

# BMJ Open Incidence, types and acceptability of pharmaceutical interventions about drug related problems in a general hospital: an open prospective cohort

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## ABSTRACT

**Objectives** To evaluate the incidence and types of drug-related problems (DRP) in a general teaching hospital and to evaluate the acceptability of pharmaceutical interventions by the medical team.

**Design** Prospective cohort study during 2 years.

**Setting** Conducted in a Brazilian University Hospital.

**Participants** The patient cohort consisted of 9303 patients with a total of 12 286 hospitalisation episodes.

**Primary outcome measures** DRP detected by pharmacists' review of 100% medication orders using Pharmaceutical Care Network Europe 6.2 classification.

**Results** Patients with a mean age of 52.6±17.7 years and 50.9% females. A total of 3373 DRP in 1903 hospital episodes were identified, corresponding to a cumulative incidence of 15.5%. 'Treatment ineffectiveness' (11.5%) and 'Treatment costs' (5.90%) were the most common DRP and 'Drug use process' (18.4%) and 'Treatment duration' (31.0%) the main causes of DRP. The medicines involved most often involved in DRP were anti-infectives (36.0%), mainly cephalosporins (20.2%), antiulcer (38.6%), analgesics/antipyretics (61.2%), propulsives (51.2%), opioids (38.5%) and antiemetics (57.4%). From 1939 pharmaceutical interventions, at least, 21.4% were not approved by the medical team.

**Conclusion** DRP detected by 100% medication order review by hospital pharmacists occur in a significant proportion of hospital episodes, the most frequent being related to treatment effectiveness and treatment costs. The medications mostly involved were cephalosporins, penicillins, antidiarrhoeals, analgesics, antipyretics, opioids and antiemetics. Pharmaceutical interventions had low acceptability by the medical staff.

## INTRODUCTION

Drug-related problems (DRP) are defined as events or circumstances involving pharmacotherapy that actually or potentially interfere with desired health outcomes.<sup>1</sup> DRP are classified as manifested or potential. They are considered adverse events and occur in patients at all levels of healthcare, whether home care,<sup>2</sup> institutional long term care,<sup>3</sup> community pharmacy<sup>4</sup> or hospital.<sup>5</sup> In the

## Strengths and limitations of this study

- Very few studies have analysed the incidence and types of drug-related problems (DRP) in patients hospitalised in general medical and surgical wards.
- A strength of this study is the prospective design based on open cohort of all adult patients hospitalised in a general hospital with DRP identified by review of 100% medication orders by clinical pharmacists.
- Another strength is the extended period of observation that allows the exclusion of seasonality bias due to changing disease incidences throughout the year.
- The main limitation was not to be able to include adverse reactions, dispensing errors and drug-administration errors, which are also considered DRP.
- Another limitation to the generalisation of the results was the conduct of the study in a single hospital.

hospital setting, incidence rates of DRP have been reported for specific patient populations, with high incidence rates in children<sup>6</sup> and the elderly,<sup>7</sup> as well as in certain clinical specialties such as cardiology,<sup>8</sup> neurology<sup>9</sup> and surgery.<sup>7</sup>

This high incidence of DRP negatively affects the quality of life of the patient and increases the economic and social burden of illnesses.<sup>5</sup> Many of the admissions to emergency departments,<sup>10 11</sup> many causes of extended hospital stays<sup>12</sup> or of patient re-admissions,<sup>13</sup> and even of deaths, are due to a DRP. It has been reported that these negative outcomes are proportional to the complexity of the drug use process,<sup>14</sup> with some of the described risk factors being polypharmacy, hepatopathies, nephropathies and the use of high-risk medicines.<sup>15</sup>

The detection and classification of potential DRP by pharmacy services is the first step to prevent harm to the patient,<sup>16</sup> contributing to a reduction in medication errors,



adverse reactions and length of stay.<sup>17</sup> Several systems have been proposed for the classification of DRP, with the Pharmaceutical Care Network Europe (PCNE) being one of the most commonly used classification systems in hospital practice.<sup>18</sup> Several DRP detection strategies have been developed, including pharmacist review of medication orders (MO), the use of computerised physician order entry (CPOE) systems couple with clinical decision support programs<sup>19–21</sup> that allow the clinical pharmacist to have an active participation within the healthcare team.<sup>5 8 22–24</sup> However, despite the clinical and economic relevance of DRP, very few studies have investigated the incidence, types and causes of DRP in patients hospitalised in general medical and surgical wards.

Therefore, the objective of the present study was to describe DRP detected by pharmacist review of all MOs issued to all patients hospitalised in medical and surgical wards throughout their stay in a general teaching hospital to evaluate the frequency, type and cause of DRP detected by this method, and the acceptability of pharmaceutical interventions by the medical staff.

## METHODS

This prospective cohort study was conducted at the University Hospital Onofre Lopes, a public hospital in Natal, Brazil, a medium-sized tertiary care hospital, during two uninterrupted years (May 2016 to April 2018). The hospital has 247 beds and approximately 8000 admissions per year. It is organised in the departments of nephrology, urology, cardiology, surgery (general, neurological, cardiovascular and oncological), endocrinology, rheumatology, neurology, gastroenterology and psychiatry.

All patients over 18-years-old who were hospitalised during the study period for more than 24 hours and for whom at least one drug was prescribed were included in the study. Patients hospitalised only for diagnostic purposes and patients admitted to an intensive care unit were excluded. Solutions of electrolytes, parenteral nutrition solutions, whole blood and blood products, oxygen therapy and diagnostic agents were not considered in the review of MO because they did not have a recommended dose. MO containing anticancer drugs were not included in the research because in our institution they are not entered into the CPOE and are evaluated by clinical pharmacists specialised in oncology.

The MO of each specialty were entered into a CPOE. The CPOE in use at our institution makes clinical data and the hospital formulary adopted at the institution available to the prescriber for selection at the time of preparation of the MO, but does not have a system for issuing electronic alerts to identify DRP. MO are sent electronically to the hospital pharmacy service for the review process by the pharmacist, a step that precedes the dispensing of the medicines.

MO review was performed by a team of hospital pharmacists composed of 21 pharmacists divided into smaller

groups of three elements. These groups took turns reviewing all individual MO that were sent to the hospital pharmacy service 24 hours a day, 7 days a week, for 2 consecutive years.

For this study, DRP were defined, according to the PCNE, version 6.2 (PCNE 6.2), as any event or circumstance involving drug therapy that would, actually or potentially, interfere with the desired health outcomes.<sup>1</sup> Pharmacist review of MO was carried out with the objective of detecting potential DRP by evaluating a predefined and standardised set of identifiable items. These included medication name, availability, dose, route of administration, pharmaceutical form, frequency of use, dilution, infusion time, duration of treatment, therapeutic duplicity, cost-effectiveness, legal aspects of the prescription, use of non-standard abbreviations in the hospital and absence of information relevant to the safe use of the drug. This type of review, in which the pharmacists looked for specific items in the MO, we call Simplified Medication Order Review (SMOR).

DRP were classified according to PCNE 6.2. The PCNE system assigns to each DRP four possible domains with respective subclassifications: (1) problem (treatment ineffectiveness, adverse reactions, treatment costs, others); (2) cause of the problem (drug selection, drug form, dose selection, treatment duration, drug use process, logistics, patient, other); (3) intervention required to solve or avoid the problem (no intervention, intervention at the prescriber level, at the patient/carer level, at drug level, others); (4) outcome of the interventions (unknown, solved, partially solved, not solved).

Based on the identification of DRP, the hospital pharmacists team issued interventions for each case using Micromedex (Truven Health Analytics, Lansing, MI, USA), Uptodate (UpToDate Inc., Waltham, MA, USA) and recommendations of the manufacturer of each drug when analysing the possibility of occurrence of a DRP due to physical–chemical and/or microbiological stability characteristics. Information on the DRP was reviewed by an experienced clinical pharmacist, and in divergent cases a third pharmacist was consulted.

All DRP were recorded manually in a log book, along with the patient identification and detailed description of the DRP, and a pharmaceutical intervention was issued, containing a proposal to change the MO in order to prevent the occurrence of DRP. The intervention proposal was written on a Pharmaceutical Intervention (PI) form and sent by messenger to the patient ward. There, the PI form was attached to the patient chart to be viewed before the next prescription.

Our study did not evaluate the outcome of DRP, considering that the problem detected by the SMOR is a potential problem, not a manifested DRP. We did, however, assess the acceptability by the medical team of the pharmaceutical interventions issued during the SMOR: changes in MO after 72 hours of follow-up, consistent with what was proposed by the pharmacist in the intervention, were considered as accepted by the notified prescriber.

All patients were observed throughout the entire hospital stay up to hospital discharge or death. All medicines prescribed to each patient were recorded and classified according to the Anatomical Therapeutic Chemical (ATC) Classification System.

### Statistical analysis

To avoid bias due to seasonality, it was determined that inclusion of patients would be carried out without interruption for 2 years. During this period it was estimated that there would be about 16 000 hospitalisation episodes, corresponding to approximately 100 000 MO and 1 600 000 prescribed items evaluated. This sample size ensured a maximum error of estimates of 0.8 percentage points with 95% confidence.

Interval variables were described by mean±SD and binary variables by absolute and relative frequency. Statistical analysis was performed using Stata V.12.

### Patient and public involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

## RESULTS

The study was conducted between May 2016 and April 2018. During this period, there were 15 005 hospital admissions and about 2 million doses of medication were dispensed. Our sample consisted of 12 286 hospitalisation episodes in 9303 distinct patients with mean age at first hospitalisation of 52.6±17.7 years, of which 6250 were women (50.9%). The hospital pharmacy reviewed 117 022 MO in these patients. The hospital offers clinical and surgical hospitalisation in different medical specialties, with cardiology (12.6%) and general surgery (8.01%) being the most common. The median length of stay was 2.93 days (range 1–474 days) (table 1).

In 1903 hospital episodes, one or more DRP was detected, corresponding to a cumulative incidence of DRP of 15.5%. A total of 3373 DRP were identified, corresponding to an incidence density of 1.71% patient-days and representing a mean of 0.27±0.81 DRP per patient. According to PCNE 6.2, DRP classified as ‘P1.Treatment

**Table 1** Demographic and clinical characteristics of the study population.

Characteristics	Descriptive statistics	
Age in years (m, SD)	52.6	17.7
Female (n, %)	6250	50.9
Length of stay (median, range)	2.93	1–474
In-hospital mortality (n, %)	666	5.42

%, relative frequency; m, mean; n, absolute frequency; SD, standard deviation.

**Table 2** Cumulative incidences of drug-related problems (DRP) according to version 6.2 of the PCNE classification.

DRP type	Cumulative incidence	
	n	%
<b>P1—Treatment effectiveness</b>		
P1.1—No effect of drug treatment/therapy failure	257	2.09
P1.2—Effect of drug treatment not optimal	1132	9.21
P1.3—Wrong effect of drug treatment	24	0.19
<b>P3—Treatment costs</b>		
P3.1—Drug treatment more costly than necessary	725	5.90
<b>P4—Others</b>		
P.4.2—Unclear problem/complaint	301	2.45

PCNE, Pharmaceutical Care Network Europe.

Effectiveness’, which includes DRP for ‘no effect of drug treatment/therapy failure ‘effect of drug treatment not optimal’, ‘wrong effect of drug treatment’ and ‘untreated indication’ was observed in 1413 (11.5%) patients, the most frequent being ‘effect of drug treatment not optimal’ (9.21% of patients) (table 2). DRP classified as ‘P3.Treatment Costs’, which are those related to the use of drugs more expensive than necessary to treat a certain disease, were identified in 725 (5.90%) patients. DRP classified as ‘P4.Others’ occurred in 301 patients (2.45%) and refers to those in which the patient is not satisfied with the therapeutic and/or economic outcome, or those whose classification system was not able to include, such as non-compliance with treatment, use of commercial name, incomplete prescription, use of non-standard abbreviations, difficulty in interpreting MO and type of pharmaceutical formulation. The SMOR process could not identify DRP of the ‘P2.Adverse reactions’ type, which encompass drug (allergic/non-allergic) adverse events and toxic adverse drug events.

Concerning the causes of DRP (table 3), the P1 type was mainly caused by inadequacies in the ‘C5. Drug use process’, which include inadequate timing of administration, inadequate or unsafe site or route of administration, insufficient dilution volume and inadequate diluent. These causes represented 18.4% of the causes of DRP, with an incidence density of 0.16% patient-days. DRP’s caused by ‘C6. Logistics’, which include drug unavailability, prescription error and dispensing error, represented 17.9% of the DRP, with an incidence density of 0.31% patient-days. ‘C3. Dose selection’ represented 16.1% of the DRP, with an incidence of 0.28% patient-days. ‘C4. Treatment duration’ was the most frequent DRP cause (31.0% of DRP and incidence density of 0.53% patient-days), associated only with the occurrence of DRPs classified as ‘P3. Treatment costs’. The only cause of the DRP

classified as 'P4. Others' was 'C6. Logistics (10.9% and 0.19% patient-days), which included how the drug would be used (infusion time, frequency, the route by which it will be administered), unavailability of the prescribed drug or prescription error.<sup>23</sup> The cumulative incidence of each DRP cause is also shown in [table 3](#).

Antimicrobials were implicated in approximately 36% of the DRP, mainly cephalosporins (J01D, 20.2%) and penicillins (J01C, 6.08%). The ATC therapeutic classes more often involved in DRP and the frequency distribution of the respective causes are shown in [table 4](#). Among anti-infectives for systemic use, 'C4. Treatment duration' was the main cause of DRP, representing from 61% to 68% of all DRP causes among the different therapeutic classes of anti-infectives. 'C6. Logistics' was another common cause of DRP in some ATC therapeutic classes, such as antipsychotic drugs (A02B, 38.6% of all causes), analgesics and antipyretics (N02B, 61.2% of all causes) and propulsive drugs (A03F, 51.2% of all causes). The DRP observed with opioids (N02A) and antiemetics (A04A) were mainly caused by 'C5. Drug use process' (38.5% and 57.4% of all causes, respectively).

From the 3373 pharmaceutical interventions performed, 1939 were followed up to assess their acceptability by the prescriber. From these, 1217 (36.10%) were considered 'approved' because there was a change in the MO in the same sense as the proposed pharmaceutical

intervention. In 722 (21.4%) cases, the interventions were classified as 'not approved' by the prescriber, since they did not generate changes on the MO ([table 5](#)).

Some pharmaceutical interventions could not be evaluated regarding acceptability by the healthcare team because they would not dictate a change in the respective MO. These include cases where the patient was discharged or died before a MO could be changed, when the pharmaceutical intervention proposed a change in the technique of drug preparation, mentioned an issue related to the physical-chemical stability of the drug, or provided instructions on the correct administration of the drug. These situations accounted for 1433 (42.5%) of cases and were classified as 'unknown'.

## DISCUSSION

Our study assessed the incidence of DRP among adult patients hospitalised in medical and surgical wards of a general hospital using an open prospective cohort for a period of 2 years. The detection of DRP was done by the review by hospital pharmacists of all MO issued by a CPOE system without alerts, according to a checklist for reviewing MO, the DRP being classified according to the PCNE version 6.2.

In this study we estimated that with this centralised simplified method of MO review, DRP are detected

**Table 3** Profile of drug-related problems (DRP) and causes according to version 6.2 of the PCNE classification

DRP type	DRP cause	Frequency distribution		Cumulative incidence	
		n	%	n	%
P1—Treatment effectiveness	C1.1—Inappropriate drug (including contra-indicated)	28	0.83	24	0.20
	C1.2—No indication for drug	12	0.36	12	0.10
	C1.3—Inappropriate combination of drugs, or drugs and food	67	1.99	47	0.38
	C1.4—Inappropriate duplication of therapeutic group or active ingredient	23	0.68	21	0.17
	C2.1—Inappropriate drug form (for this patient)	7	0.21	6	0.05
	C3.2—Drug dose too high	363	10.8	332	2.70
	C3.3—Dosage regimen not frequent enough	180	5.34	167	1.36
	C5.1—Inappropriate timing of administration and/or dosing intervals	619	18.4	530	4.31
	C6.1—Prescribed drug not available	269	7.98	246	2.00
	C6.2—Prescribing error (necessary information missing)	335	9.93	234	1.90
P3—Treatment costs	C8.1—Other cause; specify	34	1.01	32	0.26
	C1.7—More cost-effective drug available	23	0.68	22	0.18
P4—Others	C4.2—Duration of treatment too long	1044	31.0	712	5.80
	C5.7—Patient unable to use drug/form as directed	1	0.03	1	0.01
	C6.2—Prescribing error (necessary information missing)	368	10.9	301	2.45
Total		3373	100.0	—	—

PCNE, Pharmaceutical Care Network Europe.

**Table 4** Distribution of causes of drug-related problems (DRP) in the 10 ATC classes most involved in DRP

ATC class	DRP causes – n (%)							
	Cases of DRP	C1. Drug selection	C3. Dose selection	C4. Treatment duration	C5. Drug use	C6. Logistics	C8. Others	
J01D—Other beta-lactam antibacterials	682 (20.2%)	11 (1.61%)	42 (6.16%)	416 (61.0%)	64 (9.38%)	138 (20.2%)	11 (1.61%)	
A02B—Drugs for peptic ulcer and gastro-oesophageal-reflux disease	210 (6.23%)	14 (6.67%)	37 (17.6%)	0 (0.00%)	75 (35.7%)	81 (38.6%)	3 (1.43%)	
J01C—Beta-lactam, penicillins	205 (6.08%)	3 (1.46%)	10 (4.89%)	135 (65.9%)	12 (5.85%)	39 (19.0%)	6 (2.93%)	
N02A—Opioids	180 (5.34%)	7 (3.89%)	66 (36.7%)	0 (0.00%)	69 (38.3%)	38 (21.1%)	0 (0.00%)	
J01M—Quinolone antibacterials	172 (5.10%)	1 (0.58%)	5 (2.91%)	111 (64.5%)	1 (0.58%)	53 (30.8%)	1 (0.58%)	
J01X—Other antibacterials	158 (4.69%)	1 (0.63%)	18 (11.4%)	100 (63.3%)	11 (6.96%)	27 (17.1%)	1 (0.63%)	
P01A—Agents against amoebiasis and other protozoal diseases	153 (4.54%)	3 (1.96%)	2 (1.31%)	104 (68.0%)	2 (1.31%)	42 (27.5%)	0 (0.00%)	
N02B—Other analgesics and antipyretics	139 (4.12%)	0 (0.00%)	35 (25.2%)	0 (0.00%)	19 (13.7%)	85 (61.2%)	0 (0.00%)	
A03F—Propulsives	123 (3.65%)	14 (11.4%)	25 (20.3%)	0 (0.00%)	21 (17.1%)	63 (51.2%)	0 (0.00%)	
A04A—Antiemetics and antinauseants	101 (3.00%)	7 (6.93%)	11 (10.9%)	1 (0.99%)	58 (57.4%)	24 (23.7%)	0 (0.00%)	

ATC, Anatomical Therapeutic Chemical Classification System.

**Table 5** Acceptability of pharmaceutical interventions related to DRP

Acceptability	n	%
Intervention proposed, approved by prescriber	1217	36.1
Intervention proposed, not approved by prescriber	722	21.4
Intervention proposed, outcome unknown	1433	42.5

DRP, drug-related problems.

in about one-sixth of all hospital episodes. The most common DRP are related to treatment effectiveness, due mainly to inadequacies in the drug use process and inadequate selection of drug dose, and to treatment costs caused mainly by prolonged treatments, involving mostly the therapeutic groups of analgesics/antipyretics and cephalosporins, respectively. It was also found that pharmaceutical interventions, proposed indirectly by means of written communiqués, had an acceptability rate by the medical staff that may be considered rather low.

The incidence of DRP observed in this study was different from the incidence reported in other studies conducted in hospitals of different types,<sup>25–27</sup> which may be due, at least partially, to the diversity of the methodologies used to identify DRP, the classification of DRP, the communication with the medical team and the evaluation of the acceptability of pharmaceutical interventions.<sup>7 24 28 29</sup> In addition, many published studies on the DRP incidence have been done in elderly hospitalised patients who, because of the polymedication often present in that population, are at increased risk of DRP.

The number of beds assigned to cardiology patients and the greater complexity of the pathology and associated comorbidities,<sup>30</sup> especially heart failure and acute myocardial infarction, could in part explain those discrepancies. Drug-related problems predominate in clinical services, especially in cardiology, as compared with surgical services of general surgery.<sup>31</sup>

Very few studies have been published in which the analysis of all the MO of all the patients admitted to a general hospital was done. The large majority of published studies have described the frequency and type of DRP in patients of different medical specialties. Among studies conducted on a whole hospital, a prospective 18-month study between 2001 and 2003 in a university hospital examined 29016 computerised MO of 8152 patients by seven clinical pharmacists integrated in the medical team during ward rounds. The DRP identified were classified by two independent pharmacists using a checklist from the French Society of Clinical Pharmacy. In this study, the percentage of patients with one or more DRPs was significantly higher (33.0%), with non-compliance with the guidelines or contraindication (29.5%), inadequate administration (19.6%), drug interaction (16.7%) and over dosage (12.8%) being the most frequent DRP types.

Cardiovascular drugs were the most involved (22.2%), followed by antimicrobials (13.3%) and analgesics/anti-inflammatory agents (11.3%).<sup>25</sup>

Another prospective study, conducted in six departments of internal medicine and two departments of rheumatology in five hospitals in Norway between May and December 2002, evaluated the hospitalisations of 827 patients for the detection of DRP by clinical pharmacists through review of medical records and multidisciplinary meetings of therapy review, reported that 81% of patients had DRP, with an average of 2.1 clinically relevant DRP per patient. The most frequently reported DRP were dose-related problems (35.1% of patients), followed by laboratory tests (21.6%), non-optimal medications (21.4%) and need for additional medications (19.7% %), unnecessary drugs (16.7%) and errors in the medical records (16.3%). The drug classes that most often caused DRP were antithrombotic agents, non-steroidal anti-inflammatory drugs, opioids and ACE inhibitors.<sup>32</sup>

On the other hand, another study analysed all DRP identified in 44870 patients during 2014–2015 by reviewing the MO issued by a CPOE with alerts, by a team of 14 non-clinical pharmacists integrated in the ward rounds. The percentage of hospital episodes in which a DRP was observed was only 5.6%, a value much lower than the one observed in our study. The main problems related to medication were prescription errors due to incorrect use of the computerised prescription system (18.1%), drug interaction (13.3%) and dose adjustment by renal and/or hepatic function(11.5%).<sup>14</sup>

According to several studies, the implementation of CPOE systems has been responsible for a considerable increase in safety related to the use of drugs.<sup>20,33</sup> However, these systems have also been associated with the appearance of DRP as a consequence of the lack of ability to use computational tools.<sup>34,35</sup> In fact, inadequate prescription from medication errors due to confusion with decimals, lack of information about the route of administration and infusion time, use of abbreviations non-standard in the institution and the use of molecular formulas contributed to the second highest cause of DRP detected in the present study, that of treatment ineffectiveness because of inadequate drug use process. On the other hand, one of the causes of the reduced incidence rate of DRP observed in our study may be related to the absence in our institution of a computerised system that, together with the CPOE system, would provide alerts and reports resulting from cross-referencing the patient's clinical information (diagnosis, comorbidities, lab results, serum concentration of medications) with the pharmacological information on the medications (dose requested and the patient's renal/hepatic function, weight, creatinine, adequate type and volume of the diluent, infusion time, frequency and route of administration). Without such an information system, it is difficult to identify several types of DRP, such as drug interactions, dose adjustments, overdoses, subdoses, among others.

In our study, anti-infectives, especially cephalosporins and penicillins, were the drugs most involved in DRP, mainly due to overuse. The high detection of this type of DRP was probably due to the direct involvement of pharmacists in the inventory control of this class of drugs, thus facilitating the identification of divergences between the expected treatment and what was actually being administered. Other groups also involved the antidyspeptics, analgesics and antipyretics that often presented the potential problem of treatment ineffectiveness caused by logistic problems of the prescription and dispensation process, especially prescription errors due to lack of relevant information such as volume and type of diluent, dose, infusion time, frequency and route of administration and non-availability of the substance. Another relevant group was opioids and antiemetics, more frequently due to failures in the use process, such as insufficient infusion time and dilution volume.

The simplified 100% review of MO by clinical pharmacists, prior to drug dispensing, is one of the main strategies for DRP prevention in patients followed at various levels of healthcare,<sup>36–38</sup> especially in a hospital environment, where the risk of DRP is related to several factors such as polypharmacy, comorbidities, use of high-risk medication, renal/hepatic insufficiency, clinical condition, prolonged hospitalisation, among others.<sup>23,39</sup> This is a very common reality in most health services. The implementation of pharmaceutical clinical services, whether in basic care or high complexity, not only reduces hospital costs<sup>40</sup> but also minimises the occurrence of harm to the patient, of hospital admissions and readmissions and improves the quality of life of patients.<sup>45,8,24,37,41,42</sup>

After MO review, all DRPs identified were the subject of a pharmaceutical intervention via a written statement addressed to the medical staff, regardless of DRP severity. However, only the results of the interventions aimed at the prescribers could be analysed, because of the ease of identification of changes in the MO, reflecting the actual approval of the intervention on the therapeutic plan of the patient. A relatively low rate of acceptability of the interventions was observed, possibly related to the fact that the clinical pharmacists who reviewed the MO were not integrated into the healthcare team, had no direct involvement with the patient care and did not participate in ward rounds. Other studies have reported significantly higher acceptability rates, and we believe that MO review during clinical meetings, with the participation of the clinical pharmacist within the healthcare team, predisposes to this and produces better outcomes in health.<sup>3,43</sup> This stresses the importance of DRP detection before dispensing the product to the patient, thereby promoting the minimisation of harms resulting from the medication process,<sup>8,28</sup> since computer system alerts issued for MO revision do not seem sufficient to guarantee the effectiveness of the pharmaceutical interventions.<sup>44</sup>

A strength of the present study is the extended period of observation that allows the exclusion of the seasonality bias due to changing diseases characteristic throughout

the year. A major feature of the study was to perform MO review in all patients admitted to all departments of a general hospital, thus providing a better insight into the size and extent of DRP in a health facility as a whole than is provided by a study in particular populations or in specialised departments. Another strong point of the methodology was to adopt internationally recognised standards to allow easier comparison of results among studies. In this sense, the PCNE classification system was chosen for its frequent application in studies that involve the identification and categorisation of DRP<sup>22 41 45 46</sup> and because it is a frequently used tool in hospital practice,<sup>18</sup> although many other DRP classification systems have been proposed.<sup>47</sup> Very few studies have been published in the literature in which pharmaceutical interventions were made through written communication with prescribers, acting as a warning system; other studies deal only with interventions made verbally during ward rounds.

The main limitation of this study was not to be able to include adverse reactions, dispensing errors and drug administration errors, which are also considered DRP. Other limitations to the generalisation of the results are the conduct of the study in a single hospital, although in many respects it shares a number of characteristics that are common to hospitals around the world. These include being a tertiary care medium sized general hospital within the public health system, of great importance to the region where it is located, with shortage of resources at the infrastructure, human and financial level, which correspond to the reality of the vast majority of public hospitals in the world.

Future research in this topic should seek to assess the frequency of manifested DRP, their outcomes, their impact on hospital costs, as well as the identification of risk factors for potential DRP and the development of risk stratification instruments for potential DRP and/or for required pharmaceutical interventions.

According to the findings of this study, a significant part of DRP can be prevented. Therapeutic ineffectiveness related to inadequacy in the use process is likely to be minimised through constant training of health teams, especially in relation to the rational use of antimicrobials, resulting in lower cost and less occurrence of bacterial resistances. Point-of-care access to updated and quality literature on drugs, in addition to regular updating of computerised warning and prescription assistance systems, would probably decrease DRP related to treatment effectiveness, the most often observed DRP in patient wards. It is also likely that the inclusion of clinical pharmacists as members of the healthcare would contribute largely to a significant decrease in the incidence of potential DRP.

In conclusion, DRP detected by 100% MO review by hospital pharmacists occur in a significant proportion of hospital episodes, the most frequent being related to treatment effectiveness and treatment costs, with the most common causes being inadequacy in the process of use and duration of treatment. The medications mostly involved were cephalosporins, penicillin, antidiabetics,

analgesics, antipyretics, opioids and antiemetics. The acceptance rate of pharmaceutical interventions through written communication to the medical staff was relatively low.

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#### REFERENCES

- 1 PCNE Pharmaceutical Care Network Europe. The definition of drug-related problems. Available: [https://www.pcne.org/upload/files/11\\_PCNE\\_classification\\_V6-2.pdf](https://www.pcne.org/upload/files/11_PCNE_classification_V6-2.pdf). (2009) [Accessed 7 Feb 2020].
- 2 Meyer-Massetti C, Meier CR, Guglielmo BJ. The scope of drug-related problems in the home care setting. *Int J Clin Pharm* 2018;40:325–34.
- 3 Silva C, Ramalho C, Luz I, et al. Drug-Related problems in institutionalized, polymedicated elderly patients: opportunities for pharmacist intervention. *Int J Clin Pharm* 2015;37:327–34.
- 4 Szilvay A, Somogyi O, Meskó A, et al. Qualitative and quantitative research of medication review and drug-related problems in Hungarian community pharmacies: a pilot study. *BMC Health Serv Res* 2019;19:282.
- 5 Tasaka Y, Tanaka A, Yasunaga D, et al. Potential drug-related problems detected by routine pharmaceutical interventions: safety and economic contributions made by hospital pharmacists in Japan. *J Pharm Health Care Sci* 2018;4:33.
- 6 Birarra MK, Heye TB, Shibeshi W. Assessment of drug-related problems in pediatric ward of Zewditu Memorial referral Hospital, Addis Ababa, Ethiopia. *Int J Clin Pharm* 2017;39:1039–46.
- 7 Qu C, Meng L, Wang N, et al. Identify and categorize drug-related problems in hospitalized surgical patients in China. *Int J Clin Pharm* 2019;41:13–17.
- 8 Urbina O, Ferrández O, Luque S, et al. Patient risk factors for developing a drug-related problem in a cardiology ward. *Ther Clin Risk Manag* 2015;11:9–15.

- 9 Rodrigues JPV, Marques FA, Gonçalves AMRF, *et al.* Analysis of clinical pharmacist interventions in the neurology unit of a Brazilian tertiary teaching hospital. *PLoS One* 2019;14:e0210779.
- 10 Al Hamid A, Ghaleb M, Aljadhey H, *et al.* A systematic review of hospitalization resulting from medicine-related problems in adult patients. *Br J Clin Pharmacol* 2014;78:202–17.
- 11 Alghamdy MS, Randhawa MA, Al-Wahhas MH, *et al.* Admissions for drug-related problems at the emergency department of a university hospital in the Kingdom of Saudi Arabia. *J Family Community Med* 2015;22:44–8.
- 12 Jourdan J-P, Muzard A, Goyer I, *et al.* Impact of pharmacist interventions on clinical outcome and cost avoidance in a university teaching hospital. *Int J Clin Pharm* 2018;40:1474–81.
- 13 Olson CH, Dierich M, Adam T, *et al.* Optimization of decision support tool using medication regimens to assess rehospitalization risks. *Appl Clin Inform* 2014;5:773–88.
- 14 Ferrández O, Casañ B, Grau S, *et al.* [Analysis of drug-related problems in a tertiary university hospital in Barcelona (Spain)]. *Gac Sanit* 2019;33:361–8.
- 15 Kaufmann CP, Stämpfli D, Hersberger KE, *et al.* Determination of risk factors for drug-related problems: a multidisciplinary triangulation process. *BMJ Open* 2015;5:e006376.
- 16 Benson H, Lucas C, Kmet W, *et al.* Pharmacists in general practice: a focus on drug-related problems. *Int J Clin Pharm* 2018;40:566–72.
- 17 Chao S, Toibaro J, Valicenti P, *et al.* [Adverse drug reactions and prescription errors: morbi-mortality]. *Medicina* 2013;73:111–8.
- 18 Lampert ML, Kraehenbuehl S, Hug BL. Drug-Related problems: evaluation of a classification system in the daily practice of a Swiss university hospital. *Pharm World Sci* 2008;30:768–76.
- 19 Taegtmeyer AB, Curkovic I, Corti N, *et al.* Drug-related problems and factors influencing acceptance of clinical pharmacologists alerts in a large cohort of neurology inpatients. *Swiss Med Wkly* 2012;142:w13615.
- 20 Hammar T, Lidström B, Petersson G, *et al.* Potential drug-related problems detected by electronic expert support system: physicians' views on clinical relevance. *Int J Clin Pharm* 2015;37:941–8.
- 21 Tora H, Bo H, Bodil L, *et al.* Potential drug related problems detected by electronic expert support system in patients with multi-dose drug dispensing. *Int J Clin Pharm* 2014;36:943–52.
- 22 Leopoldino RD, Santos MT, Costa TX, *et al.* Drug related problems in the neonatal intensive care unit: incidence, characterization and clinical relevance. *BMC Pediatr* 2019;19:134.
- 23 Abunahlah N, Elawaisi A, Velibeyoglu FM, *et al.* Drug related problems identified by clinical pharmacist at the internal medicine ward in turkey. *Int J Clin Pharm* 2018;40:360–7.
- 24 Ma SN, Zaman Huri H, Yahya F. Drug-Related problems in patients with rheumatoid arthritis. *Ther Clin Risk Manag* 2019;15:505–24.
- 25 Bedouch P, Allenet B, Grass A, *et al.* Drug-Related problems in medical wards with a computerized physician order entry system. *J Clin Pharm Ther* 2009;34:187–95.
- 26 Blix HS, Viktil KK, Moger TA, *et al.* Characteristics of drug-related problems discussed by hospital pharmacists in multidisciplinary teams. *Pharm World Sci* 2006;28:152–8.
- 27 Roten I, Marty S, Beney J. Electronic screening of medical records to detect inpatients at risk of drug-related problems. *Pharm World Sci* 2010;32:103–7.
- 28 Semcharoen K, Supornpun S, Nathisuwan S, *et al.* Characteristic of drug-related problems and pharmacists' interventions in a stroke unit in Thailand. *Int J Clin Pharm* 2019;41:880–7.
- 29 Guignard B, Bonnabry P, Perrier A, *et al.* Drug-Related problems identification in general internal medicine: the impact and role of the clinical pharmacist and pharmacologist. *Eur J Intern Med* 2015;26:399–406.
- 30 Wong CY, Chaudhry SI, Desai MM, *et al.* Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med* 2011;124:136–43.
- 31 Urbina O, Ferrández O, Grau S, *et al.* Design of a score to identify hospitalized patients at risk of drug-related problems. *Pharmacoepidemiol Drug Saf* 2014;23:923–32.
- 32 Blix HS, Viktil KK, Reikvam A, *et al.* The majority of hospitalised patients have drug-related problems: results from a prospective study in general hospitals. *Eur J Clin Pharmacol* 2004;60:651–8.
- 33 Frisse S, Röhrig G, Franklin J, *et al.* Prescription errors in geriatric patients can be avoided by means of a computerized physician order entry (CPOE). *Z Gerontol Geriatr* 2016;49:227–31.
- 34 Slight SP, Eguale T, Amato MG, *et al.* The vulnerabilities of computerized physician order entry systems: a qualitative study. *J Am Med Inform Assoc* 2016;23:311–6.
- 35 Hellot-Guersing M, Jarre C, Molina C, *et al.* [Medication errors related to computerized physician order entry at the hospital: Record and analysis over a period of 4 years]. *Ann Pharm Fr* 2016;74:61–70.
- 36 Westerlund T, Gelin U, Pettersson E, *et al.* A retrospective analysis of drug-related problems documented in a national database. *Int J Clin Pharm* 2013;35:202–9.
- 37 Rhalimi M, Raus A, Housieaux E. Drug-Related problems identified during geriatric medication review in the community pharmacy. *Int J Clin Pharm* 2018;40:109–18.
- 38 De Bock L, Tommelein E, Baekelandt H, *et al.* The introduction of a full medication review process in a local Hospital: successes and barriers of a pilot project in the geriatric ward. *Pharmacy* 2018;6:21.
- 39 Maes KA, Tremp RM, *et al.* GSASA Working group on clinical pharmacy. Demonstrating the clinical pharmacist's activity: validation of an intervention oriented classification system. *Int J Clin Pharm* 2015;37:1162–71.
- 40 Dryden L, Dewhurst NF. Integration of a clinical pharmacist into a Canadian, urban emergency department: a prospective observational study. *Int J Pharm Pract* 2019;27:175–9.
- 41 Foroughinia F, Tazarehie SR, Petramfar P. Detecting and managing drug-related problems in the neurology ward of a tertiary care teaching hospital in Iran: a clinical pharmacist's intervention. *J Res Pharm Pract* 2016;5:285–9.
- 42 Choi KS, Lee E, Rhie SJ. Impact of pharmacists' interventions on physicians' decision of a knowledge-based renal dosage adjustment system. *Int J Clin Pharm* 2019;41:424–33.
- 43 Lenssen R, Heidenreich A, Schulz JB, *et al.* Analysis of drug-related problems in three departments of a German university hospital. *Int J Clin Pharm* 2016;38:119–26.
- 44 Verdoorn S, Kwint HF, Hoogland P, *et al.* Drug-Related problems identified during medication review before and after the introduction of a clinical decision support system. *J Clin Pharm Ther* 2018;43:224–31.
- 45 Kim MG, Jeong CR, Kim HJ, *et al.* Network analysis of drug-related problems in hospitalized patients with hematologic malignancies. *Support Care Cancer* 2018;26:2737–42.
- 46 Viprey M, Jeannin R, Piriou V, *et al.* Prevalence of drug-related problems associated with direct oral anticoagulants in hospitalized patients: a multicenter, cross-sectional study. *J Clin Pharm Ther* 2017;42:58–63.
- 47 Basger BJ, Moles RJ, Chen TF. Application of drug-related problem (DRP) classification systems: a review of the literature. *Eur J Clin Pharmacol* 2014;70:799–815.