



General Practitioner' Role in the Drug-Drug Interactions

Jose Luis Turabian*

Specialist in Family and Community Medicine, Health Center Santa Maria de Benquerencia, Regional Health Service of Castilla la Mancha (SESCAM), Toledo, Spain

Abstract

Drug-Drug interactions (DDIs) are frequent in patients taking several drugs. This problem is more important in general medicine both for the number of patients and for the number of prescriptions. Although the possible DDIs are too numerous for general practitioners (GPs) to remember, it is possible to systematize some recommendations to facilitate their identification and prevention in general medicine:

- a) Comprehensive approach (GP and patient should consider the pharmacological agents of holistic way);
- b) Know the prescribed drugs well (pharmacological arsenal not very extensive and avoid polypharmacy);
- c) DDIs can be foreseen, and prevented (doing pharmacological history including self-medication and being attentive to patient situations can increase the risk: number of simultaneous drugs, age and severity of the disease, drugs with enzyme metabolism P450);
- d) The effects of DDIs can be detected by clinical evaluation (most potentially serious outpatient interactions involve a limited number of medications);
- e) Computerized alarm and detection systems should be developed and used (especially to detect CYP450-DDIs in elderly patients);
- f) Partnership between pharmacists and GPs (community pharmacies can systematically use surveillance systems to identify patients with clinically significant DDIs);
- g) The GP must be attentive to the prescription of drugs with greater interaction potential (those that undergo biotransformation through a single metabolic pathway, those that have a high presystemic elimination or have a hepatic first-pass effect, a narrow therapeutic margin with very close therapeutic and toxic concentrations or what they have dose-dependent reactions);
- h) The GP should remember the specific and important drugs most involved in DDIs (NSAIDs, warfarin, methotrexate, antiplatelet agents, selective serotonin reuptake inhibitors, beta-2 adrenergic receptor agonists, central nervous system medicines, etc.).

Introduction

Drugs are probably the most important medical care technology to prevent diseases, disabilities, and deaths in the population. But, due to the increase in the use of medicines, the risk of problems related to them also increases [1]. In addition, most medications are prescribed and administered in outpatient settings, so drug problems, such as drug adverse reactions (DARs) and drug-drug interactions (DDIs), are treated in general medicine [2]. Pharmacological interactions 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, beverage or environmental contaminant. This modification is usually translated into a variation in the intensity (increase or decrease) of the usual effect or in the appearance of a different effect (sub therapeutic, therapeutic or toxicological) than expected. The negative effects of DDIs are essentially of two types [3]:

The appearance of ADRs

I. The decrease in the effectiveness of the treatment

Although the concept of pharmacological interaction is, strictly speaking, the modification that the action of a drug undergoes the simultaneous presence of another in the organism, however, interactions can also occur with endogenous physiological substances such as hormones, neurotransmitters, enzymes, etc., or with non-pharmacological exogenous substances, such as tobacco or coffee. Thus, although the term DDI is commonly used as a synonym for pharmacological interaction, healthcare professional must not forget the possible existence of drug-other element interactions not strictly drugs. Drug combinations

Article Information

DOI:	10.31021/ijbs.20181115
Article Type:	Review article
Journal Type:	Open Access
Volume:	2 Issue: 1
Manuscript ID:	IJBS-2-115
Publisher:	Boffin Access Limited
Received Date:	30 September 2019
Accepted Date:	05 January 2020
Published Date:	07 January 2020

*Corresponding author:

Jose Luis Turabian

Specialist in Family and Community Medicine
Health Center Santa Maria de Benquerencia
Regional Health Service of Castilla la Mancha
(SESCAM), Toledo, Spain
E-mail: jturabianf@hotmail.com

Citation: Turabian JL. General Practitioner' Role in the Drug-Drug Interactions. Int J Biopharm Sci. 2020 Jan;2(1):115

Copyright: © 2020 Turabian JL. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 international License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

can show surprising effects, given the effects of individual drugs; these are phenomena known as DDIs. Pharmacological interactions can be classified as synergistic or antagonistic, if the effect of the combination is greater or less than expected, respectively. A better understanding of drug interactions and their relationship with phenotypes offers hope for finding combinations of medications that have high therapeutic values, and may also show risk factors to avoid for adverse effects [4]. The mechanisms of pharmacological interaction can be subdivided into:

- A. Pharmacokinetic interactions
- B. Pharmacodynamic Interactions

Among the former, the interactions that involve the inhibition or induction of cytochrome P450 (CYP) enzymes are clinically very important. If such interactions cause an increase in systemic drug exposure, adverse effects are likely to occur, while a decrease in exposure may lead to treatment failure [5]. For example, protease inhibitors, a class of antiretroviral agents often used in the treatment of HIV infection, interact with numerous transport proteins, resulting in clinically significant DDIs. Proteins that carry protease inhibitors directly influence the pharmacokinetics of these drugs [6]. There is little information on the ADTs in the outpatient setting, and although only a small percentage of outpatient visits seem to result in prescription combinations with clinically important DDI potential, these interactions can have significant implications due to morbidity and mortality related to medication [7]. However, it is admitted that the prevalence and incidence of clinically observable DDIs is between 5-10% and up to 25% of patients on pharmacological treatment, and the potential DDIs is at least three to five times higher (from 15% to 50% of patients on pharmacological treatment), and even a nearby figure to 100% in geriatric patients on pharmacological treatment [8]. And an important aspect is the fact that DDI are avoidable medication errors (and yet they are associated with potentially serious adverse events and death) [9]. On the other hand, at the level of general medicine care, polypharmacy adds more risks to the use of drugs. Thus, due to the increasing frequency of polypharmacy in outpatient treatments, although a wide variance has been reported in the clinical relevance of these DDIs, it can be assumed that the prevalence of DDIs will be increasing, and trend is towards increasingly appear interactions with more serious or significant effects [10,11].

Consequently, the increasing use of prescription drugs has raised concerns about polypharmacy and its effects. Pharmacological regimens are increasingly complex and potentially harmful, and people with polypharmacy need periodic review and prescription optimization. More research is needed to better understand the impact of multiple interacting medications as they are used in real-world practice and to assess the effect of medication optimization interventions on quality of life and mortality [12]. Given the diversity of drugs, the use of new drugs with few known data about its effects, the number of associated drugs that are prescribed, the use of drugs outside of any consolidated protocol, the increasingly frequent use of drugs for unauthorized indications (off label), and the tendency to use higher doses than usual, make IDD increasingly complex and important. On the other hand, the vast majorities of IDDs are not described, or are not known, nor are there studies based on DDIs that are oriented in outpatient practice. In this scenario, one might ask, how should doctors manage patients with multiple diseases to help to prevent a cascade of problems that starts with inadequate treatment guidelines and moves through polypharmacy to an increased risk of DDIs? Providing physicians with alerts about potentially harmful DDIs is only moderately effective due to high alert override rates. And on the other hand, there is a great variation in the number of drugs prescribed by different individual doctors, for the same health problems, which suggests that individualized interventions should be performed. In addition, one of the biggest challenges in preventing DDIs is the substantial gap between theory and clinical practice. So, there are no robust methods published for formally assessing quality of evidence relating to DDIs, despite the diverse sources of information [12,13]. In this complex context there are three major

actors: the drug, the patient, and the doctor. This article aims, based on a selected narrative review and the author's experience, to reflect, synthesize and conceptualize, on how to approach IDD from the level of general medicine, and showing its possible implications for clinical practice.

Discussion

The possible pharmacological interactions in all possible combinations of drugs and chronic diseases are too numerous for doctors to remember or for the guidelines to mention. But, although it is impossible to remember all the interactions, whether these are potential or clinically relevant, pharmacokinetic or pharmacodynamic, it is possible to systematize some general recommendations, which partly overlap, useful for clinical care, that affect the drug, but also to patient, doctor, and community pharmacist, that can facilitate the identification and prevention of DDIs at the level of general medicine (Table 1, Figure 1).

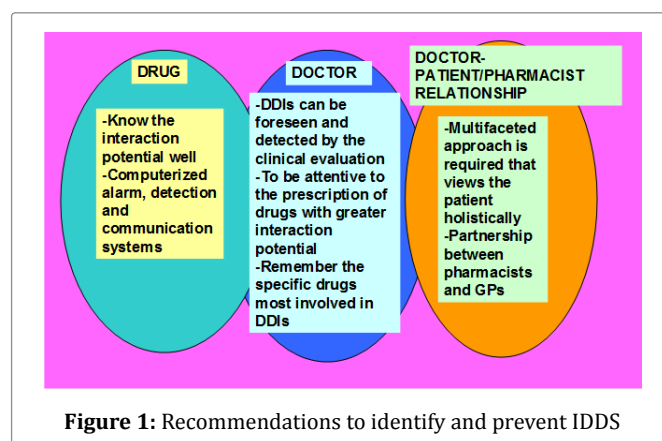
Integral approach

A multifaceted approach is required that visualizes the patient in an integral way and uses the available tools in a more effective and integrated way. The general practitioner (GP) should consider pharmacological agents holistically [15,16]. On the other hand, drug use should be avoided to treat problems that are not "master or main" problems, if possible. This would be the first rationalization of drug treatment: avoid "shooting pellets" with the dispersion experienced by them [11]. The non-pharmacological approach should always be considered as a treatment option, especially in minor problems.

It is important to know the prescribed drugs well

The GP must use a not very extensive pharmacological arsenal, which he must know in depth, including the interaction potential that these drugs entail. Because doctors find it easier to start with a new medication than to discontinue an old one, many patients end up taking a long list of prescription medications. Patient reviews should involve reviewing their medications, and may take into account patient preferences. However, a randomized trial in people over 70 who took more than six long-term medications suggests that the benefit is disappointingly small [17,18]. The GP should avoid therapeutic inertia and discuss with the patient the inertia that the same patient may have on the continuity of unnecessary, or inappropriate or contraindicated drugs.

For example, in some cases of illness (such as in most cases of depression, even severe or persistent), they can be treated successfully with psychosocial interventions, which are preferred by patients, are beneficial for self-esteem and social functioning, and have no adverse effects [19]. The use of potentially inappropriate drugs is very common among residents of nursing homes, and this increases the likelihood of DDI. Monitoring these patients for drug use and possible drug interactions could increase the quality of the prescription [20]. The GP should remember that, first of all,



Recommendations to Identification and Prevention of IDDS At the Level of General Medicine

1	A multifaceted approach is required that views the patient holistically
2	It is important to know the prescribed drugs well, including the interaction potential that they entail.
3	DDIs can be predicted (and consequently prevented)
4	The effects of DDIs can be detected by clinical evaluation
5	Computerized alarm, detection and communication systems must be developed and used
6	Partnership between pharmacists and GPs to prevent drug-drug interactions
7	The GP must be attentive to the prescription of drugs with greater interaction potential
8	The GP must remember the specific drugs most involved in DDIs

Table 1: Systematization of some recommendations that can facilitate identification and prevention of IDDS at the level of general medicine

each patient needs a comprehensive evaluation in order to develop (doctor and patient together) a personalized therapeutic regimen that balances the benefits and harms and takes into account the priorities and preferences of the patient. The same evaluation needs to consider the many factors that can influence the effectiveness of a drug, beyond the narrow efficacy that supports the specific patterns of the disease. In older patients, these factors could include cognitive and functional impairment, and lack of social support. Second, GPs must have the support of technologies properly evaluated and integrated into their daily work, such as alerts in the electronic prescription system [15].

On the other hand, it should avoid polypharmacy, keeping a close eye on clinical responses and ADRs in patients, avoiding using off-label drugs, and using the indicated drugs, for the shortest time possible and at the lowest appropriate doses. These would be the key elements to prevent and control IDD in outpatients. Further, polypharmacy is a growing problem, which leads to increased morbidity and mortality, especially in older patients with multiple diseases. Consequently, there is a need to reduce polypharmacy [21].

DDIs can be predicted (and consequently prevented)

The GP can organize and carry out its work so that it can facilitate the identification of an eventual interaction. Certain patient situations may increase the risk of having DDIs, such as the number of drugs administered simultaneously, the age and severity of the disease. Pharmacotherapy in the elderly is a challenge due to physiological changes related to age, high interindividual variability and increasing frequency of multimorbidity. The resulting polypharmacy increases the risk of drug interactions and requires an individual risk assessment. It has been documented that some drug interactions are associated with damage in older adults, such as poisoning, gastrointestinal bleeding or falls. Therefore, this evaluation is considered of special importance in the elderly. In addition, frequent risk factors and continuous physiological changes in the elderly should be taken into account during the risk assessment [22]. The prediction of DDI in elderly patients will provide better prescription and medication safety. For example, the use of non-steroidal anti-inflammatory agents, selective serotonin reuptake inhibitors and beta-2 adrenergic receptor agonists, should be closely monitored [23]. Most of these medications are subject to metabolism by CYP enzymes and transmembrane transport. This results in a considerable potential for drug interactions [24]. The decision of the GP to intervene for possible DDI mediated by CYP depends on the clinical judgment in addition to the result of the drug alert software programs [25,26]. Therefore, the incidence of DDIs-related ADRs in elderly outpatients is high, and most events have important clinical consequences and can be preventable or improvable [27], but their prevention and management require a systematic development of the prospective surveillance system service to:

- a) To identify high-risk medications that cause potential IDD in outpatients

- b) For the development of collaborative services among local doctors

- c) For academic research purposes of risk management [27].

Special care should be taken with the prescription and therapeutic follow-up of patients who have characteristics identified as predictors of IDD risk. This knowledge of possible IDD predictors could help develop preventive practices and policies that allow public health services to better manage this situation. Among these predictors of higher risk, the following have been indicated: female sex, the diagnosis of ≥ 3 diseases, and a diagnosis of hypertension. On the other hand, it has been reported that the adjusted OR increases from 0.90 in patients aged 60 to 64 years to 4.03 in those aged 75 years or older. Pharmacological therapy regimens with ≥ 2 prescribers have an OR of 1.39, those of ≥ 3 drugs have an OR of 3.21, and the prescription of ≥ 2 drugs that act on CYP an OR of 2.24 [26]. In addition, special attention should be given to patients with pharmacological treatments for arrhythmia or heart failure [26].

As rates of polypharmacy rise and medication regimens become more complex, the risk of potential CYP-mediated DDIs is a growing clinical concern (especially for older adults). The prevalence of potential CYP-mediated DDIs detected among older adults with polypharmacy is 80%. The probability of at least 1 CYP-mediated DDI is 50% for persons taking 5-9 drugs, 81% with 10-14 drugs, 92% with 15-19 drugs, and 100% with 20 or more drugs. Addition of each medication to a 5-drug regimen confers a 12% increased risk of a potential CYP-mediated DDI after adjustment for age and sex [25]. A majority (82%) of the prescriptions for potentially interacting medications occur in visits involving 5 or more medications. Patients over 44 years of age, especially elderly, Medicare beneficiaries in USA, and those patients to whom have prescribed by doctor multiple medications are at risk for receiving prescription combinations with potential for clinically important DDIs [7]. It has also been reported that odds of exposure are highest among those aged 65 years or older, males, and those with more chronic conditions. Odds of exposure increase 1.39 times with each addition of a prescription medication. A substantial number of clinically important potential DDIs have been identified among warfarin users. In summary, awareness of the most prevalent potential DDIs can help practitioners prevent concomitant use of these dangerous medication combinations [9].

The effects of IDDS can be detected by clinical evaluation

Clinically relevant DDIs refer to the pharmacological or clinical response to the administration or co-exposure of a drug with another drug that modifies, in a significant level the clinical response in the patient, and are dangerous to patient health. As already mentioned, a key point is to keep in mind that, potential IDDS increase with the increasing number of concomitant drugs. So, special attention should be drawn on patients with polypharmacy and those with drug treatments for arrhythmia or heart failure. In this sense, GPs should be more aware of possible IDD in these contexts [28,29].

IDDs contribute significantly to the occurrence of ADRs in older adults and intervention or prevention programs, such as the use of a computerized system, can reduce the burden of iatrogenic diseases, which is especially important in the elderly [30]. In any case, the GP should always suspect a possible DDI in the presence of ADR in polymedicated patients. The reported findings also indicate that most potentially serious interactions in outpatients involve a limited number of medications, particularly NSAIDs, warfarin and methotrexate [27]. Clinically meaningful DDIs are common in patients with complex medication regimens. A systematic approach for identifying DDIs, determining clinical significance, formulating patient-specific recommendations, and communicating recommendations is important in the GP clinical practice [31].

Computerized alarm, detection and communication systems must be developed and used

It is important to keep a vigilant attitude about suspicions of new or poorly known DDIs. Interactions can cause ADRs. ADRs secondary to interactions will be notified, like the rest, through the spontaneous notification of adverse reactions programs [32,33]. Spontaneous ADR notification, despite its limitations, can be an important resource for detecting ADR associated with the concomitant use of interacting drugs. The GP should apply its surveillance systems to identify high-risk medications. Patients, particularly the elderly, often receive more than one medication at a time. With each drug added to a regimen, the number of possible drug interactions (DDI) increases by a power law. Early prediction of relevant interactions using computer tools greatly helps physicians and can guide their prescription choices. However, a reliable computerized surveillance system to monitor potential IDDIs is not yet fully established [34]. Similarly, IDD detection computer systems should be developed to help pharmacists, especially to detect CYP-DDIs in elderly patients [35]. Consequently, it is desirable to develop a list of clinically important DDIs found in outpatient and community pharmacy settings, to be detected by a computerized pharmacy system. These systems should take into account the various aspects:

1. Clinical aspects of IDD (for example, clinical importance, quality and quantity of evidence, causal relationship, risk of morbidity and mortality)
2. Presence of elderly and multi-morbid
3. Generation of reports designed to optimize the Current prescriptions of older patients by applying the STOPP and START criteria, highlighting pharmacological interactions and providing non-pharmacological recommendations aimed at reducing risk [36,37].

In any case, there is evidence that guidelines and good computerized prescription support tools can alert doctors to possible problems efficiently, helping to improve prescription and reduce interactions [15]. The European Medicines Agency has already suggested that spontaneous reports of adverse events can be used to identify patterns of interactions between drugs that were not apparent before drug authorization [15]. To avoid IDDs, reliable information on all medications used by each individual should be available at the point of care. Clinically relevant DDI knowledge databases must be updated and accurate. To adapt the “magic bullet” to the individual, in the future will be necessary a new genomic and proteomic knowledge about the individual [38].

Partnership between pharmacists and GPs to prevent DDIs

Although DDIs are an important cause of ADRs and are usually predictable and preventable, for their prevention and management it is required a systematic development, and it is unclear how community pharmacists could contribute to the management of DDIs when applying its surveillance systems to identify high-risk medications. What is established is that community pharmacies can actively contribute to the management of IDDs risk and

systematically use their surveillance systems to identify patients with clinically significant IDDs. It should be borne in mind that the majority of potentially serious interactions in outpatients involve a limited number of medications, which may facilitate the organization of surveillance. Additional research should focus on the participation of community pharmacists in the management of IDDs risk in collaboration with GPs [27]. In the context of community pharmacy, pharmacist-patient communication can vary from brief counselling episodes to extensive pharmaceutical care consultations. Many community pharmacies have developed practices to facilitate the effective delivery of pharmaceutical care, particularly to chronic patients, although the nature and scope of services differ widely from one country to another. The usefulness of the pharmacist-patient, and GP-pharmacist interaction, and its involvement in the detection and prevention of IDDs should be explored to improve patient care and optimize specific results [39-41].

The GP must be attentive to the prescription of drugs with greater interaction potential

Not all drugs have the same risk profile to induce interactions. The drugs with the greatest potential for interactions are those that undergo biotransformation through a single metabolic pathway, those that have a high presystemic elimination or have a hepatic first-pass effect, those that have a narrow therapeutic margin with very close therapeutic and toxic concentrations or which present dose-dependent reactions [3]. The prescription of drugs that significantly inhibit or induce metabolizing enzymes should be avoided, and however, GP should prescribe drugs that are eliminated by several metabolic pathways or that do not have serious consequences if their metabolism is prolonged or reduced, and he could control drug plasma concentrations especially when adding an enzyme inducer or inhibitor [42,43]. It is worth highlighting the current therapeutic complexity and the difficulty of the GP to knowing by their own means the potential and described IDDs. But, thanks to the new information technologies, databases have acquired a great prominence, which thanks to their integration in prescription systems or electronic medical records allow them to be detected before they occur, or to establish control mechanisms to that, if they occur, the risk to the patient is minimal. These systems should be limited to detecting only IDDs that may cause harm to the patient and avoid the so-called “alert fatigue”, which occurs when health professionals receive a high number of alerts, including those that are trivial or inappropriate for their patients. In this sense, it is important that the GP be able to select the most suitable database of IDDs with a catalog of IDDs appropriate to clinical care practice, far from theorizing and with the minimum possibility of generating false alerts [42].

The GP must remember the specific and important drugs most involved in DDIs

A limited number of medications have been implicated in potentially severe outpatients DDIs, particularly [9,23,27,28,44-49]:

- A. NSAIDs (one of drug groups with the most commonly DDIs)
- B. Warfarin and methotrexate
- C. The interaction with digoxin and diuretics
- D. The combination of anticoagulant and antiplatelet agents
- E. The use of selective serotonin reuptake inhibitors, beta-2 adrenergic receptor agonists
- F. Drug combinations are between central nervous system medicines
- G. The combinations of theophylline / aminophylline and ciprofloxacin / fluvoxamine, warfarin and barbiturates
- H. The use of amiodarone which interacts with potassium-wasting diuretics, digoxin, simvastatin and acenocoumarol.
- I. The use of pimozide and an azole antifungal with warfarin or a nonsteroidal anti-inflammatory drug (NSAID)

- J. Cyclosporine and rifamycin
- K. The use of statins due to pharmacotherapy of co-morbidities
- L. The antineoplastic and antiretroviral therapies
- M. And the use of omeprazole, diazepam, and calcium

It should be taken into account that the frequency of IDD is usually obtained from the frequency of use of each drug and the number of serious interactions in which it has intervened, so a bias is introduced in favour of drugs frequent use, since the number of serious interactions, in which a drug intervenes, also depends on the frequency with which it is used [49].

Conclusion

In all settings, there are challenges associated with the safe drug treatment of patients, especially with multimorbidity and polypharmacy. But, this problem is more important in outpatients both for the number of patients and the number of prescriptions, and for the lack of data compared to the hospital setting. The need to characterize, understand and limit the damages resulting from the use of medications is, therefore, increasingly important in general medicine. The DDIs are frequent in patients taking several drugs. Although IDD cannot be avoided in many cases, and in routine medical practice it is often impossible to avoid them, they can present a considerable risk to the outcome of the treatment and the patient's health. However, many other IDDs can be predicted and avoided or controlled. The GP must have a vigilant role regarding IDDs. The GP must know the possible interferences between the medications taken by the patient, documenting by means of a good clinical history of the drugs that he takes including possible self-medication or that were prescribed by other doctors. If there is a risk of interaction, the GP must take the necessary precautions to detect, prevent or avoid them. In case of a suspected interaction, the pharmacological treatment should be suspended, whenever possible, communicated, document the suspicious association and reintroduce it according to the information obtained. Likewise, it is recommended not to use drugs to treat the consequences of interactions. Finally, the GP must do all that contextualizing in the particular case of each patient.

References

1. Brahma DK, Wahlang JB, Marak MD, Sangma ChM. Adverse drug reactions in the elderly. *J Pharmacol Pharmacother*. 2013 Apr;4(2):91-94.
2. Turabián-Fernández JL, Pérez-Franco B. Prescription of Medication by Family Doctors: Rational, Reason, or Relevant? *Aten Primaria*. 2005 Nov;36(9):507-509.
3. Bada Aínsa JL, Salvá Miquel JA. Reacciones adversas de los medicamentos y enfermedades yatrogénas. Barcelona: Ediciones Toray, S.A. 1980
4. Cokol M. Drugs and their interactions. *Curr Drug Discov Technol*. 2013 Jun;10(2):106-113.
5. Sawada Y, Satoh H. [Drug interactions of psychotropic drugs]. *Nihon Rinsho*. 2012 Jan;70(1):27-41.
6. Griffin L, Annaert P, Brouwer KL. Influence of drug transport proteins on the pharmacokinetics and drug interactions of HIV protease inhibitors. *J Pharm Sci*. 2011 Sep;100(9):3636-3654.
7. Aparasu R, Baer R, Aparasu A. Clinically important potential drug-drug interactions in outpatient settings. *Res Social Adm Pharm*. 2007 Dec;3(4):426-437.
8. 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 Aug;3(2).
9. Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther*. 2008 Apr;33(2):141-151.
10. Turabian JL. Polypharmacy is an Indicator of Bad Practice and Low Quality in General Medicine. *J Qual Healthcare Eco*. 2019 Jul;2(4).
11. Turabian JL, Pérez Franco B. Helping "Dr. Theseus" leave the labyrinth of multiple drug interactions. *BMJ* 2015 Mar;350:h1059.
12. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med*. 2015 Apr;13:74.
13. Cho I, Lee Y, Lee JH, Bates DW. Wide variation and patterns of physicians responses to drug-drug interaction alerts. *Int J Qual Health Care*. 2019 Mar;31(2):89-95.
14. Seden K, Gibbons S, Marzolini C, Schapiro JM, Burger DM et al. Development of an evidence evaluation and synthesis system for drug-drug interactions, and its application to a systematic review of HIV and malaria co-infection. *PLoS One*. 2017 Mar;12(3).
15. Marengoni A, Onder G. Guidelines, polypharmacy, and drug-drug interactions in patients with multimorbidity. *BMJ*. 2015 Mar;350.
16. Muth C, van den Akker M, Blom JW, Mallen CD, Rochon J et al. The Ariadne principles: how to handle multimorbidity in primary care consultations. *BMC Medicine*. 2014 Dec;12:223.
17. Verdoorn S, Kwint HF, Blom JW, Gussekloo J, Bouvy ML. Effects of a clinical medication review focused on personal goals, quality of life, and health problems in older persons with polypharmacy: A randomised controlled trial (DREAMer-study). *PLoS Med*. 2019 May;16(5).
18. Editorial Managing medication...and other stories. *BMJ*. 2019 Jun;365.
19. Brailon A, Lexchin J, Blumsohn A, Hengartner MP. Prescription of antidepressants. The "pharmaceuticalisation" of life. *BMJ*. 2019 May;365.
20. Hosia-Randell HM, Muurinen SM, Pitkälä KH. Exposure to potentially inappropriate drugs and drug-drug interactions in elderly nursing home residents in Helsinki, Finland: a cross-sectional study. *Drugs Aging*. 2008;25(8):683-692.
21. Zechmann S, Trueb C, Valeri F, Streit S, Senn O, et al. Barriers and enablers for deprescribing among older, multimorbid patients with polypharmacy: an explorative study from Switzerland. *BMC Fam Pract*. 2019 May;20(1):64.
22. Bitter K, Schlender JF, Woltersdorf R. [Drug-drug interactions in the elderly: Which ones really matter?]. *Internist (Berl)*. 2016 Jul;57(7):728-734.
23. Gören Z, J Demirkapu M, Akpınar Acet G, Çali S, Gülcebi Idriz Oğlu M. Potential drug-drug interactions among prescriptions for elderly patients in primary health care. *Turk J Med Sci*. 2017 Feb;47(1):47-54.
24. Boobis A, Watelet JB, Whomsley R, Benedetti MS, Demoly P et al. Drug interactions. *Drug Metab Rev*. 2009;41(3):486-527.
25. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. *Ann Pharmacother*. 2013 Mar;47(3):324-332.
26. Obreli Neto PR, Nobili A, Marusic S, Pilger D, Guidoni CM, et al. Prevalence and predictors of potential drug-drug interactions in the elderly: a cross-sectional study in the Brazilian primary public health system. *J Pharm Pharm Sci*. 2012;15(2):344-354.
27. Toivo TM, Mikkola JA, Laine K, Airaksinen M. Identifying high risk medications causing potential drug-drug interactions in outpatients: A prescription database study based on an online surveillance system. *Res Social Adm Pharm*. 2016 Jul-Aug;12(4):559-568.
28. Rätz Bravo AE, Tchambaz L, Krähenbühl-Melcher A, Hess L, Schlienger RG. [Prevalence of potential drug-drug interactions in ambulatory patients with statin therapy]. *Praxis (Bern 1994)*. 2006 Feb 95(5):139-146.
29. Teixeira JJ, Crozatti MT, dos Santos CA, Romano-Lieber NS.

- Potential drug-drug interactions in prescriptions to patients over 45 years of age in primary care, southern Brazil. *PLoS One*. 2012;7(10).
30. Marengoni A, Pasina L, Concoreggi C, Martini G, Brognoli F, et al. Understanding adverse drug reactions in older adults through drug-drug interactions. *Eur J Intern Med*. 2014 Nov;25(9):843-846.
31. Nelson SD, LaFleur J, Hunter E, Archer M, Steinvooort C et al. Identifying and Communicating Clinically Meaningful Drug-Drug Interactions. *J Pharm Pract*. 2016 Apr;29(2):110-115.
32. Aronson JK (ed.) *Meyler's Side Effects of Drugs*, 15th Edition: The International Encyclopedia of Adverse Drug Reactions and Interactions. Amsterdam: Elsevier. 2016 Mar-Apr;48(2);224.
33. Collignon U, Karalliedde J (Eds.) (2016) *Adverse drug interacciones: A handbook for prescribers*. Florida, United States: CRC Press.
34. Hammann F, Drewe J. Data mining for potential adverse drug-drug interactions. *Expert Opin Drug Metab Toxicol*. 2014 May;10(5):665-671.
35. Zakrzewski-Jakubiak H, Doan J, Lamoureux P, Singh D, Turgeon J. Detection and prevention of drug-drug interactions in the hospitalized elderly: utility of new cytochrome p450-based software. *Am J Geriatr Pharmacother*. 2011 Dec;9(6):461-470.
36. Malone DC, Abarca J, Hansten PD, Grizzle AJ, Armstrong EP et al. Identification of serious drug-drug interactions: results of the partnership to prevent drug-drug interactions. *J Am Pharm Assoc*. 2004 Mar-Apr;44(2):142-151.
37. Lavan AH, O'Mahony D, Gallagher P, Fordham R, Flanagan E et al. The effect of SENATOR (Software ENgine for the Assessment and optimisation of drug and non-drug Therapy in Older peRsons) on incident adverse drug reactions (ADRs) in an older hospital cohort – Trial Protocol. *BMC Geriatr*. 2019 Feb;19(1):40.
38. Astrand B. Avoiding drug-drug interactions. *Chemotherapy*. 2009;55(4):215-220.
39. Juurlink DN. Drug-drug interactions: where do we go from here? *J Am Pharm Assoc*. 2004 Mar-Apr;44(2):128, 131-2, 134.
40. Alayeto ME. Drug interaction screens are pharmacists' responsibility. *J Am Pharm Assoc*. 2005 Mar-Apr;45(2):116, 119.
41. Cavaco A, Roter D. Pharmaceutical consultations in community pharmacies: utility of the Roter Interaction Analysis System to study pharmacist-patient communication. *Int J Pharm Pract*. 2010 Jun;18(3):141-148.
42. Girona Brumós L, Juárez Giménez JC, Lalueza Broto P. Pharmacological interactions: a professional Challenger. *Farm Hosp*. 2014 May-Jun;38(3).
43. Cozza KL, Armstrong SC, Oesterheld JR. Principios de interacción farmacológica para la práctica médica. Barcelona: Ars Medica.
44. Mounier N, Katlama C, Costagliola D, Chichmanian RM, Spano JP. Drug interactions between antineoplastic and antiretroviral therapies: Implications and management for clinical practice. *Crit Rev Oncol Hematol*. 2009 Oct;72(1):10-20.
45. Leone R, Magro L, Moretti U, Cutroneo P, Moschini M et al. Identifying adverse drug reactions associated with drug-drug interactions: data mining of a spontaneous reporting database in Italy. *Drug Saf*. 2010 Aug;33(8):667-675.
46. van Heerden JA, Burger JR, Gerber JJ, Vlahović-Palčevski V. Prevalence of potentially serious drug-drug interactions among South African elderly private health sector patients using the Mimica Matanović/Vlahović-Palčevski protocol. *Int J Pharm Pract*. 2018 Apr;26(2):156-164.
47. Chatsisvili A, Sapounidis I, Pavlidou G, Zoumpouridou E, Karakousis VA et al. Potential drug-drug interactions in prescriptions dispensed in community pharmacies in Greece. *Pharm World Sci*. 2010 Apr;32(2):187-193.
48. Malone DC, Hutchins DS, Hauptert H, Hansten P, Duncan B et al. Assessment of potential drug-drug interactions with a prescription claims database. *Am J Health Syst Pharm*. 2005 Oct;62(19):1983-1991.
49. Sánchez-Muñoz LA, Monteagudo-Nogueira B, López De Juan M, Mayor-Toranzo E. Drug interactions in primary care and patient safety. *Aten Primaria*. 2012 Jan;44(1):57-58.