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6.1 Introduction

Polypharmacy has been defined by the World Health Organization as “the administration of many drugs at the same time or the administration of an excessive number of drugs” [1]. Even if the use of more drugs in many cases has been justified by concomitant diseases and complex medical situations, it is not rare, especially in old patients, the prescription of more inappropriate drugs increasing the risk of iatrogenesis defined as adverse health effects caused by medical practices or drugs prescribed by doctors for the health of the patients at the usual way or doses.

It is well known that population ageing is inducing (a) an increased prevalence of chronic diseases, in particular cardiovascular chronic diseases as congestive heart failure [2, 3]; (b) a significant increase of comorbidities, defined as the simultaneous presence of several chronic diseases, with at least one main pathology associated to disability [4–11]; (c) an increase in physical and cognitive functional decline; and (d) an increased iatrogenic risk. We need to clarify that the terms polytherapy and polypharmacy are little bit different. Polytherapy means the use of multiple prescribed medications or their excessive administration, while polypharmacy means the use of multiple, also not prescribed, drugs not strictly necessary to an

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appropriate treatment [12]. Both are directly related to demographic and epidemiological ageing trends and represent the most important risk factors for onset of adverse drug reactions (ADRs), poor quality of life, rehospitalizations, increased costs and mortality [13–16].

It is important to highlight that elderly patients receive an average of 6–7 prescribed drugs. Around 90% of these patients assume more than one drug and about 50% of them from 2 to 4 over-the-counter (OTC) drugs [12]. In addition, around 47–59% of elderly patients take vitamins or minerals and 11–14% herbal remedies [12]. For example, hepatotoxicity of herbal remedies has been well defined [18], and we have demonstrated in elderly people affected by congestive heart failure (CHF) a significant relationship between the use of laxatives/antacids and the presence of hypermagnesaemia, as well as an increased mortality risk at 3 years of follow-up [14]. Interestingly, only 58% of patients communicates to the doctors the use of OTC drugs [12], thus leading to possible interactions between OTC and regularly prescribed medications.

Drugs, even if widely indicated by clinical guidelines and best medical practice, have several potential ADRs that are related to an increased risk of hospitalization and mortality. For example, in a cohort of heart failure outpatients with a mean age >72 years and treated with spironolactone [19], it has been observed an increased prevalence of renal failure and hyperkalemia, compared to data derived from clinical trials. Of interest, there is also a great debate on the use of ACE inhibitors in patients with CHF and renal failure. In the analysis of 12 randomized controlled trials [20] enrolling patients with pre-existing chronic kidneys disease (serum creatinine >1.4 mg/dL), it has been estimated a risk of hyperkalemia that was five times higher compared to patients with normal renal function. Moreover, elevated circulating levels of digoxin, associated with clinical toxicity, are a common example of adverse reactions in the elderly population with CHF [21], initial impairment of renal function and low body weight.

The overall analysis of these data suggests that in elderly patients, it is particularly important to have a continuous supervision of the renal function, liver function, body weight and electrolyte levels in order to minimize the risk of iatrogenic injury, and the overall assessment of the elderly patient, with particular attention to comorbidities, is of great help also to identify the best individually tailored therapy. In 2011 Dungen et al. published a study comparing the tolerability and clinical effects of two proven beta-blockers in elderly patients with heart failure showing that the pattern of intolerance was different between these two beta-blockers: bradycardia occurred more often in the bisoprolol group, whereas pulmonary adverse events occurred more often in the carvedilol group [22].

6.2 Polytherapy and Polypharmacy as a Risk Factor for Adverse Drug Reactions

Epidemiological studies conducted in the elderly population have identified polypharmacy and polytherapy as a risk factor of mortality and morbidity. The combination of polypharmacy/polytherapy and the presence of multiple comorbidities

are associated with a high probability of drug-drug or drug-disease interactions. In elderly population, it is particularly frequent to observe the exacerbation of a drug-induced disease or the interaction between two or more drugs. Multidrug interactions are one of the main components of ADR, although there are several difficulties in their identification and quantification. It has been estimated that around 10–15 % of patients receiving a therapy with multiple drugs show relevant drug interactions, and these data are probably underestimated since the interactions are not always identified or reported [23, 24].

In addition, the increased use of herbal and homoeopathic medications poses the additional problem of possible interactions of these medications and other conventional drugs. The interactions between multiple co-administered drugs can be simplified into two main categories: pharmacokinetic and pharmacodynamic interactions. The higher is the number of drugs used in polytherapy, the more possible and frequent are the interactions. Based on the formula: number of interactions = [(number of drugs × number of drugs) – 1/2], with eight co-administered drugs, there are 30 possible interactions. The clinical manifestations of multidrug interactions could be mild, without clinical symptoms, or severe and are always related to the dose and to the exposure time. Most frequently, drug interactions occur at the beginning of the administration during drug absorption, distribution, metabolism or excretion. Pharmacodynamic interactions, which are related to the additive, synergistic or antagonistic effects of specific compounds, are generally more predictable. Frequently, medications interact with multiple mechanisms, although generally only one mechanism is predominant.

The incidence and frequency of adverse events caused by improper use of a polytherapy/pharmacy and their possible interactions are more common nowadays than in the past. The rise in the median age of the population, the increased possibility to face multiple coexisting diseases, the management of patient therapies by several physicians, the use of self-prescribed OTC drugs and the frequent introduction of new medications are some of the causes in the increased occurrence of drug interactions. Moreover, it has to be mentioned that the identification of ADR is complicated by the difficulty to distinguish signs and symptoms derived from adverse drug effects and from those related to pre-existing comorbidities.

For all these reasons, the identification of safe and effective therapies is essential in the modern medicine, especially in the elderly population where comorbidities and polytherapies are associated with reduced physiological reserve of organ systems [25], which strongly affect drug metabolism, pharmacokinetics and pharmacodynamics. Finally, within the complex relationship between comorbidity and polypharmacy, the possible mistakes in the medication process have to be mentioned. These mistakes can be realized at any time of the medication process, including the choice of the most appropriate medication, the prescription (the process of manually prescription of medical drugs) and the delivery of drugs to patients and their administration. Lindley et al., investigating the relationship between inappropriate drug use and the occurrence of ADR, have observed that around 50 % of the ADR was related to the use of unnecessary medications that exhibited absolute contraindications in individual cases [26].

6.3 Adverse Drug Reactions (ADRs) and Hospitalizations

About one third of hospitalizations and half of the deaths related to drug use occur in over 70-year-old subjects. Among the drugs most frequently implicated in the phenomenon, an important role is covered by neurological and non-steroidal anti-inflammatory, as well as by cardiovascular molecules such as warfarin, heparin, diuretics at higher doses, majority of anti-arrhythmics, β -blockers, digitalis and antihypertensives in general [26–30]. Many of these drugs, in addition to the known phenomena of direct toxicity, can aggravate and exacerbate chronic diseases (e.g. the prostatism by anticholinergic drugs, postural hypotension by diuretics or antihypertensives, negative inotropism and chronotropism by β -blockers).

Interestingly in hospitals and nursing homes, many elders receive routine drugs that are not essential (e.g. sedatives, hypnotics, H₂ receptor blockers, laxatives, antibiotics are not strictly necessary), which can cause ADR, directly or through complex interactions [32–35]. In confirmation of these allegations, the Italian Group of Pharmacovigilance in the Elderly (GIFA) of the Italian Society of Gerontology and Geriatrics found that at least one ADR occurred in 5.8% of the elderly during hospitalization [36]. Gray et al. also established an ADRs' incidence of 14.8% in hospitalized elderly patients [37].

Significant differences are observed in ADR rate in relation to care settings and, within the same setting, in relation to the detection method and the characteristics of the study population.

Recently by using an ADR database of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (2007–2009) for the estimation of the frequency and rate of hospitalization in the emergency department, Budnitz et al. [27] rated the contribution of specific medicines, including those identified as high risk and potentially inappropriate. They conclude that the majority of hospitalizations for recognized ADRs in elderly derives from the use of the most common drugs such as warfarin and insulin and that the improvement of antithrombotic and antidiabetic drugs management is potentially capable of reducing hospitalization rate by ADR in the elderly.

6.4 Adherence to Therapy in Elderly

The proper treatment of coexisting chronic conditions in elderly is essential to slow the progression, to prevent the development of further diseases and to reduce the risk of duplicate, inconsistent or even in conflict treatments that can negatively change the outcome. The key point in the treatment of chronic conditions is the overall accuracy of the drug prescription. In particular, the effectiveness of treatments and their long-term benefits can also depend on the adherence to the instructions of the prescriber [38].

Adherence refers to the perseverance with which the patient follows the instructions given in prescribing treatment. Proper adherence to therapy cannot be separated from sharing of choices through intense relationship between the doctor,

patient and caregiver. In general, significant positive predictors of adherence include (a) simple and short therapeutic regimens, (b) therapeutic classes that meet in favour of consumers, (c) understanding of the disease severity from patients and their families and (d) high symptom score.

The 30–60 % of patients are considered poorly adherent to pharmacological prescriptions. The main reasons for non-adherence of the elderly are represented by the potential side effects, poor education, cognitive impairment or psycho-affective disorders such as depression, but also by having difficulty paying for medications, the disagreement about the need for treatment and the relationship difficulties between the patient and professional staff in charge of care. Other reasons for non-adherence include pathological conditions silent in terms of symptoms (such as hyperlipidaemia, hypertension and osteoporosis), cultural factors and inadequate social support.

In a study of Karousel-Wood et al., predictors of adherence to antihypertensive therapy were investigated in a cohort of elderly subjects [38], identifying in women and being married characteristics favourable to a better adherence and depression a condition significantly unfavourable to a proper therapeutic adherence. Based on these considerations, interventions aimed at improving adherence to treatment of elderly patients with comorbidity are essential, also through the implementation of research oriented to identify the most appropriate strategies to this objective. Such approaches must certainly include psychosocial interventions involving both patients and caregivers in order to improve outcomes for complex diseases.

In addition, it has been reported, from both an experimental [39–43] and clinical [44–46] point of view, that physical exercise is able, even in elderly patients with CHF, to condition many pharmacokinetic parameters, modifying the effectiveness [47] and suggesting, therefore, a possible role of this important tool in the optimisation of drug therapy.

6.5 Inappropriate Prescriptions in Elderly

Several studies have documented that potentially inappropriate prescriptions are common in elderly patients, particularly in the outpatient setting, in nursing homes and in emergency departments and that exposure to inappropriate therapy is associated with an increase in terms of adverse events, morbidity, mortality and use of resources [48].

Inappropriate medications can be defined as “medications or medication classes that should generally be avoided in persons 65 years or older because they are either ineffective or they pose unnecessarily high risk for older persons and a safer alternative is available” [49]. The prevalence of inappropriateness increases with the age reaching a 70 % in a geriatric hospital setting [50].

The optimisation of drug prescription is therefore becoming an objective necessity for health systems. The therapy should be guided by the appropriateness that is accomplished through the evaluation of the risk/benefit ratio, essentially when the potential benefits of a drug outweigh the potential risks. Many studies based on the use of educative interventions demonstrated their efficacy in reducing the

inappropriate prescriptions. In particular, Corbi et al. recently showed that the use of an educative/informative instrument was able to significantly reduce the number of inappropriate prescriptions, and the length of hospitalization, suggesting as this tool could be very helpful especially in complicated patients with several comorbidities and drugs [51].

Starting from the consideration that the problems related to taking the drug include factors due to the patient (emotional factors, simple forgetfulness, lack of training/information) and the doctor (lack of information to the patient, complex therapies, bad doctor/patient relationship), in conclusion it is necessary to develop strategies involving patients, family members, caregivers and family doctors who play a vital role in the proper use of medicines, in reducing iatrogenic damage and in increasing adherence [52–60].

Elderly patients should be encouraged to discuss the medicine-related problems with their doctors and their caregivers, including through the use of simple diaries of all drugs and their changes at every doctor's visit. Physicians should exercise caution in reviewing and updating the treatment of their patients. Controlled studies, articulated through the use of electronic means, should be planned to give a correct answer to the increasing need of prescription appropriateness in elderly patients *with comorbidity and taking several different drug treatments*.

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