Strategies to Increase Opportunities to Identify and Communicate Adverse Drug Reactions and Drug Related Problems in General Medicine

Jose Luis Turabian*

Abstract

Four strategies can be described to increase the opportunities to identify adverse drug reactions (ADRs) and the problems related to them in general medicine, and to provide knowledge about their epidemiology in outpatient setting: 1. Contribute to the epidemiological knowledge by providing "numerator" and "denominator" (prevalence, incidence, risks): the position of the general practitioner as the gatekeeper of the health system allows him to know data of morbidity and mortality, as well as case rates and different types of risk (Relative Irrigation, Absolute Risk, Attributable Risk, and Individual Susceptibility); 2. Case studies at this level of general medicine allow the communication of ADRs that are especially infrequent or related to new drugs; 3. Improve the knowledge of ADRs avoiding the difficulties of interpretation of symptoms or diseases that are not due to medicines but psychosocial factors, since general practitioner in his continued attention accumulates a lot of psychosocial data of the patients which may allow him to better interpret the symptoms, and also, he can perform studies incorporating external or internal controls (the patient himself as his control); And 4. The use of all this knowledge to apply to the consultation: ADRs can also teach us important things about human biology, and so the general practitioner can observe facts and hypotheses to verify, and also using that local knowledge in the ADR prevention or epidemiological monitoring.

SHORT NOTE

Of course, nobody likes the adverse effects of medications. In any case, they are events that occur every day in the consultation. Therefore, it is necessary to recognize them, as well as to reflect on them and assess how we can find ways to improve their knowledge and prevention. It is especially important at the level of general medicine, which is the place where the vast majority of pharmacological prescriptions are made, and where patients consult for the symptoms of adverse drug reactions (ADRs). Some of these ADRs seem to occur as random events, others are predictable based on the known pharmacological properties of a drug or its metabolites, and others can be controlled after spontaneous reports or rare or infrequent cases published in the medical literature.

In this scenario, this article aims to reflect on the strategies to increase opportunities to identify ADRs and problems related to them in general medicine.

Four strategies can be described to increase the opportunities to identify ADRs and the problems related to them in general medicine, and to provide knowledge about the epidemiology of ADRs in outpatient setting:

- Contribute to epidemiological knowledge by providing "numerator" and "denominator" (prevalence, incidence, risks)
- With the high number of drugs currently used, the epidemiological study of ADRs is even more important to know their incidence, prevalence, type, and causes of them, as well as to prevent them as far as possible. The knowledge of the opportune denominators that really value the population at risk is one of the difficulties in the epidemiology of ADRs. The other related problem is the numerator used: for example, the study of all ADRs spontaneously reported in the general medicine practice, or the study for carrying out a specific and exhaustive follow-up, or the study to considering only those ADRs that motivate consultation, etc. [1].

An initial aspect to consider is the great accessibility of patients to their general practitioner (GP), and their role as first contact with the patient. Especially in healthcare systems where the GP performs a gatekeeper function of the system and healthcare is universal. In this situation, the trajectory of all patients begins and ends in the GP, which also performs a continuous care [2,3].
In addition, the GP usually attends to a list of known patients, and often with a geographical base (a neighborhood, a town, etc.). In this way, by having the “numerator” (cases diagnosed) and the “denominator” (numerical and geographic base of the population served), the GP can know morbidity data (prevalence and incidence), the cure rates and mortality, and the different types of risk (Relative Risk, Absolute Risk, Attributable Risk, and Individual Susceptibility) [4-6].

Keep in mind that rare adverse effects with a drug may only become apparent in the general community. Likewise, the position of the GP allows him to perform descriptive (cross-sectional), retrospective (case-control), prospective (cohort), clinical trials, and single case studies, seasonal variations, longitudinal studies, etc. [7-9].

Admitting that the concept of risk is the probability of a certain event occurring, it can be thought that the population at risk of presenting ADRs is only the one that takes medications, especially the one that takes them frequently. For the study of ADRs, out of the GP level of care, the primary denominator could be unknown, but a secondary denominator can be obtained as the number of sales of that drug. Obviously, obtaining data from the number of inhabitants is more accessible, and this is what is usually used. In this way, one of the advantages offered by general medicine is that studies can be carried out with denominators of population “really at risk” (subjects who take the drug) instead of the general population as the denominator, and so these studies could show differences between incidence and prevalence rates by age groups from those theoretically admitted [1,10].

On the other hand, another central aspect of the GP is its work in the early detection of the disease and its prevention [11]. General medicine presents the unique opportunity to detect new cases of disease, and study the natural history of the same as it contemplates the human life cycle continuously, and no one is in a better position to observe from the family background to the ultimate consequences of any problem of health.

In addition, the GP has a role as a guardian of health and epidemiological surveillance aimed at observation and action on any phenomenon or event that threatens the welfare of the community [12].

An obvious problem is the accuracy of the diagnosis of ADRs. This is so because of the high frequency of transient and poorly defined symptoms in general medicine, the high presence of symptoms that are due to non-pharmacological psychosocial aspects of the prescription of drugs, as well as symptoms or self-treated diseases that are not consulted by patients. Therefore, in general medicine a satisfactory estimate of the incidence and prevalence of ADRs in the population can not be assured; one could speak of “incidence or minimum prevalence”.

Case studies that allow reporting ADRs especially infrequent or related to new drugs

The case studies seek to find new evidences or situations of a phenomenon and generate theory, as well as the development and contrast of certain explanations in a representative framework of a more general context. However, it is clear that case studies do not represent a sample of a specific population or universe. So they can not be statistically generalizable, but rather give raise to theoretical propositions, since the researcher’s objective is to expand and generalize theories -analytical generalization- and do not list frequencies -statistical generalization.

The GP’s work allows him to make observations about: 1. Patients with defined clinical characteristics (for example, a certain disease or group of symptoms); 2. To describe in a simple way the clinical data without comparison groups (the data that are derived from a well-defined patient or group of individuals); 3. Formulation of hypotheses; and 4. Study the natural history of the disease, describing the “clinical experience”. Case studies of ADRs are simple and inexpensive to perform in outpatient settings, although it must be remembered that a biased selection of patients can lead to errors of interpretation [13-15].

Well-written published case reports, when widely accessible, enhance diagnostic and therapeutic practices by sharing “real-world” experiences. Case reports of ADRs, when coupled with simultaneous monitoring of drug pharmacokinetics, have also led to further investigations resulting in major advances in pharmacology, especially pharmacogenetics, mechanisms of drug–drug interactions and modulation of drug metabolism during inflammatory co-morbidities [16].

The case study approach is recommended when the level of uncertainty is high, the theory and direction are obscure and the situations are novel and complex [17]. These characteristics occur in new or little known ADRs. Case series studies are studies of “numerator” only. In addition to the “numerator approach” of the case series, only one group of patients is under study. No control group or controlled patient assignments is involved. However, apart from these inherent limitations, the series of case studies are often the only source of information on the problem of interest [17]. The presentation of a limited number of cases indicates that these cases are probably not unique, and these cases can be considered in epidemiological terms as index cases, to going beyond from them in the extension of the study [17].

Case series will remain interesting because of the intrinsic importance of observation in medicine. Although individual case reports should never be taken as definitive evidence. A case series without controls can inform about the fate of a group of patients. Such series may content extremely useful information about source, clinical course and prognosis of ADRs. Case reports and case series reports may be the "lowest" or "weakest" level of evidence, but they often remain the first line of evidence of what happened; therefore, it is at this level where the evidence begins [17-19].

**Improve the knowledge of the ADRs avoiding the difficulties of interpretation of symptoms or diseases that are not due to medicines but psychosocial factors**

Pharmacovigilance is a public health activity in which GPs are legally and medically involved. The GP plays a key role in the detection of adverse reactions to drugs, mainly by notifying the cases in which you suspect, during your usual practice, that a drug may have produced an adverse reaction, and he must send it as quickly as possible to the Authorities and Pharmacovigilance Centers [20].
Diseases and symptoms induced by drugs also occur in patients without exposure to the drug. The attribution of a symptom or sign to a ADR is a complex clinical decision [21]. It is essential to know the pharmacology of the drugs used. But also the non-pharmacological aspects, such as non-specific adverse effects (nocebo), placebo effect, noncompliance, cost, psychological meanings (symbols, beliefs, stigmas), the ethical aspects, the fact of being sometimes prescription is a way of facing the frustration of the doctor, etc. These factors produce effects on health, modify the doctor-patient encounter and can condition a change of attitude in the prescriptions in daily practice. In this way, these factors introduce elements of confusion to recognize and catalogue an ADR. But nevertheless, these variables are, at least in part, accessible to GP, which maintains a continuous attention and accumulates large amounts of psychosocial data of patients, and in this way, their knowledge may allow a better interpretation of an ADR.

On the other hand, the difficulties of interpretation of the ADRs can partly be solved, and thus acquiring its results immediate practical importance, through the use of controls. In addition to the option of studies with a control group, carefully chosen to avoid confounding factors, there is the option of using the patient as their own control, within the context of continuity of care in general medicine [1]. By means of these designs, an epidemiological view of the ADR problem is favored, and they suppose pharmacovigilance alternatives typical of general medicine.

Use all this knowledge to apply it to the consultation

GPs in clinical practice, always seeking to select the most appropriate drugs, ask themselves questions such as: Are drugs that share the same therapeutic indication equal in efficacy, safety, comfort and price? For example, are all statins the same? Are all antidepressants the same? Is there one that has more advantages than the other? Are anticholinesterases or bisphosphonates clinically relevant? [22]. The knowledge of the ADRs provides data for that wise choice of the drug to be prescribed.

In addition, GPs can learn a lot from ADRs. Adverse effects can also teach us important things about human biology, such as:

A) On the dose-toxicity relationship that can be predictable and allow the monitoring of the level of the drug.

B) On the ocular or bone marrow toxicity of certain medications.

C) On the intracellular effects of some drugs, which are only partially predictable by the levels or doses of the medication, such as colchicine, hydroxychloroquine or amiodarone.

And D) On the interruption of normal physiological homeostasis and the stimulation of counter-regulatory pathways that produce certain drugs, in such a way that unexpected biological effects occur, such as coughing with angiotensin-converting enzyme inhibitors [23].

In this sense, 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 GP could use that local knowledge. So that in addition to being aware of the interactions of aging, and concurrent comorbidities and polypharmacy which are already known, the GP can consider that their older patients do not appear to be at increased risk [24], thanks to his local knowledge and experience, and because of this, the GP can hypothesize that the incidence and prevalence of serious ADRs in the elderly are not properly rated [25,26].

Although numerous studies have sought to identify risk factors for ADRs, the only truly independent predictor is the absolute number of concurrently used medications. However, other studies indicate that there is poor doctor-patient agreement regarding a patient’s drug regimen, and interventions that aim to reduce the incidence of ADRs have failed to demonstrate a positive effect. Thus at present the most rational approach would appear to be to establish an accurate knowledge of the patients drug regimens: once this is known one can attempt to rationally minimise the number of medications without compromising therapeutic goals [25,27].

On the other hand, the GP can observe a certain fact related to the ADRs, and finally demonstrate its hypothesis as correct. Thus, for example, the fact that spontaneous communication by the patient of frequent or multiple adverse reactions to medications is associated with the presence of anxiety or depression, and that consequently this fact could be used as a marker of problems psychosocial in those patients. And besides that, this fact also advises that attention should be paid to patients with anxiety or depression when making prescriptions.

Or know likewise the fact that antibiotics, anti-inflammatories and drugs that act on the central nervous system are most likely to produce intolerances, what can be immediately translated into guidelines in the consultation [28]. Or that the main ADRs noted in pediatric population are antibiotic-associated gastrointestinal complaints and rashes, and various manifestations of CNS stimulation with bronchodilators, etc.

CONCLUSION

The role of GP in the knowledge of ADRs is fundamental. Several strategies can be described to increase the opportunities to identify ADRs and the problems related to them in general medicine, and to provide knowledge about their epidemiology in outpatient setting: 1) Contribute to epidemiological knowledge by providing “numerators” and “denominators” (prevalence, incidence, and risks); 2) Case studies that allow the communication of ADRs that are especially infrequent or related to new drugs; 3) Improve knowledge of ADRs avoiding the difficulties of interpreting symptoms or diseases that are not due to medicines but psychosocial effects, from the psychosocial data of patients that the GP accumulate, or through the use of external controls or internal (the patient himself as his control); And 4) To use all this knowledge to apply it to the consultation, so that the adverse effects can also teach us important things about human biology, and could use that local knowledge in the ADR prevention or follow-up of patients or groups at risk, as well the GP himself can observe facts and pose hypotheses to be checked.
REFERENCES


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