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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Negative clinical outcomes of medication resulting in emergency department visits

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Abstract
Purpose The results of analyses of patients' health problems related to medication use have been highly variable due to various factors, such as different study methodology, diverse variables determined, fields of study. The aim of our study was to determine the prevalence and preventability of negative clinical outcomes of medication (NCOMs).
Methods This was a cross-sectional study performed in the emergency departments (EDs) of nine Spanish hospitals during a 3-month period. A two-stage probabilistic sampling method was used , and a systematic appraisal tool was used to identify the NCOMs based on information gathered through patient interview and review of the medical records. Case evaluations were conducted in two phases by pharmacists and physicians. The prevalence and preventability of NCOM were calculated. A homogeneity test was performed to assess potential differences in the prevalence for each hospital.
Results A total of 4,611 patients were included in the study. The overall prevalence of NCOMs was 35.7 % [95 % confidence interval (CI) 33.3–38.1]. These NCOMs could be divided into three categories: ineffectiveness (18.2 %; 95 % CI 16.2–20.1), necessity (14.9 %; 95 % CI 13.4–16.6), and lack of safety (2.4 %; 95 % CI 1.9–2.8). About 81 % (95 % CI 80.1–82.3) of the NCOMs could have been prevented.
Conclusions NCOMs provoked approximately one-third of visits to the EDs, and a high percentage of these were preventable. Implementation of strategies for patient safety and pharmaceutical care could help to prevent these problems and optimize the use of medications.

Keywords Emergency department · Treatment outcomes · Medication · Prevalence · Preventability

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Introduction

Medication-related health problems in patients are a relevant issue in public health systems worldwide. Studies published over the last 20 years reveal that between 0.2 and 38 % of all health problems are related to the use of medication [1–11] and that a high percentage of these problems are preventable [1, 9, 12–24]. The high variability in the published results makes it difficult to compare data from different studies and to develop solutions to the problem.

Multiple factors contribute to generate this variability between the results of such studies. One of these is the heterogeneity of the terminology used in the studies for measuring health problems associated to the use of medication. Most of these terms are typically related to medication safety [25] (e.g., adverse drug reactions, adverse drug events, or medication errors). However, health problems arising from therapeutic ineffectiveness and/or from the lack of use can also affect medication-related morbidity and should be considered to determine the actual magnitude of negative health outcomes related to the drug therapy in the healthcare process [1, 26, 27]. The negative clinical outcomes of medication are hereby considered as those health problems related to the use (or lack of use) of medication independently of the cause that generated them (i.e., medication errors, self-medication, non-compliance, drug–drug interaction, etc.) [26, 27].

An additional factor which contributes to generate high variability between the results of different analyses of health

problems associated with medication use is the different methods of analysis applied in the studies [1, 6, 9, 12, 13, 28]. For example, the sources of information can influence the results, and the magnitude of health problems attributed to medications has been shown to be lower when medical records are used as the exclusive source of information compared to the incorporation of information from patient interviews [9, 13, 28, 29]. Studies utilizing both sources of information report higher association rates and are more consistent [1, 12, 14]. Similarly, it has been shown that the evaluation reliability influences the variability of the results [30].

Yet another factor that contributes to the variability of results is the setting of the study due to the differences in the characteristics of the populations being examined. Hospital emergency departments (EDs) are settings of interest for measuring the magnitude of health problems related to medications due to the frequent attendance of individuals with a variety of health problems. Spanish EDs are especially good settings for these studies because of their easy accessibility—patients can access EDs with no restriction and without having to first visit a family doctor or general practitioner.

Baena et al. [1] used a validated, protocolized detection method [31, 32] to investigate the prevalence of the negative clinical outcomes of medication (NCOMs) in a hospital. The results of this study showed a 33.1 % rate of NCOMs with a preventability of 73 %. However, the extrapolation of these results to other hospitals remains to be demonstrated.

We have conducted a study in nine hospitals to evaluate the prevalence and preventability of the NCOMs and have analyzed several risk factors that could be associated to these negative clinical outcomes.

Methods

A cross-sectional and multicenter study was performed in the EDs of nine Spanish hospitals from April 1 to June 30, 2003.

Study population and inclusion process

The study population was drawn from patients visiting the EDs of the nine Spanish hospitals listed in Table 1.

A two-stage probabilistic sampling method was performed at each hospital. In the first stage, a simple random sampling was used to select the sample collection days. In the second stage, a systematic sampling was performed to select patients. Sample size was estimated for a prevalence of NCOM of 33 % (based on data obtained by Baena et al. [1]), for the average number of patients visiting EDs in each hospital in 2001, with a confidence interval (CI) of 95 % and a maximum admissible error of 0.01 per hospital. The estimated sample size (n) was 3,760 (Table 1).

We considered three exclusion criteria: (1) acute voluntary drug poisoning; (2) the patient did not wait for the physician's diagnosis and was therefore not diagnosed; (3) the patient was referred to another hospital without being diagnosed. Patients who visited the ED multiple times for the same health problem during the period of the study were included only once in the analysis.

Measurements and procedure

The principal variable measured was the presence of NCOMs that resulted in a visit to the ED [1]. NCOMs were defined as "*patient health outcomes that are not consistent with the objectives of pharmacotherapy and are associated with the use or errors in the use of medicines*" [32]. NCOM refers to a negative clinical outcome (i.e., a negative change in the state of the patient health) related to the use (or lack of use) of medication independently of the cause that generated the change (i.e., medication errors, self-medication, non-compliance, etc.).

Sources of information Each patient was interviewed using a validated questionnaire [33] to collect information on the medications he/she was taking and his/her health problems. Information on the specific health problem that caused the ED visit was obtained from the medical record (i.e., the medical diagnosis).

A total of 98 pharmacists conducted interviews with the study patients. To minimize interviewer bias, all pharmacists received the same training for patient interviews and evaluations. Two pharmacists (MIB and PCF) and one physician (RM) formed the training team. Each case was evaluated using the Dáder method [31] for NCOM identification.

Case evaluations were conducted in two phases (Fig. 1). First, information on the patient was subjected to an initial evaluation by pharmacists to establish a suspected case of a NCOM was conducted by pharmacists. Secondly, a subsequent assessment to confirm this diagnosis was conducted with the assistance of a physician.

Phase 1. Preliminary evaluations by pairs of pharmacists Participant pharmacists were grouped in pairs at each hospital. Every pharmacist pair (PP1) received a number of cases for evaluation. To determine the number of patients each PP1 received, the total number of patients interviewed at each hospital was divided by the number of PP1s at the hospital. Pharmacists used basic and specialized bibliography (Appendix 1) in addition to medical record and patient interviews to study the effects of medications. Pharmacists used all of the information available to determine whether the health problem during the ED consultation was related to the medications the patient was taking (i.e., the suspected case of NCOM).

Table 1 Sample size for each hospital

Hospital	Number of visits to EDs in 2001	Number of sample collection days	Sampling interval[a]	Estimated sample size (n)	Number of patients included in this study[b]
Virgen del Rocio University Hospital (UH) (Sevilla)	188,392	4	5	414	425
UH Clínic (Barcelona)	141,608	4	3	519	429
Reina Sofía UH (Córdoba)	182,249	4	4	522	455
Carlos Haya UH (Málaga)	174,369	4	5	383	475
UH Central de Asturias (Oviedo)	88,712	4	3	326	541
Hospital Santa Creu I Sant Pau (Barcelona)	82,972	5	3	381	588
Cruces UH (Bilbao)	179,407	2	3	329	559
Gregorio Marañón UH (Madrid)	168,964	2	3	309	544
Infanta Margarita Hospital, Cabra (Córdoba)	54,000	9	2	577	595
Total (9 hospitals)	1,260,673			3760	4611

ED, Emergency department

[a] Sampling Interval: interval applied in the selection of the patients for systematic sampling

[b] Value for "Number of patients included in this study" differs from that in "estimated sample" because the number of visits to EDs used in the sample size estimation differed from the number of visits to EDs at the time of this study

Phase 2. Final evaluation Two pairs of assessors (PA1 and PA2), a physician and a pharmacist, were formed in each hospital. One of the pharmacists from the preliminary evaluation teams (PP) joined each of the two groups for the final evaluation to form a team of three reviewers. All cases that were evaluated in phase 1 were re-evaluated by each of the final evaluation teams (PA1+P and PA2+P). This second evaluation confirmed or rejected each suspected case of NCOM that was identified in the first phase. To confirm or reject a potential NCOM the PA1 and PA2 assessments had to match; otherwise, an independent third party comprising a physician and two pharmacists (the team that coordinated the study) evaluated the case and made a final decision.

Criteria were established in this study to classify a case as a NCOM of necessity, effectiveness, or safety (Table 2), as agreed upon in the Third Consensus of Granada [32]. Take, for example, the case of a patient visiting the ED who was suffering from a new health problem and who was not on medication. This case would be classified as NCOM of necessity only when the patient meeting these two criteria would have had the health problem for at least 7 days. This time frame was considered to be long enough in the Spanish National Health System for a patient to visit a family doctor or a general practitioner and therefore to obtain the medication needed.

The preventability of each NCOM was measured according to the criteria of Baena et al. [34]

The characteristics of the study population were described using the variables in Table 3. The severity of each diagnosis (mild, moderate, severe, or death) was measured according to the classification criteria of the Spanish pharmacovigilance system for adverse drug reactions [35].

The research ethics committees of the respective participating hospitals approved this study.

Statistical analysis

The prevalence and preventability of NCOMs were calculated. The chi-square (χ^2) test and Student's t test were used to compare the characteristics (for qualitative and quantitative variables, respectively) between patients who were rejected from the statistical analysis (because insufficient information was obtained with the interviews and medical records) and patients who were included in the study. The Kappa index [36] measured the level of agreement between the assessments produced by the PA1 and PA2 assessor teams for the absence/presence of a NCOM. A chi-square homogeneity test was used to assess potential differences in the prevalence of NCOMs obtained by each hospital. A multivariate analysis was performed to characterize possible risk factors for the appearance of a NCOM. The 95 % confidence interval was calculated, and a $P<0.05$ value was considered for statistical significance. The SPSS statistical package for Windows ver. 15.0 (SPSS, Chicago, Il) was used to store and analyze the data.

Results

A total of 5,380 patients were established as the sample framework once we subjected the numbers of EDs visits to each hospital during the period of the study to the two-stage probabilistic sampling method. Of these, 124 patients were excluded for one of the following two reasons: (1) the patient did not wait for the physician to diagnose the condition and

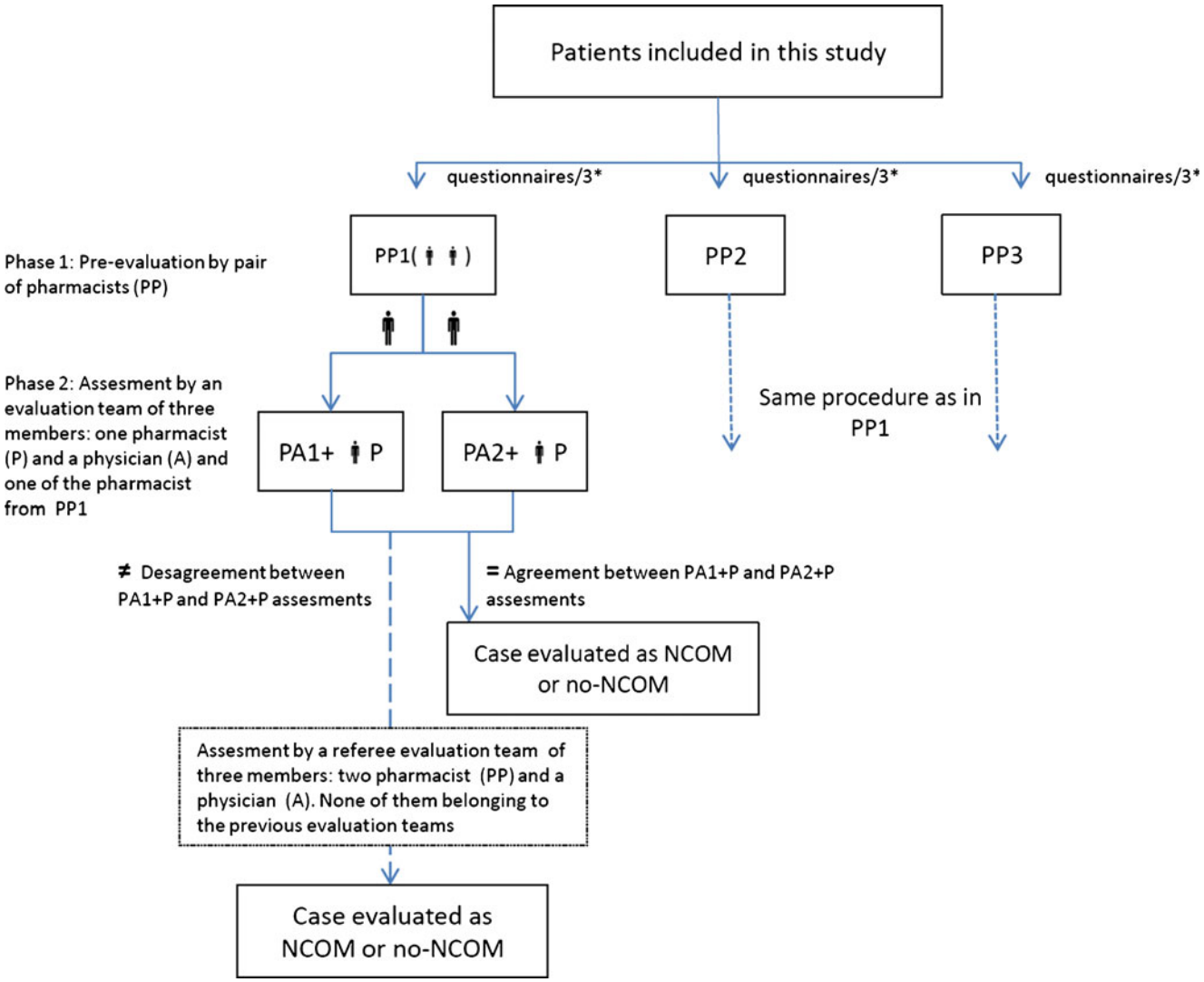

Fig. 1 The case evaluation process of negative clinical outcomes of medication (NCOM) consisted of two phases and was conducted at each hospital. Phase 1: Preliminary evaluations by pairs of pharmacists (*P*). Participating pharmacists were grouped in pairs (*PP1*) at each hospital, with each pair receiving a number of cases for evaluation. To determine the number of patients each PP1 received, the total number of patients interviewed at each hospital was divided by the number of PP at the hospital. In this phase the pairs of pharmacists evaluated the information to establish a suspected case of a NCOM. Phase 2: Final evaluation. Two pairs of assessor groups (*PA*), each consisting of a physician (*A*) and a pharmacist (*P*) were formed in each hospital. One of the pharmacists from the preliminary evaluation teams (PP1, -2, -3) joined each of the two assessor groups (PA) for the final evaluation to form a team of three reviewers. All cases that were evaluated in phase 1 were re-evaluated by each of the final evaluation teams (*PA1+P* and *PA2+P*). This second evaluation confirmed or rejected each suspected case of NCOM that was identified in the first phase. To confirm or reject a potential NCOM the PA1 and PA2 assessments had to match; otherwise, an independent third party consisting of a physician and two pharmacists (the team that coordinated the study) evaluated the case and made a final decision

therefore the patient was not diagnosed ($n=103$); (2) the patient exhibited voluntary acute drug poisoning ($n=21$). Another 167 patients (3.1 % of the sample framework) refused to participate in the study. This group of non-collaborative patients was not analyzed further due to its low percentage. In addition, 478 participants were rejected from the statistical analysis because insufficient information was obtained in the interview or present in the medical record. Therefore, 4,611 patients formed the sample population for the study. The group of rejected participants was 8.89 % of the sample and was analyzed further to determine if rejection caused a bias in the study. The variables chosen to define the characteristics of the patients in the sample are listed in Table 3.

The patients who were rejected from the statistical analysis due to insufficient information ($n=478$) differed from those patients who were included in the study in that patients in the rejected group were older ($P<0.001$) and had more severe diagnoses ($P<0.001$), their visits resulted in higher rates of hospital admissions ($P<0.001$), and a higher percentage of interviews were answered by a caregiver ($P<0.001$).

Table 2 Classification of negative clinical outcomes of medication[a]

Category of NCOM	Description
Necessity	**Untreated health problem.** The patient suffers from a health problem as a consequence of not receiving the medicine that he./she needs. (e.g., the patient suffers an hypertensive crisis as a consequence of abandonment of medication)
	Effect of unnecessary medicine. The patient suffers from a health problem as a consequence of receiving the medicine that he/she does not need. (e.g., the patient suffers an hypoglycemia caused by medication-adherence to a hypoglycemic drug that the physician suspended)
Effectiveness	**Non-quantitative ineffectiveness.** The patient suffers from a health problem associated with of a non-quantitative ineffectiveness of the medication. (e.g., the patient suffers an urinary tract infection that does not respond to the antibiotic treatment because the microorganism is resistant to that antibiotic)
	Quantitative ineffectiveness. The patient suffers from a health problem associated with of a quantitative ineffectiveness of the medication. (e.g., the patient suffers hyperglycemia due to the administration of lower doses of insulin that doses prescribed by the physician)
Safety	**Non-quantitative safety problem.** The patient suffers from a health problem associated with a non-quantitative safety problem of the medication. (e.g., the patient presents red-face after having therapeutic doses of metamizole)
	Quantitative safety problem. The patient suffers from a health problem associated with a quantitative safety problem of the medication. (e.g., a patients suffers rhabdomyolysis induced by simvastatin treatment)

[a] Classification of negative clinical outcomes of medication (NCOMs) according to the 2007 Third Consensus of Granada [32]

The prevalence of NCOMs in the nine hospitals ranged from 17.9 (95 % CI 14.7–21.1) to 41.2 % (95 % CI 36.5–45.9); the overall prevalence was 30.7 % (95 % CI 29.5–32.1) (Table 4).

The chi-square homogeneity test used to assess potential differences in the prevalence of NCOM obtained by each hospital showed a chi-square value of 134.9 ($P<0.001$). The prevalence of NCOMs was homogenous in hospitals with high involvement (>85 %) and a Kappa of >80 % (almost perfect) (Table 4) as these were the only two features that varied significantly among the hospitals. The weighted overall prevalence of NCOMs was 35.7 % (95 % CI 33.3–38.1). The weighted overall prevalence of NCOMs of *necessity*, *ineffectiveness*, and *lack of safety* was 14.9 (95 % CI 13.4–16.6), 18.2 (95 % CI 16.2–20.1) and 2.4 % (95 % CI 1.9–2.8), respectively (Table 4).

Table 3 Characteristics of patient cohort ($n=4,611$)

Variable	Values	Minimum–maximum
Male sex (%)	50.6	
Mean (±SD) age (years)	47.04±22.85	1–100
Number of medications (±SD)	2.29±2.58	0–15
Number of prescribers (±SD)	0.97±0.91	0–7
Self-medication (%)	4.6	
Non-compliance (%)	19	
Comorbidity (% healthy)[a]	73.45	
Tobacco use (%)		
Non- smoker	68.1	
<10 cigarettes/day	10	
Between 11 and 20 cigarettes/day	12.4	
>20 cigarettes/day	7.9	

SD, Standard deviation

[a] Comorbidity is expressed as the percentage of patient suffering none of following diseases: hypertension blood pressure (HBP), diabetes, chronic obstructive pulmonary disease, liver diseases, renal disease, and HBP-diabetes

Of the 1,416 detected NCOMs, 10.5 % (95 % CI 8.9–12.1) led to the patient being hospitalized, 68.2 % (95 % CI 65.7–70.6) were minor health problems, 23.2 % (95 % CI 21–25.4) were moderate events, 8.5 % (95 % CI 7–9.9) were severe events, and 0.1 % (95 % CI 0.0–0.2) caused death.

In addition, of these 1,416 detected NCOMs, 81.2 % (95 % CI 80.1–82.3) could have been prevented, with the preventability of NCOMs detected at each hospital being >70 %. NCOMs related to treatment *necessity* could have been prevented in 98.4 % (95 % CI 97.3–99.4) of cases, while those related to *ineffectiveness* were preventable in 71.1 % of cases (95 % CI 67.1–75.0) and those related to a *lack of safety* were preventable in 50.5 % (95 % CI 37.0–63.9) of cases. The preventability of any detected NCOM varied depending on the number of medications that the patient was taking. Specifically, 100 % ($\chi^2=59.5$; $P<0.001$) of the NCOMs that developed in patients not taking medications were preventable. In comparison, 77.8 and 77.2 % of NCOMs that appeared in patients taking between one and four medications and those taking more than five drugs, respectively, were preventable. The preventability of NCOMs was greater with less serious diagnoses, with 82.5 ($\chi^2=11.63$; $P<0.001$) 77.6, and 70.6 % of mild, moderate, and severe NCOMs, respectively, being preventable. Two deaths caused by preventable NCOM were recorded.

The multivariate analysis revealed associations between the appearance of a NCOM and sex, self-medication, and a

Table 4 Total prevalence of NCOMs and by category for each hospital

Hospital	Participation (%)	Kappa[a]	Total prevalence % (95 % CI)	Prevalence of necessity % (95 % CI)	Prevalence of ineffectiveness % (95 % CI)	Prevalence of lack of safety % (95 % CI)	Total preventability % (95 % CI)
Virgen del Rocío University Hospital (UH)	83.0	56.9	30.8 (26.4–35.2)	11.8 (8.7–14.9)	15.2 (11.8–8.6)	2.8 (1.2–4.4)	91.9 (81.3–94.5)
UH Clínic	71.9	94.7	41.2 (36.5–45.9)	14.2 (10.9–7.5)	22.8 (18.8–26.8)	4.2 (2.3–6.1)	79.9 (76.1–83.7)
Reina Sofía UH	95.8	98.8	38.2 (33.7–42.7)	16.9 (13.5–20.3)	19.8 (16.1–26.5)	1.5 (0.4–2.6)	90.8 (88.1–93.5)
Carlos Haya UH	82.7	96.2	33.3 (29.1–37.5)	16.8 (13.4–20.2)	14.7 (11.5–17.9)	1.7 (0.5–2.9)	82.9 (79.5–86.3)
UH Central de Asturias	84.7	99.5	21.2 (17.8–24.6)	9.6 (7.1–12.1)	9.6 (7.1–12.1)	2 (0.8–3.2)	85.2 (82.2–88.2)
Hospital Santa Creu I Sant Pau	90.2	75.2	37.6 (33.7–41.5)	15.5 (12.6–18.4)	20.1(16.9–23.3)	2 (0.9–3.1)	70.2 (66.5–73.9)
Cruces UH	95.9	72.6	17,9 (14.7–21,1)	8,2 (5.9–10.5)	8.1 (5.8–10.4)	1.6 (0.6–2.6)	79.6 (76.3–82,9)
Gregorio Marañón UH	82.4	77.6	23.5 (19.9–27.1)	9.7 (7.2–12.2)	11.9 (9.2–14.6)	1.8 (0.7–2.9)	80.8 (77.5–84.1)
Hospital Infanta Margarita	86.4	95.8	35.7 (31.9–39.5)	12.1 (9.5–14.7)	19.7 (16.5–22.9)	3.9 (2.3–5.5)	76.1 (72.7–79.5)
Total prevalence (9 hospitals)			30.7 (29.5–32.1)				81.2 (80.1–82.3)
Total weighted prevalence (9 hospitals)			35.7 (33.3–38.1)				
Weighted prevalence of necessity				14.9 (13.4–16.6)			
Weighted prevalence of ineffectiveness					18.2 (16.2–20.1)		
Weighted prevalence of lack of safety						2.4 (1.9–2.8)	

[a] Value of Kappa: very good/almost perfect, 81–100 %; good/substantial, 61–80 %; moderate, 41–60 %); fair, 21–40 %; poor, ≤20 %

high-frequency smoking habit. The risk of appearance of NCOMs was higher in women than in men [adjusted odds ratio (OR) 0.8; 95 % CI 0.68–0.99]. The risk of appearance of NCOMs increased to 70 % (adjusted OR 1.70; 95 % CI 1.49–1.95) for each different physician prescribing a medication per patient. In addition, self-medicating patients had a higher risk of suffering a NCOM than those whose medication was prescribed by a family doctor or by an emergency or a specialist doctor, with the latter associated with the lowest risk (adjusted OR 0.51; 95 % CI 0.36–0.72). A high-frequency smoking habit was associated with the NCOM variable. Patients smoking more than 20 cigarettes per day showed a higher risk of suffering a NCOM (adjusted OR 1.66; 95 % CI 1.2–2.3) (Table 5).

The other variables of the multivariate analysis, namely, the number of drugs, comorbidity, knowledge of the medication, and compliance, showed no association ($P>0.05$) with the main variable of the study (NCOM).

Discussion

The results of this study provide a valuable contribution to the knowledge of patients' health problems because the data demonstrate that more than one-third of visits to EDs at Spanish hospitals are related to the use (or lack of use) of medications, a finding that has significant implications for the country's healthcare system.

The NCOMs resulting in the highest number of ED visits were due to ineffective treatments, followed by NCOMs that resulted from the lack of required treatments. Both problems are largely due to modifiable patient behavior, such as the partial or complete compliance of treatment recommendations, and may be prevented by professional healthcare services, such as improved pharmaceutical care or health education programs [37–40].

The reliability of our results lies in the following methodologies: (1) the selection of the sample; (2) the combination of different information sources; (3) the uniform training of all researchers, interviewers, and reviewers; (4) the use of a common protocol for detecting NCOMs and the incorporation of medical assessment [31]; (5) the use of a dual assessment system for all cases and the resolution of discrepancies by a referee evaluation team. Because this study included a large number of patients from Spanish National Health System hospitals throughout Spain, the sample likely provides a reasonable approximation of the general population that visits Spanish EDs. No significant organizational differences in the various hospitals or patients from those hospitals were observed.

The data presented here are consistent with the results of a the study by Baena et al. [1] who reported a similar prevalence and distribution of NCOMs in the ED at a Spanish hospital using a similar methodology. The distribution of the different categories of NCOM (i.e., necessity, effectiveness, and safety) was similar. Other studies using comparable methods have

Table 5 Multivariate logistic regression

Variables	Categories	Adjusted odds ratio	95 % Confidence interval
Sex	Female	1[a]	
	Male	0.83	0.69–0.99
Number of prescribers		1.70	1.49–1.95
Prescriber	Self-medication	1[a]	
	Emergency Room healthcare provider	0.84	0.55–1.29
	Family doctor	0.65	0.46–0.92
	Specialist doctor	0.51	0.36–0.72
	Pharmacist	1.1	0.57–2.12
Tobacco	Low-frequency smoking habit (<20 cigarettes/day)	1[a]	
	High-frequency smoking habit (≥20 cigarettes/day)	1.66	1.20–2.29

[a] Reference categories: female; self-medication; non-smoker or smoker smoking <20 cigarettes/day

demonstrated similar results in different healthcare scenarios [12, 14]. The problems that we found to be associated with a *lack of safety* are also similar to those identified in previous studies that measured these problems exclusively in EDs [8, 13, 24, 29, 41]. Importantly, the variability in the prevalence of health problems associated with medication use was less in our study than in prospective studies that used a combination of patient interviews and medical record as their source of information [1, 7–9, 12].

The analysis of preventability showed that approximately eight of ten NCOMs resulting in ED visit could be prevented, a result that is consistent with previous studies [1, 9, 12–14, 24]. These results highlight the necessity for measures to be introduced in Health Services that aim to prevent these problems. The integration of pharmacists (i.e., professionals of Health specialized in medication) into multidisciplinary healthcare teams could minimize the occurrence of NCOMs. Indeed, among our patient cohort, some of the pharmaceutical care activities that are typically performed by pharmacists could have prevented the visit to the ED. Therefore, many of these problems could have been solved in a primary care setting had pharmacists been involved in the decision-making process [37]. Importantly, the preventability of NCOMs increases in patients who did not take the medication. All cases involving patients with NCOMs but who did not take medications could have been prevented because these visits were primarily the result of the abandonment of medication (non-compliance) by the patient. This result emphasizes the importance of improving patient adherence to the treatment regimen and patient knowledge regarding their medications.

The cases that were rejected from the our study included patients who were older, exhibited more severe diagnoses and whose interview was answered by someone else. Some of these features have been previously shown to be associated with an increased risk of NCOMs [1, 8, 13]. Therefore, the inclusion of these cases in the dataset would have produced an even greater prevalence of NCOM. However, the multivariate analysis performed in this study showed no association of those factors with NCOMs.

In our study, the case of patients visiting the ED with a new health problem and not having medication would be considered to be a NCOM of necessity only if the patient suffered the health problem for at least 7 days and had not received the necessary medication prior to time of the ED visit. This time frame was considered to be long enough in the Spanish National Health System for a patient to visit a family doctor or a general practitioner and therefore to obtain the medication needed. This criterion avoided the overestimation of NCOM prevalence because the accessibility of Spanish EDs makes them the primary gateway for treatment and, consequently, we could have classified many more cases as NCOM of necessity.

The multivariate analysis showed that self-medicated and smoking women belong to the patient group with the highest risk of NCOMs.

Several studies have shown an association between sex and NCOMs, while several others have found no association between these two variables [41–43], thereby illustrating the variability in the obtained results mentioned in the Introduction. Interestingly, in those studies (with the exception of the Courtman and Stallings study [44]) that showed an association between gender and NCOM, females were found to have the higher risk of NCOMs [41–43].

The association between self-medication and NCOM variables could be explained by the implications of the self-medication—i.e., it is when the patient selects a drug without the assessment of a healthcare professional, leading to a NCOM. Self-medication is a modifiable behavior, and it is therefore important that this problem receive the appropriate attention.

The association of tobacco and NCOM could be explained based on the implied effect of substances in cigarette smoke on the metabolism of drugs, which would directly affect their effectiveness and/or their safety [45, 46]. However, a more complete study that would consider the singularities of smoking patients (ex-smoker's diseases, time being a ex-

smoker, chronic smoker vs. sporadic one, etc.) should be performed to determine the reliable association of tobacco and NCOMs.

The results of this study focused on the Spanish population, but the data may be of general interest because of the relevance to clinical practice. The prevalence of NCOMs that result in ED visits may vary between countries due to differences in healthcare systems, but this problem likely affects the healthcare systems and patients of all countries. Therefore, our study serves as a starting point for other countries to evaluate the magnitude of NCOMs within their own hospitals. An improved knowledge of the magnitude and effects of these problems on the health of the general population may encourage healthcare administrations to undertake action on these issues.

Conclusion

Approximately 35 % of ED visits are produced by NCOMs, and approximately 15 % of these visits are associated with the need for treatment, while 20 % are associated with drug ineffectiveness. Our results indicate that > 80 % of these NCOM are preventable. The magnitude of medication-related health problems and the high degree of preventability demand the establishment and implementation of patient safety strategies aimed at optimizing the use of medications.

The relevant prevalence of NCOMs determined in this study reveals the necessity of evaluation methods of public health systems. The high preventability of NCOMs that we found in our study demonstrates that it is worthwhile to implement evaluation methods that produce comparable results among European countries. This task should be taken by various health and economic European authorities, such as the European Medicines Agency and the Organization for Economic Co-operation and Development. Actions taken in this direction would benefit millions of European patients.

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