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Mini Review

The Increase of Adverse Drug Reactions and Drug Interactions are Changing the Clinical Symptoms of Diseases

Jose Luis Turabian*

Specialist in Family and Community Medicine, Spain

Abstract

The circumstances of matching the concepts of risk factor and disease, increase in medicalization with more drugs treatments, the effect of creating a growing set of multimorbidity and polypharmacy, and the changes in the perceived severity of the disease, produce a dramatic increase of the adverse drug reactions (ADRs) and the drug-drug interactions (IDDs), as an intermediate consequence of the previous reasons. This situation is changing disease symptoms because of ADRs and DDIs, and it can have important consequences, and can give rise to, among others, the following effects:

1. There are more symptoms of ADRs initially classified as very rare or not described.

2. They are "disorganized" symptoms where no way to achieve an overall diagnosis that order to the whole.

3. There are symptoms in a lighter degree in some diseases, so that they can go unnoticed with the consequent risk.

4. There are confusing between symptoms of a new disease or an ADR, which makes it difficult to achieve a diagnosis.

5. The appearance of a second disease as a result of the treatment of the first, or increased aggressiveness of one disease.

6. The appearance of drug-induced systemic processes.

7. The appearance of yatrogenic infections; and,

8. Drug interference with laboratory tests. Due to changing the symptoms that were previously considered as indicators of certain diseases, especially in general medicine, where there were already some circumstances that make the diagnosis more complex, will be increasingly difficult to understand, detect, diagnose, prevent, and treat diseases reasonably and within a biopsychosocial framework.

Keywords: General practitioner; Drug-related side effects and adverse reactions; Drug interactions; Disease; Diagnosis; Medications; Multimorbidity; Polypharmacy; Symptom; Medically unexplained symptoms; Symptom assessment

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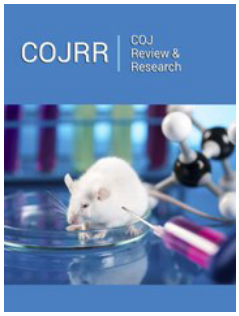

***Corresponding author:** Jose Luis Turabian, Specialist in Family and Community Medicine, Toledo, Spain

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Introduction

The classic description of symptoms of new diseases is less and less useful. At present, the symptoms of many diseases are changing. And this phenomenon is produced by the conjunction of several causes, such as:

A. The greater access to medical services and the early treatment of many diseases or symptoms causes only early or lighter symptoms to be observed, the florid observation of a clinical picture being rare; even some tend to disappear (rheumatic fever, tofaceous gout, etc.)

B. The health paradox. The feeling of being sick grows while global health improves dramatically. The feeling of being sick is greater the better the objective data, such as life expectancy. It is the frustrating search for "perfect health" [1]. In developed countries, the obsession with perfect health has become a predominant pathogen. The medical system, in a world impregnated with the instrumental ideal of science, constantly creates new needs for medical care. But the greater the supply of health, the more people have problems, needs and diseases. Everyone demands that progress put an end to the suffering of bodies, that they maintain the freshness of youth as long as possible and prolong life to infinity [2].

C. The evolution of the cultural context causes all the phenomena of life to be experienced, including those of the disease, in an urgent, demanding, excessive, and exaggerated way, both by the patient and by the doctor, changing the symptoms experienced (the odynophagia "of a few minutes", or the symptoms of gastroenteritis, or the bite of an insect, are lived as serious situations, motivate to going the emergency room, and the patient usually requests to be treated pharmacologically, even by parenteral route, thinking that the effect will be faster) [3,4].

D. The medicalization of symptoms and risk factors (the pre-diabetes, or the increasingly broad criteria of primary prevention treatments for cardiovascular diseases with statins, according to which the number of adults ages 60 to 75 without cardiovascular disease who now are qualify for statin therapy, is significantly increased (from 30% to 87% in men and from 21% to 54% among women) [5], or of the criteria of treatment of arterial hypertension (and that motivate criticism by important journals when this rhythm of relaxing inclusion criteria is not followed) [6], and in the same line a mild ankle sprain requires low molecular weight heparin for three weeks, a headache without risk signs precise an urgent brain MRI, etc. The practical imprecision of the term "risk factors", that is, the characteristics statistically associated with a disease or injury (not a cause, but a simple statistical association), has made any variable that can predict the value of the disease be called "risk factor", and then assigned the same meaning as "causal factor." Consequently, this medicalist transformation entails the logic of the intervention on the risk factor, which ends up becoming a disease. But in reality, for example, hypertension is not a disease, osteoporosis is not a disease, hypercholesterolemia is not a disease, etc. However, the medicalist force makes impossible to reverse this trend. In addition, the prevalence of prevention based on risk factors destroys many of the possibilities of clinical and social prevention. It also medicalizes the response to many diseases and health problems that have their best response outside the system since they are related to the "conditions" of life or social determinants [7].

E. And last but not least, and as an intermediate consequence of the previous reasons, the high frequency of adverse drug reactions (ADRs) and drug-drug interactions (DDIs). Of every 100 courses of drug treatment, there are 20 adverse drug reactions (ADRs), between 5 and 25 of clinically observable drug interactions (DDIs) (of which 5 are due to ADRs) 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, produces a logarithmic spiral or "the wonderful spiral" or "growth spiral." This spiral follows a geometric progression, not arithmetic: every health problem that health system "cure" leads us, not to another new problem, but to many more. And so, it is increasingly complex to leave this labyrinth that grows and tangles like a knot or ball [8,9].

Therefore, we are witnessing a situation of changes in the expression of disease symptoms. This modification of the clinic is due to changes in the social context and in the use of medical services, and to the geometric growth of medical interventions, which lead to multimorbidity, and in 100% of cases to some type of pharmacological prescription and often as polypharmacy [10].

Consequently, a modification of the symptoms of the diseases is attending, by early treatment, by the treatment of asymptomatic risk factors, by the polypharmacy, and in patients with multimorbidity. In addition, this transformation of the clinic will probably be increasingly intense. And for these new expressions of diseases there are no guidelines; there are no diagnostic nor intervention guidelines on syndromes not yet fully described or are totally new.

It can be pointed out as one of the main factors causing this transformation of the clinic to the increase in multimorbidity and polypharmacy that brings with it a dramatic increase in adverse reactions to drugs and drug-drug interactions, whose new symptoms, not described above, not even in pre-marketing studies. And this set of symptoms appear by the coincidence of patient factors (age, sex, presence of co and multimorbidity, etc.) and the presence of multiple, sometimes many, drugs administered at the same time.

In this scenario, the objective of this article, based on the review of selected articles, and personal experience of the author, is to reflect, conceptualize, synthesize, and discuss the possible implications, for the understanding of the clinical physician and for research, on the symptoms specifically related to ADRs and DDIs in general medicine.

Discussion

Traditionally, the diagnosis has focused on the physical complaint. The doctor's objective is to move in the direction of ordering the symptoms and signs, the reasons for consultation and the diseases that may appear disorderly, so that they can be integrated and arranged in an intelligible set. A symptom is a deviation from normal function or sensation noticed by a patient, which reflects the presence of an unusual state or a disease [11].

On the other hand, disease is a medical entity characterized by specific signs and symptoms. Symptoms represent a somatic manifestation of the disease or a consequence of treatment. Symptoms are of vital importance, as they are a signal for a person that there is a threat to health, side effects of treatment or a manifestation of an acute illness or disease progression that requires medical attention. People often experience multiple symptoms simultaneously, which increases the burden of suffering. The symptoms usually appear in groups, defined as two or more symptoms that occur simultaneously and are related. These groups of symptoms, interestingly, were studied for the first time in patients who received chemotherapy and radiation for cancer, that is, in symptoms due to ADRs [12]. On the other hand, the evaluation and management of symptoms is a main task in general medicine [13].

However, if the symptoms used for the diagnosis of diseases in general medicine, present variations or changes, and could there be both a difficulty in cataloguing diseases in this level of care, where all patients converge. This new and dramatic situation of transformation of the symptoms that can identify the clinic of the diseases brings with it an increase of the diagnostic uncertainty, letting pass without cataloguing diverse sets of symptoms, and favoring empirical treatments, which aggravate the problem. Therefore, in general medicine vs. hospital, there is a starting situation that results in even greater difficulties to observe, understand, diagnose and cataloguing the symptoms; two of these factors are:

A. In general medicine there is already a number of characteristics that modify the clinical conditions of patients. The diseases seen in the hospital and general medicine "are not the same." In general medicine there are a number of characteristics that modify the clinical conditions of the patients seen, with respect to those described in the classic books, whose descriptions are usually based on patients in the hospital setting [14]:

i. Problems are seen instead of diseases.

ii. The first phases of the disease are observed.

iii. There are self-limited symptoms and signs, which disappear spontaneously.

iv. There is a different vision clinic from the hospital where are selected and severe patients.

B. Work environments are different in general medicine and in the hospital. In the hospital the patient is treated decontextualized of their environment; there is a greater emphasis on the biological, the technology, and the quantitative. The opposite occurs in general medicine (the patient is studied contextually in his life and work environment, with a biopsychosocial and qualitative emphasis) [14].

Diseases change over time

Diseases have their own rhythms that change over the centuries; each society builds its way of thinking and feeling diseases. The interdependence between the biological and social conditions of civilized life has caused, each historical moment, to living the disease differently [15]. Diseases change over time, with economic development, culture, environmental changes, and other factors. Thus, in the last 50 years there have been important changes in infectious diseases, new diseases have appeared, others have disappeared, etc. For example, climate change increases temperatures throughout the planet, and with that there are areas that allow vectors to exist that can infect to people with infectious diseases not previously present in those areas. Likewise, epidemiological transitions and the high prevalence of chronic non-communicable diseases involve major changes in the presentation of the disease worldwide [16].

The transformation of the clinic is not a new phenomenon, but its current accelerated change is:

General medicine has traditionally tried to identify, catalog, treat, and eliminate the causative agents of diseases and health problems. However, this traditional approach is becoming inadequate to face a changing disease landscape. Although the evolution of the clinic and medicine has been pointed out for some time [17-20], currently we are witnessing a tremendous acceleration of such evolution favored by the presence of a series of factors, where the tremendous frequency of ADRs and DDIs, which are due to polypharmacy, it is one of the main. That is, the presence of multimorbidity and polypharmacy, gives rise to different clinical expressions of diseases.

The increase in ADRs and DDIs as a cause of transformation of symptoms seen in general medicine:

The increase in multimorbidity and polypharmacy brings with it a dramatic increase in adverse drug reactions and drug-drug interactions, which change disease symptoms. IDD is a particularly important health problem because of its growing potential frequency, which will also increase, due to the wide variety of factors involved, due to the limited knowledge currently available, due to the implications for health and cost outcomes, and for the possibilities of prevention, on which, surprisingly, excessive attention is not paid.

Every time a drug is administered to treat an ailment, no matter whether it is acute or chronic manifestation, it usually goes together with some other prescription medicine, over the counter formulation, herbs or even food. All the xenobiotics such as drugs, toxins and food components as well as the endogenous compound that are formed in the body, exert a stimulatory or inhibitory effect on the different physiological and biochemical processes going in the body. These effects may alter the normal metabolism and / or drug transport or its efficacy drastically and thus expose the patient to the risk of a potentially dangerous interaction [21].

Drugs prescribed in combinations causing frequently DDI and ADR. DDIs are an important clinical and public health concern. Although DDI screening now occurs during drug development, it is difficult to predict clinical importance based on in vitro experiments. Furthermore, older drugs that were not screened may have interactions that have not yet been identified [22]. And in any case, they have not been analyzed in the current actual circumstances of coexistence of multiple diseases and other drugs. DDI is a major cause of morbidity and mortality. DDI research includes the study of different aspects of drug interactions, from in vitro pharmacology, which deals with drug interaction mechanisms, to drug-epidemiology, which investigates the effects of DDI on drug efficacy and adverse drug reactions [23].

Drug-drug interactions can also contribute substantially to differences in drug response. Drug-induced inhibition of drug

metabolising enzymes is usually competitive and causes an increased exposure of the drug whose metabolism is inhibited. This usually results in a higher incidence of adverse drug reactions and an increased severity. Conversely enzyme induction increases the metabolic capacity thereby reducing the exposure of a drug with sometimes loss of drug effects (non-response) [24].

Of every 100 courses of drug treatment, there are 20 ADRs, between 5 and 25 of clinically observable DDIs and between 15 and 50 potential DDIs, which arrive to 100 in geriatric patients. And 30% of IDDs contribute to ADRs [25]. The current approach to the disease, risk factors and prevention, within the biomedical framework, seem to produce a logarithmic spiral or "the wonderful spiral" or "growth spiral" [8,26-31]. Thus, pharmacological interactions represent a new causal factor of great significance in the transformation of the disease burden, the expression of symptoms, and the modification of the effects of therapeutic interventions.

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

a) The appearance of ADRs

b) The decrease in the effectiveness of the treatment [32]. But another effect must be included that until now was not paid attention:

c) The modification of the symptoms of the diseases, either of the disease that theoretically receives the drug treatment, or about the rest of the patient's co-or multimorbidities, and the modifications of their interactions.

The growing clinical importance of drug interactions is justified by the fact that it is currently rare for a patient to receive a single drug. At the outpatient level, which is where most of the pharmacological prescriptions are made, the escalating use of prescribed drugs has increasingly raised concerns about polypharmacy. Drug regimens are increasingly complex and potentially harmful, and people with polypharmacy need regular review and prescribing optimization. Research is needed to better understand the impact of multiple interacting drugs as used in real-world practice and to evaluate the effect of medicine optimization interventions on quality of life and mortality [33,34].

Thus, the changing symptoms can have important consequences [35], and ADRs and DDIs can give rise to, among others, the following effects [32]:

1. There are more easily symptoms of ADRs initially classified as very rare or not described, with the consequent diagnostic difficulty [36].
2. They present as disorganized symptoms or diseases: where doctor and patient are not of agreement in a diagnosis, organic or psychological, where doctor has the intuition or feeling that there is hidden data that should come to light, and where several medical problems, at the same time, are treated,, in a patient (eg, peptic ulcer, anorexia, depression, atrial fibrillation, etc.), but there is no way to achieve an overall diagnosis that order to the whole.
3. There are symptoms of a disease in a lighter degree, so that they can go unnoticed with the consequent risk (for example, in chronic congestive heart failure).
4. There are confusing symptoms, which makes it difficult to achieve a diagnosis (for example, the hematuria in a patient with direct-acting anticoagulants, and prostatic pathology, it is difficult to add it to the latter pathology or to an ADR).
5. The appearance of a second disease as a result of the treatment of the first (such as tumors after treatment with cytostatics and immunosuppressants), or increased aggressiveness of the disease (such as the appearance of very aggressive prostate cancer in a patient treated with methotrexate due to cutaneous lymphoma)
6. The appearance of drug-induced systemic processes (such as the appearance of vasculitis, systemic lupus erythematosus, etc.)
7. The appearance of yatrogenic infections (such as superinfections by antibiotic resistant bacteria, which are using in an excessive and unnecessary way)
8. Drug interference with laboratory tests (such as contraceptives or acetylsalicylic acid and determination of blood thyroxine)

Conclusion

Matching the concepts of risk factor and disease has led to some disturbing and generally underestimated consequences that could be subject to greater reflection and clinical response. The increase in medicalization causes some puzzling trends in medical decision making, such as the steep and uniform increase in the number of certain treatments. The effect of creating a growing set of multimorbidity and polypharmacy results in an increasing number of people with diseases/risk factors, resulting in an expanded market for biomedical interventions and greater influence for defenders of diseases. Changes in the perceived severity of the disease produce a domino effect on how people experience and understand their disease and the risk of disease.

In these circumstances there is a dramatic increase in ADRs and IDDs, which are changing the symptoms that were previously considered as indicators of certain diseases, especially in general medicine, where there were already some circumstances that make the diagnosis more complex. Consequently, it is and will be increasingly difficult to understand, detect, diagnose, prevent and treat diseases reasonably and with biopsichosocial framework in general medicine.

And yet, to understand the clinical effect of ADRs and DDIs, where 2+2 is not 4, but a much higher figure, a holistic view is needed: the way to see whole things, in their entirety, in their as a whole, in its complexity, because in this way it is possible to seeing interactions, particularities and processes that are usually not perceived if you study the aspects that make up the whole, separately. Each ADE and DDI in certain circumstances have its individual properties, but by forming a whole in patients with multimorbidity and polytherapy, this new system has different properties from those that were known with respect to each of the parts that comprise it.

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