Impact of non-formulary drugs on pharmacological prescription in hospitalised patients

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ABSTRACT

Objectives The growing number of drugs on the market makes it necessary to adapt hospital formularies in order to ensure consistent drug coverage. The aim of this study was to evaluate the impact of the prescription of non-formulary drugs (NFD) on the therapeutic management of admitted patients.

Methods This retrospective observational study included NFD prescriptions in patients hospitalised in a tertiary university hospital during the period 2012–2015. NFD prescriptions are displayed on the computerised medical order as a pending alert to be reviewed by the clinical pharmacists, who make a notation to the clinical course that includes a recommendation for an available therapeutic alternative when available in the hospital formulary. The degree of acceptance of the recommendation by physicians is recorded.

Results Approximately 0.5% of patients hospitalised during the study period were affected by an NFD prescription. A total of 52 (9.5%) NFD were of doubtful therapeutic efficacy, five (0.9%) were non-replaceable drugs and 490 (89.4%) were prescriptions for drugs with an alternative available in the hospital formulary. The acceptance rate for the recommended alternative was 34.9% in the evaluable NFD prescriptions. No correlation was observed between the number of NFD prescriptions or the number of NFD and the availability index (drugs included in the hospital formulary in relation to the total number of drugs marketed).

Conclusions The number of patients with a NFD prescription was very low. The lack of correlation between the number of NFD or NFD prescriptions and the availability index demonstrated that the hospital formulary covers practically all therapeutic needs.

INTRODUCTION

Hospital formularies are a key element of medication management and aim to ensure effective, safe and cost-effective treatment.[1]

In recent years, the rapid increase in the number of molecules belonging to the same therapeutic family has increased treatment complexity.[2] This, together with the need for more rational medication use and greater control of drugs and healthcare-associated costs, has helped to highlight the role of therapeutic interchange.[1 3] In hospitals, this function is supported by the Pharmacy Commission and consists of replacing a non-formulary drug (NFD), received by the patient prior to admission, with a therapeutic equivalent with a different chemical structure, available at the hospital formulary once the patient is hospitalised.[1 3] Several studies have reported that this strategy has not affected treatment effectiveness.[4–7]

Nevertheless, the effect of prescription of NFD on the therapeutic approach to patients is still unknown.

The main objective of this study was to evaluate the impact of prescription of NFD on the therapeutic management of hospitalised patients.

METHODS

This retrospective observational study was performed in a tertiary university hospital with 431 beds (413 conventional beds and 18 critically-ill patient beds) during a 4-year period (2012–2015). Prescriptions of NFD detected in hospitalised patients were included.

A computerised physician order system was implemented throughout the hospital.

NFD prescriptions appear in the medical order as an alert waiting for review by a clinical pharmacist. After evaluation, the clinical pharmacist makes an annotation in the patient's electronic medical record, providing information on an alternative in the hospital formulary, when available, purchasing the prescribed drug if not included in the hospital formulary, or recommending removing the prescribed drug if it is of doubtful therapeutic efficacy.

The result of the recommendation is evaluated following the physician's response to the clinical pharmacist's recommendation in the electronic medical record of the computerised physician order entry system. The recommendation is considered to be accepted when the physician switches from the NFD to the therapeutic alternative recommended. In some circumstances (death, discharge, transfer to another centre or a self-limiting situation) the acceptance rate cannot be evaluated.

Non-replaceable NFD (NFD-NR) were defined as those drugs with an indication without a therapeutic alternative and with clinical evidence of their effectiveness in the evaluated indication.

NFD with doubtful therapeutic efficacy (NFD-DTE) were defined as those drugs with limited evidence of their effectiveness.

Admissions to the emergency department without hospital admission were excluded because this unit lacked the computerised physician order entry system in the study period.

Variables

The principal variable was NFD with a therapeutic alternative (NFD-ALT). The following variables were also collected: age and sex of hospitalised

patients prescribed NFD-ALT, hospital stay, number of different drugs the patients received during their stay, comorbidities (Charlson index), medical or surgical department, and type of admission (emergency or elective admission). We also calculated the acceptance rate of recommendations (accepted, not accepted, not evaluable) and the Anatomical Therapeutic Chemical (ATC) group of the NFD-ALT.

The availability index was defined for each ATC group as the quotient between drugs included in a particular ATC group available in the formulary in relation to the total number of commercialised drugs in the same ATC group in Spain, giving correlation between the drugs included in the formulary with respect to the total number of drugs commercially available.

Statistical analysis

Quantitative variables are described as the median ±SD. Categorical variables are described as frequency tables (number and percentage).

The distribution between prescriptions and the number of different drugs for each ATC group was evaluated based on the availability index by a simple linear regression analysis.

Possible associated factors for acceptance were evaluated by the chi-square test for categorical variables and the non-parametric Mann–Whitney *U* test for continuous variables. The odds ratios (OR) for variables associated with the acceptance of recommendations were calculated by univariate and multivariate binary logistic regression, to evaluate potential confounding factors.

Associations with a P-value<0.05 were considered statistically significant. Statistical analyses were performed with the STATA 15.0 software (Stata Corp., College Station, Texas, USA).

RESULTS

During the study period, a total of 571 648 prescriptions were issued by physicians, of which 547 (0.09%) were NFD in 384 hospitalised patients. Of 69 686 patients hospitalised during the study period, 0.5% of them were affected by an NFD prescription.

Of all 547 NFD, 490 (89.4%) had an alternative available on the formulary, 52 (9.5%) were of doubtful therapeutic efficacy and five (0.9%) were non-replaceable drugs.

Clinical pharmacists made an annotation on the electronic medical record offering an alternative in all 490 NFD-ALT prescriptions. The alternative was accepted in 152 (31.0%), was not accepted in 283 (57.8%) and was not evaluable in 55 (11.2%).

The 435 evaluable NFD prescriptions corresponded to 140 different drugs (online supplemental table). The ATC groups involved in more than 5% of the NFD prescriptions were: ATC G04: urologicals (71), R03; drugs for obstructive airways diseases (47), C09; agents acting on the renin-angiotensin system (47), S01; ophtalmologicals (43); and C10: lipid modifying agents (25).

Referring to the availability index (which represents the number of drugs included in the hospital formulary in relation to the total number of drugs marketed), it ranged from 0% (groups ATC A08 (antiobesity preparations), A13 (tonics), A14 (anabolic steroids), D04 (antipruritics), D10 (antiacne preparations), M09 (other drugs for disorders of the musculo-skeletal system), R01 (nasal preparations), R07 (other respiratory system products), V01 (allergens), V09 (diagnostic radiopharmaceuticals) and V10 (therapeutic radiopharmaceuticals)) to 100% (groups ATC B05 (blood substitutes and perfusion solutions), D02 (emollients and protectives), H04 (pancreatic hormones), J02 (antimycotics of systemic use), J04 (antimycobacterials), L04 (immunosupressants), M04 (antigout preparations), N03 (antiepileptics), P01 (antiprotozoals) and P03 (ectoparasiticides, incl. scabicides, insecticides and repellents)).

No other correlation was observed between the number of NFD prescriptions or the number of NFD and the availability index (figures 1 and 2).

When the 435 evaluable NFD prescriptions alone were analysed, the acceptance rate for the recommended alternative was 34.9% (152/435). Patients with accepted alternatives received a higher number of drugs during stay (20.5% vs 18.8%), but no differences between groups were observed (P=0.110). Besides, patients staying in a medical ward seemed to follow pharmacists' recommendations compared with surgical admissions (55.9% vs 49.5%) but also no differences between groups were observed (P=0.421). Even patients with a higher value of morbidity seemed to present more acceptance by physicians yet again presenting no differences (P=0.350).

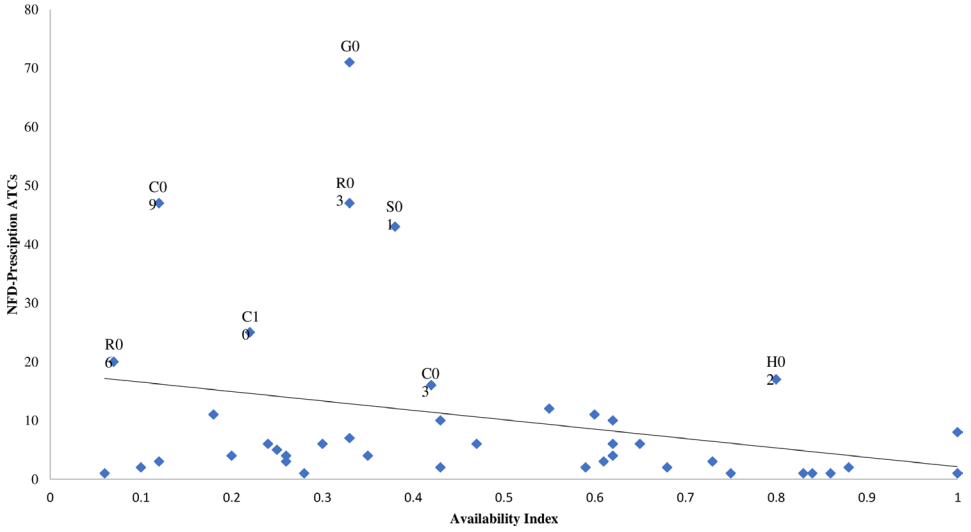

Figure 1 Correlation between number of NFD prescriptions and availability index for each ATC group. r= 0,0861. Prescriptions = 18,15 -16,02 *(availability index).

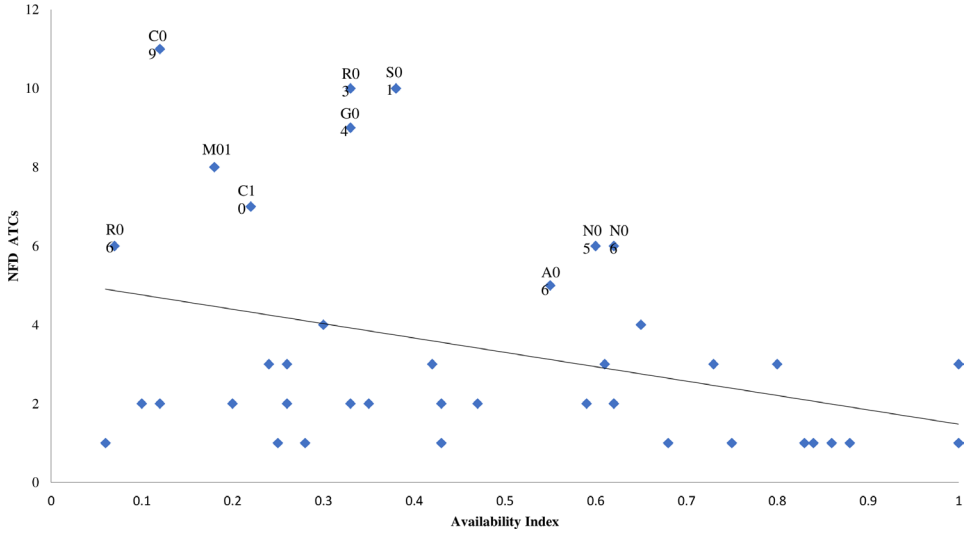

Figure 2 Correlation between prescribed NFD and availability index. r= 0,1284. Prescriptions = 5,12 -3,84 *(availability index).

The only variable associated with acceptance of the recommended therapeutic alternative was prolonged hospital stay, but this association disappeared on multivariate analysis (tables 1 and 2).

The prescription of these 140 NFD led to the inclusion in the formulary of apixaban (B01) and tolterodine (G04), both of which were prescribed only once.

DISCUSSION

In the present study, only 0.5% of hospitalised patients were affected by a NFD. The acceptance rate was 34.9% when considering NFD with an alternative and there was no correlation between NFD or NFD prescriptions and the availability index in the hospital formulary. Although hospital stay was identified as being independently associated with the acceptance rate in the univariate analysis, none of the variables were associated with this rate on multivariate analysis. The ATC groups most frequently involved in NFD prescriptions were urological drugs (G04), drugs for obstructive airway diseases (R03), agents acting on the renin-angiotensin system (C09), ophthalmological drugs (S01) and lipid-modifying agents (C10). NFD prescription has not prompted the inclusion of new drugs in the formulary, since just two new drugs have been admitted (1.4%) and both were prescribed just once.

Other studies have reported higher percentages of patients affected by NFD prescription than the present study. For example, in a study conducted between 2009 and 2012, a total of 223,266 NFD prescription alerts were generated relating to 184 258 hospitalised patents, representing 1.2 NFD prescriptions per hospitalised patient.[8] Similar values were obtained in other studies, which reported 1.3[9] and 1.2[10] NFD prescriptions per patient. The two hospitals had 793 and 365 beds, respectively.

In this work, we analysed the availability index, which was not evaluated in other studies. This variable allows assessment of the real coverage rate of a hospital formulary, given that it correlates the drugs included in the formulary with respect to the total number of drugs commercially available. For 13 ATC groups, the availability index was 0%, and no NFD prescriptions for these groups were observed during the study period. In fact, this could indicate the limited clinical relevance of the lack of availability of these ATC groups in patients hospitalised in acute hospitals, such as groups A08 (antiobesity preparations), A13 (tonics), A14 (anabolic agents for systemic use), D04 (topical antipruritics), D10 (anti-acne preparations), V01 (allergens), M09 (other drugs for disorders of the musculo-skeletal system) and/or R07 (other respiratory products). Moreover, use of the R01 group (nasal preparations) for rhinosinusitis has been questioned on several occasions, due to its association between prolonged administration and the rebound effect or nasal hyperactivity.[11] Last, radiopharmaceutical management (groups V09 and V10), including their prescription and administration, are controlled by a specific application at the radiology department.

Table 1 Univariate statistics of hospitalised patients whom the alternative to NFD proposed was accepted vs no accepted

	Total (n=435)	Hospitalised patients with accepted NFD alternative (n=152)	Hospitalised patients with no accepted NFD alternative (n=283)	P-value
Age (years, SD)	69.73 (14.34)	69.75 (13.22)	69.72 (14.93)	0.610
Sex (females) (%)	204 (46.9%)	70 (46.1%)	134 (47.3%)	0.796
Hospital stay (days, SD)	10.90 (15.89)	13.48 (21.61)	9.52 (11.52)	0.004
Number of drugs received during stay (n, SD)	19.53 (11.46)	20.5 (12.29)	18.81 (10.95)	0.110
Charlson Index(%)				
0	157 (36.1%)	51 (33.6%)	106 (37.5%)	0.350
1	112 (25.7%)	36 (23.7%)	76 (26.9%)	
2	166 (38.2%)	65 (42.8%)	101 (35.7%)	
Medical admission (vs surgical) (%)	225 (51.7%)	85 (55.9%)	140 (49.5%)	0.421
Scheduled admission (vs urgent) (%)	244 (56.1%)	83 (54.6%)	161 (56.9%)	0.647

Table 2 Factors associated with the degree of acceptance of the recommended alternative to the prescription of a NFD (univariate and multivariate statistics)

	Univariate	P-value	Multivariate	P-value
Age (years, SD)	OR 1.00 (CI 95% 0.99–1.01)	0.982	OR 0.99 (CI 95% 0.98–1.01)	0.986
Sex (females) (%)	OR 0.95 (CI 95% 0.64–1.41)	0.796	OR 1.02 (CI 95% 0.67–1.53)	0.938
Hospital stay (days, SD)	OR 1.02 (CI 95% 1.00–1.03)	0.026	OR 1.01 (CI 95% 0.99–1.03)	0.212
Number of drugs received during stay (n, SD)	OR 1.01 (CI 95% 1.00–1.03)	0.079	OR 1.01 (CI 95% 0.99–1.04)	0.255
Charlson Index (%)				
0	Reference category	–	Reference category	–
1	OR 0.98 (CI 95% 0.59–1.65)	0.953	OR 0.99 (CI 95% 0.58–1.70)	0.984
2	OR 1.34 (CI 95% 0.85–2.11)	0.212	OR 1.21 (CI 95% 0.73–1.98)	0.461
Medical admission (vs surgical) (%)	OR 1.31 (CI 95% 0.88–1.95)	0.176	OR 1.53 (CI 95% 0.92–2.54)	0.098
Scheduled admission (vs urgent) (%)	OR 0.91 (CI 95% 0.61–1.35)	0.647	OR 1.08 (CI 95% 0.69–1.68)	0.736

The most frequent NFD prescribed belonged to the ATC groups G04 (71 prescriptions, nine drugs), C09 (47 prescriptions, 11 drugs), R03 (47 prescriptions, 10 drugs), S01 (43 prescriptions, 10 drugs) and C10 (25 prescriptions, seven drugs). Nevertheless, there was no association between more frequent NFD prescription and a lower availability index in the hospital formulary, which excludes the non-availability of alternatives as the reason for prescribing an NFD. Furthermore, only tolterodine (which belongs to ATC group G04) and apixaban (ATC group B01), both involved in just one NFD prescription, were included in the formulary.

The acceptance rate for an alternative was similar to the rates reported in other studies.[10] In one of them, the acceptance rate reached 33% in the surgery department and 45% in the home hospitalisation service.[10]

The lower value observed in this study could be due to physician reluctance to switch to an alternative drug,[12] and to the fact that patients often take their own medication.[13] According to the results of a survey performed in 300 American hospitals, 90% allow patients to bring their usual medication when hospitalised.[13] In addition, another study showed that patients brought their own medication on 34 (16.5%) occasions in a sample of 206 NFD prescriptions.[9] However, the acceptance rate was higher in other studies conducted in American hospitals.[14 15]

In this work, longer hospital stay was related to higher acceptance of a recommended alternative. This finding could be because, during longer stays, patients have greater difficulties in bringing in their own medication and are visited by physicians from different specialties: consequently, adjustment of drugs included in the formulary could be more frequent in prolonged hospital stays. Nevertheless, this difference did not appear in the multivariate analysis.

In conclusion, although the acceptance rate of alternatives was limited, the number of patients with a NFD prescription was very low. Moreover, the hospital formulary covers practically all the therapeutic needs, which is demonstrated by the lack of correlation between the number of NFD or NFD prescriptions and the availability index.

What this paper

What is already known on this subject

- Little research has been performed about the impact of non-formulary drugs' prescription on the therapeutic management in hospitalised patients.
- A few studies have evaluated therapeutic interchange and suggest that this strategy does not affect the effectiveness of treatment.

What this study adds

- The availability index, not previously evaluated, provides guidance on the drug availability of a specific ATC.
- A longer hospital stay is associated with a greater degree of therapeutic interchange acceptance.
- Less than 1% of inpatients are affected by non-formulary drugs prescription.

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REFERENCES

1 ASHP Expert Panel on Medication Cost Management. ASHP guidelines on medication cost management strategies for hospitals and health systems. *Am J Health Syst Pharm* 2008;65:1368–84.
2 European Medicines Agency's (EMA). Human medicines. Available: https://www.ema.europa.eu/en/medicines
3 Gray T, Bertch K, Galt K, *et al*. Guidelines for therapeutic interchange – 2004. *Pharmacotherapy* 2005;25:1666–80.
4 Sodorff MM, Galt KA, Galt MA, *et al*. Patient perceptions of a proton pump inhibitor therapeutic interchange program across the continuum of care. *Pharmacotherapy* 2002;22:500–12.
5 Boix Montañes A, Barrera Puigdollers MT. Sustitucion Y seleccion de equivalentes terapeuticos. *Farm Hosp* 1996;20:351–8.
6 Carroll NV. Therapeutic interchange in community pharmacies in Virginia. *Am J Health Syst Pharm* 2000;57:882–6.
7 Sodorff MM, Galt KA, Galt MA. Pharmacists' perceptions of a therapeutic – interchange program. *Am J Health Syst Pharm* 2000;57:999–1000.
8 Her QL, Seger DL, Amato MG, *et al*. Development of an algorithm to assess appropriateness of overriding alerts for nonformulary medications in a computerized prescriber-order-entry system. *Am J Health Syst Pharm* 2016;73:e34–45.
9 Her QL, Amato MG, Seger DL, *et al*. The frequency of inappropriate nonformulary medication alert overrides in the inpatient setting. *J Am Med Inform Assoc* 2016;23:924–33.

10 Corrales L, Segura M, Gasanz I, *et al*. Analysis of prescriptions of drugs not included in the formulary. *Eur J Hosp Pharm* 2012;19:214–5.
11 Graf P. Long-term use of oxy- and xylometazoline nasal sprays induces rebound swelling, tolerance, and nasal hyperreactivity. *Rhinology* 1996;34:9–13.
12 Poole TA. Survey of pharmacists' and physicians' perceptions of therapeutic interchange. *Adv Ther* 2005;22:1–9.
13 Norstrom PE, Brown CM. Use of patients' own medications in small hospitals. *Am J Health Syst Pharm* 2002;59:349–54.
14 Schachtner JM, Guharoy R, Medicis JJ, *et al*. Prevalence and cost savings of therapeutic interchange among US hospitals. *Am J Health Syst Pharm* 2002;59:529–33.
15 Galt KA, Galt MA, Sodorff MM, *et al*. Patient-perceived outcomes of an inpatient PPi therapeutic interchange program. *Formulary* 2001;36:340–54.