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EDITORIAL

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1. Definition and occurrence of polypharmacy

Polypharmacy is, in simple terms, the concomitant use of multiple medications. This impreciseness opens up for controversies already in the basic definition of the concept and makes the term a continuous matter of debate [1]. Most definitions of polypharmacy are, however, numerical. The most commonly reported definition of polypharmacy is concurrent use of five or more medications, but definitions vary. Because of the increase in medication use, the term excessive polypharmacy (10 or more medications) has also emerged [1]. To add to the complexity, there are also polypharmacy measures focused on specific therapeutic areas, e.g. concurrent use of three or more psychotropics [2]. Polypharmacy should be kept separate from potentially inappropriate medication (PIM) use although these terms are sometimes confused. PIMs describe drugs where the risks generally outweigh the benefits whereas polypharmacy usually defines the sheer number of medications regardless of appropriateness. Nonetheless, polypharmacy is consistently reported as a main driver for PIM use [3].

In general, about half of the population aged 65 years and older are exposed to polypharmacy [4]. Thus, use of five or more medications is common practice and may therefore not be judged as 'use of multiple medications' anymore. The prevalence of polypharmacy varies, however, between countries, settings and patient groups. The highest occurrence of polypharmacy can be found in nursing homes where also excessive polypharmacy is common [4]. Hence, the most frail older people who are most likely to suffer from adverse drug effects are the ones who use the most medications. There is a need for more research in nursing homes to identify the main drivers of polypharmacy in this special setting.

2. Methodological challenges

The already mentioned inexactness of polypharmacy stems from the inherent methodologically difficulties in measurement and assessment. The timeframe for concomitant multiple medication exposure varies greatly between studies, often guided by the available data. Survey data typically have predefined time periods for medication use, e.g. daily use or within the last 2 weeks, that is measured at each survey wave with often years in between measurements. These data, on the other hand, have the advantage of coming closer to adherence than register data. Register data rely on calculations and algorithms for medication exposure and can examine use during 1 year, 1 month or even 1-day prevalence. These continuously measured administrative kinds of data have the advantage of reducing selection and recall bias, but are limited by the lack of information about secondary adherence. Hence, the data source and the timeframe will have a major impact on the estimated occurrence of polypharmacy.

Another challenge is which medications to include in the calculations of polypharmacy. Usually prescribed regularly used medications are included, but whether to count over-the-counter medications, PRN (as needed) medications, and herbal drugs varies between studies. Also here is the assessment often driven by the available data and will have an impact on the results.

Finally, polypharmacy studies struggle – together with all other pharmacoepidemiological research – with confounding by indication, which in the case of polypharmacy is complicated by confounding by multimorbidity [4]. It is essential to acknowledge this type of confounding as inherent in all studies of polypharmacy and address this limitation as appropriately as possible to obtain reliable findings.

3. Meaningfulness of the concept of polypharmacy

Polypharmacy has been associated with adverse outcomes such as adverse drug reactions, hospitalization, and mortality [5]. Yet, polypharmacy has been criticized because of the inherent impreciseness and methodological challenges outlined above, but also because multiple medication therapy may not be wrong per se as long as all medications are reviewed and relevant and the patient is not suffering from side effects. Indeed, older individuals often have multiple diseases and impairments [6] and therefore use multiple medications according to single-disease guidelines. Still, polypharmacy is an indicator of the need for medication review and reevaluation of the medication list. Polypharmacy poses challenges during transitions of care and warrants medication reconciliation. Multiple medication use can be the result of lack of follow-up of treatments and prescribing

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cascade [7]. It is also difficult to foresee the net effects (e.g. drug–drug interactions) of multiple medication use in the individual patient. Thus, from a clinical point of view, polypharmacy can be considered as a 'red flag' that requires a medication review by each physician seeing the patient.

4. Lack of evidence for the prescribing practice of polypharmacy

Exclusion criteria for participation in randomized clinical trials (RCTs) typically include multiple diseases and multiple medication use, which in practice prohibit older adults with polypharmacy from enrolling. RCTs also investigate only one drug for one disease at the time, not reflecting the reality of drug treatment in old age. This complicates the translation of clinical trial results to the treatment of older patients with polypharmacy [8]. In addition, it is neither ethical nor feasible to conduct RCTs where elderly patients are randomized to either polypharmacy or no drug treatment. Thus, the composite effects of polypharmacy are difficult to predict in the individual patient.

However, there is an emerging and promising literature on deprescribing trials. Deprescribing is the procedure of tapering or discontinuing medications to minimize polypharmacy and improve patient outcomes [9]. These trials have shown encouraging results but are still pioneer work. This is evidently one important way forward in polypharmacy research and interventions.

5. Personalized medication therapy – a way to minimize polypharmacy?

In the era of personalized medicine, older adults with polypharmacy are one of the patients groups in the greatest need of personalized medication therapy [10]. Inter-individual differences in drug response are large and difficult to predict in this group [11]. Thus, these older patients are clearly a case of 'one size does not fit all.' Personalized medication therapy could be a way of minimizing polypharmacy and guide prioritization for deprescribing of drugs.

Because of the ethical and feasibility reasons prohibiting the usual pharma RCTs, one way forward might be to employ a translational design with integration of basic science, clinical and epidemiological research to improve medication strategies for elderly patients with polypharmacy [12]. Indeed, in a first polypharmacy mouse study [13], polypharmacy impaired mobility, balance and strength in old male mice compared to no effect in young male mice. None of the individual drugs have previously showed these outcomes when used as monotherapy in rodents.

Thus, a translational 'bedside to bench and back again' approach [14] may provide tailor-made medication therapy where it is needed the most – among multimorbid older patients with complex needs for care.

6. Expert commentary

The concept of polypharmacy remains elusive despite numerous studies on the topic. However, great efforts are being made addressing the methodological challenges of polypharmacy moving the pharmacoepidemiological development

forward [4]. Polypharmacy is criticized for being a concept that is inherently too general and imprecise. However, in clinical practice, polypharmacy does raise concerns because the net effects of multiple medication use are unpredictable and can be harmful to an already impaired older adult with many diseases, organ failure and functional decline.

The field of polypharmacy research needs new ways forward to gain more robust evidence. This includes deprescribing trials and translational efforts, which requires interdisciplinary collaboration and large long-term programs. With the aging of the population, polypharmacy is on the rise and will become an even larger challenge in the future [15]. Hopefully, authorities and funding bodies will acknowledge this and support these important efforts moving forward.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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