



Reporting adverse drug reactions: contribution, knowledge and perception of German pharmacy professionals

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Abstract

Background The detection, assessment and prevention of adverse drug reactions along the product's life cycle is known as pharmacovigilance. German pharmacists are obliged by law to conduct pharmacovigilance measures, a specific training is not required. **Objectives** To assess the knowledge, contribution and perception of German pharmacy professionals regarding pharmacovigilance activities, in order to identify their needs to report better on the issue. **Setting** A semi-quantitative survey among German pharmacy professionals was conducted in November 2017. **Method** A questionnaire with 20 questions was developed and distributed to pharmacy professionals in four different German regions. **Main outcome measures** To assess the knowledge the number of right answered questions were examined; for perception a six-point-Likert was used and for contribution, yes or no questions. **Results** The participation ratio was 64.5% (n = 127). Nearly half of the participants (47.2%, n = 60) stated that they had already reported adverse drug reactions. Regarding the knowledge questions, there was neither a statistically significant difference between the correct answers of pharmacists and pharmacy technical assistants ($p = 0.7209$), nor between the different regions ($p > 0.5054$). For better reporting, the participants recommended better training, shorter forms to fill in and/or a contact person to call. **Conclusion** For the successful integration of pharmacovigilance reporting in daily practice, we suggest the following: (1) A structured, mandatory training of the pharmacy team. (2) The preparation of a standard operating procedure for the pharmacy or its integration into the pharmacy software.

Keywords Adverse drug reactions · Community pharmacy · Germany · Pharmacovigilance · Questionnaire · Survey

Impacts on Practice

- Pharmacists are drug specialists with a good understanding of clinical symptoms; they have their focus on the complete medication including OTC drugs. Thus, they play an important role in the detection of suspected adverse drug reactions, but need additional training on pharmacovigilance.
- Up to now there is no data available for Germany concerning this matter. Further research in this field has to be done to customise training programs based on the determined needs.

- Our results are similar to those from other countries and show that there is room for improvement among pharmacy professionals concerning pharmacovigilance matters.

Introduction

The detection, assessment and prevention of adverse drug reactions (ADRs) along the product's life cycle is known as pharmacovigilance (PV). Drug exposure during pregnancy or breast-feeding and medication errors such as overdose, abuse or misuse are also of interest in pharmacovigilance activities, as they might contribute to ADRs. In Europe, PV is regulated by the commission implementing regulation (EU) No. 520/2012 [1] that was converted into German law by the German Medicines Act (AMG) [2] and is therefore valid in Germany. According to §63 c AMG, the holder of the marketing authorization is legally obliged to report suspected ADRs within a more or less short time frame to the

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regulatory authority, depending on the categorisation of the ADR as being serious or not [2]. Therefore, it is not surprising that in Germany more than 80% of the suspected ADRs are reported to authorities by the pharmaceutical industry [3]. ADRs are defined in §4 (13) AMG as any unintended, harmful response to a drug. Serious ADRs are defined as responses to a drug that cause immediate danger to life or death, inpatient treatment in the hospital, extension of a hospital stay, congenital malformation or birth defects, permanent or severe disability or invalidity or medically significant events that would meet the aforementioned criteria if left untreated [2]. German health care professionals (HCPs) including pharmacists have to report adverse events according to their respective professional code. For German pharmacists §21 of the “Apothekenbetriebsordnung”, the law that describes how to operate a pharmacy [4], describes the duty of the pharmacy owner to put procedures in place that allow for reporting ADRs and other irregularities concerning drugs immediately when they occur. These procedures affect pharmacists and pharmacy technical assistants (PTA) alike. The Federal union of German associations of pharmacists has 864 community pharmacies and 54 hospital pharmacies as reference pharmacies whom they contact to answer emerging questions about pharmacovigilance [5]. However, there is no mandatory continuing education programme for PV in place for German pharmacy professionals, which could be used to train them on reporting adverse events in an appropriate way. Such training could increase spontaneous reporting, as drug safety surveillance strongly relies on these spontaneous reports [6]. If HCPs would report each ADR experienced by their patients, probably most of the ADRs that occur could be registered. However, in daily practice, only 5–10% of serious ADRs are reported and probably even less of the non-serious ADRs [7], although reporting possibilities are easily accessible (Fig. 1).

Aim of the study

The knowledge about, the contribution to and the perception of pharmacovigilance of German pharmacy professionals in different German geographical regions was assessed in order to identify their specific needs to report better on the issue.

Ethics approval

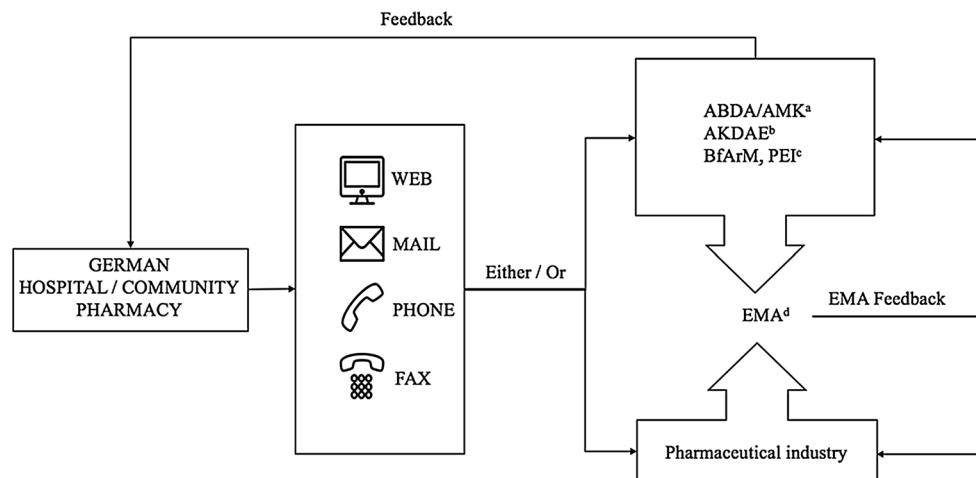
For this kind of anonymous research, no ethics approval was needed in Germany.

Method

Study setting

In November 2017, a semi-quantitative survey, using a structured questionnaire, was conducted amongst German pharmacists and PTA who attended regular continuing education seminars on pharmacological topics in four different geographic regions of Germany that also corresponded to different chamber of pharmacists: Central Germany, Western Germany, Eastern Germany and Southern Germany, during which the questionnaires were distributed. Hence, no formal recruiting took place for the purpose of the study at hand. The questionnaire was developed by two pharmacists (LA, SK) and reviewed by a pharmacovigilance expert (FWH). It contained four single-choice questions about demographics (Questions 1–4), one single-choice question, one question that combined an open field and a multiple-choice question, and one multiple-choice question, about the reporting behaviour of pharmacy professionals (Questions 5–7), eight multiple- and single-choice questions about their pharmacovigilance knowledge (Questions 8–15), four questions

Fig. 1 Reporting lines for German pharmacy professionals. ^aDrug commission of the federal union of German associations of pharmacists [8]. ^bDrug commission of the medical profession [9]. ^cFederal institute for medicines and medicinal products (BfArM), Paul-Ehrlich Institute (for sera, vaccines and test allergens) [10, 11]. ^dEuropean Medicines Agency [12]



about their perception of pharmacovigilance (Questions 16–19) and one question about future reporting (Question 20). Multiple-choice questions were only classified as correct if all answers were given correctly. Two researchers (LA, SK) clustered the answers to the open question and formulated the results. For the questions on perception, a Likert scale was used. The questions were translated from German to English and are displayed in Fig. 2. The participation was anonymous and not mandatory. Participants were informed about the scientific evaluation and publication of the results and they agreed by submitting their completed questionnaires. They had the possibility to ask questions for the better comprehension of the questionnaire and about the evaluation and the publication of the study at hand.

Statistical methods

A statistical analysis of the results of the questionnaire was conducted. The results from the pharmacists and the PTAs were summed up and translated into percentage format for comparability in relation to different number of participants. The same procedure was conducted in relation to the geographic regions. The results are described as absolute frequencies and percentages. A Wilcoxon-Rank sum test was used to evaluate the differences between groups using the percentage-based significance level of $\alpha=0.05$. p values were not adjusted for multiple testing. R-studio version 3.3.2 was used [13].

Results

Participants

Between the 6th and 23rd of November 2017, a total number of 197 participants were asked to take part in the survey. 127 answered the questionnaire. The courses took place in the German cities of Potsdam (Eastern Germany), Muenster (Western Germany), Mannheim (Central Germany), Berlin (Eastern Germany) and Landshut (Southern Germany). In Potsdam, 29 out of 30 (96.7%) course participants completed the survey, in Muenster, 42 out of 80 (52.5%) participants answered and 37 out of 60 (61.67%) in Mannheim. Berlin and Landshut had smaller sized groups with answers from 12 out of 12 (100%) and 7 out of 15 (46.7%) of survey participants, respectively. Hence, Landshut was exempt from statistical analysis when comparing the geographical regions due to the small number of participants in Southern Germany. In total, there was a participation ratio of 64.47% ($n=127$). The characteristics of participants are displayed in Table 1. The majority of the study participants were female, between 40 and 60 years old and worked in community pharmacies.

Contribution

Former experiences with ADR reporting were assessed. Table 2 provides a detailed overview of the reporting strategies that the participants had used and the bodies to which they had reported ADRs. Nearly half of the participants (47.2%, $n=60$) stated to having already reported an ADR. The majority of these cases were reported by pharmacists: 59.5% ($n=50$) of the participating pharmacists already reported an ADR but only 23.3% ($n=10$) of the PTAs. The most frequently named bodies for reporting an ADR to were

1. The marketing authorisation holder,
2. The drug commission of the federal union of German associations of pharmacists (AMK) and
3. The German federal agency for medicines and medicinal products (BfArM).

Other reporting channels were mentioned, for example the attending physician, the chamber of pharmacists or the drug commission of the medical profession. For ADR research and reporting, pharmacists used multiple websites such as the website of

1. The AMK (63.1%, $n=53$),
2. The pharmacovigilance and counselling centre for embryonal toxicology of the Charité Hospital Berlin (Embryotox [14]; 61.9%, $n=52$) and
3. The BfArM (60.7%, $n=51$),

whereas PTAs mainly focused on the website of the AMK (62.8%, $n=27$).

Pharmacists used all communication methods nearly equally, while PTAs concentrated on fax and telephone for communication of ADRs.

Knowledge

Question 15 was answered correctly by the majority of participants (79.5%, $n=101$). Questions 8 and 12 were answered correctly by nearly half of the participants (48.0% $n=61$; 47.2% $n=60$), while all other questions varied between 8% and 30% (Question 14: 7.9%, $n=10$; Question 9: 10.2%, $n=13$; Question 13: 18.1%, $n=23$; Question 11: 26.0%, $n=33$; Question 10: 29.9%, $n=38$) correct answers. There was neither a statistically significant difference between the correct answers of pharmacists and PTAs ($p=0.7209$, Fig. 3), nor between the different regions ($p>0.5054$, Fig. 4, Table 3).

A. Demographics						
1. You are	☐ ≤20 y	☐ 21–30 y	☐ 31–40 y	☐ 41–50 y	☐ 51–60 y	☐ Over 60 y
2.	☐ male	☐ female				
3.	☐ pharmacist	☐ pharmacy technician				
4. You work in ...	☐ community	☐ hospital	☐ pharmaceutical industry	☐ elsewhere (specify)		
5. You already reported an adverse drug reaction	☐ Yes			☐ No		
6. If you answered question 5 with yes, please specify to whom and how you reported:						
			☐ online	☐ Mail	☐ Phone/Fax	
7. Which websites have you visited at least once in connection with reporting or researching about adverse drug reactions?						
☐ bfarm.de	☐ embryotox.de	☐ ema.europa.eu	☐ pei.de	☐ akdae.de	☐ abda.de	
B. Knowledge questions						
8. Knowledge of the medicinal product is limited at the time of its authorization. This concerns in particular the knowledge about its ...						
☐ Safety	☐ Efficacy	☐ Chemical composition	☐ Dosage	☐ Metabolism		
9. An adverse event must be reported ...						
☐ only if it occurs immediately after taking a medicine						
☐ if it occurs as a reaction to a drug and is harmful and unintentional						
☐ as a result of intended use, i.e. the application is carried out according to the information in the instruction leaflet						
☐ as the result of the use of the medicine at a higher dosage than indicated in the instruction leaflet						
☐ due to the use of the medicine in other target groups than approved (e.g. in children) or in other indications						
10. Please tick the only correct statement.						
☐ Medication errors that could have caused harm to the patient are subject to reporting requirements						
☐ Knowledge of adverse drug reactions in children, adolescents and elderly patients should not be reported to the authorities if the product is authorized.						
☐ Lack of efficacy is not an undesirable drug effect.						
☐ If a medicine is prescribed, dispensed or administered incorrectly, for example due to confusion, this is not reportable.						
☐ Suspected cases are only to be documented if no suspicion of an adverse reaction has occurred.						
11. Please tick all groups of persons that you believe are required by law to report suspected adverse drug reactions (multiple answers possible):						
☐ Physicians	☐ Pharmacists	☐ Nurses	☐ Patients	☐ Lawyers		
12. Suspected cases of adverse drug reactions include a distinction between serious and non-serious events. Which of the events mentioned here is serious (multiple answers possible)?						
☐ Immediate danger to life or death						
☐ Outpatient treatment						
☐ Shortening of a hospital stay						
☐ Congenital malformation or birth defects						
☐ Permanent or severe disability or invalidity						
13. In the case of suspected adverse drug reactions, the following information must be provided (multiple answers possible):						
☐ Details of the temporal link between the intake of a preparation and the side effect that occurs						
☐ Information on the preparation (trade name, strength, etc.)						
☐ Details of the event that occurred						
☐ Initials, gender, age and, if applicable, address of the person concerned						
☐ Your contact information for inquiries						
14. In the case of suspected adverse drug reactions, pharmacists and pharmacy technicians can report to the following authorities or companies (multiple answers possible):						
☐ Federal institute for medicines and medicinal products						
☐ Drug commission of the federal union of German associations of pharmacists						
☐ Drug commission of the medical profession						
☐ Marketing authorisation holder						
☐ Treating physician						
15. If a patient assures me that (s)he has already talked about his adverse effects with his attending physician, I am exempt from the obligation to report						
☐ Yes ☐ No						
C. Self-assessment						
16. My knowledge about reporting obligations under the German Medicines Act is very good.						
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	
Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree	
17. My knowledge about reporting obligations under the German Medicines Act is very good.						
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	
Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree	
18. My knowledge about reporting obligations under the German Medicines Act is very good.						
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	
Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree	
19. My knowledge about reporting obligations under the German Medicines Act is very good.						
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	
Strongly disagree	Disagree	Somewhat disagree	Somewhat agree	Agree	Strongly agree	
20. What, in your opinion, would facilitate your personal reporting behaviour?						

Fig. 2 Pharmacovigilance questionnaire (translated from German to English)

Table 1 Characteristics of participants

Characteristics	n	%
Gender		
Male	19	15.0
Female	108	85.0
Age		
< 20 years	1	0.8
21–30 years	12	9.4
31–40 years	24	18.9
41–50 years	41	32.3
51–60 years	42	33.1
> 60 years	7	5.5
Profession		
Pharmacists	84	66.1
Pharmacy technical assistants	43	33.9
Workplace		
Community pharmacy	125	98.4
Hospital pharmacy	1	0.8
Others	1	0.8

Perception

The mean values of the self-assessment questions per profession and per region are shown in Figs. 5 and 6. There is no statistical significant difference between the results ($p > 0.1986$, Table 4). Participants mostly answered that they rather agree or rather disagree with the statements, which means that they are not adopting any clear position.

Making reporting easier

31 out of 127 (24.41%) participants answered the question about what they think would better facilitate their personal reporting behaviour. Nine participants mentioned better training, eight suggested shorter forms to fill in and/or a contact person whom they could call. Further suggestions were standard operation procedures for reporting (4), more time within the daily routine (6), more contact and discussion with colleagues about pharmacovigilance matters (6), financial benefit (1) and a link for reports to be included in the pharmacy software (2). Four participants answered that they do not know what could help and one participant stated that s/he doesn't need support.

Discussion

Main results

The survey revealed the situation of German pharmacists and PTAs in relation to pharmacovigilance. Two-thirds of

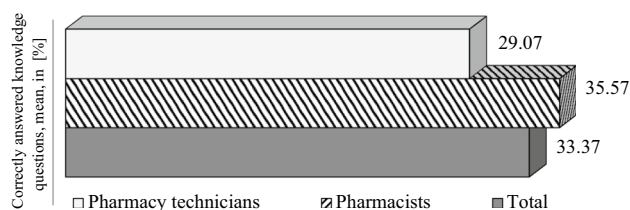
the invited participants answered the questionnaire. The latter is indicative of a strong interest in the matter: the survey was lengthy in nature and many of the participants had to stay 15–20 min longer after the termination of an all-day training to fill in the questionnaire. In concordance with the general view that ADRs are underreported [15], the study shows only some of the participants had reported ADRs in the past despite the fact that the study group consisted mainly of dedicated professionals with a longstanding professional experience, voluntarily taking part in continuing education courses.

When reporting, legal guidelines [4] were found to having been followed, as a large proportion of the participants had used the AMK and the BfArM websites. Therefore, it is not surprising that the websites of these institutions were among the most widely used sources for reporting and research of ADRs. Embryotox was the second frequently used source due to the information provided for the highly vulnerable group that consists of pregnant and breastfeeding women. However, many participants also stated that they had reported ADRs to the MAH. When analysing the answers to the open question that asked about the entity to which the report was being submitted to, many participants answered “AMK and pharmaceutical industry”. Thus, we can assume that some of the ADRs might have been double-reported. It is important to understand that double-reporting might jeopardise the statistics if the forms are not entirely filled in correctly so that duplications of the same ADR event would be erroneously registered. Knowledge about pharmacovigilance reporting within our study group cannot be reported as strong, however, our rating criteria were very strict, as multiple-choice question had to be answered fully correctly, and were otherwise rated as wrong. Partly correct answered questions were not analysed.

On a positive note, the participants were aware of being responsible for reporting ADRs themselves, as nearly 80% answered question 15 correctly. Although no further questions could be answered correctly by a majority of participants, almost half of them were aware of the fact that the data on the safety of a medicine were not yet finalised at the time of approval and therefore, awareness in relation to pharmacovigilance issues is existent. We can assume that with adequate training and a good support structure at work, pharmacy professionals would be willing to participate more in pharmacovigilance activities. Interestingly, nearly 50% of the participants could distinguish serious from non-serious ADRs. However, in daily practice, all reports should be forwarded after occurrence, as it is not the duty of a German pharmacy professional to categorise ADRs. Having them categorise ADRs might lead to even more underreporting of non-serious ADRs. The study shows that many participants did not know that reports

Table 2 Contribution to adverse drug reaction (ADR) reporting

	Total (n)	Total (%)	Pharmacists (n)	Pharmacists (%)	Pharmacy technicians (n)	Pharmacy technicians (%)
Former ADR reporting						
Yes	60	47.2	50	59.5	10	23.3
No	65	51.2	33	39.3	32	74.4
Not answered	2	1.6	1	1.2	1	2.3
Reported to						
AMK ^a	21	16.5	17	20.2	4	9.3
MAH ^b	25	19.7	22	26.2	3	7.0
BfArM ^c	13	10.2	12	14.3	1	2.3
Others	12	9.4	8	9.5	4	9.3
Not answered	77	60.6	43	51.2	34	79.1
Communication method						
Online	23	18.1	21	25	2	4.7
Mail	21	16.5	19	22.6	2	2.7
Fax/phone	32	25.1	25	29.8	7	16.3
Not answered	68	53.5	35	41.7	33	76.7
Websites used for ADR research or reporting						
BfArM ^c	62	48.8	51	60.7	11	25.6
Embryotox ^d	67	52.8	52	61.9	15	34.9
EMA ^e	8	6.3	8	9.5	0	0
PEI ^f	26	20.5	22	26.2	4	9.3
AKDAE ^g	9	7.1	8	9.5	1	2.3
AMK ^a	80	63.0	53	63.1	27	62.8
Not answered	13	10.2	4	4.8	9	20.9

^aDrug commission of the federal union of German associations of pharmacists^bMarketing authorisation holder^cFederal institute for medicines and medicinal products^dPharmacovigilance and counselling centre for embryonal toxicology of the Charité Hospital Berlin^eEuropean medicines agency^fPaul-Ehrlich Institute^gDrug commission of the medical profession**Fig. 3** Correct answered knowledge questions, mean, in %, total and per profession (see Fig. 2 for the questions)

from a pharmacy might also be submitted to the drug commission of the medical profession, which led to poor results in answers to question 14. Furthermore, as indicated by answers to question 13, the participants were not aware of all details to be reported. However, this would not cause problems in daily routine, as it suffices to know one

recipient of reports and the details to report are outlined in the form. More problematic is the fact that the reporting obligations for both medication errors or delayed ADRs were not understood fully. The study results in relation to knowledge about pharmacovigilance show that there is room for improvement. This is underlined by the results of the perception questions (Questions 16–19) showing that participants do not have a specific opinion about the issues outlined. Future training initiatives should take this latter point into account both for pharmacists and PTAs all over Germany, as there were no differences between professions or geographic regions.

Comparison with other studies

The response rate of our study is similar or lower than previously conducted studies in other countries, that reported

Fig. 4 Correct answered knowledge questions in %, total and per region (see Fig. 2 for the questions)

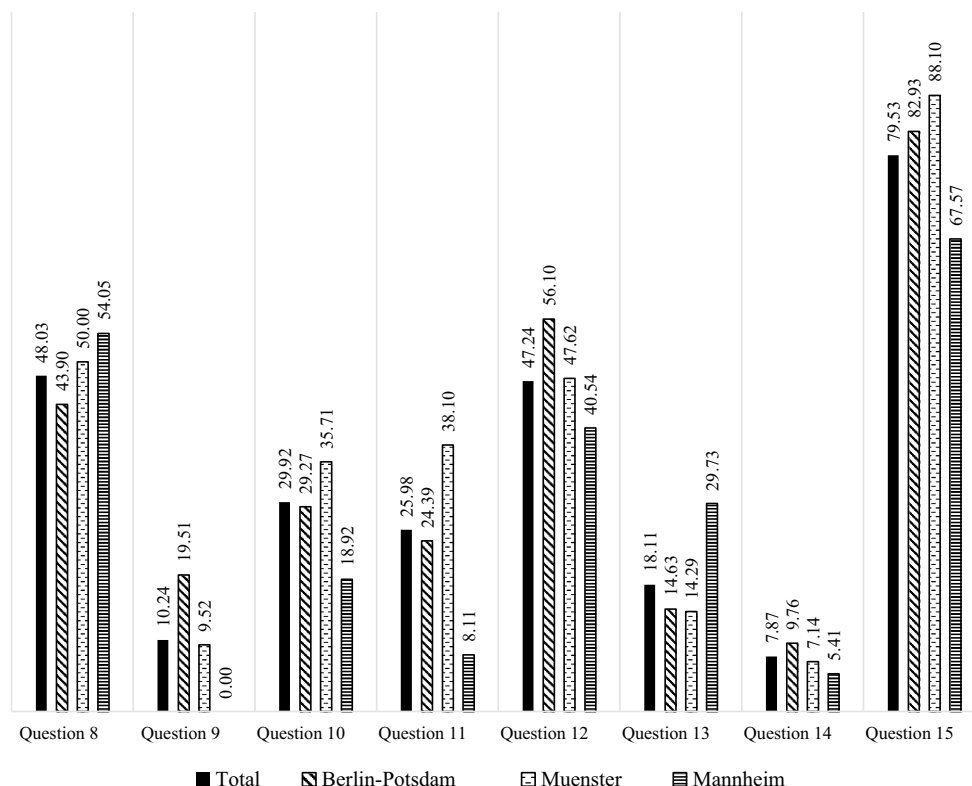


Table 3 P-values knowledge

	Pharmacists versus pharmacy technicians	Mannheim versus Muenster	Mannheim versus Berlin-Potsdam	Muenster versus Berlin-Potsdam
Mean	0.7209	0.5737	0.5054	0.9591

a response rate from 65 to 85% [16–20]. The percentage of German pharmacy professionals who already reported an ADR seems to be low at about 50%. It is, however, higher than international report rates (Kuwait, 26.8% [16]; China, 14.6% [17]; Nepal, 20.1% [19]; India, 25% [21]; Saudi-Arabia, 34% [20]). The latter figures show

that awareness of pharmacovigilance differs internationally. However, the knowledge of healthcare professionals including pharmacists is lacking [18, 22]. These findings are similar to our findings. International studies containing suggestions about how to increase reporting mentioned better understanding of ADRs [23, 24], better training on pharmacovigilance and/or clinical outcomes [17, 23, 24], more confidence to discuss ADR with colleagues and/or patients [16, 23, 24], more time and better management [16, 17, 24] and remuneration [21, 23]. These findings largely correlate with our study results.

Fig. 5 Self-assessment questions, mean, total and per profession (see Fig. 2 for the questions)

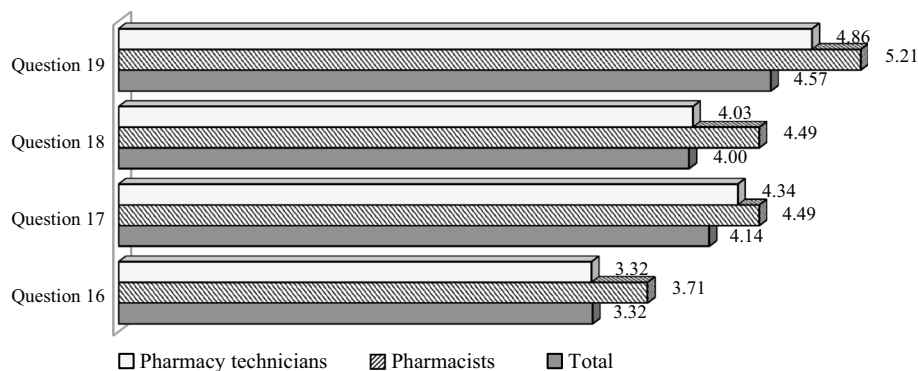


Fig. 6 Self-assessment questions, mean, total and per region (see Fig. 2 for the questions)

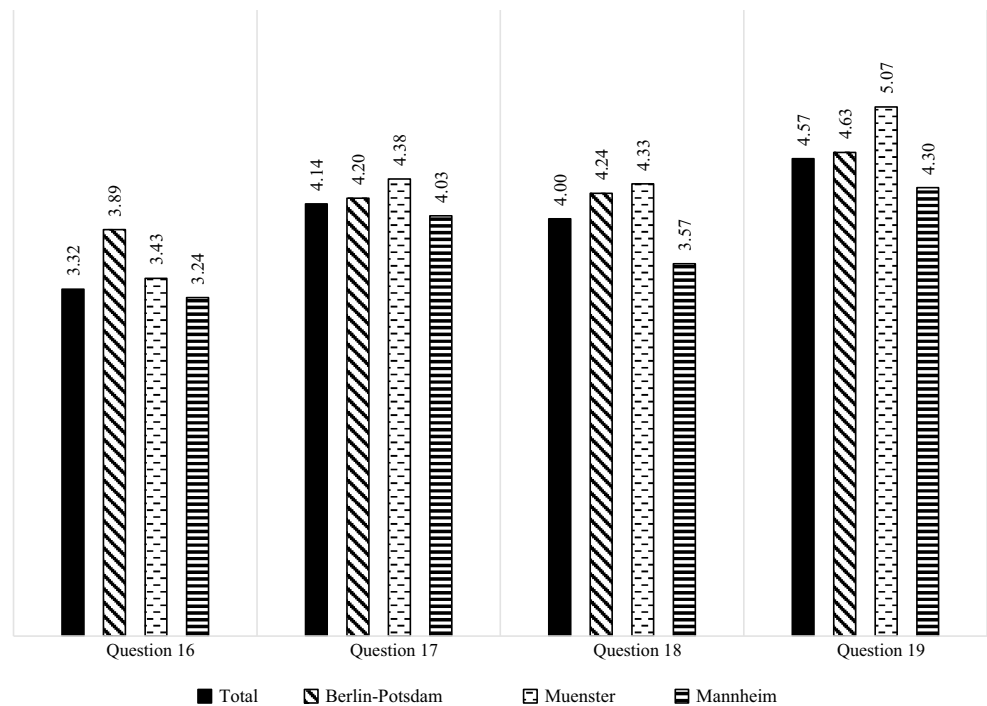


Table 4 P-values self-assessment

	Pharmacists versus pharmacy technicians	Mannheim versus Muenster	Mannheim versus Berlin-Potsdam	Muenster versus Berlin-Potsdam
Question 16	0.8095	0.9355	0.9354	0.8072
Question 17	0.5676	1	0.8068	1
Question 18	0.1986	0.7475	0.8095	1
Question 19	0.5683	1	1	1

Strengths and weaknesses of the study

Only the participants of a continuing education seminar took part in the survey, thus, we can assume that they were more interested than the average pharmacy professional might be. This could potentially have resulted in a false positive outcome of our survey. Although we can assume that there is some double-reporting of ADRs from individual pharmacies, we had no explicit question in our study about double-reporting, which can be considered a limitation of this assumption. Because of the coincidental nature of this research study and the continuing education courses that the participants attended, there was an inherent time limitation in preparing for and validating the qualitative part of this study. Therefore, a validation of the questionnaire was not executed beforehand. The fact, however, that the participants had no comprehension questions about the questionnaire, and that our results correspond to those of international studies, exemplifies the validity of the study at hand.

Generalisability

Our survey is a snapshot of the situation in community pharmacies, which is a reflection of reality but can only be generalised to a limited extent. Reflecting the German pharmacy sector demographic in general, most study participants were female and worked in community pharmacies, however, hospital and industrial pharmacists were underrepresented. Participants were older than the national average. The study group was small and might not represent all German pharmacies. Additionally, 60% of the study group examined were pharmacists, thus highly over-representing the profession in comparison to the usual distribution of about 40% pharmacists and 60% other pharmaceutical specialists in German pharmacies such as PTAs [25]. This would also impact the survey in a false positive way.

Conclusion

In an effort to identify mechanisms that could improve reporting by pharmacy professionals, the study results can be summarised as follows: Pharmacy professionals seem to be destined for a stronger involvement in pharmacovigilance measures. For successful integration and progress, we suggest the following:

1. Introduction of a structured, mandatory training of the pharmacy team, which is repeated annually. On the one hand, such a training will equip them to make them better understand how to report ADRs and on the other hand, it will support the minimisation of double-reporting.
2. The preparation of a standard operating procedure for the pharmacy or its integration into the pharmacy software.

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Conflicts of interest Both LA and SK work for Pharmabrain, a company specialising in continuing education for pharmacy teams. FWH declares that he has no conflict of interest.

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