PERSONAL VIEW

Reactions Adverse to Drugs and Drug-drug Interactions: A "Wonderful" Spiral of Geometric Growth Produced by Multimorbidity and Polypharmacy

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ABSTRACT

The attempt to solve multimorbidity using tools of the biological framework makes us return to the origin: It is like a boomerang. Doctor is punished to strive uphill on a mountain to climb the heavy burden of multimorbidity when it seems to be reaching the top that burden of disease rolls back down, and again, the doctor is at the point of departure and that seems to be repeated infinitely: It is like the Myth of Sisyphus. Diagnosis and medical treatment are the "weapons" used by the professional to "cure" or "solve" health problems. However, overdiagnosis and drug overtreatment are weapons that, if they do not impact their objective, return to their point of origin, creating more problems than they intended to solve overdiagnosis and polypharmacy. Of every 100 courses of drug treatment, there are 20 adverse drug reactions, between 5 and 25 of clinically observable drug-drug interactions (DDIs) and between 15 and 50 potential DDIs, which arrive to 100 in geriatric patients. The current approach to the disease, risk factors, and prevention, within the biomedical framework, seems to produce a boomerang effect or Sisyphus effect. However, it is even worse: It is a logarithmic spiral or "the wonderful spiral" or "growth spiral." This spiral follows a geometric progression, not arithmetic: Every health problem that we "cure" leads us, not to another new problem, but to many more. And so, it is increasingly complex to leave the labyrinth of multimorbidity and polytherapy. And yet, the DDIs are often predictable and preventable, and the biomedical framework for addressing health problems can be extended to a biopsychosocial framework.

Key words: Disease, drug-related side effects and adverse reactions, general practitioner, metaphor, multimorbidity, over diagnosis, polypharmacy, prescriptions

INTRODUCTION

The analogy between a certain phenomenon observed in a certain artistic, sociological, anthropological, or scientific field and a certain phenomenon pending to be understood and observed in medicine, supposes an important support to understand the latter. Metaphors are analogy devices to illuminate reality. Thus, we have the metaphor of the boomerang: A weapon that after being launched, if it does not impact the target, returns to its point of origin due to its aerodynamic profile and special launching form.[1] Moreover, the Myth of Sisyphus: Sisyphus, in Greek mythology, is known for his punishment: Pushing a stone up a mountain that, before reaching the top, rolled back down, repeating again and again the frustrating and absurd process.[2]

The attempt to solve multimorbidity using tools of the biological framework makes us return to the origin. The doctor is punished to strive up a mountain to climb the heavy burden of multimorbidity when he seems to be reaching the

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top that burden of disease rolls back down and the health-care professional returns to the point of departure and that seems to be repeated infinitely.

Diagnosis and medical treatment are the "weapons" used by the professional to "cure" or "solve" health problems. However, overdiagnosis and pharmacological overtreatment are weapons that, if they do not impact their objective, return to their point of origin, creating more problems than they intended to solve.

Overdiagnosis can be defined as the diagnosis of a condition that, if unrecognized, would not cause symptoms or harm a patient during his or her lifetime, and it is increasingly acknowledged as a consequence of screening for cancer and other conditions and by medicalization of everyday life and the medical emphasis on the biological approach to health problems. Overdiagnosis in primary care is an important problem from a public health perspective and has far-reaching implications.[3]

Prescription medications are a cornerstone of community-based health care, especially in the first world countries. They are used to successfully manage a broad range of health conditions that appear in general medical practices including bacterial infections, chronic conditions such as diabetes, mental health conditions, and everyday needs such as contraception. However, some classes of prescription medications (e.g., opioids) carry risk to the community if their prescription or use is inappropriate. Inappropriate prescribing includes a variety of potentially harmful prescribing practices such as inappropriate dosage and prescribing medications that interact with others or lead to adverse events. Inappropriate prescribing of medications, especially those that are opioid-based analgesics and psychoactive, can be harmful and even fatal to patients by potentially facilitating inappropriate use. Inappropriate use of prescription medications is a growing problem globally.[4]

Overtreatment refers to the unnecessary treatment of a condition. It occurs whenever overdiagnosed disease is treated and can affect the individual patient as well as the wider health-care system. Overdiagnosed disease provides no opportunity for treatment benefit so it incurs only harms. These potential harms include direct negative consequences of the unnecessary treatment itself (such as a wound infection after thyroidectomize to treat an overdiagnosed thyroid cancer) and indirect harms related to the consequences of resultant downstream services (such as palpitations resulting from an incorrect dose of replacement levothyroxine after thyroidectomize).[3,5]

The practices of using drug combinations could also be included in the concept of overtreatment for problems for which only one drug could be used (for example, associate two antidepressants initially for the treatment of depression, or associate two benzodiazepines, or associate at the beginning two hypo tensors, or two analgesics, etc.). It could also be included in the concept of overtreatment the practice of to using maximum doses of the drugs without clear indication or drugs that may be contraindicated or to using higher risk drugs from the start versus other lower risk alternatives (such as doses higher than those recommended by nonsteroidal anti-inflammatory drugs [NSAIDs] or paracetamol, or starting with opioids from the beginning of symptoms of low back pain, etc.).

In this age, where multimorbidity appears to be infinite in everyday work in medical primary and hospital settings, multimorbidity is more the norm than an exception, and its presence is an indicator of polypharmacy.[6,7] 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 five drugs used chronically, a figure from which, there is a relationship with the inappropriate use of medicines.[8,9] In short, the concept of the use of multiple medicines (polypharmacy) or of "polymedicated patient" is quite simple: The prescription of more medications then is clinically appropriate.[6,10-14]

All patients, especially elderly patients, those with certain pathologies, those with multimorbidity, or those who live in institutions, are more exposed to polypharmacy. It is admitted that the prevalence general of polypharmacy is high and could reach 20%.[15]

Many efforts have been made to understand and treat multimorbidity. This is very important and complex objective, which despite their difficulty and their different approaches ranging from pure quantitative approaches to strict qualitative guidelines, create great agreements regarding the search for new approaches that offer more utility. However, the importance of the side effects of multimorbidity and polypharmacy is often forgotten: The drug-drug interactions (DDIs) and adverse drug reactions (ADRs). These are phenomena that are rooted in multimorbidity and polypharmacy and that feedback on these problems.

In this scenario, this article aims, based on a selected narrative review and the author's experience, to reflect, synthesize, and conceptualize, about the phenomenon of ADRs and DDIs, showing its possible implications for clinical practice, mainly from the level of medicine general.

DISCUSSION

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. At this level of primary care, can be frequent inappropriate prescribing, for example of medications in elderly patients; so, has been communicated that virtually 100% of older patients have at least one drug-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.[16-19]

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.

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.[20,21] However, in any case, DDIs are a significant cause for ADRs. The risk of a DDI in any particular patient increases with the number of coexisting diseases and the number of drugs prescribed. It should be noted that the frequency of ADRs is 6% when a patient takes two medications, 50% when he takes five, and almost 100% when he takes eight or more medications.[8,9]

Hence, ADRs and drug allergies – as a subset of ADRs – make a significant public health concern, complicating 5–15% 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.[22] In general, the assessment of the severity and preventability of ADRs reveals that 1% of ADRs are severe and 2% are preventable reactions.[23] The incidence of ADRs has particularly increased among patients 65 years and older with as many as 1 in 20 persons.[24]

The importance of ADRs becomes bigger and bigger in relation to the current increase in the use of drugs, polypharmacy, and multimorbidity. 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. It has been reported that about 60% of patients may be exposed to at least one potentially inappropriate medication, 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 (i.e., ≥5 medications). Exposure to potentially harmful medications, as identified by DBI >0 and by polypharmacy (i.e., ≥5 medications) is associated with lower self-rated quality of life. 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.

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]

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), it could be clarified in studies at the level of general medicine, and the general practitioner could use that local knowledge. Hence, the incidence and prevalence of serious ADRs in the elderly could be not properly rated.[25]

The incidence and prevalence of ADRs and DDIs increase with the number of drugs used. It can be admitted that ADRs occur in approximately 20% of the patients in drug treatment.[26] One-quarter of these patients have possible adverse events or diminished treatment effectiveness that may have been at least partly caused by DDIs.[27]

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 as follows:

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

The incidence of DDI increases with the number of drugs used and with age. The prevalence and incidence of clinically observable DDIs are between 5% and 10% and up to 25% of patients on pharmacological treatment, and potential DDIs are at least 3–5 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

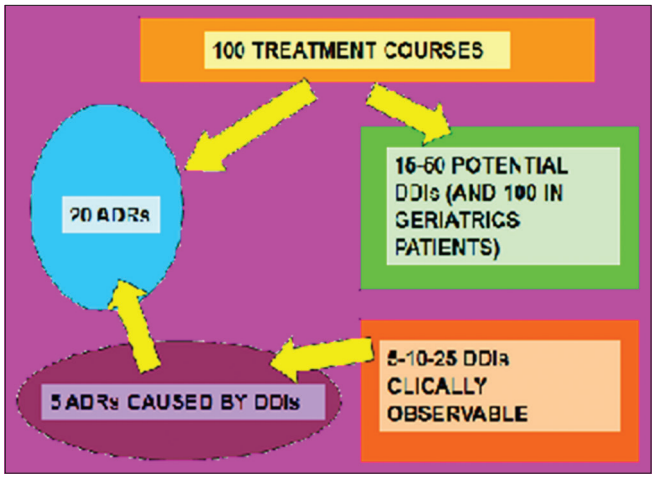

Figure 1: Flowchart of adverse drug reactions and drug-drug interactions

Figure 2: The spiral of adverse drug reactions and drug-drug interactions

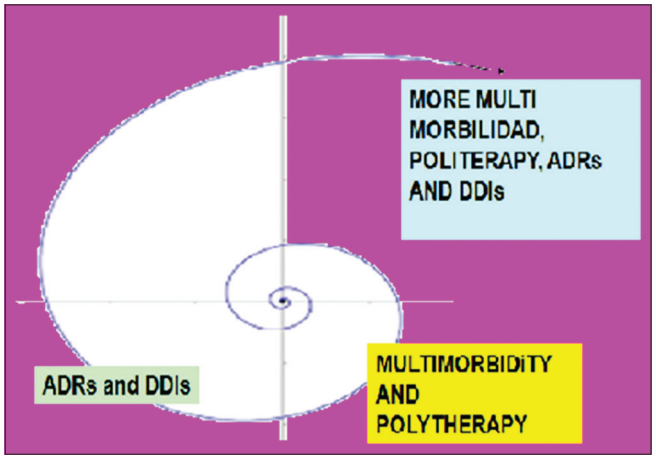

Figure 3: The "wonderful" spiral of geometric growth of adverse drug reactions and drug-drug interactions produced by multimorbidity and polypharmacy

potentially serious DDIs is relatively low (perhaps, <1%) among ambulatory patients. However, the absolute number of patients involved is high, its serious potential risks, and its tendency is to increase rapidly.[28]

Other authors report higher numbers of IDDs identified: From 20% to 30%. No difference between men and women regarding the mean number of DDIs identified per prescription. A persistently obvious fact is that the incidence of ADRs and DDIs increases with the number of drugs used, being 20% in patients taking two drugs, and 80% in those taking six or more.[28] 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.[29,30]

CONCLUSION: THE METAPHOR OF THE GEOMETRIC SPIRAL

ADRs and DDIs are a real problem in clinical practice, which may partly remain hidden. Figure 1 shows an approximation to the flow of ADRs and DDIs in pharmacological treatments in general medicine. The current approach to the disease, risk factors, and prevention, within the biomedical framework, seems to produce a boomerang effect or Sisyphus effect. Doctors work tirelessly to reduce the set of disease and increasingly "create" more disease. The task of diagnosis and treatment becomes overdiagnosis and overtreatment, and "returns" to health services, in part, such as ADRs and DDIs, which increase the disease burden for the health system, for patients, and for the community in general. In addition, it is not uncommon for doctors to treat ADRs with drugs, thereby creating a boomerang subsystem as well (more polypharmacy, more ADRs and DDIs, which, in turn, are treated with more drugs, etc.).

However, in reality, the effect of ADRs and DDIs exceeds the concept of boomerang effect or the Sisyphus Myth. Certainly, the effect of wanting to address morbidity, with an exclusively biomedical framework, causes multimorbidity and polypharmacy, and consequently ADRs and DDIs, etc. It is not so much a boomerang effect or Sisyphus effect since it is not returning to the place of departure, but returning to the place of departure in worse conditions; ADRs and DDIs that appear in the attempt to resolve the disease burden create more disease then were intended to be resolved. It is certainly a logarithmic spiral or "the wonderful spiral" or "growth spiral." This spiral follows a geometric progression, not arithmetic: Every health problem that we "cure" leads us, not to another new problem, but to many more. The arms of tropical cyclones, such as hurricanes, storms, galaxies, and spider webs, form logarithmic spirals. And so, it is increasingly complex to leave the labyrinth of multimorbidity and polytherapy [Figures 2 and 3]. An important distinction must be made

between returning boomerangs and the Myth of Sisyphus, and the geometric spiral. And yet, the DDIs are often predictable and preventable, and the biomedical framework for addressing health problems can be extended to a biopsychosocial framework.

REFERENCES

1. Boomerang. From Wikipedia, the Free Encyclopaedia. Available from: https://www.en.wikipedia.org/wiki/Boomerang.
2. The Editors of Encyclopaedia Britannica. Sisyphus. Greek Mythology. Available from: https://www.britannica.com/topic/Sisyphus.
3. Kale MS, Korenstein D. Overdiagnosis in primary care: Framing the problem and finding solutions. BMJ 2018;362:k2820.
4. Kunstler BE, Lennox A, Bragge P. Changing prescribing behaviours with educational outreach: An overview of evidence and practice. BMC Med Educ 2019;19:311.
5. McCaffery KJ, Jansen J, Scherer LD, Thornton H, Hersch J, Carter SM, *et al*. Walking the tightrope: Communicating overdiagnosis in modern healthcare. BMJ 2016;352:i348.
6. Turabián JL, Pérez Franco B. A way of helping "Mr. Minotaur" and "Ms. Ariadne" to exit from the multiple morbidity labyrinth: The master problems. Semergen 2016;42:38-48.
7. Turabian JL. Notes for a theory of multimorbidity in general medicine: The problem of multimorbidity care is not in practice, but in the lack of theoretical conceptualization. J Public Health Gen Med 2018;1:1-7.
8. Rodríguez Del Río E, Martínez Agüero M, Arias Fernández L, Martín-Sánchez FJ. Global intervention in the polymedicated patient. Gac Sanit 2016;30:402.
9. Turabian JL, Franco BP. Helping "Dr. Theseus" leaves the labyrinth of multiple drug interactions. BMJ 2015;350:h1059.
10. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. BMC Geriatr 2017;17:230.
11. Turabian JL. Why do patients not meet the pharamalogical treatment? Arch Pharmacol Ther 2018;1:1-8.
12. Turabian JL. Doctor-patient relationship in pharmacological treatment: Discontinuation and adherence. COJ Rev Res 2018;1. Available from: https://www.crimsonpublishers.com/cojrr/pdf/COJRR.000521.pdf.
13. Hillen JB, Vitry A, Caughey GE. Medication-related quality of care in residential aged care: An Australian experience. Int J Qual Health Care 2019;31:298-306.
14. Monégat M, Sermet C, Perronnin M, Rococo E. Polypharmacy: Definitions, Measurement and Stakes Involved Review of the Literature and Measurement Tests. Questions D'économie de la Santé; 2014. Available from: http://www.irdes.fr/english/issues-in-health-economics/204-polypharmacy-definitions-measurement-and-stakes-involved.p.
15. Turabian JL. Polypharmacy is an indicator of bad practice and low quality in general medicine. J Qual Healthcare Eco 2019;2:130.
16. Roughead EE, Semple SJ, Gilbert AL. Quality use of medicines in aged-care facilities in Australia. Drugs Aging 2003;20:643-53.
17. Gheewala PA, Peterson GM, Curtain CM, Nishtala PS, Hannan PJ, Castelino RL. Impact of the pharmacist medication review services on drug-related problems and potentially inappropriate prescribing of renally cleared medications in residents of aged care facilities. Drugs Aging 2014;31:825-35.
18. Kosari S, McDerby N, Thomas J, Naunton M. Quality use of medicines in aged care facilities: A need for new models of care. J Clin Pharm Ther 2018;43:591-3.
19. Stafford AC, Tenni PC, Peterson GM, Jackson SL, Hejlesen A, Villesen C, *et al*. Drug-related problems identified in medication reviews by Australian pharmacists. Pharm World Sci 2009;31:216-23.
20. Fernández RP, Rojo EV. Reacciones Adversas Medicamentosas. Valoración Clínica. Madrid: Ediciones Díaz de Santos S.A; 1992.
21. Gutiérrez-Islas E, Báez-Montiel BB, Turabián JL, Bolaños-Maldonado M, Herrera-Ontañón JR, Villarín Castro A, *et al*. Patients with adverse drug reactions have a higher prevalence of emotional disorders. Aten Primaria 2012;44:720-6.
22. Pourpak Z, Fazlollahi MR, Fattahi F. Understanding adverse drug reactions and drug allergies: Principles, diagnosis and treatment aspects. Recent Pat Inflamm Allergy Drug Discov 2008;2:24-46.
23. Gholami K, Ziaie S, Shalviri G. Adverse drug reactions induced by cardiovascular drugs in outpatients. Pharm Pract (Granada) 2008;6:51-5.
24. Bourgeois FT, Shannon MW, Valim C, Mandl KD. Adverse drug events in the outpatient setting: An 11-year national analysis. Pharmacoepidemiol Drug Saf 2010;19:901-10.
25. Turabian J. Strategies to increase opportunities to identify and communicate adverse drug reactions and drug related problems in general medicine. J Fam Med Community Health 2018;5:1165.
26. Turabian JL. The role of general practitioner in the study of adverse drug reactions epidemiology in ambulatory care setting. Arch Community Med Public Health 2019;5. DOI: 10.17352/2455-5479.000045.
27. Tulner LR, Frankfort SV, Gijsen GJ, van Campen JP, Koks CH, Beijnen JH. Drug-drug interactions in a geriatric outpatient cohort: Prevalence and relevance. Drugs Aging 2008;25:343-55.
28. Turabian JL. Approach to the epidemiology of drug interactions in primary health care. The visible part of a dangerous great iceberg growing rapidly. Epidemiol Int J 2019;3:126.
29. Parekh N, Gahagan B, Ward L, Ali K. They must help if the doctor gives them to you: A qualitative study of the older person's lived experience of medication-related problems. Age Ageing 2019;48:147-51.
30. Turabian JL. Relevant characteristics for elderly patient biopsicosocial care in general medicine. Arch Community Fam Med 2019;2:48-55.

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