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Off-label drug prescriptions in French general practice: a cross-sectional study

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ABSTRACT

Objectives Off-label drug prescribing is a public health and economic issue. The aim of this study was to describe off-label prescription in general practice in France, in terms of frequency and nature, and to identify its main determining factors.

Design Multicentre cross-sectional study

Setting Twenty-three training general practice offices

Participants All the voluntary patients coming for a medical consultation or visited at home over a cumulative period of 5 days per office between November 2015 and January 2016.

Methods Eleven interns, acting as observers, collected data. Two reviewers analysed the drugs prescribed by the trainers, in order to identify those prescribed off-label in terms of their indication or the age of the patient. We used a univariate, then a multivariate model, based on hierarchical mixed-effects logistic regression.

Results Among the 4932 drug prescriptions registered, 911 (18.5%[95% CI17.4% to 19.6%]) were off-label, of which 865 (17.6%) due to the indication of the drug and 58 (1.2%) due to the age of the patient. The prescription never mentioned the off-label use, neither was the patient informed of it, as required by the French law. With the multivariate analysis, variables contributing to off-label prescription were the number of drugs (OR=1.05 for each additional drug), the initiation of new drug therapy (OR=1.26) and the non-specific goal of the prescription (OR=1.43); the age of the patient ≤14 years (OR=1.42); the rural location of the physician's practice (OR=1.38) and the low frequency of the visits of national health insurance representatives (OR=0.93).

Conclusion Almost one out of five drugs prescribed in French general practice was off-label. It seems necessary to better train physicians in clinical pharmacology, to provide them with more effective drug prescription software, to reinforce postmarketing surveillance and to clearly define off-label use by consensus.

Strengths and limitations of this study

- ► No data were missing from the database we used.
- ► The off-label status of each drug prescription was double assessed.
- ► The study involved general practice trainers, which could entail a selection bias.
- ► We only studied off-label prescribing in terms of indication and age, without including the dosage, route of administration and drug interaction risks.

INTRODUCTION

Marketing authorisation (MA) is mandatory before marketing medicine, thus ensuring the safety, the quality and the efficacy of the drug.[1 2] In the USA, the Food and Drug Administration (FDA) issues the MA since 1962, and is competent on the entire federal state.[2] The FDA-approved labelling for a drug provides the prescribing information or package insert (PI) to the practitioners and the patient package insert to the patients. The PI contains two main components: the highlights of PI (HPI) and the full PI.[3] In Europe, the European Medicines Agency (EMA) issues the MA since 1995.[4] National MA exists in France since 1941,[5] and has been completed by three procedures to harmonise drug approval between the European Union countries: centralised, mutual recognition and decentralised.[6] The European MA has three annexes: the summary of product characteristics (SPC) for healthcare professionals, the medication leaflet for patients and the label with the packaging. Both the HPI and the SPC include the name of the medicinal product, the composition, the pharmaceutical form, the therapeutic indications, the clinical particulars (posology and method of administration), warnings and precautions for use, contraindications and adverse effects of the product.[7] However, there has been substantial disagreement in the information available to prescribers and patients in different countries.[8]

Drugs are not always used according to the MA criteria in medical practice. Any intentional use of an authorised product not covered by the terms of its MA is considered an off-label prescription. This may, for example, be the use for a different indication, use of a different dosage, dosing frequency or duration of use, use of a different method of administration or use by a different patient group.[1] Off-label prescribing is a public health and economic issue. The quality and

the safety of a prescribed drug are not ensured outside of its MA. Off-label prescribing increases iatrogenic risks by a factor of 1.4, whether in adults or children.[9 10] Besides, there is not always scientific studies to assess its effectiveness. Finally, many off-label prescribed drugs are more expansive for the patient and/or the community.[11]

Evaluations on off-label drug prescribing performed until now were limited to a setting (mostly the hospital setting[12]), or a target population (mostly children[13]), or to some drug classes[14] or some specialty (such as oncology,[15] psychiatry[16] or rare diseases[1]).

The aim of this study was to describe off-label prescribing in French general practice, in terms of frequency and nature, and to identify its main determining factors.

METHODS

It was a multicentre cross-sectional study, carried out on general practice patients, in the French Rhône-Alpes region, as part of the Objectives of PREscriptions in general Medicine research programme.[17] It involved 23 training offices for interns from Lyon 1 University.

Inclusion criteria

Eleven general practice interns, acting as observers, have collected data during their training with a practitioner, and every intern was investigating in two to three different offices. We calculated a sample size of 2119 consultations, based on estimates of 2.9 drugs prescribed per consultation on average[18] and of 20% of drugs prescribed off-label[19] with a CI of ±1%. All the 2149 patients coming for a medical consultation or visited at home over a cumulative period of 5 days per office, between the second of November 2015 and the sixth of January 2016, were requested to the study. Eight patients refused to participate in the study. The database contained 2141 consultations, of which 1649 (77.0%) included at least one drug prescription.

Data collection and data entry

Investigating interns benefited from training meetings for data collection and entry according to the International Classification of Primary Care (ICPC-2).[20 21] At the end of each consultation, they collected the following variables on a free text questionnaire: consultation length, age, gender, socioprofessional category, potential fee exemption status (for low income or for long-term conditions), seniority of the patient (new or already known), health problems managed, and for each health problem, the prescribed drugs, their anteriority (new or renewed prescription) and the main goal of their prescription. Prescription goals were divided into three categories: specific (to decrease the risk of mortality or morbidity, to cure or provide remission of the disease), non-specific (to improve symptoms, quality of life or functional status) and unspecified. Following data have been collected on trainers: age, gender, practice location (rural, semirural or urban), type of practice (solo or collective), visits of pharmaceutical representatives and public health insurance representatives. Investigating interns have entered anonymous data previously collected on the paper questionnaires in a centralised database available on a dedicated website. They have entered the data on health problems managed according to the ICPC-2, using an online encoding engine. They have entered prescribed drugs using a search engine combined with the Thériaque drug database,[22] which includes the Anatomical Therapeutic Chemical classification system.[23] They entered the professions data according to the eight items of the French classification of professions and socioprofessional categories,[24] before regrouping the data into five categories.

Data analysis

Each of the two reviewers (AN and FD) have analysed the 5036 drug prescriptions registered to identify drugs prescribed off-label in terms of indication or the age of the patient. In case of discrepancy, the two reviewers have consulted each other to find a compromise. In case of a disagreement, another author (LL) acted as arbitrator. We excluded 104 unusable drug prescriptions of the data analysis, due to indication inconsistencies (n=33) or to drugs missing in the Thériaque database (n=71). Our database contained 4932 drugs in the end. We used univariate, then multivariate analysis, based on hierarchical mixed-effects logistic regression to take into account the data structure. We selected the variables to include in the final model by doing a backward stepwise selection of the clinically relevant variables or those with a p value less than 0.25 after the univariate analysis. The statistical significance threshold was set to 5% and p values were obtained using likelihood ratio tests. We used R software V.3.1.0 to carry out the analyses.

Patient and public involvement

Patients and the public were not involved in the design of the study.

RESULTS

Among the 4932 drug prescriptions registered, 911 (18.5% [95% CI 17.4% to 19.6%]) were off-label, of which 865 (17.6%) due to the indication of the drug and 58 (1.2%) due to the age of the patient. The proportion of consultations with at least one off-label drug was of 38.2% (95% CI 35.8% to 40.6%). The patient was never informed when prescriptions were off-label and prescriptions never mentioned the off-label use. The 10 most prescribed off-label drugs were: acetylsalicylic acid, omeprazole, diclofenac, salbutamol, prednisolone, amoxicillin, esomeprazole, mometasone, vitamin D and bisoprolol. Among them, the proportion of off-label prescriptions ranged from 17.8% to 76.2% (table 1). With the univariate analysis, variables contributing to off-label drug prescribing were the initiation of a new drug therapy (OR=1.27) and the non-specific goal of

Table 1 Top 10 most prescribed off-label drugs in descending order (n=4932)

	Off-label prescriptions			
	Yes n (%)	No n (%)	Total n (%)	Main indication for off-label prescription
Acetylsalicylic acid per os	48 (55.2)	39 (44.8)	87 (1.76)	Atherosclerosis/peripheral vascular disease
Omeprazole per os	41 (55.4)	33 (44.6)	74 (1.50)	Preventing NSAIDs*-induced lesions
Topical diclofenac	28 (49.1)	29 (50.9)	57 (1.16)	General pain/multiple pain locations
Inhaled salbutamol	21 (46.7)	24 (53.3)	45 (0.91)	Acute bronchitis and bronchiolitis
Prednisolone per os	20 (45.4)	24 (54.6)	44 (0.89)	Cough
Amoxicillin per os	18 (24.0)	57 (76.0)	75 (1.52)	Acute upper respiratory infection
Esomeprazole per os	17 (30.4)	39 (69.6)	56 (1.14)	Epigastric/abdominal pain
Nasal mometasone	16 (76.2)	5 (23.8)	21 (0.43)	Acute upper respiratory infection
Vitamin D per os	16 (17.8)	74 (82.2)	90 (1.83)	Osteoporosis
Bisoprolol† per os	16 (39.0)	25 (61.0)	41 (0.83)	Uncomplicated hypertension

*Non-steroidal anti-inflammatory drugs.
†This bisoprolol off-label prescription only concerned Cardensiel and Bisoce, which have no MA for high blood pressure.

the medical prescription (OR=1.48); the age below or equal to 14 years (OR=1.44) and the profession of worker (OR=2.11) or the professional inactivity (OR=2.38) of the patient (table 2).

With the multivariate analysis, variables contributing to off-label prescribing were the number of drugs (OR=1.05 for each additional drug), the initiation of a new drug therapy (OR=1.26) and the non-specific goal of the prescription (OR=1.43); the age of the patient below or equal to 14 years (OR=1.42); the rural location of the physician's practice (OR=1.38) and the low annual frequency of the visits of national health insurance representatives (OR=0.93) (table 3). Using the receiver operating characteristic curve equation, the multivariate model explained 44.7% of the variance.

DISCUSSION

Almost one out of five drugs prescribed in general practice (18.5%) was off-label in France, without informing the patient. Generally, a prescription has a higher risk of being off-label if it includes many newly prescribed drugs with a non-specific goal, for a patient less than 14 years old known by his GP, who is practising in a rural area and not meeting public health insurance representatives.

Strengths and limitations

No data were missing from the database we used. The off-label status of each drug prescription was double assessed. The multivariate analysis allowed us to take into account data hierarchy and to explain nearly 45% of the off-label prescription variance from the drug features, but also the patients and physicians characteristics. To the best of our knowledge, no previous study analysed all these combined factors. The study involved general practice trainers, which could entail a selection bias underestimating the off-label prescribing frequency. However, we observed that their patients and drug prescriptions were not very different from other GPs.[25] In addition, mean age and gender of the participating GPs did not differ from French GPs (data not presented). We only studied off-label prescribing in terms of indication and age, without including the dosage, route of administration and drug interaction risks. Non-inclusion of these criteria allows us to believe that the estimation of off-label prescribing frequency was minimal.

Comparison with existing literature

Our estimation of off-label prescribing frequency (18.5%) is close to the estimation of an American reference study (21%) in community medicine in 2001, based only on the indication criteria.[19] A French study in 2012, limited to 11 clinical situations, found that 19.3% of general practice prescriptions were off-label.[26] Our results are even more significant given the high average level of drug prescribing in France, with more than 80% of general practice consultations resulting in at least one drug prescription.[18] To the best of our knowledge, no previous study has examined patient information when they receive off-label prescriptions.

We can identify two types of off-label prescriptions: whether they are scientifically justified or not. Only 27% of off-label prescriptions were considered justified in the USA in 2001.[19] Off-label prescribing is indeed not always wrong or harmful, especially when complying with clinical practice guidelines, since they are usually elaborated according to SPC. Available recommendations are in principle more adaptive and regularly updated, whereas indications remain most often unchanged after the MA, except for temporary recommendations for use. Moreover, most SPC labelling texts address regulatory or industrial issues rather than public health or clinical goals. They are, therefore, often limited or imprecise

Table 2 Factors associated with off-label prescribing in univariate analysis

Characteristics	Off-label prescription				
	Yes (n=911) n (%)	No (n=4021) n (%)	Total (n=4932) n (%)	OR (95% CI)	P
Drug					
Anteriority					<0.01
Renewed	444 (48.7)	2177 (54.1)	2621 (53.2)	Reference	
Initiated	467 (51.3)	1844 (45.9)	2311 (46.8)	1.27 (1.08 to 1.48)	
Main goal					<0.01
Specific	326 (35.8)	1791 (44.5)	2117 (42.9)	Reference	
Non-specific	572 (62.8)	2164 (53.8)	2736 (55.5)	1.48 (1.26 to 1.73)	
Unspecified	13 (1.4)	66 (1.6)	79 (1.6)	1.14 (0.58 to 2.07)	
Patient/consultation					
Age (years)					0.01
0–14	145 (15.9)	477 (11.9)	622 (12.6)	1.44 (1.13 to 1.83)	
15–64	381 (41.8)	1726 (42.9)	2107 (42.7)	1.05 (0.88 to 1.24)	
65–100	385 (42.3)	1818 (45.2)	2203 (44.7)	Reference	
Gender					0.95
Female	525 (57.6)	2310 (57.4)	2835 (57.5)	Reference	
Male	386 (42.4)	1711 (42.6)	2097 (42.5)	1.01 (0.86 to 1.18)	
Seniority					0.20
New	33 (3.6)	194 (4.8)	227 (4.6)	Reference	
Known	878 (96.4)	3827 (95.2)	4705 (95.4)	1.30 (0.88 to 1.98)	
Fee exemption status for long-term condition					0.09
No	623 (68.4)	2611 (64.9)	3234 (65.6)	Reference	
Yes	288 (31.6)	1410 (35.1)	1698 (34.4)	0.86 (0.73 to 1.02)	
Fee exemption status for low income					0.17
No	864 (94.8)	3852 (95.8)	4716 (95.6)	Reference	
Yes	47 (5.2)	169 (4.2)	216 (4.4)	1.30 (0.89 to 1.86)	
Socioprofessional category					<0.01
Executive, intellectual profession	13 (1.4)	114 (2.8)	127 (2.6)	Reference	
Farmer/craftsman/shopkeeper/ business owner/intermediate profession/ employee	193 (21.2)	916 (22.8)	1109 (22.5)	1.73 (0.96 to 3.37)	
Worker	46 (5.0)	166 (4.1)	212 (4.3)	2.11 (1.07 to 4.38)	
Pensioner	402 (44.1)	1966 (48.9)	2368 (48.0)	1.64 (0.92 to 3.17)	
Inactive	257 (28.2)	859 (21.4)	116 (22.6)	2.38 (1.33 to 4.63)	
Duration≥10 min					0.75
Yes	813 (89.2)	3619 (90.0)	4432 (89.9)	Reference	
No	98 (10.8)	402 (10.0)	500 (10.1)	1.04 (0.80 to 1.35)	
Number of health problems managed (m [SD])	2.9 (2.0)	3.1 (2.1)	3.0 (2.1)	0.97 (0.93 to 1.01)	0.09
Number of drugs (m [SD])	4.9 (3.1)	4.8 (3.1)	4.8 (3.1)	1.02 (0.99 to 1.05)	0.22
Physician					
Age (years)	49.9 (7.7)	49.7 (8.5)	49.8 (8.3)	1.00 (0.99 to 1.02)	0.61
Gender					0.66
Male	596 (65.4)	2685 (66.8)	3281 (66.5)	Reference	

Continued

Table 2 Continued

Characteristics	Off-label prescription Yes (n=911) n (%)	No (n=4021) n (%)	Total (n=4932) n (%)	OR (95% CI)	P
Female	315 (34.6)	1336 (33.2)	1651 (33.5)	1.07 (0.79 to 1.44)	
Location of practice					0.15
Urban or semirural	515 (56.5)	2435 (60.6)	2950 (59.8)	Reference	
Rural	396 (43.5)	1586 (39.4)	1982 (40.2)	1.22 (0.93 to 1.61)	
Type of practice					0.29
Solo	118 (13.0)	619 (15.4)	737 (14.9)	Reference	
Collective	793 (87.0)	3402 (84.6)	4195 (85.1)	1.24 (0.83 to 1.87)	
Pharmaceutical representatives per week (m [SD])	0.80 (1.2)	0.78 (1.2)	0.78 (1.2)	1.03 (0.91 to 1.16)	0.65
PHIR visits per year (m [SD])	2.3 (2.2)	2.5 (2.1)	2.5 (2.1)	0.95 (0.90 to 1.01)	0.12

m, mean; PHIR, public health insurance representatives.

Table 3 Factors associated with off-label prescribing in multivariate analysis

Characteristics	OR (95% CI)	P
Drug		
Anteriority		0.02
Renewed	Reference	
Initiated	1.26 (1.04 to 1.54)	
Main goal		0.0001
Specific	Reference	
Non-specific	1.43 (1.21 to 1.67)	
Unspecified	1.16 (0.62 to 2.18)	
Patient/consultation		
Age (years)		0.04
0–14	1.42 (1.07 to 1.88)	
15–64	1.07 (0.87 to 1.30)	
65–100	Reference	
Seniority		0.049
New	Reference	
Known	1.51 (1.00 to 2.27)	
Number of drugs* (m [SD])	1.05 (1.02 to 1.09)	0.002
Physician		
Practice location		0.02
Urban or semirural	Reference	
Rural	1.38 (1.08 to 1.75)	
PHIR visits per year† (m [SD])	0.93 (0.88 to 0.98)	0.02

*For each new drug per consultation, the probability of off-label prescribing was multiplied by 1.05.
†PHIR, public health insurance representatives. Off-label prescribing probability decrease by 7% for each additional visit per year.
m, mean.

and not well suited for clinical use, especially in general practice.[1] For example, among the 10 most prescribed off-label drugs identified in our study, acetylsalicylic acid has no indication for peripheral artery disease while it is recommended by the French National Authority for Health (HAS) in that indication,[27] and it is even a criterion of the public health pay-for-performance system.[28] Omeprazole is also not indicated for the prevention of non-steroidal anti-inflammatory drugs (NSAIDs)-induced lesions, while it is one of the proton pump inhibitors (at full dose) recommended by the HAS in this indication.[29] In these situations, should the physician respect the regulation, the patient would not be reimbursed for a drug with no MA in this indication. On the opposite, some off-label prescriptions in our study were not justified. Salbutamol was prescribed off-label to treat bronchiolitis in infants and acute bronchitis in adults, while it is not recommended in these two indications.[30] Amoxicillin was prescribed off-label for upper respiratory tract infections, acute nasopharyngitis in particular, contrary to clinical practice guidelines.[31] Prednisolone was also prescribed off-label as cough treatment, despite no proven efficacy in reducing the symptoms duration or severity.[32] Esomeprazole was prescribed off-label for epigastric pain, despite the suspicion of serious adverse effects when using proton pump inhibitors for an extended period.[33]

Off-label prescribing is legal in France and physicians can freely prescribe if their prescription is in line with the 'current scientific knowledge'.[34] However, the physician is liable for off-label prescribing, and has to justify the validity of his prescription by the lack of alternative drugs and the absolute necessity of the treatment. He must also inform the patient on potential risks and that the prescription is non-reimbursable, before obtaining his informed consent.[35] Not informing the patient has already been considered a prejudice punishable by law in France.[36] We can assume that in some situations the physician did not intentionally prescribe off-label. This

can partly be explained by the lack of clarity of some SPC that is hard to remember for practitioners. Indications can change within a therapeutic class, or between an original drug and its generics. For example, different topical NSAIDs have specific indications in terms of aetiology (trauma, osteoarthritis, etc) and of location (knee, finger, etc). The branded versions of bisoprolol (Cardensiel) do not have an MA to treat high blood pressure, but its generics are indicated in uncomplicated high blood pressure. On the contrary, the branded versions of pregabalin (Lyrica) are indicated to treat neuropathic pain, but its generics are not.

We observed more frequent off-label prescriptions when they did not have a specific goal. More than half of the drugs are prescribed without a specific goal in general practice, mostly to alleviate symptoms.[17] The patients' high expectations in these situations could explain these off-label prescriptions. Our study confirms that children are especially exposed to off-label prescriptions (23.3%). Previous studies mainly included children and did not compare children and adults. In 2011, a French study estimated that almost 38% of community medicine prescriptions for children were off-label, based on indication, dosage, age or route of administration.[37] A systematic literature review found that 11%–37% of community medicine prescriptions for children were off-label.[13] This can be explained by the lack of clinical trials for this population deemed at risk.[38] In the field of analgesics, in particular, many drugs are recommended, although they have not been tested in children and thus, have no MA.[39] On a European level, new rules have been established as part of 'The European Regulation on medicines for paediatric use' programme, to promote drug development for children.[40] Some drugs may later obtain an MA for use in children although such use was originally off-label. In addition, real-world evidence on use in such off-label populations is sometimes used to providing supporting evidence for MA applications in new populations.[41]

The more drugs prescribed during a consultation, the higher the chances of being off-label. This cumulative risk could contribute to increase the probability of adverse effects linked to polypharmacy (estimated to be between 6% and 15% per additional drug).[42] Our results confirm a higher off-label frequency in rural areas, already observed in a study in German children.[43] Difficulties to access continuing education because of isolation may explain this finding. The lower frequency of off-label prescriptions observed in physicians meeting with public health insurance representatives is probably linked to the fact that they remind them of good medical practices and provide them with prescribing guidelines based on current recommendations.[44] In our study, meeting with pharmaceutical industry representatives did not increase off-label prescribing, but it was shown that it increased the amount and cost of prescribed drugs, and lowered the quality of drug prescriptions.[45]

Implications for practice and research

These results raise issues in terms of education and prescription support systems. According to a French report on promoting and monitoring the proper use of medicinal products, physicians do not have enough training on basic rationales that are the foundation of good prescribing and relevant use of drugs. The authors of this report recommend improving initial medical training, to make the prescribing physician aware of what he is prescribing, to whom, how and why. In their opinion, the lack of continuing education and of the hierarchy of its content regarding health and economic priorities are significant factors of improper prescribing, particularly off-label.[46]

Practitioners' drug prescription software are not effective enough, even those certified by the HAS.[46] It would be advisable that these software include a prescribing support system displaying every data available on drug benefits and risks for each indication. In principle, the physician should associate the drug to the diagnosis justifying his prescription.[47] His software should then be able to indicate if this diagnosis is part of the drug MA, considering the patient's age. Whether or not the drug has an MA in the intended indication, the software should be able to suggest the treatment options supported by clinical practice recommendations or by scientific data.[48] In the USA, Drugdex system is a national reference standard for drug use, describing the level of evidence of their efficacy and their safety in every indication, covered by an MA or not. The Medicaid software uses this tool to approve the reimbursement of treatments prescribed in off-label indications based on a sufficient level of evidence.[49]

Developing a postmarketing drug surveillance system that measures the drug effectiveness and risks in routine practice would secure prescriptions, and in particular off-label prescriptions, that involve major adverse effect risks.[50] In France, there is a 'temporary recommendation for use' process allowing to monitor temporary off-label prescribed drugs for indications for which they are not licenced yet, and to evaluate them to prepare an MA application. This regulatory process is intended for specific groups of patients and rare diseases, and does not really concern GPs.[51]

There is no official definition for off-label prescribing and various definitions are used.[52] An international or European common definition would allow better off-label prescriptions evaluation and comparison. The intentionality requirement, by the EMA, in particular,[1] can be an obstacle as this criterion is hard to assess.

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