The influence of drug use in university hospitals on the pharmaceutical consumption in their surrounding communities

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Hospital doctors influence pharmaceutical consumption outside the hospital, directly by initiating treatments or indirectly by informing general practitioners about drugs.
- Pharmaceutical companies sell loss leaders to hospitals for the treatment of chronic diseases, expecting a return on investment in the community in the long term.

WHAT THIS PAPER ADDS

- This paper is the first to test and quantify the extent of the influence of hospital consumption of nine competitive pharmacological classes on the ambulatory care market on a national scale.
- The influence strongly varied according to the class of drugs. It was maximal for the studied cardiovascular classes (ACEIs, ARBs and statins).

AIM

To investigate the influence of hospital drug choices on pharmaceutical consumption for nine competitive classes in the surrounding community.

METHODS

Ecological study. Data from the national survey on drugs in hospitals were used to extract quantities purchased by 25 French university hospitals for three 'hospital classes' (EPOs, LMWHs and setrons) and six 'ambulatory classes' (PPIs, ACEIs and ARBs, statins, α -adrenoreceptor antagonists (AAAs) and selective serotonin re-uptake inhibitors SSRIs). Re-imbursed quantities for patients living in the hospital's catchment area were extracted from the national health insurance database. The relationship between the use of a brand in hospitals and their catchment areas was assessed using multivariate linear regressions with instrumental variables.

RESULTS

An increase of 1 day of treatment with one brand in the hospital was associated with a significant increase of 2.8 days of treatment with the same brand in the catchment area. However, results strongly varied according to classes. An increase of 1 day of treatment in the hospital was significantly associated with an increase of 0.21 day for 'hospital classes' and 21.8 days for 'ambulatory classes' in the catchment area. Strong variations were seen across 'ambulatory classes'. The effect was maximal for cardiovascular classes and not significant for AAAs and SSRIs. The size of the effect also varied with hospital characteristics: small and proximity university hospitals exerted the greatest influence.

CONCLUSIONS

Hospital consumption influences the use of drugs in the community. A significant effect was found, especially for competitive classes used on a long-term basis. The economic consequences of these findings need to be addressed.

Introduction

Microscopic studies have shown that specialists, in particular hospitalists, influence the prescribing behaviour of general practitioners (GP), directly by initiating treatments or indirectly by informing GPs about drugs [1–11]. Hospitalization of patients is also the occasion to take stock of their drug regimen and very frequently results in changes in medications [12–21]. However, some modifications are not clinically motivated and are only made to match the hospital formulary.

Drug availability and pricing mechanisms differ between the hospitals and the ambulatory care setting in France (Table 1). In France, pharmaceutical companies make great efforts to have their products included in the formulary by the hospitals. In particular, manufacturers of brand name drugs faced with competition dramatically reduce their prices. Thus, for long term conditions and competitive classes (such as antihypertensive drugs), the drugs selected in the hospital formularies are usually brand name drugs and are not the cheapest equivalents available on the ambulatory care market [22]. Pharmaceutical companies expect a return on investment on their product sales in the community in the long term. This strategy is likely to be associated with extra costs for insurers or society (in case of public insurance) that cover drug use in the community.

Little is known about the consequences at the macro level of the hospitals' influence on drug use in the community. Few studies are available and those that are only focused on a few drugs in a limited geographical area. Pryce and colleagues [23] reported the influence of a single hospital on the increase in glyceryl trinitrate prescriptions in the catchment area of the hospital in Great Britain. A recent Canadian paper has shown that the vast majority of patients continued the medication initiated for their chronic condition during hospitalization. It also reported the potential savings in Ontario if discharged patients were using the cheapest equivalent considering outpatient formulary prices for three classes [24].

The aim of our study was to quantify the influence of hospital use of drugs on the pharmaceutical consumption

in its surrounding community for nine competitive pharmacological classes in France.

Methods

We conducted an ecological study linking the consumption of drugs in university hospitals with pharmaceutical use in the surrounding community in 2008 in France.

Data

Classes Nine pharmacological classes were chosen because of their high level of competition (Table 2) and were divided into two groups according to the share between their hospital and ambulatory markets: 1) 'hospital classes': serotonin antagonists (setrons), low molecular weight heparins (LMWH), erythropoietins (EPO) and 2) 'ambulatory classes': proton pump inhibitors (PPI), angiotensin converting enzyme antagonists (ACE inhibitors), angiotensin receptor blockers (ARB), HMG-CoA reductase inhibitors (statins), α -adrenoreceptor antagonists (AAAs) used in benign prostatic hyperplasia and selective serotonin re-uptake inhibitors (SSRIs). Little or no influence was expected for the 'hospital classes' while the effect was thought to be paramount for the 'ambulatory classes'.

Hospital use Purchased quantities in 2008 for 25 of the 27 metropolitan French university hospitals were extracted from the national survey on drugs in hospitals (Direction de la recherche des études, de l'évaluation et des statistiques DREES). One hospital did not entirely complete the survey (Marseilles) and one was excluded because of its very particular characteristics (Paris, whose university hospital is located in 37 different sites and has more than 800 000 inpatient hospitalizations vs. 100 000 on average in the other university hospitals).

Community use Re-imbursed quantities in 2008 for prescriptions issued by non-hospital doctors and filled by patients living in the hospital's 'département' (French territorial division) and catchment area (Figure 1) were

Table 1

Comparison of pharmaceutical policies between ambulatory care and hospital settings

	Ambulatory care setting	Hospital setting
Drug availability	All drugs with market authorization unless their use is restricted to hospitals	All drugs with market authorization. In practice, only the drugs listed in the hospital formulary
Drug formulary	None	Each hospital draws its formulary, more or less restrictive
Substitution	Only from brand name products to their generic equivalents by pharmacists without physician's permission	Within the pharmacological or therapeutic class to match the formulary
Drug price	Nationally set	Varies by hospital

Table 2
Competition and price variations for the selected pharmacological classes in 2008

Drug classes	Available entities	Available brands	Price for 1DDD in the university hospitals			Price for 1DDD in the ambulatory care setting		
	<i>n</i>	<i>n</i>	Minimum	Median	Maximum	Minimum	Median	Maximum
Hospital classes								
Setrons	3	11	0	2.92	17.91	1.59	17.17	37.73
LMWHs	4	4	0	0.66	3.5	2.09	3.36	4.73
EPOs	5	5	4.37	6.71	8.51	6.72	9.33	11.45
Ambulatory classes								
PPIs	5	10	0	0	6.21	0.62	1.32	8.87
ACE inhibitors	13	27	0	0.05	0.53	0.08	0.36	1.19
ARBs	7	12	0	0	0.80	0.02	0.45	1.35
Statins	5	14	0	0	1.26	0.19	0.76	3.03
AAAs	4	12	0.01	0.03	0.65	0.20	0.59	1.13
SSRIs	6	12	0	0.16	0.55	0.34	0.55	1.11

AAAs: α -adrenoreceptor antagonists, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers, DDD: defined daily dose, EPO: erythropoietins, LMWHs: low weight molecular heparins, PPIs: proton pump inhibitors, SSRIs: selective serotonin re-uptake inhibitors.

Figure 1
Geographic areas used for defining the community: 'département' (A) and catchment area (B). Each black circle symbolizes a university hospital. Départements belonging to the same catchment area are indicated using the same colour. White departments belong to the excluded hospitals' catchment areas (Paris and Marseilles)

extracted from the national health insurance database (90% of the population). The 'département' was the smallest geographical unit at our disposal. The hospital's catchment area was constituted by the merging of departments whose inhabitants preferentially attended that hospital in 2008.

Measures Quantities consumed for each brand were expressed in defined daily doses (DDD) and converted per 1000 inhabitants-day (DID). DDD is the assumed average

maintenance dose per day for a drug used for its main indication in adults [25]. Thus, one DDD represents 1 day of treatment on average. It allows standardizing the consumption of different drugs whatever their differences in the mean prescribed daily dose.

Pharmaceutical consumptions were collected at the brand level. The brand consisted in grouping together the various strengths and presentations of the same brand of a drug entity. In the case of generic drugs, we grouped all the available generics into one brand (regardless of the

Table 3

Effect of hospital use on pharmaceutical consumption in the community

	Département				Catchment area			
	b	SE	t	P	b	SE	t	P
Hospital classes	0.13	0.03	4.41	<10 ⁻⁴	0.21	0.05	4.41	<10 ⁻⁴
Ambulatory classes	13.64	2.56	5.33	<10 ⁻⁴	21.81	3.95	5.53	<10 ⁻⁴

b: estimation of the parameter, SE: standard error of the parameter, t: t-statistic, P: t-statistic probability.

pharmaceutical company, strength or presentation). That brand was different from the brand name equivalents.

Analysis

The relationship between consumption in the hospital and in the community, at the level of the drug brand, was assessed using multivariate linear regression models. As community use is also likely to influence hospital use, we needed to account for simultaneous causality using a multivariate two-stage least squares model with instrumental variables.

Instrumental variables We identified the selectivity of hospital (percentage of brands selected in the class) and a price ratio (price of brand divided by the mean price of other brands from the same class in the hospital) as valid instrumental variables for hospital quantities. A valid instrument must be uncorrelated with the error term of our model or exogenous. This condition may be tested with a Sargan test [26]. Our instruments matched that condition, with a Sargan test *P* value of 0.82. Second, a valid instrument must be relevant, i.e. significantly and sufficiently correlated with the hospital quantities. This was checked by regressing the hospital quantities on our instruments and all other exogenous covariates using a linear regression. Our instruments were significantly (joint test, $P < 10^{-4}$) and strongly associated with hospital quantities (F statistic = 52, F statistic above 10 being commonly viewed as the threshold [26]).

Covariates Characteristics of drugs (pharmacological class, generic alternatives available [27]), of hospitals (size, activity, geographical competition [28]) and of geographical areas (percentage of inhabitants suffering from at least one chronic disease [29]) were used as covariates. We classified hospitals into three groups according to a previously published typology [30]: 1) 'state-of-the-art' hospitals located in ageing communities where hospital supply is scarce, 2) 'state-of-the-art' hospitals located in dynamic and competitive areas and 3) 'proximity' hospitals (i.e. a high part of their activity is dedicated to non-specialized care) located in competitive areas. Originally, other covariates were used as well, but were found to be insignificant at a 5% threshold: percentage of inhabitants over 65 years of age, percentage of inhabitants with low income, density

of physicians, and density of public and private hospitals [29]. We used a manual backward method, controlling for confounding at each step, to select variables with a 5% significant threshold. Additionally, interactions between the selected variables were tested.

Analyses We built separate models for the geographic scales ('département' or catchment area) and for the 'hospital' or 'ambulatory' pharmacological classes. In exploratory analyses, we tested whether the effect remained constant among pharmacological classes and hospitals by adding interaction terms between these variables and hospital quantities in the models. Statistical analyses were performed with SAS® software version 9.1 (SAS institute, Cary, NC, USA).

Results

Data regarding the selection of drugs by university hospitals for these nine classes have been presented elsewhere [22]. Table 2 presents a brief overview of the competition within the studied classes and of price variations. For five classes, drugs were free or almost free in hospitals. Large variations existed between the cheapest and most expensive alternatives available in the ambulatory care setting. For instance, for cardiovascular classes, the most expensive drugs cost 15 times more than the cheapest options.

Crude correlations Overall, a significant positive correlation existed between quantities of each brand consumed in the hospital and in the surrounding community (Spearman rank correlation coefficient $r = 0.41$, $P < 10^{-4}$). Correlation coefficients were significant and above 0.47 for six out of the nine classes. The strongest correlation was seen for LMWHs with $r = 0.79$ ($P < 10^{-4}$).

Multivariate models An increase of 1 day of treatment with brand *i* in the hospital was associated with a significant increase of 1.5 and 2.8 days of treatment respectively with the same brand *i* in the 'département' and the catchment area of the university hospital.

The hospital-community influence was significant even for the 'hospital classes' (Table 3) where brands selected in the hospital were preferentially prescribed in the commu-

Table 4

Effect of hospital use on pharmaceutical consumption in the community according to classes

Ambulatory classes	b	Catchment area		
		SE	t	P
PPIs	13.75	7.04	1.95	0.051
ACE inhibitors	51.76	9.66	5.36	<10 ⁻⁴
ARBs	33.51	15.11	2.22	0.027
Statins	28.09	5.05	5.56	<10 ⁻⁴
AAAs	8.03	17.49	0.46	0.646
SSRIs	17.90	22.04	0.81	0.417

b: estimation of the parameter, SE: standard error of the parameter, t: t-statistic, P: t-statistic probability. AAAs: α -adrenoreceptor antagonists, ACE: angiotensin converting enzyme, ARBs: angiotensin receptor blockers, PPIs: proton pump inhibitors, SSRIs: selective serotonin re-uptake inhibitors.

nity, but close to 0 as the essential part of their market is in the hospital.

The effect was much more marked in 'ambulatory classes' (Table 3): an increase of 1 day of treatment in the hospital was associated with increases of respectively 14 and 22 days of treatment in the département and the catchment area.

This average effect also varied with drug groups for the 'ambulatory classes' (Table 4). It was positive for all classes but did not reach statistical significance for AAAs and SSRIs. The effect was particularly strong and significant for the three cardiovascular classes: statins, ARBs and ACE inhibitors.

The hospital-community effect was greater for the 'proximity' university hospitals. In addition, a negative insignificant trend was seen in relation to the hospital activity and influence on the community: the smaller the hospitals, the greater the influence on the community.

Discussion

Our study has three main findings. Firstly, for the nine studied classes, we observed an overall positive influence of hospital use of drugs on the community (on both scales). Secondly, this influence varied according to the class of drugs. It was weak but significant for hospital classes and more pronounced for 'ambulatory classes'. Among 'ambulatory classes', the magnitude of the effect varied strongly by class with the strongest influences for cardiovascular classes. Lastly, the level of influence varied according to the hospitals' characteristics and was greater for small and proximity hospitals.

Out of all the studied classes, the strongest effects were seen for the three cardiovascular classes (ACE inhibitors, ARBs and statins) that are used in the long term treatment of the most frequent diseases. For an average stay of 7 days in the university hospital, initiation or switch to ACE inhibi-

tor *i* would result in an increase of 1 year of treatment with the same brand *i* for the patient in the community. For ARBs and statins, the increase in the community would be approximately 200 days of treatment. In fact, this increase may be shared between different patients as GPs may adopt the use of a product initially prescribed for another patient.

The effects were positive, but not statistically significant for AAAs and SSRIs, which may be explained by the fact that nearly all hospitals selected the same AAA (alfuzosin) and nearly all selected all the SSRIs available. It is thus likely that we lacked power to detect a positive impact. Also, these drugs are commonly initiated by GPs who may rely on their personal preferences.

Small and proximity hospitals were exerting the greatest influence on the drug use in their surrounding community. In these settings, hospitalists and GPs may have closer relationships, as well as a higher proportion of people living around the hospital may indeed have been hospitalized or referred to that hospital. Thus, one can wonder how the influence of university hospitals compares with the influence of local hospitals.

The use of instrumental variables techniques allowed us to account for simultaneous causality. Naïve models using ordinary least squares models resulted in overestimating the effect of the hospital [data not shown].

Yet the effect on the community market in our study is certainly underestimated. Firstly, numerous unobserved factors also influence community use. Among them, the most important may be the influence of pharmaceutical representatives, prescribing habits of other hospital doctors (working in other types of hospitals), prescribing habits of other specialists, etc. We were unable to adjust our analyses for these factors.

Secondly, only the brand dispensed in the community was recorded in the database. The hospitals tend to select and consume few generic drugs in France [22], while their penetration rate is high in the community (because of pharmacists' substitution) [31]. Hence, the hospital use of a brand name drug and the community use of its generic equivalent are not considered as the use of the same drug at the brand level. Analyses at the drug entity (molecule) level would have shown a stronger influence of hospitals.

Lastly, prescriptions from hospital doctors (i.e. at discharge, outpatient visits or emergency room prescriptions) and dispensed in a community pharmacy are excluded from our measure of community use. Therefore, we only measured the indirect influence of hospitals on community use and are conservative in the size of the influence we report.

This is the first published study assessing the influence of hospital consumption of drugs on GPs' prescriptions on a national scale. Our results confirm what was anticipated following observation of pharmaceutical companies' behaviour and experts' statements [32]. Promotional actions targeting the hospital are good investments for the

companies as they consecutively influence GPs' behaviour. On the other hand, insurers may face extra costs for re-imbursing quite expensive drugs in the long term in the community. For instance, French university hospitals chose mainly to use some of the most expensive drugs in the community market for the classes of ACE inhibitors and statins (respectively brand name perindopril and atorvastatin).

In conclusion, hospital consumption influences community use of drugs and *vice versa*. A significant effect of the hospital on the community was found, especially for competitive classes used on a long term basis. This is in line with pharmaceutical companies' strategies to get their products selected by hospitals. This influence is likely to be associated with extra cost for insurers in the long run in the community.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare this study was funded by the French Department of Health (Direction de la recherche, des études, de l'évaluation et des statistiques DREES, ministères chargés de la santé, des solidarités et des comptes publics, France) and the University Hospital of Toulouse, Toulouse, France. The sponsor provided data and was actively involved. One of the DREES employee is a co-author of the manuscript. The authors declare no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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