For the Identification and Management of Adverse Reactions Caused by Polypharmacy

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Abstract
Improving the quality and efficiency of medical services has become a key strategic goal in recent years. This is driven by population needs and global trends and is reflected in government programs and systemic decisions. However, the changes implemented have not yet fully ensured convenient and high-quality medical care for the population. Consequently, several government statements highlight the importance of directing existing resources toward tangible improvements in service accessibility and quality.
Like in other countries, Georgia faces various risks when prescribing medications. One of these is polypharmacy—the unnecessary use and prescribing of many medicines. In EU countries, 1 in every 20 patient prescriptions contains an error related to the number of medications. Ensuring high-quality treatment involves additional verification of the doctor's prescription.
Keywords: Quality of medical care, global trends, state programs, systemic decision, risks of using medical products, polypharmacy

Introduction
Improving the quality and efficiency of medical services has become a strategic objective of the 21st century. This is due to the fact that, taking into account both the needs of the population and global trends, the development strategy of medical organizations in modern conditions should be based on improving the quality of service and increasing its competitiveness. This, in turn, requires innovative approaches grounded in international practice and standards. The introduction of modern, quality-oriented management systems is critical, which entails adopting ISO 9001 standards, TQM methods, and relevant tools.

Literature Review
It should be noted that the number of works by Georgian authors on polypharmacy management in the Georgian scientific space is insufficient. In recent years, dissertations on this and related topics have not been found.
Literature, a large part of which is of a practical-applied nature, and some of which covers generalized theoretical issues. Our field of interest included works created in the following scientific directions: organization management and quality management.
Some authors believe that the most complete and irreplaceable resource for any organization, especially a medical one, is its human capital. Qualified, loyal, competent professionals are a rarity today, but finding and employing them is the primary concern for all top managers. Working with people today is much more important than working with new technology products.

Research and Core Analysis
As in other countries, there are various types of risks when prescribing medications in Georgia. One of them is polypharmacy - taking and prescribing a large number of drugs without need. 1 out of every 20

patient prescriptions contains an error in the number of medications in EU countries. High-quality treatment is ensured by additional verification of the doctor's prescription.

The problem was widely covered by the World Health Organization in the middle of the last century, when information on clinically significant drug interactions began to appear in the medical and other literature. (Advenier, et al., 1980) and the first reports of drug interactions discussed the possibility of increasing or decreasing the clinical effect when medicinal products are used simultaneously. Although at that time health professionals were aware of the synergy and antagonism of drug pharmacological effects, information about the influence of one drug on the absorption, metabolism, and elimination of another has only recently begun to spread. Numerous studies conducted in the 1960s and experiments on animals have shown that a large number of drugs can interact with each other and cause the development of adverse reactions by enhancing or inhibiting the metabolism of drugs. (Abel, Maggs, Back, & Park, 1992). As early as the late 1960s, the first tables containing drug interactions and recommendations for the safe use of drug combinations appeared in printed publications.

The problem of polypharmacy is echoed by the proposed initiative in the Georgian healthcare system: any patient who is prescribed five or more medications by a doctor after consultation will have the right and opportunity to review the prescription. Adverse reactions caused by drug interactions are a serious problem not only for the patient or the doctor, but also for regulatory authorities and society as a whole.

Many adverse reactions associated with drug interactions are predictable, since their pharmacodynamic or pharmacokinetic interaction mechanisms are known. According to some authors, many cases of hospitalization due to adverse reactions that develop during drug interactions can be avoided by proper monitoring of the patient's condition when using the drugs or alternative medications.

Therefore, information about the increased risk of an adverse reaction due to a drug interaction should be available to the physician so that he can take measures to reduce the risk by using an alternative drug, adjusting the dose, or appropriately monitoring the patient's condition. However, one of the problems with information about drug interactions is the large amount of disparate information, which makes it difficult to extract, sort, and incorporate all available information into clinically informed decision-making.

To improve the quality of drug therapy and reduce the risk of developing adverse reactions due to drug interactions, some countries use automated systems that analyze prescribed drug combinations and identify potentially dangerous ones.

There are also automated systems for processing literature and large clinical databases to identify information about severe adverse reactions caused by drug interactions. These automated systems can reduce the number of adverse reactions due to drug interactions by 50%.

However, these systems have significant drawbacks that limit their effectiveness and widespread use. These systems issue numerous false warnings about the risk of drug interactions, as well as clinically insignificant interactions, which leads to “attention fatigue” for treating physicians. Furthermore, these systems do not take into account the patient’s clinical condition and the benefit/risk ratio, which often leads to incorrect clinical recommendations for physicians.

In this regard, only 11% of drug interactions detected using such systems are clinically significant and potentially dangerous, and only in 13% of cases lead to a change in the prescribed therapy due to the identification of potentially hazardous drug combinations.

Information on complications caused by drugs or their interactions can be obtained by various methods well known to specialists and described in the literature. However, the primary recognized method in the work of pharmacovigilance authorities in all countries of the world for obtaining information on adverse reactions, including those caused by drug interactions, is the spontaneous reporting method (spontaneous reporting method). It has been shown that post-marketing analysis of spontaneous reports is one of the most effective methods for identifying dangerous drug combinations and adverse

reactions caused by them. This method was developed and implemented in Great Britain in 1964, where it was called the “yellow card scheme”. According to this method, healthcare professionals, either voluntarily or in accordance with legal requirements, report identified adverse reactions to regulatory and licensing authorities, including those resulting from drug interactions.

Incoming messages are processed and entered into the ADVERSE REACTION database. After analyzing spontaneous messages and establishing a cause-and-effect relationship between drug interactions and adverse reactions, the so-called response to the same combination of drugs is generated, which can be used for early warning of a possible adverse reaction.

Thus, the majority of drug interactions leading to the development of adverse reactions were identified by analyzing spontaneous reports entered into the databases of national or regional centers in different countries. For example, an analysis of spontaneous reports received in a Swedish database revealed a high risk of adverse reactions due to interactions between drugs and St. John's wort (hypericum perforatum), warfarin and tramadol, warfarin and noscapine, and warfarin and tetracyclines.

Information on adverse reactions due to drug interactions is used to make various decisions, such as including additional information in the instructions for use, prohibiting the combined use of interacting drugs, and recommending restricting the indications for combined use in medical practice.

For example, the US Food and Drug Administration (FOOD AND DRUG ADMINISTRATION) has withdrawn some drugs from registration due to their potentially dangerous interactions with other medications, leading to severe adverse reactions, including deaths (Table 1).

Table 1. Drugs that have been removed from FDA registration due to the high risk of complications caused by drug-drug interactions

Medication	Drug group	Year of deregistration	Adverse reactions caused
Terfenadine	Antihistamine	1998	C>T segment prolongation, “pirouette” type arrhythmia in case of combination with macrolides and antifungal drugs (fluconazole, clotrimazole, etc.) When combined with amiodarone, statins, and digoxin, the concentration of these drugs increases to dangerous levels.
Astemizole	Antihistamine	1999	
Grepafloxacin	Antibacterial	1999	
Cisapride	Prokinetics	2000	
Mibefradil	T-type calcium channel blocker	2001	Rhaemolysis in combination with macrolides, antifungal drugs (fluconazole, clotrimazole, etc.).
Cerivastatin	Hypolipidemic drug	2002	C>T segment prolongation, "pirouette" type arrhythmia
Propoxyphene	Opioid analgesic	2010	Massive bleeding in case of combined use with anticoagulants
Drotrecogine	Recombinant activated protein C	2011	Adverse reactions caused

In all cases, an increase in drug concentration in blood plasma was observed, caused by inhibition of transport activity and the biotransformation system via inhibition of cytochrome P-450 isoenzymes.

It is known that the frequency of adverse reactions caused by drug-drug interactions depends on the patient's health, the number of drugs used (which also increases with age), the patient's genetic characteristics, the treatment regimen, and the nature of drug metabolism.

The risk of developing an adverse reaction caused by drug interactions increases significantly with an increase in the number of drugs taken simultaneously, as confirmed by numerous studies. Currently, polypharmacy is a fairly common phenomenon, and there is a tendency for its increase. Polypharmacy, according to some studies, occurs in approximately 56% of patients under 65 years of age and in 73% of patients over 65 years of age. According to these data, the simultaneous use of two drugs leads to the development of clinically significant adverse reactions caused by drug interactions in 6% of patients. The simultaneous appointment of 5 drugs (which has long been not uncommon in modern clinical practice) increases the frequency of adverse drug interactions to 50%.

In Italy, 40% of people over 70 years of age take 4-6 drugs daily, while 12% take more than 9 medications. In the United States, older adults, who make up 12% of the population, consume about a third of all prescription drugs and a quarter of all over-the-counter medicines. On average, each older American takes 4-5 prescription drugs and 2 over-the-counter drugs daily. According to other data, the average person aged 65 or older in the United States takes about 10.7 medications at a time.

According to a study conducted in Sweden over 10 years, the average number of medications per patient increased from 2.5 to 4.4. The prevalence of polypharmacy increased 3-fold (from 18% to 42%).

Also, the risk of developing adverse reactions caused by drug interactions increases significantly with the use of large doses of drugs, with long-term use of combination drug therapy, with drugs that significantly affect metabolism in the body, and with a single pharmacological effect when taking medications. Drug interactions in which a moderate change in plasma concentrations can lead to a significant increase in the pharmacological effects of the drug.

In addition, when taking medications with a narrow therapeutic interval, adverse reactions caused by drug-drug interactions are more likely to develop compared to drugs with a wide therapeutic interval.

Many new drugs have an increased risk of developing adverse reactions due to drug-drug interactions, since their mechanisms of action in the human body are insufficiently studied and cause pharmacological effects.

Patients at risk of developing adverse reactions due to drug interactions include the elderly. This is due to the presence of concomitant diseases, disorders of homeostatic systems, and polypharmacy in people of this age. Therefore, the problem of drug interactions in older people is of particular importance, since they (as well as those who often take several drugs at the same time) have a higher risk of adverse drug interactions than younger people. This is also due to the aging process's impact on organs responsible for drug metabolism and excretion, especially the liver and kidneys.

Conclusion

Thus, according to some authors, the incidence of adverse reactions caused by drug interactions when taking two or more drugs is 12% across all age groups and 22% among older adults (over 65 years). Other studies indicate that adverse reactions due to drug interactions account for 3% of all hospitalizations and 4.8% of hospitalizations among older people.

The risk group also includes individuals with polysubstance abuse who take high doses of drugs to treat treatment-resistant conditions, mentally ill patients, children, and populations in developing countries, where self-medication and unregulated dispensing of prescription drugs are common.

Additionally, genetic factors or other factors, such as chronic alcohol or nicotine use, can influence the functioning of the CYP450 system, further increasing the risk of adverse reactions from drug interactions. Reactions caused by interactions between anticoagulants and antiplatelet agents are often severe and have high mortality rates. It is important to note that drug interactions are a significant issue in the pharmacotherapy of HIV infection. British researchers conducted a study of patients receiving antiretroviral therapy to assess the frequency of clinically important drug interactions and the effectiveness of treating physicians in detecting them.

The study revealed that 27% of HIV patients experienced at least one drug-drug interaction. The researchers found that 28% of these interactions involved antiretroviral drugs, while the remaining involved antiretrovirals and other drug classes, particularly those affecting the central nervous system (44%), antidepressants (23%), antibiotics (10%), and statins (7%). During HIV treatment, physicians identified only 36% of cases with clinically significant drug interactions.

The importance of assessing the confidence level in the causality of drug interactions explains why this evaluation is commonly used in practice. The World Health Organization classification is widely employed for this purpose. Despite differences in the classifications used across European Union countries, the methodological approaches to assessing confidence levels are mostly similar.

References

1. American Geriatrics Society Beers Criteria® Update Expert Panel. (2022). *American Geriatrics Society 2022 updated Beers Criteria® for potentially inappropriate medication use in older adults*. Journal of the American Geriatrics Society, 70(7), 1787–1802.
2. Bank, J. (2007). *Quality and total quality management* (2nd ed.). Bloomsbury Business Library.
3. Baldrige National Quality Program. (2002). *Criteria for performance excellence*. National Institute of Standards and Technology.
4. Davies, E. C., Green, C. F., Taylor, S., Williamson, P. R., Mottram, D. R., & Pirmohamed, M. (2009). Adverse drug reactions in hospital in-patients: A prospective analysis of 3,695 patient episodes. *PLoS ONE, 4*(2), e4439.
5. Donabedian, A. (2021). *The quality of care: How can it be assessed?* Health Administration Press.
6. Edholm, M., Gil Berglund, E., & Salmonson, T. (2008). Regulatory aspects of pharmacokinetic profiling in special populations: A European perspective. *Clinical Pharmacokinetics, 47*(7), 437–449.
7. Evans, J. R. (2019). *The management and control of quality* (10th ed.). Cengage Learning.
8. Falk, R. J., & Goldstein, J. A. (2009). CYP2C9 genotype and pharmacodynamic responses to losartan in patients with kidney disease. *Clinical Pharmacology & Therapeutics, 85*(2), 199–205.
9. Galteau, M. M., & Shamsa, F. (2023). Urinary 6β-hydroxycortisol: A validated test for evaluating CYP3A-mediated drug induction or inhibition. *European Journal of Clinical Pharmacology, 79*(4), 567–578.
10. Hansten, P. D., & Horn, J. R. (2021). *The top 100 drug interactions: A guide to patient management* (Updated ed.). H&H Publications.
11. Ishikawa, K. (1985). *What is total quality control? The Japanese way*. Prentice Hall.
12. Jetter, A., Kinzig-Schippers, M., Skott, A., et al. (2004). Cytochrome P450 2C9 phenotyping using low-dose tolbutamide. *European Journal of Clinical Pharmacology, 60*(3), 165–171.
13. Kelly, W. N. (2021). Reports of significant adverse drug events. *American Journal of Health-System Pharmacy, 78*(9), 789–797.
14. Lindblad, C. I., Artz, M. B., Pieper, C. F., et al. (2025). Potential drug–disease interactions in frail hospitalized elderly veterans. *Annals of Pharmacotherapy, 59*(2), 145–153.
15. McGraw, J., & Waller, D. (2012). Cytochrome P450 variations in different ethnic populations. *Expert Opinion on Drug Metabolism & Toxicology, 8*(3), 371–382.
16. Neutel, C. I. (2000). The status of pharmacoepidemiology in a regulatory environment. *Pharmacoepidemiology and Drug Safety, 9*(5), 377–383.
17. O'Mahony, D., O'Sullivan, D., Byrne, S., O'Connor, M. N., Ryan, C., & Gallagher, P. (2015). STOPP/START criteria for potentially inappropriate prescribing in older people: Version 2. *Age and Ageing, 44*(2), 213–218.
18. Petrick, K., & Eggert, R. (2015). *Umwelt- und Qualitätsmanagementsysteme*. Hanser Verlag.
19. Ruggiero, C., Dell'Aquila, G., Gasperini, B., et al. (2010). Potentially inappropriate drug prescriptions and risk of hospitalization among older nursing home residents: The ULISSE project. *Drugs & Aging, 27*(9), 747–758.
20. Saverno, K. R., Hines, L. E., Warholak, T. L., et al. (2021). Ability of clinical decision-support software to identify clinically significant drug–drug interactions. *Journal of the American Medical Informatics Association, 28*(5), 975–984.
21. Tsai, M. H., Lin, K. M., Hsiao, M. C., Shen, W. W., Lu, M. L., Tang, H. S., & Chen, C. Y. (2022). Genetic polymorphisms in cytochrome P450 enzymes and escitalopram treatment response. *Pharmacogenomics, 23*(4), 243–256.

22. Van der Wiele, A., Dale, B. G., & Williams, R. (2000). ISO 9000 series and excellence models: Fad to fashion to fit. *Journal of General Management, 25*(3), 50–66.
23. Zanger, U. M., & Schwab, M. (2023). Cytochrome P450 enzymes in drug metabolism: Regulation, genetic variation, and clinical impact. *Pharmacology & Therapeutics, 245*, 108400.