

The knowledge and experience with the off-label use – results of a survey

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Received 19 September 2019 ♦ Accepted 21 October 2019 ♦ Published 31 December 2019

Citation: Drenska M, Naseva E, Getov IN (2019) The knowledge and experience with the off-label use – results of a survey. *Pharmacia* 66(4): 217–221. <https://doi.org/10.3897/pharmacia.66.e46687>

Abstract

Introduction: The aim of this survey is to assess the current knowledge and experience of medical doctors in regard to off-label use and to determine whether it is legal, according to them, as the local current legislation on medicinal products does neither prohibit nor explicitly permit such use.

Materials and methods: One hundred medical doctors from inpatient and outpatient medical care participated and answered 10 questions. The inclusion criteria were to have a degree in medicine and right to prescribe medications. Statistical analysis was performed using the SPSS v19.0 statistical program.

Results: The results show that 8 out of 10 medical doctors have knowledge in regard to the meaning of the term “off-label”. More than half (62%) stated they have prescribed off-label medicine in their medical practice. Half of the respondents (49%) experienced some kind of trouble when prescribing off-label. In regard to whether the law allows this practice, opinions were divided. To a larger extent (88%), medical doctors support the introduction of clearer rules for off-label use in Bulgaria.

Conclusion: Medical doctors have significant knowledge about off-label use, but feel uncertainty in their actions when they use medicines off-label. It is necessary to consider regulating this use at a national level, following the good examples of other European Union (EU) member states, until a harmonized solution within EU is found.

Keywords

off-label, pharmacovigilance, survey

Introduction

The off-label use refers to use of medicinal products not in accordance with the terms specified in the product information (i.e. the summary of product characteristics -SmPC). It is a common practice, especially in some medical areas such as pediatrics, oncology, neurology, orphan diseases, cardiology, ophthalmology, etc. (Chalumeau et. al. 2000; Ekins-Daukes et. al. 2004; Casali 2007;

Weda et. al. 2017; ECRD 2018). According to some European studies the extent of the off-label use is between 13–69% (Weda et. al. 2017).

In Bulgaria, recently published study on the off-label use among pediatric patients reveals that the frequency of the off-label use is 39% (Drenska et. al. 2019). There is also data for common off-label use in obstetrics and gy-

necology, but further studies are needed to establish more accurate data on a national level (Bozhinova et. al. 2008; Sirakov 2012a, b).

The aim of this survey is to assess the current knowledge and experience in regard to off-label use and to determine whether it is legal, according to medical doctors, as the local current legislation on medicinal products does neither prohibit nor explicitly permit such use.

Materials and methods

This prospective, multicenter face-to-face questionnaire based survey was performed between 2016–2018. One hundred medical doctors from inpatient and outpatient medical care participated and answered 10 questions. The questionnaire was specially developed in order to evaluate the knowledge and experience of medical doctors in regard to off-label use and to reveal whether it is legal according to them.

Questions were closed-ended or multiple choice questions, in order to be easy to answer and time saving for participants. The inclusion criteria were to have a degree in medicine and right to prescribe medications. The questionnaire was paper based. It was provided personally, by the interviewer. All medical doctors participated anonymously and voluntarily.

Patient and personal data were not included in this survey. The following variables were collected: sex, age and medical specialty. Qualitative data are presented as numbers and percentages, whilst quantitative as median and interquartile range (25 and 75 percentiles) due to their distribution (not matching normal distribution).

Assessing the relations between qualitative variables was performed by using χ^2 test or Fisher's exact test when appli-

cable. The difference in a quantitative variable between two groups was assessed by Mann-Whitney test and between more than 2 groups by Kruskal-Wallis test. The data analysis was performed using the SPSS v19.0 statistical program.

Results

Majority of participants were medical doctors with post-graduate medical specialty (82%), at an average age of 42 years (range 25–74). They were almost equally divided by gender (49,5% male and 50,5% female), which corresponds to their distribution in the population. The distribution of participants by their specialty is shown in Figure 1.

Answers to the questions posed in the survey, differentiating between General practitioners (GPs) and Specialist, are shown in Table 1.

Two-thirds of respondents (72%) associate the off-label use with use for "another indication", followed by use of an "unauthorized medicine". Only 16% gave the right definition for off-label use – "when used not in accordance with the authorised product information".

More than half stated they have prescribed off-label medicine in their medical practice (62%). The main reasons are shown in Figure 2.

Opinions were divided as to whether the law allows this practice, with 59% saying that the law does not allow the off-label use of medicines. To a large extent (88%), respondents believe that there should be clear rules and guidelines for the off-label use. Half of them (49%) experienced some kind of trouble when prescribing off-label (e.g. refusal of funding, patient doubts, sanctions, bans, comments from colleagues, etc.). The opinion was also divided as to whether off label use is common practice or not (51% and 49%). The main off-label medical areas are shown in Figure 3.

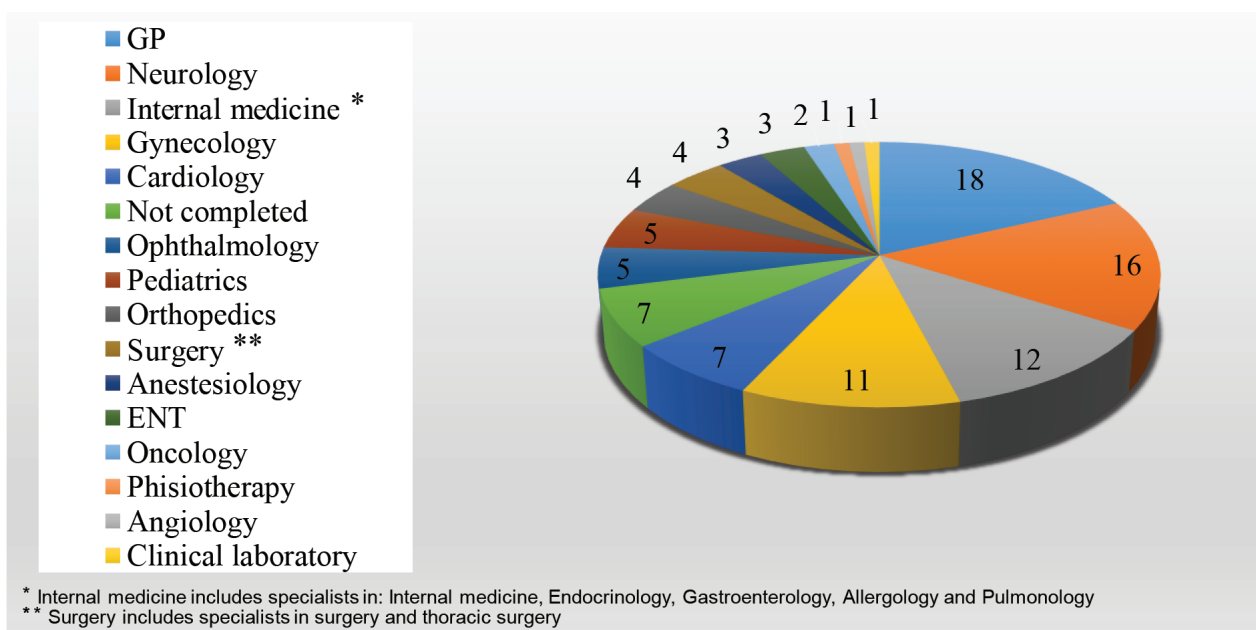


Figure 1. Distribution of participants by their medical specialty.

Table 1. Responses to the survey.

Question	Answers	GP		Specialist		p
		n = 18	%	n = 82	%	
In your opinion, which of the following is most appropriate for defining “off-label” i.e. the “use of a medicinal product not in accordance with the approved summary of product characteristics (SmPC)”	When authorized medicine is used for indication, other than that specified in the summary of product characteristics	11	61	60	73	0.486
	When not authorized medicine for use in humans is used to treat patients	2	11	10	12	
	When authorized medicine is used not in accordance with the summary of product characteristics	5	28	11	13	
	When authorized medicine is used in unapproved subpopulations and indications	0	0	1	1	
	Other	0	0	0	0	
In your opinion, which of the following terms in Bulgarian corresponds most closely to the English term „off-label use“	Use beyond the summary of product characteristics	13	72	50	61	0.651
	Use outside the marketing authorisation	1	6	14	17	
	Use not in accordance with the instructions	2	11	3	4	
	Use outside the terms of the Marketing Authorisation	1	6	6	7	
	Use beyond the summary of product characteristics	1	6	5	6	
	Use beyond authorized product information	0	0	3	4	
Have you ever prescribed a medicine outside the SmPC	No	8	44	30	37	0.596
	Yes	10	56	52	63	
What reasonable reasons would lead you to prescribe a medicinal product beyond the approved information in its SmPC	Lack of alternative treatment	7	39	47	57	0.195
	Other answer	11	61	35	43	
	New data and evidence in the scientific literature	10	56	53	65	0.591
	Other answer	8	44	29	35	
	Personal experience	5	28	22	27	0.999
	Other answer	13	72	60	73	
	Economic reasons (if off-label drug is cheaper than available therapeutic alternatives)	2	11	11	13	0.999
	Other answer	16	89	71	87	
Do you think you have access to sufficient scientific information to support the administration of medicinal products beyond the approved SmPC	No	6	33	25	30	0.786
	Yes	12	67	57	70	
In your opinion, does the Bulgarian legislation allow the use of medicinal products outside the approved SmPC	No	12	67	47	57	0.599
	Yes	6	33	35	43	
Do you think that there should be clear rules and guidelines in which situations can medicinal products be prescribed outside the approved SmPC	No	3	17	9	11	0.448
	Yes	15	83	73	89	
If you have been prescribed a medicine outside the SmPC, have you experienced any of the following issues: refusal of funding, patient doubts, sanctions, bans, comments from colleagues, etc. in your practice?	No	11	61	40	49	0.438
	Yes	7	39	42	51	
Do you think that prescribing medicines outside the approved SmPC is a widespread practice in Bulgaria	No	13	72	40	49	0.116
	Yes	5	28	41	51	
Which of the following medical specialties are most commonly prescribed medicines outside the approved SmPC	Oncology	8	44	50	61	0.291
	Other answer	10	56	32	39	
	Psychiatry	2	11	16	20	0,515
	Other answer	16	89	66	80	
	Neurology	5	28	27	33	0,785
	Other answer	13	72	55	67	
	Ophthalmology	5	28	10	12	0,138
	Other answer	13	72	72	88	
	Pediatrics	3	17	12	15	0,731
	Other answer	15	83	70	85	
	Other	2	11	12	15	0,999
Other answer	16	89	70	85		

Discussion

The results from this survey show that 8 out of 10 medical doctors have knowledge in regard to the meaning of the term off-label when applied to the specific use of a certain medication, which is comparable to results from another EU (European Union) survey (Piñero Pérez 2014). However, the majority relates the off-label use with the use of medicines for another therapeutic indication and not to the other terms specified in the SmPC (i.e dosage, method of administration, age, etc.).

This survey also shows that medical doctors have experience in regard to off-label use and more than half admit they prescribed off-label medicine in their practice, but almost half experienced some trouble. In terms of legality medical doctors are divided, and while half of them think that this is a legal practice, the other half is of the opposite opinion.

In fact, the EU as well as Bulgarian legislation does not explicitly prohibit or allow the off-label use of medicines (Drenska et. al. 2017). The lack of clear rules can cause confusion and can have unpleasant consequences. This was

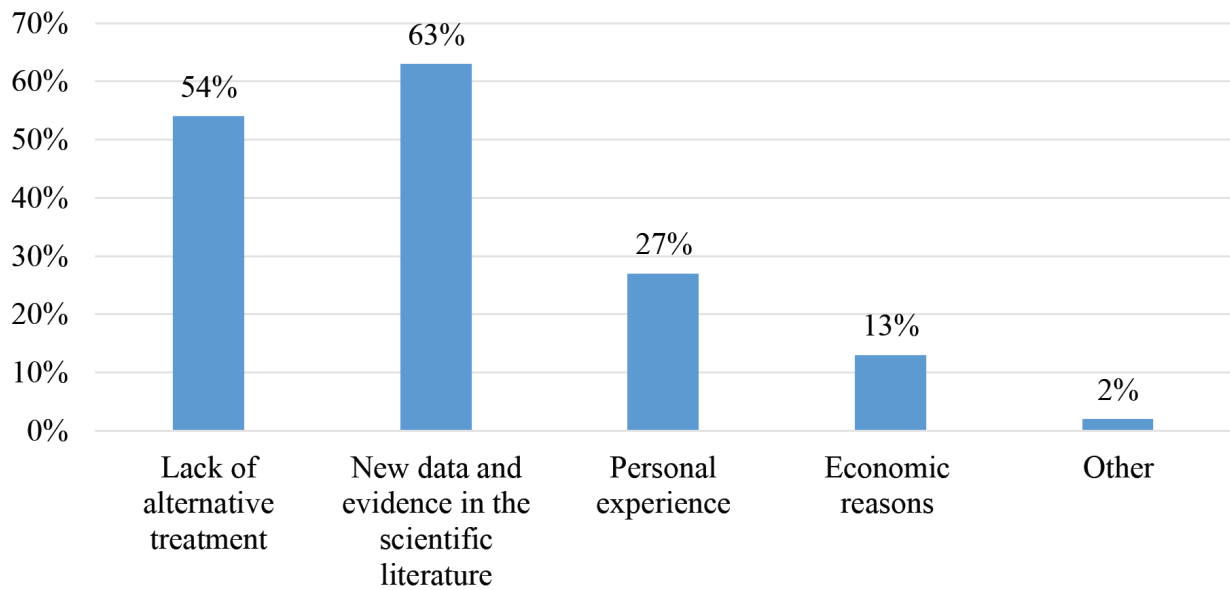


Figure 2. The main reasons for off-label use.

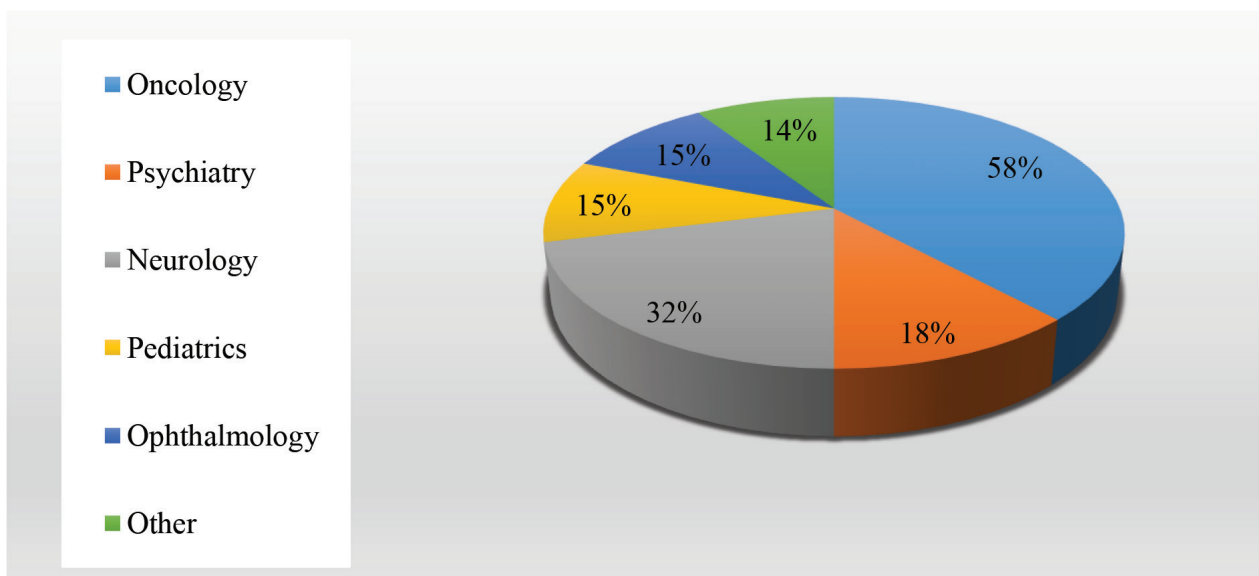


Figure 3. The main off-label medical areas.

the case, when in 2014, the Bulgarian Medical Audit Agency banned the use of medicine bevacizumab for treatment of macular degeneration in ophthalmology (off-label) and threatened to impose fines on medical institutions in case of violation. This action affected one-third of people over the age of 75 (Petrova 2014). Quite opposite to a case from Italy, where a huge fine was imposed on pharmaceutical companies Roche and Novartis because they didn't promote the same medicine (bevacizumab) for treatment of the same disease (macular degeneration) (Jolly 2014).

Uncertainty and confusions could be avoided only by introducing rules for prescribing medicines off-label. Some European countries do have special policies and

guidelines (e.g. Italy, France, Spain, United Kingdom, etc.) (Drenska et. al. 2017). The medical doctors from this survey support the introduction of clearer rules in Bulgaria for off-label use.

This survey has limitations and possible biases. It is a relatively small sample size and the analysis is based on trusted responses. Also, there might be differences between what medical doctors say and what they really do. However, despite limitations, the authors of the present work consider that the results of this survey reflect a current local situation in which the off-label use of medicines is real and common but at the same time a legally unclear practice.

Conclusion

Off-label prescribing appears widely in present daily medical practice. Medical doctors have significant knowledge about off-label use, but feel uncertainty in their actions when they use medicines off-label. It is necessary to

consider regulating this use at a national level, following the good examples of other EU member states, until a harmonized solution within EU is found.

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