

Editorial

Misuse of drugs and personalized treatment in geriatric patients

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Many voices from different sectors of the medical and scientific community have been warning us for decades about the disastrous consequences of the misuse and abuse of certain pharmacological treatments in medical practice. This is particularly alarming in the case of geriatric patients. Cardiovascular disorders, cancer and brain disorders are the principal causes of death and disability in developed societies. All these medical conditions are age-related, with increased prevalence and incidence in parallel with aging. Furthermore, the costs attributed to pharmacological treatment in these pathologies represent about 10-20% of the direct cost of disease, depending upon the country. Among brain disorders, neuropsychiatric disorders (psychotic syndromes, major depression, bipolar disorder, anxiety, sleep disorders, epilepsy, chronic pain, migraine), neurodegenerative disorders (Alzheimer's disease, Parkinson's disease) and stroke account for approximately 80% of the outlay in chronic pharmacological treatments. Additionally, only 20-30% of the drugs administered for the treatment of chronic disorders of the central nervous system are cost-effective, and most of them are not devoid of adverse drug reactions (ADRs). In this context, the medical community, the pharmaceutical industry and the regulatory agencies (FDA, EMA, Koseisho) should revise current treatment protocols and decision-making strategies to reverse this unacceptable situation.

The elderly population with chronic disorders may consume 6-10 different drugs per day with the consequent risk of drug-drug interactions (DDIs). Approximately 10-20% of prescriptions in the general population are susceptible to DDIs [1-3]. Especially dangerous is the association of anticoagulants (warfarin) and non-steroidal anti-inflammatory drugs (NSAIDs) [2,4,5]. In elderly patients, DDIs are prevalent in the USA and Europe with a frequency ranging from 12% to 40% [6,7]. Preventable ADR rates in ambulatory care surpass 15% and in hospital care reach 50-75% [8]. In patients with DDIs, the median DDI prevalence for hospital admissions ranges from 4% to 20% [9,10]. Incorrect prescription of NSAIDs is the most frequent cause of hospital admission [9], together with inappropriate medications for cardiovascular disorders in adults and elderly patients [2,11]. In geriatric patients, the most frequent symptoms that require hospitalization include gastrointestinal complaints and metabolic and hemorrhagic complications associated with the misuse of diuretics, calcium channel blockers, NSAIDs and digoxin [12,13]. In these cases, the most important determinant of risk for ADR-related hospital admissions is the number of inappropriate drugs prescribed to the

patients, and self-medication [12-15]. Cardiovascular drugs, analgesics, and hypoglycemic agents account for over 85% of preventable ADRs in ambulatory care, and about 77% of these preventable ADRs result in CNS symptoms [16]. The rate of preventable ADRs in intensive care units is about 19 events per 1000 patient days, and almost twice that rate in non-intensive care facilities [17]. It has also been reported that admissions caused by preventable ADRs represent an additional cost of \$6685 per event [18].

These figures have been passively accepted by the medical community and health authorities for decades, and no apparent reduction in ADR- or DDI-related events has been observed in recent times, despite spectacular progress in medical technologies and management procedures. Accidental risks in medical practice are unavoidable in many instances, especially in fragile patients with chronic and/or terminal diseases. However, nowadays, the incorporation of predictive biomarkers and pharmacogenetic procedures may help health professionals to improve the efficacy and safety of pharmacological treatments in both ambulatory and hospital settings [19-26].

There is a clear parallelism between the efficacy and safety of drugs and the pharmacogenetic profile of patients. It is estimated that only one-third of drugs are cost-effective and only 20% of the Caucasian population is extensive metabolizer for the gene cluster integrated by major polymorphic variants of the CYP2D6-CYP2C9-CYP2C19-CYP3A4/5 genes (involved in the metabolism of 60-80% of current drugs worldwide) [19,27-30]. According to these estimations, it is likely that the administration of a drug at random, by trial-and-error, following conventional protocols, will result in a lack of effect or in toxicity, assuming that 80% of the population is intermediate, poor or rapid metabolizer for phase-I reaction enzymes encoded by CYP genes [30].

Pharmacogenetics accounts for a 60-80% variation in drug pharmacokinetics and pharmacodynamics. The genes involved in the pharmacogenetic cascade include (i) pathogenic genes associated with the etiology and pathogenesis of a given disease, (ii) mechanistic genes associated with the mechanism of action of drugs, (iii) metabolic genes encoding phase-I and phase-II enzymes responsible for the metabolism of drugs, (iv) transporter genes that encode transporter proteins; and (v) and pleiotropic genes involved in multiple metabolomic cascades [29,30]. The expression of all these genes is under the control of the epigenetic machinery (DNA methylation, chromatin/histone modifications, microRNA regulation) [31]. The

normal functioning of this complex apparatus is essential for the optimization of therapeutics, and genomic and/or epigenetic defects in this regulatory network are responsible for drug efficacy and safety, and drug resistance as well [32].

At present, the implementation of pharmacogenetic procedures in clinical practice is the only effective way to optimize therapeutics, to reduce ADRs and DDIs, and to eliminate unnecessary costs associated with ADR/DDI events. However, pharmacogenetics is still an immature discipline, with a need for substantial improvement in specificity and sensitivity. The *World Guide for Drug Use and Pharmacogenomics* [19] provides basic information on the pharmacogenetics of over 1000 FDA-approved drugs, and some other excellent sources from the academia and public and private websites [33,34] are contributing to educate physicians and scientists on the utility of pharmacogenomics in drug prescription and drug development.

Despite the documented benefits provided by pharmacogenetics, there is still reluctance in the medical community and administration to incorporate pharmacogenetics into current therapeutic protocols. The rejection of novelty is a typical behavior of the human species. However, in any case, a personalized treatment, based on pharmacogenetic principles, will always be better than the personal preferences or the intuition of the medical prescriber, and naturally much more honest and accurate than the guidelines dictated by the pressure of industrial marketing.

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