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DETERMINING THE KNOWLEDGE ABOUT PHARMACOVIGILANCE OF DENTISTS FROM THE REPUBLIC OF NORTH MACEDONIA

УТВРДУВАЊЕ НА ЗНАЕЊЕТО ЗА ФАРМАКОВИГИЛАНЦА НА СТОМАТОЛОЗИТЕ ОД РЕПУБЛИКА СЕВЕРНА МАКЕДОНИЈА

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Abstract

Introduction: Pharmacovigilance is defined as the science of detection, assessment, understanding, and prevention of the adverse effects of drugs or other related problems. Clinicians play a crucial role in preventing ADRs by recognizing, managing, and reporting ADRs to the national pharmacovigilance centers (NPCs). The majority of dentists are not aware, nor do they participate in the FDA's MedWatch program directed at drug safety. Given the fact that dentists play a crucial role in preventing and reporting adverse drug reactions, as well as the broad spectrum of pharmacotherapy agents being used in dentistry, the aim of our study was to determine the knowledge of dental professionals regarding pharmacovigilance in the Republic of North Macedonia. Material and Methods: This study included 100 doctors of dental medicine, employed in public and private healthcare institutions in the city of Skopje. The research was conducted using an anonymous survey questionnaire intended for healthcare professionals. For this purpose, a modified version of the questionnaire, according to Gupta et al., was used. The collected data were statistically processed using SPSS Statistica v23 for Windows, with tests adequate to the sample characteristics. **Results:** Less than half of the dentists (12-45%) correctly answered the questions concerning dentists' knowledge of pharmacovigilance systems (Q1-Q4, Q7, Q11-Q13). More than half of the dentists (58-70%) answered correctly to only two questions (Q5 and Q6) concerning dentists' knowledge of pharmacovigilance systems. **Conclusion**: Dentists have insufficient knowledge regarding pharmacovigilance. Taking into account the fact that healthcare professionals, including doctors of dental medicine, have a key role in reporting adverse drug reactions, their education and more active involvement in pharmacovigilance processes is essential for an ideal functioning of the healthcare system. **Key words:** dentists, pharmacovigilance, adverse drug reactions.

Апстракт

Вовед: Фармаковигиланцата е дефинирана како наука за откривање, проценка, разбирање и спречување на несаканите реакции на лековите (НРЛ) или други поврзани проблеми. Лекарите играат клучна улога во спречувањето на НРЛ преку препознавање, управување и известување за НРЛ до националните центри за фармаковигиланца (НЦФ). Мнозинството стоматолози не се свесни, ниту пак учествуваат во програмата MedWatch на FDA насочена кон безбедноста на лековите. Со оглед на фактот дека стоматолозите играат клучна улога во спречувањето и пријавувањето на несаканите реакции на лекот, како и широкиот спектар на фармакотераписки агенси кои се користат во стоматологијата, целта на нашата студија беше да го утврдиме знаењето за фармаковигиланцата на стоматолозите во Република Северна Македонија. **Материјал и методи:** Оваа студија опфати 100 доктори по дентална медицина, вработени во јавни и приватни здравствени установи во Скопје. Истражувањето беше спроведено со помош на анонимен анкетен прашалник наменет за здравствените работници. За таа цел, се користеше модифицирана верзија на прашалникот според Gupta и сор.. Собраните податоци беа статистички обработени со помош на SPSS Statistica v23 за Windows, со тестови соодветни на карактеристиките на примерокот. **Резултати:** Помалку од половина од стоматолозите (12-45 %) одговорија точно на прашањата кои се однесуваат на знаењето на стоматолозите за системите на фармаковигиланца (Q1-Q4, Q7, Q11-Q13). Повеќе од половина од стоматолозите (58-70 %) одговорија точно на само две прашања (Q5 и Q6) кои се однесуваат на знаењето на стоматолозите за системите на фармаковигиланца. **Заклучок:** Стоматолозите имаат недоволно знаење за фармаковигиланца. Имајќи го предвид фактот дека здравствените работници, вклучително и докторите по дентална медицина, имаат клучна улога во пријавувањето на несаканите реакции на лековите, нивната едукација и поактивно вклучување во процесите на фармаковигиланца е од суштинско значење за идеално функционирање на здравствениот систем. **Клучни зборови:** стоматолози, фармаковигиланца, несакани реакции од лекови.

Introduction

Pharmacovigilance is defined as the science of detection, assessment, understanding, and prevention of adverse effects of drugs or other related problems[1]. The importance of pharmacovigilance was first highlighted in 1848, when a girl named Hannah Greener from England passed away after being administered chloroform for anesthesia to remove an infected toenail. Due to concerns around the safety of using anesthetics, the Lancet set up a commission to tackle this issue, encouraging doctors to report deaths caused by anesthesia[2].

Clinicians play a crucial role in preventing ADRs by recognizing, managing, and reporting ADRs to the national pharmacovigilance centers (NPCs). Safe and rational prescription of drugs require therapeutic reasoning and appropriate selection of drugs for each patient[3]. The Food and Drug Administration (FDA) constantly tries to balance the promotion of greater drug safety with a quicker drug-review process[4]. The director of the Center for Drug Evaluation and Research, which now includes the Center for Biologics Evaluation and Research, oversees the balance of drug safety versus innovation through science. Dentists have traditionally not been included in this process. Drug utilization by dentists has not been determined by the pharmaceutical industry. However, the recent FDA opioid drug-safety initiative program[5] has shown that dentists contribute to the overprescribing of opioids, which led to stricter prescription patterns already in place in some states. The majority of dentists are not aware, nor do they participate in the FDA's MedWatch program[6] directed at drug safety. As more targeted drugs, aimed at reducing drug-adverse effects are developed, the US drug safety net would require the participation of all prescribers, especially for the completeness of all electronic medical records. One example of dentists participating in this process was the reporting of osteonecrosis of the jaw[7-9].

The medical histories dentists keep are, for the most part, isolated and remain in their offices. Electronic dental records, as part of the patient's electronic health record or electronic medical record under the broader banner of the electronic medical home, will forever change how dentists record medical histories[4]. Pharmacotherapy is playing an important role in the treatment and therapy for the management of different oral and dental diseases, such as periodontal disease[10], diseases of the dental pulp[11-12], aphthous ulcerations[13-14] as well as immune mediated diseases affecting the oral mucosa[15-17].

Given the fact that dentists play a crucial role in preventing and reporting adverse drug reactions, as well as the broad spectrum of pharmacotherapy agents being used in dentistry, the aim of our study was to determine the knowledge about pharmacovigilance of dental professionals in the Republic of North Macedonia.

Material and method

This study included 100 doctors of dental medicine, employed in public and private healthcare institutions in the city of Skopje.

The research was conducted using an anonymous survey questionnaire intended for healthcare professionals. For this purpose, a modified version of the questionnaire, according to Gupta et al. [18], was used.

Limitations of the study (possible risks and errors)

Measures were taken for two common limitations in this type of study:

- Selective bias. Doctors were selected from health institutions from different municipalities in the territory of the city of Skopje, in order to obtain a representative sample.
- Incomplete and involuntary disclosure of data – when filling in the anonymous questionnaire by the subjects, there is a risk of inadequate response.

The collected data were statistically processed using SPSS Statistica v23 for Windows, with tests adequate to the sample characteristics.

Results

This study included 100 doctors of dental medicine. The average age of the respondents in the whole group was 48.3±13 years. The majority of respondents were female 87.0%, while only 13.0% were men.

Questions about dentists' knowledge of pharmacovigilance:

1.To the first question (Q1) "Define the term pharmacovigilance", the correct answer was given by 12.0% of the surveyed doctors of dental medicine (table 1).

2. To the second question (Q2) "The most important goal of pharmacovigilance is:", the correct answer was given by 27.0% doctors of dental medicine (table 1).

3. To the third question (Q3) "Is there a mandatory obligation to report adverse drug reactions", the correct answer was given by 25.0% of the doctors of dental medicine (table 2).

4. To the fourth question (Q4) "Which of the listed health professionals has the obligation to report the adverse reactions of a drug that is put on the market", the correct answer was given by 22.0% of the doctors of dental medicine (table 2).

Table 1. Questions 1 and 2 of the questionnaire

answers Q1	Doctors of dental medicine		answers Q2	Doctors of dental medicine	
	N	%		N	%
A	24	24.0	**A**	27	27.0
B	48	48.0	**B**	30	30.0
C	16	16.0	**C**	15	15.0
D	12	12.0	**D**	27	27.0
Total	100	100.0	**Total**	100	100.0
*correct answer: D. A system for detecting, collecting, monitoring, evaluating and ensuring the appropriateness of new data on drug safety and the risk-benefit ratio related to the use of the drug or its interaction with other drugs			*correct answer: D. Determination the hitherto unknown adverse drug reactions		

Table 2. Questions 3 and 4 of the questionnaire

answers Q3	Doctors of dental medicine		answers Q4	Doctors of dental medicine	
	N	%		N	%
A	25	25.0	**A**	62	62.0
B	16	16.0	**B**	0	0.0
C	59	59.0	**C**	16	16.0
/	/	/	**D**	22	22.0
Total	100	100.0	**Total**	100	100.0
*correct answer: A. yes			*correct answer: D. All of the listed		

5. On the fifth question (Q5) "Does the Republic of Macedonia have an established system of pharmacovigilance", the correct answer was given by 70.0% of the doctors of dental medicine (table 3).

6. To the sixth question (Q6) "If you consider that the system of pharmacovigilance has been established, which regulatory body is responsible for monitoring adverse drug reactions", the correct answer was given by 58.0% of the doctors of dental medicine (table 3).

7. To the seventh question (Q7) "Where is the international center for monitoring adverse drug reactions", the correct answer was given by 19.0% of the doctors of dental medicine (table 4).

8. To the question (Q8) "Has any of your patients experienced an adverse reaction from a drug", 45.0% of the surveyed doctors of dental medicine answered in the affirmatively (table 4).

9. To the question (Q9) "Have you ever submitted a report for an adverse reaction to a drug", only 16% of the doctors of dental medicine answered affirmatively (table 5).

10. To the question (Q10) "Have you seen the application form for an adverse reaction to a drug", 21.0% of the doctors of dental medicine answered affirmatively (table 5).

11. To the question (Q11) "Serious adverse reactions and events (without fatal outcome) from the use of med-

Table 3. Questions 5 and 6 of the questionnaire

answers Q5	Doctors of dental medicine		answers Q6	Doctors of dental medicine	
	N	%		N	%
A	70	70.0	**A**	58	58.0
B	6	6.0	**B**	2	2.0
C	23	23.0	**C**	10	10.0
/	/	/	**did not answer because of lack of accurate information**	30	30.0
Total	100	100.0	**Total**	100	100.0
*correct answer: A. yes			*correct answer: a. MALMED		

Table 4. Questions 7 and 8 of the questionnaire

answers Q7	Doctors of dental medicine		answers Q8	Doctors of dental medicine	
	N	%		N	%
Did not answer	29	29.0	**Yes**	45	45.0
A	20	20.0	**No**	25	25.0
B	20	20.0	**I do not know**	30	30.0
C	12	12.0	**/**	/	/
D	19	19.0	**/**	/	/
Total	100	100.0	**Total**	100	100.0
*correct answer: D. Sweden			No correct answer (opinion/statement)		

Table 5. Questions 9 and 10 of the questionnaire

answers Q9	Doctors of dental medicine		answers Q10	Doctors of dental medicine	
	N	%		N	%
Yes	16	16.0	**Yes**	21	21.0
No	42	42.0	**No**	61	61.0
I do not know where to submit this report	40	40.0	**I do not know**	18	18.0
I do now know how to fill this report	2	2.0	**/**	/	/
Total	100	100.0	**Total**	100	100.0
No correct answer (opinion/statement)			No correct answer (opinion/statement)		

Table 6. Questions 11 and 12 of the questionnaire

answers Q11	Doctors of dental medicine		answers Q12	Doctors of dental medicine	
	N	%		N	%
A	20	20.0	**A**	0	0
B	18	18.0	**B**	8	8.0
C	35	35.0	**C**	50	50.0
D	27	27.0	**D**	42	42.0
Total	100	100.0	**Total**	100	100.0
*correct answer: D. 15 days			*correct answer: D. During Phase 4 of the clinical trial		

Table 7. Questions 13 and 14 of the questionnaire

answers Q13	Doctors of dental medicine		answers Q14	Doctors of dental medicine	
	N	%		N	%
A	15	15.0	**Yes**	17	17.0
B	45	45.0	**No**	37	37.0
C	32	32.0	**I do not know**	46	46.0
D	8	8.0	**/**	/	/
Total	100	100.0	**Total**	100	100.0
*correct answer: B. Spontaneous reporting			No correct answer (opinion/statement)		

icine are reported within", 27.0% of the surveyed doctors of dental medicine gave the correct answer (table 6).

12. To the question (Q12) "Rare adverse drug reactions can be detected in the next stages of a clinical trial", the correct answer was given by 42.0% of the surveyed doctors of dental medicine (table 6).

13. To the question (Q13) "Which of the following methods is most often used to monitor adverse reactions to new drugs placed on the market", 45.0% of the surveyed doctors of dental medicine gave the correct answer (table 7).

14. To the question (Q14) "Does your facility have a person/committee who/which is monitoring adverse drug reactions", 17.0% of the doctors of dental medicine answered affirmatively (table 7).

Discussion

The system of pharmacovigilance in the Republic of North Macedonia is regulated by the Law on Medicines and Medical Devices (Official Gazette of the Republic of Macedonia No. 106/07, 88/10, 36/11, 53/11, 136/11, 11/12, 147/13, 164/13, 27/14, 43/14 and 88/15) and the Rulebook on the method of reporting, the content of the form for reporting adverse drug reactions, and the method of organization of the pharmacovigilance system[19].

Organization and monitoring of the collection and assessment of adverse drug reactions, processing and assessment of the obtained data on drug safety is carried out by the Agency for Drugs and Medical Devices, through the National Center for Monitoring Adverse

Drug Reactions[19]. The Agency for Medicines and Medical Devices of the Republic of Macedonia (MALMED) was established on September 16, 2014, based on the Law on Medicines and Medical Devices, as an independent body of the state administration. The founder of MALMED is the Government of the Republic of Macedonia.

Spontaneous reporting of adverse drug events in the post-marketing phase is crucial for registering adverse drug reactions[20]. However, clinical studies make it possible to determine the frequency of adverse reactions reliably, as well as to assess the toxic potential of the drug. It is necessary for pharmacovigilance to be planned in detail, to be systematically implemented and to have an equally important role both in clinical trials, before the drug is put on the market, and after the drug is put on the market, after it has been approved. The importance of drug safety should be the same as the importance of drug efficacy[21]. For this reason, regulatory bodies are of crucial importance. However, the functioning of the system requires the active participation of both health professionals and patients. Therefore, our research examined the knowledge of dental medicine doctors related to pharmacovigilance.

The results obtained from the survey on question no. 1 and no. 2, and which refer to the assessment of the knowledge of healthcare workers about the concept and purpose of pharmacovigilance indicate that the knowledge of doctors of dental medicine is not sufficient (table 1). The obtained results for the knowledge of dentists in our research, compared to other researches[22,23], indicate that dentists do not know enough about the concept and purpose of pharmacovigilance.

Our survey showed that 25.0% of the doctors of dental medicine know that there is a mandatory obligation to report adverse drug reactions (table 2). In the available literature, a large number of health professionals declare that the reporting of adverse drug reactions is a professional obligation and they recognize it as such[24-29]. In order to obtain more detailed information about the knowledge of doctors of dental medicine, regarding their obligation to report adverse drug reactions, the survey questionnaire also contained a question on the exact determination of healthcare professionals who have the obligation to report adverse drug reactions. The results showed that only 22.0% of the doctors of dental medicine answered positively - that all health professionals have an obligation to report an adverse reaction to a drug (table 2).

The results obtained in our research indicate that the largest number of doctors of dental medicine know that a system of pharmacovigilance has been established in the Republic of North Macedonia, and more than half (58%) know that the Agency for Medicines and Medical Devices (MALMED) is a regulatory body responsible for monitoring adverse reactions to drugs (table 3). However, a small number of respondents in our survey correctly answered the question that the international center for monitoring adverse drug reactions is located in Uppsala, Sweden (table 4). Similar results were obtained in the study conducted by Nisa et al.[30].

From Table 4 we can observe that doctors of dental medicine, in their daily clinical practice, face the problem of "adverse drug reactions". Then again, what was significant for us was whether the health workers submitted a report on an adverse reaction to a drug, for which the question was also incorporated in the survey questionnaire. Only 16% of the surveyed doctors of dental medicine answered positively (table 5). However, a large percentage of those surveyed do not know where to submit and how to fill out the reports for an adverse reaction to a drug (table 5). The obtained results indicate that a large part of the adverse drug reactions that have occurred remain unreported, which is actually indicated by the available literature[31-35].

When asked if they have seen the report form for an adverse drug reaction, 21.0% of the doctors of dental medicine answered positively to this question (table 5). This form is part of the legal regulations of our country and is provided as a mandatory form of reporting adverse drug reactions in accordance with the Regulation on the method of reporting, the content of the form for reporting adverse drug reactions and the manner of organizing the pharmacovigilance system[36].

Adverse drug reactions can occur both in clinical trials of the drug and after the drug has been put on the market. In order to assess the knowledge of dental professionals, we surveyed them regarding the deadline for reporting serious adverse reactions and events (without fatal outcome) from the use of a drug. To this question, 27.0% of the doctors of dental medicine gave the correct answer, that is, that these adverse reactions and events should be reported within 15 days (table 6). We also asked them at what stage of clinical trials can rare adverse drug reactions be detected. 42.0% of the doctors of dental medicine gave the correct answer to this question, i.e. that during phase 4 of the clinical trial, the rare adverse reactions to the drug can be detected (table 6).

Conclusions

Based on the results from our research and the data from the available literature, we can conclude that dentists have insufficient knowledge regarding pharmacovigilance. Taking into account the fact that healthcare professionals, including doctors of dental medicine,

have a key role in reporting adverse drug reactions, their education and their more active involvement in pharmacovigilance processes is essential for an ideal functioning of the healthcare system.

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