Master of Public Health

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Off-Label Prescribing in French Oncology Patients: A Multilevel Observational Study of Hospital Variation in *Liste en sus* Medications Using 2023 PMSI Data

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List of Acronyms

- AMM - Autorisation de Mise sur le Marché
- ANSM - L'Agence Nationale de Sécurité du Médicament et des produits de santé
- ATIH - Agence Technique de l'Information sur l'Hospitalisation
- CAQES - Le Contrat d'Amélioration de la Qualité et de l'Efficience des Soin
- CCI – Charlson Comorbidity Index
- CI – Confidence Interval
- CH - Centre Hospitalier
- CHR - Centre Hospitalier Régional
- CHU- Centre Hospitalier Universitaire
- CLCC – Centre de Lutte Contre le Cancer
- CNS – Central Nervous System
- DRG- Diagnosis Related Groups
- ICC – Intra Class Coefficient
- ICD 10 - International Classification of Diseases 10th Revision
- IRDES - Institut de Recherche et Documentation en Economie de la Santé
- LES – Listee En Sus
- MOR – Median Odds Ratio
- PL – Privé à but Lucratif
- PMSI - Programme de Médicalisation des Systèmes d'Information
- PNL – Privé Non Lucratif
- PTT - Protocole Thérapeutique Temporaire
- RTU - Recommandation Temporaire d'Utilisation
- SAE - Statistique annuelle des établissements de santé
- TR - Tarif de Responsabilité

Abstract

Background

Off-label prescribing is commonly seen in cancer patients. Progressive diminishing of regulations around off-label prescribing on the liste en sus in France may contribute to higher rates of off-label prescribing. Though often warranted, inappropriate off-label use of medications can result in worse patient outcomes and higher healthcare spending.

Objectives

In the context of rising costs of medications on the liste en sus, we wished to identify patient and hospital level factors predisposing to off label prescribing in cancer patients, and explore variation in healthcare facilities across the country.

Methods

We used 2023 PMSI hospital prescribing data to analyse off label prescribing trends in 1543716 hospital admissions across France. Using R we assessed association of patient level factors, initially with bivariate analysis with Chi square/Wilcoxon rank sum tests and subsequently using a generalised linear model. We then used a multilevel logistic model to explore patient and facility level factors and variation across hospitals.

Results

Lower patient age and female sex were associated with off-label prescribing. Admissions with CNS cancers had 107 times the odds of off-label prescribing compared to those with respiratory cancers. Different probability of off-label prescribing was seen across different types of healthcare facilities, with teaching hospitals and cancer centres being more likely to have off label prescribing than general hospitals. When accounting for patient and facility level characteristics, we noted persistent variation in off-label prescribing practices between different hospitals.

Conclusions

There appears to be significant variation in off-label prescribing practices in cancer across hospitals in France, which may be due to unmeasured factors such as hospital culture. Unwarranted variability in care is associated with poorer patient level, economic and environmental outcomes. These results warrant further investigation in order to guide future policy to improve prescribing practices.

Introduction

The liste en sus

In France, as in many other countries which finance hospitals via diagnosis-related group (DRG) payments, the costs of some innovative and expensive drugs are paid separately, with the intention of supporting equal access to innovation.(1) In 2005, a list was set up at the national level (*liste en sus*) to define expensive medications to be reimbursed retrospectively (out of DRG payment) based on a maximum standard price. Total expenditure on these drugs tripled between 2007 and 2022, reaching €6 billion in 2022. (2) The same year, over 80% of the costs of medications administered to hospitalised patients are financed outside of DRG payments. (3)

Overall, the cost of medications on the liste en sus (LES) represent 18% of the total medication spending covered by the national health insurance, and this spending has increased annually by 10-20% since 2019, with the public and not-for-profit private sectors representing 85% of this spending. (2,3) This significant growth is concerning as, within a fixed sectorial budget, these costs come at the detriment of other expenses. Several issues regarding the regulatory measures of the LES have been flagged- the list is considered stagnant, with very few drugs having been dropped from the list in the past 20 years (4) and the degree of innovation of some medications has been called into question (5). Moreover, the combination of two levels of price negotiation has been challenged. Prices are negotiated at a national level through the setting of Tarifs de Responsabilité (TRs), which are reimbursement caps set by national health insurance, and at a local level through direct negotiations between hospitals and pharmaceutical companies. Though TRs are not official prices, they often become the de facto price ceiling, which can discourage hospitals from negotiating lower local prices. Consequently, this can limit competition and reduce incentives to negotiate, and can ultimately allow suppliers to capture the savings originally intended for the health system. (6)

Finally, and most significantly, the question of the appropriateness of prescriptions has been raised.

Appropriate prescribing:

Appropriate care refers to the degree to which provided healthcare is relevant to the medical needs of the patient given the current best evidence, and requires that health benefits of a procedure or medication exceed any associated risks. (7) Appropriateness of care is a pertinent issue in France as well as worldwide, since inappropriate care offers no benefit to

patients, may cause harm, and consumes valuable healthcare resources. (8,9) Reducing so-called low-value care is essential for enhancing the quality of healthcare, while ensuring the sustainability of the health system. (10) Medication appropriateness is an important facet within appropriateness of care and broadly means whether each patient receives the correct medication at the correct dose and administration for the correct indication.(11) Inappropriate prescribing has a significant prevalence, with a quarter of French community dwelling older people estimated to have an inappropriate prescription. (12)

Inappropriate prescribing can have a significant clinical impact on patients: the IATROSTAT report estimates a 136% rise in hospital admission related to adverse drug events between 2007 and 2018.(13) As well as the issue of patient safety, inappropriate prescribing can lead to significantly increased healthcare costs.(14)

Appropriate prescribing has been investigated in other studies in France and elsewhere by the development of indicators of appropriateness, such as in the case of oral anticoagulants (15) and psychotropics.(16)

Off-label prescribing:

A significant factor involved in the assessment of appropriateness of prescriptions of medications is the issue of off-label prescribing. Off-label (or hors AMM in France, that is outside of the marketing authorisation) prescribing refers to prescribing of medications that is outside the principal conditions for use approved by marketing authorisation (e.g. clinical indication, patient population, dose, route of administration). (17)

Off-label prescribing is not necessarily inappropriate prescribing. It can be warranted in certain cases, for example in certain populations such as older people, or in rarer diseases where clinical trials may not be feasible. Often there is good evidence to support the use of off-label prescribing, and this use is well accepted. (18,19)

It is relatively common in cancer treatment. In the US, a 2024 analysis of real-world data of cancer patients found that 18.6% of patients had received one line of off-label cancer medication, with prevalence being higher among younger patients, patients with worse performance status and those treated in academic centres. (20) Frequency is also reported to vary according to cancer site and stage of disease. (21) Additionally, it is seen more commonly in cancer medications with narrow indications but with a broad spectrum of activity. (21)

However, off-label prescribing can be come with a risk to patient safety- the use of medications outside of trialled use means that the full risk-benefit ratio is not completely understood. Off-label prescribing has been demonstrated to be associated with adverse drug events (22), and can result in negative outcomes without clinical benefit.

While off-label prescribing can often be considered acceptable where there is sufficient evidence to support its use, there exists significant concern where off-label use occurs in the absence of scientific support. In 2002, a panel of external experts analysed evidence for 124 off-label prescriptions in cancer patients in France and deemed only 62% of these to be justified. (23)

Off-label prescribing on the LES.

Off-label prescribing of the medications on the LES has been permitted since its creation in 2005. It has been obligatory to code the prescribing indications for these medications since 2019. From this data we know that off-label prescriptions represent an average of 19% of the prescriptions of these medications and 15% of spending.(23)

The regulation of this off-label prescriptions on the LES has progressively weakened over recent years.

Between 2005 and 2015, off-label prescribing on the LES was subject to regulation by way of temporary treatment protocols (PTT) determined by the national agency of medication safety (l'ANSM). These were then removed at the end of 2015 due to the introduction temporary recommendations of use (RTU). These recommendations however were not plentiful and did not cover the breadth of indications of their predecessors, leaving French healthcare facilities without national guidance for certain off label indications.(24)

Second, modifications of care quality contracts (CAQES) in certain healthcare facilities shifted the focus of hospitals to prescriptions delivered in community settings.(25) Moreover, from 2022 the national indicators for good use of medications on the LES disappeared, along with the possibility of financial sanctions for healthcare facilities, which would reduce reimbursement rates for facilities not respecting the terms set out in the contract.(26)

Variation in medical practice

Given this progressive weakening in regulation of off label prescribing on the LES over previous years, including the lack of good practice guidelines for healthcare facilities and the disappearance of financial incentives, we postulated that there is likely to be variation in off-label prescribing across healthcare facilities in France, at a potential detriment to both healthcare costs and to patient outcomes.

Variation in care in different settings is known to exist in France. (27) While a certain degree of clinical variation is expected and some is appropriate(28), unwarranted or inappropriate clinical variation can worsen patient outcomes, increase healthcare costs, and increase healthcare waste.(29,30)

Objective of the research

This project aims to identify potential variation in off-label prescribing amongst healthcare facilities in France and estimate the impact of patient and hospital level factors determining the variations in off-label prescriptions.

We concentrated on a subset of 2023 cancer related hospital admission/stays and aimed to identify predisposing factors to this off-label prescribing.

We hypothesised that there was likely to be clustering at a hospital level with regard to prescribing practices.

The ultimate objective of this project is to work towards improving appropriateness of prescribing and consequently quality of care while optimising healthcare spending.

This work was carried out as part of a larger project on appropriate care at IRDES, using different medication databases to generate different indicators of prescribing. It was complementary to my internship at IRDES in 2023-2024, where with my supervisors I carried out a scoping review on deprescribing interventions. My role as intern has been carrying out a literature review, data management and data analysis of 3 different databases encompassing hospital and community prescribing, under the guidance of and with the support of my supervisors.

Methodology

Data source

For the purposes of our analysis, we used 2023 French PMSI hospital prescribing data for all medications prescribed on the LES, throughout France. We excluded observations pertaining to overseas departments in France as it was felt that differing practices would limit comparability.

Data was accessed securely through l'Agence technique de l'information sur l'hospitalisation (ATIH). Data was accessed and tables were merged in SAS. Exploration and analysis of data was performed in R.

We used PMSI data to access data relative to medications financed on the LES and data about the associated hospital admissions/visits. Data regarding healthcare facility level characteristics was accessed by the annual statistics of facilities (SAE).

Tables used to compile full dataset were as follows:

- VALO_DGF
- VALO_OQN
- DIAG_2023
- MCO_2023
- CANCERO_2023

The initial dataset therefore included all prescriptions for medications on the LES in 2023. Each observation in the initial dataset represented a LES medication prescribed to a patient in a specific hospital admission. The initial dataset was cleaned to ensure no duplicate observations for each medication and indication pair per admission/ visit which could skew analysis.

The dataset was then aggregated to admission/stay level to facilitate statistical analysis as we wished to explore clustering at the hospital level while retaining as much granularity as possible.

Each admission/visit stay was specific to one patient. There was no patient identifying data, with each patient being classified in the database by an anonymised code classified as "ident". There were no ethical concerns.

The initial dataset, comprising of all hospital admissions/visits pertaining to prescription of LES medications, was then sub-setted to include only cancer admissions/visits. We achieved this by including only hospital admissions/visits whose principal or first linked diagnosis were a cancer diagnosis- that is, pertaining to a malignant neoplasm as per the International Classification of Diseases, 10th version (ICD-10) code.(31)
As adult and paediatric cancers differ significantly in prevalence and in treatment,(32) we included only adult patients (that is, patients of age 18 or over).

Some observations had missing data in relation to hospital site and Charlson Comorbidity Index. Given the relatively low proportion of observations missing these data and the categorical nature of this data we did not impute any values for this missing data.

Variables

Dependent variable:

The indication for each medication prescribed was available in our dataset. Off label (hors AMM) prescriptions were indicated by the code I999999. This permitted us to generate a binary variable for prescriptions – off-label or not.
Once data was aggregated at an admission level, we then created a binary outcome variable "any_offlabel" which demonstrated whether any medication was prescribed off-label during the hospital admission/visit.
Additionally, we created a variable totalling the number of off-label prescriptions per admission/ visit using the original off-label variable which was used for descriptive statistics.

Independent variables:

Variables of interest relevant to appropriate prescribing in cancer were identified following review of the literature.
For our analysis we wished to consider the effect of clustering by hospital level, and as such covariates can be considered as level 1 (i.e. patient level) and level 2 (hospital level).

Patient level (level 1 covariates):

- Patient age at time of prescription, in years (continuous). As indicated previously we only included admissions/visits for patients 18 years of age or older.

- Patient sex

- Charlson Comorbidity Index (CCI) – this is a weighted score generated from a defined list of patient's concurrent medical conditions which is commonly used as a prognostic indicator in certain diseases.(33) A higher score represents more medical comorbidities and predicts higher mortality. In the most recent adjusted CCI, conditions are assigned a score of 1, 2, 3 or 6 according to their impact on mortality. Non metastatic tumours (excluding some skin cancers), lymphoma and leukaemia correspond to 2 points on the index. We used the comorbidity package in R(34) to generate the adjusted CCI for each hospital admission/visit using the principal and linked diagnoses associated with each hospital admission. As the score is weighted, it was deemed not appropriate for use as a continuous variable. Given that the vast majority participants would have a score of at least 2 and after assessing the distribution, we categorised this variable as a factor with 2 levels- score of less than or equal to 2, and greater than 2.

- Cancer primary- site of cancer primary was identified for each patient using the ICD-10 codes provided for their principal and linked diagnosis. For use in our analysis, we sub-categorised these diagnoses these in terms of broad anatomical sites, as categorised in the ICD-10, to balance clinical relevance and ensure sufficient power for meaningful analysis. Cancer sites of low prevalence in our dataset and of similar distribution with regard to off-label prescribing were grouped into an "other" category to maintain statistical power. We used respiratory/intrathoracic malignancy as a reference category, with lung cancer being the second and third most prevalent cancer amongst men and women respectively in 2022(35), and with this cancer site having similar rates of off-label prescribing in our dataset as compared to our whole dataset.

- Metastatic disease- we used ICD-10 diagnosis codes to create a binary variable to signify the presence of metastatic disease or not, as indicated by the principal or linked diagnosis for the hospital admission/visit.

- Medication prescribed- in the initial dataset we had detailed information regarding each medication prescribed. When aggregating data at the admission level we created binary variables for each ATC2 class present in the dataset.

Facility level:

- Finess code of each establishment

- Hospital legal status – each facility's legal status was present in the database. We then grouped these categories into a categorical variable with 5 levels, namely university hospitals/regional hospitals (CHU/CHR), general hospitals (CH), cancer centres (for profit private- CLCC) other non-profit private hospitals (PNL) and for-profit private hospitals (PNL). Hospitals with similar profiles were grouped to balance relevance and ensure sufficient observation for analysis. We excluded army hospitals from analysis due to their distinct structure and patient population, limiting comparability to a more general civilian population.

- Location of healthcare facility- for the purposes of our analysis we described location at regional and departmental level

- Oncology activity- using the SAE cancer database we created a variable demonstrating annual chemotherapy sessions for each healthcare facility. We then categorised this into a 4-level factor variable. This information served as a proxy for oncology activity for each healthcare facility.

- Facility size- we created a variable with the total beds and day-based medical care spots for each facility. We then categorised this variable into a 4-level factor variable.

Empirical strategy

Descriptive and bivariate analysis

Continuous variables were summarised by median and interquartile range, due to non-normality of distribution. Between group differences were tested for using the Wilcoxon rank-sum test. Categorical variables were summarised by counts and proportions and between group differences were assessed using Chi-squared test. A cut-off p value of 0.05 was accepted for statistical significance.

Off-label prescribing data was aggregated at a department level to present a proportion of hospital admissions/ visits with an off-label prescription per each department, presented in a choropleth map generated using R.

Multivariate analysis

In our analysis we wished to explore factors relating to off-label prescribing while accounting for clustering at the hospital level.
Due to convergence issues when fitting the multilevel model, we employed a dual analytic strategy.

Firstly, we fitted a full generalised linear model with all patient covariates to estimate overall associations, here without accounting for clustering at hospital level. This was carried out on our full dataset.

Secondly, we fitted a simplified multilevel logistic model with fewer patient covariates which allowed for full convergence. As sensitivity analysis we performed a generalised linear model with only these covariates to compare estimates.

Generalised Linear Model

We used a generalised linear model (GLM) with a binomial distribution and logit link function to assess associations between patient-level covariates and the outcome of interest.
Covariates were selected based on clinical relevance and support from the literature: patient age, sex, site of cancer primary, presence of metastatic disease, and Charlson Comorbidity Index (CCI).
We initially performed bivariate analysis between each covariate and the outcome to confirm the presence of an association. Given clinically significant differences in treatment patterns and outcomes across some cancer primary sites by sex, we tested for effect modification between sex and site of cancer primary. This interaction was statistically significant and therefore the final model was stratified by sex.
Model selection was carried out using stepwise selection based on Akaike Information Criterion (AIC). The final model included age, sex, site of cancer primary, with an interaction term between sex and site of cancer primary, metastatic disease, and CCI.
Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

$$\log\left(\frac{Y}{1-Y}\right) = \beta_0 + \beta_1 \cdot \text{Age} + \beta_2 \cdot \text{Sex} + \sum_{j=1}^{7} \beta_{2+j} \cdot \text{CancerSite}_j + \beta_{10} \cdot \text{Metastasis} + \beta_{11} \cdot \text{CCI} + \sum_{j=1}^{7} \beta_{11+j} \cdot (\text{Sex} \times \text{CancerSite}_j)$$

Multilevel Logistic Model

To explore the potential impact of hospital-level clustering, we developed a multilevel logistic regression model using the lme4 R package (36) with a random intercept for each hospital. This approach allowed us to account for both patient-level and hospital-level variables.

We initially created a null model, with random intercept for hospitals only. We then created a model with level 1 covariates only, and subsequently included level 2 covariates in the full model. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

The full multilevel model included:

- Level 1 covariates: centred patient age, patient sex, and CCI.
- Level 2 covariate: legal status of the hospital.
- Random intercept for hospital

$$\text{logit}\left(\Pr(Y_{ij}=1)\right) = \beta_0 + \beta_1 \cdot \text{Age}_{ij} + \beta_2 \cdot \text{Sex}_{ij} + \beta_3 \cdot \text{CCI}_{ij} + \beta_4 \cdot \text{LegalStatus}_j + u_j$$

$$u_j \sim \mathcal{N}(0, \sigma_u^2)$$

Site of primary cancer and metastatic disease were excluded from the final multilevel model due to data sparsity within hospitals, which affected model convergence and stability.

A further analysis was performed on a subset of the data restricted to larger/teaching hospitals and cancer centres, to explore variation in off-label prescribing within these types of institutions. In this subset, site of primary cancer was included.

As previous, we initially carried out a null model, with random intercept for hospitals, then a model with level 1 covariates only, then the full model. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported.

The full model for this subset included

- Level 1 covariates: centred patient age, patient sex, site of cancer primary and CCI.
- Level 2 covariate: legal status of the hospital
- Random intercept for hospital

$$\text{logit}\left(P(Y_{ij}=1)\right) = \beta_0 + \beta_1 \text{Age}_{ij} + \beta_2 \text{Sex}_{ij} + \sum_{l=1}^{2} \delta_l \text{CCI}_{ijl} + \sum_{k=1}^{7} \gamma_k \text{CancerSite}_{ijk} + \beta_3 \text{LegalStatus}_j + u_j$$

For all multilevel models we calculated the intraclass correlation coefficient (ICC) and the median odds ratio (MOR), using the following parameters(37):

- σu^2: the variance of the random intercept (i.e., between-hospital variance),
- $\pi^2/3 \approx 3.29$: the fixed level 1 residual variance for logistic models,
- 0.6745: the median of the absolute value of a standard normal distribution.

Where $ICC = \sigma u^2 / (\sigma u^2 + \pi^2/3)$ and $MOR = \exp(\sqrt{(2 \times \sigma_u^2)} \times 0.67$

Results

The final sample consisted of 1543716 cancer- related hospital admissions or sessions, corresponding to a total of 203,219 patients, across 581 different healthcare facilities in Metropolitan France. Hospital admissions/visits with off label prescribing represented 19% of the total sample. Admissions with off-label prescribing differed from those without across all assessed categories with significant results from Chi square testing.

Patient Characteristics

Table 1: Patient Characteristics

Overall admissions/visits n (%) median [IQR]			**Off label prescribing?**		**p value**
			No n (%) median [IQR]	**Yes n (%) median [IQR]**	
Total	**1543716**		1250757 (81)	292 959 (19)	
Age		68 [59,75]	68 [60,75]	67 [58,74]	<0.001[1]
Sex	Male	781342 (51)	626300 (80)	155042 (20)	<0.001[2]
	Female	762374 (49)	624457 (82)	137917 (18)	
Charlson Index	0-2	955549 (62)	759792 (80)	195757(20)	<0.001[2]
	> 2	385589 (25)	324795 (84)	60794 (16)	
	Unknown	202578 (13)	166170 (82)	36408 (18)	
Cancer primary	Haematological	384971 (25)	291595 (76)	93376 (24)	<0.001[2]
	Breast	243461 (16)	208472 (86)	34989 (14)	
	CNS	26163 (2)	1063 (4)	25100 (96)	
	Digestive tract	263643 (18)	213202 (81)	50441 (19)	
	Urinary	87038 (6)	82068 (94)	4970 (6)	
	Respiratory/ intrathoracic	301611 (20)	254332 (84)	47279 (16)	
	Skin	56626 (4)	46549 (82)	10077 (18)	
	Oral	53282 (3)	48330 (91)	4952 (9)	
	Other	57944 (4)	105146 (83)	21775 (17)	
Metastatic	Yes	34490 (2)	28630 (83)	5860 (17)	<0.001[2]
	No	1509226 (98)	1222127 (81)	287 099 (19)	

[1]Wilcoxon rank sum test; [2]Chisquared test

Table 1 demonstrates patient characteristics across the total sample of admissions:
51% of admissions were of male patients and 49% concerned female patients.
20% of admissions concerning men had off label prescribing, compared to 18% of admissions involving women.

The median age of patients included in the analysis was 68 years with an interquartile range of 59-75. Median age in admissions/ visits with off-label prescribing was 67 versus 68 in those without, with a significant p value from Wilcoxon rank sum testing.

Most admissions concerned patients with a Charlson Comorbidity Index (CCI) two or less, with 62% of admissions. 25% of admissions involved patients with a CCI of greater than two, while 13% were unknown. 20% of admissions involving patients with a CCI of two or less had off-label prescribing compared to 16% of admissions involving patients with a CCI of greater than two.

In terms of the cancer primary, a quarter of admissions had a diagnosis of cancer of lymphoid, hematopoietic and related tissue, and a fifth concerned cancer of respiratory or intrathoracic origin. 17% of admissions concerned digestive tract primary cancer, 16% a breast primary, 6% urinary organs and 4% skin. 2% of admissions/sessions concerned a cancer with a central nervous system primary (excluding eye). Other primaries with sparsity of data were combined into an “other” category to retain statistical power and comprised the remaining 4% of observations. This category included primaries of bone, thyroid and other endocrine glands, mesothelial and soft tissue, female and male genital organs and cancers classified as other/unknown by ICD diagnosis.
Distribution of off-label prescribing in admissions varied significantly with regard to site of cancer primary. Notably, 96% of admissions involving patients with a CNS primary had at least one off-label prescription. Conversely, only 6% of admissions involving patients with a urinary cancer had any off-label prescribing. In terms of other primary sites, 24% of admissions involving haematological or lymphoid primary involved off label prescribing, 14% of those related to breast cancer, 19% of those related to a digestive tract primary, 16% of those relating to a respiratory or intrathoracic malignancy, 18% of those relating to skin cancer, 9% of those relating to oral cancers and 17% of those cancers in the other category.

Only 2% of admissions reportedly involved a diagnosis of metastatic cancer. 17% of admissions involving a diagnosis of metastatic cancer had off label prescribing, compared to 19% of admissions that did not involve a diagnosis of metastatic cancer.

In terms of medications prescribed, 98% of admissions/visits involved the prescription of antineoplastic agents. 99% of admissions/visits with off label prescribing involved these agents and 98% of admissions/visits which did not involve off label prescribing.

Total medications prescribed per admission ranged from 1 to 9 prescriptions, with a median of 1 prescription and a mean of 1.1 prescriptions.

Regarding number of medications, total prescriptions in admissions without off label prescribing ranged from 1-6, with a median of 1 and a mean of 1.06. Total prescriptions in admissions with off label prescribing ranged from 1 to 9, with a median of 1 and a mean of 1.24 prescriptions.

Healthcare Facility Characteristics

Table 2: Facility Characteristics

Overall admissions/ visits n (%)			**Off label prescribing?**		**p value**
			No n (%)	**Yes n (%)**	
Total		**1543716**	1250757 (81)	292 959 (19)	
Legal status	General	498093 (33)	420494 (84)	77599 (16)	<0.001[1]
	Teaching/ regional	387497 (25)	269846 (70)	118011 (30)	
	Private for profit	345925 (22)	307532 (89)	38393 (11)	
	Cancer centre	203488 (13)	163101 (80)	40387 (20)	
	Private non- profit	103848 (7)	86597 (83)	17251 (17)	
Cancer activity (Annual chemotherapy sessions)	0-10,000	579565 (38)	506156 (87)	73409 (13)	<0.001[1]
	10,000-20,000	455139 (29)	373723 (82)	81406 (18)	
	20,000-50,000	372718 (24)	278697 (75)	94021 (25)	
	>50,000	88688 (6)	75444 (85)	31244 (35)	
	Unknown	47606 (3)	34737 (73)	12869 (27)	
Facility size (number of beds/day case spots)	0-100	117917 (8)	101900 (86)	16017 (14)	<0.001[1]
	101-500	799712 (52)	682762 (85)	116950 (15)	
	>500	607003 (39)	449795 (74)	157208 (26)	
	Unknown	19084 (1)	16300 (85)	2784 (15)	
Region	Ile de France	145697 (9)	124424 (85)	21273 (15)	<0.001[1]
	Centre Val de Loire	55123 (4)	45755 (83)	9368 (17)	
	Bourgogne Franche Comté	68266 (4)	56656 (83)	11570 (17)	
	Normandie	81559 (5)	71659 (88)	9900 (12)	
	Hauts de France	214681 (14)	156631 (73)	58050 (27)	
	Grand Est	133729 (9)	104862 (78)	28867 (22)	
	Pays de la Loire	101306 (7)	83502 (82)	18204 (18)	
	Bretagne	99419 (6)	84869 (82)	14346 (18)	
	Nouvelle-Aquitaine	164752 (11)	133775 (81)	30977 (19)	
	Occitanie	149489 (10)	117780 (81)	31709 (19)	
	Auvergne-Rhone-Alpes	188856 (12)	147443 (78)	41413 (22)	
	Corse	133410 (9)	117459 (88)	15951 (12)	
	Provence-Alpes Cote d'Azur	2931 (0.2)	2660 (91)	271 (9)	
	Unknown	4865 (0.3)	3547 (73)	1318 (27)	

[1]*Chisquared test*

Table 2 shows characteristics of healthcare facilities involved in the analysis. 58% of admissions were in public hospitals, with 33% of the sample concerning general hospitals (CH) and 25% of admissions taking place in university or regional centres (CHU/CHR). 42% of the sample concerned private hospitals. 22% concern for profit private hospitals, 13% were cancer centres and the remainder were other not-for-profit facilities. Less than 1% of admissions did not have information regarding the category of the facility.

16% of admissions in general hospitals had off label prescribing, as contrasted to 30% of admissions in regional or teaching hospitals. Regarding private hospitals, 11% of admissions/visits in for-profit private involved off-label prescribing. 20% of admissions in non-profit cancer centres involved off-label prescribing compared to 16% of admissions in other non-profit private hospitals.

Cancer activity was described using annual chemotherapy sessions. 37% of admissions occurred in centres with 0-10000 chemotherapy sessions a year, 29% were in facilities with 10,000-20,000 sessions a year, 24% in facilities with 20,000-50,000 a year and just under 6% in facilities that performed over 50,000 chemotherapy sessions a year.
Admissions in hospitals with higher rates of chemotherapy sessions per year and higher proportion of off-label prescribing, with 35% of admissions in hospitals with >50,000 annual chemotherapy sessions involving off-label prescribing, compared to 13% of admissions in hospitals performing 0-10,000 chemotherapy sessions per year.

In terms of facility size, 8% of facilities had 100 beds and out-patient spots or less, just over half had 101-500 and 39% had over 500. Just over a quarter of admissions in hospitals with over 500 beds or day case spots involved off-label prescribing, compared to 14 and 15% in hospitals with 0-100 beds/spots and 101-500 beds/spots respectively.

Hauts de France was the most represented region accounting for 14% of admissions, then Auvergne-Rhone-Alpes with 12%, Nouvelle-Aquitaine with 11% and Ile-de France with 9%. Provence-Alpes-Cote d'Azur was the least represented region accounting for 0.19% of admissions/sessions. Variation in distribution of off label prescribing in admissions was also seen across regions, with 27% of admissions in hospitals in Hauts-de-France involving off label prescribing and 22% in admissions in hospitals in Grand Est, compared to 15% in admissions in hospitals in Ile-de-France, 12% in admissions in hospitals in Corsica, and 9% in Provence- Alpes Cote d'Azur.

Departmental variation

We further explored geographical variation in off label prescribing at a departmental level.

Figure 1:

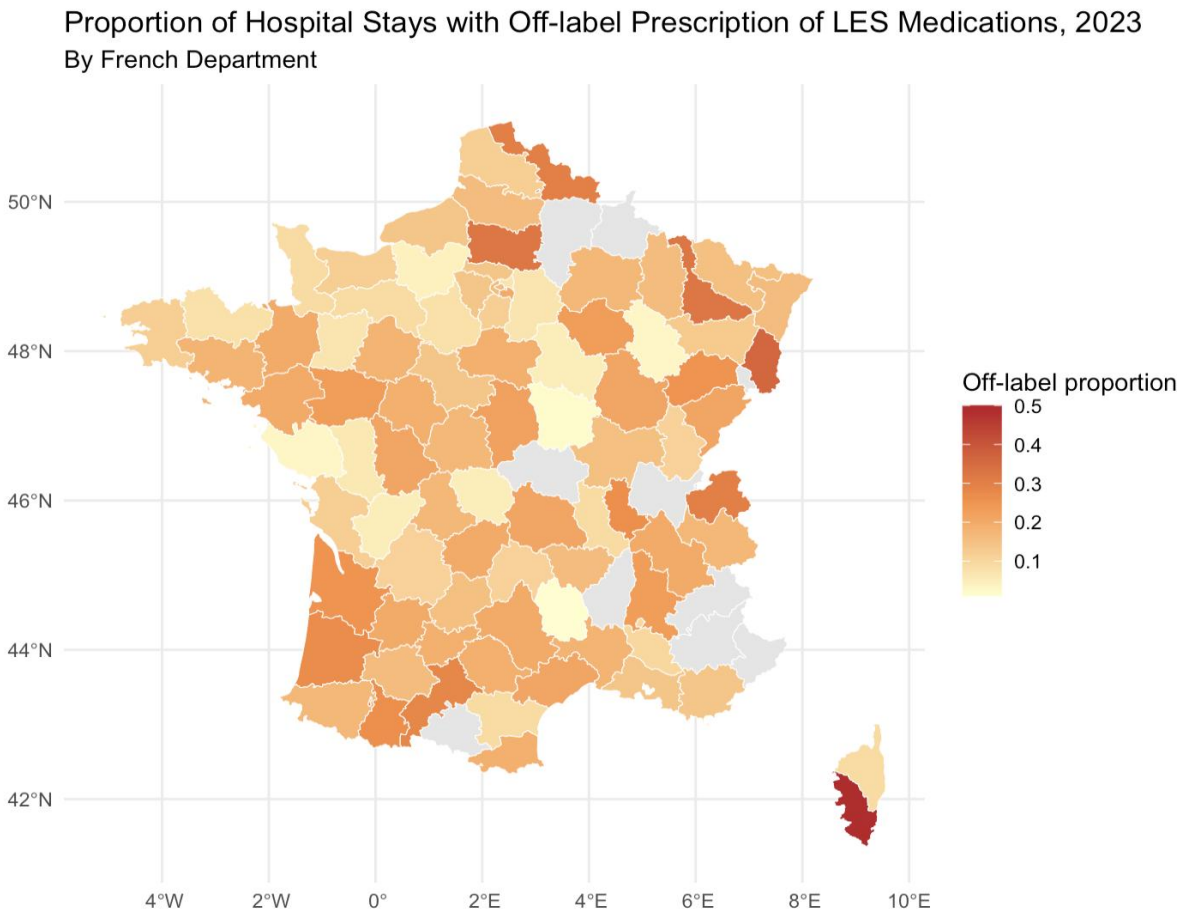

Figure 1 shows variation in off label prescribing at a departmental level, with the choropleth demonstrating the proportion of hospital admissions with any off label prescribing per department. The proportion of hospital admissions/visits with off label prescribing ranged from 0.01 to 0.5. The department with the highest proportion was Southern Corsica however it should be noted that this was over only 4 total hospital admissions/visits. The department with the next highest proportion was Haut-Rhin with a proportion of 0.38. On the lower end, Lozère had a proportion of 0.01 admissions/visits with off label prescribing, and Nièvre had a proportion of 0.02 hospital admissions/visits with off label prescribing.

Generalised linear model

Table 3: Generalised linear model with outcome of off-label prescribing, stratified by sex

	Female (n= 662,134)		Male (n =679,004)	
Predictor	**OR [95% CI]**	**p value**	**OR [95% CI]**	**p value**
Age (years)	0.99 [0.99-0.99]	<0.001	0.98 [0.98-0.98]	<0.001
CCI				
Zero - 2	Ref		Ref	
Over 2	1.05 [1.03-1.07]	<0.001	0.82 [0.81-0.84]	<0.001
Metastatic disease				
No	Ref		Ref	
Yes	1.17[1.12-1.23]	<0.001	0.87 [0.82-0.92]	<0.001
Site of cancer				
Respiratory/thoracic	Ref		Ref	
Breast	0.74 [0.72-0.75]	<0.001	1.04 [0.89-1.20]	0.6
CNS	106 [95-118]	<0.001	113 [104-123]	<0.001
Digestive tract	0.87 [0.85-0.89]	<0.001	1.65 [1.62-1.68]	<0.001
Oral	0.57 [0.53-0.61]	<0.001	0.56 [0.54-0.58]	<0.001
Skin	0.90 [0.87-0.94]	<0.001	1.44 [1.39-1.48]	<0.001
Urinary	0.33 [0.31-0.35]	<0.001	0.34[0.33-0.35]	<0.001
Haematological/lymphoid	1.48 [1.45-1.51]	<0.001	1.89[1.85-1.92]	<0.001
Other	0.98 [0.95-1.00]	0.074	1.34 [1.29-1.39]	<0.001

OR= odds ratio, CI= confidence interval

Table 3 shows a generalised linear model with outcome off label prescribing across admissions, stratified by sex. Amongst admissions involving female patients, for every one year increase in patient age there is a 1% decrease in odds of having an off-label prescription.

Regarding the Charlson Comorbidity Index, compared to women with a score of two or less, no relevant comorbidities), admissions involving women with a score of greater than two had 5% higher odds of having an off-label prescription.

Admissions involving women with metastatic disease had 17% higher odds of an off-label prescription than those without metastatic disease.

Compared to women with a cancer of respiratory or intrathoracic origin, women with a cancer of breast primary had 26% lower odds of having an off-label prescription. Women with cancer of central nervous system primary had 105 times the odds of having an off-label prescription than those with cancer of respiratory/intrathoracic primary. Women with haematological and lymphoid cancers had higher odds of off-label prescribing than

respiratory/intrathoracic cancers. Women with digestive organ, oral, skin and urinary cancers all had lower odds of off label prescribing than women with respiratory/intrathoracic cancer.

With regard to admissions involving male patients, every one year increase in age conferred a 2% decrease in odds of an off-label prescription.
Admissions involving men with a CCI of greater than two had 18% lower odds of an off-label prescription than those involving men with a score of two or less.
Metastatic disease in men conferred lower odds of off-label prescriptions, with admissions involving men without metastatic disease having 13% lower odds of off-label prescribing than admissions involving men without metastatic disease.
Compared to admissions involving men with respiratory/intrathoracic origin, admissions involving men with CNS cancer had 109 times higher odds of off-label prescribing.
Admissions involving men with haematological and lymphoid cancer had 89% higher odds of off label prescribing than admissions involving men with respiratory/ intrathoracic cancer, and admissions involving men with digestive cancer had higher odds than those involving men with respiratory/ intrathoracic cancer. Admissions involving men with oral and urinary cancer had lower odds of off-label prescribing than those involving men with respiratory cancer.
No significant difference in off-label prescribing was demonstrated between admissions involving men with breast or skin cancer and admissions involving men with respiratory/intrathoracic cancer.

Multilevel Model:

Table 4: Multilevel logistic model for off label prescribing (n=153876)

	Null model	Level 1 covariates	Full model
Fixed effects (OR [CI])			
Age (centred)	—	0.87[0.86-0.87]*	0.87[0.86-0.87]*
Sex			
Male	—	Ref	Ref
Female	—	0.90 [0.89-0.91]*	0.90[0.89-0.91]*
Charlson Comorbidity Index			
0-2		Ref	Ref
>2		0.74[0.73-0.75]*	0.74 (0.73-0.75)*
Legal status			
General hospital	—	—	Ref
Teaching/regional	—	—	3.46 [2.58-4.65]*
Cancer centres	—	—	1.97 [1.35-2.86]**
Private non-profit	—	—	1.09 [0.63-1.88]
Private for profit	—	—	0.54 [0.44-0.66]*
Random effects			
Hospital variance (sd)	1.60(1.27)	1.51(1.23)	1.25(1.12)
ICC	0.33	0.32	0.28
MOR	3.34	3.23	2.90

*OR= odds ratio, CI=confidence interval,*p value <0.001, **p value<0.005*

Table 4 shows the results of our full multilevel logistic model. Here when accounting for hospital level clustering, female sex was associated with 10% lower odds of off label prescribing compared to male sex. For every increase in standard deviation of age, odds of off label prescribing decreased by 13%. Compared to a Charlson Comorbidity Index of two or less, a score of greater than two was associated with 26% lower odds of off label prescribing.

At the hospital level, admissions/visits in teaching or regional hospitals had 3.5 times the odds of having an off-label prescription as compared to admissions in general hospitals. Cancer centres had 1.97 times the odds of off label prescribing as compared with general hospitals. Admissions in private for-profit hospitals were 46% less likely to have off-label prescribing than admissions in general hospitals. There was no significant association in off label prescribing for other non-profit private hospitals, as compared to general hospitals.

The MOR reduced from 3.34 in the null model to 2.91 in our final model. This suggests that some of the variation in off-label prescribing seen between hospitals can be explained by the factors included in our model (i.e. patient age and sex, and hospital legal status). The final MOR of 2.91 suggests that while accounting for age, sex, comorbidities and hospital category, between two randomly selected hospitals, the median difference in odds of off label prescribing due to unmeasured or uncaptured hospital level effects is nearly 3-fold.

Table 5: Multilevel logistic model for off label prescribing- only CHU/CHR and CLCC (n=590985)

	Null model (model 0)	**Level 1 covariates (model 2)**	**Full model (model 2)**
Fixed effects (OR [CI])			
Age (centred)	—	0.90[0.89-0.90]*	0.90[0.89-0.90]*
Sex			
Male	—	Ref	Ref
Female	—	0.87 [0.86-0.88]*	0.87[0.86-0.88]*
Charlson Comorbidity Index			
0-2	—	Ref	Ref
>2	—	0.92[0.90-0.94]*	0.92 [0.90-0.94]*
Cancer site			
Respiratory	—	Ref	Ref
Breast	—	0.97[0.94-1.00]**	0.97[0.94-1.00]**
Digestive tract	—	1.47[1.43-1.51]*	1.47[1.43-1.51]*
CNS	—	280[246-319]*	280[246-318]*
Oral	—	0.67[0.64-0.70]*	0.67[0.64-0.70]*
Skin	—	0.82[0.79-0.85]*	0.82[0.79-0.85]*
Urinary	—	0.25[0.23-0.26]*	0.25[0.23-0.26]*
Haematological	—	1.26[1.23-1.29]*	1.26[1.23-1.29]*
Other	—	1.15[1.11-1.18]*	1.15[1.11-1.18]*
Hospital status			
Teaching/regional	—	—	Ref
Cancer centre	—	—	0.59[0.36-0.96]**
Random effects			
Hospital variance (sd)	0.74(0.85)	0.77(0.87)	0.70(0.83)
ICC	0.18	0.19	0.18
MOR	2.24	2.31	2.22

Table 5 shows our focused multilevel model, which involved 590,895 observations (i.e. hospital admissions/visits) which were related to 84507 patients across 49 hospitals including only teaching hospitals and cancer centres. As previously seen, age and female sex were both negatively associated with off-label prescribing in this subset, with odds ratios of 0.90 and 0.87 respectively.
Increasing severity of Charlson Comorbidity Index was also demonstrated to have a modest negative association with off-label prescribing, with a score of greater than two having 8% lower odds of off label prescribing than a two or less.

In terms of cancer site primary, as compared to cancers of respiratory/intrathoracic origin, CNS cancers were positively associated with off-label prescribing, with 270 times higher odds. Higher odds of off-label prescribing compared to respiratory was also seen in digestive tract cancers and haematological/lymphoid cancers, though with more moderate effects, with 1.47 times higher odds and 1.26 times higher odds respectively. Breast, oral, skin and urinary cancers all had lower odds of off-label prescribing than respiratory and intrathoracic cancers, with 3%, 33%, 18% and 75% lower odds respectively.

Admissions or visits in cancer centres had 0.58 times lower odds of having off-label prescribing than those in teaching centres.

In terms of between hospital variability, hospital variance reduced slightly with a mild decrease in ICC and MOR between our null model and final model, suggesting that incorporation of these patient and facility factors partly but not fully explains the variability in off label prescribing between these healthcare facilities. A MOR of 2.23, suggests that while accounting for age, sex, comorbidities and hospital category, when randomly selecting 2 hospitals, the median difference in odds of off label prescribing due to unmeasured or uncaptured hospital level effects is 2.2-fold.

Discussion:

Main findings

Our study of a large sample of 2023 French cancer related hospital admissions/visits produced significant results relating to off-label prescribing at the level of patient characteristics and hospital level clustering. Estimates were stable across all models suggesting robustness of our results.

Patient factors

Cancer site was a predictor of off-label prescribing, which is consistent with results previously described in the literature. Previous reviews showed higher rates of off-label prescribing in bladder and prostate cancer, and lower rates of off-label prescribing in breast cancer. (21) In our study, cancers of urinary organ origin were negatively associated with off-label prescribing in both sexes, and haematological malignancy was positively associated with off-label prescribing in both. Female breast cancer was negatively associated with off label prescribing while no association was seen with breast cancer in males. Previous work has described high rates of off label prescribing in male cancer, due to the paucity of evidence in this population. (20) It is possible that the lack of association in our study could be related to the relatively low prevalence of male breast cancer.

We demonstrated a significant association between central nervous system cancers and off-label prescribing, with a 100-fold increase in odds as compared to respiratory/ intrathoracic cancers. An association between CNS cancers and off label prescribing does seem to have been previously described. Though our study focused on adults, a previous review of off-label prescribing in paediatric cancers reported high rates of off label prescribing in neuro-oncology cases.(38) Additionally, a 2019 UK report used glioblastoma as an example to make the case for using real world evidence to guide off label use. (39) Evidence may be lacking in patients with CNS tumours as randomised controlled trials may not be feasible or indeed not ethical to perform.

This initial association warrants further, more detailed analysis of this sub-group, and exploration of specific diseases and medications implicated in this association.

Interestingly, in our sample metastatic disease was positively associated with off-label prescribing in women and negatively associated with off-label prescribing in men, and the same pattern was seen for the CCI. Previous evidence has described a positive association between more advanced disease and off-label prescribing. (40,41)
We had no information in our data regarding patients' performance status, which is a term referring to cancer patients' ability to take care of themselves and perform their usual activities of daily living. Performance status is a commonly used metric in cancer care with regard to treatment decisions (42) and worse performance status has been associated with off-label prescribing. (20)

Younger age is associated with off-label prescribing which is consistent with previous findings.(20) It is postulated that this is because younger patients are felt more likely to be able to tolerate potential adverse events. The same reasoning could be extended to the negative association seen between rising Charlson Comorbidity Index and off-label prescribing. Patients with fewer comorbidities may be seen as more robust and thus more able to tolerate potential unwanted side effects or drug reactions.

Facility factors

Private for-profit hospitals had lower probability of off-label prescribing compared to general public hospitals. Previous evidence has shown differing general prescribing practices in public versus private hospitals.(43)

Compared to general hospitals, teaching/regional hospitals had significantly higher probability of off label prescribing. This is consistent with previous evidence showing higher rates of off label prescribing in academic centres. (20) Additionally, cancer centres had higher probability of off label prescribing than general hospitals. It is reasonable to infer that practitioners in specialist centres would be more confident in prescribing specialist cancer medications off label, likely having more experience in treating rarer diseases and having more experience using specialist anti-cancer medications.

Another consideration that could potentially contribute to this association is the cultural transmission of clinical practice and larger hierarchical team structures in teaching hospitals versus smaller more local centres. In larger or more specialist facilities, senior clinicians may supervise more trainees, which is likely to increase the reach and influence of their individual prescribing habits, which may be consistent with guidelines or not. (44,45) The "hidden curriculum" of medical training, defined as "set of influences that function at the level of

organizational structure and culture" has been previously described in the literature. Previous research in the UK has shown an influence of team dynamics on prescribing decisions, with some prescribers reporting prescribing outside of hospital guidelines in order to maintain relationships with their colleagues.(46)

Between hospital variation

After adjusting for patient factors and legal status of hospitals, we saw significant between hospital variability in off label prescribing practices of medications on the LES, and when focusing on solely academic and specialist centres we still demonstrated between hospital variation. This suggests the presence of unmeasured factors contributing to differing practices, consistent with previous studies showing differing practices across healthcare establishments, though in a more general setting.

Variations in medical practice across similar hospitals (i.e. of the same category) could be due to different medical cultures across different facilities. A 2019 paper suggested a framework of warranted vs unwarranted variation which incorporated main themes of capacity, agency and evidence. Unwarranted variation is postulated to arise where providers' needs and preferences are prioritised, when decision making is contrary to available evidence, and where variation in practice is due to disparities in training and competency levels of care providers.(47) It would be of interest to further explore the variation in these hospitals by examining patient outcomes and exploring whether variation is present in metrics such as mortality, complications and adverse drug events.

While a degree of variation in care is expected, and desirable, mitigation of unwarranted variation is vital. The evidence suggests that standardisation of care is important in improving outcomes(48), with some researchers calling for a harmony between standardisation and customisation of care, (49) balanced by available evidence and funding.

Strengths & Limitations

To our study's strength, we had a large sample size, giving substantial statistical power. Our models showed stable estimates, suggest robustness of our findings.

This paper is not without limitations. Our findings serve as a gross overview of off label prescribing of LES medications in cancer admissions in 2023 France. As a result, direct inferences about practices cannot be made from these findings alone. However, we wished

to capture a global picture of off-label prescribing of these medications in the first instance. From here we would like to further explore specific diseases and specific medications in more detail.

We acknowledge missing data in some instances which may skew results, particularly regarding the CCI. Observations missing this information were examined in more detail and had a similar distribution profile to the general sample, though in those missing this data teaching and general hospitals were slightly over-represented and other private non-profit hospitals were slightly underrepresented, which could skew results.

As we are reliant on hospital coding data, errors in coding could also potentially contribute to inaccuracies in our results.

Additionally, there is likely to be residual confounding in our multilevel model. Case-mix is not fully accounted for in the model which is likely to contribute significantly to between hospital variation(50). However, the inclusion of the Charlson Comorbidity Index should serve as a proxy to this to some degree. Indeed, though we suspect residual confounding, the result of 2.9 suggests that even were this adjusted for, there is likely to still exist significant between hospital variability.
Site of primary cancer in our second multilevel model should also somewhat serve as a proxy for case-mix, and we note that we still demonstrated between hospital variability in off-label prescribing when adjusting for this in our second more focused multilevel model.

In some cases where metastatic disease was present, the primary diagnosis was coded as a chemotherapy session, and the only available linked diagnosis was coded as the secondary tumour. This means that for some metastatic disease we did not have information regarding the primary tumour. As a result, some cancer primary sites may be underrepresented in our analysis which we must acknowledge when taking our findings into account.

Further directions

Off the basis of our findings, going forward we would like to investigate these associations in further detail. As discussed above; to advance from this general overview, it would be of interest to explore specific diseases and specific medications with more granularity.

As mentioned previously, off-label regulations have weakened progressively and considerably over the previous years. Moreover, this has happened in an uneven fashion,

with some facilities subject to regulations that others are not. It is plausible that between hospital variation could be at least in part related to this disappearance of guidance. We would like to explore trends in previous years to further explore this potential reasoning.

Variation in off-label prescribing on the LES amongst hospitals in France could be justified in the context of different patient needs, however it is possible that some of this variation is due to different hospital cultures or the radiation of undesirable behaviours.

Given that off-label prescribing is known to be related to adverse drug events, or potential harm to patients in the absence of clinical benefit, unwarranted variation in off-label prescribing in cancer patients could have nefarious effects on an already vulnerable patient population. Additionally, it could result in unjustified higher costs at the expense of other services in the health system.

It would be prudent to further investigate variations of across these hospitals in terms of other factors, namely patient outcomes such as mortality rates, to further elucidate the nature of this between-hospital variation. We would like to further explore this phenomenon, with a view to contributing to the improvement of quality of care in France.

Conclusion

From our study we have demonstrated significant patient related factors and facility factors predisposing to off-label prescribing of medications on the LES. When accounting for patient and facility level factors, significant between hospital variability persists. This suggests unmeasured factors, potentially such as cultural factors causing variation across facilities.

More research is warranted to further explore this variation and explore related patient outcomes. The identification of unwarranted variation in care could help to guide further policy. These findings could suggest a need to re-introduce guidelines regarding off-label prescribing on the LES, to aid prescribers in decision making and promote standardised care. Previous studies have shown that national policies are more effective than those at a hospital level for effecting real change. (51)

We hope that with ongoing research we can contribute to bettering patient outcomes, improving healthcare spending, and reducing healthcare waste

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Résumé

Contexte

La prescription hors autorisation de mise sur le marché (hors AMM) est courante chez les patients atteints de cancer. L'affaiblisement progressif des réglementations encadrant la prescription hors AMM sur la liste en sus en France pourrait contribuer à une augmentation de ces prescriptions. Bien que parfois justifiée, une utilisation inappropriée de médicaments hors AMM peut entraîner de moins bons résultats pour les patients et une hausse des dépenses de santé.

Objectifs

Dans un contexte de hausse des coûts des médicaments inscrits sur la liste en sus, nous avons cherché à identifier les facteurs, au niveau des patients et des établissements hospitaliers, qui prédisposent à la prescription hors AMM chez les patients atteints de cancer, et à explorer les variations entre structures de soins à l'échelle nationale.

Méthodes

Nous avons utilisé les données de prescription hospitalière PMSI de 2023 pour analyser les tendances de la prescription hors AMM dans 1 543 716 séjours/séances à travers la France. À l'aide de R, nous avons d'abord évalué l'association entre les facteurs individuels des patients et la prescription hors AMM via des analyses bivariées (tests du chi carré / Wilcoxon), puis au moyen d'un modèle logistique. Nous avons ensuite utilisé un modèle logistique multiniveau pour explorer les facteurs liés aux patients et aux établissements, ainsi que la variation interhospitalière.

Résultats

Un âge plus jeune et le sexe féminin étaient associés à une probabilité plus élevée de prescription hors AMM. Les admissions pour cancers du système nerveux central (SNC) présentaient une probabilité 107 fois plus élevée de prescription hors AMM comparées à celles pour cancers respiratoires. La probabilité de prescription hors AMM variait selon le type d'établissement de santé, les hôpitaux universitaires et les centres de lutte contre le cancer étant plus susceptibles de prescrire hors AMM que les hôpitaux généraux. En tenant compte des caractéristiques des patients et des établissements, nous avons observé une variabilité des pratiques de prescription hors AMM entre les hôpitaux.

Conclusions

Il existe une variation significative des pratiques de prescription hors AMM dans le traitement du cancer selon les hôpitaux en France, possiblement liée à des facteurs non mesurés tels que la culture institutionnelle. Une variabilité injustifiée des soins est associée à des résultats moins favorables pour les patients ainsi qu'à un impact économique et environnemental négatif. Ces résultats justifient des investigations supplémentaires pour orienter les politiques futures visant à améliorer les pratiques de prescription.