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Prevalence of narcolepsy in two European countries -France and Germany

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Table of Contents

1.	List of abbreviations
2.	Amendments and updates
3.	Milestones
4.	Rationale and background
5.	Research question and objectives
6.	Research methods4
6.1.	Study design4
6.2.	Setting and study population4
6.3.	Variables4
6.4.	Data sources and management4
6.5.	Statistical methods5
6.6.	Quality control5
7.	Results
7.1.	Prevalence of narcolepsy in France and Germany5
8.	Discussion6
8.1.	Key results6
8.2.	,
	, Data from other sources
8.3.	, Data from other sources
8.3. 8.4.	Data from other sources
8.3. 8.4. 8.5.	Data from other sources
8.3. 8.4. 8.5. 8.6.	Data from other sources
8.3. 8.4. 8.5. 8.6. 9.	Data from other sources
 8.3. 8.4. 8.5. 8.6. 9. 10. 	Data from other sources
 8.3. 8.4. 8.5. 8.6. 9. 10. Anne 	Data from other sources

1. List of abbreviations

СОМР	Committee for Orphan Medicinal Products
МАН	Marketing Authorisation Holder
EMA	European Medicines Agency
PRAC	Pharmacovigilance Risk Assessment Committee
RDA	Rapid Data Analysis
US	United States

2. Amendments and updates

NA

3. Milestones

Milestone	Planned date
Feasibility feedback with analysis proposal shared with Requesting Office	15 October 2021
Analysis report by EMA circulated to Requesting Office by	25 October 2021
Internal review	11 th April 2022
Reviewed by COMP	20 th April 2022
Registration in the EU PAS register (including study report)	30 th May 2022

4. Rationale and background

The prevalence of narcolepsy in Europe is unclear at the moment due to contradictory studies and to the impact of the H1N1 vaccination on the overall prevalence. An updated prevalence for this condition is required for regulatory purposes.

5. Research question and objectives

The main objective of this study was to provide the yearly prevalence of narcolepsy in France and Germany primary care settings, between 2011 and 2019. The yearly prevalence was stratified by sex and age group.

6. Research methods

6.1. Study design

This was a descriptive study of prevalence of narcolepsy in two European countries (France, Germany) using *in-house* accessible databases. Study results were complemented with incidence rate data for narcolepsy obtained from the ACCESS study and incidence data from Sweden, using publicly accessible data [1].

6.2. Setting and study population

The study was undertaken in France and Germany primary care setting and included both general practices and paediatric practices in Germany, as paediatricians act as primary care physicians for the health care of children in Germany.

The study period was between 2011 and 2019.

All patients in selected practices that were observable during the study period (2011 to 2019) were included in the study.

For data quality reasons patients were excluded from the study if their sex or age was not recorded or if their birth date occurred after their first visit to the practice.

6.3. Variables

- Narcolepsy diagnosis: The WHO ICD 10 code G47.4 was used to identify patients with narcolepsy
- Date of diagnosis
- Prevalence year
- Age
- Sex

6.4. Data sources and management

The data sources were IMS® Disease Analyzer (Germany and France) version June 2021.

IMS® Disease Analyzer Germany collects computerised information from specialised and general primary care practices throughout Germany since 1992. Around 3% of GPs in GP practices are included in IMS® Disease Analyzer Germany from the different regions in Germany. There is a slightly higher coverage of paediatricians (between 4.5% and 5%). Data from IMS® Disease Analyzer Germany have been shown to be reasonably representative of German healthcare statistics for demographics and certain diseases [2, 3].

IMS® Disease Analyzer France collects anonymised patient medical records since 1997 through a representative panel of GPs. The physician sample represents approximately 2 % of physicians, and is weighted by age and gender of the physician, doctor region and the SNIR of the physician (National Official Indicator of the GP volume of activity in terms of visits and consultations) [4]. The age distribution of patients has been shown to be similar to France social security data (SNIIRAM) [4].

In both the IMS® Disease Analyzer Germany and France databases diagnoses are coded using WHO ICD 10 codes, and prescriptions are coded using EphMRA ATC codes and substance names.

6.5. Statistical methods

The numerator for the yearly prevalence consisted of patients that were diagnosed with narcolepsy during the year or that already had a history of narcolepsy at the start of the year.

The denominator consisted of patients that were observable for at least one day during the respective year. The observability for a patient started on the date of the first visit to the practice and ended on the date of the last visit to the practice.

The prevalence was expressed as number of narcolepsy cases per 10,000 persons. Yearly prevalence was stratified by sex and age group.

As narcolepsy is a lifelong condition, we assessed the timepoint of the narcolepsy diagnosis in relation to the starting point of the yearly prevalence period. We also assessed the average time to a narcolepsy diagnosis from the first patient visit, and we compared the duration of the lookback period in patients with narcolepsy vs. all patients in the denominator (i.e. the time between the first patient visit and the start of the yearly prevalence period).

The statistical analyses were performed with SAS Enterprise Guide version 7.15

6.6. Quality control

The quality of IMS® Disease Analyzer data is ensured by a series of continuous QA controls and data refinement. These include checking incoming data for criteria such as completeness and correctness, (e.g. linkage between diagnoses and prescriptions), and standardizing certain data values such as laboratory test results.

7. Results

7.1. Prevalence of narcolepsy in France and Germany

The yearly prevalence of narcolepsy per 10,000 in the population varied from 0.77-0.98 In IMS® Disease Analyzer France and from 1.83-3.16 in IMS® Disease Analyzer Germany, please see Figures 1 and 2 below. In IMS® Disease Analyzer France the prevalence seemed to be stable or slightly decreasing, whereas in IMS® Disease Analyzer Germany prevalence increased over time. The trends were not formally tested. For prevalence stratified by sex and age groups, please see Annex 1.



Figure 1 Yearly prevalence of narcolepsy per 10,000 patients in IMS® Disease Analyzer France

Figure 2 Yearly prevalence of narcolepsy per 10,000 patients in IMS® Disease Analyzer Germany



The yearly study population increased over time, from around 400,000 (year) to around 800,000 (year) in IMS® Disease Analyzer France and from around 3 million (year) to around 4.5 million (year) in IMS® Disease Analyzer Germany, please see Annex 2 for descriptive information on background population and narcolepsy cases. Narcolepsy cases had a longer average time available for collection of medical history information compared to the average for the entire population.

8. Discussion

8.1. Key results

Using data from two primary care databases in France and Germany, the overall yearly prevalence of narcolepsy between 2011 and 2019 was found to be within the expected range of 2.5-5 per 10,000 persons [5] for Germany and lower than the previously published prevalence of 2.1-2.6 per 10,000

persons in France [6, 7]. The prevalence was increasing over time from 1.83 to 3.16 per 10,000 persons in the German database whilst it was stable or slightly decreasing in the French database, varying between 0.77 and 0.98 per 10,000 persons. The prevalence in both France and Germany was below the threshold of 5 per 10,000 inhabitants.

8.2. Data from other sources

Using publicly available data, the estimated overall prevalence of narcolepsy in Sweden in 2019 was 2.09 per 10,000 persons, i.e. at lower end of the expected range. In the 2020 yearly report from the Swedish narcolepsy register in Sweden, [8], the estimated prevalence of narcolepsy in 2019 was 2,15. The size of the Swedish population as estimated on 1 January 2019 was 10,230,185 and on 1 January 2020 it was 10,327,589 [9], i.e. an average of 10,278,887 persons during 2019.

The yearly overall incidence rate of narcolepsy obtained from the ACCESS studies [1] using data sources that had access to primary care data seemed to decrease slightly over time, but this was difficult to assess due to sparse data: data from Denmark was only available between 2010 and 2013 whereas the other data sources provided data between 2017 and 2019-2020. Incidence rates ranged from 0.24 to 0.4 per 10,000 person-years in Denmark, 0.16 to 0.24 per 10,000 person-years in Spain BIFAP, 0.07 to 0.1 in Spain SIDIAP and 0.07 to 0.12 per 10,000 person-years in UK CPRD. The overall incidence of narcolepsy was generally below 0.25 per 10,000 per year, except between 2010 and 2012, which were the years immediately following the H1/N1 pandemic. Rates from hospital only data sources were lower, ranging from 0.012 to 0.05 per 10,000 persons per year.

A large European network of clinicians and scientists dedicated to promote research on narcolepsy founded in 2008 in Zurich cite in a publication from 2016 a prevalence of narcolepsy within Europe, US and Asia of between 2-5 per 10,000 [25].

8.3. Other information to contextualize the findings

Narcolepsy is a chronic sleep disorder with a typical onset during adolescence [8]. The most common form of narcolepsy is associated with a reduction in orexin (hypocretin-1) producing neurons, possibly on the basis of an autoimmune reaction [5, 8-10], mainly in individuals with HLA type DQB 0602. There is limited data on the prevalence of narcolepsy and it is difficult to obtain correct estimates due to the risk of selecting a potentially biased population and/or inadequacy in the data required to estimate the presence or not of narcolepsy in the population [13]. Also, there is evidence that the prevalence of narcolepsy, which is generally cited at around 5 per 10,000, varies geographically and with ethnicity with a lower prevalence in Israeli Jews [13]. There is also evidence that occurrence of narcolepsy shows significant variation over time and varies with etiologic factors such as H1N1 infection or vaccination [12-18]. No publication could be identified that provides data on the lifetime risk of narcolepsy. Recent estimates of prevalence from the US showed an increase in the prevalence of narcolepsy between 2013 and 2016 from 3.89-4.43 per 10,000 [19]. In contrast, a recent estimate of prevalence in Slovakia was as low as at 0.1 per 10,000 (10 per million) [20].

Narcolepsy patients have been shown to have higher mortality compared to the general population and an increased risk of cardiovascular disease [24].

8.4. Limitations

There are several issues that impact on estimates of prevalence that need to be considered. One issue is that patients with narcolepsy tend to have a long time from symptoms to diagnosis with a mean time to diagnosis of around 3-4 years. Most patients were also diagnosed before the year when the prevalence was calculated, meaning that it was important to capture data from earlier years.

Furthermore, patients diagnosed with narcolepsy had longer observation times compared to the entire population in the database. All these findings indicate that narcolepsy may be underdiagnosed in patients with short follow-up times and indicate a degree of uncertainty around the obtained estimate. However, a long observation time is indicative of chronic health issues, and patients who have a long observation time in the database are therefore not representative of the general population. The population denominators are based on patients seeking health care and not on the total population denominators (the population in the geographic area covered by the practices), which may lead to an overestimation of the prevalence of narcolepsy.

Another issue is that it is not mandatory to record a diagnosis in the French database whereas it is recommended to record a diagnosis and it is in the interest of the physician to document a diagnosis for budget reasons in the German database. This can lead to a relative under-recording of narcolepsy in the French database compared to the German database and to an absolute under-recording of narcolepsy in the French database. On the other hand, because of the free doctor's choice both in France and Germany, and non-uniqueness of the patient identity across different practices, data for an individual patient may be duplicated across practices, which can potentially lead to an over-recording of diagnoses (i.e. a diagnosis in the same patient is provided from multiple practices appearing as multiple patients with the same diagnosis), but also to incomplete patient records in an individual practice.

As data in the database become increasingly longitudinal over time (because each practice that contributes data has one more year of data for each year) it would seem possible that an increase in the prevalence of narcolepsy could be expected over time. This might contribute to the observed increasing prevalence over time in the German database but does not explain the stable or slightly decreasing prevalence in the French database.

8.5. Interpretation

The data on overall prevalence of narcolepsy between 2011 and 2019 from the IMS® Disease Analyzer France and Germany databases, and the estimated overall prevalence of narcolepsy in Sweden are in keeping with and below the threshold of 5 per 10,000 inhabitants.

8.6. Generalisability

This study was restricted to a limited number of countries within the EU, and findings may not be generalisable to the entire EU population.

9. Conclusion

This study assessed the overall yearly prevalence of narcolepsy in France and Germany between 2011 and 2019 using two primary care databases. The estimated overall yearly prevalence of narcolepsy in France seemed to be underestimated in the database, varying between 0.77 and 0.98 per 10,000, which is lower than previous prevalence estimates from France of between 2.1 and 2.6 per 10,000 [6, 7]. No existing published prevalence could be identified in Germany, but results were in keeping with the expected range of 2.5-5 per 10,000 [5], varying from 1.83 to 3.16 per 10,000. These results, as well as published results from other European countries, indicate that the prevalence of narcolepsy is currently below the threshold of 5 per 10,000 inhabitants in the countries studied. However, these results should be interpreted in the light of all limitations mentioned above.

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Annex 1 - Stratified analyses of prevalence per 10,000 patients



Figure S 1 Prevalence of narcolepsy per 10,000 patients by sex in IMS® Disease Analyzer France

Figure S 2 Prevalence of narcolepsy per 10,000 patients by sex in IMS[®] Disease Analyzer Germany



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Figure S 3 Prevalence of narcolepsy per 10,000 patients by age group in IMS® Disease Analyzer France



Figure S 4 Prevalence of narcolepsy per 10,000 patients by age group in IMS® Disease Analyzer Germany

Annex 2 – Tables with descriptive information on background population and narcolepsy cases

Table 1. Size of yearly population, average look back time, and distribution of cases with narcolepsy in IMS® Disease Analyzer France

Year	Total population	Time in years (mean, SD) for collection of medical history	Total no of narcolepsy cases (cases diagnosed during the year)	Time in years (mean, SD) for collection of medical history in narcolepsy cases	Time in years to narcolepsy diagnosis (mean, SD)	Time in years (mean, SD) between narcolepsy and starting point of year	Time in years (25 th – 75 th perc) between narcolepsy and starting point of year	Time in years (min;max) between narcolepsy and starting point of year ¹
2011	410,714	3,3 (3.1)	38 (12)	5.3 (3.1)	3.3 (3.1)	2.0 (2.7)	0.0-3.2	-0.8; 9.2
2012	470,371	3,4 (3.4)	46 (10)	5.7 (3.3)	3.4 (3.1)	2.4 (2.8)	0.2-3.7	-0.8; 10.2
2013	548,112	3,3 (3.6)	47 (<10)	6.3 (3.6)	3.4 (3.2)	2.9 (3.1)	0.5-4.4	-1.0; 11.2
2014	655,887	3,1 (3.8)	57 (12)	6.2 (4.3)	3.2 (3.4)	3.0 (3.2)	0.5-4.4	-0.8; 12.2
2015	730,816	3,2 (3.9)	65 (14)	6.4 (4.5)	3.2 (3.3)	3.2 (3.4)	0.6-4.7	-0.9; 13.2
2016	777,958	3,4 (4.0)	67 (<10)	7.2 (4.7)	3.6 (3.7)	3.6 (3.6)	0.5-5.5	-0.9; 14.2
2017	802,205	3,7 (4.2)	73 (11)	7.4 (5.1)	3.7 (3.8)	3.7 (3.7)	0.7-5.7	-0.8; 15.2
2018	805,966	3,9 (4.4)	69 (<10)	7.6 (5.2)	3.6 (3.7)	4.1 (3.9)	1.1-6.3	-0.9; 16.2
2019	808,973	4,1 (4.6)	62 (11)	6.9 (5.5)	2.6 (3.2)	4.3 (4.2)	1.2-6.5	-0.8; 17.2

¹ A negative value indicates that the patient was diagnosed with narcolepsy during the year (i.e. after the starting point of the year).

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Year	Total population	Time in years (mean, SD) for collection of medical history	Total no of narcolepsy cases (cases diagnosed during the year)	Time in years (mean, SD) for collection of medical history in narcolepsy cases	Time in years to narcolepsy diagnosis (mean, SD)	Time in years (mean, SD) between narcolepsy and starting point of year	Time in years (25 th - 75 th perc) between narcolepsy and starting point of year	Time in years (min;max) between narcolepsy and starting point of year ¹
2011	2,964,526	4,1 (4.7)	543 (137)	6.4 (5.3)	3.6 (4.3)	2.7 (3.5)	0.0-4.4	-1.0; 18.5
2012	3,259,066	4,2 (4.9)	656 (154)	6.3 (5.4)	3.5 (4.3)	2.8 (3.6)	0.1-4.5	-1.0; 19.5
2013	3,559,112	4,4 (5.0)	764 (171)	6.5 (5.7)	3.6 (4.5)	2.9 (3.6)	0.2-4.5	-1.0; 20.5
2014	3,742,296	4,7 (5.2)	847 (153)	6.9 (5.7)	3.7 (4.5)	3.2 (3.8)	0.5-4.9	-1.0; 21.5
2015	3,895,360	5,0 (5.3)	946 (173)	7.3 (5.9)	3.9 (4.7)	3.5 (3.9)	0.5-5.2	-1.0; 22.5
2016	4,372,578	4,8 (5.5)	1122 (242)	7.5 (6.0)	4.0 (4.8)	3.5 (4.1)	0.2-5.2	-1.0; 23.5
2017	4,579,277	5,0 (5.7)	1246 (229)	7.9 (6.1)	4.2 (4.9)	3.6 (4.2)	0.4-5.5	-1.0; 24.5
2018	4,584,953	5,3 (5.8)	1337 (222)	8.4 (6.3)	4.5 (5.1)	4.0 (4.4)	0.6-6.1	-1.0; 25.5
2019	4,490,966	5,6 (6.1)	1418 (244)	8.9 (6.5)	4.8 (5.3)	4.2 (4.6)	0.5-6.5	-1.0; 26.5

Table 2. Size of yearly population, average look back time, and distribution of cases with narcolepsy in IMS® Disease Analyzer Germany

¹ A negative value indicates that the patient was diagnosed with narcolepsy during the year (i.e. after the starting point of the year).