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Short Communication

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ADRs and Clinical Toxicology

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Medications unquestionably have provided tremendous benefits to society. Whether preventing childhood illness through vaccination, treating or preventing infections with antimicrobials, or forcing cancer into remission with antineoplastic agents, the benefits of modern drug therapy are immense. However, such therapy is not without risk. Encephalitis has been associated with vaccines; allergic reactions to antimicrobials are well documented; and antineoplastic agents can severely impair a patient's immune system, exposing them to life-threatening infections. The negative and undesirable effects of drug therapy are adverse drug reactions or ADRs. About 5–10% of hospital admissions can be attributed to ADRs [1]. All medical products, whether drugs, biologicals, diagnostic agents (eg, radiocontrast dye), natural products, or nutritional agents can cause adverse reactions. The majority (≥ 85%) of ADRs are type A (non-immunological), resulting from the pharmacological activity of the drug [2]. These reactions may be caused by the drug itself or one of its metabolites; from an interaction between two or more drugs or between a drug and food; or may be caused by an excipient in the product, such as a dye or preservative. Some reactions occur with most or all drugs in the class, so called "class effects," for example cough from ACE inhibitors. Despite the risk of bleeding is a well-known adverse effect of oral anticoagulants that requires constant monitoring in a real-life context [3]. Other reactions are unique to the drug. Among antibiotics, chloramphenicol causes aplastic anemia, a reaction rarely seen with other antimicrobials. Some drugs can affect multiple organ systems; for example, amiodarone may cause pulmonary fibrosis, dermatological reactions, hyper- or hypothyroidism, ophthalmologic changes, and arrhythmias [4]. ADEs from other drugs can be highly specific, for example, toxicity from aminoglycoside antibiotics is limited primarily to the kidney and vestibular/cochlear systems. And while drugs and biologicals marketed in the US are required to be proven safe and effective, safe does not mean risk-free. Thus, the decision to use any medicinal product is always the result of examining its risk to benefit ratio. As progress is made toward better assessment and management of drug risk, the line between ADRs and ADEs blurs. While much of the research in recent years have documented risk factors, including age, gender, comorbidities, polypharmacy, inappropriate use of drugs, poor cognitive function, alcohol intake, length of stay and depression, as associated with ADRs [5]. Indeed, comprehensive management of drug risk requires that ADRs and ADEs be considered equally. To this end, FDA has identified four sources of risk from medical products: known side effects (both avoidable and unavoidable), medication errors, product defects, and "remaining uncertainties," which include side effects not yet known or reported, long-term effects, and unstudied uses and unstudied populations. All sources of risk must be considered and evaluated to truly improve drug safety. An exact incidence rate for adverse drug reactions is difficult to determine for several reasons. Different trials and national re- porting programs have used differing definitions of an ADR, resulting in varying reporting rates. Differing means of gathering ADR data (eg, computerized vs manual surveillance), differing areas of research (eg, all hospitalized patients vs a specific unit within a hospital vs an ambulatory setting), differences in reporting statistics (eg, adverse reactions may be reported as a percentage, a rate per unit of time, or a rate per number of doses dispensed), underreporting of reactions, and difficulty in determining numerators and denominators for drug exposure and drug use, all lead to heterogeneous results and difficulty in defining a precise figure or comparing figures. Polypharmacy and inappropriate medication have been shown to contribute substantially to the burden of morbidity, hospitalization and death. Up to 50 % of ADE and ADE-related hospitalizations are judged to be preventable by avoiding inappropriate prescribing [6]. Use of a simple interdisciplinary medication review has been shown to lead to the reduction of inappropriate prescribing and costs, but there was no effect

on clinically relevant patient outcomes, possibly due to a lack of power and insufficient observation time. The cost associated with ADRs is considerable and takes many forms. The economic cost of ADRs in US is 30.1 billion dollars annually [7] and more than 21% of admissions to an oncology service are ADR-related [8]. Studies have consistently shown that patients experiencing an ADR have longer hospitalizations, sometimes doubling the length of stay, relative to the non-affected population. Not surprisingly, the cost of hospitalization for such patients is greater as more resources are used to manage and treat drug-induced illnesses. In addition to the direct increase in the cost of hospitalization, there is the cost to patients themselves in terms of lost time at work, decreased productivity, and possibly permanent disability. Patients or their families may utilize legal means to seek financial remuneration if a serious ADR is experienced. Litigation costs can be significant and place a burden on the court system, individual practitioners, and health care institutions. For example, in 2009 Pfizer Inc. resolved all but three of 35,000 claims over its withdrawn diabetes drug Rezulin for a total of about $750 million and also paid $325 million in 2004 for fraudulently marketing gabapentin, an anti-seizure drug marketed under the name Neurontin [9,10]. Although uncommon, some manufacturers have filed for bankruptcy as a result of ADR-related litigation. Additionally, litigation influences liability and malpractice insurance costs for health care providers and institutions, contributing to the malpractice insurance crisis experienced in several states. A final consideration is the cost of lost confidence and distrust of health care providers and the health care system. A patient's fear of drug-related untoward effects may cause delays in seeking medical assistance at some future point when it is truly needed, possibly causing prolonged illness and severe outcome. The total annual cost to the nation of ADRs is difficult, if not impossible, to quantify but is certainly quite large and is likely in the billions of dollars.

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