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Asthma and Rhinitis

Heterogeneity of the pharmacologic treatment of allergic rhinitis in Europe based on MIDAS and OTCims platforms

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Abstract

Background: The practice of allergology varies widely between countries, and the costs and sales for the treatment of rhinitis differ depending on practices and health systems. To understand these differences and their implications, the rhinitis market was studied in some of the EU countries.

Methods: We conducted a pharmaco-epidemiological database analysis to assess the medications that were being prescribed for allergic rhinitis in the years 2016, 2017 and 2018. We used the IQVIA platforms for prescribed medicines (MIDAS[®]—Meaningful Integration of Data, Analytics and Services) and for OTC medicines (OTC International Market Tracking—OTCims). We selected the five most important markets in the EU (France, Germany, Italy, Poland and Spain).

Results: Intranasal decongestants were excluded from the analyses because they are rarely prescribed for allergic rhinitis. For both Standard Units (SU) and costs, France is leading the other countries. In terms of SU, the four other countries are similar. For costs, Poland is lower than the three others. However, medication use differs largely. For 2018, in SU, intranasal corticosteroid is the first treatment in Poland (70.0%), France (51.3%), Spain (51.1%) and Germany (50.3%), whereas the Italian market is dominated by systemic antihistamines (41.4%) followed by intranasal corticosteroids (30.1%). Results of other years were similar.

Discussion: There are major differences between countries in terms of rhinoconjunctivitis medication usage.

KEYWORDS

allergic rhinitis, costs, medications, MIDAS, units

1 | INTRODUCTION

Allergic rhinitis (AR) is one of the most common chronic conditions. Available treatments include allergen avoidance, pharmacotherapy with H₁-antihistamines or intranasal corticosteroids (INCS) and allergen-specific immunotherapy (AIT).¹ Many patients are dissatisfied with their treatment for various reasons. Management does not consider the patients' needs, no cure is available, adherence to long-term therapy is poor, and/or the patients do not fully understand their condition. Real-world data obtained via mobile technology have suggested that there are differences in medication use between countries.^{2,3}

MASK-air⁴⁻⁶ is a Good Practice of DG Santé concerning the digital transformation of health.^{7,8} The practice of allergology varies widely between countries, and the costs and sales for the treatment of rhinitis differ depending on practices and health systems. To understand these differences and their implications, it is important to have an overall view of the rhinitis market in some of the EU countries.

The goal of this paper was to assess practices in different EU countries in order to better implement the Good Practice of DG Santé (MASK-air). The secondary goal was to understand some of the differences and to propose mitigation strategies. This study will

serve as a baseline status for possible future measures to be taken at the country level.

2 | METHODS

2.1 | Study design

This ARIA study evaluated the market for allergic rhinitis (AR) treatment (prescribed and over-the-counter (OTC) medications) in five EU countries in the years 2016–18. We conducted a pharmaco-epidemiological database analysis to assess the medications that were prescribed for allergic rhinitis during the years 2016, 2017 and 2018. We used the IQVIA (collaboration between Quintiles and IMS Health under the name 'IQVIA') platforms for prescribed medicines (MIDAS[®]—Meaningful Integration of Data, Analytics and Services)⁹⁻¹¹ and for OTC medicines (OTC International Market Tracking—OTCims).¹² PharMetrics Plus database (IQVIA), a large health claims database, captures demographics, physician visits, hospitalizations and prescription drugs. All medical diagnoses are captured through the International Classification of Diseases, Ninth and Tenth Editions (ICD-9 and ICD-10). This database also captures all outpatient prescription drugs and includes drug identification,

dose prescribed and treatment duration. We used manufacturing costs rather than costs for the healthcare system as, in some countries, there are rebates that are not publicly available.

2.2 | Medications

2.2.1 | Definitions used

We used SU (Standard Units) and LEU/MNF (Local Currency Euro/Manufacturer Price Level) to compare data between countries.

An SU is a unit defined by IQVIA to represent the smallest daily unit of consumption, for example one tablet, one vial/ampoule or 5 ml of liquid. As an example, a pack of 100 tablets with a dosage recommendation of two tablets a day will lead to Unit = 1, Counting Units = 100 and SU = 50.

LEU/MNF per year represents the total sales in Local Currency Euro at Ex-Manufacturer Price Level per Calendar Year.

We chose Manufacturing Cost of the drugs, and it was not possible to mention healthcare system costs due to rebates that are not publicly available.

2.2.2 | Selection of medications

We selected medications registered for AR, as well as nasal or ocular decongestants which may also be administered for AR.

The World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classifies drugs by their active ingredients¹³ and their defined daily dose (DDD), a fixed attribute that allows the conduct of national or international drug use studies.¹⁴ This ATC system is based on the earlier Anatomical Classification System, which was intended as a tool for the pharmaceutical industry to classify pharmaceutical products (as opposed to their active ingredients).¹⁵ This system was initiated in 1971 by the European Pharmaceutical Market Research Association (EphMRA).^{16,17} In the present study, we used the EphMRA system and gave the ATC correspondence.

For prescribed medications, the study was performed by IQVIA Ltd., London, England, using de-identified prescription data from MIDAS[®] for 2016, 2017 and 2018 (in € for sales) as well as numbers of treatments. MIDAS[®] provides connectivity and international standardization of national-level pharmaceutical audits to allow the cross-country analysis of company and product performance, as well as additional insights and attributes not available at a local level. MIDAS[®] captures and harmonizes the data from 92 countries worldwide, mainly for registered medicines (prescription and non-prescription) in pharmacy and hospital channels. MIDAS[®] integrates and extends IMS National Audits that accurately detail estimated product volumes, trends and market share by product and therapy class, through retail and non-retail channels. MIDAS[®] tracks the direct sales (i.e. sales invoices) of pharmaceuticals from the manufacturer to pharmacies or hospitals. MIDAS[®] also tracks indirect sales (sales going through a middleman, i.e. the wholesaler)

to pharmacies and hospitals. MIDAS[®] tracks inflow or what these different channels are purchasing (i.e. the sales made into those outlets). It represents the full European market through representative panel projections for both retail and hospital channels.

The following subgroups include symptomatic AR drugs and ophthalmic drugs (since rhinitis is often associated with conjunctivitis). Montelukast was not used as it is an asthma and a rhinitis treatment and is only indicated in patients with both rhinitis and asthma. The following medications were considered (Table 1).

For OTC medications, the QuintilesIMS OTCims (OTC International Market Tracking) database was used. OTCims is a Customized Global Information Offering that provides granular data for the effective tracking of company and competitor performance in the Consumer Health marketplace. It uses IQVIA Consumer Health Classification based on Market Positioning. Data are available across four main market segments: OTC, Personal Care, Patient Care and Nutrition. Data are included for 36 countries from Europe, Asia Pacific, and North and Latin America. Clients are supported in both own as well as competitor product/pack performance tracking against key performance indicators.

The MIDAS[®] database does not identify the disease for which the medication has been used. This is the case for systemic antihistamines (R06A0) which include treatments for the nose, skin and other organs. They cannot be distinguished. INCS (R01A1) can also be administered for AR, non-allergic rhinitis and rhinosinusitis.

The list of OTC medications is given in Table 2. The four OTC therapy classes include 'oral H1-antihistamines' and 'INCS'. The list is too far from ATC to propose any correspondence.

2.3 | Allergen-specific immunotherapy

The only country where AIT is mostly delivered in pharmacies is Germany. We only provided data for AIT in Germany (allergens, V1A0).

2.3.1 | Selection of countries

The market for prescribed medications (in costs for patients) for 2018 in all EU countries was ranked in order to choose the markets with the highest sales (Table S1). OTC medications were not considered in the country selection because a single database cannot be used in all countries. AIT was not considered in the country selection since large variations exist between countries in terms of supply (pharmacies, hospitals, Named-Patient Products, etc.).

The first six countries with the highest sales for AR medications and nasal decongestants were France, Germany, Italy, Spain, Poland and the UK. There was a big gap between UK N°6 and Sweden N°7. Thus, we considered only the first six countries. In the UK, a significant proportion of sales took place in supermarkets and these were not considered by IQVIA. Thus, the country had to be excluded.

TABLE 1 Codes of prescribed medications

Description	EphMRA code	ATC code	Application form
Nasal corticosteroids without anti-infectives	R01A1	R01AD	Nasal spray, drops, ointment
Nasal anti-allergic agents	R01A6	R01AC	Nasal spray, drops, ointment
Nasal decongestants ^a	R01A7	R01AA + R01AB	Nasal spray, drops, ointment
Other topical nasal preparations	R01A9	R01AX	Nasal spray, drops, ointment
Systemic rhinologic preparations (including oral decongestants)	R01B0	R01BA	Systemic
Systemic antihistamines	R06A0	R06AA + R06AB + R06AD + R06AE + R06AX	Systemic
Ophthalmologic anti-allergic antihistamines	S01G1	S01GX	Eye drop
Ophthalmologic anti-allergic mast cell stabilizers	S01G2		Eye drop
Other ophthalmologic anti-allergic agents	S01G3		Eye drop
Ophthalmologic decongestants with sympathomimetics ^a	S01G5	S01GA	Eye drop

^aIncluded although not indicated in allergic rhinitis but may be used.

TABLE 2 Codes of over-the-counter (OTC) medications

Description	OTC class
Nasal decongestants	01B2
Respiratory & general antiallergics	01E1
Eye antiallergics	07A2
Eye decongestants & anti-inflammatories	07A5

The 'Sell-Out' (Medication dispensed in pharmacies) data and, if not available, the 'Sell-In' (Medication delivered in pharmacies) data were obtained from IQVIA. For the countries selected, the databases were from different origins, and the data type differed taking into account the country specificities on drug dispensing (Table 3).

2.4 | Collection of information

There are different methods of collecting the information, and we needed to make assumptions.

It is possible to compare 'Sell-in' (from wholesaler to retail pharmacy, effects like stocking are included) and 'Sell-out' (from retail pharmacy to patient) data, bearing in mind some biases. Therefore, for one quarter, the 'Sell-in' data might be higher when compared to 'Sell-out' due to stock, but these effects are minimized for yearly data. In the countries tested, 'hospital' means hospital consumption from hospital to patient.

For the OTCims Panel, all panels are 'Sell-out'.

2.5 | Analyses

We conducted a descriptive analysis to evaluate the medications used in different countries. To derive figures for anti-rhinitis

consumption per person over the three years, we linked consumption by SU to population estimates.

Stratification: The analyses were performed separately for prescription data and OTC data. In some countries, the same products could be prescribed and were also available OTC. Thus, in order to prevent multiple counts, a complex merger process between prescriptions and OTC was necessary.

Data periods: The analyses covered the periods 2016, 2017 and 2018. Results were processed on a yearly basis.

Analyses were performed once at the same time.

Projection: The results were projected yearly per country.

3 | RESULTS

3.1 | Intranasal decongestants (R1A7 and 01B2)

Intranasal decongestant sales (R1A7 and 01B2) are extremely variable, with low sales in France (from 612,073 to 751,739 kSU per year, 12.6%–14.8% of total sales) and high sales in Germany (from 6,586,460 to 6,890,822 kSU per year, 71.6%–79.6%) (Table 4). We checked the monthly variation of R1A7 in Germany in 2018 and found that they were purchased less often during the pollen season than outside (Figure S4). In Germany, although the majority of products were available in pharmacies, they were non-prescribed. We therefore excluded R1A7 and 01B2 from further analyses as they are unlikely to represent patients with allergic rhinitis.

3.2 | Overall results without intranasal decongestants (R1A7 and 01B2)

The results are presented in Table S2, Table 5 and Figure 1. For both SU and costs, France is leading the other countries. In terms of SU,

TABLE 3 Origin of the databases

Countries/Panels:	Country	Channel	Data type
OTCIMS	France	Pharmacy	Sell-out
		Para-pharmacy	Sell-out
	Germany	Pharmacy	Sell-out
		Pharmacy mail order	Sell-out
		Discounter	Sell-out
		Drugstores	Sell-out
		Supermarkets	Sell-out
	Italy	Pharmacy	Sell-out
		Para-pharmacy	Sell-out
		Supermarkets & hypermarkets-corner	Sell-out
		Supermarkets & hypermarkets-non corner	Sell-out
	Poland	Pharmacy	Sell-out
	Spain	Pharmacy	Sell-out
Para-pharmacy		Sell-out	
MIDAS	France	Hospital	Sell-in
		Retail	Sell-in
	Germany	Retail/mail order	Sell-out
		Hospital	Sell-in
	Italy	Hospital	Sell-in
		Retail	Sell-in
	Poland	Hospital	Sell-in
		Retail	Sell-in
	Spain	Hospital	Sell-in
		Retail	Sell-out
		Retail	Sell-in

the four other countries are similar. For costs, Poland is lower than the three others. However, medication use differs largely. For 2018, in SU, INCS is the first treatment in Poland (70.0%), France (51.3%), Spain (51.1%) and Germany (50.3%), whereas the Italian market is dominated by systemic antihistamines (41.4%) followed by INCS (30.1%). Results of other years are similar. MPAze-Flu (DYMISTA) is represented from less than 1% in Spain to 1.5% in Poland and Germany and to around 2.6% in France of SU in 2018.

In costs for 2018, INCS represent 20.7% of the market in Poland, around 26–28% in Germany, Italy and Spain, and up to 38.6% in France. Systemic antihistamines represent from 45.8% (Italy) to 49.3% (France), 57% to 59% (Germany, Spain) and 67% (Poland).

3.3 | Rhinoconjunctivitis medication consumption per person in Europe

There are very large differences in medication consumption (SU) per person in Europe depending on the country (Table 6). In France,

there are 4.3 times more INCS sold per inhabitant than in Germany. On the other hand, in Germany, there are 9.25 times more nasal decongestants sold per inhabitant than in France.

Although the proportion of reimbursement/out of pocket differs between countries, and even in the same country, for different classes of drugs, reimbursement and OTC availability of medications differ in EU countries (Table S3).

3.4 | Allergen immunotherapy

In Germany, AIT represents between 33.2% and 37.3% of LEU/MNF (Table 4).

4 | DISCUSSION

The present paper shows that there is a great heterogeneity in AR medications across Europe. Some explanations may be proposed including reimbursement strategies.

TABLE 4 Overall units and costs obtained by MIDAS and OTCims

	Annual SU (thousands)			Annual LEU/MNF (million €)		
	2016	2017	2018	2016	2017	2018
France						
All without R1A7 + 01B2	4,345,542 (85.2%)	4,232,505 (85.8%)	4,262,629 (87.4%)	297,502 (91.1%)	289,445 (91.7%)	290,265 (92.6%)
R1A7 + 01B2	751,739	697,063	612,073	29,107	25,742	23,134
Total	5,097,281	4,929,568	4,874,702	326,609	315,187	313,399
Germany						
All without R1A7 + 01B2	1,873,427 (28.4%)	1,813,819 (20.4%)	1,988,758 (22.4%)	148,607 (50.2%)	136,762 (46.9%)	154,858 (48.8%)
R1A7 + 01B2	6,586,460	6,763,831	6,964,445	147,137	155,700	162,511
R1A7 prescribed	4	2	0	14	6	0
Total	8,459,887	8,577,650	8,879,580	295,744	292,462	317,369
Allergens (V1A0)	896,439	841,312	964,073	107,746	94,514	107,138
Italy						
All without R1A7 + 01B2	1,584,524 (63.5%)	1,560,315 (63.5%)	1,560,179 (62.3%)	163,988 (75.6%)	163,317 (74.8%)	167,595 (74.5%)
R1A7 + 01B2	908,777	897,072	945,276	52,739	55,042	57,843
Total	2,493,301	2,457,387	2,505,455	216,727	218,359	225,438
Poland						
All without R1A7 + 01B2	1,725,720 (62.4%)	1,804,554 (63.5%)	1,806,021 (63.7%)	98,413 (69.1%)	98,622 (67.5%)	101,771 (67.8%)
R1A7 + 01B2	1,039,763	1,037,053	1,029,205	44,063	47,571	47,989
Total	2,765,483	2,841,607	2,835,226	142,476	146,193	149,960
Spain						
All without R1A7 + 01B2	1,659,893 (71.1%)	1,696,172 (72.4%)	1,746,283 (73.4%)	158,275 (83.5%)	160,797 (83.5%)	168,842 (72.8%)
R1A7 + 01B2	675,098	645,544	631,286	31,317	31,703	32,392
Total	2,334,991	2,341,716	2,377,569	189,592	192,500	232,852

4.1 | Limitations

Although the IQVIA platform appears to be a good source of data for estimating drug consumption in different countries, there are several limitations.

First, we can only use the classification of medications proposed by IQVIA and some classes assess medications for multiple diseases such as 'Systemic antihistamines'. It is likely that their use differs between countries and that the results reported in this paper may not be totally comparable.

Second, in the IQVIA database, medications are not classified by disease and there are overlaps between skin and respiratory diseases. Furthermore, in respiratory diseases, there are different indications such as allergic and non-allergic rhinitis or rhinosinusitis.

Third, we had to make assumptions that were discussed in the methods. It does not seem that these estimations may have led to significant problems.

Fourth, another limitation is non-adherence to prescribed drugs in patients that cannot be estimated. Thus, the results of the study do not consider lack of adherence to medication which was reported to be quite high.¹⁸

Finally, the exclusion of nasal decongestants was proposed because they are not indicated in AR and are largely used for common cold and cough in some countries. The BSCAI guidelines (the only European guidelines)¹⁹ and ARIA (global guidelines)²⁰ - used in most European countries - do not recommend the regular use of intranasal decongestants. In ARIA, the last recommendation was made in 2010; there have not been any other important papers on the subject since. In adults with AR and severe nasal obstruction, we suggest a very short course (no longer than 5 days, and preferably shorter) of intranasal decongestants while co-administering other drugs (conditional recommendation, very low-quality evidence). We suggest that clinicians should not administer and that parents should not use intranasal decongestants in preschool children

TABLE 5 Standard units (SU) and costs of medications (LEU/MNF, absolute for fiscal year) in five European countries based on MIDAS and OTCims

	Standard units 2016 (Absolute)	Standard units 2017 (Absolute)	Standard units 2018 (Absolute)	LEU/MNF 2016 (Absolute)	LEU/MNF 2017 (Absolute)	LEU/MNF 2018 (Absolute)
France	5,097,280,885	4,929,568,274	4,874,702,206	326,609,288	315,187,283	313,398,985
Hospital	24,443,211	22,347,969	24,131,960	3,994,101	3,930,879	4,164,317
R1A1	4,430,987	3,142,635	3,408,948	323,730	307,361	336,467
R1A7	4,165,245	3,735,215	3,600,270	61,833	52,174	48,840
R6A0	12,383,393	12,163,848	12,668,770	3,124,229	3,209,892	3,284,036
*Dymista	0	720	144,840	0	74	13,948
S1G1	14,980	13,119	20,349	1198	1095	1636
S1G2	3,376,938	3,251,404	4,251,647	126,016	124,745	153,377
S1G3	63,456	35,431	170,362	2455	1587	7990
Retail	4,690,535,231	4,530,115,204	4,493,777,976	303,069,376	292,933,322	290,997,700
R1A1	2,281,980,628	2,205,997,152	2,182,679,986	119,602,835	114,537,298	111,803,786
R1A7	382,849,348	334,644,594	289,028,123	12,324,480	10,578,877	9,086,817
R6A0	1,259,075,253	1,250,282,248	1,284,035,579	140,023,134	137,490,816	139,313,337
*Dymista	796,680	34,165,320	114,622,080	113,530	3,444,710	11,462,208
S1G1	50,009,780	47,470,270	48,741,660	4,633,682	4,569,464	4,788,785
S1G2	592,278,142	570,187,400	570,438,348	20,262,676	19,507,566	19,794,182
S1G3	124,342,080	121,533,540	118,854,280	6,222,569	6,249,301	6,210,793
Off-Take	360,521,721	352,837,569	333,455,785	19,074,984	17,810,498	17,700,707
01B2	343,489,664	332,041,918	297,306,639	16,300,087	14,656,459	13,563,859
01E1	5,346,125	7,039,683	23,249,372	821,915	938,080	1,998,837
07A2	400	0	0	13	0	0
07A5	11,685,532	13,755,968	12,899,774	1,952,969	2,215,959	2,138,011
Para pharm	21,780,722	24,267,532	23,336,485	470,827	512,584	536,261
01B2	21,236,429	23,640,960	22,138,035	421,973	454,114	434,148
01E1	341,703	422,512	978,770	44,419	52,036	96,827
07A2	400	0	200	8	0	4
07A5	202,190	204,060	219,480	4427	6434	5282
Germany	8,474,999,252	8,595,106,633	8,898,547,120	691,220,202	686,781,024	707,408,598
Hospital	249,496,527	255,184,305	250,282,157	8,711,628	7,863,795	8,272,906
R1A1	5,474,147	5,439,325	5,575,688	324,277	282,455	299,298
R1A7	228,397,070	234,976,448	229,199,632	2,923,767	2,942,361	2,909,478
R6A0	13,346,015	12,761,105	13,384,968	2,066,290	1,923,863	2,484,365
V1A0	17,442	12,954	13,269	3,335,043	2,668,134	2,524,879
*Dymista	64,240	44,400	72,120	10,675	7400	12,154
S1G1	291,274	303,232	410,628	10,349	11,407	11,025
S1G2	1,387,085	1,278,129	1,156,591	16,949	13,627	14,754
S1G3	583,494	413,112	541,381	34,953	21,948	29,107
Phmscope	7,867,016,585	7,966,630,528	8,257,235,986	674,286,284	669,888,195	689,539,848
R1A1	775,921,033	755,819,069	829,008,199	37,308,422	37,331,516	42,471,934
R1A7	6,231,082,998	6,396,953,648	6,486,356,795	139,382,223	148,708,228	155,314,296
R6A0	564,852,155	543,717,940	608,321,693	92,324,525	80,342,707	88,917,806
V1A0	15,095,779	17,444,001	18,953,549	392,140,744	391,651,448	387,486,192
*Dymista	36,562,768	34,240,092	36,755,760	6,093,972	5,706,703	6,165,471
S1G1	39,119,160	33,719,080	44,437,320	2,479,823	2,128,481	2,849,695

(Continues)

TABLE 5 (Continued)

	Standard units 2016 (Absolute)	Standard units 2017 (Absolute)	Standard units 2018 (Absolute)	LEU/MNF 2016 (Absolute)	LEU/MNF 2017 (Absolute)	LEU/MNF 2018 (Absolute)
S1G2	106,793,840	94,276,360	104,978,800	2,957,406	2,544,410	2,862,850
S1G3	134,151,620	124,700,430	165,179,630	7,693,141	7,181,405	9,637,075
Pharmacy	193,137,402	210,177,201	216,417,121	5,093,515	5,681,215	5,846,784
01B2	83,858,450	98,444,811	103,622,407	2,281,585	3,043,918	3,246,814
07A5	100,576,690	104,101,960	105,335,380	2,088,516	2,002,415	2,000,027
O1E1	5,926,522	4,475,960	4,168,654	578,025	481,892	452,820
07A2	2,775,740	3,154,470	3,290,680	145,389	152,990	147,123
Discounter	8,832,814	8,353,946	8,590,854	257,229	197,507	193,400
01B2	8,832,814	8,353,946	8,590,854	257,229	197,507	193,400
Drugstore	113,170,473	114,023,434	124,054,013	1,999,975	2,237,524	2,572,119
01B2	86,313,303	89,465,439	100,583,488	1,727,111	1,780,528	1,795,086
O1E1	26,857,170	19,024,460	15,197,810	272,864	184,562	174,842
07A2	0	4,272,160	4,959,840	0	71,889	80,231
07A5	0	1,261,375	3,312,875	0	200,545	521,960
S/Market	38,898,835	36,600,671	37,537,948	778,642	823,753	893,062
01B2	30,506,765	30,122,121	32,530,143	733,210	724,048	766,362
O1E1	8,392,070	4,216,660	3,629,200	45,432	51,778	51,792
07A2	0	2,176,640	1,022,880	0	34,308	18,346
07A5 E	0	85,250	355,725	0	13,619	56,562
Small SMKT	4,446,616	4,136,548	4,429,041	92,929	89,035	90,479
01B2	3,781,336	3,682,438	3,562,601	89,961	85,649	82,075
O1E1	665,280	372,290	680,470	2968	1762	3051
07A2	0	81,120	172,320	0	1512	3166
07A5	0	700	13,650	0	112	2187
Italy	2,493,701,426	2,460,288,900	2,508,148,909	221,605,769	224,095,406	230,723,070
Hospital	19,268,623	20,624,634	22,896,801	7,307,742	8,225,054	7,737,864
R1A1	2,637,698	3,097,120	6,309,450	215,073	247,465	522,799
R1A7	6,402,915	6,575,175	6,376,050	152,228	158,388	162,177
R6A0	6,641,693	7,132,653	6,905,066	2,345,114	2,494,632	2,189,101
V1A0	2,307,100	2,676,768	2,454,872	4,557,923	5,291,088	4,839,904
*Dymista	12,628	18,840	90,240	1854	2762	13,228
S1G1 O	1,120,848	1,033,981	791,298	31,163	27,931	20,146
S1G2	8931	18,846	3785	448	750	179
S1G3	149,438	90,091	56,280	5793	4800	3558
Retail	1,883,436,191	1,844,094,607	1,881,117,488	176,870,734	177,557,354	184,265,292
R1A1	496,427,232	485,212,020	499,795,900	43,107,606	42,304,966	44,205,554
R1A7	683,174,377	678,502,447	689,459,915	40,119,423	42,168,247	44,414,520
R6A0	372,064,000	370,177,978	377,874,748	73,414,490	72,901,327	74,732,272
V1A0	162,692	225,659	238,380	320,549	445,196	470,630
*Dymista	30,759,112	31,069,200	36,225,840	6,041,621	6,102,510	7,115,358
S1G1	230,409,525	214,051,423	215,322,465	10,608,676	10,101,835	10,384,357
S1G2	35,852,210	31,149,190	31,040,290	2,588,674	2,362,103	2,352,370
S1G3	65,346,155	64,775,890	67,385,790	6,711,316	7,273,680	7,705,589
Off-Take	420,390,759	426,548,277	441,534,997	29,617,267	30,277,427	30,776,362
01B2	183,808,168	183,945,839	177,617,076	8,938,640	9,011,910	8,847,760

(Continues)

TABLE 5 (Continued)

	Standard units 2016 (Absolute)	Standard units 2017 (Absolute)	Standard units 2018 (Absolute)	LEU/MNF 2016 (Absolute)	LEU/MNF 2017 (Absolute)	LEU/MNF 2018 (Absolute)
O1E1	18,147,917	15,335,022	13,921,881	1,525,029	1,454,974	1,373,791
07A2	23,223,460	24,866,070	25,146,300	1,345,096	1,761,222	2,005,317
07A5	195,211,214	202,401,346	224,849,740	17,808,502	18,049,321	18,549,494
Para pharm	41,399,851	42,567,200	42,588,137	2,863,821	2,865,082	2,796,401
01B2	15,199,665	15,112,203	13,707,888	754,197	760,555	722,685
O1E1	3,130,451	2,712,157	2,786,754	300,695	289,792	304,747
07A2	811,270	1,139,910	856,970	50,091	72,531	72,711
07A5	22,258,465	23,602,930	25,236,525	1,758,838	1,742,204	1,696,258
Mass market	113,035,642	110,123,888	104,234,591	4,326,080	4,470,655	4,382,715
01B2	62,842,213	61,141,481	57,418,452	2,703,120	2,737,765	2,643,213
O1E1	1,971,259	2,292,072	2,124,944	231,160	347,777	372,003
07A2	6,867,550	6,237,605	5,858,435	244,540	227,324	215,782
07A5	41,354,620	40,452,730	38,832,760	1,147,260	1,157,789	1,151,717
Mass MKT-NC	16,170,360	16,330,294	15,776,895	620,125	699,834	764,436
01B2	2,236,235	1,796,525	1,461,621	72,318	67,713	52,786
O1E1	26,030	37,499	36,434	3186	5115	5743
07A2	62,585	66,140	67,690	2572	2929	2599
07A5	13,845,510	14,430,130	14,211,150	542,049	624,077	703,308
Poland	2,765,988,564	2,842,199,367	2,835,908,301	155,134,749	160,226,726	164,378,170
Hospital	15,137,626	16,445,222	16,028,988	1,596,145	1,627,760	1,654,806
R1A1	2,298,952	2,749,104	2,513,696	37,254	38,483	38,328
R1A7	7,500,858	8,190,886	7,891,661	132,630	154,203	158,718
R6A0	4,753,783	4,890,510	5,023,220	672,903	699,454	790,018
V1A0	18,573	17,682	17,331	745,406	726,527	658,504
*Dymista	360	1080	4680	59	176	663
S1G1	376,200	407,800	388,700	4560	5658	5468
S1G2	160,400	154,620	162,200	1578	1622	1783
S1G3	28,860	34,620	32,180	1814	1813	1987
Retail	2,366,366,557	2,417,153,496	2,431,208,428	146,144,714	150,426,738	153,779,672
R1A1	653,132,400	703,686,012	713,149,704	22,924,341	20,705,341	20,673,273
R1A7	1,004,863,014	1,011,149,604	992,832,758	42,197,935	45,819,743	46,349,359
R6A0	486,694,708	493,734,398	503,733,894	64,423,901	66,049,824	67,696,276
V1A0	468,615	573,662	665,272	11,912,466	13,306,862	13,759,838
*Dymista	6,561,360	8,876,280	21,715,680	972,582	1,273,403	2,772,401
S1G1	32,080,900	28,343,000	26,681,800	565,844	519,091	490,397
S1G2	142,996,760	131,793,440	139,948,300	1,440,042	1,259,054	1,311,795
S1G3	46,130,160	47,873,380	54,196,700	2,680,185	2,766,823	3,498,734
Offtake	384,484,381	408,600,649	388,670,885	7,393,890	8,172,228	8,943,692
01B2	27,399,224	27,711,821	27,479,770	1,732,406	1,596,898	1,479,956
O1E1	70,555,480	59,164,147	59,134,467	2,684,702	2,764,934	3,395,491
07A2	19,943,700	40,539,400	52,760,100	562,182	1,057,186	1,368,100
07A5	266,585,977	281,185,281	249,296,548	2,414,600	2,753,210	2,700,145
Spain	2,335,455,930	2,342,195,399	2,378,256,266	190,665,883	193,609,689	202,734,323
Hospital	9,112,183	11,052,976	10,225,055	1,513,651	1,645,761	1,560,387
R1A1	2,172,526	3,357,987	2,535,450	50,334	86,924	75,791

(Continues)

TABLE 5 (Continued)

	Standard units 2016 (Absolute)	Standard units 2017 (Absolute)	Standard units 2018 (Absolute)	LEU/MNF 2016 (Absolute)	LEU/MNF 2017 (Absolute)	LEU/MNF 2018 (Absolute)
R1A7	2,005,927	2,283,341	2,158,777	88,131	93,613	92,522
R6A0	4,027,829	4,395,427	4,440,996	1,309,209	1,392,995	1,316,609
*Dymista	0	0	0	0	0	0
S1G1	119,460	150,960	183,220	6728	8488	10,080
S1G2	9300	5300	11,700	378	208	459
S1G3	777,141	859,961	894,912	58,871	63,533	64,926
Sell-out	2,194,730,398	2,195,372,883	2,242,126,707	180,353,377	182,800,026	191,487,364
R1A1	855,946,916	889,440,180	919,688,976	42,155,216	45,579,352	47,849,302
R1A7	627,535,576	601,079,486	590,371,990	28,513,887	29,012,900	29,795,483
R6A0	457,352,438	465,876,773	487,974,761	91,904,533	91,040,256	96,059,459
V1A0	465,028	479,164	686,600	1,074,098	1,110,096	1,584,551
*Dymista	9,252,292	11,344,080	12,349,804	1,233,993	1,596,132	1,852,831
S1G1	111,263,360	102,285,020	107,474,200	5,855,324	5,514,404	5,680,404
S1G2	33,539,100	29,905,100	29,050,300	772,194	681,761	669,877
S1G3	108,627,980	106,307,160	106,879,880	10,078,125	9,861,257	9,848,288
Off-Take	129,508,699	131,988,535	122,727,936	8,702,319	8,969,019	9,517,896
01B2	46,051,527	42,168,335	38,740,393	2,714,808	2,595,648	2,513,212
O1E1	4,814,504	4,447,039	5,056,991	1,025,215	760,457	834,638
07A2	184,714	434,790	2,210,500	57,610	131,428	218,062
07A5	78,457,954	84,938,371	76,720,052	4,904,686	5,481,486	5,951,984
Parapharm	2,104,650	3,781,005	3,176,568	96,536	194,883	168,676
01B2	4050	13,875	14,850	256	817	1038
O1E1	1640	4660	11,710	308	1505	3941
07A5	2,098,960	3,762,470	3,150,008	95,972	192,561	163,697

(conditional recommendation, very low-quality evidence). A report by Statista (<https://www.statista.com/statistics/417727/cough-and-cold-self-medication-market-sales-in-europe/>) showed the same ranking order for cold and cough drugs as the IQVIA data for nasal decongestants. Germany ranked first (1,557 million € for 2017), followed by Italy (718), Poland (609), Spain (552) and France (490). In Germany, in 2018, the months with the highest pollen counts were those with the lowest use of nasal decongestants.

4.2 | Interpretation

Although many papers dealt with AR costs, we were not able to find any that analyzed the units sold. Moreover, costs are difficult to compare between papers as OTC and prescribed drugs vary between countries, and direct AR costs reduced considerably when OTC medications became available. In the present paper, we found large differences between EU countries and particularly between France (low nasal decongestants, high INCS consumption) and Germany (the opposite).

In a Swedish study, it was found that 71.6% of patients with AR were using OAH, 44% INCS and 41% nasal decongestants.²¹

In France, most medications are reimbursed if prescribed. A long wait to consult French medical specialists encourages the quick purchase of OTC drugs, during pollen seasons, for example. French pharmacists are often well trained for offering OTC drugs: easy-to-use, inexpensive oral OAH, nasal sprays and eye drops. ENT physicians and allergists traditionally prescribe these molecules and train general practitioners to also do so. These molecules were prescribed very early by pediatricians, also to children of atopic families who present nasal signs. These children are used to these methods from the age of 3.

In Germany, the situation is more complex than in other countries. The general reimbursement strategy is outlined in Table 4. 8.7% of the population are privately insured; this is only possible for people who are self-employed or for employees who earn an above-average salary. For privately insured patients, all allergic rhinitis medications are usually reimbursed but this depends very much on the individual contracts. Some privately insured patients, for instance, have a contract where they are only reimbursed for medications and other healthcare costs above a chosen limit, for example 1,000€ per year. This is a contract which young people very often choose, with the monthly costs being lower and the speculation of not having to use this fixed rate in the year. These patients often tend

FIGURE 1 Comparison between countries for 2018 of the number of standard units sold (SU) and costs (LEU/MNF) Incs include dymista

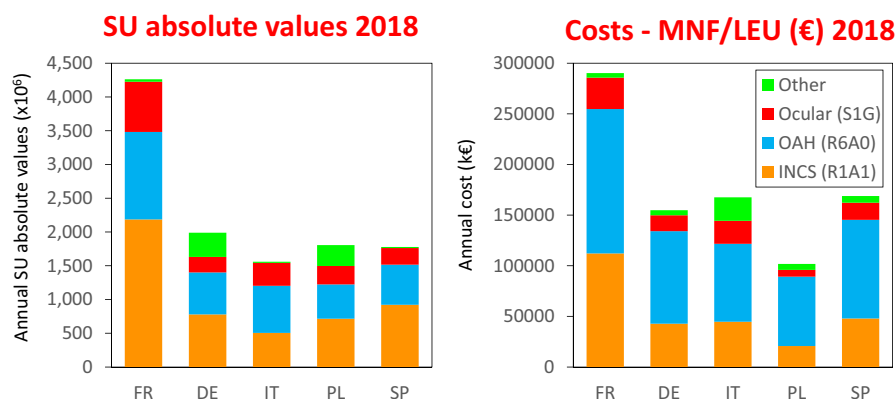


TABLE 6 Rhinoconjunctivitis medication consumption in Europe per inhabitant (results in SU per year, 2018)

	Population 2015 (in thousands)	All without nasal decongestants	Nasal decongestants	INCS
France	66,352	64.2	9.2	33
Germany	81,175	24.5	85.1	7.6
Italy	60,795	25.7	15.6	8.3
Poland	38,005	47.5	27.0	18.8
Spain	46,440	36.5	13.7	20.0

not to buy medications recommended by the physician. The rest of the population is under the statutory health insurance (Gesetzliche Krankenversicherung) but can choose between policies of different companies. Also, the official healthcare insurance companies have different reimbursement strategies, and details vary. The general reimbursement strategy is outlined in Table 4 but another variable comes into play. Physicians treating patients under the statutory health insurance scheme in Germany have a fixed budget for medication costs and can be made liable if they do not adhere to the very strict economic prescription pathways. Although OAH can be reimbursed for severe allergic rhinitis, even if over-the-counter products are available, physicians often choose not to prescribe these medications on a panel prescription allowing reimbursement. They choose rather to give a private prescription to the patient which means that he/she has to cover the full costs. Last but not least, another limiting factor in Germany is the fact that all patients above 12 years of age also have to pay a cost share fee for every drug at the pharmacy (10% of the price of the product), with a minimum of 5 € and maximum of 10 €.

In Italy, most medications for rhinoconjunctivitis are provided through medical prescription. OAH are reimbursed by the NHS (National Healthcare System), whereas INCS (including INCS + INAH) are not, except in the region of Tuscany.

In Poland, the situation is similar to France. The medications for Allergic Rhinoconjunctivitis are reimbursed if prescribed by the physician. Everyone is covered by the National Health Fund (NHF), but the private sector is also very active. Patients can visit specialists working under the NHF for free, but they have to wait for a few months to consult. Otherwise, they can choose to visit a private doctor and pay out of pocket for the service without having

to wait. Physicians in private and public sectors can prescribe reimbursed medications. Many medications which are reimbursed if prescribed also have an OTC version, including INCS and OAH. Similar to France, these molecules were prescribed very early by pediatricians, also to children of atopic families who present nasal symptoms. These children are used to these methods from the age of 2. In Poland, nasal washing with isotonic saline is also very common.

In Spain, most medications for rhinoconjunctivitis are provided through medical prescription. Nevertheless, there are a few formulations which may be acquired as OTC, including some OAH, such as cetirizine, and INCS, such as fluticasone propionate. A recent study has calculated the direct and indirect costs of AR in patients attending specialized clinics in Spain.²² Data showed that the mean drug treatment per year was significantly higher in persistent AR (77.88 ± 134.22€) compared to intermittent AR (45.62 ± 78.93€). On the other hand, no significant differences were found when comparing mild, moderate and severe AR (41.77 ± 86.02€, 70.36 ± 127.07€ and 72.16 ± 114.60€, respectively). Direct costs accounted for 24% of total costs, and drug therapy was only 10%–13% of the direct costs.

Cultural and reimbursement differences between countries may explain trends in treatment.

Many studies reported that OAH are more often used than INCS^{23–25} and this accords with the results of the present study. However, this is the first multi-national study to compare medication delivery.

The large differences between countries in INCS use are surprising since the guidelines of ARIA,²⁶ the British Society of Allergy and Clinical Immunology¹⁹ and the US Practice parameters²⁷ all recommend INCS as the first-line treatment for moderate to severe AR and

it is likely that AR severity is similar between countries. However, the reimbursement strategies of some countries may impair the implementation of guidelines. Moreover, although most AR patients consulting a physician have moderate to severe rhinitis, the low level of ICNS prescribed is surprising. These data may at least partly explain the poor satisfaction of AR patients.

There are also very large differences between countries in intranasal decongestants. Although the indications cannot be assessed using the IQVIA database, it is likely that many patients in Germany use intranasal decongestants for AR. This does not accord with guidelines. In ARIA, 'in adults with AR and severe nasal obstruction, we suggest a very short course (no longer than 5 days, and preferably shorter) of intranasal decongestants while co-administering other drugs (conditional recommendation, very low-quality evidence).'²⁰

5 | CONCLUSIONS

With the limitations discussed, this study is of great interest for assessing the heterogeneity of pharmacotherapy in some European countries and can be used as a baseline for future studies to show treatment trends.

CONFLICT OF INTEREST

CB reports personal fees from Meda. JB reports personal fees from Chiesi, Cipla, Hikma, Menarini, Mundipharma, Mylan, Novartis, Purina, Sanofi-Aventis, Takeda, Teva, Uriach, other from KYomed-Innov, outside the submitted work. VC reports personal fees from ALK, Allergopharma, Allergy Therapeutics, Diater LETI, Thermofisher, Stallergenes, outside the submitted work. PD reports personal fees and non-financial support from Astra Zeneca, Chiesi, personal fees from Mylan, personal fees from Sanofi, GlaxoSmithKline, Menarini, outside the submitted work. LK reports grants and personal fees from Allergopharma, LETI Pharma, MEDA/Mylan, Sanofi, personal fees from HAL Allergie, Allergy Therapeut, grants from ALK Abelló, Stallergenes, Quintiles, ASIT biotech, Lofarma, AstraZeneca, GSK, Immunotk outside the submitted work; and Membership: AeDA, DGHN, Deutsche Akademie für Allergologie und klinische Immunologie, HNO-BV GPA, EAACI. OP reports grants and personal fees from ALK-Abelló, Allergopharma, Anergis S.A., Stallergenes Greer, HAL Allergy Holding B.V./HAL Allergie GmbH, Bencard Allergie GmbH/Allergy Therapeutics, Lofarma, ASIT Biotech Tools S.A., Laboratorios LETI/LETI Pharma, grants from Biomay, Circassia, Glaxo Smith Kline, personal fees from MEDA Pharma/MYLAN, Mobile Chamber Experts (a GA2LEN Partner), Indoor Biotechnologies, Astellas Pharma Global, EUFOREA, ROXALL, NOVARTIS, SANOFI AVENTIS, Med Update Europe GmbH, streamedup! GmbH, outside the submitted work. BS reports grants from AstraZeneca, personal fees from Mylan, Polpharma, outside the submitted work. GS reports personal fees from ALK- Abello, Mylan, GSK, Bayer outside the submitted work. EVG reports personal fees from PELyon, outside the submitted work. TZ reports: Organizational affiliations:Committee

member: WHO-Initiative 'Allergic Rhinitis and Its Impact on Asthma' (ARIA), Member of the Board: German Society for Allergy and Clinical Immunology (DGAKI); Head: European Centre for Allergy Research Foundation (ECARF); President: Global Allergy and Asthma European Network (GA²LEN). Member: Committee on Allergy Diagnosis and Molecular Allergology, World Allergy Organization (WAO).

AUTHOR CONTRIBUTIONS

Jean Bousquet designed and interpreted the study data and wrote the paper. Detlef Schröder-Bernhardi co-designed the study and participated in the analysis interpretation. Claus Bachert, G. Walter Canonica, Victoria Cardona, Elisio M Costa, Wienczyslawa Czarlewski, Philippe Devillier, Joao A. Fonseca, Ludger Klimek, Piotr Kuna, Olga Lourenco, Joaquim Mullol, Oliver Pfaar, Nhat Pham-Thi, Boleslaw Samolinski, Glenis Scadding, Sophie Scheire, Eric Van Ganse, Torsten Zuberbier interpreted the data and reviewed the paper. They all gave their agreement for the publication. Julia Saueressig, Ann-Kathrin Stroh analyzed the data.

DATA AVAILABILITY STATEMENT

The data is the property of IQVIA.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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