not be used to include/exclude studies as most of the studies are likely to be of poor quality. [52] Apart from high-quality studies, poor quality studies can also generate potentially valuable insights. Together, they can lead to a richer understanding of the research phenomenon.

Data extraction

Data will be extracted from papers included in the review using the standardized data extraction tool incorporated within JBI SUMARI,[47-52,54-55] independently by two reviewers (NK and KC/JLB). Any disagreements that arise between the two reviewers will be resolved through discussion. If consensus is not reached, then a third reviewer (KC/JLB) will be involved. The data extracted will include specific details about the epidemiological study design, definition of polypharmacy (including details like prescribed medicine, over-the-counter medicine, western medicine, traditional medicine), country, population (e.g., age, sex, general population/disease-specific group), setting (e.g., community, residential care, primary care, secondary care, tertiary care), inclusion and exclusion criteria, sample size, data collection procedure and tool (e.g., participant-reported method, case/medical note, prescription), data analysis and incidence/prevalence of polypharmacy, risk factors of polypharmacy and health consequences of polypharmacy, depending on the review question.

Where possible, we will attempt to differentiate between problematic and appropriate polypharmacy and the types of medications (prescribed medicines and over-the-counter medicines, both western and traditional medicines) being used. We will follow the authors' reported opinion in this regard.

Data synthesis

We will initially use a narrative synthesis approach to look systematically at the data and to describe each study based on the three separate review questions. Patterns in the data will be identified through tabulation of results, and content analysis using an inductive approach (where the concepts are derived from the data) will be used to translate the data to identify areas of commonality between the studies.[52] We will assess the reasons for differences in the magnitude of the outcomes for polypharmacy practice through investigating within-study differences (including different settings and different population groups) and between study differences (including study design, age groups, gender and definition of polypharmacy).

Question 1: Incidence/prevalence of polypharmacy

Where possible, for each study, we will calculate raw proportions using the number of events divided by the total number of people in the study to estimate the incidence/prevalence of polypharmacy practice. Variances of the raw proportions will be stabilized using the Freeman-Tukey variant of the arcsine square root transformation to bound 95% confidence intervals (CIs) between 0 and 1.[56] Where possible, we will perform random effects meta-analysis to estimate pooled incidence/prevalence with 95% CIs to allow for heterogeneity resulting from inherent biases within the different study designs.

Question 2: Risk factors of polypharmacy

Where possible, for each study, we will extract estimates of risk with 95% CIs. Adjusted estimates will be used in preference to crude estimates. Where only raw data is presented, we will use this to estimate either odds ratios for case-control studies or risk ratios for other study designs. Odds ratios and risk ratios will be pooled together and reported as pooled relative risks (RR) with 95% CIs using random-effects meta-analysis models. For exposures reported in categories or as quantiles, we will use the most exposed group compared to the least exposed.

Question 3: Health consequences of polypharmacy

Where possible, for each study, we will extract estimates of risk with 95% CIs. Adjusted estimates will be used in preference to crude estimates. Where only raw data is presented, we will use this to estimate either odds ratios for case-control studies or risk ratio for other study designs. Odds ratios and risk ratios will be pooled together and reported as pooled RR with 95% CIs using random-effects meta-analysis models. For exposure reported in categories, we will use the most exposed group compared to the least exposed.

Investigations of heterogeneity and reporting biases

For all the three reviews, we will quantify and explore heterogeneity using the methods described below. Heterogeneity will be quantified using I^2.[54] Data permitting, we will explore reasons for heterogeneity using subgroup analyses based on age (65+ years only versus 18+ years), gender, problematic/appropriate polypharmacy, types of medications, specific disease groupings, country and healthcare setting. Also, where data permit, we will conduct sensitivity analyses by excluding poor methodological quality studies to assess the robustness of the conclusions. Statistical analysis will be performed using JBI SUMARI and Stata 15.[54,57] Where there are at least 10 studies in the meta-analysis, we will assess for the presence of publication bias using funnel plots.

Assessing certainty in the findings

A modified version of the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method will be used to determine the strength of evidence for each finding related to the categorization of risk factors,[58] and reported within a summary of findings table. Due to the observational nature of the study designs included in this review, findings will be initially ranked as low and will be downgraded to very low if there is evidence of any of the following - 1. Risk of bias, 2. Imprecision, 3. Inconsistency of evidence, 4. Indirectness, 5. Publication Bias. We will upgrade further based on the magnitude of association, evidence of a dose-response relationship, and where residual confounding

would increase the magnitude of the effect. We will follow the below-mentioned summary (Table 1) to evaluate the quality of evidence:

Insert Table 1

Three reviewers (NK, KC and JLB) will be involved in this process.

Conflict of interest
The authors declare no conflict of interest.

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Appendix I

Search strategy

1. exp Polypharmacy/
2. Polypham*.mp. [mp=title, abstract, original title, the name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. Polymedication or poly-medication.mp.
4. Polymedicine or poly-medicine.mp
5. Polydrug* or poly-drug*
6. Multipharm*.mp. [mp=title, abstract, original title, the name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. Multiple drugs or multiple-drugs.mp.
8. Multiple medications or multiple-medications.mp.
9. Multimedicat* or Multi-medicat*
10. Multidrug* or multi-drug*
11. Overprescrib*
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. South Asia*.mp. or South Asia/
14. Afghanistan*.mp. or Afghanistan/
15. Bangladesh*.mp. or Bangladesh/
16. Bhutan*.mp. or Bhutan/
17. India*.mp. or India/
18. Maldives*.mp. or Maldives/
19. Nepal*.mp. or Nepal/
20. Pakistan*.mp. or Pakistan/
21. Sri Lanka*.mp. or Sri Lanka/
22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 12 and 22

Table 1: Measurement of quality of evidence using GRADE method

Certainty	What it means
Very Low	The true effect is markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect