

Reporting rates for severe hypersensitivity reactions associated with prescription-only drugs in outpatient treatment in Germany

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ABSTRACT

Purpose To determine which 10 prescription-only drugs used in outpatient treatment in Germany are most frequently reported to induce severe drug hypersensitivity reactions taking into account their prescription numbers. In addition, the reader should be made aware of respective databases available to the public and their limitations.

Methods Reports of anaphylactic and severe cutaneous adverse reactions were identified in the adverse drug reaction database of the German competent authority for the time period January 1998 to December 2012. For frequently reported drugs, the total number of reports was matched with their total number of prescriptions resulting in the reporting rate.

Results Among the 10 drugs with the highest reporting rate for anaphylactic reactions, there were six antibiotics (moxifloxacin, levofloxacin, clindamycin, ciprofloxacin, cefuroxime and amoxicillin), three of which were fluoroquinolones. The other four drugs were glatiramer, metamizole and two angiotensin-converting-enzyme inhibitors. Concerning severe cutaneous adverse reactions, four out of ten drugs were antibiotics (clindamycin, sulfamethoxazol + trimethoprim, ciprofloxacin and amoxicillin), and three were anticonvulsives. Because dental prescription numbers were not available to the public, the real reporting rates for clindamycin and to a lesser extent for amoxicillin are presumably lower.

Conclusions The predominance of antibiotics among the reports of severe immediate and delayed-type drug hypersensitivity reactions is largely in accordance with literature although fluoroquinolones seem to be slightly overrepresented concerning anaphylactic reactions. The reader should be aware of the limitations of adverse drug reaction and prescription databases available to the public, and that over-the-counter drugs, such as non-steroidal anti-inflammatory drugs, and drugs typically administered in hospitals could not be considered. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—drug hypersensitivity; severe cutaneous drug reactions; anaphylactic reactions; reporting rates; pharmacoepidemiology

Received 11 February 2015; Revised 22 June 2015; Accepted 21 July 2015

INTRODUCTION

Severe drug hypersensitivity reactions (DHRs) can be classified clinically in immediate and delayed-type reactions depending on their time to onset. Anaphylactic and severe cutaneous adverse reactions (SCARs) like toxic epidermal necrolysis or Stevens–Johnson syndrome represent the most severe clinical entities of these DHRs.^{1,2}

In Germany, physicians and pharmacists are obliged by their professional conduct code to report suspected adverse drug reactions (ADRs) either directly to one of the competent authorities, the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul-Ehrlich-Institut, or to their professional councils, which forward these reports to BfArM. Another considerable amount of cases received by BfArM is sent by the pharmaceutical industry, which is obliged to report all suspected serious ADRs originating from Germany to the competent authorities. A small amount is reported directly by consumers.

The reports are stored in BfArM's ADR database and coded using MedDRA terminology and the Anatomical Therapeutic Chemical classification system.^{3,4} BfArM's ADR database is open to the public.⁵ In

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analogy, prescription numbers for prescription-only drugs used in outpatient treatment are available to the public in Germany.⁶

The aim of the present study was to determine which prescription-only drugs used in outpatient treatment are most frequently reported to induce severe DHRs taking into account their prescription numbers. In addition, the reader should be made aware of the respective data sources and their limitations.

METHODS

BfArM's ADR database

BfArM's ADR database and the limitations of the spontaneous reporting system are described elsewhere.^{5,7}

Only ADR reports informing about at least one suspected drug (but not interactions) were included in this analysis. Reports originating from clinical trials and published literature were excluded. Because of the large amount of reports included, these were not assessed with regard to the causal association or the correctness of diagnosis. Thus, the data set may contain a small amount of ADR reports for which the causal association or the diagnosis is improbable or not assessable.

Identification of ADR reports informing about anaphylactic reactions or SCARs

First, all ADR reports informing about anaphylactic reactions or SCARs within the time period January 1998 to December 2012 were identified in the ADR database using a standardised MedDRA query (SMQ) (Annex). The reports were then ranked according to their number for the individual drug. In principle, for the SMQ, a narrow (only the diagnosis) or a broad search profile can be applied. The latter additionally identifies reports, which inform about symptoms occurring in context with and thus suggesting either potential anaphylactic reactions or SCARs such as toxic epidermal necrolysis/Stevens–Johnson syndrome although these diagnoses are not explicitly stated. Consequently, the broad search profile also identifies reports representing milder clinical variants and not the full spectrum anaphylactic reactions or toxic epidermal necrolysis/Stevens–Johnson syndrome. The SMQ ‘anaphylactic reaction’ combines a narrow and broad search with an algorithm.³ The algorithm can improve the identification of cases of interest when more than one MedDRA term of the SMQ is represented in a single case.³ For the SMQ ‘SCARs’, no algorithm was available, and hence, the broad search profile was applied.

Figure 1 illustrates how the ADR data were collected, selected and finally matched with prescription data.

RESULTS

Prescription numbers and reporting rate

The total number of reports for the identified drugs was matched with the respective total prescription number during the same time period in order to calculate the reporting rate (number of reports/defined daily doses (DDDs)). The reporting rate is a more robust parameter than the absolute number of ADR reports because the latter may rise with proportionally increasing exposure, whereas the reporting rate would remain unchanged. The prescription numbers were compiled from a data source available to the public in Germany, which is restricted to prescription-only drugs.⁶ Therefore, over-the-counter (OTC) drugs had to be excluded from further analysis. Concerning the SMQ ‘anaphylactic reactions’, this resulted in the exclusion of diclofenac ($n=333$ reports) and ibuprofen ($n=99$ reports) placed 2nd and 16th with regard to the total number of reports. Concerning the SMQ ‘SCARs’, the following drugs had to be excluded: paracetamol (place 2; $n=213$ reports), acetylsalicylic acid (place 5; $n=201$ reports), diclofenac (place 6; $n=189$ reports), ibuprofen (place 15; $n=100$ reports) and acetyl cysteine (place 16; $n=97$ reports) (Table 1).

Drugs, which preferentially or in large quantities are administered in hospitals, had to be excluded for the same reason. These were, for example paclitaxel (place 3; $n=289$ reports) and iopromide (place 4; $n=269$ reports) regarding the SMQ ‘anaphylactic reactions’ and pantoprazole (place 13; $n=101$ reports) and heparin (place 17; $n=96$ reports) concerning the SMQ ‘SCARs’.

Additionally, terbinafine (OTC status for some indications; SMQ ‘SCARs’: place 12, $n=101$ reports) and rofecoxib were excluded (because of the withdrawal from the market in 2004; SMQ ‘anaphylactic reactions’: place 12, $n=101$ reports).

Because of the aforementioned exclusion criteria, 35 drugs with the highest number of reports for the SMQ ‘anaphylactic reactions’ and 20 drugs with the highest number of reports for the SMQ ‘SCARs’ had to be identified in order to result in 10 drugs with the highest reporting rate.

Prescriptions by dentists have been recorded in the prescription reports available to the public from the year 2012 onwards only.⁶ For clindamycin, the total numbers of prescriptions were 6.3 million DDDs in 2011 and 19.1 million DDDs in 2012, including prescriptions by dentists. Because clindamycin seems to be frequently prescribed as an antibiotic by dentists,⁸

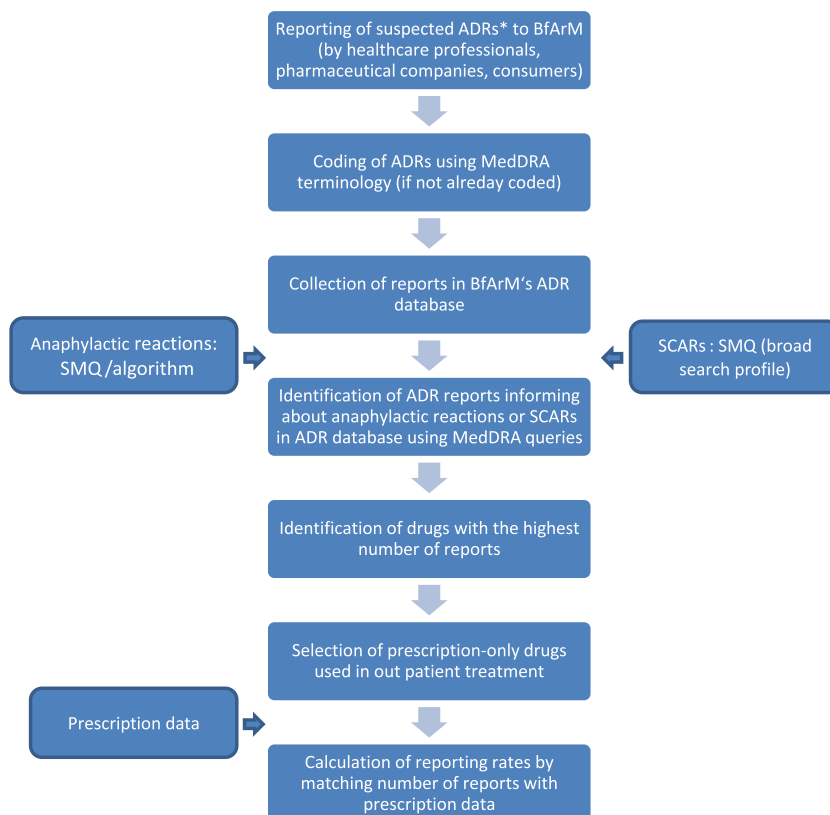


Figure 1. The workflow with regard to the collection and selection of adverse drug reactions (ADRs) and the final match with the prescription data. SMQ, standardised MedDRA query; SCARs, severe cutaneous adverse reactions

the real total prescription numbers including dental prescriptions in the period 1998 to 2012 is very likely to be higher. In consequence, the real reporting rate for clindamycin will become substantially smaller. However, the magnitude of this deviation cannot be determined.

The total numbers of amoxicillin prescriptions were 71.8 DDDs in 2011 and 81.3 DDDs in 2012 including prescriptions by dentists. Therefore, the real reporting rate for amoxicillin will become smaller although to a lesser extent than for clindamycin.

Concerning prescriptions by dentists besides antibiotics, also analgesics have to be considered.⁸ However, in the data source available to the public in 2012, metamizole prescriptions by dentists were 0.69 DDDs compared with 142.2 DDDs by physicians.⁶ Thus, their non-consideration is very unlikely to have an impact on the reporting rate.

Total number of ADR reports for the SMQs 'anaphylactic reactions' or 'SCARs'

The ADR database contained 190.971 ADR reports for the time period January 1998 to December 2012.

Among these, 9.992 (5.2%) referred to the SMQ 'anaphylactic reactions' and 5.526 (2.9%) to the SMQ 'SCARs'. Table 1 lists 35 drugs with the highest number of reports for the time period January 1998 to December 2012.

Reporting rates for the SMQ 'anaphylactic reactions'

The 10 drugs with the highest reporting rates for prescription-only drugs without relevant in-hospital use for the SMQ 'anaphylactic reaction' for the time period January 1998 to December 2012 are shown in Table 2.

The reporting rates cover a range from 7.18 (moxifloxacin) to 0.004 (ramipril), differing by a factor of 1.700. Except for moxifloxacin (7.18) and glatiramer (4.17), the reporting rates are below one. Moxifloxacin is in first place regarding the reporting rate and the total number of reports ($n=481$). The total number of reports for the drugs placed second to tenth is rather close between 190 (metamizole) and 52 (enalapril), differing by a factor of four. Hence, for these drugs, the differences of their reporting rates are mainly driven by differences in the total number of

Table 1. Thirty-five drugs with the highest number of reports concerning the SMQ anaphylactic reactions* and severe cutaneous drug reactions (SCARs)** within the ADR database for the time period January 1998 to December 2012

Ranking of the drugs according to highest number of reports for the respective SMQ	SMQ anaphylactic reactions	SMQ severe cutaneous drug reactions (SCARs)
1	Moxifloxacin (481)	Allopurinol (276)
2	Diclofenac (333)	Paracetamol (213)
3	Paclitaxel (289)	Metamizole (205)
4	Iopromide (269)	Sulfamethoxazole + trimethoprim (202)
5	Gadopentetat (199)	Acetylic salicylic acid (201)
6	Iomeprol (191)	Diclofenac (189)
7	Metamizole (190)	Furosemide (183)
8	Glatiramer (164)	Carbamazepine (173)
9	Oxaliplatin (146)	Lamotrigine (133)
10	Gadoteridol (125)	Amoxicillin (118)
11	Levofloxacin (109)	Ciprofloxacin (110)
12	Rofecoxib (101)	Terbinafine (101)
13	Gadobenic acid (100)	Pantoprazole (101)
14	Carboplatin (99)	Docetaxel (100)
15	Acetylic salicylic acid (99)	Ibuprofen (100)
16	Ibuprofen (99)	Acetyl cysteine (97)
17	Gadubutrol (93)	Heparin (96)
18	Iobiditrol (91)	Clindamycin (94)
19	Ramipril (90)	Methotrexate (94)
20	Docetaxel (79)	Phenytoin (93)
21	Amoxicillin (61)	Tramadol (88)
22	Articain hydrochloride + epinephrine hydrochloride (61)	Prednisolone (81)
23	Heparin (61)	Ambroxol (80)
24	Prednisolone (60)	Moxifloxacin (70)
25	Clindamycin (59)	Clarithromycin (64)
26	Hetastarch + sodium chloride (58)	Metoclopramide (63)
27	Iopamidol (58)	Dexamethasone (62)
28	Cefuroxime (57)	Doxycycline (62)
29	Iohexol (55)	Phenprocoumon (61)
30	Ciprofloxacin (54)	Enoxaparin (60)
31	Pantoprazole (54)	Metoprolol (59)
32	Certoparin (52)	Omeprazole (57)
33	Enalapril (52)	Levofloxacin (53)
34	Gelatine polysuccinat (52)	Ramipril (50)
35	Propofol (52)	Oxazepam (48)

SMQ, standardised MedDRA query.

*Combined approach SMQ plus algorithm.

**Broad search profile.

prescriptions (39.3 million DDDs for glatiramer compared with 21300.4 DDDs for ramipril, differing by a factor of 600).

Four out of the first five (80%) and six out of the ten (60%) are antibiotics (moxifloxacin, levofloxacin, clindamycin, ciprofloxacin, cefuroxime and amoxicillin), three of which being fluoroquinolones. Two of 10 (20%) are angiotensin-converting enzyme inhibitors (enalapril (place 9), ramipril (place 10)) and two single representatives of their respective class: the

immunomodulator glatiramer in second place (high number of reports and comparably low number of prescriptions) and the analgesic metamizole in seventh place (high number of reports and prescriptions).

Reporting rates for the SMQ 'SCARs'

The 10 drugs with the highest reporting rates for prescription-only drugs without relevant in-hospital use for the SMQ 'SCARs' for the time period January 1998 to December 2012 are shown in Table 3.

The reporting rates cover a range from 0.93 (clindamycin) to 0.06 (allopurinol), differing by a factor of 15. The range is therefore considerably smaller than for the SMQ 'anaphylactic reactions' (where the wide range is mainly caused by the comparably low reporting rate for ramipril).

The total number of reports for the SMQ 'SCARs' extends from 94 to 276 (around factor 3), and the total prescription numbers range from 101.6 to 4350 million DDDs (around factor 43). Hence, the difference in the reporting rates is mainly driven by the prescription numbers.

Four out of the ten drugs (40%) are antibiotics (clindamycin, sulfamethoxazol + trimethoprim, ciprofloxacin and amoxicillin), and three (33%) are anticonvulsives (lamotrigine, phenytoin and carbamazepine). Single representatives of their respective class are metamizole (analgesic), methotrexate (immunosuppressive) and allopurinol (anti-gout drug). The number of ADR reports for individual drugs within the SMQ 'SCARs' ranges between 94 (clindamycin) and 276 (allopurinol), which is similar in magnitude as for the SMQ 'anaphylactic reaction' (52 (enalapril) to 481 (moxifloxacin)). The highest reporting rate for the SMQ 'SCARs' (0.93 for clindamycin) is by a factor of eight below the highest reporting rate for the SMQ 'anaphylactic reactions' (7.18 for moxifloxacin). Some drugs are among the 10 drugs with the highest reporting rate in both SMQs, that is, clindamycin, ciprofloxacin, amoxicillin and metamizole.

DISCUSSION

Reporting rates for anaphylactic reactions

The percentage of ADR reports informing about anaphylactic reactions among all ADR reports in the respective period was 5.2%, which is similar to results reported for Portugal (6%) and Italy (2.7%).^{9,10} According to an anaphylaxis register in Germany, drugs come second as cause for anaphylaxis in adults (insect stings in first place).¹¹ However, concerning the absolute incidence of drug-induced anaphylaxis, only

Table 2. Ranking of the 10 drugs with the highest reporting rates for the SMQ anaphylactic reactions*, the total number of reports and the total number of prescriptions for the time period January 1998 to December 2012

Ranking according to reporting rate	Drug	Total number of reports for the SMQ anaphylactic reactions	Total number of prescriptions in million defined daily doses (DDD)	Reporting rate** (total number of reports per 1 million DDD for the SMQ* anaphylactic reactions)
1	Moxifloxacin	481	67	7.18
2	Glatiramer	164	39.3	4.17
3	Levofloxacin	109	112.5	0.97
4 ***	Clindamycin	59	101.6	0.58
5	Ciprofloxacin	54	179.7	0.30
6	Cefuroxime	57	259.8	0.22
7	Metamizole	190	1123.9	0.17
8***	Amoxicillin	61	1064.7	0.06
9	Enalapril	52	8561.8	0.01
10	Ramipril	90	21344.8	0.00
				(0.004216484)

SMQ, standardised MedDRA query.

*Combined approach SMQ plus algorithm.

**Rounded.

***The total number of prescriptions by dentists was recorded in prescription reports available to the public from the year 2012 onwards but not for the previous years. Because antibiotic prescription by dentists in particular refers to clindamycin and to a lesser extent to amoxicillin, the real total prescription number for clindamycin is likely to be higher. In consequence, the real reporting rate for clindamycin will become substantially smaller. The same applies for a lesser degree to amoxicillin. The extent of this deviation cannot be determined. The rows for clindamycin and amoxicillin are marked to highlight this limitation.

Table 3. Ranking of the 10 drugs with the highest reporting rates for the SMQ severe cutaneous drug reactions (SCARs)*, the total number of reports and the total number of prescriptions for the time period January 1998 to December 2012

Ranking according to reporting rate	Drug	Total number of reports for the SMQ SCARs	Total number of prescriptions in million defined daily doses (DDD)	Reporting rate** (total number of reports per 1 million DDD for the SMQ* SCARs)
1***	clindamycin	94	101.6	0.93
2	sulfamethoxazole + trimethoprim	202	318.6	0.63 (0.6340)
3	lamotrigine	133	212.5	0.63 (0.62588)
4	ciprofloxacin	110	179.7	0.61
5	phenytoin	93	237.7	0.39
6	carbamazepine	173	914.5	0.19
7	metamizole	205	1123.9	0.18
8	methotrexate	94	755.99	0.12
9***	amoxicillin	118	1064.7	0.11
10	allopurinol	276	4350	0.06

SMQ, standardised medDRA query.

*Broad search profile.

**Rounded.

***The total number of prescriptions by dentists was recorded in prescription reports available to the public from the year 2012 onwards but not for the previous years. Because antibiotic prescription by dentists in particular refers to clindamycin and to a lesser extent to amoxicillin, the real total prescription number for clindamycin is likely to be higher. In consequence, the real reporting rate for clindamycin will become substantially smaller. The same applies for a lesser degree to amoxicillin. The extent of this deviation cannot be determined. The rows for clindamycin and amoxicillin are marked to highlight this limitation.

approximate estimations are available. In Switzerland, the incidence of drug-induced anaphylaxis with circulatory symptoms was reported as 1.6 per 100,000 inhabitants per year.¹² Hence, anaphylaxis may occur 10 times more often than the most severe syndromes within the spectrum of SCARs, that is, toxic-epidermal necrolysis/Stevens–Johnson syndrome with a population-based incidence of 1 per 1 million per year.¹³

The majority of fluoroquinolone-induced DHRs are of the immediate-type; among these, anaphylactic

reactions are most frequent.^{14,15} In the present analysis, moxifloxacin had the highest reporting rate for the SMQ ‘anaphylactic reactions’ (place 1; 7.18), followed by levofloxacin (place 3; 0.97) and ciprofloxacin (place 5; 0.3). In literature, the incidence of fluoroquinolone-induced anaphylaxis was described as 0.2 per 1 million days of treatment.¹⁶ However, in our analysis besides anaphylaxis, also milder variants of anaphylactic reactions were included. Therefore, the reporting rates found in our analysis seem to be

broadly in accordance with the data described in literature even taking underreporting into account.

Regarding anaphylactic reactions, a higher reporting rate for moxifloxacin compared with other fluoroquinolones has been described before in case series^{17,18} and a previous analysis in the ADR database.¹⁹ Although a subsequent analysis in a large managed care organisation in the USA did not demonstrate an increased incidence of moxifloxacin-induced anaphylaxis (1 per 100,000 prescriptions) compared with other fluoroquinolones,²⁰ a higher rate of moxifloxacin-related hypersensitivity reactions compared with levofloxacin or ciprofloxacin was found in a recent study in the USA based on admissions to hospital emergency departments in conjunction with prescription data.²¹ However, because the risk of moxifloxacin-induced anaphylactic reactions is already addressed in its summary of product characteristics,²² no new signal arises from this data.

It is noted that three out of six antibiotics with the highest reporting rates for the SMQ 'anaphylactic reactions' are fluoroquinolones. Whether this finding is due to a differential reporting concerning the different classes of antibiotics, a different potential of these drugs to induce anaphylactic reactions, differences in the predisposition of the targeted patient population for such reactions or other reasons cannot be determined.

Concerning glatiramer, which comes second in our analysis, anaphylactic reactions with varying degrees of severity are described in its summary of product characteristics.²³ Therefore, no new signal arises from these data.

The high reporting rate for clindamycin (place 4) is unexpected but very likely because of the non-consideration of prescriptions by dentists up to 2011, which resulted in a misleading smaller total number of prescriptions (Section on Results). However, the magnitude of this deviation cannot be determined. According to an exploratory analysis in PubMed and personal experience, clindamycin does not frequently induce anaphylactic reactions¹⁵ and in contrast is recommended as safe alternative in patients with beta-lactam allergy.²⁴

Beta-lactam antibiotics are reported as the most frequent inducers of immediate-type reactions with varying degrees of severity.^{25,26} In our analysis, cefuroxime took sixth place in accordance with current literature reporting an increasing frequency of cephalosporin-induced immediate-type reactions due to their rising use.²⁷

Amoxicillin took only eighth place in our analysis possibly because this association is already known and thus less often reported.

Similarly, it is well known that angiotensin-converting enzyme inhibitors can induce angioedema. Since angioedema is one search term of the SMQ 'anaphylactic reactions' and in 50% of the reports of enalapril-induced anaphylactic reactions, angioedema, edema or swellings (e.g. tongue or lips) were described, the reporting rates for enalapril and ramipril do not represent a new signal.

Metamizole-associated anaphylactic reactions have also been described before.²⁵ Therefore, the reporting rate for metamizole does not constitute a new signal.

In general, non-steroidal anti-inflammatory drugs are considered to be among the drugs most frequently causing anaphylactic reactions.^{10,25} However, as non-steroidal anti-inflammatory drugs are usually dispensed OTC to a considerable extent, they had to be excluded from the further analysis in the context of this study. This results in a higher representation of other classes of drugs such as antibiotics among the drugs with the highest reporting rates.

Reporting rates for SCARs

Five out of the ten drugs with the highest reporting rates for SCARs in our analysis were also among the nine high-risk drugs for toxic epidermal necrolysis/Stevens–Johnson syndrome identified in a case control study by Mockenhaupt *et al.*,²⁸ that is, sulfamethoxazol+trimethoprim, allopurinol and the anticonvulsives lamotrigine, phenytoin and carbamazepine.

In that study, no causal association was suspected for metamizole because it was possibly administered immediately before the occurrence of skin symptoms in order to ease the pain (confounding by indication). The ranking of metamizole in our analysis (place 7) may partly reflect that some symptoms reported in context with metamizole-induced DHRs are also represented in the SMQ 'SCARs', although the reactions do not equate SCARs.

Concerning fluoroquinolones (ciprofloxacin) and aminopenicillins (amoxicillin), a significantly increased risk for SCARs was described by Mockenhaupt *et al.*,²⁸ which, however, was less than for the high-risk drugs.

Conversely, oxycamers and nevirapine were not among the top 10 in our analysis. For nevirapine, which was first marketed in Germany in 1998,²⁹ this may be due to its low prescription numbers. With regard to oxycamers, it remains unclear.

Allopurinol, which is reported to carry the highest risk for toxic epidermal necrolysis/Stevens–Johnson syndrome³⁰ in Europe, took only 10th place in our analysis, possibly because such an association is well-known and therefore less often reported.

The high reporting rate for clindamycin (place 1) is unexpected because clindamycin was not mentioned by Mockenhaupt *et al.* at all.²⁸ Its real reporting rate will be substantially lower because prescriptions by dentist were not considered up to 2011. The magnitude of this deviation cannot be determined. However, an analysis of the FDA's public ADR database found a signal of an increased reporting rate for toxic epidermal necrolysis/Stevens–Johnson syndrome for clindamycin.³¹

Concerning methotrexate (place 8), the finding is not unexpected as SCARs are listed as ADRs in the product information of methotrexate-containing drugs.

The population-based incidence for toxic epidermal necrolysis/Stevens–Johnson syndrome, that is, the most severe variants of SCARs, is reported as 1/1 million inhabitants/year,¹³ whereas the drug-related incidence for high-risk drugs (e.g. carbamazepine and allopurinol) is 1/1000 to 1/100,000 users.²⁸ These frequencies are broadly in accordance with the reporting rates found in this analysis ranging from 0.06 to 0.93 per 1 million DDDs if underreporting is taken into account.

Strengths and limitations of the analysis

The large number of ~190,000 ADR cases with 9992 reports referring to the SMQ 'anaphylactic reactions' and 5526 reports referring to the SMQ 'SCARs' is one strength of this study. A further strength is the linkage with the prescription numbers because the reporting rate is a more relevant parameter than the total number of ADR reports only.

The total number of prescriptions was compiled from a data source available to the public, which informs about prescriptions at the expense of the statutory health insurance, which applies to 90% of the German population. Ten percent are members of private health insurances. However, the authors are not aware of any evidence suggesting that certain drugs considered in this analysis are preferentially prescribed to members of the private health insurances. A complete recording of all prescriptions would by trend diminish the reporting rates.

It should be kept in mind that reporting rates are different from absolute ADR frequencies because not all ADRs will be reported (underreporting). Additionally, for certain drugs or ADRs, reporting may be higher for different reasons (e.g. stimulated reporting with new drugs). It is thus mandatory to consider that analysis based on spontaneous reports may only generate signals, which may then trigger further investigations. Otherwise, the frequency of rare ADRs like

anaphylactic reactions or SCARs is difficult to analyse in studies. In principle, their frequency may be determined in cohort studies; however, because of their rareness, the studies would have to include large numbers of patients and follow them for a long time. Case-control studies only provide relative risks but not absolute incidence figures. Adequately designed analysis of big data bases (e.g. the General Practice Research Database (GPRD) in the UK) in which prescription data are linked with medical diagnosis may allow with some curtailment to generate both relative and absolute figures. However, in Germany, analysis in such data-bases is currently restricted and in addition would be based on much smaller data sets.

In summary, the set of drugs identified in the present analysis of BfArM's ADR database as most frequently being reported to induce anaphylactic reactions and SCARs is broadly in accordance with respective findings in literature. This accordance to some extent supports the reliability of the database. Fluoroquinolones were slightly overrepresented among the drugs with the highest reporting rates for anaphylactic reactions. Whether this is due to a reporting bias, a differential potential of the different classes of antibiotics to induce anaphylactic reactions or other reasons may trigger further investigations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- In Germany, reports of adverse drug reactions are stored in a database available to the public. Likewise, drug prescription numbers are available to the public.
- The reader should be aware of the limitations of adverse drug reaction and prescription databases available to the public.
- The predominance of antibiotics among the reports of severe immediate and delayed-type drug hypersensitivity reactions is largely in accordance with literature although fluoroquinolones seem to be slightly overrepresented concerning anaphylactic reactions.

ACKNOWLEDGEMENTS

The authors would like to thank Barbara Koch and Uschi Gibbert-Pilar for the analysis in the ADR database and Jutta Krappweis, Norbert Paeschke and Kimberley Sherwood for critically reading the manuscript.

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