Prescription of antibiotics and anxiolytics/hypnotics to asthma patients in general practice: A cross-sectional study based on French and Italian prescribing data.

David Darmon1*

*Corresponding author

Email: david.darmon@unice.fr

Postal address: Département d’enseignement et de recherche en médecine générale, UFR médecine, Université de Nice Sophia-Antipolis, 28 avenue Valombrose 06 107 Nice Cedex 02, France

Telephone: +33 6 60 59 86 42
Fax number: +33 9 58 61 39 15

Laurent Laforest2
Email: laurent.laforest@univ-lyon1.fr

Eric Van Ganse2
Email: eric.van-ganse@univ-lyon1.fr

Ferdinando Petrazzuoli3
Email: ferdinando.petrazzuoli@gmail.com

Chris van Weel4,5,
Email: C.vanWeel@elg.umcn.nl

Laurent Letrilliart6
Email: laurent.letrilliart@wanadoo.fr

1. Département d’enseignement et de recherche en médecine générale, Faculté de médecine, Université de Nice Sophia-Antipolis, France.

2. Unité de Pharmaco épidémiologie, Faculté d’Odontologie, UMR 5558 CNRS – Université Claude-Bernard Lyon, CHU-Lyon, France.
3. SNAMID Caserta (Italian Society of General Practice), Caserta, Italy.

4. Department of Primary and Community Care, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

5. Australian Primary Health Care Research Institute, Australian National University, Canberra, Australia.

6. Département de médecine générale, Faculté de médecine, Université Claude-Bernard Lyon I, France.
Abstract:

Background: Asthma is often poorly controlled and guidelines inadequately followed in medical practice. In particular, the prescription of non-asthma specific drugs can affect the quality of care. The goal of this study was to measure the frequency of the prescription of antibiotics and anxiolytics/hypnotics to asthma patients and to look for association between gender or age and the prescriptions of these drugs.

Methods: A cross-sectional study was conducted using computerised medical records from French and Italian general practitioners’ (GPs’) networks. Patients were selected according to criteria adapted from the HEDIS (Healthcare Effectiveness Data and Information Set) criteria. The outcome measure was the number of antibiotics or of anxiolytics/hypnotics prescriptions per patient in one year. Parallel multivariate models were developed.

Results: The final sample included 3,093 French patients (mean age 27.6, 49.7% women) and 3,872 Italian patients (mean age 29.1, 48.7% women). In the univariate analyses, the French patients were prescribed fewer antibiotics than the Italian patients (37.1% vs. 42.2%, p<0.00001) but more anxiolytics/hypnotics (17.8% vs. 6.9%, p<0.0001). In the multivariate models, the female patients were more likely to receive antibiotics (OR: 1.5 [1.3-1.7]) and anxiolytics/hypnotics (OR: 1.8 [1.5-2.1]).

Conclusions: The prescription of antibiotics and anxiolytics/hypnotics to asthma patients is frequent, especially in women. GPs should follow the same rules that apply to non-asthma patients to contain the prescription of these drugs. Asthma guidelines should address this issue by referring to other guidelines covering the prescription of non-asthma-specific drugs, and alternative non-pharmacological interventions should be considered.

Keywords: Asthma, antibiotics, anxiolytics, hypnotics, drug prescription, primary care.

Word count: 2351
Background

Despite international guidelines [1], the proportion of patients with uncontrolled asthma remains high, independent of disease severity [2, 3]. Among asthma-specific drugs, inhaled corticosteroids are often underused, and rescue medication is frequently over-used [4, 5]. Studies investigating insurance claims data have suggested that non-asthma-specific drugs such as antibiotics [6] or anxiolytics/hypnotics are widely prescribed to asthma patients [7] and to the general population [8, 9]. First line antibiotics, prescription in primary care increases population carriage of resistant organisms in the community and use of second line antibiotics [10]. Anxiolytics and hypnotic prescription in primary care leads to addiction and other side effects (such as daytime fatigue, ataxia, falls, and road traffic incidents) [11]. Importantly, the actual prescribing of these drugs to asthma patients has been little studied in primary care practice. This study aimed to measure the frequency of the prescription of antibiotics and anxiolytics/hypnotics to asthma patients and to look for association between gender or age and the prescriptions of these drugs. We specifically compared the prescription profiles in general practice in two European countries with different healthcare systems for which comparable databases are available, namely France and Italy.

Methods

Data sources

We conducted a cross-sectional study using data from computerised French and Italian primary care databases. These two clinical databases, operated by Cegedim Strategic Data, collect consultation data from a network of 1200 general practitioners (GPs) (3% of French GP) [12] distributed across France and a network of 700 GPs (1.3% of Italian GP) [13] across Italy. Participating GPs continuously and voluntarily provided anonymised and coded patient data to a centralised database using an electronic health record system that is common within each country. In both countries participating GPs are selected to be representative of the French population according to three main criteria, namely, geographical area, age and gender. Activity and prescription habits of the panel have also been compared with national data and shown to be representative [14, 15]. This procedure has been approved in France by the National Data Protection Authority (ethics committee) since 2002 (reference number: 770334) and in Italy by the National Data Protection Authority since 2004 (no reference number). The data include
patient demographic characteristics and the diagnoses and prescriptions related to each consultation. The quality of these databases has been checked regularly, and they have been frequently used for pharmaco-epidemiological studies [16, 17].

**Data extraction**

The following variables were extracted from the databases: patient age and gender, number of visits to the GP and prescribed drugs, classified according to the Anatomical Therapeutic Chemical classification (ATC) [18]. Asthma drug categories belong to the ATC class R03 (Drugs for obstructive airway diseases) and include short-acting inhaled beta-agonists, long acting inhaled beta-agonists (R03AC), oral beta-agonists (R03CC), theophylline (R03DA04), cromoglicic acid (R03BC), inhaled corticosteroids (R03BA), anticholinergics and leukotriene receptor antagonists (alone or in combination) (R03DC). We also extracted data on the use of oral corticosteroids (HA02AB). The following antibiotics were used for respiratory tract infections: tetracyclines (J01A), amphenicols (J01B), macrolides (J01F), beta-lactams (J01C), sulphonamides (J01E), cephalosporins (J01D), aminoglycosides (J01G) and quinolones (J01M). We also extracted data on all anxiolytics (N05B), hypnotics/sedatives (N05C), nasal preparations (R01) and antidepressants (N06A).

**Inclusion criteria**

From a pre-selected group of patients with at least one R03 prescription in 2007, we included in the analyses all patients between the ages of 13 and 40 on the first of January 2008 who consulted during the year 2007 or 2008 and who fulfilled the asthma criteria derived from Health Employer Data and Information Set criteria (HEDIS criteria) [19]. These criteria based on prescription have shown to be more accurate to retrieve asthma patient than criteria based on diagnostic label [20]. These criteria consisted of the prescription of four or more units of any ATC R03 class drug (alone or in combination), or four or more outpatient visits with a diagnosis of asthma and two or more drug prescriptions used in the treatment of asthma, within a year. Patients with any prescription of tiotropium bromide (R03BB04) in 2007 or 2008 were excluded as well as the age range selection was intended to limit the risk of confusion with Chronic obstructive pulmonary disease (COPD) diagnosis.

**Statistical analyses**

First, the proportion of patients who received at least one prescription of antibiotics or anxiolytics/hypnotics in 2008 was estimated for France and Italy. Then, these patients were
compared with the other patients using univariate and multivariate analyses using SAS software. In the univariate analyses, we estimated the prescription frequencies of at least one antibiotic and one hypnotic/sedative or anxiolytic in 2008. Using chi-square tests, we compared these frequencies between France and Italy and assessed the influence of patient age and gender, as well as the influence of the prescription of nasal preparations and antidepressants, as indicators of conditions frequently associated with asthma, such as rhinitis and depression.

Multivariate analyses were then conducted, based on logistic regression models combining the French and Italian samples. We estimated odds ratios adjusted for asthma control criteria and severity, i.e., more than six prescriptions of short-acting inhaled beta-agonists (R03AC excluding R03AC12, R03AC13, R03AC14 and R03AC18) in 2008; the prescription of at least one inhaled corticosteroid (R03BA) in 2008, one inhaled asthma controller (R03AC12, R03AC13, R03AC14, R03AC18, R03AK06, R03AK07, R03BA, R03BC, R03DC, R03DA, R03DB or R03DX05), one oral corticosteroid (HA02AB) or the number of asthma drug units (R03; 1-7, 8-14, ≥15); and more than 12 visits to the GP with a prescription of an ATC R03 class medication in 2008.

**Results**

The final samples included 3,093 French patients (mean age 27.6, 49.7 % women) and 3,878 Italian patients (mean age 29.1, 48.7 % women) (Figure 1).

**Prescription of antibiotics**

The proportion of asthma patients having at least one prescription of antibiotics in 2008 was higher in Italy than in France (42.1 % vs. 37.1 %, P<0.0001). These prescriptions were more frequent in older patients in Italy and in female patients in both France and in Italy (Table 1).

**Prescription of anxiolytics/hypnotics**

The proportion of asthma patients with at least one prescription of anxiolytics or hypnotics in 2008 was more frequent in France than in Italy (17.8 % vs. 6.9 %, P<0.0001). The prescription of anxiolytics or hypnotics was more frequent in older and female patients in both countries (Table 2).

In the multivariate analyses (Table 3), the prescription of antibiotics was less frequent in France than in Italy (aOR=0.8) and more frequent in female than in male patients (aOR=1.1). The prescription of antibiotics was also associated with the prescription of nasal preparations.
The prescription of anxiolytics or hypnotics was more frequent in France than in Italy (aOR=5.0), in female patients (aOR=1.8) and in older patients (aOR=1.9 between 18 and 30 years and 3.3 between 31 and 40 years). The prescription of these drugs was associated with the prescription of antidepressants (aOR=9.6).

Discussion

Main Findings

Using the data from two large computerised databases, we observed that non-asthma-specific drugs are commonly prescribed to asthmatic patients in France and Italy. In particular, in 2008, 37.1% of the French patients and 42.1% of the Italian patients were prescribed antibiotics, and 17.8% of the French patients and 6.9% of the Italian patients were prescribed anxiolytics or hypnotics. A higher frequency of prescription was observed for females for these two drug categories in both countries and in older patients for anxiolytics or hypnotics in France. These results are comparable to known rates of prescription for antibiotics, anxiolytics and hypnotics in non-asthmatic patients.

Strengths and limitations

A strength of this study is the use of accurate drug prescription data from community-based general practice, where asthma patients are treated most of the time. Our data come from France and Italy, countries with poor documentation of primary care performance [21]. Our analyses are based on prescription data, not on claims data or on data on drugs dispensed OTC. Although they do not capture the OTC drug consumption or perfectly document adherence to prescribed drug regimens, these prescription data reflect the actual practice of French and Italian GPs [22]. Although we selected antibiotics typically indicated for respiratory tract infections, their prescription may have also been for other reasons than asthma exacerbation. We could not take into account some severity factors, which were not available (like socioeconomic factors or spirometry) or reliable (like smoking status) [23]. Because the derived HEDIS criteria are partly based on drug prescriptions to identify patients with persistent asthma, we may have underestimated the proportion of asthmatic patients in the GPs’ lists and the frequency of non-asthma-specific drug prescriptions [24].
From our database, we could estimate the baseline proportions of patients aged from 13 to 40 in 2008 being prescribed at least one box of antibiotics at 34.4% in France and 38.0% in Italy. For anxiolytics/hypnotics, the respective estimate were 9.7% in France and 3.2% in Italy. These figures suggest a higher prescription of these two drug (categories) classes in asthma patients in both countries.

**Antibiotics prescription**

In asthma exacerbation, GPs are likely to prescribe antibiotics, due to an overestimation of the risk of bacterial infection [25, 26]. This trend is associated with the underuse of inhaled CS likely due to the believe of an immunosuppressive effect [27]. However, antibiotics are frequently not useful in asthma exacerbations (for those caused by viral infections, for example), unless they are of bacterial origin or are associated with bacterial acute sinusitis in children [1, 28]. A CT scan is recommended for confirmation when sinusitis is suspected in adult patients. However, because the clinical features of sinusitis lack diagnostic precision [29, 30], GPs can face delays in getting access to a CT scan for their patients and may prescribe antibiotics as a precautionary measure. Independently, evidence is lacking on the actual role of the use of antibiotics, such as macrolide treatment for at least 4 weeks, in the treatment of chronic asthma [31]. The over-prescription of antibiotics to asthma patients may cause adverse events, increase costs and contribute to the development of antibiotic resistance in microbes [16]. Interestingly, antibiotic use in the first year of life represents a risk factor for asthma [32].

France and Italy belong to the group of European countries with a high level of antibiotics consumption (17 to 24 daily doses per day per 1000 inhabitants); France is currently ranked second and Italy third, behind Greece [33]. The small difference that we observed in the numbers of antibiotics prescriptions between France and Italy may be because such prescriptions are specific for respiratory tract infections. Our results confirm that women are prescribed more antibiotics than men [34, 35], which may be due to poorer control of their asthma [3].

**Anxiolytics and hypnotics prescriptions**

Our estimation of the frequency of the prescription of anxiolytics or hypnotics in French asthma patients (17.8%) is consistent with observations from the available dispensation data (25.6% for anxiolytics and 13.0% for hypnotics) [25]. In Italy, we observed less frequent prescription of this
drug category (6.9 %). A possible explanation for this finding is that patients must pay for all benzodiazepine prescriptions [36]. Thus, a GP may preferentially prescribe other reimbursable drugs. The high prevalence of anxiety disorders and insomnia in France, especially in elderly people, may explain the high numbers of prescriptions for anxiolytics and hypnotics [37]. More specifically, these prescriptions may be related to poor asthma control [3, 38–40]. This relationship could be interpreted in two ways: asthma exacerbation could induce anxiety [41] or psychiatric disorders could be risk factors for asthma exacerbations [42].

There are guidelines that promote the provision of psychological support to asthma patients and that recommend the limited prescription of psychotropic drugs [30]. The long-term use of anxiolytics and hypnotics should be avoided because of their addictive effect [43], and their use should be avoided during asthma exacerbations because of their respiratory depressant effects, which are potentially lethal [42]. Although cognitive-behavioural therapies focused on worry-proneness and the overvaluation of worry and uncertainty may be as effective as drug treatment and may be more durable for treating anxiety disorders [44], these results remain to be confirmed in asthma patients [45].

In Europe and North America, women are generally prescribed twice as many psychotropic drugs as men [46]. Psychiatric disorders and complaints are indeed more common in women than in men [47]. Women are also exposed to specific situations such as pregnancy, which can both worsen asthma and generate anxiety [25, 48]. In addition, women have fewer opportunities than men to control anxious symptoms through activities outside the home, including the social use of alcohol [49–51].

**Implications for research, policy, and practice**

The high prevalence of antibiotic prescription in asthma patients suggests a likely antibiotic overprescription in France as well and Italy. While anxiety is frequent in asthma patients, the prescription of anxiolytics and hypnotics should be avoided and the use of non-pharmacological interventions be considered in these patients. Anxiolytics/hypnotics are contraindicated during asthma exacerbations, but international guidelines remain unclear about whether to prescribe antibiotics and anxiolytics/hypnotics between asthma exacerbations [1].

**Conclusions**
While it is known that many asthma patients do not take specific controllers, the prescription of non-asthma-specific drugs is common, especially in women. Asthma patients often have additional health and life concerns, and GPs should manage them using safe interventions in a global perspective. The prescription of antibiotics and anxiolytics/hypnotics to asthma patients should follow the same rules that apply to their prescription in non-asthmatic patients. Asthma guidelines should address this issue and refer to other guidelines covering the prescription of these drugs, and alternative non-pharmacological interventions should be considered.

**Abbreviations**

aOR: adjusted odds ratios; ATC: Anatomical Therapeutic Chemical classification; GP: General practitioner; HEDIS: Health Employer Data and Information Set;

**Conflict of interest**

EVG reports a non-conditional grant from Cegedim Strategic Data and consultancy fees from Danone, ALK, ABELLO, and expertise fees from UCB, grants from IMS, personal fees Boeringher. CVW reports grants from Böhringer Ingelheim, personal fees from Novartis, grants from GSK. DD, LLa, FP and LLe report no conflicts of interest

**Authors’ contributions**

DD, LLa, EVG and LLe had the original idea together. DD and LLa, contributed to the statistical analysis. DD and LLe drafted the manuscript, which was reviewed and approved by DD, LLa, EVG, FP, CVW and LLe approved the manuscript.

**Acknowledgements**

We thank Marie Sophie Schwalm for her support and CSD Cegedim strategic data for allowance us to use these data.
References

1. GINA report, global strategy for asthma management and prevention. updated 2012. [http://www.ginasthma.org/]


17. Scientific Publications Bibliography [www.cegedimstrategicdata.com]


Table 1: Prescription of antibiotics in France and in Italy (at least one prescription in 2008) according to patient age, gender, and nasal preparation and antidepressant prescriptions (univariate analyses).

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Italy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patients</td>
<td>1147 (37.1) 1946 (62.9)</td>
<td>1634 (42.1) 2244 (57.9)</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[13-17]</td>
<td>169 (14.7) 316 (16.2)</td>
<td>0.09  180 (11.0) 238 (10.6) &lt;0.01</td>
</tr>
<tr>
<td>[18-29]</td>
<td>433 (37.7) 784 (40.3)</td>
<td>528 (32.3) 839 (37.4)</td>
</tr>
<tr>
<td>[30-40]</td>
<td>545 (47.5) 846 (43.5)</td>
<td>926 (56.7) 1167 (52.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>686 (59.8) 852 (43.8)</td>
<td>&lt;0.001  902 (55.2) 983 (43.9) &lt;0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>461 (40.2) 1094 (56.2)</td>
<td>731 (44.8) 1256 (56.1)</td>
</tr>
<tr>
<td>Nasal preparations prescription*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>293 (25.5) 1055 (54.2)</td>
<td>&lt;0.001  1428 (87.4) 2007 (89.4) &lt;0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>854 (74.5) 891 (45.8)</td>
<td>206 (12.6) 237 (10.6)</td>
</tr>
<tr>
<td>Antidepressants prescription*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1038 (90.5) 1831 (94.1)</td>
<td>&lt;0.001  1503 (92.0) 2112 (94.1) &lt;0.05</td>
</tr>
<tr>
<td>Yes</td>
<td>109 (9.5) 115 (5.9)</td>
<td>131 (8.0) 132 (5.9)</td>
</tr>
</tbody>
</table>
Data are presented as n (%). *At least one prescription in 2008

**Table 2: Prescription of anxiolytics/hypnotics (at least one prescription in 2008) in France and in Italy according to patient age, gender, and nasal preparation and antidepressant prescriptions (univariate analyses).**

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th></th>
<th>Italy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>P-value</td>
<td>Yes</td>
</tr>
<tr>
<td>Patients</td>
<td>551 (17.8)</td>
<td>2542 (82.2)</td>
<td></td>
<td>267 (6.9)</td>
</tr>
<tr>
<td>Age (yrs.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[13-17]</td>
<td>28 (5.1)</td>
<td>457 (18.0)</td>
<td><strong>&lt;0.0001</strong></td>
<td>9 (3.4)</td>
</tr>
<tr>
<td>[18-29]</td>
<td>185 (33.6)</td>
<td>1032 (40.6)</td>
<td></td>
<td>56 (21.0)</td>
</tr>
<tr>
<td>[30-40]</td>
<td>338 (61.3)</td>
<td>1053 (41.4)</td>
<td></td>
<td>202 (75.6)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>359 (65.15)</td>
<td>1179 (46.4)</td>
<td></td>
<td>186 (69.7)</td>
</tr>
<tr>
<td>Male</td>
<td>192 (34.8)</td>
<td>1363 (53.6)</td>
<td><strong>&lt;0.0001</strong></td>
<td>81 (30.3)</td>
</tr>
<tr>
<td>Nasal preparations*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>222 (40.3)</td>
<td>1126 (44.3)</td>
<td>0.09</td>
<td>237 (88.8)</td>
</tr>
<tr>
<td>Yes</td>
<td>329 (59.7)</td>
<td>1416 (55.7)</td>
<td></td>
<td>30 (11.2)</td>
</tr>
<tr>
<td>Prescription of antidepressants*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>401 (72.8)</td>
<td>2468 (97.1)</td>
<td><strong>&lt;0.0001</strong></td>
<td>169 (63.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>150 (27.2)</td>
<td>74 (2.9)</td>
<td></td>
<td>98 (36.7)</td>
</tr>
</tbody>
</table>
Table 3: Prescription of antibiotics and of anxiolytics/hypnotics (at least one prescription in 2008) according to country, patient age, gender, and nasal preparation and antidepressant prescriptions, after adjusting for asthma control and severity criteria (multivariate logistic models).

<table>
<thead>
<tr>
<th>Factors</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prescription of at least one antibiotic in 2008 (n=6965)</td>
<td>Prescription of at least one anxiolytic/hypnotic in 2008 (n=6965)</td>
</tr>
<tr>
<td>France (vs. Italy)</td>
<td>0.76 (0.66-0.87)</td>
<td>5.00 (3.45-5.26)</td>
</tr>
<tr>
<td>Age 18-30 (vs. 13-18)</td>
<td>0.98 (0.83-1.16)</td>
<td>1.92 (1.33-2.76)</td>
</tr>
<tr>
<td>Age 31-40 (vs. 13-18)</td>
<td>1.10 (0.93-1.30)</td>
<td>3.31 (2.33-4.72)</td>
</tr>
<tr>
<td>Female (vs. Male)</td>
<td>1.48 (1.34-1.65)</td>
<td>1.81 (1.53-2.14)</td>
</tr>
<tr>
<td>Nasal preparations*</td>
<td>1.99 (1.75-2.27)</td>
<td>0.98 (0.81-1.19)</td>
</tr>
<tr>
<td>Antidepressants*</td>
<td>1.22 (1.00-1.49)</td>
<td>9.56 (7.69-11.89)</td>
</tr>
</tbody>
</table>

Data are presented as adjusted odds ratios (aOR), with their 95% confidence interval.
*At least one prescription in 2008

Figure 1. Sample selection in France and Italy

Data are presented as n (%). * At least one prescription in 2008
Patients with at least one prescription of ‘R03’ in 2007

France (n=119 265)
Italy (n=138 057)

Excluded because age <13 or >40

France (n=82 701)
Italy (n=98 470)

France (n=36 564)
Italy (n=39 587)

Excluded because of a prescription of tiotropium bromide

France (n=403)
Italy (n=557)

France (n=36 161)
Italy (n=39 355)

Excluded for not meeting criteria derived from the HEDIS criteria

France (n=33 068)
Italy (n=35 477)