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ORIGINAL ARTICLE

Doctors' acceptance of recommendations for patients with the opportunity for pharmacotherapy improvement☆

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KEYWORDS
Pharmacotherapy recommendation;
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Abstract
Objective: To identify and quantify the influence of different variables on the implementation of pharmacotherapy optimisation measures in hospitalised patients.
Method: Descriptive transversal study. Period: 2000-2007. Environment: public university general hospital (25,000 patients admitted/year).

The Programme implemented to improve pharmacotherapy quality and patient safety covers 30% of all patients. Using records from the Atefarm® Farmis application, we analysed pharmacotherapy recommendations (PRs) made by pharmacists to doctors. The selected variables were the following: Risk of the medication for ADE (1-high, 0-low), ADE category, (0-indication, 1-effectiveness, 2-safety), potential severity (scale of 1 to 5), impact of the PR (0-effectiveness, 1-safety, 2-efficiency) and implementation of the PR (yes/no).

We calculated the frequency (%) and 95% CI for the categorical variables and performed a multivariate logistical regression analysis to identify the variables' degree of influence on implementing the PRs.
Results: We identified 7920 ADEs in 4680 patients. A PR was issued in 85% of the cases (6762), and it was implemented in 83% (95% CI 74.2-89.8). Potential severity of the ADE ≥2 (OR 1.57; 95% CI 1.27-1.94), and ADE category for effectiveness and safety (OR 1.19; 95% CI 1.02-1.39) were shown to be determining factors for implementing the PR for the patient.
Conclusions: The probability that a PR will be implemented for a patient is related to the potential severity and the category of the identified ADE. Therefore, recommendations intended to improve effectiveness of pharmacotherapy or patient safety, and those with potential clinical consequences have a greater chance of being applied to a patient.

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PALABRAS CLAVE
Recomendación farmacoterapéutica;
Seguridad del paciente;
Calidad farmacoterapéutica

Aceptación de recomendaciones en el paciente con oportunidades de mejora farmacoterapéutica

Resumen

Objetivo: Identificar y cuantificar la influencia de diferentes variables en la implantación de medidas de optimización farmacoterapéutica en pacientes ingresados.

Método: Estudio descriptivo, transversal. Período: 2000-2007. Ámbito: hospital general universitario público (25.000 pacientes ingresados/año).

El Programa de Mejora de la Calidad de la Farmacoterapia y la Seguridad del Paciente implantado da cobertura al 30%de los pacientes. A partir de los registros del aplicativo Atefarm® Farmis, se analizaron las recomendaciones farmacoterapéuticas (RF) realizadas por los farmacéuticos al médico. Las variables seleccionadas fueron las siguientes: riesgo del medicamento (problema relacionado con el medicamento [PRM]) (0, bajo; 1, alto), categoría del PRM (0, indicación; 1, efectividad; 2, seguridad), gravedad potencial (escala 1-5), impacto de la RF (0, efectividad; 1, seguridad; 2, eficiencia) e implantación de la RF (sí/no).

Se calculó la frecuencia (%) y el intervalo de confianza del 95% (IC 95%) de las variables categóricas y se realizó un análisis de regresión logística multivariante para identificar el grado de influencia de las variables en la implantación de las RF.

Resultados: Se identificaron 7.920 PRM en 4.680 pacientes. En el 85% (6.762) de los PRM se realizó una RF, que se implantó en el 83% (IC 95%: 74,2-89,8). La gravedad potencial del PRM superior o igual a 2 (OR: 1,57; IC 95%: 1,27-1,94) y la categoría del PRM de efectividad y seguridad (OR: 1,19; IC 95%: 1,02-1,39) se manifestaron como determinantes de la implantación de la RF en el paciente.

Conclusiones: La probabilidad de implantación de RF en el paciente está relacionada con la gravedad potencial y la categoría del PRM identificado. Así, las recomendaciones orientadas a mejorar la efectividad de la farmacoterapia o la seguridad del paciente, y con consecuencias clínicas potenciales presentan mayor éxito en su aplicación al paciente.

Introduction

Patient care is a complex process involving many disciplines, designed to resolve health problems and improve quality of life. However, this process is not risk-free, as has been proven by several studies conducted in different health care environments, quantifying the incidence and consequences of health care-related adverse events.[1-3] Most of these events are drug-related and frequently restrict optimal patient health care outcomes, with significant clinical, social and economic consequences.

In this vein, a common objective of various institutions and professional and scientific societies[4-6] has been to implement pharmacotherapy quality improvement and patient safety programmes (PhQI&PSP), so that pharmacists can continue contributing to a safer and more appropriate drug use. Therefore, one of the *Sociedad Española de Farmacia Hospitalaria* (Spanish Society of Hospital Pharmacy)'s objectives for 2020 is to ensure that pharmacists are more involved in optimising personalised pharmacotherapy. This objective represents the pharmacist's involvement as a member of the interdisciplinary health care team, identifying, preventing and resolving adverse drug events (ADE), which represent opportunities to improve pharmacotherapy, and implement pharmacotherapeutic optimisation measures in patients.[7,8]

The added value that pharmacists bring to the drug-use process has been proven as ADE-associated clinical complications, hospital stays and treatment costs have significantly reduced, according to various national and international studies published.[9-11] Acceptance of pharmacists' pharmacotherapeutic recommendations (PR) to other professionals involved in patient care varies greatly, between 60%-95%.[12-14] Acceptance is often the last step towards implementing pharmacotherapeutic optimisation measures in the patient.

Some studies suggest that different variables related to ADE, proposed PR, clinical departments or professionals involved,[15-17] can determine the pharmacotherapeutic optimisation recommendations and their implementation in the patient. As such, examining such variables can help make pharmacists more efficient and improve pharmacotherapy.

In this context, this study aims to identify and quantify the influence that different variables related to the identified ADE and the PR made have on implementing pharmacotherapeutic optimisation measures in hospitalised patients.

Method

Study design. Observational, descriptive and cross-sectional study conducted over an 8-year period, from 2000 to 2007.

Patients and scope. The study population comprised all patients admitted to a general, public, university hospital (25 000 patients admitted/year). ADE have been identified in patients by reviewing their clinical history during the hospital stay, or by means of pharmacotherapeutic monitoring performed using an integral system for personalised medication dispensing in the *Servicio de Farmacia* (Pharmacy Department).

The PhQI&PSP implemented in the hospital since 2000 covers approximately 30%of hospitalised patients and is based on laser© methodology.[18] It completes the following phases: identifying patients with ADE, pharmacist intervention, pharmacotherapeutic monitoring, assessing the individual results in the patient, analysis and circulation of population results. After identifying an ADE in a patient, a pharmaceutical action plan was defined; then, if necessary the pharmacist would make a recommendation (PR) to the rest of the interdisciplinary team, with the aim of implementing a pharmacotherapeutic optimisation measure in the patient. The recommendation was made within 24 hours after ADE identification; either *verbally*, face-to-face or by telephone to the medical professional caring for the patient; or in *writing,* by recording it on the patient's clinical history. A 48h-period was given to assess acceptance and apply the PR to the patient. All pharmaceutical actions were recorded on a personalised pharmacotherapeutic monitoring sheet and later entered in the Atefarm® Farmis computer application (IMF, 2008).

The variables analysed were classified into two categories depending on the type of ADE identified or the PR made, as shown in Table 1.

Criteria from the Institute for Safe Medication Practices[19] and the Spanish Ministry of Health and Consumer Affairs[20,21] were used for classifying the drugs involved in ADE as high- or low-risk. Drugs that needed personalised dosage regimens and pharmacokinetic monitoring in the hospital were also considered high-risk (vancomycin, aminoglycoside).

We classified 4 types of ADE and a scale of potential severity from 1-5, (1 being less severe clinical consequences in the patient), in accordance with the methodology approved in the hospital (Table 2).[18,22,23]

Statistical analysis. Descriptive analysis was conducted for the variables included in this study. The categorical variables have been represented as relative frequencies expressed as percentages and the quantitative variables using indices depending on the distribution: *average and standard deviation* (symmetric distribution), and *median and interquartile range* (asymmetric distribution).

We performed a multivariate logistic regression analysis to identify the variables that influence whether the pharmacotherapeutic optimisation recommendations were to be implemented or not, defining PR implementation as a response variable. Explanatory or dependent variables were as follows: drug (high or low risk), ADE category, potential ADE severity, impact of PR. Explanatory variables with three or more categories were re-classified into two to simplify the analysis: ADE category, (0-indication, 1-effectiveness or safety), potential severity of ADE (0-severity=1; 1-severity≥2) and impact of PR (0-efficiency, 1-effectiness or safety).

For developing the logistic regression model,[24] the explanatory variables were screened, using the univariate regression analysis, to select the potential prognostic factors that would be included in the multivariate model ($P<.25$). Using the resulting variables, the various multivariate models were examined using inclusion and exclusion sequential sampling methods, considering the P value to be significant at .05 and inclusion and exclusion of variables at .10. Secondly, the interaction terms were introduced to confirm whether the adjustment indices improved (significant changes to the verisimilitude logarithm). We performed the statistical analysis with SPSS software, version 12 (SPSS Inc., Chicago, IL).

Results

The PhQI&PSP has provided 55 123 patients with pharmacotherapeutic monitoring during the period analysed (2000-2007). The study included 4680 patients, in which 7920 ADE were identified. A PR was made for 85% (6762) of them, which was implemented in the patient for 83.0%of cases (95% confidence interval [95%CI]: 74.2-89.8). Table 3 shows the relative frequency for the predictive categorical variables evaluated with its 95% CI.

Table 4 presents the univariate regression results. According to the results of this analysis, we selected the variables ADE effectiveness/ safety against indication, potential ADE severity ≥2 against potential severity 1, and PR impact on safety/ efficacy against efficiency, to construct

Table 1 Variables analysed

Category	Variable/description
ADE	Drug risk: high or low
	ADE Category: indication, effectiveness, safety or adherence
	Potential severity of ADE: scale of 1-5
Pharmacotherapeutic recommendation	Impact: effectiveness, safety or efficiency
	Implementation (yes/ no)

ADE indicates adverse drug event.

Table 2 Scale of potential severity of the adverse drug events and examples of pharmacotherapeutic recommendations

Grade	Description
1	*ADE/ME that would not damage or cause reversible damage (with no change in vital signs) requiring increased monitoring* Examples: change from levofloxacin 500 mg/24 h IV to levofloxacin 500 mg/24 h orally without removing the IV access; change from linezolid 600 mg/12 h IV to vancomycin 1 g/12 h IV in patients with methicillin-resistant *Staphylococcus aureus* infection, sensitive to both drugs
2	*ADE/ME that would cause reversible damage (with no change in vital signs) requiring treatment modification* Examples: change from imipenem 1 g/8 h to imipenem 500 mg/6 h adjusted to the patient's renal function; change from gentamicin 240 mg/24 h IV to vancomycin 180 mg/24 h IV adjusted to the patient's renal function
3	*ADE/ME which would cause reversible damage requiring additional treatment, hospital admission or longer hospital stay* Examples: change from ceftriaxone 1 g/12 h IV to levofloxacin 500 mg/24 h IV in patients with reported beta-lactam antibiotic allergy, change from vancomycin 1 g/12 h IV to vancomycin 1 g/24 h IV adjusted to the patient's renal function
4	*ADE/ME which would cause irreversible or disabling damage* Examples: change from morphine 300 mg IV perfusion/24 h to morphine 30 mg IV perfusion/24 h due to prescription error; change from tacrolimus 3 mg/12 h IV to tacrolimus 1.5 mg IV perfusion/24 h
5	*ADE/ME which caused the death of the patient* No case has been reported

ADE indicates adverse drug event; IV, intravenous; ME, medication error.

a predictive model, as they presented a $P<.25$ and a correct sign on the coefficient.

Table 5 shows the results from the final logistic regression model. The predictive multivariate logistic regression model included the variables ADE safety/effectiveness and potential severity ≥2.

Table 3 Descriptive characteristics of categorical variables

Variable	Relative frequency, %	95% CI
Drug risk		
High	58.0	57.2-59.7
Low	42.0	40.0-42.8
ADE Category		
Indication	27.0	26.0-28.0
Effectiveness	17.0	16.5-18.3
Safety	55.0	54.2-56.6
Potential severity of ADE		
Grade 1	9.6	8.9-10.4
Grade 2	65.0	64.2-66.5
Grade 3	24.7	23.7-25.9
Grade 4	0.3	0.2-0.5
Grade 5	0	—
Impact of PR		
Effectiveness	20.6	19.7-21.6
Safety	60.0	58.9-61.3
Efficiency	12.6	11.9-13.5

95% CI indicates 95% confidence interval; ADE, adverse drug event; PR, pharmacist recommendation.

The predictive equation (Figure) for the chosen model is represented by the logistic regression model and gives us the probability that a pharmacotherapeutic optimisation recommendation is implemented in a patient in accordance with the explanatory variables: ADE safety/effectiveness and potential ADE severity ≥2.

The probability that the pharmacotherapeutic optimisation measures would be implemented in ADE due to safety/effectiveness was 0.59 when the ADE presented a potential severity ≥2, and 0.31 if severity was <2. The probability that the pharmacotherapeutic optimisation measures were implemented due to indication problems was less: 0.49 for ADE with severity ≥2 and 0.17 if severity was <2.

Discussion

The PhQI&PSP's end objective was to optimise pharmacotherapy to improve the probability of obtaining optimum results and reducing the probability of patient

Table 4 Univariate analysis results

Variable	*P*	OR	95% CI of OR
High-risk drug	.549	0.961	0.843-1.095
ADE category: safety/effectiveness	<.001	1.307	1.13-1.512
Potential ADE severity ≥2	<.001	1.666	1.360-2.040
Impact of PR safety/effectiveness	<.001	1.666	1.438-1.93

95% CI indicates 95% confidence interval; ADE, adverse drug event; OR, odds ratio; PR, pharmacist recommendation.

Table 5 Final logistic regression model

Variable	B	*P*	OR	95%CI of OR
ADE category safety/ effectiveness	1.076	.025	1.192	1.022-1.390
Potential severity of ADE ≥2	0.449	<.001	1.567	1.268-1.936
Constant	1.189	<.001	3.284	

95% CI indicates confidence interval of 95%; ADE, adverse drug event; OR, odds ratio.

risks. To do so, a pharmacotherapeutic action plan was designed based on patient needs and pharmacotherapy improvement opportunities identified. The implementation of these measures is a complex and multifactorial process, which firstly depends on the clinical team accepting the PR.

In this study we analysed 6762 PR made for patients admitted to a general hospital. More than 85% of the pharmacotherapeutic optimisation measures proposed were implemented. This result is similar to that obtained by Kloper et al[25] in the meta-analysis on 23 studies conducted in different health care environments. Their acceptance percentages varied between 58.1%-97.5%. Other studies, such as that by DeName et al,[12] which assesses the pharmacotherapy optimisation recommendations in diabetic outpatients, or that by Arroyo et al[26] in critical oncology patients, which obtained acceptance percentages of 61.4% and 94%, respectively. The wide variability found suggests the need to identify which factors most influence the level of recommendation acceptance in the health care environment, with the aim of prioritising those pharmacotherapeutic optimisation measures that the health team considers of greater relevance for patients' outcomes.

After conducting the univariate analysis, we observed that the categorical variables ADE safety/ effectiveness, potential ADE severity ≥2, and impact of PR safety/ effectiveness, presented a statistically significant relationship with PR implementation. However, the predictive variables finally chosen by the multivariate analysis because of their greatest influence on whether pharmacotherapeutic optimisation measures are implemented on the patient were ADE category and severity. This shows that they should be the ADE priority variables when creating a pharmaceutical action plan.

The final prediction model for our study observed that the PR related to ADE with a severity ≥2 were twice more likely to be accepted than those related with severity 1. This relationship was statistically significant. The relationship between PR acceptance and the severity of ADE has been widely studied,[16,26] however, it is difficult to compare them given that the studies performed are very different in nature. Barber et al,[15] concluded that acceptance depends on the severity, but they determined ADE severity indirectly, relating it to the clinical department where the patient is registered. They therefore found that recommendations made in intensive care units were more likely to be accepted than those in other units. Our study, using an individual analysis of the potential ADE severity based on the drug characteristics involved and the patient's clinical situation (Table 3), showed that this variable is the one that seems to have the most influence on pharmaceutical decision making, as this variable had different sub-groups: ADE with no relevant clinical consequences (severity 1) and those that could be potentially relevant for the patient (severity ≥2).

$$Pr\,(Y=1/X) = \frac{1}{1 + e^{-(1{,}19 + 0{,}2\ X\ PRM\_ES\_I + 0{,}5\ X\ G \geq 2)}}$$

Figure Equation to predict the probability that a pharmacist recommendation is implemented.

The ADE category is closely related to PR implementation in our model. Therefore, a PR related to drug safety/ effectiveness is 20% more likely to be implemented than if it is indication-related (Table 5). Similarly, Bedouch et al[27] concluded that recommendations of personalised dosage, equally related to treatment safety and effectiveness, present an acceptance probability 3.86 times greater (95% CI: 1.63-8.86). This suggests that indication-related recommendations are possibly considered less relevant from a clinical point of view, and are mainly aimed at reducing pharmacotherapy costs. Involving pharmacists in pharmacotherapeutic decision making and strengthening professionals' education could contribute to a more appropriate drug use, based on safety criteria, efficacy and cost, as has been shown in a recent systematic review published by Ostini et al.[28]

Meanwhile, other variables studied which have not shown a relationship with PR implementation have been the type of drug involved and the impact of the action. In our study, 58% of the ADE were related to "high-risk" drugs, but no statistically significant relationship was observed with PR implementation (*P*=.549). However, a relationship with ADE severity was obtained, which considers the drug risk and the patient's clinical situation. The impact of the action was generally related with the ADE category. In our study, most of the pharmacists' actions were related with safety (60%), effectiveness (20.6%) and lastly, efficiency (12.3%). This distribution is similar to that obtained in other studies.[26,29,30] After grouping the impact of PR in safety-effectiveness compared to efficiency, a statistically significant relationship was observed with recommendation implementation. However, it was not included in the final model, possibly given the strong relationship with the variable ADE caterogy.

Quantifying all of the factors related to implementing pharmacotherapeutic optimisation recommendations is complicated, and can sometimes be difficult to measure. One of the limitations of our study was that we did not consider other factors studied in the literature, such as the professional involved or the way that the recommendation was communicated. In general, some authors noted that recommendations made verbally were accepted more

often than those given in writing.[17,27] In our environment, most recommendations are communicated verbally, meaning that we are not able to study its relationship with implementation. Meanwhile, other studies observed differences depending on the professional involved (e.g. student-junior doctors, specialist doctors),[16,25] which proves that the pharmacist's communication skills and professional experience may influence whether they take part in pharmacotherapeutic decisions effectively. We were not able to study this factor in our study, since the PR were only made by specialist pharmacists and junior doctors being supervised by the specialists, meaning that a bias could have been produced when interpreting potential differences.

Lastly, the prediction model obtained concludes that the pharmacotherapeutic optimisation recommendation implementation is significantly related with the category, especially the severity of the pharmacotherapy improvement opportunity identified in the patient. As such, when the ADE identified may affect the treatment's effectiveness or the patient's safety, the acceptance probability increases by 20% (95% CI: 0%-40%), and when the ADE severity is ≥2, i.e. with notable clinical consequences for the patient, the acceptance probability increases by 50% (95% CI: 30%-100%). This fact proves the need to prioritise PR for pharmacotherapy improvement opportunities with severity ≥2 and based on effectiveness and safety, so as to reduce the acceptance variability and ensure that relevant pharmacotherapeutic optimisation measures are implemented in patients.

Conflict of interest

The authors affirm that they have no conflict of interest.

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