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Research Article
The role of general practitioner in the study of adverse drug reactions epidemiology in ambulatory care setting

Abstract
Adverse drug reactions (ADRs) cause considerable mortality and morbidity. Its importance becomes greater in relation to the current increase in the use of drugs and multimorbidity. Premarketing studies do not allow a complete knowledge of the safety of a medicine. Many ADRs occurring in the outpatient setting, but there is a significant lack of information regarding the epidemiology of ADRs in this level of healthcare. Thus, guidance on how to direct attention to effective targets for improvement of medication safety in ambulatory care settings is missing. In this scenario, the general practitioner (GP) is in a rare, special position in the health system, which allows him to combine the clinical tasks of diagnosis and treatment on individuals with epidemiological and public health tasks on communities, including an important role in the study of ADRs’s epidemiology. Among the methods aimed at identifying and quantifying the ADRs, in the GP consultation, we have: 1) Data derived from pure clinical observation; 2) Voluntary spontaneous notification systems; 3) Effective local initiatives for improving the collection of reports on ADRs; 4) Careful epidemiological studies, which may include descriptive studies (cross-sectional), retrospective (case-control), prospective (cohort), clinical trials, and single-case studies, seasonal variations, longitudinal studies, etc.; 5) Patient reporting of ADRs; 6) The use of algorithms for the diagnostic of ADRs; 7) Intensive telephone surveillance; 8) Collaborative work with Pharmacists working in the community; 9) From the position of the GP (where the entire medical care process begins and ends) the incidence rate of ADRs caused by hospital prescribed drugs can also be observed and collected from discharge of the hospital admissions; And 10) Genetics and electronic health records can go together to identify heritable traits to predisposition to ADRs.

"The scientific purist, who will wait for medical statistics until they are nosologically exact, is no wiser than Horace’s rustic waiting for the river to flow away." Major Greenwood, 1948.

Introduction
Medications are probably the most important health care technology in preventing illness, disability, and death in the population. But, on the other hand, the problem of the use of medications is one of the most socially relevant in all countries and adverse drug reactions (ADRs) are an important part of it. ADRs cause a lot of suffering to the patient with considerable mortality and morbidity, as well as an increase in medical care expenses. Its importance becomes greater in relation to the current increase in the use of drugs, polypharmacy and multimorbidity [1,2].

An ADR is any response to a drug that is harmful and unintentional, and that takes place at doses that are normally applied in humans for the prophylaxis, diagnosis or treatment of diseases, or for the restoration, correction or modification of physiological functions. This term also includes all the harmful clinical consequences derived from the dependence, abuse and misuse of medications, including those caused by use outside the authorized conditions and those caused by medication errors [3]. So, ADRs and drug allergies- as a subset of ADRs- make a significant public health concern, complicating 5 to 15% of therapeutic drug courses. They may result in diminished quality of life, increased physician visits, health care costs, hospitalizations, and even death [4].

Most medications are prescribed, and administered in ambulatory care settings, but little information exists on the adverse effects of drugs in this setting. In this way, its epidemiology is unknown, but it is admitted that the burden of ADRs is substantial in ambulatory care. Consequently, the...
systematic comparison of ADRs in inpatient and outpatient care is lacking, even though there is a prescription pattern difference [5]. On the other hand, neither the studies prior to the commercialization, nor the spontaneous notification of the ADR, however carefully they are carried out, allow a complete knowledge of the safety of a medicine.

In this scenario, despite a recent increase in publications on ADEs in the ambulatory care setting, most studies remain hospital based, and only there are a few studies that assess ADRs which occurring in the outpatient setting. Furthermore, these limited numbers of studies that were performed in the outpatient setting identify a lack of information regarding the epidemiology of ADRs in this setting. But, what can be said is that, based on the review of studies, the burden of ADRs, in both in- and outpatient settings, is substantial. Therefore, studies in all countries about ADR occurrence in the outpatient setting are needed [6,7].

Although as has been said, population level estimates of outpatient ADRs are limited, the visits due to ADRs in outpatient clinics substantially increased from 9.0 to 17.0 per 1000 persons between 1995 and 2005. Both patient age and polypharmacy use are risk factors for ADR-related. So, the incidence of ADRs has particularly increased among patients 65 years and older with as many as 1 in 20 persons [8]. However, although it is recognized that the incidence of adverse drug reactions increases with age, this increase is mainly due to altered pharmacodynamics and pharmacokinetics, as well as multiple prescription and the effect of the disease instead of the effect of age itself [9].

This situation of lack of studies, leads to not having clear data on the differences in prevalence rates by age groups and by responsible drug categories to can provide guidance on how to direct attention to effective targets for improvement of medication safety in ambulatory care settings. This lack of useful epidemiological data results in the reduction of our ability to understand fully the characteristics of clinically important adverse drug reactions and by a lack of knowledge on biological mechanisms, patient susceptibility factors and long-term outcomes [10]. However, it can be admitted that ADRs occur in approximately 20% of the patients. In general, the assessment of the severity and preventability of ADRs reveals that 1% of ADRs are severe and 2% are preventable reactions [11]. In short and in other words, the lack of information means that no useful actions are implemented in ambulatory level of healthcare.

Discussion

ADRs and pharmacovigilance

Considering increased use of drugs (for example, cardiovascular, psychotropic drugs, etc.) and limitations in pre-marketing trials for drug safety evaluation, since clinical trials are done with a very small number of people, so they can not detect all the ADRs, post marketing evaluation of ADRs seems necessary.

In this context, pharmacovigilance is the process of identifying, monitoring, and effectively reducing adverse drug reactions. ADRs are an important factor to take in consideration when assessing a patient’s health. Further, the proliferation of new pharmaceuticals means that the incidence of ADRs is increasing. The goal for all health care providers must be to minimize the risk of ADRs as much as possible [12].

The distribution of ADRs in the population

Are ADRs distributed homogeneously in the community and do people present a similar number of problems (perhaps the arithmetic mean)? Or alternatively, the number of ADRs per person is distributed as a “normal” form in the population (following a Gaussian curve)?

The disease is not randomly distributed among people in the population: 20% of patients present 50% of health problems [13]. The disease tends to occur in clusters, and it is estimated that at least one third of diseases are influenced to some degree by individuals’ attempts to adapt to events and situations. In people with a high frequency of diseases, this probably occurs due to their inability to adequately adjust to their problems. The fact that a relatively small proportion of people experience a disproportionately large number of diseases suggests both that these people have an unusually high tendency to disease processes and that that group of people repeatedly somatize.

Similarly, the fact that a relatively small proportion of people experience a disproportionately large number of ADRs to drugs suggests both that these people have an unusually high tendency to adverse drug effects or that that group of people repeatedly somatize [14]. Patients diagnosed with “neurosis” -as well as those diagnosed with hysteria who exhibit a multiplicity of symptoms, including a history of excessive surgical interventions-, probably exhibit a history of excessive ADRs of all types and with multiple symptoms [15].

Regarding the symptoms that are adverse effects of the medication, the difficulty to separate ARDs “true” from “false”, and the possible influence of psychic and social factors to experience ARDs or communicate them to a greater degree. In any case, it has been suggested that the fact of multi-drug intolerance should be assessed as a hallmark or marker of patients with neurosis, including somatization.

Therefore, pharmacological treatment is a special problem when facing the patient with hysteria. These patients often take several prescribed drugs for questionable reasons, and this high number of drugs increases the likelihood of iatrogenic symptoms due to ADRs or drug interactions. An important problem of these patients is the tendency to abuse narcotic, hypnotic and tranquilizing analgesic drugs.

The doctor-patient relationship works like a drug

For Balint, the drug most used in general practice is the doctor himself; the interview itself is therapeutic. In his writings on “the doctor as a medicine” he establishes the fact that himself as a drug can be dosed, prescribed, and is able to producing intoxication like any drug. This medicine called...
“doctor” is powerful and can have many side effects. You have to know how to dose and prescribe. In any case, it is accepted unanimously that the chances of success in a treatment are directly proportional to the quality of the doctor–patient relationship [16,17].

The doctor–patient relationship works like a drug, and likewise has the capacity to affect beneficially, as well as causes adverse reactions. Adverse reactions in placebos (dry mouth, nausea, headache, dizziness, etc.) occur in 9–25% of patients. Anxiety is the only factor in the individual that has been identified as an element that affects the placebo response [14].

**The epidemiological position of the general practitioner**

The general practitioner (GP) is in a rare, special and specific position in the health system, which allows him to combine the clinical tasks of diagnosis and treatment on individuals and families, with the epidemiological and public health tasks on families and communities. In addition both roles of the GP feed each other [18–20].

The essence of general medicine / family medicine is the assistance to individuals in family and community units, and this implies, on the one hand, a good continuity of care, and on the other, knowledge of the nature of the disease in the community. Many of the health problems can be successfully identified only within a population: excessive incidence or prevalence of a specific health problem, discontinuity of care, coordination of care, therapeutic adherence, etc. The exclusive focus on individual attention would lead us to work “successfully and in vain”, since risk factors and individual diseases are a consequence of community factors [21,22].

For the sensible practice of general medicine, not only the traditional diagnostic and treatment skills are necessary, but also the application of the understanding of the frequency and distribution of the disease in the community and its natural history [23].

This special position of the GP, between individual and group attention, allows a whole network of possibilities to extend different methods to identify and quantify the ADRs. This network of methods from general medicine is related and can overlap or favour each other.

**Methods to identify and quantify the epidemiology of ADRs at the general practitioner’s level**

Pharmacovigilance must be effectively practiced by all health care providers in order to avoid ADRs. Among the methods that tend to identify and quantify the adverse reactions of medications, in the GP consultation, we have:

1. The data derived from the pure clinical observation and in this aspect, the role played by GP is fundamental.

2. Related to the clinical observation data, there are voluntary spontaneous notification systems (Yellow Card System). These have the negative aspect of Infra-communication, due to the uncertainty that the observer has between cause and effect [24,25]. Voluntary notification systems rely on attentive medical professionals who are well informed about the possibility that medications can produce ADRs and are prepared to inform others about their observations [26]. The true approach to ADRs epidemiology should also include the less serious ADRs, as a prior step to assess their real involvement in community health and public health and individual treatments, in order to improve therapeutic management and generate research hypotheses in this area.

3. Effective local initiatives for improving the collection of reports on adverse drug reactions [27].

4. Careful epidemiological studies, which may include descriptive studies (cross-sectional), retrospective (case-control), prospective (cohort), clinical trials, and case studies, seasonal variations, longitudinal studies, etc., which can encompass large numbers of drug users. An example can be an epidemiological screening for potentially carcinogenic drugs in large cohorts of patients with recorded full information sets [28].

5. Patient reporting of ADRs could supplement the existing reporting system and contribute to early detection of ADRs. It has been communicated that the outpatients can report a high proportion of potential ADRs and with high confidence and accuracy. Patient reporting of ADRs has the potential to support the pharmacovigilance system [29].

6. The use of algorithms for the diagnostic of ADRs. The incidence and impacts of ADRs have been extensively studied, but there is an emerging focus on real-time detection systems. These can play an important role, along with systems pharmacology and population-level epidemiology, in a multipronged approach to prevent ADRs and mitigate their harm. Tailoring ADRs detection systems to a particular health care setting can improve predictive accuracy, but the added complexity reduces its wider applicability. As this approach becomes increasingly used we can imagine detection algorithms of greater complexity but also a set of algorithms encompassing the full range of health care settings and ADR types, thus creating a system that is both accurate and widely applicable. [30,31].

For example, it has been suggested that the interaction of two common medications, a cholesterol-lowering drug called pravastatin and the antidepressant paroxetine, could raise blood sugar levels dangerously close to diabetes levels. Tatonetti, designed an algorithm to extract a large database of adverse drug reactions administered by the US Food and Drug Administration (FDA) and detect side effects reported in patients taking any combination of two drugs. The practical conclusion is that computer generated hypotheses could be reliable, and the use of algorithms to identify significant relationships hidden in giant databases, and genetics and adverse drug reactions are special interests of these systems [32].

7. Intensive telephone surveillance program to monitor all courses of prescription and nonprescription drug therapy in general practice for a certain time [33].
8. Collaborative GPs’ work with Pharmacists working in the community, that are in a unique position to become involved in ADR monitoring and reporting [34].

9. From the position of the GP (where the entire medical care process begins and ends) the incidence rate of ADRs caused by hospital prescribed drugs can also be observed and collected from discharge of the hospital admissions and know the problems related to them, such as hospital readmissions for ADRs, and prevent these events [35].

10. Genetics and electronic health records come together to identify heritable traits to predisposition to ADRs. Although scientists have suspected a genetic component of traits such as ADRs, few studies have shown whether such traits are hereditary. Therefore, an important field of interest is to know if a certain predisposition to ADRs is hereditary. This is exploit electronic health records to first identify markers of ADRs and then see if there is a genetic component in these reactions [32].

**Conclusion**

The fact of obtaining information which increases our knowledge of the frequency and cost of adverse drug reactions is important in enabling both more rational therapeutic decisions by individual clinicians and for a more optimal social policy. The GP has several strategies to promote the opportunities to identify ADRs and the problems related to them in general medicine, and to provide knowledge on the epidemiology of ADRs in outpatient setting [36].

But there seems to be some doubt as to whether the role of GP can contribute something to the scientific accuracy of the epidemiology of ADRs, and there are many who doubt the usefulness of attempts to compile these data, at general medicine setting, due to the difficulties of detection and classification. To these, one can quote Major Greenwood: “The scientific purist, who will wait for medical statistics until they flow away” [37]. Fortunately, for the progress of epidemiological knowledge of ADRs, by incorporating the role of GP, it can be greatly improved.

The factors reviewed above lead to a series of practical actions that the GP can incorporate in its daily work (Figure 1).

In short, these could be: 1. The follow-up of patients and groups at greatest risk for developing ADRs such as elderly, children, and pregnant patients, as well as others; 2. Monitoring ADRs in patients using certain drugs (for example, cardiovascular) that pose a matter of importance since this class of medicines is usually used by patients with critical conditions and underlying diseases [38]; 3. Early diagnosis: predicting and diagnosing ADRs, for example in old age who have significant challenges for the clinician, even when specific risk scoring systems are available, or patients diagnosed with neurosis who exhibit a history of excessive ADRs of all types and with multiple symptoms. 4. Monitoring the risks of ADRs that occur in the fragmentation of care (eg, increased number of treating doctors and care transitions) experienced by patients (especially older) during their clinical journey [39].

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