Arch Pharmacol Ther. 2024;6(1):21-23.

Archives of Pharmacology and Therapeutics Editorial

The Domino Effect of Polypharmacy. A Dangerous Catalyst That Starts Numerous Bio-Psycho-Social Chain Reactions

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Received date: March 28, 2024, **Accepted date:** April 01, 2024

Citation: Turabian JL. The Domino Effect of Polypharmacy. A Dangerous Catalyst That Starts Numerous Bio-Psycho-Social Chain Reactions. Arch Pharmacol Ther. 2024;6(1):21-23.

Keywords: Drug interactions, Drug-related side effects and adverse reactions, Polypharmacy, Practice patterns, Inappropriate prescribing, General practice

Editorial

Increasing medicalization causes some disconcerting trends in medical decision making. Polypharmacy is one of its most important consequences. The tendency to equate the concepts of risk factor and disease, the changes in the biomedical assessment of the severity of many health problems, and the increase in the number of pharmacological treatments create a growing set of multimorbidity and polypharmacy, and this produces a dramatic domino effect, with an increase in adverse drug effects (ADR) and drug-drug interactions (DDI), which feed on themselves: the more biomedically defined morbidity, the more polypharmacy, the more morbidity, the more polypharmacy, etc.

Polypharmacy defined as the chronic co-prescription of several drugs, is often the consequence of the application of disease specific guidelines, targeting disease specific goals, to patients with multiple chronic diseases. The basic concept of the use of multiple medicines (polypharmacy) is quite simple: the prescription of more medications than are clinically appropriate. From 1999 to 2007, the proportion of mild and severe polypharmacy cases increased from 41% (1999) to 51% (2003) and 57% (2007). And the trend continues to rise, with up to 92% in the elderly (2020) [1]. Medical utilization increased with the severity of polypharmacy, as did the use of advanced medical resources (i.e., the number of hospitalizations). In particular, the increase in incidence rate ratio was more significant in 3 aspects: number of pharmacy visits, number of emergency room admissions, and number of hospitalizations [2].

One common consequence of polypharmacy is the high rate of ADR, mainly from DDI. So, DDI are a significant cause for ADR [3,4]. DDI are defined as quantitative or qualitative modifications or alterations of the effect of a drug caused by the simultaneous or successive administration of another drug, medicinal plant, food, drink, or environmental contaminant. This modification usually results in a variation in the intensity (increase or decrease) of the usual effect or in the appearance of a different effect (subtherapeutic, therapeutic or toxicological) than the expected one [5,6].

The incidence of DDI increases with the number of drugs used. Prevalence and incidence of clinically observable DDI is between 5- 25% of patients on pharmacological treatment. DDI also contributes substantially to differences in drug response. 10% of ADR are due to DDI. 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 ADR is 6% when two medications are taken, 50% when five are taken, and almost 100% when eight or more medications. In this scenario, it could be said that the presence of polypharmacy is an indicator of malpractice and poor quality especially in family medicine practice [7].

To following the recommendations for prescription in clinical guidelines (NICE clinical guidelines for type 2 diabetes, heart failure, and depression) would result in numerous potentially serious drug interactions: 32 potentially serious drug-disease interactions between drugs recommended in the guideline for type 2 diabetes, 6 for drugs recommended in the guideline for

depression and 10 for drugs recommended in the guideline for heart failure. Few of these DDI are highlighted in the usual guidelines [8].

It is important to clarify some aspects of confusion; 1. Polypharmacy does not depend exclusively on multimorbidity; 2. Polypharmacy does not depend on the size of the general practitioner (GP) patient list (large lists may have little polypharmacy and small lists may have a lot of polypharmacy); 3. There is a great variability between doctors in the prevalence of polypharmacy (all this means that the predictable prevalence of polypharmacy could be between 10% and 20%, although there is a great variability per GP: from 4-5% up to 18-30% according to the family doctor), 4. The main cause of polypharmacy (excessive use of medications) is the professional. Taking into account the great variability in the prevalence of polypharmacy between general medicine offices within the same geographical area and subject to the same health policies and budgets, and which does not seem to be justified by differences in the characteristics of the list of patients treated (age, sex, social level, morbidity), we must think that the medical action is responsible, and 5. The majority of clinical guidelines, although they invoke their support on evidence-based medicine, are biased in favor of the biomedical approach over the biopsychosocial one, are influenced by the pharmaceutical industry and are, in short, dangerous for individual and community health without a reflective contextualization for each case [9].

DDR and DDI can have important consequences, and may give rise to, among others, the following domino effects: 1. There are more symptoms of ADR initially classified as very rare or undescribed; 2. The symptoms of ADR can be "disorganized" where there is no way to achieve a global diagnosis that puts the whole thing in order; 3. In some diseases the symptoms are milder, so they can go unnoticed with the consequent risk; 4. There is confusion between the symptoms of a new disease or an ADR, making it difficult to achieve a diagnosis; 5. The appearance of a second disease as a consequence of the treatment of the first, or the increase in the aggressiveness of a disease; 6. The appearance of drug-induced systemic processes; 7. The appearance of iatrogenic infections; 8. DDI may also contribute substantially to differences in drug response resulting in a higher incidence of ADR and greater severity or sometimes loss of its effects (lack of response); 8. The interference of medications with laboratory tests; and, 9. Increases in costs at all levels of the health system, with an increasingly lower cost-benefit ratio of the health system [10-14].

The GP should consider pharmacological agents in a holistic way (biopsychosocial, contextualizing all clinical guidelines and treatment). Each patient needs a comprehensive assessment with a view to developing a personalized therapeutic regimen [3]. Not all drugs have the same risk profile for inducing interactions. The drugs with the greatest potential to present DDI are those that undergo biotransformation through a single metabolic pathway, those that have a high presystemic elimination or have a first-pass hepatic effect, those that have a narrow therapeutic range with therapeutic and toxic concentrations very close or that present dose-dependent reactions [5,15].

Furthermore, some techniques could be suggested for judiciously avoid polypharmacy in general medicine: 1) Use drugs only in authorized indications; 2) Use only indicated drug combinations; 3) Avoid starting treatment with two drugs from the same pharmacological group; 4) Avoid prescribing drugs that significantly inhibit or induce metabolizing enzymes, prescribe drugs that are eliminated by several metabolic pathways or that do not have serious consequences if their metabolism is prolonged or reduced, and monitor plasma concentrations of the drug subject to pharmacokinetic interaction, especially when adding an enzyme inducer or inhibitor and suspending it, taking into account that the period in which the induction or inhibition is maintained is variable; 5) avoid using the last commercialized drug, of which there is almost no experience; 6) Avoid using higher doses than indicated at the beginning of prescription; 7) Avoid using a drug longer than indicated; 8) Not treating ADR with other drugs, and, 9) Be a thoughtful and independent thinker from the pharmaceutical industry [7,9,16].

In short, in medicine the first thing is "primum non nocere" (do no harm) [17]; Polypharmacy is a dangerous catalyst that starts numerous harmful bio-psycho-social chain reactions. It is an indicator of poor and dangerous medical practice.

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