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IM - COMMENTARY

Drug–drug interaction knowledge to save the patient from iatrogenic disease and to improve the diagnostic process

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A drug interaction occurs when a patient's response to a drug is modified by other drugs, disease, food, nutritional supplements, formulation excipients, and environmental factors, and it may be harmful or beneficial. Altered compliance, pharmaceutic, pharmacokinetic and pharmacodynamic interactions are the main mechanisms involved.

A huge part of the related literature deals with harmful potential drug–drug interactions (PDDIs), but polypharmacy is potentially problematic rather than being often inappropriate. In fact, sometimes multiple drug regimens represent a price worth paying for health benefits. For example, Shi et al. [1] document the effect of sildenafil as an inhibitor of the transporter function of *P*-glycoprotein, suggesting a possible strategy to enhance the distribution and, therefore, the activity of anticancer drugs. Another example of drug–drug interaction-intended benefit, in emergency or cardiology setting, is the rapid control of rhythm in some supraventricular tachydysrhythmias due to the co-administration of amiodarone and metoprolol (for additive cardiac effects, possible CYP2C9 inhibition of beta-adrenergic blocker metabolism by amiodarone).

Clinicians are responsible to ensure the safe prescribing and use of drug regimens involving drug combinations potentially interacting and causing adverse events of different grades of severity.

In the past 50 years, a great deal of data on drug interactions has been published. Although PDDIs are commonly described, only a few of them are clinically manifested, often in predisposed patients. Clinically important events due to exposure to PDDIs are estimated in 5.3–14.3% of inpatients [2]. The majority of them are avoidable.

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The clinical management of PDDIs generally implies monitoring of symptoms related to possible side effects, laboratory parameters or instrumental elements to prevent potentially serious adverse patient outcomes.

Adverse events by drug–drug interactions represent a considerable amount of iatrogenic disease for which numerous North American and European studies report 2–10% of outpatient consultations and 3–10% of hospital admissions. Nowadays, iatrogenic disease is included in the clinical reasoning for the differential diagnosis to identify the real health problem of a patient. After constructing a complete problem list of the patient, consisting of chief complaints, other acute symptoms and physical examination abnormalities, altered laboratory tests, chronic active problems and important past problems, a deep analysis of the drug therapy regimen is needed to reveal suspected drug-related events.

The relationship between the evidence that establishes a PDDI and the information that can help clinicians to assess the risk within a given patient is quite complex. Many of the developers of PDDI databases are using the Eric van Roon model to determine the clinically useful PDDI information for discerning whether some action should be taken with respect to PDDI [3] (Fig. 1).

The paper by Pejčić et al. [4] in the current issue is interesting for all the clinicians because it evaluates PDDIs and their risk factors in a cardiology center during the patient's entire stay affected by acute coronary syndrome (ACS). Exposition to PDDIs in ACS patients is higher than in patients of medical wards and intensive care units, given the high incidence of cardiovascular disease in developed countries and the use of multiple drugs during and after percutaneous coronary intervention. Multiple comorbidities, longer hospitalization, multiple drug prescription by different specialists, and classes of drugs associated with a lot of PDDIs, such as antidysrhythmics, anticoagulants, antidiabetics, antidepressants, antipsychotics, analgesics, ACE-inhibitors, beta-blockers, diuretics and bronchodilators, are involved in increased risk of PDDIs.

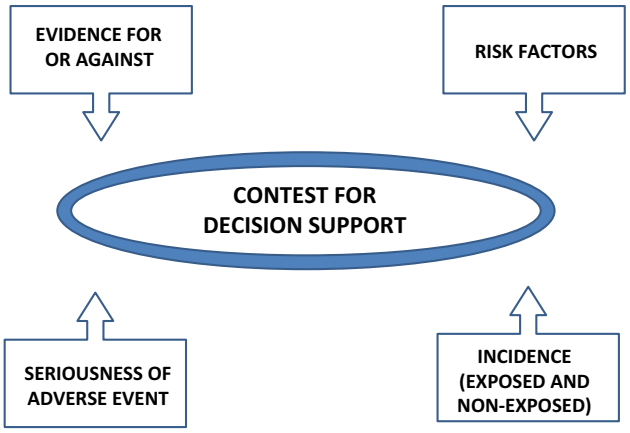

Fig. 1 Van Roon model, the principal information domains for clinically useful PDDIs knowledge

On this basis, the clinician has to face with "the best therapy for the right patient" every day and in every setting. To prevent harm by PDDIs, it is necessary to know at least those interactions which are contraindicated and responsible for major and moderate adverse events. A lot of PDDIs are theoretical or exist only in pharmacokinetic form, where the post-marketing registry reports are sometimes the only source of the clinical evidence to support the relevance of the issue.

Given the spreading of cardiovascular disease and its associated pharmacotherapy, more support from regulatory authorities and scientific organizations is needed to more systematically examine the clinical relevance of PDDIs.

On the other hand, there are several reasons why the rates of prescribing are increased and probably will continue to increase, including the greater availability of effective drugs, the promotion of concomitant treatment of many chronic conditions by guidelines and other quality improvement interventions, and change in patient's expectations.

Some guidelines recommend multiple drug therapy to achieve tight intermediate outcomes such as blood pressure and glycemic control.

Moreover, despite widespread multimorbidity, clinical guidelines are largely written as though patients have a single condition and the burden of disease and treatment recommendations from multiple guidelines is not generally considered.

While improving these actions, interventional providers need to be aware of the PDDIs and associated harm to minimize or, if possible, avoid medication-related adverse events, decrease risk of hospitalization and longer stay in hospital in addition to avoiding higher health care costs.

Although software checkers for drug interactions are widely available, they have limited the clinical utility. Some help may be given by drug information services that use reference information such as Stockley's Drug Interactions and Micromedex. Moreover, to reduce patient harm from drug interactions, the clinician may use a personal formulary (with few drugs but well known), and should recognize drugs that are major perpetrators of interactions and drugs that have a narrow therapeutic index. About these last drugs, warfarin is a typical example to strictly monitor when it is co-administered with drugs that bind to site I of albumin during the pharmacokinetic distribution phase. It is known that drugs that have a high degree of plasma protein binding are more likely to be displaced by drugs with greater affinity for the same binding site. From a clinical point of view, the displacement might be associated with symptoms, side effects or toxicities when the displaced drug has a higher degree of binding to plasma proteins, reduced volume of distribution, a rapid onset of the effect, and a long half-life, besides a narrow therapeutic index.

Applying clinical pharmacology principles is another and important means to prevent adverse events. When knowledge of clinical pharmacology is poor, the clinician may require assistance by the clinical pharmacologist or the clinical pharmacist, where the first is not present.

The several "take home messages" given by Pejčić et al. [4] in the discussion induce the clinician to reflect on the complexity of a patient management along the complete health care pathway. The precise analysis on PDDIs in a specialist setting like cardiology should be an example of good clinical practice to apply to every setting.

Ameliorating drug prescription from admission to discharge is an essential step of decision making for the best therapy tailored to the single patient, in accordance with the characteristics of each one, as inter-individual variability, fragility and reduced homeostasis, as in the elderly.

Compliance with ethical standards

Conflict of interest The author declares that she has no conflict of interest.

Statement of human and animal rights The article does not contain any study on human participants or animals.

Informed consent Informed consent was not required.

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