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SHORT COMMUNICATION

The Additional Value of an E-Mail to Inform Healthcare Professionals of a Drug Safety Issue: A Randomized Controlled Trial in the Netherlands

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Abstract

Background The usefulness and the impact of Direct Healthcare Professional Communications (DHPCs, or 'Dear Doctor letters') in changing the clinical behaviour of physicians have been debated. Changes in the current risk communication methods should preferably be based on the preferences of the healthcare professionals, to optimize the uptake of the message.

Objective The aim of this study was to assess whether safety issues are communicated more effectively with an additional e-mail sent by the Dutch Medicines Evaluation Board (MEB) than with the DHPC only.

Methods A randomized controlled trial was conducted amongst ophthalmologists and hospital pharmacists in the Netherlands, who were the target group of a DHPC that was issued for pegaptanib, a drug that is administered intra-ocularly in patients with macular degeneration. The intervention group ($N = 110$) received the pegaptanib DHPC, as well as the MEB e-mail. The control group ($N = 105$) received the traditional paper-based DHPC only. Two weeks later, the study population received an invitation to fill out an online questionnaire. Questions were asked about the respondents' knowledge and attitude regarding the pegaptanib issue, and any action they had consequently taken. Additional questions were asked about their satisfaction with the DHPC and the e-mail, and their preferred source of such information.

Results Forty respondents (18.6 %) completed the questionnaire. Eighty-one percent of the respondents in the intervention group ($N = 21$) and 47 % of the control group ($N = 19$) correctly indicated that a serious increase in intra-ocular pressure could be caused by pegaptanib injections (Fishers' exact test, $p = 0.046$). Nine respondents in the intervention group versus none of the control group respondents indicated that they had taken action in response to the pegaptanib safety issue (Fishers' exact test, $p = 0.01$). The majority of both the intervention group and the control group confirmed that they would like to receive an MEB e-mail with safety information about drugs in the future (90 and 95 %, respectively).

Conclusion The results of this study indicate that an additional e-mail might strengthen the uptake of the safety information provided to healthcare professionals, who prefer to receive an e-mail from the MEB as a source of such information, as well as the DHPC. This study may serve as a starting point for new strategies to improve risk communication regarding safety issues associated with drugs and its impact on prescribing.

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1 Background

The usefulness and the impact of Direct Healthcare Professional Communications (DHPCs, or 'Dear Doctor letters') in

changing the clinical behaviour of physicians have been debated [1–3]. Currently, very little is known about the effect of communication efforts other than the DHPC to rapidly inform healthcare professionals about newly identified safety issues associated with drugs. Such information would provide a much needed knowledge base—in particular since evaluation of the impact of risk-minimization measures became mandatory in July 2012 in Europe, when the new European pharmacovigilance legislation [4, 5] came into force. What is known, though, is that any change in the current risk communication methods should preferably be based on the preferences of the healthcare professionals, to optimize the uptake of the message [6].

Previous research has shown that healthcare professionals prefer to receive safety information electronically and from an independent, trustworthy source [7–12]. Strengthening the safety message by repetition through different means might be very effective in getting the information across, especially when the message is similar but not identical [13]. For this reason, the Dutch Medicines Evaluation Board (MEB) has offered, from October 2010 onwards, an additional e-mail newsletter, to which interested parties can subscribe. With this e-mail, healthcare professionals are informed of drug safety issues for which a DHPC is issued.

Recently, the MEB planned to send such an e-mail in conjunction with a DHPC that was issued for pegaptanib (a drug that is administered intra-ocularly in patients with macular degeneration), as a serious adverse drug reaction had occurred. The aim of this study was to assess whether safety issues are communicated more effectively with an additional e-mail than with a DHPC only, by studying the impact of this e-mail—in particular on the knowledge and action taken by the healthcare professionals, their attitude to this safety issue, and their satisfaction with this additional information. For this reason, a special questionnaire was developed.

2 Methods

2.1 Study Population

The study population was chosen in agreement with the target population (as stated in the communication plan of the pegaptanib DHPC), consisting of ophthalmologists and hospital pharmacists in the Netherlands (Fig. 1). The study population was not selected from a list of previous subscribers to the newsletter. The e-mail addresses of the hospital pharmacists ($N = 84$) were obtained from the Dutch Pharmacist Association (KNMP). For the e-mail addresses of ophthalmologists ($N = 131$), the websites of Dutch hospitals were reviewed. The healthcare professionals were randomly assigned to the control group ($N = 105$) or the intervention group ($N = 110$). In addition to the traditional paper-based DHPC, the intervention group received the e-mail newsletter (which is shown as a figure in the Electronic Supplementary Material [ESM]). The control group received the DHPC only. Two weeks later, both groups received an invitation by e-mail to fill in an online questionnaire (Questback EFS survey 9.0). The questionnaire could be accessed by clicking on a personalized link in the invitation e-mail. Reminders were sent 1 and 2 weeks after the original invitation, including the same personalized link.

2.2 The Study Drug

Pegaptanib was approved in January 2006 for the treatment of neovascular (wet) age-related macular degeneration in adults [14]. It should only be administered by ophthalmologists experienced in giving intravitreal injections [15]. Due to reports of a serious adverse drug reaction, consisting of increased intraocular pressure caused by administration of the excess volume of pegaptanib present in the pre-filled syringe, a DHPC was instigated at the EU level [15]. In the Netherlands, the DHPC was sent to all ophthalmologists and hospital pharmacists [16], advising ophthalmologists to expel the excess volume of pegaptanib from the syringe before administration. The DHPC was accompanied by the amended Summary of Product Characteristics [17] and a visual representation of the correct administration method [18].

2.3 Questionnaire Development

The main outcome measures of this intervention study were knowledge of the issue, the attitude towards the issue, and action taken to minimize the risk. Additionally, satisfaction with the risk communication was assessed. Since an explorative literature search did not result in any usable validated questionnaires, we developed a questionnaire (which is shown as a table in the ESM) using the 'knowledge, attitudes, behaviour' model of Cabana et al. [19], representing possible barriers to physicians' adherence to guidelines. To minimize the respondent burden, some questions were skipped automatically where appropriate (e.g. respondents who did not know what safety issue was identified were not asked if they took any consequent action). In addition, they were asked about their sex, age, whether they worked full time or part time in a general or academic hospital, and how many years they had been professionally registered.

2.4 Data Analysis

Data were exported from the online survey program (Questback EFS survey 9.0) to be analysed in SPSS (IBM

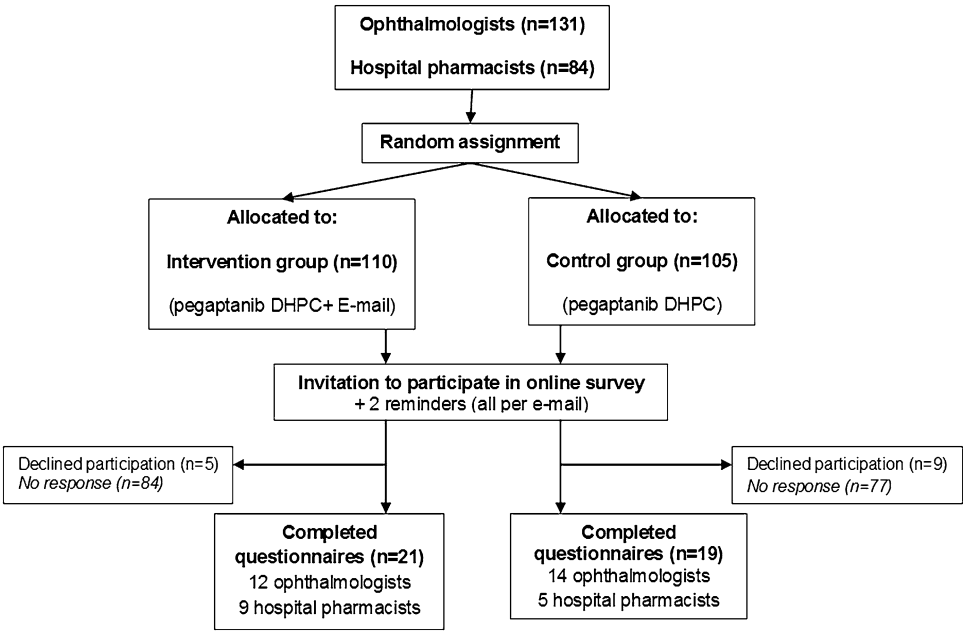

Fig. 1 Study flow chart. *DHPC* Direct Healthcare Professional Communication

SPSS Statistics 20.0). Descriptive statistics were used to describe demographic characteristics. Percentages were calculated based on the number of respondents who answered each specific question. Mann–Whitney *U* tests, χ^2 tests and Fishers' exact tests (FETs) were used to compare the intervention group with the control group and the responders with the non-responders.

3 Results

Forty respondents (19 %) completed the questionnaire (intervention group $N = 21$; control group $N = 19$; Table 1; Fig. 1). An additional 14 healthcare professionals notified us that they would not fill out the questionnaire, 11 of whom did not administer or provide pegaptanib. The remaining three gave no reasons or gave other reasons for not participating. The majority of the respondents were male (73 %), ophthalmologists (65 %), working full time (93 %), in a general hospital (83 %). The mean age was 52 years (range 36–64 years), and most (90 %) had been professionally registered for more than 10 years. No significant differences were observed when comparing responders with non-responders with regard to sex, occupation and hospital type (χ^2, $p = 0.273$; $p = 0.359$; $p = 0.894$, respectively). Respondents in the intervention group did not differ significantly from those in the control group (Table 1). Eighteen intervention group respondents (86 %) and thirteen control group respondents (68 %) indicated that they had received the DHPC (FET, $p = 0.265$). In both groups, one respondent had not read the DHPC. Twelve respondents (67 %) in the intervention group and ten (77 %) in the control group reported that they had skimmed through the DHPC. The remaining respondents had read the DHPC carefully. Ten intervention group respondents (48 %) indicated that they had received the initial e-mail, and four of them had read it carefully. The remaining six reported skimming through the e-mail.

3.1 Knowledge

Eighty-one per cent of the respondents in the intervention group correctly identified the pegaptanib issue, versus 47% in the control group (FET, $p = 0.046$; Fig. 2a). Over two thirds of both groups who were aware of the issue identified the correct recommendation (FET $p = 0.674$; Fig. 2b). Overall, 11 respondents were already aware of the issue before the DHPC was issued (no significant difference between groups; FET $p = 0.444$), either from personal experience and/or common sense ($N = 6$), from the scientific literature ($N = 2$), from colleagues ($N = 2$) or from an electronic newsletter ($N = 1$) [Table 2]. Thirty percent of all respondents were of the opinion that generally it takes too much time to keep up with all new safety issues.

3.2 Attitudes

Almost all respondents (93 %) considered drug safety information important or very important for their work in daily practice. Most intervention group respondents (72 %) agreed with the warning. In the control group, 50 % of the respondents agreed with the issue. All but one control group respondent indicated that their own patients were not

Table 1 Demographic characteristics of the survey respondents ($N = 40$)

	Intervention group ($N = 21$)	Control group ($N = 19$)	Total ($N = 40$)	P value
Response [N (%)][a]				
Before reminders	13 (12)	9 (9)	22 (10)	
After reminder 1	5 (5)	5 (5)	10 (5)	
After reminder 2	3 (3)	5 (5)	8 (4)	
Age [years; mean (range)]	51.1 (36–64)	52.6 (40–63)	51.8 (36–64)	0.668[b]
Male sex [N (%)][a]	14 (67)	15 (79)	29 (73)	0.385[c]
Occupation [N (%)][a]				0.273[c]
Hospital pharmacist	9 (43)	5 (26)	14 (35)	
Ophthalmologist	12 (57)	14 (74)	26 (65)	
Full time employment [N (%)][a]	18 (86)	19 (100)	37 (93)	0.233[d]
Hospital type [N (%)][a]				0.689[d]
General	18 (86)	15 (79)	33 (83)	
University	3 (14)	4 (21)	7 (18)	
Duration of professional accreditation [N (%)][a]				0.108[d]
<5 years	4 (19)	0 (0)	4 (10)	
5–10 years	0 (0)	0 (0)	0 (0)	
>10 years	17 (81)	19 (100)	36 (90)	

[a] Differences in percentages may exist due to rounding

[b] Mann–Whitney U test

[c] χ^2 test

[d] Fishers' exact test

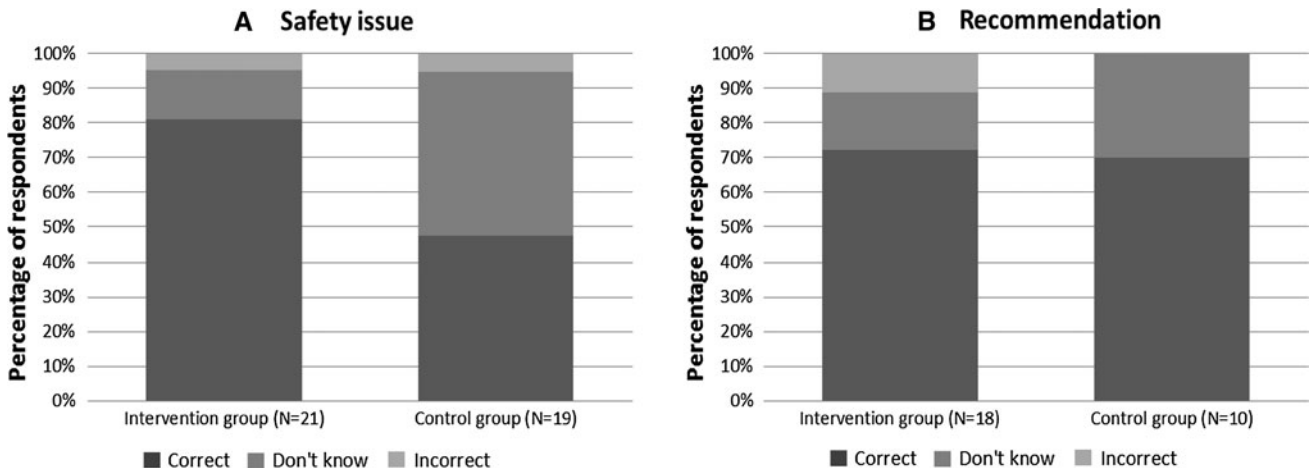

Fig. 2 Healthcare professionals' knowledge of **a** the pegaptanib safety issue (Fisher's exact test, $p = 0.046$); and **b** the corresponding recommendation (Fisher's exact test, $p = 0.674$). The 'recommendation' question was not presented to respondents who had indicated that they did not know which safety issue had been identified for pegaptanib

at risk of the issue. Twenty-five of the 28 respondents who answered this question did not administer or provide pegaptanib (intervention group 94 %; control group 80 %).

3.3 Action Taken

Nine respondents (six ophthalmologists, three hospital pharmacists) in the intervention group versus none in the control group indicated that they had taken some form of action in response to the issue (FET $p = 0.01$). The issue was mainly discussed with colleagues. One ophthalmologist mentioned that he had discussed with colleagues that close attention should be paid to the volume administered with intravitreal injections in general. Two respondents had searched for more information (both had visited the MEB website), one respondent had discussed it with a patient, and two ophthalmologists indicated that they had changed their patients' treatment. One hospital pharmacist had recorded the issue in a computerized physician order entry system. Of note, the remaining ophthalmologist had reported the issue to the marketing authorization holder and the Dutch Pharmacovigilance Center.

Table 2 Results of the questionnaire

Questions	Intervention group		Control group	
	N^a	n^b (%)^c	N^a	n^b (%)^c
Knowledge				
Does it take you too much time to keep up with new drug safety issues? [Answered yes]	21	6 (29)	19	6 (32)
Can you specify which new safety issue was identified for Macugen (pegaptanib)? [Answered correctly]	21	17 (81)	19	9 (47)
Can you specify which recommendation was made in connection with this safety issue? [Answered correctly]	18	13 (72)	10	7 (70)
Were you aware of the Macugen (pegaptanib) safety issue before the DHPC and/or e-mail were sent? [Answered yes]	18	6 (33)	10	5 (50)
Attitude				
Do you think information about drug safety by means of DHPCs is important for your work in daily practice? [Answered yes]	21	19 (90)	19	18 (95)
Do you agree with the message about this safety issue? [Answered yes]	18	13 (72)	10	5 (50)
Are you of the opinion that one or more of your patients are at risk of the safety issue? [Answered yes]	18	0 (0)	10	1 (10)
Action taken				
Did you search for more information regarding the safety issue? [Answered yes]	18	2 (11)	10	0 (0)
If so, did you visit the MEB website for more information regarding the safety issue? [Answered yes]	16	2 (13)	10	0 (0)
Did you discuss the safety issue with one or more of your colleagues? [Answered yes]	18	8 (44)	10	0 (0)
Did you discuss the safety issue with (some of) your patients? [Answered yes]	18	1 (6)	10	0 (0)
(*Ophthalmologists only*) Did you change the treatment of one or more of your current patients? [Answered yes]	10	2 (20)	9	0 (0)
(*Hospital pharmacists only*) Did you advise one or more physicians to adjust treatment of one or more current patients? [Answered yes]	6	0 (0)	1	0 (0)
Did you take any other action in response to the safety issue? [Answered yes]	18	2 (11)	10	0 (0)
Satisfaction with DHPC/e-mail				
Does the DHPC offer you specific support for your work in daily practice? [Answered yes]	17	13 (76)	12	6 (50)
Does the e-mail offer you specific support for your work in daily practice? [Answered yes]	9	7 (78)	NA	NA
How satisfied are you in general with the provision of information by letter (DHPC)? [On a visual analogue scale of 1–10; mean score (SD)]	21	7.1 (1.1)	19	5.0 (2.9)
How satisfied are you with the provision of information by e-mail? [On a visual analogue scale of 1–10; mean score (SD)]	10	7.2 (1.8)	NA	NA
Do you think the link in the e-mail that provides access to the DHPC on the MEB website is useful? [Answered yes]	10	6 (60)	NA	NA
In future, would you like to receive e-mails with similar information in addition to the letter (DHPC)? [Answered yes]	21	19 (90)	19	18 (95)
Would you rather receive safety information via a letter, e-mail, or both?	19		18	
DHPC		3 (16)		3 (11)
E-mail		10 (53)		10 (56)
Both		6 (32)		6 (33)
Would you rather receive such an e-mail from the pharmaceutical company or from the MEB?	16		16	
Pharmaceutical company		0 (0)		0 (0)
MEB		12 (75)		11 (69)
Both		4 (25)		5 (31)
Would you rather receive the letter (DHPC) from the pharmaceutical company or from the MEB?	11		9	
Pharmaceutical company		1 (9)		1 (11)
MEB		7 (64)		5 (56)
Both		3 (27)		3 (33)

DHPC Direct Healthcare Professional Communication, *MEB* Medicines Evaluation Board, *NA* not applicable

[a] *N* represents the number of respondents who answered each question. The total number of respondents per question could differ; depending on answers given to previous questions, some subsequent questions were skipped in the online questionnaire. For example, all questions regarding 'action taken in response to the DHPC' were automatically skipped if a respondent indicated that they had not been aware of the safety issue and the recommendations that were given in the DHPC

[b] *n* represents the number of respondents who gave the answer specified for each question

[c] Differences in percentages may exist due to rounding

3.4 Satisfaction with Risk Communication

The DHPC in general was rated with a mean score of 7.1 (standard deviation [SD] 1.1) out of 10 by the intervention group and 5.0 (SD 2.9) by the control group (Mann–Whitney U test, $p = 0.024$). The intervention group rated the e-mail with a score of 7.2 (SD 1.8). Fifty percent of the respondents in the control group and 76 % of the intervention group thought that the traditional DHPC offered sufficient support for their work in daily practice (FET $p = 0.236$). The intervention group valued the e-mail similarly to the DHPC, with 78 % stating that the e-mail alone offered adequate support. The link to the DHPC as provided in the e-mail was rated useful by 60 % of the intervention group respondents. Almost all respondents in both groups stated that they would like to receive an e-mail with safety information. Two thirds of them preferred to receive only e-mails about drugs that are relevant to their daily practice. Slightly more than half of the respondents who stated that they would like to receive an e-mail preferred not to receive the DHPC, and about a third preferred both. Thirteen percent indicated that they favoured the traditional DHPC despite wanting to receive the e-mail. The MEB was the preferred source of such information for both the DHPC as well as the e-mail (60 and 72 %, respectively).

4 Discussion

Risk communication is increasingly receiving attention in pharmacovigilance, partly due to an increased call for transparency. The new European pharmacovigilance legislation has become operational, in which risk communication plays an important role, and in 2007 an EU DHPC template became available [4, 5, 35]. Despite these improvements, much can still be learned and optimized by addressing multiple factors. This study offers valuable information, as an additional e-mail may lead to better uptake of the information than only the DHPC. In general, uptake of a message is improved by repetition, especially when the message is similar but not identical [13]. This fits with the intervention group respondents being more knowledgeable about the pegaptanib issue and taking action more often than the control group respondents. The issue was mainly discussed with colleagues and appears to have been a reminder that pegaptanib should be administered carefully. In general, people want to make informed decisions about risks [20]. Two respondents searched for more information about the issue, underlining that additional information is desired and should be provided. Most respondents stated that they would like to receive an additional MEB e-mail in the future. This confirms that healthcare professionals have more trust in an objective information source, like the MEB, than in the pharmaceutical industry [8, 9, 11]. Successful risk communication largely depends on a trustworthy information source and might be an important contribution to the impact of the intervention, as pharmaceutical companies are often distrusted [8, 21–23.[1]] When the trust and credibility of the source of the information are questioned, the message may not be heard, believed and acted upon [21, 24, 25]. Many factors play a role in constructing and deconstructing trust and, according to the so-called asymmetry principle, trust is lost more easily than it is rebuilt [21].

The DHPC was rated higher by the intervention group than the control group. Thus, the e-mail may have influenced the intervention group's opinion about the DHPC. Repetition of a message does improve its uptake [13], but it is unclear if satisfaction with the message is improved at the same time. Also, the link to the DHPC as provided in the e-mail may have improved its rating, as it was rated useful by 60 % of the respondents. The fact that they rated the DHPC similarly to the e-mail confirms that DHPCs remain an important communication tool [8, 10].

The question is raised as to when a DHPC can be considered sufficiently effective. Although the intervention group respondents were more knowledgeable and took action more frequently than the control group, not everyone in the intervention group could identify the correct recommendation. The challenge will be to develop evidence-based thresholds as to what knowledge and action levels are achievable and acceptable. Additional measures can be demanded whenever a threshold is not reached.

4.1 Strengths and Limitations

To our knowledge, this is the first randomized controlled study comparing the impact of an additional risk communication tool with that of the DHPC. Several national authorities provide an e-mail service informing subscribers of safety issues concerning drugs [26–29], but their impact has not yet been assessed. These results therefore offer valuable insights to improve current risk communication.

This was a small study restricted to ophthalmologists and hospital pharmacists, and the response rate was fairly low despite two reminders, which limits its representativeness and generalizability. The low response rate may have caused bias, e.g. healthcare professionals who are unfamiliar with DHPCs or who are not specifically interested in drug safety issues may have been underrepresented. The control group consisted of slightly more ophthalmologists than the intervention group. Ophthalmologists could have had different opinions about the issue than the hospital pharmacists, but this was not the case (Mann–Whitney U test, $p = 0.900$). Low response rates are not uncommon, especially in the case of online surveys

[30–32]. In this case, it may have been attributable to the limited use of pegaptanib in the Netherlands [33] as shown by 11 healthcare professionals who indicated that they had not filled out the questionnaire for that reason. Also, pegaptanib is a product with a very specific indication, and a highly educated group of prescribers (as was demonstrated by the 11 respondents) were already aware of the safety issue before the DHPC was issued. This might have been a reason for the non-responders to disregard the questionnaire. Yet no significant differences were observed between responders and non-responders. In view of its limitations, our study should be considered a starting point for future risk communication evaluations. Eleven intervention group respondents indicated that they had not received the pegaptanib e-mail, yet those respondents did fill out the questionnaire by using the link in the invitation e-mail that was sent to the same e-mail address and by the same sender. Those respondents might have overlooked the previous e-mail. The same issue holds for the DHPC, with nine respondents indicating that they had not received the DHPC. Previously, several physicians indicated that they often mistakenly throw away the DHPC together with direct mail advertising from pharmaceutical companies [9]. Also, electronic messages may be lost. A recall bias could be another possible explanation.

In order to minimize biased results, we did not perform an assessment before the DHPC was issued, nor did we provide detailed information about the study at the time of sending the e-mail, nor did we offer any incentives to increase response rates. Still, taking part in the study itself may have altered the attitude, knowledge and behaviour of the healthcare professionals. We are not able to verify to what extent this might have occurred.

Ultimately, measuring intended behaviour is just the start of evaluating the impact of risk communication, which should be supported by measurement of actual behaviour (removing the excess volume from the pre-filled pegaptanib syringe before administration) and ultimately the impact on clinical outcome, i.e. occurrence of the safety event (increased ocular pressure) [34].

4.2 Recommendations

Improving the impact of future risk communication, based on these results, will benefit public health and, ultimately, the patient. To this end, an additional e-mail sent by a national authority can be considered a promising additional tool. Healthcare professionals could be sent e-mails only about safety issues that are relevant to their specialization in order to prevent 'warning fatigue'. They should, however, still be given the opportunity to receive all e-mails, as was preferred by one third of the respondents in this study. Ideally, risk communication is a two-way process [36, 37], emphasizing the need for close involvement of healthcare professionals who are working in daily practice at the time when the DHPC is drafted. They know from experience what practising healthcare professionals already know about the drug and the safety issue. They are aware of the concerns, needs and aspects that deserve to be emphasized in the DHPC [38, 39]. With their input, the information can be tailored, e.g. by omitting information that is considered common knowledge, or by providing relevant background information.

Previous studies have shown that optimization of the format and content of DHPCs is possible [9, 40, 41] and that it can influence the impact of DHPCs [42]. A clear subject header on the e-mail or a notable symbol on the DHPC's mailing envelope could make it stand out and prevent it from being discarded [41, 43]. The content should be formulated to ensure that it is as readable and unambiguous as possible to make sure that it will be interpreted as intended and to avoid any confusion [9, 44, 45]. The most important aspects of the warning and clear recommendations should be mentioned first [20]. This is emphasized by the fact that a total of five respondents in our study who were aware of the pegaptanib issue could not correctly identify the recommendation, with two respondents in the intervention group incorrectly indicating that treatment with pegaptanib should be stopped.

Sending an additional e-mail is only one option. Other options, such as safety alerts in medical journals or computerized physician order entry systems, should also be explored, as these are also highly valued by healthcare professionals [8]. The impact of DHPCs may also be improved by taking the characteristics of the drug and the safety issue into account [42].

Risk communication can be evaluated in different ways, including formative evaluation to assess the content of a message, process evaluation to determine whether the audience has received the message, and outcome evaluation to determine whether the intended effect of the message was achieved [38]. Each method has its methodological challenges, and studies should be carefully designed. When evaluating impact by means of surveys, low response rates should be anticipated, especially when the surveys are conducted online. Pilot tests should be carried out to provide a basis for thorough sample size calculations. Several respondents in our study indicated that they had not received the pegaptanib DHPC and/or e-mail. This should be investigated more thoroughly, as reaching the target audience is a prerequisite of effective risk communication. Since risk perception may differ between countries and there may be cultural differences regarding drug use [46, 47], it is necessary to compare the impact of DHPCs, as well as the experiences and preferences of healthcare professionals, with regard to DHPCs in different countries.

5 Conclusion

The results of this study indicate that an additional e-mail may strengthen the uptake of a written DHPC, as healthcare professionals' awareness of the safety issue was increased and more action was taken in response to the issue. This study may serve as a starting point for new strategies to improve risk communication regarding safety issues associated with drugs and its impact on prescribing.

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