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RESEARCH

Association between polypharmacy and death: A systematic review and meta-analysis

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ABSTRACT

Objective: Polypharmacy has been linked to a myriad of adverse consequences, and escalating rates of polypharmacy present an emerging concern, particularly among older adults. This systematic review and meta-analysis summarizes the existing literature concerning the association between polypharmacy and mortality.

Data sources: A systematic literature review was done by searching the EMBASE, PubMed, Scopus, and International Pharmaceutical Abstract databases to identify studies assessing the association between polypharmacy and death published until June 2016.

Study selection: Studies that investigated the association between polypharmacy and mortality were eligible for this systematic review and meta-analysis.

Data extraction: Data were extracted by the first and second authors independently using a data extraction form. Disagreement was resolved by consensus. A meta-analysis was performed using random effect models. Heterogeneity was assessed using the I^2 statistic.

Results: Forty-seven studies were included in this meta-analysis. The underlying populations were heterogeneous (I^2= 91.5%). When defined as a discrete variable, pooled risk estimates demonstrated a significant association between polypharmacy and death (pooled-adjusted odds ratio [aOR] 1.08 [95% CI 1.04-1.12]). When defined categorically, a dose-response relationship was observed across escalating thresholds for defining polypharmacy. Categorical thresholds for polypharmacy using values of 1-4 medications, 5 medications, and 6-9 medications were significantly associated with death (P <0.05; aOR 1.24 [1.10-1.39], aOR 1.31 [1.17, 1.47], and aOR 1.59 [1.36-1.87], respectively). Excessive polypharmacy (ie, the use of 10 or more medications) was also associated with death (aOR 1.96 [1.42-2.71]).

Conclusions: Pooled risk estimates from this meta-analysis reveal that polypharmacy is associated with increased mortality risk, using both discrete and categorical definitions. The causality of this relationship remains unclear, but it emphasizes the need for approaches to health care delivery that achieve an optimal balance of risk and benefit in medication prescribing.

Polypharmacy is a general concept referring to the concurrent use of multiple medications by the same individual; however, there is no consensus in the biomedical literature regarding a precise operational definition for polypharmacy.[1] Some studies consider polypharmacy as a discrete variable that is synonymous to the number of drugs a patient is taking at a point in time, or has taken over a specified period of time. Alternatively, some studies define polypharmacy as a categorical variable for which the number of drugs is dichotomized at some arbitrarily selected threshold. For example, it is common to label patients taking 5 or more drugs as being exposed to polypharmacy, although individual studies have used higher and lower thresholds.[2,3] Another common threshold is 10 or more drugs, which has been labeled

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Key Points

Background:

- Conceptually, polypharmacy is the concurrent use of multiple medications by the same individual; however, no precise operational definition has been universally accepted.
- Though variously defined, polypharmacy is often associated with increased risk for poor clinical outcomes.

Findings:

- Polypharmacy is significantly associated with increased mortality risk.
- Mortality risk increases in a dose-dependent fashion as threshold values for the number of drugs defining polypharmacy increases. Polypharmacy is more appropriately conceptualized and measured as a discrete variable, rather than by the imposition of an arbitrary categorical threshold.

as *excessive polypharmacy*.[4] In other contexts, the term *polypharmacy* carries the additional requirement of being clinically inappropriate, such as the presence of unnecessary therapeutic duplication (e.g., concurrent use of 2 beta blockers).[5]

Definitional quandaries aside, polypharmacy has been associated with a host of adverse consequences, including increased direct[6,7] and indirect[8] health care costs and increased risk for poor clinical outcomes such as bleeding,[9] renal failure,[4] falls,[10] fracture,[11] depression,[12] cognitive decline,[7] functional decline,[7] and delirium.[13] Most alarmingly, an emerging body of literature has linked polypharmacy to mortality.[14] This association is of growing concern as the prevalence of polypharmacy is on the rise, particularly among older adults.[15-18] Polypharmacy could affect mortality risk through several pathways, including inappropriate drug prescribing,[19,20] adverse drug events,[5,7,21] drug–drug interactions,[7,22,23] and reduced medication adherence.[24,25] However, a systematic review of health outcomes in community-dwelling older adults showed an inconclusive relationship between polypharmacy and adverse outcomes including mortality.[26]

The primary objective of this systematic review and meta-analysis is to summarize the existing literature concerning the association between polypharmacy and death. We have included studies that define polypharmacy as a discrete variable and studies using categorical thresholds. Thus, the secondary objective is to describe the dose-response relationship between the number of drugs and mortality risk, using both discrete and categorical approaches.

Methods

Data source and search strategy

Search terms were defined, and a systematic literature search was performed by the first and fourth authors using MEDLINE/PubMed, EMBASE, Scopus, and International Pharmaceutical Abstract from inception to June 2016 using the terms “polypharmacy” (e.g., multiple drugs used) and “death” (e.g., mortality, survival) without applying language or study design restrictions. Synonyms of polypharmacy and death suggested by the search engines and 2 studies[1,27] were used. The MEDLINE database was searched through PubMed by using medical subject headings and text words. EMBASE was searched using Emtree terms and synonyms. The full search strategies are provided in the Supplementary Material 1. Potential pertinent studies were also searched from references of review articles, letters, and relevant excluded studies.

Inclusion and exclusion criteria

Studies were included in this meta-analysis if they were human studies, defined polypharmacy as multiple medication use, and explicitly indicated death as an outcome. Studies were excluded if they 1) were review articles, 2) were case reports or case series, 3) had data that could not be used to calculate risk ratios (odds ratio, relative risk, and hazard ratio), 4) did not explicitly define the number of medications that were considered as a criteria for polypharmacy, or 5) were conducted in a pediatric population. Rationales for the exclusion criteria are provided in Supplementary Material 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) diagram of the systematic literature search and review process is shown in Figure 1.

Data extraction

Articles retrieved by the search were stored in a citation manager (EndNote X7; Thomson Reuters, New York, NY). After the removal of redundant articles, titles, and abstracts, the remaining articles were reviewed by the first author by searching for specific words for exclusion (e.g., to exclude reviews, terms such as *review* and *systematic* were searched). The remaining abstracts were reviewed. For non–English-language articles, English abstracts and result sections in full texts were used to determine whether further translation would be necessary. For the abstraction process, the abstraction form (Supplementary Material 3) was designed by the first author and reviewed by coauthors. Information on study design, location, patient demographics, polypharmacy definition, and potential confounders in every study were independently extracted by the first and second authors. In case of disagreement, the third and the last author were consulted, and the disagreement was resolved by consensus.

Assessment of study quality

Study quality was independently evaluated using the Newcastle-Ottawa Quality Assessment scale[28] by the first and second authors. Disagreement was also resolved with consultation and by consensus. The scale was used because it is valid, reliable, and easy to use.[29] Studies were categorized by the scores to studies with low quality (score 1-3 out of 9), medium quality (score 4-6 out of 9), and high quality (score 7-9 out of 9).