Original Article

Frequent Adverse Drug Reactions, and Medication Groups under Suspicion

A Descriptive Analysis Based on Spontaneous Reports to the German Federal Institute for Drugs and Medical Devices from 1978 to 2016

Diana Dubrall, Matthias Schmid, Eva Alešik, Norbert Paeschke, Julia Stingl, Bernhardt Sachs

Summary

Background: The adverse drug reaction database of the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) contains reports of suspected adverse drug reactions (ADRs) that are spontaneously submitted by physicians, pharmacists, or patients. The aim of the present study was a descriptive analysis of all of these spontaneous reports.

Methods: 345 662 spontaneously submitted reports were analyzed with respect to the number of reports per year, the sources of the reports, demographic variables, the most commonly reported ADRs, and the drug classes most commonly suspected.

Results: The number of reports submitted spontaneously each year has grown steadily since 1978. At the least detailed level of analysis, “drugs for the treatment of nervous system disorders” were the most common class of drugs under suspicion of causing the reported adverse drug reactions (23.1%). In a more detailed analysis by therapeutic subgroup, the three subgroups most commonly reported as suspected of causing side effects were antithrombotic agents, systemic antibiotics, and psycholeptics—causing thrombocytopenia, diarrhea, and drug dependency as the most frequently reported ADRs, respectively. The order of drug classes most commonly causing ADRs differed markedly between the physicians’ reports (diazepines, fluoroquinolones, heparins) and the patients’ reports (interferons, antithrombotic drugs, selective immunosuppressant drugs). Patients more commonly reported subjectively perceived ADRs, while physicians more commonly reported findings or diagnoses that require medical expertise.

Conclusion: The increasing number of spontaneous reports is mainly due to reports forwarded from pharmaceutical companies to the BfArM. This, in turn, is probably a result of increasingly strict legal reporting requirements in Germany. The detected differences between physicians’ and patients’ ADR reports can be taken to indicate that patients should be more specifically informed and questioned about potential ADRs. By reporting adverse drug reactions, physicians may improve drug safety.

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German Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany: Diana Dubrall, Dr. med. vet. Eva Alešik, Dr. med. Norbert Paeschke, Prof. Dr. med. Julia Stingl, Prof. Dr. med. Bernhardt Sachs

Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE), University Hospital of Bonn, Germany: Diana Dubrall, Prof. Dr. rer. nat. Matthias Schmid

Center for Translational Medicine, Universität Bonn, Germany: Prof. Dr. med. Julia Stingl

Clinic for Dermatology and Allergology, University Hospital (RWTH), Aachen, Germany: Prof. Dr. med. Bernhardt Sachs

One of the central tasks of the German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM) is to monitor the safety of medicinal products. An essential methodological element in the regulatory monitoring of medicinal product safety is the spontaneous reporting system (1–3). Spontaneous reports are unsolicited reports by physicians, pharmacists, patients, or other sources, of suspected cases of adverse drug reactions (ADRs) with widespread, everyday use of a medicinal product, which is not in the context of systematic investigations (for example, studies).

Spontaneous reports play an important role, as clinical trials prior to medicinal product approval can include only a limited number of selected patients. The limitations of these studies means that rare ADRs, as well as those that only occur in certain vulnerable patients or after prolonged use, cannot be reliably detected (1, 2, 4, 5). Additionally, new ADRs may occur during the drug lifecycle, such as in the event of other indications for use or novel co-medications (1, 6).

Complementary, active programs for medicinal product safety monitoring have increasingly been developed in the past decade, including the analysis of so-called Big Data (7) (from electronic health records [from insurance companies], scientific literature, and social media). These systems, like the spontaneous reporting system, are subject to method-inherent limitations (7, 8). Thus, analysis of spontaneous reports still is of central importance (3, 7–9).

Signals from spontaneous reports can provide a major impetus for regulatory action (for instance, leading to changes in product information or to new studies) (10). A 2013 study found that 44% (11/25) of safety-related withdrawals of medicinal products in the USA or the EU were due to spontaneous reports (1).

In Germany, spontaneous reports can be submitted directly to the competent federal authorities via the BfArM/ Paul-Ehrlich-Institut (PEI) website according to the respective area of responsibility (BfArM, chemically-defined active substances, among others; PEI, monoclonal antibodies and vaccines, among others) (11, 12, 13). However, reports may also be directed to the medicinal product commissions of the drug commissions of healthcare professions or to

Number of spontaneous reports received per year according to primary reporting source. (The primary source refers to the person who generated the ADR report, not to the sender [such as the pharmaceutical company] who submitted the report to the German Federal Institute for Drugs and Medical Devices). The color-coded curves indicate the respective 95% confidence intervals. In 6% of the 345 662 cases, more than one reporting source was named (for example, physician and patient both reported the same case independently from each other). To avoid double counting, this analysis was based on reports that only named one source. HCP, healthcare professionals

pharmaceutical companies, which then forward them (14). Physicians are required by their professional code to report ADRs (15). An overview of what physicians should be aware of when reporting ADRs is given in *eBox 1*.

Since 22 November 2017, pharmaceutical companies send their reports exclusively to the European database EudraVigilance at the European Medicines Agency (EMA) (16, 17) (restricted access rights: www.adrreports.eu/en/access_policy.html). The BfArM forwards the adverse reaction reports that it receives directly (e.g. from physicians) to EudraVigilance. Future analyses within the framework of monitoring medicinal product safety will be carried out in EudraVigilance; country-specific analyses are also possible. Therefore, direct reports, e.g. from physicians and pharmacists in Germany, to the BfArM continue to be of great importance, as these may differ from ADR reports from other EU countries, for example due to difference in frequency of use of medicinal products.

The aim of this investigation was to determine the importance of ADR reports and databases for ensuring safety of medicinal product use by carrying out a retrospective descriptive analysis of all spontaneous reports contained in the adverse drug reaction database.

Methods

The starting point of the analysis comprised of all suspected ADR reports contained in BfArM's adverse drug

reaction database, from the first registration in 1978 until 31 December 2016 ($N = 528\,539$). Of these suspected ADR reports, about 70% ($n = 369\,778$) were spontaneous reports, about 28.2% ($n = 149\,034$) were from systematic investigations/studies ("solicited reports"), and about 1.8% ($n = 9728$) were of unclear origin. This analysis only included spontaneous reports within Germany of ADRs due to suspected or interacting medicinal product(s) (herein termed "drugs under suspicion") that did not report unintended use. The final analysis dataset contained 345 662 spontaneous reports (65.4% of all reports of the ADR database, and 93.5% of all spontaneous reports) (*eFigure 1*, *eMethods*).

All spontaneous reports were of suspected ADRs of medicinal products. Case numbers were determined by computer-based database queries; no single-case evaluation was performed (for example, for causality assessment). Active substances are coded in the ADR database according to the official classification for active pharmacologically ingredients according to the ATC code (anatomic therapeutic chemical classification system) (18) (*eFigure 2*) and the World Health Organization's Drug Dictionary (19), and ADRs according to MedDRA terminology (MedDRA, Medical Dictionary for Regulatory Activities) (20) (*eMethods*). Suitable hierarchy levels were selected for each evaluation.

The primary reporting source provides information from whom the report originated (e.g. physician) regardless of the reporting channel (e.g. pharmaceutical company). Healthcare professionals (HCPs) are defined as those with medical qualifications; this includes physicians, pharmacists, and nurses (21). Consumers and non-HCPs are defined as people who are not HCPs; this includes patients and relatives (herein referred to as "patients"). Ratios were calculated as appropriate to investigate possible associations between the number of reports and population size (22), number of prescriptions (23), or number of physicians (24) in Germany.

The classification "serious adverse drug reaction" takes into account criteria from the legal definition (e.g., it results in death, is life-threatening, requires inpatient hospitalization, results in permanent disability, and/or is a congenital anomaly). These criteria differ from clinical criteria (11).

Approval for the study protocol was obtained from the ethics committee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn (Lfd. Nr. 009/17).

Results

The 345 662 spontaneous reports comprised more than 904 242 ADRs, which were associated with 421 581 drugs under suspicion or combinations of drugs under suspicion. The primary reporting sources were physicians (64.1%; 221 427) and pharmacists (10.3%; 35 776), other HCPs (2.6%; 9011), patients (9.5%; 32 992), and lawyers (0.6%; 2138).

The total number of spontaneous reports per year has been rising steadily since 1978 (Figure 1). Reporting from physicians has had a slower rate of increase since 2002; in contrast, reporting has noticeably increased from pharmacists and other HCPs since 2005, and from patients since 2008. Reporting from lawyers show peak levels that can be traced back to special factors (for example, the case of rofecoxib in 2007).

The time course of spontaneous reports in total and of those sent to the BfArM by pharmaceutical companies has been very similar since 1988 (Figure 2). In contrast, there are no clear associations between the increasing number of spontaneous reports and changes in population size (22), prescription data (23), or the number of working physicians (24) (Figure 3).

The observed increase in the number of spontaneous reports from 1989 to 1996 is not reflected in the number of spontaneous reports sent to the BfArM from other sources. This increase could therefore be the result of other statutory reporting obligations in this period (25), as pharmaceutical companies also were required to report non-serious ADRs to the BfArM during that time (eBox 2).

Around 66.9% of all spontaneous reports are classified as serious (11). The proportion of spontaneous reports including the serious criterion “fatal” was 5.5%.

Stratification according to patient age shows a continuous increase in accumulated reports for patients from 11 to 70 years of age (eFigure 3). The most spontaneous reports refer to the age group 66–70 years.

Overall, 54.6% of spontaneous reports refer to females, and 38.8%, refer to males (with 6.6% not specified). For children aged ≤ 15 years, more spontaneous reports are made for males.

For this age group the most frequent ADRs are for the drug group of “nervous system disorders” with the most reports for the subgroup of “psychostimulants, ADHD medication, and nootropics” (11.9%, 830). The most commonly reported ADRs are aggression (6.1%; 51), suicidal thoughts (6.1%; 51), and headache (5.9%; 49).

For adolescent women (> 15 to ≤ 20 years), the most frequent ADRs are for the drug group of “hormonal contraceptives for systemic use” (23.7%; 1046). The most commonly reported ADRs are pulmonary embolism (20.1%; 217), deep vein thrombosis (17.4%; 182), and pelvic vein thrombosis (11.9%; 124).

The three ADRs that were cumulatively reported most frequently for all groups (irrespective of age or sex) during the observation period were nausea, pruritus, and dizziness (eTable 1). Many other nonspecific general symptoms (such as vomiting, headache, and pyrexia) are also among the 15 most common ADRs. Three of these 15 ADRs are visible cutaneous ADRs (skin rash, erythema, and urticaria); two others (hypersensitivity and pruritus) may show visible cutaneous symptoms.

FIGURE 2

Number of spontaneous reports per year that are forwarded by pharmaceutical companies to the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM).

If the reported drugs under suspicion are analyzed at the highest hierarchical level of the ATC drug groups, the drugs for nervous system disorders are clearly in first place (23.1%), as four of the ten most reported therapeutic subgroups, all of which are listed in Table 1 (psycholeptics, psychoanaleptics [anti-depressants], analgesics, and antiepileptics) are comprised in this drug group. This is followed by drugs for the treatment of cardiovascular disorders (13.0%) and “antineoplastics and immunomodulating agents” (12.4%) (eTable 2).

Table 1 shows the ten therapeutic subgroups that are most frequently reported as suspicious, with their most commonly reported ADRs. The aim of this study was to obtain a descriptive analysis of all spontaneous reports. Therefore, Table 1 lists many known associations, such as bleeding events related to antithrombotic agents.

Reported ADRs from physicians and patients are similar in terms of the most commonly reported ADRs but differ in ranking (eTable 3). However, among the 50 ADRs most frequently reported by physicians, those that are typically diagnosed by physicians, such as specific diagnoses (e.g., pulmonary embolism, ranked #35) and laboratory findings (e.g., leukopenia, ranked #14), are prevalent. In contrast, ADRs reported by patients are mainly those that can be subjectively perceived (e.g., anxiety, ranked #29; taste disturbances, ranked #45) and/or those that limit individual quality of life (e.g., weight increased, ranked #40; alopecia, ranked #28). This distinction is also evident when the medicinal products most frequently reported by either physicians or patient are directly compared (Table 2). On average,

Quotient of spontaneous reports per 100 000 population, per 100 000 prescriptions, or per 100 physicians, over time.
Limitations of the analysis over time are described in eBox 3.

FIGURE 3

patients report more ADRs per report than physicians (3.5 versus 2.5) as well as more serious ADRs (75.6% versus 65.8%). Only three of the drug groups most frequently reported by physicians as suspicious were also among the top ten from patients. Notably, patients were more likely than physicians to report immunostimulants (e.g., interferons, ranked #1) and contraceptives (progestogens and estrogens, fixed combination, ranked #5; intrauterine contraceptives, ranked #6); these were ranked #18, #16, and #21, respectively, by physicians.

Discussion

To our knowledge, this is the first and largest cumulative evaluation of spontaneous reports from Germany in the BfArM adverse drug reaction database, and it revealed a continuous increase in reports from 1978 to 2016. Furthermore, the number of reports increased with patient age (11–70 years), and more reports involving women. The three most commonly reported medication groups (with the most common ADRs in parentheses) were: antithrombotic agents (thrombocytopenia, gastrointestinal hemorrhage, and hemorrhage), antibacterials for systemic use (diarrhea, skin rash, and pruritus), and psycholeptics (drug dependence, leukopenia, and pyrexia).

The steady increase in number of spontaneous reports in the BfArM database is mainly due to more reports being sent to the BfArM by pharmaceutical companies. Various factors could be behind this, such as a general increase in willingness to report by physicians and patients (as primary reporting sources); this could be due to increased awareness of ADRs and of reporting options, and having more information sources (Internet). However, the proportion of direct reports to the BfArM (spontaneous reports without reports from pharmaceutical companies) did

not show a comparably strong increase (Figure 2). Likewise, there was no clear association between the increase in spontaneous reports and population size, the number of prescriptions made, or the number of working physicians (Figure 3), although certain limitations must be taken into account (eBox 3). Therefore, modified or tightened legal requirements for reporting ADR reports to the BfArM were probably more important for increasing the number of reports sent to the BfArM by the pharmaceutical companies (eBox 3).

About every tenth spontaneous report comes from a patient. Reports from this source have increased substantially since 2008. This could be due to increased sensitivity to the topic due to high-profile medicinal product scandals, the possibility since 2009 to report ADRs online to the BfArM, and the calls for reporting suspected ADRs in the package leaflet (26). Patients in other European countries also have reported more frequently over time (27, 28).

The relatively high proportion of reports classified as serious (66.9%) (11) is likely due to regulatory reporting requirements for pharmaceutical companies. It is not possible to determine how many ADRs were fatal, as the calculated proportion (5.5%) does not provide any statement about the cause of death. In other words, many reports do not indicate whether death was due to the ADR itself, to the consequences of the ADR, or to underlying diseases.

ADRs are known to increase with age (from 11 to 70 years) (29–31) and may be due to increased medicinal product use in older people (32, 33). A higher risk of ADRs in older people may also be the result of comorbidity, polymedication, and/or decreased liver or kidney function (32, 34–36).

A prevalence of the female sex in ADR reports (54.6% versus 38.8%) has also been described

TABLE 1

The most frequently reported medication groups under suspicion, and their most frequently reported ADRs, in the total dataset (N = 345 662)

Rank	Therapeutic subgroup under suspicion (pharmacological subgroup)*1	Proportion of generated dataset (N = 345 662), in %*2 (number of spontaneous reports)	Proportion of most frequently reported ADRs in medication subgroups under suspicion, in %*2 (number of spontaneous reports)
1 st	Antithrombotic agents (heparin group, factor Xa inhibitors/ direct thrombin inhibitors*3)	8.4% (29 185)	7.1% thrombocytopenia (2074) 5.9% gastrointestinal hemorrhage (1722) 4.9% hemorrhage (1430)
2 nd	Antibacterials for systemic use (quinolones, other beta-lactam antibacterials [e. g. cephalosporin])	8.4% (29 014)	6.5% diarrhea (1885) 6.2% skin rash (1803) 6.0% pruritus (1741)
3 rd	Psycholeptics (antipsychotics)	7.9% (27 363)	4.0% drug dependence (1098) 3.7% leukopenia (1025) 3.5% fever (947)
4 th	Psychoanaleptics (antidepressants)	6.0% (20 828)	5.4% nausea (1125) 4.7% dizziness (975) 3.1% headache (640)
5 th	Antineoplastic agents (other antineoplastic agents [e. g. protein kinase inhibitors], antimetabolites)	6.0% (20 793)	6.2% dyspnea (1284) 5.4% fever (1125) 5.2% thrombocytopenia (1087)
6 th	Antiinflammatory and antirheumatics (antiinflammatory and antirheumatic non-steroids [coxibs, e. g. rofecoxib; acetic acid derivatives, e. g. diclofenac])	5.7% (19 650)	6.2% hypertension (1209) 5.0% nausea (980) 4.5% cerebral infarction (887)
7 th	Analgesics (salicylic acid and derivatives [e. g. ASA], pyrazolones [e. g. phenazone], anilides [e. g. paracetamol], opioids)	4.0% (13 723)	7.9% nausea (1085) 5.1% drug dependence (695) 4.8% agranulocytosis (657)
8 th	Antiepileptics (other antiepileptics [e. g. levetiracetam, lamotrigine], carboxamide derivatives [e. g. carbamazepine])	3.7% (12 898)	7.1% seizure (920) 4.4% dizziness (575) 4.3% hyponatremia (557)
9 th	Agents acting on the renin-angiotensin system (ACE inhibitors plain, angiotensin II antagonists plain)	3.7% (12 713)	9.0% angioedema (1139) 7.0% cough (893) 6.2% dizziness (782)
10 th	Sex hormones and modulators of the genital system (hormone contraceptives for systemic use)	3.4% (11 906)	9.5% pulmonary embolism (1132) 8.1% deep vein thrombosis (961) 4.4% unintended pregnancy (519)

*1 For the analysis presented in Table 1, medications were grouped according to the 2nd level of the ATC code (the therapeutic subgroup), with the most frequent pharmacological subgroups shown in brackets; for the analysis presented in Table 2, medications were grouped according to the 4th level of the ATC code.

Adverse drug reactions (ADRs) were analyzed at the 4th level of MedDRA (Medical Dictionary for Regulatory Activities) terminology (as preferred terms).

*2 When interpreting percentages, it should be noted that a report may contain several drugs under suspicion and multiple ADRs.

*3 For definition of the therapeutic/pharmacological subgroup "factor Xa inhibitors/direct thrombin inhibitors", please see eFigure 2.

previously in other analyses (29–31). Explanations for this could be more frequent visits to the physician by women (34, 37), a higher use of medicines by women (29, 33), and sex differences in pharmacokinetics (38).

Thirteen of the 15 most commonly reported ADRs were nonspecific general symptoms. This could be due to the fact that, in addition to the ADR leading to the report, nonspecific general symptoms associated with the main ADR were (co-)reported and therefore appeared overly frequently in the analysis.

One-fifth of the most common ADRs are cutaneous, and one-third of the reported ADRs were related to skin. Adverse drug reactions should therefore be considered when making a differential diagnosis of skin lesions.

It is striking that in our study, as well as in other studies (29, 31), "medicinal products for the treatment of the nervous system disorders" were most frequently reported as suspect in the top-level drug groups. However, based on these data, no conclusions can be made about whether these medicines actually cause more ADRs or are only reported more frequently, as the corresponding frequency of use is not known (among other reasons). Nonetheless, in Germany in the period from 2008 to 2011, the highest prevalence of medicinal product use was observed for treating cardiovascular disorders (28.4%), followed by varia (22.5%), and then for nervous system disorders (21.2%) (33).

The importance of medical expertise becomes clear with regard to ADRs typically determined by a

TABLE 2

Physician reports (n = 221 427) compared to patient reports (n = 32 992): Comparison of the most frequently reported ADRs in the ten most frequently reported medication groups under suspicion (based on physician reporting)*¹

Rank: physicians	Most frequent medication groups under suspicion in physician reports	Frequency in physician reports in % (n = 221 427)	Physicians: Proportion of most common ADRs in reported medication groups under suspicion in % (number of spontaneous reports)	Rank: patients	Frequency in patient reports in % (n = 32 992)* ²	Patients: Proportion of most common ADRs in reported medication groups under suspicion in % (number of spontaneous reports)
1 st	Diazepine* ³ , oxazepine, thiazepine, oxepine (e. g. clozapine, olanzapine)	3.3% (7324)	8.5% leukopenia (626) 8.4% pyrexia (615) 5.8% agranulocytosis (426)	22 nd	1.1% (361)	14.1% weight increased (51) 8.6% dizziness (31) 8.0% fatigue (29)
2 nd	Fluoroquinolones	3.0% (6577)	5.5% nausea (359) 5.4% diarrhea (357) 5.1% dyspnoea (333)	4 th	2.7% (880)	13.6% arthralgia (120) 13.6% tendinopathy (120) 10.3% dizziness (91)
3 rd	Heparins	2.6% (5861)	24.1% thrombocytopenia (1 411) 14.6% drug-specific antibodies (856) 13.5% pulmonary embolism (792)	26 th	1.0% (321)	7.2% thrombocytopenia (23) 6.2% thrombosis (20) 5.9% hematoma (19)
4 th	HMG CoA reductase inhibitors	2.4% (5343)	27.6% myalgia (1477) 16.6% blood creatine phosphokinase increased (887) 10.0% rhabdomyolysis (535)	12 th	1.4% (475)	28.0% myalgia (133) 11.2% muscle weakness (53) 10.1% muscle spasms (48)
5 th	Factor Xa inhibitors/direct thrombin inhibitors* ⁴ (e.g. rivaroxaban, lepirudin)	2.2% (4912)	6.3% cerebral hemorrhage (311) 6.2% gastrointestinal hemorrhage (304) 5.5% hemoglobin decreased (271)	2 nd	3.0% (1006)	13.1% epistaxis (132) 8.8% dizziness (89) 7.5% blood in urine (75)
6 th	Antithrombotic agents	2.1% (4752)	12.8% gastrointestinal hemorrhage (608) 7.9% melena (374) 7.5% thrombocytopenia (358)	20 th	1.1% (371)	7.3% dizziness (27) 6.2% hematoma (23) 5.9% bleeding (22)
7 th	Non-selective monoamine reuptake inhibitors, and other antidepressants (e. g. venlafaxin, mirtazapine)	2.1% (4708)	4.5% nausea (210) 4.0% dizziness (187) 3.5% alanine aminotransferase increased 167)	9 th	1.8% (590)	11.4% nausea (67) 10.2% dizziness (60) 9.7% fatigue (57)
8 th	ACE inhibitors, plain	2.0% (4373)	13.7% angioedema (599) 8.8% cough (387) 4.1% nausea (180)	25 th	1.0% (328)	11.6% cough (38) 10.1% dizziness (33) 7.9% dyspnea (26)
9 th	Other antipsychotics (e.g. risperidone)	1.8% (4002)	5.2% extrapyramidal symptoms (208) 4.6% dyskinesia (185) 4.5% akathisia (180)	42 nd	0.7% (231)	14.3% weight increased (33) 8.7% restlessness (20) 6.9% fatigue (16)
10 th	Selective serotonin reuptake inhibitors (SSRI) (e. g. citalopram, fluoxetine)	1.7% (3865)	6.2% nausea (238) 3.7% dizziness (144) 3.7% drug interaction (143)	18 th	1.3% (420)	10.0% dizziness (42) 7.6% nausea (32) 7.4% headache (31)

*¹ To avoid double counting, this analysis was based on reports with only one reporter source.

*² Ranking of the most commonly reported medication groups under suspicion in patient reports: 1st, interferons (5.1%); 2nd, other antithrombotic agents (3.0%); 3rd, selective immunosuppressants (2.9%); 4th, fluoroquinolones (2.7%); 5th, progestogens and estrogens, fixed combinations (2.4%); 6th, intrauterine contraceptives (2.2%); 7th, other immunostimulants (1.9%); 8th, dopa and dopa derivatives (1.9%); 9th, other antidepressants (1.8%); and 10th, angiotensin II antagonists, plain (1.7%).

*³ These refer to diazepam that are assigned to antipsychotics, such as clozapine and olanzapine, but not to benzodiazepines.

*⁴ For definition of the therapeutic/pharmacological subgroup "factor Xa inhibitors/direct thrombin inhibitors", please see eFigure 2.

physician, such as specific diagnoses (pulmonary embolism) or laboratory findings (thrombocytopenia). Patients, on the other hand, are more likely than physicians to report ADRs that are subjectively perceived, as well as those that may be of particular importance to their personal quality of life (for example, weight changes, sleep disorders, or alopecia). In this respect, patient reports can be an important supplement to reports from physicians. Furthermore, ADRs that affect the patient's quality of life may affect adherence. Together with an appropriate

patient education, patient knowledge about such ADRs and their significance can be relevant to the success of a therapy.

The benefits of the spontaneous reporting system include monitoring the full spectrum of medicinal products (including over-the-counter [OTC] medications), a large population coverage that includes high-risk groups (e.g., children and pregnant women), and acquisition without a time limit. Among the inherent limitations of the spontaneous reporting system is underreporting (3, 14, 39); while this is

estimated to be around 90% (40), it depends on the type, severity, and familiarity of the ADR, and of the drug under suspicion (old/new), as was shown in a German study (e1). Other limitations include partially incomplete documentation of case reports and the inability to determine ADR frequency.

The BfArM regularly informs about new risks identified within the framework of medicinal product safety monitoring. Analysis of spontaneous reports contributes substantially to risk recognition of new medical products and can provide the basis for a range of various regulatory measures, such as intensified surveillance, obligation of studies, inclusion of new contraindications in the product information of medicinal products, and revocation of authorization.

Examples of BfArM measures that were based on spontaneous reports include:

- changes in monitoring requirements due to progressive multifocal leukoencephalopathy with the use of fumarates (e2);
- obligation to determine liver values during treatment with kava-kava-containing medicinal products due to hepatotoxic events (e3);
- withdrawal of approval of topically applied bufexamac-containing medicinal products due to contact allergic reactions (e4).

As regulatory measures required to ensure medicinal product safety are based on relevant data and information, ADR reports and the quality of these reports are of major importance for medicinal product safety. Therefore, the BfArM would also like to use this article to strongly encourage reporting of suspected ADRs (14).

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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Key messages

- Spontaneous reports of ADRs from physicians, pharmacists, or patients in everyday use of an already approved medicinal product are crucial for ensuring drug safety.
- The number of spontaneous reports registered annually with the German Federal Institute for Drugs and Medical Devices (BfArM; *Bundesinstitut für Arzneimittel und Medizinprodukte*) has increased steadily since 1978. This is mainly due to an increase in reports sent to the BfArM by pharmaceutical companies. Stricter legal requirements for reporting ADRs are likely to be behind this increase.
- At the top hierarchy level, drugs for treatment of nervous system disorders are the most common to be reported as drugs under suspicion (23.1%). At the level of the specific drug groups, the most commonly reported medicinal products are anti-thrombotics, systemic antibiotics, and psycholeptics.
- Physicians typically report ADRs that can be detected by a physician, such as specific diagnoses or laboratory findings. In contrast, patients often report ADRs that are perceived subjectively and/or that affect their quality of life.

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Corresponding author

Prof. Dr. med. Bernhardt Sachs
German Federal Institute for Drugs and Medical Devices (BfArM)
Kurt-Georg-Kiesinger Allee 3
53175 Bonn, Germany

► Supplementary material

For eReferences please refer to:
www.aerzteblatt-international.de/ref2318

eBoxes, eFigures, eTables, eMethods:
www.aerzteblatt-international.de/18m0393

Supplementary material to:

Frequent Adverse Drug Reactions, and Medication Groups under Suspicion

A Descriptive Analysis Based on Spontaneous Reports to the German Federal Institute for Drugs and Medical Devices from 1978 to 2016

by Diana Dubrall, Matthias Schmid, Eva Alešik, Norbert Paeschke, Julia Stingl, and Bernhardt Sachs

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What should physicians be aware of when reporting ADRs?

● Why should ADRs be reported after approval?

Clinical trials prior to approval of a medicinal product include a limited number of preselected patients. In this situation, ADRs that are rare or that only occur in certain vulnerable patients or after prolonged use cannot be reliably detected. Therefore, spontaneous reports of ADRs from physicians with everyday use of a medicinal product on a wide range of patients after its approval are of major importance for medicinal product safety.

● To whom can ADRs be reported in Germany?

ADRs can be reported to:

- a) the Drug Commission of the German Medical Association (AkdÄ; *Arzneimittelkommission der deutschen Ärzteschaft*);
- b) the competent federal authorities according to their respective areas of responsibility (for the German Federal Institute for Drugs and Medical Devices [BfArM], chemically-defined active substances, among others; and for the Paul-Ehrlich-Institut [PEI], monoclonal antibodies and vaccines, among others);
- c) pharmaceutical companies, which then forward them.

As the reports are exchanged between institutions, parallel reports to several institutions are not required.

● How can ADRs be reported?

ADRs are best reported via the online platforms of AkdÄ, BfArM, or PEI, respectively. If this is not possible, reporting can alternatively be done either using the reporting form, which should be printed and filled out and then sent by fax, scan, or postal mail, or directly (without a form) by postal mail, fax, or email. Nonetheless, using the online platforms is explicitly recommended, as all relevant information is specifically queried there.

● Which information should be included in the ADR report?

The relevant information is requested in the reporting form. Of particular importance are the following:

- a) the demographic background of the patient (including initials, age, and sex), to allow detection of double reporting, among other things;
- b) the type of ADR, time of occurrence, duration, and outcome;
- c) the suspected (or, where appropriate, interacting) medicinal product(s) and its use (exact name [active substance, trade name], and if available, lot number), route of administration (oral, intravenous, etc.), dose used, starting and (if appropriate) stopping time/date of therapy, and indication;
- d) any concomitant medication (exact name [active substance, trade name] and if available, lot number), route of application (oral, intravenous, etc.), dose used, starting and (if appropriate) stopping time/date of therapy, and indication;
- e) medical history, potential risk factors, and accompanying factors (e.g., comorbidities, nicotine or alcohol abuse);
- f) information for assessment of a causal relationship (for example, description of the temporal association, course, and treatment of the ADR [including discontinuation of the suspect medicine]), re-exposure, assessment of a causal relationship by the reporting physician;
- g) information that provides a more detailed description of the ADR, such as laboratory parameters;
- h) information about the reporter (including address, e-mail, and qualifications).

Treating physician letters and hospital discharge letters can be very helpful if they contain relevant information.

● Which ADRs are of particular interest?

All ADRs can be reported. A causal relationship with the use of the medicinal product does not have to be clearly demonstrated; it is sufficient if it is assessed as "possible". Of particular interest are reports on:

- all serious ADRs
- all ADRs in children and pregnant or breast-feeding women
- ADRs of newly introduced active substances (e.g., up to five years after approval)
- previously unknown ADRs, or those that are not listed in the product information
- ARs occurring after prolonged use or after a medicinal product has been discontinued (long-term effects)
- observed accumulation of a certain AR (for example, allergic reactions as an indication of possible defects in pharmaceutical quality)
- ADRs in case of use outside of the approved indications (off-label use)
- medication errors, abuse

● What happens to the report?

- After pseudonymisation, the report is stored in EudraVigilance (*European Union Drug Regulating Authorities Pharmacovigilance*, the European database for adverse drug reaction), where analyses are continuously performed to ensure drug safety. Signals from ARs can be a major cause of regulatory action (for example, changes in product information, conducting trials).

Authors

Felix Wolfrum¹, Diana Dubrall^{2,3}, Norbert Paeschke², Eva Alešik², Bernhardt Sachs^{2,4}, Rainer Riedel¹, Maria Wittmann^{1,5}

¹ Institute for Health-Economics & Health-Care Research, University of Applied Sciences, Cologne, ² BfArM, Bonn, ³ Institute for Medical Biometry, Informatics, and Epidemiology (IMBIE), University Hospital of Bonn, Germany, ⁴ Clinic for Dermatology and Allergology, University Hospital (RWTH), Aachen, Germany, ⁵ Department of Anesthesiology and Intensive Care Medicine, University of Bonn, Germany

ADR reporting by pharmaceutical companies

Changes to the statutory reporting obligations of 1987–2016. The following aspects must be taken into consideration with respect to Figure 2:

The increasing number of spontaneous reports in the database of the Federal Institute for Drugs and Medical Devices (BfArM) over time is mainly due to an increase in reports forwarded to the BfArM by pharmaceutical companies. In particular, modified or tightened legal requirements for pharmaceutical companies to forward ADRs which they have become aware of, may have contributed to this increase. The reporting obligation for pharmaceutical companies—that is, their obligation to forward spontaneous reports—to the competent federal authorities, has existed since 1987. Various legislative changes were made up to 2016. For example, in October 2012, the second law amending medicinal products and other legislation redefined the term „ADR“. In the 1987 definition, unintended ADRs under the intended use of a medicinal product had to be reported; the definition of ADRs since 2012, in contrast, includes any reaction to the use of a medicinal product, including, for example, those due to medication errors.

Modifications in the form and scope of the reporting requirements of individual cases (serious/non-serious) could have influenced the course as well. Specifically, in 1987, ADRs with temporary, minor harm that did not impair health were not yet notifiable. In stark contrast, in the period 1989–1995, all ADRs (serious and non-serious) had to be reported. Differences also existed in the reporting forms and the timing of the deadlines, depending on whether the reported ADR was known or not. Starting from 1996, non-serious ADRs could be listed in periodic safety reports (instead of submitting an ADR report). The new EU legislation in 2012 (e7) created the conditions for suspected non-serious ADRs to be reported regularly as single-case reports. The obligation to forward such suspected cases from the EU Member States to the EudraVigilance database applies both to the respective competent authorities in the EU and to pharmaceutical companies (for the latter, since 22 November 2017) across the EU.

With the beginning of the legal reporting obligations, ADR reports were required to provide information about the so-called „identifiability“ of the data source and the patient (to exclude multiple registrations of one case report from different reporting sources), in addition to information about at least one medicinal product under suspicion of inducing an ADR and about at least one ADR due to use of the product. The requirements of providing a minimum criteria of information for identifiability have been reduced over time, in part for data protection reasons but also to ensure that not having certain information does not obstruct reporting an ADR. However, this has made merging information about the same case from different reporting sources much more difficult, and having multiple registrations cannot be ruled out for all individual cases. In addition, the general monitoring and documentation requirements for pharmaceutical companies have been increasingly tightened. These now includes the obligation to perform a weekly literature search in at least one literature database (since 2005), and the obligation to report ADRs that have become known; the obligation to notify was (and is) also valid for ADRs reported via the Internet.

Other reasons for the increased volume of reporting are: the obligatory inclusion since 2013 of a reference in the product information and patient information leaflets for reporting ADRs, as well as the labeling of newly approved medicinal products with additional monitoring (black triangle).

Explanations for the terms used:

Medicinal products under additional monitoring ▼

Since 2013 (26), medicinal products under additional monitoring are marked with a black triangle ▼ in all EU member states (e8). Additional monitoring usually covers medicinal products when there is less available information about them than for other medicines, which may be due to the product being new to the market or having insufficient data for its long-term use. The black triangle indicates that this medicinal product is being monitored even more strictly than others. Notably, it does not mean that the medicinal product is not safe. The black triangle urges patients to report any suspicion of a possible ADR when using the medicine. The black triangle is printed both in the patient information leaflet and in the prescribing information for healthcare professionals (the so-called summary of medicinal product characteristics). It is not shown on the outer wrapper or on the product label.

eBOX 3

Limitations on the evaluation of the time course of the quotient of spontaneous reports per 100 000 population, 100 000 prescriptions, and 100 physicians in Germany

Overview of the evolution of population size, prescriptions, and number of working physicians over time

Since the reunification of Germany (1990), the population size has remained almost constant (data: German Federal Statistical Office [Statistisches Bundesamt]) (22). In contrast, the number of spontaneous reports has increased over time. This has led to an increase in the ratio of spontaneous reports/100 000 population in Germany.

The total number of prescriptions (data: drug prescription report [Arzneiverordnungsreport]) (23) increased in the years 1991/1992 (this is not visible in the quotient) and then slowly decreased. In 2004, the total number of regulations decreased sharply (due to the Statutory Health Insurance Modernization Act [GKV-Modernisierungsgesetz]) and then began to slowly rise again. The number of spontaneous reports has greatly increased over time. Therefore, the quotient of spontaneous reports/100 000 prescriptions shows a slight increase.

The number of working physicians in the out- and inpatient areas (data: physician statistics of the German Medical Association [Bundesärztekammer]) (24) has steadily increased. The number of spontaneous reports has greatly increased over time. Therefore, the quotient of spontaneous reports/100 physicians shows a slight increase.

For interpreting the quotients in Figure 3, various limitations must be taken into account:

The data on the population are provided by the German Federal Statistical Office (Statistisches Bundesamt) (22). In particular, there may be restrictions in the accuracy in recent years due to the increased level of immigration and the consequent problems in registration. Another aspect is an increase in the aged population in Germany over the analysis period (1978–2016) and increased life expectancy, as an older population is associated with higher prevalence rates for the presence of disease. The presence of disease or comorbidity, and the therapies for these (and in particular polypharmacy), may be associated with an increase in ADRs and reports of ADRs.

The total number of prescriptions was taken from the *Arzneiverordnungsberichte* (drug prescription reports) (23). This included finished medicinal products that have been prescribed for outpatients and covered by the statutory health insurance funds; among other things, data on medicinal product prescriptions for private patients are missing. Further, over-the-counter (OTC) use is not included. In addition, data do not allow any conclusion to be drawn as to whether the medicines were actually used. The indication of the total number of prescriptions in DDD (defined daily dose) is also problematic, as using DDD is not suitable for all medicinal products and may not correspond to the actual prescribed/applied daily dose.

Data on the number of working physicians come from the medical statistics of the German Medical Association (Bundesärztekammer) (24). The increase in the number of working physicians in the out- and inpatient sectors did not take into account the individual disciplines. Due to different prescription frequencies in the various disciplines, this may also be of importance.

Explanations for the terms used:

DDD (defined daily dose)

The defined daily dose is based on the amount of active substance or medicinal product that should typically be used for the main indication per day. It should be noted that the DDD does not necessarily reflect the recommended or actual daily dose of a medicinal product but mainly provides a technical means of measurement and comparison (23).

eFIGURE 1

Flow chart depicting generation of final dataset

German Federal Institute for Drugs and Medical Devices (*Bundesinstitut für Arzneimittel und Medizinprodukte*, BfArM); SMQ, standardized MedDRA queries; MedDRA, Medical Dictionary for Regulatory Activities

eFIGURE 2

Description and schematic depiction of ATC* (anatomical, therapeutic, chemical) classification using morphine as an example

Example: morphine

The ATC classification system has a hierarchy with five different levels. * There are fourteen major anatomical groups (for example, 1st level: the nervous system). Active substances are each assigned to the anatomical systems in which they are effective. The 2nd level identifies the associated pharmacological/therapeutic subset (for example, analgesics). The 3rd and 4th levels reflect the chemical, pharmacological, or therapeutic subgroup (3rd level, opioids; 4th level, natural opium alkaloids). At the last (5th) level, the chemical substance is described (morphine). Graphical depiction using the example "Medicinal products for the treatment of diseases of the nervous system" (not given in full).

* ATC-Structure and Principles: www.whooc.no/atc/structure_and_principles/

Clarification for Tables 1 and 2: Other antithrombotic agents

In the ADR database (and deviating from the ATC code classification), the active substances rivaroxaban and lepirudin (4th level ATC code) are assigned to the pharmacological subgroup "other antithrombotic agents". Other direct factor Xa inhibitors (e.g., apixaban, edoxaban) are included in the pharmacological subgroup "factor Xa inhibitors", while another direct thrombin inhibitor (dabigatran) is included in the pharmacological subgroup "direct thrombin inhibitors". To facilitate understanding, the term "other antithrombotic agents" in Tables 1 and 2 has been renamed "Factor Xa inhibitors/direct thrombin inhibitors". Thus, only the name of the group, but not the assigned substances, was changed. Note that there was no summation of the three pharmacological subgroups.

eFIGURE 3

Stratification of spontaneous reports by age and sex

eFigure 3 shows the cumulative stratification of spontaneous reports with respect to age (in 5-year age groups) of affected patients and their sex. Reports within one age group can be from different years. In addition to the sex ratio (female/male), the odds ratio for each age group with respect to the other age groups was calculated using the Bonferroni confidence interval adjustment.

eTABLE 1

The 15 most frequently reported ADRs in the generated dataset

Rank	Most frequently reported ADRs	Proportion of generated dataset (N = 345 662) in % (number of spontaneous reports)
1 st	Nausea	5.2% (18 074)
2 nd	Pruritus	3.8% (12 984)
3 rd	Dizziness	3.7% (12 833)
4 th	Dyspnea	3.4% (11 762)
5 th	Vomiting	2.8% (9781)
6 th	Skin rash	2.8% (9610)
7 th	Headache	2.7% (9353)
8 th	Diarrhea	2.7% (9338)
9 th	Pyrexia	2.5% (8709)
10 th	Hypersensitivity	2.4% (8225)
11 th	Urticaria	2.3% (7985)
12 th	Thrombocytopenia	2.1% (7279)
13 th	Fatigue	2.0% (7044)
14 th	Erythema	1.9% (6508)
15 th	Tachycardia	1.8% (6150)

The fifteen most frequently reported ADRs are shown as the proportion of the generated dataset of 345 662 spontaneous report (as percentage) and their absolute number (in brackets).

As a report may describe several ADRs, the number of reported ADRs exceeds the total number of reports.

For the analysis presented in eTable 1, ADRs were chosen at the 4th level (PT, preferred term) of the MedDRA (Medical Dictionary for Regulatory Activities) terminology.

eTABLE 2

The ten most frequently reported medication groups under suspicion at the top level

Rank	First level medication groups under suspicion (and the three most frequent therapeutic subgroups of medication under suspicion)	Proportion in generated dataset (N=345 662) in %- (absolute number of spontaneous reports)
1 st	Nervous system (psycholeptics; psychoanaleptics [antidepressants]; analgesics)	23.1% (79 976)
2 nd	Cardiovascular system (agents acting on the renin-angiotensin system; lipid modifying agents; cardiac therapy)	13.0% (44 787)
3 rd	Antineoplastic and immunomodulating agents (antineoplastic agents; immunosuppressants; immunostimulants)	12.4% (43 006)
4 th	Blood and blood forming organs (antithrombotic agents; blood substitutes and perfusion solutions; antianemic preparations)	10.9% (37 661)
5 th	Antiinfectives for systemic use (antibacterials; antivirals; antimycotics)	10.5% (36 327)
6 th	Musculo-skeletal system (antiinflammatory and antirheumatic products; drugs for treatment of bone diseases; muscle relaxants)	8.7% (30 217)
7 th	Alimentary tract and metabolism (drugs used in diabetes; drugs for acid related disorders; drugs for functional gastrointestinal disorders)	7.3% (25 139)
8 th	Genitourinary system and sex hormones (sex hormones and modulators of the genital system; other gynecologicals; urologicals)	6.1% (21 223)
9 th	Various (contrast media; all other therapeutic products; dental preparations)	4.7% (16 089)
10 th	Respiratory system (drugs for obstructive airway diseases; cough and cold preparations; antihistamines for systemic use)	3.9% (13 365)

The ten most frequently reported medication groups under suspicion are shown as their percentage share of the generated dataset of spontaneous reports ($n = 345\,662$), and as absolute numbers (in brackets). The three most frequent therapeutic subgroups of medication under suspicion are shown in brackets. As a report may describe several drugs under suspicion, the number of reported ADRs exceeds the total number of reports.

The analysis presented in eTable 2 is based on the ATC code and depicts the most frequent 1st level (anatomical main group) medication groups and their three most frequent 2nd level medication subgroups.

eTABLE 3

The ten most frequent ADRs reported by physicians and patients

Rank	Physicians: most frequently reported ADRs	Proportion in physician reports (n= 221 427) in % (number of spontaneous reports)	Rank	Patients: most frequently reported ADRs	Proportion in patient reports (n=32 992) in % (number of spontaneous reports)
1.	Nausea*	4.7 % (10 382)	1.	Dizziness*	7.1% (2346)
2.	Pruritus*	3.5% (7734)	2.	Nausea*	6.3% (2074)
3.	Dyspnea*	3.1% (6876)	3.	Headache	5.3% (1747)
4.	Vomiting	2.8% (6267)	4.	Fatigue	5.1% (1696)
5.	Pyrexia	2.8% (6262)	5.	Dyspnoea*	4.6% (1527)
6.	Dizziness*	2.8% (6256)	6.	Diarrhea*	4.1% (1353)
7.	Thrombocytopenia	2.7% (6009)	7.	Pruritus*	3.7% (1209)
8.	Urticaria	2.6% (5721)	8.	Visual impairment	3.4% (1135)
9.	Skin rash	2.6% (5681)	9.	Asthenia	3.3% (1088)
10.	Diarrhea*	2.3% (5180)	10.	Arthralgia	3.1% (1038)

The ten most frequently reported ADRs in spontaneous reports from physicians (n = 221 427) and patients (n = 32 992) are shown as the percentage share of the corresponding dataset (e.g., for physicians or patients) and their absolute number (in brackets).

ADRs that are in the top ten for both physicians and patients are indicated with an asterisk (*). As a report may describe several ADRs, the number of reported ADRs exceeds the total number of reports. The remaining ADRs (until #50) are not listed here.

For the analysis presented in eTable 3, ADRs were chosen at the fourth level (PT, preferred term) of the MedDRA (Medical Dictionary for Regulatory Activities) terminology.

eMETHODS

Explanation of terms used

To facilitate understanding, the following terms were used in the article “Frequent Adverse Drug Reactions, and Medication Groups Under Suspicion”:

- “ADR/s” as an abbreviation of “adverse drug reaction/s”
- “patient” rather than “consumer and non-healthcare professional”;
- “pharmaceutical company” rather than “holder of the authorization” or “marketing authorization holder”. Differences in reporting obligations are not further discussed within the article.

OTC medicinal products:

OTC (over-the-counter) refers to all non-prescription medications (e5).

Generation of the final analysis dataset (N = 345 662)

Only spontaneous reports were used for the analysis, to produce a homogeneous database. Spontaneous reports (including reports from the Internet and digital media) are unsolicited reports about suspected ADRs that occur under everyday conditions (and not in the framework of clinical trials, for instance). According to the guidelines of the European Medicines Agency (EMA) (21), however, the definition of “unsolicited reports” covers both spontaneous reports and literature reports.

Solicited reports

According to an EMA guideline (21), solicited reports are all ADR reports that arise from organized data collection systems, including clinical trials, non-interventional studies, and surveys of patients or healthcare professionals. These reports are not considered to be spontaneous.

Causality assessment

Because of the high volume of ADR reports, no routine causality assessment can be made of all submitted spontaneous reports. Instead, causality assessments are conducted on an *ad hoc* basis, for instance when a signal arises in the context of computer-based signal detection. Such a signal may result, for example, from a relatively high number of ADR reports on a particular medicinal product within a given time span.

MedDRA terminology

MedDRA terminology (MedDRA, Medical Dictionary for Regulatory Activities) is a standardized medical terminology that can be used to index reported ADRs, for example in an ADR database (20). Keywording makes it easier to standardize such research and to perform it in a reproducible manner.

SMQ (standardized MedDRA queries)

SMQs are a predefined set of terms used in the MedDRA catalog for summarizing ADRs (e6).

Preferred term (PT)

A PT is a self-contained descriptor (a single medical concept) for a symptom, sign, disease, diagnosis, therapy indication, examination, or surgical or medical intervention. A PT is also an independent descriptor for a medical, social, or family history characteristic (according to MedDRA).

Restriction to medicinal products used as intended

The aim of this study was to generate a dataset of ADRs that were due to the intended use of the medicinal products. In the case of unintended use, for example in the case of suicide, much higher doses are typically taken, so that ADRs can be significantly different from those with the intended use. For this purpose, using SMQs (e6) removed ADR reports from the dataset that were based for instance on a medication error or an intended overdose (such as a suicide attempt).

Exclusion of ADR reports associated with medication errors

Spontaneous reports of ADRs that were coded as medication errors were excluded from the

analysis using the SMQ *medication errors* ($n = 9304$)*^{1,2}. However, one can assume that this does not exclude all ADR reports that were due to medication errors, as some ADRs contained in the database can be related to a medication error that is neither explicitly stated in the report nor can be directly deduced from the report.

Exclusion of cases with intentional overdoses

The SMQs *depression and suicide/ self-injury* and *drug abuse and dependence* identified 32 013 cases*^{1,2}. Of these, 18 919*^{1,2} reports were excluded that were of ADRs after intentional overdose (e.g., suicide attempts). For this exclusion process, two reviewers of the SMQs *depression and suicide/ self-injury* and *drug abuse and dependence* (total $n = 32\,013$ cases)*^{1,2} identified subordinated preferred terms (PTs; referred to herein as “adverse drug reactions” or “ADRs”) that indicated suicide or intentional overdose. In this way, 5345*² and 11 682*² cases were identified with the SMQs *depression* and *suicide/ self-injury*, respectively, and 15 408*² cases were identified with the SMQ *drug abuse and dependence*.

Cases with ADRs that were also detected with these SMQs, and that reported suicidality or suicide as a ADR but without a detectable indication of intentional use, were not excluded ($n = 13\,097$)*^{1,2}. This applies for instance to cases that reported depression ($n = 3804$) or suicidal thoughts ($n = 1417$) as ADRs.

Due to the high number of cases, it was not possible to evaluate individual cases. Therefore, it could be possible that some cases of intentional overdose were included in the final dataset.

Cases with unknown primary reporting source

Spontaneous reports in which the primary reporting source was unknown (6.9% of the 345 662 cases; e.g., those from an anonymous reporting source) were analyzed separately. As this separate analysis did not reveal any substantial differences as compared to the overall dataset, these reports were not excluded from the final analysis.

*¹ Within the framework of an internal review process, a recommendation was made after the first analysis had been completed to list the overall number of cases identified for the SMQ *depression and suicide/ self-injury* and the SMQ *drug abuse and dependence*, to facilitate understanding ($n = 32\,013$ cases). Since this analysis was performed at a later date, there is a minimum deviation of three cases from the summation of 18 919 (= cases excluded by this SMQ) and 13 097 (= cases included in the analysis). ($18\,919 + 13\,097 = 32\,016$, rather than 32 013). There was also a minimal deviation of ten cases for cases that had been coded as medication error, between the first and the most recent case retrieval (from 9304 cases to 9294, respectively). These marginal deviations may have been caused by, for example, re-coding as a result of follow-up reports.

*² A single report can be included in multiple SMQs, hence the sum of reports collected via different SMQs is not the same as the number of excluded cases.