

## ORIGINALES

# Factors related with the appropriateness of pharmacological treatment in polypathological patients

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### Abstract

**Objective:** To evaluate the association between the number of pharmacological inappropriateness and possible factors related with it.

**Methods:** All polypathological patients of the *IMPACTO* project in a tertiary hospital were included (July 2010-March 2012). The pharmacist performed the interventions based on a combined strategy that included the modified MAI and the STOPP-START criteria. A greater number of interventions indicated smaller treatment appropriateness. In the analysis of the strength of association between two continuous variables the Pearson correlation coefficient was used. Test of Student's t or Mann-Whitney comparisons of quantitative data between two groups were applied. Subsequently, a multivariate analysis was performed to study possible variables which explain the inappropriateness of the pharmacological treatment.

**Results:** 242 patients were included. 838 inappropriateness were detected (average per patient of  $3\pm 2$ ). The appropriateness was associated with: number of diagnoses, medications, and categories of polypathology, Charlson Comorbidity Index, sex, and categories A1 and B2. When diagnosing collinearity in the multivariate model, we observed that there was collinearity between "Charlson Comorbidity Index" and "number of categories of polypathological patients", so it was decided to conduct two multivariate models variables, one each. The number of drugs, the number of diagnoses and the gender remained significant in both multivariate models.

**Conclusions:** The appropriateness of pharmacological treatment decreases with increasing number of drugs and number of diagnoses, as well as female gender. However, both multi-

### Factores relacionados con la adecuación del tratamiento farmacológico en pacientes pluripatológicos

#### Resumen

**Objetivo:** evaluar la asociación entre el número de inadecuaciones farmacológicas y posibles factores relacionados con la misma.

**Métodos:** Se incluyeron todos los pacientes pluripatológicos del proyecto *IMPACTO* en un hospital de tercer nivel (Julio 2010-Marzo 2012). El farmacéutico realizó las intervenciones en base a una estrategia combinada que incluía el MAI modificado y los criterios STOPP-START. A mayor número de intervenciones menor adecuación del tratamiento. En los análisis de la fuerza de asociación entre dos variables continuas se utilizó el coeficiente de correlación de Pearson. Se aplicó el test de la t de Student o U de Mann-Whitney en comparaciones de datos cuantitativos entre dos grupos. Posteriormente, se realizó un análisis multivariante, para estudiar posibles variables que explicasen las inadecuaciones del tratamiento farmacológico.

**Resultados:** Se incluyeron un total de 242 pacientes. Se detectaron un total de 838 inadecuaciones, siendo la media por paciente de  $3\pm 2$ . La adecuación del tratamiento farmacológico se asoció con el número de diagnósticos, el número de medicamentos, el número de categorías de paciente pluripatológico, el índice de comorbilidad de Charlson, el sexo y las categorías A1 y B2. Al realizar el diagnóstico de colinealidad, en el modelo multivariante, de las variables se observó que existía colinealidad entre las variables "índice de comorbilidad de Charlson" y "número de categorías de paciente pluripatológico", por lo que se decidió realizar dos modelos multivariantes, uno con cada una de ellas. Se mantuvieron significativos con el multivariante y para ambos modelos el número de medicamentos, el número de diagnósticos y el sexo.

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variate models explain a low percentage of variability in the number of inappropriateness.

#### KEYWORDS

Multimorbidity; Polyphatological; Appropriateness

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## Introduction

Appropriateness is a general term that includes a wide range of characteristics and behaviours related to the quality of the prescription<sup>1</sup>. A prescription is considered adequate when there is clear evidence that supports its use for the given indication, is well tolerated and has a favourable cost-effectiveness profile<sup>2</sup>.

Inappropriate prescribing also includes the use of drugs with incorrect duration, interactions and duplications. Additionally, in elderly patients, criteria should be considered such as prognosis, life expectancy and functional state so as to promote the use of treatments with better risk-benefit ratios<sup>3,4</sup>.

Inappropriate drug prescribing in chronic patient is considered a public health issue related to morbidity, mortality and use of healthcare resources<sup>5</sup>.

Within this framework, polypathological patients are defined as those with two or more chronic diseases from a list of specific clinical categories that take into account the severity of or incapacity produced by the disease<sup>6</sup>. The prevalence of these patients is low in the general population, but can be high in the hospital setting<sup>7</sup>.

These patients are susceptible to suffer inadequate pharmacological treatment, since polypharmacy, high morbidity rates, and continuous health care transitions increase this risk<sup>8,9</sup>.

Our research group, in a previous work<sup>10</sup>, identified by a panel of experts, following the Delphi methodology, potentially useful tools for appropriateness in this group of patients. As implicit method, the modified *Medication Appropriateness Index* (MAI) was selected, and as explicit method, the *Screening Tool of Older Person's potentially inappropriate Prescription/Screening Tool to Alert doctors to the Right* (STOPP-START). Once we validated the modified MAI<sup>11</sup>, our group applied this combined approach for assessing the appropriateness of the pharmacological treatment in a cohort of polypathological patients<sup>12</sup>. The primary endpoint of this study was the number of inappropriateness detected. An average of 3 inappropriateness per patient was detected.

The main objective of this study was to evaluate the association between the number of pharmacological inappropriateness (number of interventions for the appropriateness of drug treatment performed by the pharmacist) and possible factors related with it.

**Conclusiones:** La adecuación del tratamiento farmacológico disminuyó al aumentar el número de medicamentos y el número de diagnósticos, así como en mujeres. No obstante, ambos modelos multivariantes, explicaron un porcentaje de variabilidad del número de inadecuaciones leve.

#### PALABRAS CLAVE

Multimorbilidad; Pluripatología; Adecuación

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## Methods

All polyphatological patients in an integrated care project, *IMPACTO* project, in a tertiary hospital were included (July 2010-March 2012). This is a multidisciplinary macro project, whose main objective is to evaluate the clinical impact of a multilevel intervention model based on shared care between the internist of reference and the primary care service in a multicenter population of polypathological patients.

The pharmacist performed the interventions based on a combined strategy that included the modified MAI<sup>11</sup> and the STOPP-START<sup>13</sup> criteria. Each intervention was considered as a pharmacological inappropriateness, so, a greater number of interventions indicated smaller treatment appropriateness.

For each of the patients was collected: age, sex, number of diagnoses, number and types of categories of inclusion as polypathological patients, number of drugs, Charlson Comorbidity Index, number of admissions at 3 and 12 previous months and number of interventions for the appropriateness of drug treatment performed by the pharmacist.

The dates were statistically analyzed in the IBM ® SPSS Statistic software (version 19.0 for Windows). The description of the qualitative variables was performed by distribution of absolute frequencies and percentages. Quantitative variables were described by mean and its standard deviation.

To analyze the association between the variable numbers of interventions with respect to the other quantitative variables the Pearson correlation coefficient was used. And to analyze qualitative variables the test of Student's t or Mann-Whitney was applied as they were normal or not (Kolmogorov-Smirnov). It was assumed that the differences were statistically significant when  $p < 0.05$ .

With those variables significant association was obtained in the univariate analysis, we performed a multivariate analysis in order to study possible variables that explain inappropriateness of the drug therapy. We realized the collinearity diagnosis, in the multivariate model, in order to detect possible variables which were associated. Regression coefficients (B) and their confidence intervals (CI) at 95% were obtained. An assessment of the goodness of fit by the determination coefficient was performed, and the diagnosis of

independence (Durbin-Watson) errors and verification of homogeneity and normality of these through the scatter plots.

## Results

A total of 242 patients were included. Baseline characteristics are shown in Table 1.

The number of diagnoses, drugs, categories of inclusion as polypathological patients and Chalon index showed a statistically significant association with the

number of interventions, being the Pearson correlation coefficient of 0.322 ( $p < 0.001$ ), 0.369 ( $p < 0.001$ ), 0.162 ( $p = 0.012$ ) and 0.183 ( $p = 0.004$ ) respectively.

The mean difference of interventions in women ( $3.82 \pm 1.77$ ) and in men ( $3.11 \pm 1.88$ ) was significant ( $p = 0.003$ ). This also occurred with the category A1 (chronic heart failure), the presence ( $3.65 \pm 1.86$ ) versus the absence ( $3.00 \pm 1.77$ ) of the same was significant ( $p = 0.012$ ); and with the category B2 (chronic renal disease), its presence implies a number of interventions of  $3, 92 \pm 1.99$  and the absence of  $3.16 \pm 1.70$  ( $p = 0.002$ ).

**Table 1.** Baseline characteristics of patients

Characterization of polypathological patients included (n= 242).	
Age, mean (years $\pm$ SD)	76 $\pm$ 8
Sex, n (%)	
– Men	122 (51%)
– Women	120 (49%)
Number of drugs, mean $\pm$ SD	12 $\pm$ 4
Number of diagnoses, mean $\pm$ SD	8 $\pm$ 3
Global Charlson index, mean $\pm$ SD	4 $\pm$ 2
Number of admissions at 3 previous months, mean $\pm$ SD	1 $\pm$ 1
Number of admissions at 6 previous months, mean $\pm$ SD	1 $\pm$ 1
Number of interventions per patient, mean $\pm$ SD	3 $\pm$ 2
Number of categories of inclusion as polypathological patients, mean $\pm$ SD	3 $\pm$ 1
Categories of inclusion as polypathological patients, n (%):	
– A1	171 (71%)
– A2	112 (46%)
– B1	6 (2%)
– B2	97 (40%)
– C1	115 (47%)
– D1	2 (1%)
– D2	10 (4%)
– E1	70 (29%)
– E2	11 (4%)
– E3	22 (9%)
– F1	41 (17%)
– F2	56 (23%)
– G1	62 (26%)
– G2	2 (1%)
– H1	29 (12%)

SD: standard deviation

A1. Chronic heart failure with past/present stage II dyspnea of NYHA.

A2. Coronary heart disease.

B1. Vasculitides and/or systemic autoimmune diseases.

B2. Chronic renal disease (creatininaemia N1.4/1.3 mg/dL in men/women or proteinuria, during  $\geq 3$  months).

C1. Chronic lung disease with past/present stage 2 dyspnea of MRC, or FEV1 $\leq$ 65%, or basal SatO<sub>2</sub> $\leq$ 90%.

D1. Chronic inflammatory bowel disease.

D2. Chronic liver disease with evidence of portal hypertension.

E1. Stroke.

E2. Neurological disease with permanent motor deficit, leading to severe impairment of basic activities of daily living (Barthel index  $\leq 60$ ).

E3. Neurological disease with permanent moderate–severe cognitive impairment (Pfeiffer's test with  $\geq 5$  errors).

F1. Symptomatic peripheral artery disease.

F2. Diabetes mellitus with proliferate retinopathy or symptomatic neuropathy.

G1. Chronic anemia (Hb $\leq$ 10 g/dL during  $\geq 3$  months) due to digestive-tract losses or acquired hemopathy not tributary of treatment with curative intention.

G2. Solid-organ or hematological active neoplasia not tributary of treatment with curative intention.

H1. Chronic osteoarticular disease, leading to severe impairment of basic activities of daily living (Barthel index  $\leq 60$ ).

When diagnosing collinearity in the multivariate model, the variables "Charlson Comorbidity Index" and "number of categories as polypathological patients", demonstrated collinearity between them so it was decided to conduct two multivariate models variables, one each. Both models are detailed in Table 2, and verification that the waste meets the assumption of homogeneity and follows a normal distribution is shown in the graphs in Figure 1.

The first predictive model based on the Charlson Comorbidity Index would be:

Number of interventions =  $-0.140 + 0.92 \times \text{number of diagnosis} + 0.156 \times \text{number of drugs} + 0.627 \times \text{sex} + 0.297 \times \text{categorie of inclusion A1} + 0.468 \times \text{categorie of inclusion B2} + 0.055 \times \text{Charlson Comorbidity Index}$

And the second, based on the number of categories as polypathological patients:

Number of interventions =  $-0.69 + 0.95 \times \text{number of diagnosis} + 0.157 \times \text{number of drugs} + 0.599 \times \text{sex} + 0.310 \times \text{categorie of inclusion A1} + 0.548 \times \text{categorie of inclusion B2} + 0.19 \times \text{number of categories as polypathological patients}$

Both models explain 23.4% and 23.3% respectively of the total variability in the number of interventions.

## Discussion

In this study potential predictors of lower appropriateness of pharmacological treatment in a group of patients who, because of their vulnerability, are susceptible to numerous pharmacological inappropriateness, are evaluated<sup>8</sup>.

It is known that the appropriateness decreases with increasing number of drugs<sup>14</sup>. Importantly, in numerous studies, the polypharmacy has been identified as the main risk factor that determines the appearance of the incidents that gave rise to hospitalization or emergency care<sup>15,16</sup>.

On the other hand, a relationship between inappropriateness and adverse drug reactions (ADRs) has been established. The risk of suffer an ADRs increases with age, due to physiological changes of the aging, changes in the pharmacokinetic and pharmacodynamic behavior of drugs, the influence of diseases, functional problems and social issues<sup>17,18</sup>.

Despite the magnitude of the problem, there is no consensus nor is there solid scientific evidence to help prevent inappropriate prescribing, especially in older people. As far as the authors know this study is the first attempt to study variables related to a lower appropriateness in polypathological patients, hence its importance.

Our population of polypathological patients was characterized by an average of over 65 years of age, be considerably polymedicated (mean number of drugs per patient of 12) so as to present a high disease burden. This profile has previously been described in numerous publications<sup>19,20</sup>.

In this study, when we did the diagnosis of collinearity, it was observed that it exists between "Charlson Comorbidity Index" and "number of categories of polypathological patients". This situation determined that two multivariate models were realized. This collinearity is logical because both variables are conceptually linked, as they determine in one or another way the disease burden.

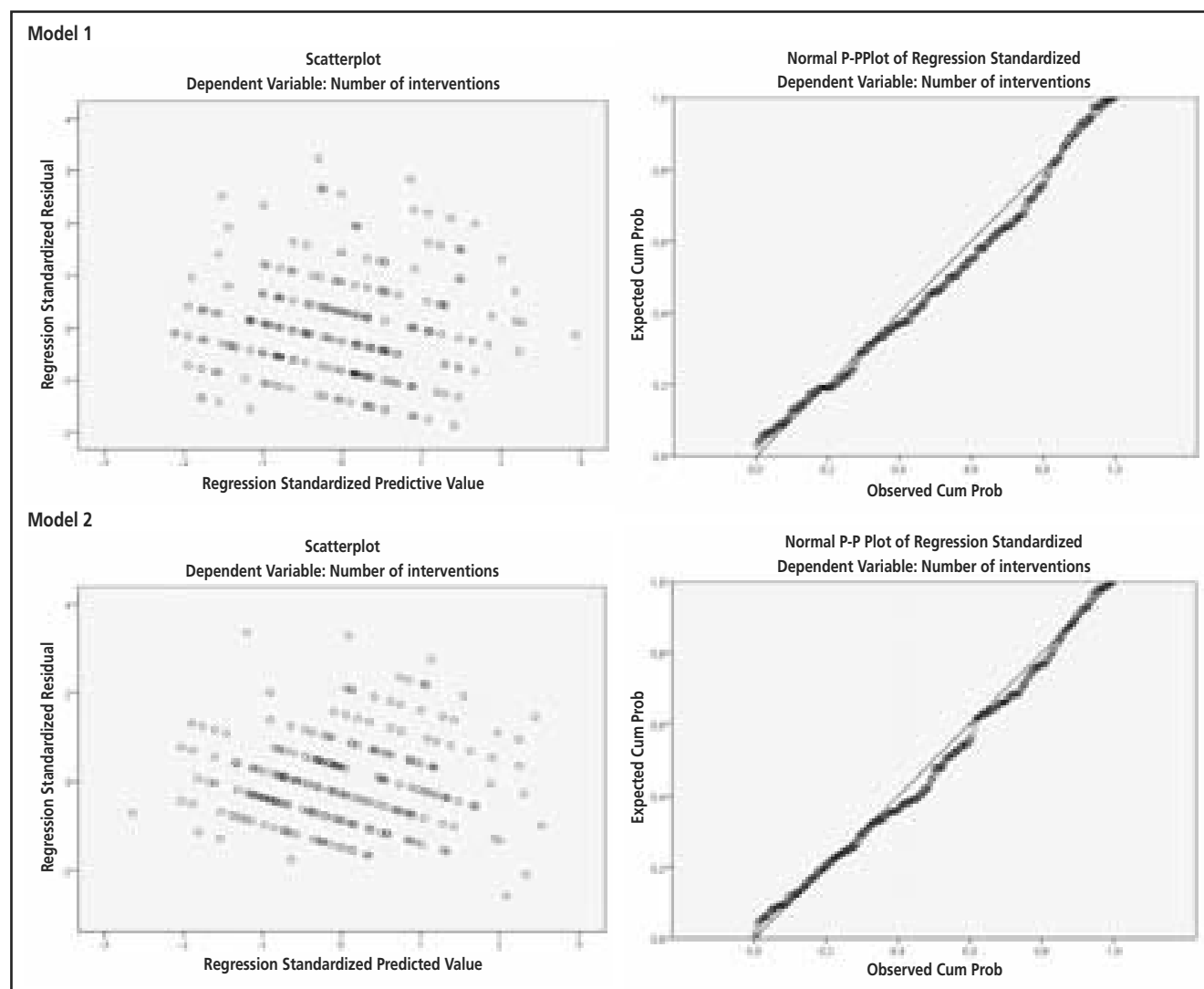
**Table 2.** Results of multivariate analysis for both models

Model 1					Model 2				
	B*(95% CI)	p	Diagnosis collinearity			B*(95% CI)	p	Diagnosis collinearity	
			T <sup>&amp;</sup>	VIF <sup>#</sup>				T <sup>&amp;</sup>	VIF <sup>#</sup>
(Constant)	-0.140 (-1.075; 0.795)	0.768			(Constant)	-0.069 (-1.072; 0.934)	0.892		
Number of diagnoses	<b>0.092</b> (0.009; 0.175)	0.030	0.734	1.363	Number of diagnoses	<b>0.095</b> (0.009; 0.181)	0.031	0.680	1.470
Number of drugs	<b>0.156</b> (0.093; 0.219)	<0.001	0.868	1.152	Number of drugs	<b>0.157</b> (0.094; 0.220)	<0.001	0.871	1.148
Sex (woman)	<b>0.627</b> (0.194; 1.060)	0.005	0.926	1.079	Sex (woman)	<b>0.599</b> (0.174; 1.025)	0.006	0.960	1.042
Categorie of inclusion A1 (yes)	<b>0.297</b> (-0.184; 0.778)	0.225	0.904	1.106	Categorie of inclusion A1 (yes)	<b>0.310</b> (-0.171; 0.791)	0.205	0.907	1.102
Categorie of inclusion B2 (yes)	<b>0.468</b> (-0.056; 0.992)	0.080	0.659	1.517	Categorie of inclusion B2 (yes)	<b>0.548</b> (0.085; 1.012)	0.021	0.842	1.187
Charlson index	<b>0.049</b> (-0.102; 0.200)	0.525	0.618	1.619	Number of categories	<b>0.019</b> (-0.251; 0.289)	0.889	0.742	1.347

\*: B= Regression Unstandardized coefficients; &: T= Tolerance; #: VIF= Variance inflation factor.

Model 1: Durbin-Watson = 1.959; R<sup>2</sup>=0.234.

Model 2: Durbin-Watson = 1.956; R<sup>2</sup>= 0.233



**Figure 1.** Scatter plots for models 1 and 2.

The results of the multivariate analysis show that, for both models, variables such as the number of drugs or the number of diagnoses may determine the appropriateness, so that a greater number of drugs and number of diagnoses increases the presence of inappropriateness. This is reasonable and is in line with data available in the literature, pointing to polypathological patients as the most vulnerable among chronic patients. Moreover, being a woman seems to determine a greater presence of inappropriateness, although the clinical relevance of this difference between men and women is questionable, since the mean difference of interventions is one.

In one of the models (based on the number of categories as polypathological patients) the presence of category B2 (chronic kidney disease) determines a lower appropriateness. This can be justified based on the need for dose adjustment of drugs.

However, both models explain 23.4% and 23.3% respectively of the total variability in the number of interventions. More covariates would be necessary to arrive

at an appropriate percentage which explains the variability of this variable.

Other studies, such as the REPOSI group, show results on the same line. Nobili et al 2011<sup>21</sup>, on the basis that the multimorbidity and polypharmacy are associated with hospitalization rates assessed whether certain groups of diseases carried a greater polypharmacy. The strongest association between clusters of diseases and polypharmacy was found for diabetes mellitus plus coronary heart disease plus cerebrovascular disease, diabetes plus coronary heart disease, and heart failure plus atrial fibrillation. In our study, the average of drugs per patient was approximately of 12, and the cardiac pathology constitutes the majority.

This study is not without limitations. First, the strategy developed for pharmaceutical interventions includes a clear subjective component, which is the modified MAI. Moreover, the study is conducted at local level in a tertiary hospital, which may influence the external validity of the results.

In conclusion, the appropriateness of pharmacological treatment decreases with increasing the number of drugs and the number of diagnoses, as well as in female gender. The presence of the B2 category also seems to determine a minor appropriateness. However, both multivariate models explain a low percentage of the variability in the number of interventions.

Given these results, new lines of research are open. A very interesting study could be whether interventions to improve the appropriateness of pharmacological treatment in patient's candidates to the same mean better health outcomes, ie, evaluate the effectiveness of these intervention models.

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