

The Emergency Division as a strategic center for pharmacovigilance activities. The role of hospital pharmacist experience at the Hospital "Gaetano Rummo" of Benevento

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Abstract

The Emergency Division represents a strategic hospital headquarter to implement pharmacovigilance activities. The ease of access, the care availability of 24 hours to 24 and the patient's multidisciplinary approach make Emergency Division is the ideal access to health care. Since 2006, the Lombardy region in Italy joined "MEREAFaPS Project": Epidemiological Monitoring Adverse Drug Reactions/Events in Emergency Department. Following the success of Lombardy region, the Italian Drug Agency (AIFA) has proposed an extension of this project to the other Italian regions as Campania. So in April 2010, "Gaetano Rummo" Hospital in Benevento joined MEREAFaPS Project. It is clear that the presence of the hospital pharmacist in Emergency Division is an important resource for the spontaneous reporting system. A pharmacist infact, reports and supports physician to identify ADR/ADE in Emergency Division, increasing the number of ADR/ADE report forms.

In addition, the professional role of hospital pharmacist is an useful tool to create an important network of hospital pharmacovigilance and to increase the number of ADR report forms, their quality and the awareness in safety pharmacology.

Keywords: Emergency Division, MEREAFaPS Project, Epidemiological, pharmacology, hospital pharmacist, ADR/ADE

Introduction

The Emergency Division represents a strategic hospital headquarter to implement pharmacovigilance activities. The ease of access, the care availability of 24 hours to 24 and the patient's multidisciplinary approach make Emergency Division is the ideal access to health care [1]. In the past few years, the Scientific Community considers the drugs as possible inducers of iatrogenic disease and one of the major cause of access to Emergency Division [2]. Since 2006, the Lombardy region in Italy joined "MEREAFaPS Project": Epidemiological Monitoring Adverse Drug Reactions/Events in Emergency Department, involving 15 hospitals in Lombardy Emergency Division Services. The aim of this project is to introduce pharmacists in Emergency Division to collect data on adverse drug reactions or events (ADR/ADE) admissions. From June 2006 to May 2008, 3997 ADR report forms were collected: ADR severe were 17% (0.25% death, 15% hospitalization, 2% life-threatening). In this study, the drugs mainly involved were: non steroidal anti-inflammatory (NSAIDs), platelet inhibitors, anticoagulants and antibiotics. Following the success of Lombardy region, the Italian Drug Agency (AIFA) has proposed an extension of this project to the other Italian regions as Campania. So in April 2010, "Gaetano Rummo" Hospital in Benevento joined MEREAFaPS Project. It is clear that the presence of the hospital pharmacist in Emergency Division is an important resource for the spontaneous reporting system. A pharmacist in fact, reports and supports physician to identify ADR/ADE in Emergency Division, increasing the number of ADR/ADE report forms.

The presence of pharmacist contributes so to establish a mechanism to ensure that adverse drug reactions or events are systematically reported and reviewed. Several studies confirm the importance of hospital pharmacist's figure as a pharmacovigilance monitor in Emergency Divisions [3,4] including MEREAFaPS project too. The aim of this study is to confirm that a pharmacist who supports medical staff and nurses to signalling ADR, should be im-

prove the national system of Pharmacovigilance involving (where possible) the patient in order to understand better the dynamics of suspected drugs' use. "Gaetano Rummo" Benevento Hospital direct care staff, in cooperation with the pharmacist, has the responsibility of reporting, documenting and monitoring adverse drug reactions that occur within the ED population.

In all hospital divisions, the monitoring activities in response to signals provided by reports of Emergency Division were determinant. The Emergency Division is in fact an important center of immediate hospitalization of all patients with more or less serious pathological phenomena. Some specific targets (indicators) were considered: the percentage of ED visits due to ADR (adverse drug reaction) or ADE (adverse drug event), the percentage of hospital admissions due to acute ADR and ADE, suspected drugs which caused reaction and other drugs taken in association, the type and frequency of observed adverse drug reactions and events, the type of population involved (age, sex, comorbidities), how many of these ADRs and ADEs are predictable and therefore preventable and their classification in severe, non severe and life-threatening. In addition, the professional role of hospital pharmacist is an useful tool to create an important network of hospital pharmacovigilance and to increase the number of ADR report forms, their quality and the awareness in safety pharmacology.

Materials and methods

In the first 3 months of project (January-May 2010), pharmacist and medical staff took part in a course to acquire the theoretical aspects of the recognition and reporting of suspected ADR/ADE and the technical and operational aspects of the MEREAFaPS project too. The ADR/ADE report form presents a part concerning patient details: patient identifier initials, date of birth, sex, ethnic origin, weight and a part relates to the date of reaction started, the date of recovery, the description of the observed reaction or problem, a list of suspected

medications (name, manufacturer, number of lot, Exp. date (if known), dose used, route used, frequency), the reason for use or prescribed for, if reaction was abated after drug stopped or dose reduced or if reaction was reappeared after reintroduction, the relative degree of severity of ADR/ADE according to the criteria of the EMEA, if therapy was prescribed by a doctor and if there is a personal or family history for previous adverse reactions to drugs. Another part of ADR/ADE report forms relates to alternative causes of reactions/events, concomitant medical products and therapy dates including self medication and herbal remedies (exclude those used to treat reaction), relevant tests/laboratory data when available including dates and other relevant history, including pre-existing medical conditions (e.g., allergies, race, pregnancy, smoking-alcohol use, hepatic/renal dysfunction, etc.). Finally it is necessary to describe the seriousness of the reaction (death, congenital anomaly, life-threatening, required intervention, hospitalization-initial to prevent permanent or prolonged impairment/ damage, disability or other) and its outcomes (fatal, recovering etc etc). Any health care professional (doctors including dentists, nurses and pharmacists present in Emergency Division) can report and it's possible to report even if it's not certain the product caused adverse reaction. The licensed nurses can observe, report, document and begin ADR report. Psychiatrists/physicians observe, assess, prescribe, document and complete ADR report. Pharmacist evaluates report, presents ADR report to Pharmacy. Information provided in this form is handled in strict confidence. Hospital Pharmacist will forward this form to the National Pharmacovigilance Centre and data entered the network database of Niguarda Ca' Granda Hospital in Milan, the leader of this national project. This reporting form was established with key principles: all suspected ADRs should be reported; reporters do not need to prove that the drug caused the reaction; all medical and paramedical staff have the responsibility to report; reporters could be made in confidence. Finally the data is statistically analysed and forwarded to the

Global Pharmacovigilance Database. Data is periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health (AIFA). Moreover, the software allows a real-time statistical analysis of the collected data in order to highlight the homologies or discrepancies among the different Italian hospitals. Monthly, the Hospital Pharmacist proceeds to expound paper reports about the number of reports he/she made during the month, the description of ADR/ADE with the triage color (red, yellow, green or white) and the description of suspected drugs in order to give all medical and paramedical staff constant data about the progress of the project.

Results

Considering the reporting period from May to December 2010 it was an increase of ADR/ADE report forms (Fig 1)

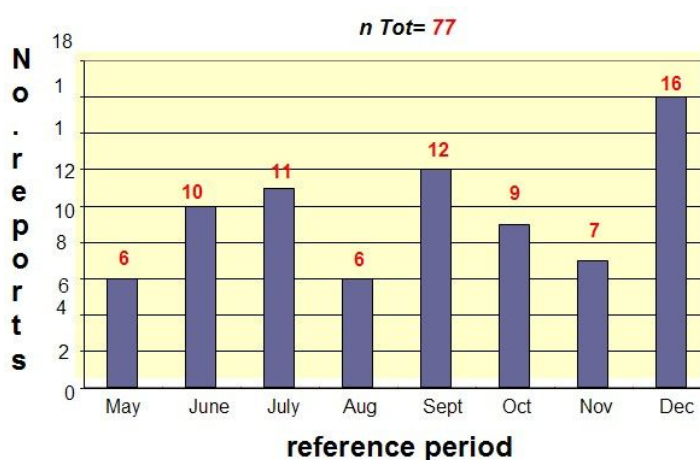


Fig 1 Increasing reports (n = 77) evaluated in the period May-December 2010

ADR report forms don't take into account the period preceding the month of May 2010: a training period for the hospital pharmacist and the medical and paramedical staff of Emergency Division. As you can see in the graph, only in the first 10 months, since the MEREAFaPS Project was initiated, the number of ADR report forms was increased (6 ADR report forms in May while in December there was an three-fold increase of ADR report forms). Clearly

in the month of August the number of ADR report forms is similar to that found at the beginning of this project because the hospitalization at this time was very limited even if the monitoring service has continued. The population was divided in three different age categories (Fig 2). 52% of adverse drug reactions involved adults aged 65 years, 45% were patients older than 65 years while only 3% of the events were connected to children older than 12 years. The latter figure is, as discussed below, controversial for location of Emergency Division compared to the monitored pediatric emergency departments.

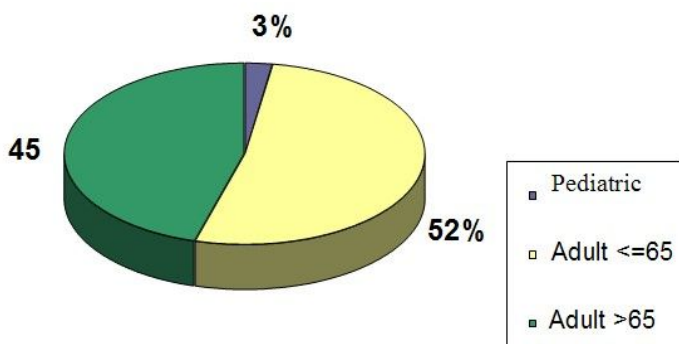


Fig. 2 Percentage of reports in relation to age

57% of patients were woman while 43% of ADR report forms were referred to men (Fig 3)

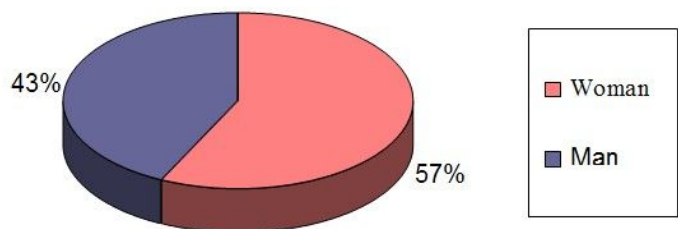


Fig.3 Percentage of reports in relation to gender

The top ten of drugs involved in ADR report forms are also represented with the number of events they caused (Fig. 4). The most reported drug was aspirin, that is the active ingredient that has caused the major number of ADR report forms.

Active substances

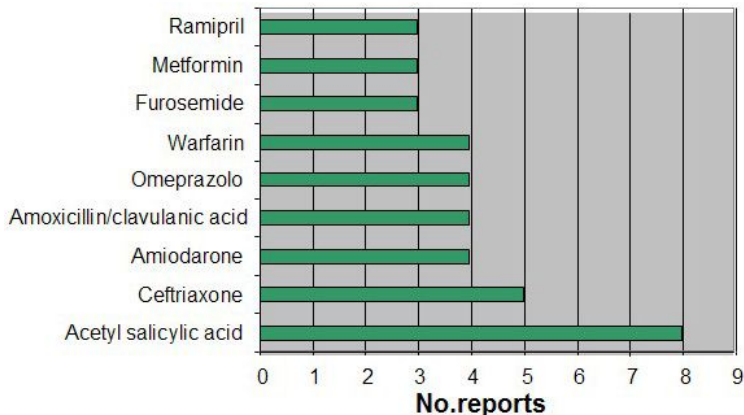


Fig. 4 Active ingredient that caused ADR/ADEs (top ten)

According to the System Organ Class (SOC), 166 ADR report forms were analysed: skin reactions and subcutaneous tissue reactions were 26.5% of the events (44 cases); 11.4% (19 cases) were disturbs of central nervous system, 10.8% (18 cases) gastrointestinal problems; 8.4% (14 cases) were respiratory reactions with mediastinal involvement – chest (Fig 5)

see fig. 5

In detail, the classification of Preferred Term (PT) shows skin reactions and subcutaneous tissue events: 13 cases of urticaria and 8 of erythema and generalized pruritus; in addition, among the disorders of the central nervous system, we highlight 7 of dizziness, 4 cases of anxiety and headache (Fig. 6)

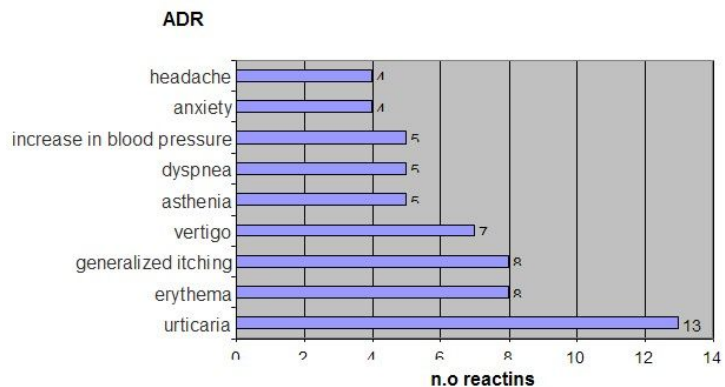


Fig.6 Analysis of ADR through the Preferred Term

48% of adverse drug reactions were severe but without interfering with vital signs while 4% of adverse drug reactions have endangered the life of the patient requesting the hospitalization (life-threatening) (Fig.7)

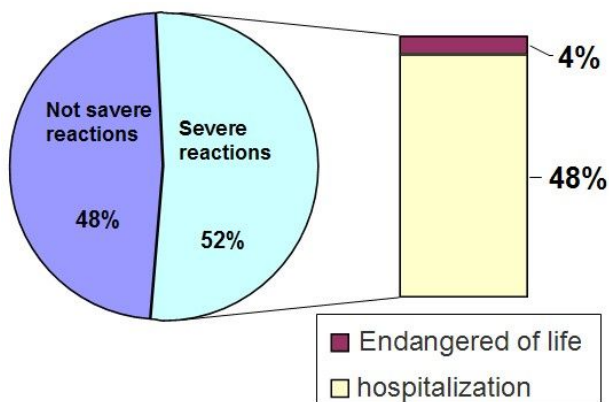


Fig.7 Analysis of the severity of adverse drug reactions we obtained

58% of ADR report forms (96 cases) indicated polytherapy as the first cause of ADR/ADEs. 42% of the reported reactions (70 cases) is attributable to a single agent (Fig. 8).

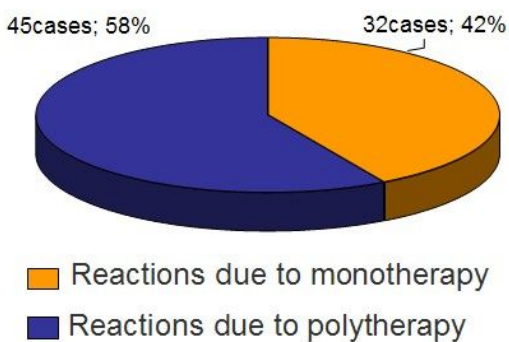


Fig.8 Distribution of ADR caused by mono or polytherapy

Specifically, figure relates the number of involved drugs in polytherapy with the number of suspected ADR/ADE associated with them. In particular 14 cases of ADR report forms are attributable to polytherapies of 2 and 3 drugs and 14 cases are attributable to an association of 3 and 4 drugs (Fig. 9)

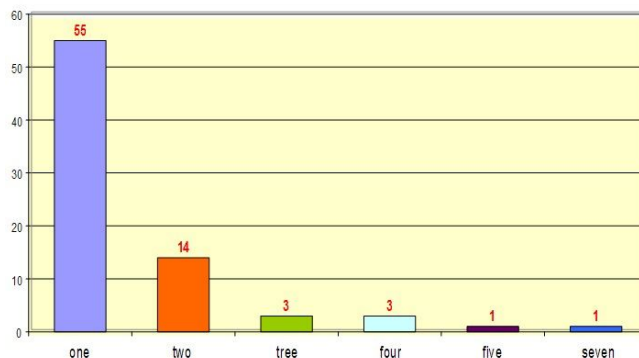


Fig.9 Distribution for n° reactions drugs suspected

Discussion

All drugs, including those administered for the treatment of genetic trivial (common cold, pain of various types, etc..) present a risk to cause adverse reactions [6]. It's important to use all drugs considering their risk/benefit ratio, starting from a correct understanding of the potential adverse events and the severity of the condition for which each drug is used. It must, therefore, make a close watch on the true incidence of adverse drug reactions/events that may occur in the course of drug therapy, particularly in Emergency Division: its ease of access, its availability and the patient's multidisciplinary approach are necessary to implement the strategic drug surveillance [7]. Epidemiological data of the literature report an estimate of 106.000 deaths/year due to adverse drug reactions in the U.S., with more than 2 million of patients with adverse drug reactions. This figure is completely unknown in Italy but if adverse drug reactions have the same estimated incidence in the U.S., we could hypothesize about 30.000 deaths/year in Italy for adverse drug reactions/events. It's very difficult to determine the incidence of iatrogenic morbidity and mortality for the inability to calculate the denominator. Within the MEREAFaPS project, the calculation of the total hospitalization was very difficult and inaccurate for several logistic factors (constant loss of data, errors about patient's data, etc etc). So it was impossible to calculate the incidence of hospital admissions due to ADR/ADEs. After the MEREAFaPS project there was an increase of ADR/ADE report forms higher than the results

presented after 12 months of the starting project in other Italian hospitals [8]. The ADRs were the most important cause of visits in the ED (63.8%) [9]. During years 2004-2005, in the U.S. 21,298 patients used Emergency Division for adverse drug reactions (2.4 subjects with suspected ADR/ADE in 1000 accesses to the ED). 16.7% of patients required hospitalization. Patients with more than 65 years old had a greater frequency of adverse drug reactions than the general population (4.9 vs 2 in 1000 accesses to ED) and often had required hospitalization (1.6 vs 0.23 in 1000 accesses to ED [9]). A lot of studies have shown that the geriatric patients (≥ 65 years), the polytherapy and the female gender may represent the major factors of risk for the occurrence of ADE/ADR [11,12]. The data show a clear majority of suspected adverse drug reactions attributable to a monotherapy (71.4% of ADR report forms are attributable to a single drug) compared with 28.6% of ADR report forms attributable to polytherapy. The majority of ADR report forms involve adult patients (52%) between 18 and 65 years old while only 42% of the monitored patients are older than 65 years. The remaining 3%, as discussed later, represents pediatric patients [13]. The data on the sex of monitored patients are in line with the international literature: infact 57%, $n = 44$ of patients are female. In U.S. every year 177,504 patients over 65 years visit ED for adverse drug reactions/events.

33.5% of adverse drug reactions are caused by three drugs: warfarin (17.3%), insulin (13%) and digoxin (3.2%) with 3.6% of ADR for potentially inappropriate medications in the elderly [14] and a further 5.2% of ADR for potentially inappropriate medications in specific circumstances. The risk of recourse to the ED for warfarin, insulin and digoxin is 35 times higher than the ED visits for inappropriate medications. After the first 12 months of MEREAFaPS project, we note a different thing: only 5.2% of ADR report forms refers to warfarin while there is no ADR report forms about digoxin and insulin.

28.5% of ADR report forms in ED has showed that the main suspected drugs are acetylsalicylic acid (10.4%), amoxicillin (alone or in combination with

clavulanic acid, 6.5%), ceftriaxone (6.5%) and amiodarone (5.2%). Annually in the U.S. it is estimated that 7091 patients under 12 years old are treated in the ER for adverse drug reactions/events and the drugs are used to treat cough and flu syndrome (5.7%). 64% of children are 2-5 years old. Approximately 5-10% of patients has these ADRs and just under 1% is hospitalized [15]. Only 3% of ADR report forms involved "pediatric" patients (0-18 years); this deviation from the international literature is due to the location of pediatric ED compared to other departments in the hospital (located in one pavilion).

MEREAFaPS project showed the validity and importance of hospital pharmacist's professionalism for realization of pharmacovigilance system and as a valuable source of information and support to medical and paramedical staff. The problem of awareness the medical and paramedical staff in ED was in this way, immediately solved thanks to the constant presence of the hospital pharmacist: a part of this task force. However there is an "old" problem about all spontaneous reporting systems: the under-reporting or the failure to report is a more or less significant fraction of all adverse drug reactions or events that are manifested in patients during a drug treatment. [16] The causes of failure to report ADR or ADE are numerous and very heterogeneous.

The experience of MEREAFaPS project shows infact that for a lot of time ADR/ADEs are considered of little clinical significance, causing under-reporting and some time medical and paramedical staff were uncertain about the causal relationship with the drug and suspected adverse events or reactions they noted.

In addition, the frenetic rhythm of emergency department is another obstacle for capturing the interest of operators on the reporting practice. ADR/ADE report forms are also analyzed as a bureaucratic practice that interfere in terms of time offered for patient care. Particularly the value that professional hospital pharmacist has acquired in the ED (and later also in other hospital departments,

particularly those in emergencies) seems to be very “innovative”. Following the example of MEREAFaPS project and thanks to his/her cultural background on medication, the hospital pharmacist is identified not only as a reference in the legislative practices of drugs dispensation (in discharge or departments) but as a consummate professional for prescribing appropriateness, for the interactions and toxicity of drugs, for pharmacovigilance practices and active medical device-vigilance too. These dynamics have been favored by specific guidelines of the hospital pharmacist with the aim to involve medical and paramedical staff in the ED and highlight how good and beneficial work the hospital pharmacist had undertaken in the perspective to improve the quality of patient's care. Hospital pharmacist supports medical and paramedical staff with recent scientific literature, EMEA and AIFA updates that could resolve all suspected cases of ADR/ADEs.

Adverse drug reactions don't only affect the health of population but also have an high economic costs. Investigations on this subject have been conducted only in recent times probably because it is entered into an era of cost containment for health care. In fact some recent works have tried to quantify the costs of ADRs based on increased incidence of medical visits and hospitalizations, the use of additional therapies and the extended duration of hospitalization [17,18,19]. In Italy, it is interesting to note the proposed aspect in the Lombardy region: the estimated cost of the ADR in ED for the year 2007, calculating simply the cost of treatment in ED and DRG cost in case of hospitalization, was € 20,178,000. The cost of avoidable ADR is estimated of € 3,228,000. In light of the obtained results from MEREAFaPS project, it's possible to conclude that the implementation of an efficient structure of pharmacovigilance and the cultural and professional competence of the hospital pharmacist can open and encourage many future scenarios. In fact, creating a dense monitoring network, we can improve the appropriateness of drugs' use in all the Italian territory to protect population's life and to save hospital costs related to ADR/ADEs. Pharmacovigilance is a crucial source for reporting

the inadequacies of pharmacokinetic/pharmacodynamic characteristics of all drugs that are on the market but that aren't observed during the previous phases of clinical trials.

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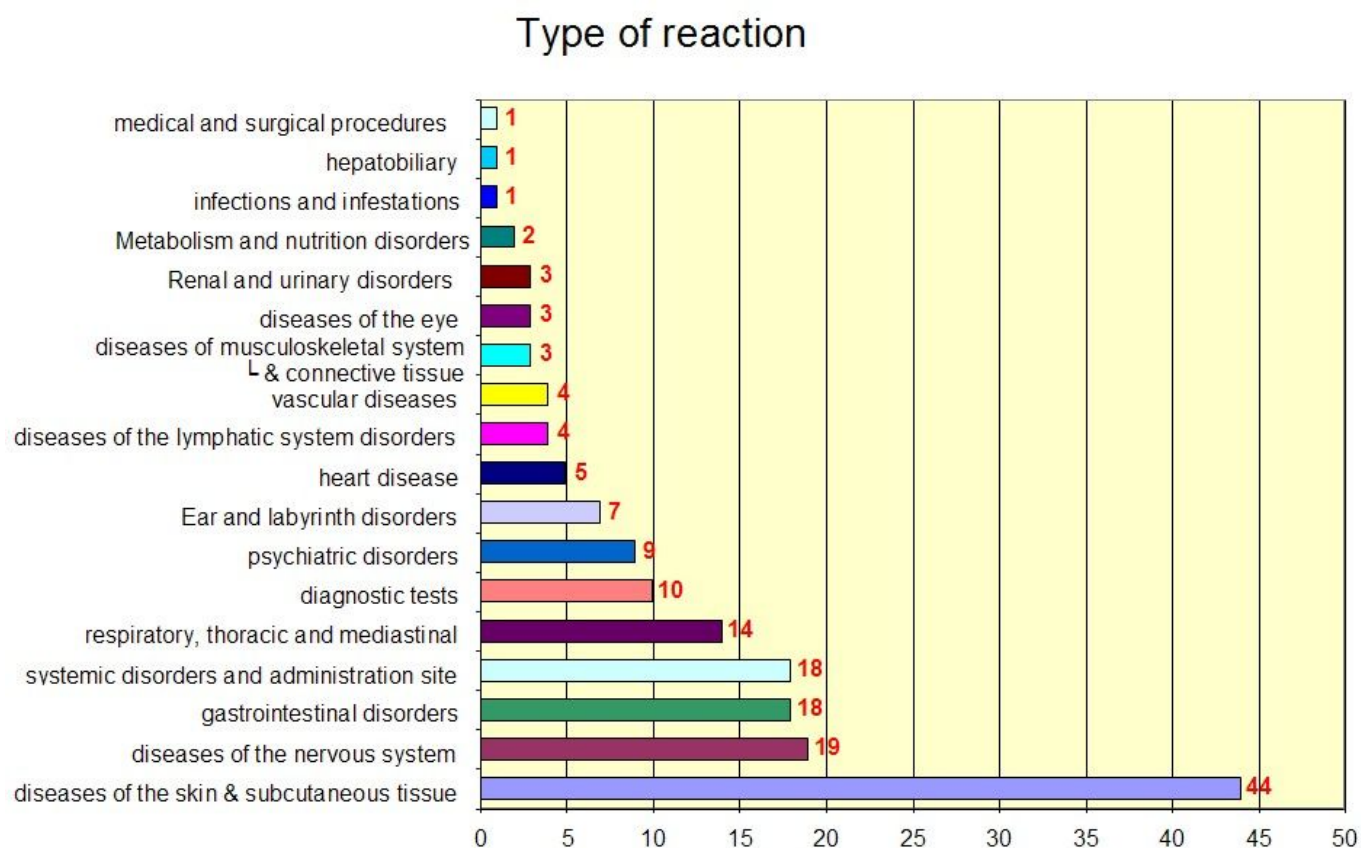


Fig. 5 Types of ADR/ADE that are reported and classified according to the terminology of System Organ Class (SOC)