

# Polypharmacy: volume or value, quantity or quality? The high quantity originates low quality. There is no adequate and valuable polypharmacy

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## Abstract

All patients, especially elderly patients, those with certain pathologies, those with multimorbidity, or those who live in institutions, are exposed to polypharmacy. The prevalence of polypharmacy is high (18-30%) and the prevalence of excessive polypharmacy (10+ drugs) is 12%. Polypharmacy affects between 40% and 50% of all older adults. The incidence rate of polypharmacy is 20% person-years, ranging from 17% in individuals aged 65–74 years to 33% in those aged  $\geq 95$  years. From this point of view, polypharmacy seems to be a concept of quantity or volume of prescriptions. It can lead to serious adverse events related to a wide variety of drug-drug interactions (DDIs) and adverse drug reactions (ADRs): the frequency of ADR is 6% when a patient takes two medications, 50% when he takes five and almost 100% when he takes eight or more medications. Of every 100 courses of drug treatment, there are 20 adverse drug ADRs, between 5 and 25 of clinically observable DDIs and between 15 and 50 potential DDIs, which arrive to 100 in geriatric patients. But on the other hand, low-quality pharmacological care reports are not uncommon. About 60% of patients may be exposed to at least one potentially inappropriate medication: benzodiazepines, psychotropics, proton pump inhibitors, analgesics (including opiates), laxatives, NSAIDs, antacids, etc. Adverse health outcomes related to inappropriate medications for the population, and especially the elderly, include falls, strokes, delirium and death. The quantity of drugs as a defining concept of polypharmacy implies poor quality. The more drugs that are prescribed to a patient, not only there are more possibilities of inappropriate prescriptions or of little value, but even suitable prescriptions tend to lose their indication, and from a certain level of quantity or volume of prescriptions, the increase in DDIs and ADRs makes their value decrease in such prescriptions, and they begin to be inappropriate and give rise to poor quality. In other words, there is no adequate and valuable polypharmacy; the high quantity originates low quality.

**Keywords:** drugs; older adults, polypharmacy; drug utilization; drug therapy; prescribing pattern; general practice

## Introduction

Polypharmacy is the concomitant use of several drugs by a single patient [1]. It often reflects the coexistence of many chronic diseases (multimorbidity), including chronic diseases (eg, diabetes, heart failure, chronic obstructive pulmonary disease, osteoarthritis, depression, benign prostatic hypertrophy, etc.), acute conditions (eg, infections), and symptoms (eg, pain), which accumulate with age. Consequently, polypharmacy is considered an indicator of multimorbidity [2, 3].

In addition, the application of evidence-based prescribing guidelines designed for the management of single disease to individuals with multimorbidity can result in complex drug regimens [4-7]. So, the number of drugs is higher among older people than among middle-aged adults [8]. The use of multiple drug treatments can be clinically appropriate if they improve health and quality of life. However, it poses important challenges to clinicians because many older adults are exposed to polypharmacy beyond the point where drug therapy is beneficial [9-14]. That is,

therefore, the concept of the use of multiple medicines (polypharmacy) or of "polymedicated patient" varies depending on the source consulted, but the basic definition seems to be quite simple: the prescription of more medications than are clinically appropriate. All patients, especially elderly patients, those with certain pathologies, those with multimorbidity, or those who live in institutions, are exposed to polypharmacy [15-17].

From this point of view, polypharmacy seems to be a concept of quantity or volume of prescriptions. It is potentially problematic because it can lead to serious adverse events related to a wide variety of drug-drug interactions (DDIs) and adverse drug reactions (ADRs). But on the other hand, low-quality pharmacological care reports are not uncommon. Adverse health outcomes related to inappropriate medications for the population, and especially the elderly, include falls, strokes, delirium and death [15, 18]. And so, it could be thought that the main problem of polypharmacy derives from the fact that some of these prescriptions

include some inappropriate, of little value, not indicated or contraindicated, which give rise to the problem of the dangers of polypharmacy.

In addition, polypharmacy is an important cause of increased health costs, both by the use of drugs and indirectly by the iatrogenic effects of pharmacological interactions, adverse drug reactions, and greater morbidity and hospitalizations [4, 16]. Therefore, it is imperative to monitor and optimize the use of medications, especially in general medicine which is the level of care where the prescriptions of different providers are received, to minimize adverse outcomes related to the use of medications to improve the quality of care, as well as for possible cost savings and improve clinical outcomes [19].

In this sense, in some places the volume of polypharmacy data is given prominence, as in primary care in Spain, where general practitioners (GPs) are informed of the frequency of patients with polypharmacy in their patient list, what allows to see the great discrepancy and variability of this prevalence among GPs: it can vary from 4-5% until 18-30% according to GP, in the same geographical area and with lists of random and similar patients. So, it is hypothesized that prevalence of polypharmacy does not justify itself exclusively by the presence of the multimorbidity or of elderly people, neither is randomly distributed; polypharmacy does not depend on the size the GP patients list (large lists may have little polypharmacy and small lists a lot of polypharmacy). Therefore, it is imperative to monitor and optimize the use of medications in general medicine [15].

On the other hand, a great variation between geographical areas has also been reported [20]. And also variations of polypharmacy have been reported according to the pathologies: The most common multi-drug combinations is to treating manifestations of metabolic syndrome [21] and the cardiovascular diseases (31%) followed by the infectious diseases (24 %) and gastrointestinal disorders (24%), and the lowest prevalence of polypharmacy in dermatological diseases (1% -2%), and infectious diseases (20%) [21].

But, there is another point of view that gives more importance to the value of prescriptions than to their volume. There are experiences in which are suggested that paying for the value over the volume is considered a key part of reducing the cost of prescription drugs. It is about the health system maintaining value-based drug coverage, and that include only those medications that an independent source considers valuable [22].

In this scenario, where exists the dichotomy of seeing and assessing polypharmacy as a matter of drug volume, or as a matter of drug quality, this article, which is a personal view, aims, based on a selected narrative review and the author's experience, has as a goal to reflect, conceptualize and synthesize the elements that constitute polypharmacy and show some clues to apply them in daily work, especially in general medicine.

## Discussion

### Volume of the polypharmacy

In general, polypharmacy has been defined in quantitative terms, although there seems to be no consensus on where to establish the limit from which we would be talking about polypharmacy, and in any case they are almost always arbitrary criteria. For some authors, taking only two medications would be polypharmacy, and for others it would be the daily consumption of four, five or even eight drugs. The most widespread number seems to be that of 5 drugs used chronically, a figure from which, there is a relationship with the inappropriate use of medicines. It should be noted

that the frequency of adverse drugs reactions (ADR) is 6% when a patient takes two medications, 50% when he takes five and almost 100% when he takes eight or more medications.

So, drug-related problems are common in general medicine, and even more in aged care. Despite all the progress in medical care, including care for the elderly, it is still reported that drug-related problems occur frequently (and very often in elderly patients), are important factors for hospitalization and reduced quality of life in older adults [15]. It can therefore be said emphatically that problems related to medication, and especially to polypharmacy, are common in adults (especially among elderly patients) and it can cause harm [5, 23-25].

One common consequence of polypharmacy is the high rate of ADRs. An ADR is any response to a drug that is harmful and unintentional, and that takes place at doses that are normally applied in humans for the prophylaxis, diagnosis or treatment of diseases, or for the restoration, correction or modification of physiological functions. This term also includes all the harmful clinical consequences derived from the dependence, abuse and misuse of medications, including those caused by use outside the authorized conditions and those caused by medication errors.

Polypharmacy increases the risk of adverse drug-related events, especially in older adults [26-28]; first of all because a higher number of drugs come a higher risk of harmful DDIs [29]; Further, because the high prevalence of chronic multimorbidity in old age leads to an enhanced risk of drug-disease interactions [30-32].

The prevalence of polypharmacy is high, and could reach 20%. But, the main thing is that there is a great variability among general practitioners (GPs), which can vary from 4-5% until 18-30% according to GP, in the same geographical area and with lists of random and similar patients. Thus, the main cause of polypharmacy (of excessive use of drugs) is the professional; the prevalence of polypharmacy does not justify itself exclusively by the presence of the multimorbidity or of elderly people, neither is randomly distributed [15]. In high-income countries, population-based surveys and cross-sectional studies have shown that polypharmacy affects between 40% and 50% of older adults [33-35].

Several risk factors have been identified, such as recent nursing home admission, number of prescribers, and frailty. Recent studies have also suggested an inverted U-shaped association between age and number of drugs, with a pronounced decline in the burden of medications after the age of 85 years. However, only few of these studies had the possibility to account for the confounding effect of chronic multimorbidity (confounding by indication), thus most likely overestimating the role of sociodemographic risk factors. Moreover, surprisingly little is known about incident polypharmacy, which is the development of polypharmacy over time. This lack of evidence from longitudinal, prospective studies limits our understanding of the epidemiology of polypharmacy and most likely leads to underestimating the true burden of medication use among older adults. Previous studies have shown that, on average, polypharmacy affects between 40% and 50% of all older adults. It has also been reported that the prevalence of polypharmacy (5+ drugs) is 44%, and the prevalence of excessive polypharmacy (10+ drugs) is 12%. The incidence rate of polypharmacy is 20 per 100 person-years, ranging from 17% in individuals aged 65-74 years to 33% in those aged  $\geq 95$  years. The incidence rate of excessive polypharmacy is 8 per 100 person-years (36).

Many ADRs are due to DDIs, but others cannot be strictly assigned to pharmacological effects, so other non-specific mechanisms, such as

nocebo effects or cultural factors, also give rise to ADRs experienced by patients (37). But, in any case, DDIs are a significant cause for ADRs. The risk of a DDI in any particular patient increases with the number of co-existing diseases and the number of drugs prescribed. ADRs and drug allergies- as a subset of ADRs- make a significant public health concern, complicating 5 to 15% or even 20% of therapeutic drug courses. They may result in diminished quality of life, increased physician visits, health care costs, hospitalizations, and even death (38).

In general, the assessment of the severity and preventability of ADRs reveals that 1% of ADRs are severe and 2% are preventable reactions (39). The incidence of ADRs has particularly increased among patients 65 years and older with as many as 1 in 20 persons (40). Of every 100 courses of drug treatment, there are 20 adverse drug ADRs, between 5 and 25 of clinically observable DDIs and between 15 and 50 potential DDIs, which arrive to 100 in geriatric patients (41). However, there are certain aspects of ADRs that are not well known (such as the exact efficacy and safety profile of the drugs in older patients, because the older patients are not included in the large randomized trials, and so much of the information used to determine the age-associated risks of drugs come from observational studies). So, the incidence and prevalence of serious ADRs in the elderly could be not properly rated (42).

In any case, the incidence and prevalence of ADRs and DDIs increases with the number of drugs used. It can be admitted that ADRs occur in approximately 20% of the patients in drug treatment (20). One-quarter of these patients have possible adverse events or diminished treatment effectiveness that may have been at least partly caused by DDIs (43).

DDI is the modification that the action of a medicine undergoes due to the simultaneous presence of another in the organism. The effects of the DDIs are:

1. The appearance of pharmacological adverse reactions
2. The decrease in the effectiveness of the treatment

Too, the incidence of DDI increases with the number of drugs used and with age. The prevalence and incidence of clinically observable DDIs is between 5-10% and up to 25% of patients on pharmacological treatment, and potential DDIs is at least three to five times higher (from 15% to 50%), and even a nearby figure to 100% in geriatric patients on pharmacological treatment. Pharmacodynamic DDIs are more prevalent (80%) than pharmacokinetic. However, the incidence of potentially serious DDIs is relatively low (perhaps less than 1%) among ambulatory patients. But, the absolute number of patients involved is high, its serious potential risks, and its tendency is to increasing rapidly. A persistently obvious fact is that the incidence of ADRs and DDIs increases with the number of drugs used. The use of 5 drugs used chronically is a figure from which there is an independent relationship with the inappropriate use of medicines: the frequency of ADRs is 6%-20% when a patient takes two medications, 50%-80% when he takes five, and almost 100% when he takes eight or more medications (24, 25, 41, 44, 45).

### **Polypharmacy quality**

Low-quality pharmacological care reports are not uncommon. Adverse health outcomes related to medications for the population, and especially the elderly, include falls, strokes, delirium and death, as well as a wide variety of adverse drug reactions and drug-drug interactions (18). On the other hand, only a limited number of studies have been published explicitly using indicators of quality use of medicines, including the

construction of indicators for monitoring the quality of prescriptions in general practice (46).

Anyway, various data of quality use of medicines have been reported, or indicators for measuring quality of medicines in clinical areas (geriatrics and obstetrics) or in specific diseases, such as diarrhea and pneumonia, quality indicators for assessing antimicrobial prescribing and proton pump inhibitors written by GPs, or quality indicators for antibiotic treatment of respiratory tract infections in general practice, among others (47-50).

The combination of the expansion of elderly populations and concerns about variability in the quality of care has driven the development of sets of indicators of quality of care with the aim of monitoring and improving the use of medicines. Indicators are the gold standard for evaluating the quality of many aspects of health care. More specifically, quality indicators of medication-related care are summary measures that should be used as a guide to monitor, evaluate, and improve the use of medication that affects the quality of care and patient outcomes. However, it is common that quality indicators of medical care do not always focus on the use of medications. This lack of recognition of medicines in the current sets of health care quality indicators may reflect an uncertainty (especially in the sector of care for the elderly, which is the segment with the highest prevalence of polypharmacy), with respect to the best way to evaluate use of drugs (51).

It has been reported that about 60% of patients may be exposed to at least one potentially inappropriate medication (identified by the Beers criterion), 80% of patients may be exposed to drugs that contribute to the Drug Burden Index (DBI) > 0, and 90% of patients may be exposed to polypharmacy (ie  $\geq 5$  medications). Exposure to potentially harmful medications, as identified by DBI > 0 and by polypharmacy (i.e.  $\geq 5$  medications) is associated with lower self-rated quality of life (52).

At this level of primary care, can be frequent inappropriate prescribing, for example of renally cleared medications in elderly patients; Thus, has been communicated that virtually 100% of older patients have at least one drugs-related problem as a factor to be highlighted, the chronic renal failure has a prevalence of 50% in these patients, and the prescription for renal elimination drugs can be identified in more than 15% of them. All medications can potentially lead to medication-related problems. A greater number of medications received, and the identification of more than 2 medication-related problems in a patient, are signs of very high risk of medication misadventure (15, 57). On the other hand, it has been described, especially in elderly people, the excessive use of high-risk medications associated with falls (70%), medications with moderate to strong anticholinergic properties (50%), benzodiazepines (40%) and antipsychotics (30%) (53-56).

In addition to the elders in the community, patients with dementia, and especially those who live in residential care centers for the elderly, have a particularly high risk of harm with medications. In these patients, polypharmacy has been identified in 90% of them (with a very high average of 10 drugs per person); one third of these patients were prescribed an antipsychotic medication; and it was found that 50% were taking at least one potentially inappropriate medication. The combination of antipsychotics and antidepressants was the pharmacological interaction observed more frequently, and it was prescribed in 16% of patients. Besides the inappropriate use of benzodiazepines and psychotropics in general, this inappropriate use of drugs has been also reported in proton pump inhibitors, analgesics (including opiates), laxatives, NSAIDs, antacids, etc. (15).

The potential harms of some medications can outweigh their potential benefits (inappropriate use of medications). Despite recommendations to avoid the use of potentially inappropriate medications in older adults, their prevalence is high in different settings, including residential care for the elderly. In addition, of course, the use of potentially inappropriate medications (especially for older adults) represents a substantial cost that can be reduced. In addition to the elders in the community, patients with dementia, and especially those who live in residential care centers for the elderly, have a particularly high risk of harm with medications. In these patients, polypharmacy has been identified in 90% of them (with a very high average of 10 drugs per person); one third of these patients were prescribed an antipsychotic medication; and it was found that 50% were taking at least one potentially inappropriate medication (15). Polypharmacy increases the risk of adverse drug-related events in, especially in older adults because the aging process is associated with physiological changes (eg, weight loss, deterioration of liver and renal excretion, decrease of cardiac output, body composition remodelling) that make that older adults are more prone to adverse drug reactions (58-62).

Initiatives have been proposed to address the quality of polypharmacy. In this way, three areas of polypharmacy have been reported that may be subject to special monitoring to improve the value of polypharmacy (63, 64):

1. The use by polypharmacy of multiple anticholinergic medications in older adults

It is known that the anticholinergic burden increases the risk of cognitive impairment in particular, but it is also associated with an increased risk of falls, a greater number of hospitalizations and decreased physical function. Reducing the concurrent use of these medications, including the use of tricyclic antidepressants, particularly nortriptyline, has been proposed as a priority objective.

2. The use of multiple active drugs in the CNS in older adults

It is known that these drugs cause greater risk of falls and fractures when

taken simultaneously. Taking one or more of the CNS medications may cause a 1.5-fold increase in the risk of falls, and that risk increases to 2.5 times if two or more medications are taken. In addition, a high dose of these medications can lead to a three-fold increase in the risk of recurrent falls.

3. Concurrent prescription of opioids and benzodiazepines

It is known that taking these two drugs at the same time is associated with a four-fold increase in the risk of opioid overdose and death, compared to the use of opioids without a benzodiazepine

**Conclusion**

All patients, especially elderly patients, those with certain pathologies, those with multimorbidity, or those who live in institutions, are exposed to polypharmacy. The prescription of contraindicated or potentially inappropriate medications is also common. It must be taking into account that the issue of polypharmacy, and within this, the attention of the quality and meaning of polypharmacy, is a crucial and complex issue. It is crucial because its increase, in relation to the multimorbidity, the over-diagnosis, the medicalization and the increase in costs, shows a rapid growth. It is a complex issue because of the very nature of these variables and because of the inherent difficulties in the criteria and the measurement of quality

The quantity of drugs as a defining concept of polypharmacy implies poor quality (FIGURE 1, FIGURE 2). The more drugs that are prescribed to a patient, not only are there more possibilities of inappropriate prescriptions or of little value, but even suitable prescriptions tend to lose their indication, and from a certain level of quantity or volume of prescriptions, the increase in probability of IDD and ADRs makes their value decrease in such prescriptions, and they begin to be inappropriate and give rise to poor quality. In other words, there is no adequate and valuable polypharmacy; the concept of polypharmacy makes the quantity of drugs, even of value, causes a reduction in that value, and poor quality, increased risks of iatrogeny, poor health outcomes and increased costs begin to predominate. The high quantity originates low quality.

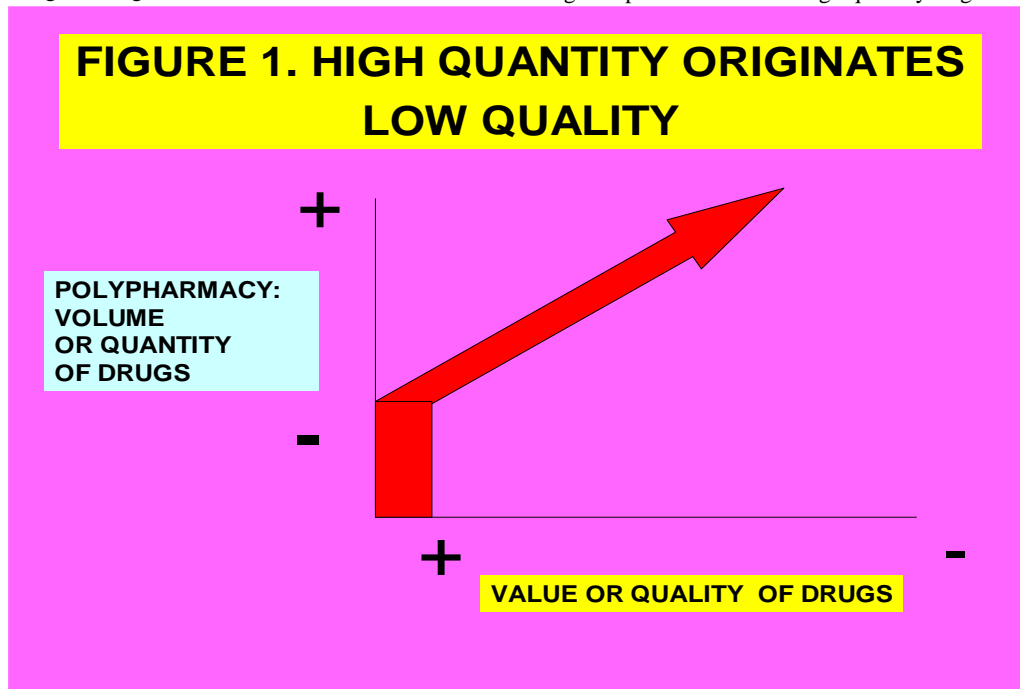
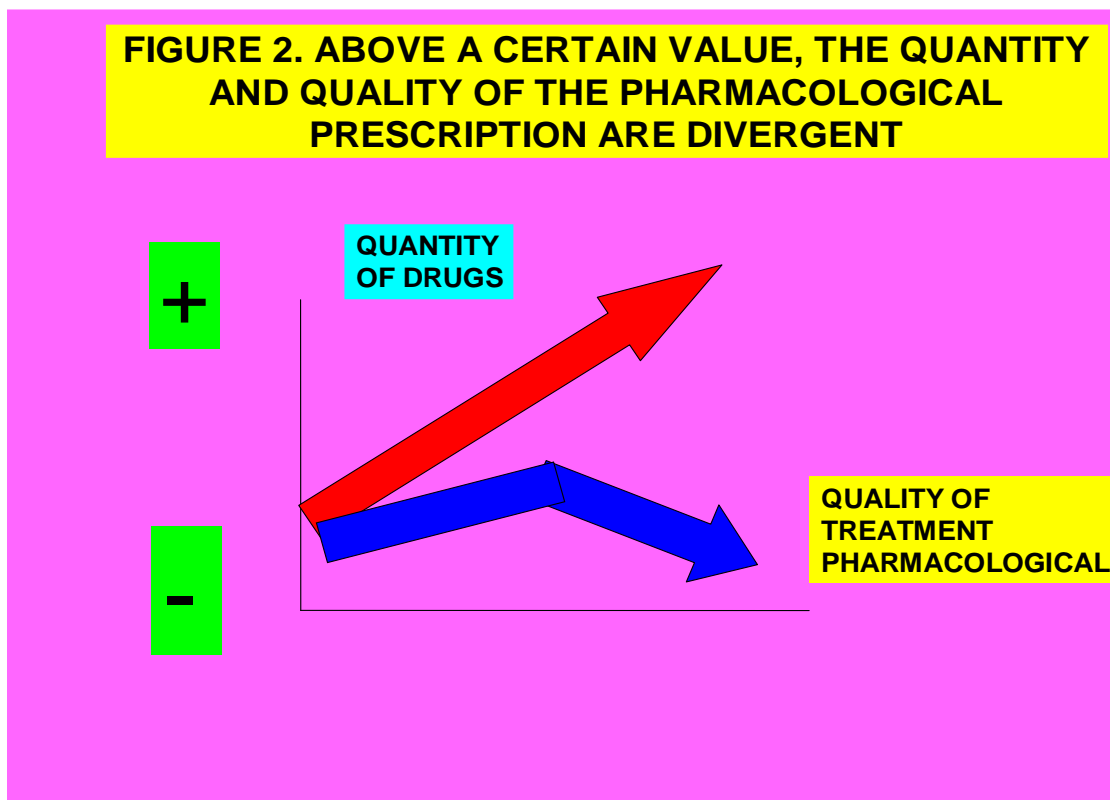


Figure 1 Polypharmacy Implies Poor Quality





**FIGURE 2 above a Certain Value, the Quantity and Quality of the Pharmacological Prescription Are Divergent**

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