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Clinical Practice and Knowledge of Primary Health Care Physicians Toward Adverse Drug Reactions: Can We Recognize Adverse Drug Reactions and What Should We do to Maximize Patient Safety and to Improve Self-confidence of Doctors When Prescribing Medicines?

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Authors' contributions

This work was carried out in collaboration between all authors. Author AJ designed the study, wrote the protocol, and wrote the first draft of the manuscript, managed the literature searches, analyses of the study results, and wrote to the health authorities of every institution for study approval. Authors VP, AP, SM and MM distributed and collected all questionnaires within their institutions, read the first draft version of the manuscript, including literature, and gave their suggestions for improving manuscript, as did author DB who designed statistical processing of data and applied it together with author AJ. All authors read and approved the final manuscript.

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ABSTRACT

Aim: A suspicion about adverse drug reactions is sufficient for adverse drug reactions reporting. However, assessing the causal drug-disturbance(s) relation is the primary issue in physicians' clinical practice, due to their principal responsibility among health care workers for patients' health, including patients' safety, while the far more studied adverse drug reactions reporting is the secondary one. Thus, adverse drug reactions, and the need for introducing activities for physicians toward adverse drug reactions.

Study Design: It was a prospective, multicentric, questionnaire based, self-administered, and anonymous study, conducted during two months among physicians employed in five public (state) primary health care centers in the Republic of Serbia settled in Sombor, Mladenovac, Pozarevac, Cacak and Pirot.

Results: It was questionnaired 238 out of 461 employed physicians. Doctors declared to diagnose adverse drug reactions *(n* = 213) but rarely report them (*n* = 49). They usually withdrew the drug suspected for adverse drug reactions (*n* = 212) and seldom introduce it to the same patient in the future (*n* = 5). They claimed to have difficulties in both the adverse drug reactions diagnosing (*n* = 146) and treating (*n* = 113). Almost all considered the improvement of the knowledge about adverse drug reactions beneficial for their clinical practice, adverse drug reactions diagnosing and treating (*P* < .001 for all the statements). With a very few exceptions, answers were not influenced by physicians' ages and medical education.

Conclusion: Physicians recognized the dimension of their problems in the field of adverse drug reactions, especially diagnosing, which is crucial for patient health. Better education and training are the most important strategies for improving existing weaknesses, which have to be translated into routine clinical practice.

Keywords: Adverse drug reactions; diagnosing; knowledge; primary health care physicians; clinical pharmacologist.

1. INTRODUCTION

Adverse drug reactions (ADRs) are often the focus of attention of scientists and health authorities and have been studied extensively. Such a great interest was created because of the increasing drug related morbidity [1,2,3], and mortality [1,3], as well as due to the facts that many of ADRs can be avoided / prevented [4,5,6]. Furthermore, the ADRs are under-reported [7], and represent a substantial economic burden for the health system and the whole society [8].

Out of all the health care workers, physicians have the primary (leading) responsibility for the patient's health as a whole, which also implies safety. Their activities relating to ADRs include detection, analysis, interpretation and evaluation, treating and documentation [9]. These activities are obligatory taken because doctors must promptly solve the current health problems of the concrete patient. The reporting of ADRs to the relevant health and drugs authorities comes only after this, i.e. it is secondary to the diagnosing and, if necessary, the ADRs treating.

Despite all the above mentioned, the diagnostic and therapeutic problems in clinical practice related to ADRs have been insufficiently investigated neither among physicians in general, nor among doctors in primary health care settings. Moreover, if the doctors are subjected to education programs about ADRs, the guiding idea is usually focused on the improvement of the reporting of ADRs [10,11,12], not primarily on ADRs diagnosing and treating. Furthermore, the overwhelming majority of healthcare is delivered in primary care settings and most of the medicines are prescribed and dispensed in outpatient care settings (primary care). Bearing in mind all the above mentioned, it was quite justified that the primary objectives of this study were to examine physicians' experience and knowledge regarding ADRs in real-world clinical practice. Special attention was placed at ADRs diagnosing and treating, as well as at drug suspension, together with assessing whether there is a need to introduce in physicians' clinical practice the intervention and / or improvement regarding ADRs.

2. METHODS

2.1 Design and Settings

This study was prospective, multicentric and questionnaire based. It was approved by health

authorities in five primary health care centers (PHCs). In brief, a letter of intentions, research plan, and a request for research approval was sent to all directors of the institutions to which PHCs belonged. It was obtained written consent for running research in response to every letter.

The study was conducted during two months among physicians employed in public (government established) PHCs in the Republic of Serbia (RS) located in different geographical regions, except the province of Kosovo and Metohija (Fig. 1). Health services obtained in public institutions are financially covered through compulsory national health insurance, which almost all inhabitants of the country have.

Starting from the north to the south of the country, PHCs in which research was conducted were in the municipalities of Sombor, Mladenovac, Cacak, Pozarevac and Pirot. Ambulatory units of the involved PHCs were located both in the cities and the surrounding villages.

2.2 Questionnaire

In total, the structured questionnaire survey was 33 questions. The anonymous study questionnaire was distributed to all employed physicians, excluding dentists, because they do not often prescribe medication.

Questions (Q) referred to demographic, professional and ADRs facts, which included diagnosing, treating, and reporting of the ADRs. Multiple choice answers (A) were provided for each question. For some issues, both correct and incorrect answers were offered. Doctors were free to choose one or multiple options. The possibility of "No answer" was not offered to any question.

2.3 Comparison

A number of comparisons were conducted: between female and male physicians, afirmative and negative answers, and correct or incorrect answers. Also, it was performed between younger (up to 45 years old) and older doctors (46 to 65 years old) to examine whether younger doctors could receive more information about ADRs during graduate and postgraduate studies of medicine than those of older age.

Another comparison was based on the formal medical education of doctors, to see how medical education gained after completing medical school improved physicians' perception and knowledge on ADRs. Thus, one group of physicians was consisted of general practitioners without specialization (GPs), while the other one of specialists, regardless of the field of medicine. Specialzation is a formal medical education after finished medical faculty that lasted between three and four years, after which it is taken the final, specialistic exam.

Fig. 1. The Republic of Serbia: the capital (Belgrade) and the municipalities in whose primary health centers the study was conducted

2.4 Statistics

The score of responses to each question was expressed as a frequency in absolute numbers and/or percentages. When no answer was given, that answer was treated as missing.

SPSS Statistics 17.0 was used for statistical analysis. The comparisons were made using chi-square test for all discrete variables, rejecting the null hypothesis at a value $P \leq .05$.

3. RESULTS

The results are presented in five tables. Table 1 refers to personal and professional characteristics of questionnaired physicians, Table 2 to ADRs diagnosing, treating, reporting, knowledge and training, Table 3 to recognizing ADRs. Table 4 shows what measures doctors take to the drug suspectd for the ADRs, Table 5 gives elements for the withdrawal of the drug suspected of ADRs.

3.1 Personal and Professional Characteristics of Questionnaired Physicians

Selected PHCs covered a population of 389173 inhabitants [13]. From a total of 461 eligible physicians who were employed in all five PHCs, 238 of them responded to the questionnaire. The overall response rate was 51.6%. In the PHC in Sombor it was involved 46.1%, of physicians i.e. 47 out of 102 physicians *(n* = 47/102), in Mladenovac 62.7% (*n* = 42/67), in Požarevac 43.2% (*n* = 41/95), in Čačak 43.5% (*n* = 57/131), and in Pirot 77.3% (*n* = 51/66) (Table 1).

Out of 238 respondents, 181 were women ($P <$ .001 for comparison female *vs*. male). The equal gender differences were also found within comparable subgroups, except within the group of GPs over 45 years of age.

A similar number of physicians participated in the group up to 45 years of age and in the older one (46-65 years of age). No physicians older than 65 participated, probably because of the pension policy in the government established health care institutions.

It was participated 148 general practitioners [without (*n* = 99) and with (*n* = 49) specialization in general medicine]. The remaining of 238 physicians (*n* = 90) were specialists in other areas of medicine, such as in pediatrics (*n* = 41), occupational health (*n* = 19), gynecology (*n* = 12), internal medicine (*n* = 6), neurology / psychiatry (*n* = 4), emergency medicine (*n* = 3), otorynolaryngology (*n* = 2), ophthalmology (*n* = 2), and physical medicine (*n* = 1).

There were statistically significant differences between the total number of physicians with (*n* = 139) and without (*n* = 99) specialization ($P = .01$), as well as between the number of female *vs.* male physicians ($P < .001$ for all comparisons).

3.2 ADRs: Diagnosing, Treating, Reporting, Knowledge and Training

Almost all the doctors diagnosed ADRs ($P <$ .001), but more than two thirds of them did not report ADRs ($P < .001$) (Table 2, Q1 and Q2). The largest number of doctors had difficulty in the diagnosing ($P = .01$, Q6), and almost half of them in the treating ADRs (Q9). The majority of respondents had no formal training in diagnosing and treating ADRs after graduation ($P < .001$ for both Q7 and Q10). Thus, the additional questions about training (not shown) became meaningless.

The greatest proportion of physicians pleaded to be trying to find causality between the drug and registered disturbances ($P < .001$; Q3), and were dissatisfied with their own knowledge about ADRs which they needed in their clinical practice ($P < .001$; Q4). Almost all of them have recognized that improving the knowledge on ADRs would be helpful in their clinical practice, diagnosing and treating ADRs ($P < .001$ for Q5, Q8 and Q11).

Only 6% of all questionnaired physicians knew anything about the tools established for diagnosing ADRs ($P < .001$, Q12). Therefore, two other issues related to the skills toward tools turned out to be irrelevant.

In consideration of criteria for the recognition of the relationship between the drug and the registered disturbance(s) the most common response was the combination of some answers, whether it was specified (*n* = 111) or not (*n* = 59; this option was not offered as an answer) (Table 3). However, out of these 111 specified combinations, only 17 physicians selected the combination of all the answers (A1-A4) that must be considered in order to assess adequately whether the drug could be the reason for the registered disturbance(s) or not ($P < .001$ in comparison to expected frequency 50%:50%).

The claim under A1 (clinical manifestation) was selected 55 times, either as the only answer (*n* = 38), or as a part of specified combinations (*n* = 17). The laboratory and radiological findings was included in the 37 specified combinations of answers.

However, significant differences between the compared ages (A1: *P* = .05) and between different medical education (A6: *P* = .01) were found only once.

3.3 Drug Suspension (Withdrawal)

The largest number of physicians suspended the drug suspected for ADRs (Q1: 89.8%, *P* < .001), 77.5% of them replaced it with another drug (Q2: *P* < .001), and 77.7% of doctors did not introduce it to the same patient any time in the future (Q3: *P* < .001) (Table 4).

Among the five offered answers (A1-A5), most doctors based drug suspension on a single reason (*n* = 164/238, 73%) (Table 5). The A4 claim, the only correct answer, was chosen only by 31% of physicians (*P* < .001 compared to expected frequency, see explanation below Table 5). Apart from being chosen as a single reason, A4 answer was also found in 27 combinations of answers. Thus, the correct answer was selected 97 times (43%) in total. However, 94 doctors (nearly 42%) based the drug suspension on another single reason (A1, A2, A3 or A5), which was not sufficient for such a decission.

The decision to withdraw the drug based on a combination of more than one reason was frequent (27% of physicians). The A1 claim (*n* = 40) was the most common of all responses that existed in the combinations.

The greatest number of physicians did not give any answer either about the number of levels of causality between the drug and the disturbances on the World Health Organization (WHO) probabilty scale [14] or about the levels of ADRs severity given by the Food and Drug Administration [15] (*n* = 135 and *n* =141, respectively). Furthermore, when correct (*n* = 21 and *n* = 24, respectively) and incorrect (*n* = 82 and *n* = 73, respectively) answers were compared, it turned out that, for both the questions, incorrect answers were far more frequent (*P* < .001). These answers were influenced by neither the age nor the medical education.

4. DISCUSSION

The detection and the diagnosing drug-related disturbances is the first and crucial step in the ADR process from the standpoint of patients' health, physician's clinical practice, the health system, the ADRs reporting systems, as well as drug manufacturers, since the life cycle of a drug is influenced by its safety profile. The failure in recognizing ADRs can lead to physicians' inappropriate clinical decisions and measures concerning the treatment of registered disturbance(s) and the application of the accused drug both at the current moment and in the future.

In accordance with the statement of failure in recognizing ADRs are the most important results yielded by our study. They relate to the difficulty in diagnosing ADRs, drug suspension and ADRs reporting as well. These findings were not dependent on the age and medical education of doctors. Furthermore, doctors recognized their insufficient knowledge on ADRs diagnosing, treating and throughout their clinical practice. That could be in harmony with McGavock statement [3]: "There is no structure for continuing medical education in this rapidly changing field (pharmacology) – it is left to the individual doctor to attend whatever postgraduate classes he or she wishes".

4.1 Diagnosing ADRs

Diagnosing ADRs is a complex and highly challenging task [16]. The routine identification of drug-related problems might be difficult, quite subjective, imprecise, and vary quite a lot due to individual factors, like doctor's knowledge, background and experience in the field of ADRs. This is not the case only in the physicians' daily clinical practice, but even in the institutions to which ADRs are reported, where pharmacovigilance professionals, who need not necessarily be doctors, have far more training, time and tools to assess the causality of drug-related disturbances than doctors in their daily clinical practice [17].

Table 1. Personal and professional details of surveyed physicians in five primary health centers in the Republic of Serbia included in study (*n* = 238 physicians)

Primary health care centers settled down in municipalities:	Medical education	Participants (absolute numbers)				
		≤ 45 years		≥ 46 years		Total (Male/Female)
		Male	Female	Male	Female	
Sombor, Mladenovac, Pozarevac, Cacak, Pirot	GPs	13	48***	15	23	99 (28/71***)
	Spec	6	38***	23	72***	139** (29/110***)
	GPs+Spec	19	86***	38	95***	238 (57/181***)

*Comparison between GPs and Spec, and between male and female within the same group (chi-square, expected frequency 50%:50%). **, *** - P = .01, P<.001; Abbreviations: GPs: general practitioners without specialization in any field of medicine; Spec: specialists in any medical field*

There is no doubt that ADR reporting is far easier than dealing with consideration drug-disturbance causality in a concrete patient. In the first case, attribution of causality is not a prerequisite for ADRs reporting, i.e. suspicions on drug-related disorder is sufficient for that (suspected ADRs) [18]. After setting a doubt, filling in the forms and handling them are technical in nature.

In the latter case, however, the physician must assess and clarified whether there is association or causation between the drug and the registered disturbance(s), the level of causality and the degree of severity if registered disturbances are related to drug. Thus, they have to establish the clinical diagnosing of ADRs at the first.

In our study the greatest number of physicians claimed to diagnose ADRs (*n* = 213/235) (Table 2). Having in mind their answers on how to establish ADRs diagnosis, including gradation of causality between the drug and registered disturbances, it is undoubtedly obvious that diagnostic processes were based on insufficient facts which actually led to a diagnostic failure, probably ADRs over diagnosis. The both, under diagnosing and over diagnosing of ADRs, inevitably leads to numerous wrong decisions with potentially harmful consequences regarding the health of the individual, the whole society and pharmaceutical industry. Because of that, the accuracy in the diagnosing of drug-related disturbances is an imperative.

4.2 Reporting ADRs

Much attention all over the world has been paid to the ADRs reporting. Under-reporting exists worldwide without exception [7]. The crucial question is whether it is because ADRs are not recognized or they are not reported despite the timely recognition [19,12]. The findings of Dormann et al. [4] stating that up to 57% unrecognized community acquired ADRs on hospital admission by the attending physicians are in compliance with the first statement. Our results are in accordance with the second one since most doctors in our study did not report ADRs (79%), despite the fact that 90% of them cited they had diagnosed them (Table 2).

Our findings of reporting ADRs was consistent with the data on the ADRs reporting in our country as a whole: from 781 reports in 2010 to the national pharmacovigilance center, 255 were related to vaccines [20]. In the remaining reports, physicians accounted for 38% and pharmacists for 16%. The rest, making up 46%, were reports from pharmaceutical industry. Not even one of ADRs was reported by physicians from PHCs that participated in this study. However, the search for the causes of ADRs under-reporting was beyond the scope of this study.

4.3 Drug Suspension (Withdrawal)

In the present study almost 90% of physicians withdrew the drug suspected of ADRs, although they did not have enough arguments for such a decision (Table 4). For example, for making such a decision: a) only 70 of 224 physicians chose the statements that were sufficient (Table 5); b) too many of them selected only one, but insufficient criterium, or made a large number of criteria combinations; and c) an extremely small number of doctors was familiar with the ADRs severity scale, as well as d) with gradation levels on causality scale.

However, in the case of drug suspension, especially if it is inappropriate, measurement and valuation of decision-making outcomes are poorly investigated [16]. It must be emphasized that basic and clinical pharmacologists have the fundamental place in improving physicians' clinical practice, including overcoming problems in the field of ADRs, among which is the drug withdrawal as well [21- 24].

Table 2. Attitude toward diagnosing, treating, reporting, training and knowledge about adverse drug reactions (ADRs) (*n* = 238 physicians)

Questions (Q)		Responses						
		All answers (absolute numbers)			Age (answer Yes, %)		Education (answer Yes, %)	
		Yes	No	NA	≤ 45 years	≥ 46 years	GPs	Spec
Q1	Do you diagnose ADRs	213	22***	3	90	91	89	92
Q2	Do you report ADRs to the official pharmacovigillance centers	49	187***	2	21	20	20	21
Q3	Do you try to find causality between the registered disorder and the applied drug	197	27***	14	87	90	90	86
Q4	Is information that you have about ADRs sufficient for your clinical practice	85	151***	2	36	36	37	35
Q5	Would the improvement of your knowledge of ADRs be beneficial for your clinical practice	233	5***	0	99	97	97	98
Q6	Do you have difficulty in diagnosing ADRs	146	88**	4	59	65	68	58
Q7	Did you have any formal training (except during regular university programme) teaching you how to diagnose ADRs	13	224***	1	7	5	8	4
Q8	Would the improvement of your knowledge of ADRs be beneficial for your diagnosing ADRs	229	9***	0	96	96	98	94
Q9	Do you have difficulty in ADRs treating	113	119	6	50	48	38	57
Q10	Did you have any formal training (except during regular university programme)) teaching you how to treat ADRs	10	226***	2	6	3	8	2
Q11	Would the improvement of your knowledge of ADRs be beneficial for your treating ADRs	231	7***	0	96	98	98	96
Q12	Are you informed about the tools for assessing causality between the registered disturbance and the drug	14	218***	6	8	5	6	6

*Comparison within the same question between answers Yes and No (chi-square, expected frequency 50%:50%). **, *** - P = .01, P < .001. Significant statistical diffrences within the same question were not found either between physicians of ≤45 and ≥46 years of age, or between GPs and Spec (chi-square, expected frequency 50%:50%).*

Abbreviations: GPs: general practitioners without specialization in any field of medicine; NA: no answer; Q: question; Spec: specialists in any medical field.

Table 3. Elements for consideration on how to recognize adverse drug reaction (*n* = 238 physicians)

Offered answers (A)		Responses (absolute numbers)				
		All	Age		Education	
			≤ 45 years	≥ 46 years	GPs	Spec
A1	Clinical manifestation	38	12	26*	15	23
A2	Laboratory and radiological findings	0	0	0	0	0
A3	Time from the start of drug administration to the appearance of the distrurbance	13	4	9	5	8
A4	Time from the discontinuating of the drug use to the appearance of the distrurbance	4	2	2	0	4
A5	The combination of the above answers (specified-stating the specific combination: A1+A3 ...)	111	46	65	54	57
A6	The combination of the above answers (unpecified-not stating the specific combination of answers)	59	32	27	18	41**
A7	No answer	13	9	4	7	6

*Comparison within the same question between physicians of ≤ 45 and ≥ 46 years of age, or between GPs and Spec (chi-square, expected frequency 50%:50%). *, ** - P = .05, P = .01. Abbreviations: A: answer; GPs: general practitioners without specialization in any field of medicine; Spec: specialists in any medical field*

Table 4. The prospects for the drug suspected of inducing adverse reaction (n=238 physicians)

Questions (Q)		Physicians		Responses (absolute numbers)							
				Yes		No		Sometimes		No answer	
Q1	Do you withdraw the drug suspected for ADRs induction	Age	≤ 45 y	212	97	3***	1	21	6	2	1
			≥ 46 y		115		2		15		1
		Education	GPs		87**		1		9		2
			Spec		125		2		12		0
2	Do you replase the withdrawn drug with another one	Age	≤ 45 y	148	66	13***	9	30	13	47	17
			≥ 46 y		82		4		17		30
		Education	GPs		64		5		13		17
			Spec		84		8		17		30
Q3	Do you introduce the suspended drug again any time in the future to the same patient	Age	≤ 45 y	5	3	160***	69	41	16	32	17
			≥ 46 y		2		91		25		15
		Education	GPs		3		71		16		9
			Spec		2		89		25		23

*Comparison between answers Yes and No within the same question (chi-square, expected frequency 50%:50%, *** - P < 0.001); Comparison between GPs and Specialists within the same question (chi-square, expected frequency 50%:50%, ** - P < 0.01). Abbreviations: y: years; GPs: general practitioners without specialization in any field of medicine; Q: question; Spec: specialists in any medical field*

Table 5. Elements for the withdrawal of the drug suspected of adverse reactions (*n* = 238 physicians)

Offered answers (A)		Responses (absolute numbers)				
		All	Age		Education	
			≤ 45 years	≥ 46 years	GPs	Spec
A1	Causality between the drug and the registered health disturbance	39	9	30**	13	26
A2	The time from the start of the drug administration to the appearance of distrurbance	35	21	14	12	23
A3	The time from the discontinuating of the drug use to the appearance of the distrurbance	3	1	2	1	2
A4	The severity of the health disturbance and causality between the drug use and the disturbance	70***	27	43	28	42
A5	The severity of the health disturbance	17	6	11	13	4
A6	The combination of the above answers (for example: A1+A3...)	60	35	25	29	31
A7	No answer	14	5	9	7	7

*Column All: Comparison between the chosen answer and expected frequency (chi-square, expect frequency 14.3%, *** - P < .001). Column Age: Comparison between the chosen answer and expected frequency (chi-square, expected frequency 50%:50%, ** - P = .01); Abbreviations: A: answer; GPs: general practitioners without specialization in any field of medicine; Spec: specialists in any medical field*

4.4 Knowledge about ADRs

We registered insufficient knowledge in a number of aspects concerning ADRs. That was obtained both directly, through affirmative responses, and indirectly, as evidenced by weaknesses in the answers related to ADRs diagnosing and suspension, as well as tools in the ADRs diagnosis (Table 2-5).

With the intention to facilitate and improve recognizing ADRs and assess the probability of drug-related disturbance(s), a number of different pharmacovigilance methods, algorithms and techniques (from short questionnaires to comprehensive algorithms) has been created and established [25]. Based on the results obtained in our study where most physicians were not familiar with such methods, one could conclude that these tools, including this one proposed by the WHO, could have only academic character, but not practical and applicable in clinical practice.

So, a need to improve the knowledge of doctors about ADRs is suggested in many studies [21,22]. Agrawal and coworkers [23], for example, have been drew an improvement strategy for decreasing medicinal errors that was consisted of 15 recommendations applicable to all physicians. This model could be applied for overcoming weaknesses in the ADRs field found in our study since about 95% of physicians had not been trained in ADRs, and they cited to have insufficient knowledge of ADRs in clinical practice (64%), difficulty in ADRs diagnosing (62%) and treating (49%). Also, almost all of them realized that improvement of their knowledge on ADRs would be useful for their clinical practice (98%), ADRs diagnosing (96%), and ADRs treating (97%).

4.5 Strengths and Limitations of the Present Study

There are both strengths and some weaknesses (limitations) in the present study. The number of participating physicians may be a weak point. Although the questionnaire comprised 43-77% of physicians employed in the public PHCs, it is obvious that the results would be more powerful if all the doctors were questionnaired. Moreover, many doctors did not give an answer to some questions. Thus, the sample for the statistical analysis was additionally reduced. However, it could be seen that quite a small number of questions remained unanswered. It is interesting that this modality was found particularly in the issues which required reliable knowledge on ADRs. Two of them were related to the number of levels of drug-disturbances causality and

ADRs severity. Among the eight offered answers to the first question and six to the second, only one answer was correct. It is possible that too many answers could be confusing for doctors with insufficient knowledge and thus could be the reason for not giving the answer.

In addition, some of the obtained results must be interpreted very carefully and appropriately. That is the case of affirmative answers on diagnosing, treating, withdrawing and replacing the accused drug, as well as negative answers on reintroducing the suspended drug. All these answers require conclusively established existence of causality and level of probability between the drug and the registered disorder, and the properly assessed severity of the disorder, which was not the case in the present study.

However, our study had several important strengths. They are determined by at least three features. Namely, the study was a) prospective, b) multicentric and c) have looked at physicians, *a priori*, to determine their experience, knowledge and the difficulty they have in the field of ADRs, especially diagnosing. This study also showed that physicians' recognized the need for improving their knowledge on ADRs as well.

5. CONCLUSION

Despite some limitations, the present study clearly drew attention to the difficulties the physicians employed in primary health care centers in the Republic of Serbia without the province of Kosovo and Metohija have in the diagnosing, treating, recognizing, and reporting ADRs,and determining the appropriate conditions for cessasion of a particular therapeutic agent or drug. The results were not dependent on the physicians' age and medical education, but were sufficient to suggest the need for systemic educational intervention in the field of ADRs among physicians who participated in the survey. Since this study was multicentric, it is possible that these suggestions could be extended to the physicians employed in other primary health care centers in the Republic of Serbia. This would bring a great benefit primarily to the safety and health of patients, and also, not less importantly, to the self-confidence of doctors in prescribing drugs in their daily clinical practice, since none of the other health care workers have such a great responsibility for the health of the patients as doctors do. The proposed measures will undubtedly bring about positive effects in the entire health care system of the state and in the pharmaceutical industry, too.

ETHICAL APPROVAL

This study was questionnaire-based and anonymously Thus, it could not cause any harm to participants.

A letter of intentions, of the research plan and for the research approval was sent to all the authorities of the institutions to which PHCs belonged. In response to our letters, it was given written consent for the conduct of research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA. 1998;279: 1200-5.
2. Wetzels R, Wolters R, van Weel C, Wensing M. Harm caused by adverse events in primary care: a clinical observational study. J Eval Clin Pract. 2009;15:323-7.
3. McGavock H. Prescription-related illness--a scandalous pandemic. J Eval Clin Pract. 2004;10:491-7.
4. Dormann H1, Criegee-Rieck M, Neubert A, Egger T, Geise A, Krebs S, et al. Lack of awareness of community-acquired adverse drug reactions upon hospital admission: dimensions and consequences of a dilemma. Drug Saf. 2003;26:353-2.
5. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions--a meta-analysis. PLoS One. 2012;(7): e33236.
6. Marcum ZA, Pugh MJ, Amuan ME, Aspinall SL, Handler SM, Ruby CM, et al. Prevalence of potentially preventable unplanned hospitalizations caused by therapeutic failures and adverse drug withdrawal events among older veterans. J

Gerontol A Biol Sci Med Sci. 2012;67:867-74.

7. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385-96.
8. de Rezende BA, Or Z, Com-Ruelle L, Michel P. Economic evaluation in patient safety: a literature review of methods. BMJ Qual Saf. 2012;21:457-65.
9. Makeham M, Dovey S, Runciman W, Larizgoitia I. (on behalf of the Methods & Measures Working Group of the WHO World Alliance for Patient Safety, 2008). Methods and measures used in primary care patient safety research. Results of a literature review. Accessed 22 January 2012.
10. Available:http://www.who.int/patientsafety/research/methods_measures/makeham_dovey_full.pdf
11. Figueiras A, Herdeiro MT, Polónia J, Gestal-Otero JJ. An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. JAMA. 2006; 296:1086-93.
12. Gerritsen R, Faddegon H, Dijkers F, van Grootheest K, van Puijenbroek E. Effectiveness of pharmacovigilance training of general practitioners: a retrospective cohort study in the Netherlands comparing two methods. Drug Saf. 2011;34:755-62.
13. Desai CK, Iyer G, Panchal J, Shah S, Dikshit RK. An evaluation of knowledge, attitude, and practice of adverse drug reaction reporting among prescribers at a tertiary care hospital. Perspect Clin Res. 2011;2:129-36.
14. Statistical Office of the Republic of Serbia. Natural Changes of Population in the Republic of Serbia 1961–2010 (by municipalities) Belgrade; 2012. Serbian.
15. World Health Organization. The use of the WHO–UMC system for standardised case causality assessment. Accessed 28 February 2009.
16. Available:http://who-umc.org/Graphics/24734.pdf
17. Food and Drug Administration. Expedited Safety Reporting Requirements for Human Drug and Biological Products. WAIS Document Retrieval [Federal Register: October 7, 1997 (Volume 62, Number 194)]. Accessed 20 March 2010.
    Available:http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm120262.htm
18. Edwards IR. Decision dilemmas: worse in emerging economies. Drug Saf. 2012;24: 41-54.
19. Théophile H1, Arimone Y, Miremont-Salamé G, Moore N, Fourrier-Réglat A, Haramburu F, et al. Comparison of three methods (consensual expert judgement, algorithmic and probabilistic approaches) of causality assessment of adverse drug reactions: an assessment using reports made to a French pharmacovigilance centre. Drug Saf. 2010;33:1045-54.
20. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36:75-81.
21. González-Rubio F1, Calderón-Larrañaga A, Poblador-Plou B, Navarro-Pemán C, López-Cabañas A, Prados-Torres A. Underreporting of recognized adverse drug reactions by primary care physicians: an exploratory study. Pharmacoepidemiol Drug Saf. 2011;20:1287-94.
22. Medicines and Medical Devices Agency of Serbia. Spontaneous reporting of adverse effects of drugs in 2010 year. Accessed 11 September 2011.
    Available:http://www.alims.gov.rs/ciril/files/2012/10/rezultat2010.pdf Serbian.
23. Rehan HS, Vasudev K, Tripathi CD. Adverse drug reaction monitoring: knowledge, attitude and practices of medical students and prescribers. Natl Med J. India. 2002;15:24-6.
24. Williams D. Monitoring medicines use: the role of the clinical pharmacologist. Br J Clin Pharmacol. 2012;74:685-90.
25. Agrawal A, Aronson JK, Britten N, Ferner RE, de Smet PA, Fialová D, et al. (Members of EMERGE, Erice Medication Errors Research Group). Medication errors: problems and recommendations from a consensus meeting. Br J Clin Pharmacol. 2009;67:592-8.
26. British Pharmacological Society. A prescription for the NHS: Recognising the value of clinical pharmacology and

therapeutics. Accessed 11 November 2014.
Available:http://www.bps.ac.uk/details/news/6901701/BPS-Warns-More-Clinical-Pharmacologists-Needed-to-Improve-Health-of-Patients-and.html

27. Agbabiaka TB, Savović J, Ernst E. Methods for causality assessment of adverse drug reactions: a systematic review. Drug Saf. 2008;31:21-37.

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