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ORIGINAL RESEARCH ARTICLE

Factors Influencing Preferences and Responses Towards Drug Safety Communications: A Conjoint Experiment Among Hospital-Based Healthcare Professionals in the Netherlands

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Abstract

Introduction Healthcare professionals (HCPs) are informed about new drug safety issues through Direct Healthcare Professional Communications (DHPCs). The influence of DHPC content on the impact of the communication is unclear.

Objectives The aim of this study was to assess the effect of content elements 'frequency of the safety issue', 'seriousness of the safety issue', 'need to take action', 'life span of drug involved' and 'type of evidence supporting the safety issue' on hospital-based HCPs' preferences and responses towards DHPCs.

Methods A survey study including a conjoint experiment was performed among hospital-based HCPs in the Netherlands. Hypothetical DHPCs varying on the five content elements were constructed. Each respondent received eight out of 16 hypothetical DHPCs and was asked about (1) importance to be informed (fixed-point scale), (2) preferred communication timing (multiple options) and (3) their stated actions (multiple options). Associations were tested using generalized linear mixed models.

Results In total, 178 HCPs participated. DHPCs concerning more frequent or serious safety issues, or requiring action, were associated with a higher perceived importance to be informed and a preference for immediate communication. Periodic communication was preferred for DPHCs concerning less frequent or serious safety issues. The most commonly stated action was to discuss the DHPC with colleagues. Monitoring was common when this was recommended. High frequency and seriousness were associated with more prescribing-related actions.

Conclusion Frequency and seriousness of the safety issue and the recommended action are likely to influence the impact of DHPCs. The timing of communication could be tailored depending on the content, where less urgent safety issues might be communicated periodically.

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Key Points

Hospital-based healthcare professionals prefer immediate communications, mostly for safety issues that occur relatively frequently or are irreversible and life threatening, whereas they prefer less urgent issues to be communicated periodically.

The most common action following a Direct Healthcare Professional Communication (DHPC) is discussing the issue with colleagues.

Actions with regard to changing prescribing for existing and new users were more influenced by safety issues with the highest frequency and that were life threatening.

1 Introduction

Distribution of Direct Healthcare Professional Communications (DHPCs) is the key regulatory tool to inform healthcare professionals (HCPs) urgently of important new drug safety information [1]. The impact of safety warnings on drug utilization or drug monitoring was found to be variable [2], even when methodological variation was restricted [3]. Several communication factors have been identified that influence the adoption of new drug safety information, which are related to the message, the medium and the sender [4]. A structured message, repetition of the message as well as an email additional to the paper-based DHPC may improve the uptake and impact of drug safety issues [5, 6]. Where the uptake refers to the awareness of the DHPC and the drug safety issue, the impact refers to the changes in behaviour following the DHPC. In general, HCPs prefer safety messages coming from national authorities [5, 7, 8], which may improve their uptake and impact as the message is considered more trustworthy [4]. However, if the clarity and clinical relevance of messages conveyed in DHPCs is less clear, this may negatively affect their impact [9–11]. HCPs prefer explicit risk data and actionable recommendations to inform their decisions [12]. Communications including recommendations for action showed more impact on prescribing than those without [13].

Currently, it is insufficiently clear to what extent content elements of the message influence the impact of the communication. DHPCs concerning more serious safety issues resulted in less prescribing of the drug involved [6]. One qualitative study indicated that the effect size of the risk is important for HCPs when assessing and processing drug safety information [9]. Other factors mentioned in the same study were biological plausibility, the type of evidence supporting the safety issue, personal experience as well as the experience and opinion of colleagues with the safety issue; however, their impact needs to be confirmed [9]. Experience with the drug itself and the availability of alternative treatment options may also influence the impact of DHPCs [14]. DHPCs for psychotropic drugs or drugs that require a specialist to initiate prescribing appeared to have less impact as compared with DHPCs for other drugs [2, 6]. The belief that newer drugs are more likely to have safety issues can influence the assessment of the new safety information [9]. Nevertheless, DHPCs for newer or more innovative drugs did not show a greater impact on drug utilization than those for older or less innovative drugs [6].

In order to improve the effectiveness of the DHPC, a better understanding of factors related to the message that influence the adoption of safety information is needed [2, 3]. With hospital-based HCPs being the largest target population for DHPCs in the Netherlands [15], and DHPCs for specialist medication showing less impact [6], this study is focused on their preferences and responses towards DHPCs. The following questions are addressed: to what extent are content elements of the message (i.e. 'frequency of the safety issue', 'seriousness of the safety issue', 'need to take action', 'life span of the drug involved' and 'type of evidence supporting the safety issue') associated with hospital-based HCPs' (1) stated importance to be informed about the drug safety issue, (2) preferred timing of such communication and (3) stated action after receiving a DHPC about the safety issue?

2 Methods

2.1 Study Design

We conducted a conjoint experiment to assess the associations between the five content elements related to the drug safety issue and the HCPs' preferences and responses towards DHPCs. We developed an online survey, which was distributed among Dutch medical specialists and hospital pharmacists, including those in training, between November 2019 and June 2020.

2.2 Survey Study Population and Recruitment

In order to recruit participants for the survey, professional associations from the Netherlands were approached and requested to mail their members a pre-composed email concerning our survey, to include it in their newsletter and/or to promote it on their website. This was followed by a reminder after a month. We specifically targeted internists

(particularly oncologists and haematologists), neurologists, gynaecologists, pulmonologists, cardiologists, nephrologists and urologists, as well as hospital pharmacists and polyclinic pharmacists, as they were the most frequent recipients of DHPCs in the Netherlands from 2016 to 2018. All approached organisations were willing to participate.

As the effect of the content elements on the included outcomes was unknown, no formal sample size was determined. With the respondents answering questions regarding multiple hypothetical DHPCs, we aimed at reaching as many respondents as possible via the professional organisations and including at least 100 respondents for the analyses following the rule of thumb of Pearmain [16].

2.3 Survey Development

The survey consisted of two parts: (1) general questions concerning demographics of the respondents and background information on their sources of drug safety information and familiarity with DHPCs and (2) a series of eight hypothetical DHPCs with the following three main questions: 'How important is it to you to be informed about this drug safety issue?', 'What would you do in response to the DHPC?' and 'Which moment would you like to receive the information?' (Supplementary Table 1 and Supplementary Fig. 1, see electronic supplementary material [ESM]). The survey was pilot-tested for readability and flow among 14 colleagues with various backgrounds, including a hospital pharmacist and a medical specialist. Based on their feedback, general information concerning the disease and patient population was added to the hypothetical DHPCs, such as 'slowly progressive condition within your patient population' (Supplementary Fig. 1, see ESM).

2.3.1 Part 1: Background Information

After a short introduction on DHPCs, including one real-world example, respondents were asked the following questions concerning DHPCs: if they were familiar with them, if they read them, if they considered them useful and through which channel they preferred to receive them (Supplementary Table 1, see ESM). At the end of the survey, respondents were asked about their personal characteristics, including age, working experience and the type of hospital they were employed by. Furthermore, respondents were asked which sources they used to obtain general drug information.

2.3.2 Part 2: Hypothetical DHPCs

From a total of 48 possible hypothetical DHPCs, a random subset of 16 hypothetical DHPCs was selected using the orthogonal design function in SPSS version 25 (IBM Corp.). Each respondent received a random selection of eight hypothetical DHPCs from this subset.

2.4 Determinants

The hypothetical DHPCs varied on five content elements that are usually addressed in DHPCs: frequency of the safety issue, seriousness of the safety issue, need to take action, life span of the drug and type of data that was provided as evidence to support the safety issue (Table 1). These elements were selected for their expected relevance to HCPs, according to previous studies [6, 9–14]. Information concerning the frequency of the safety issue, when presented, is not consistently presented in DHPCs. Therefore, we used the classification from the Summary of Product Characteristics as the level presented in the hypothetical DHPCs (i.e. uncommon [≥ 1/1000 to < 1/100], rare [1/10,000 to 1/1000] and very rare [< 1/10,000]) [17]. For the levels of seriousness, the World Health Organisation's classification was used (i.e. leads to hospital admission or prolonging of current admission, and leads to irreversible invalidity and is potentially life threatening) [18]. The levels used for type of evidence (i.e. epidemiological research and spontaneous

Table 1 Levels for content elements used in the hypothetical DHPCs

	Levels		
Frequency of the drug safety issue (SmPC classification)	Very rare (< 1/10,000)	Rare (≥ 1/10,000 to < 1/1000)	Uncommon (≥ 1/1000 to < 1/100)
Seriousness of the drug safety issue (WHO classification)	Leads to hospital admission or prolonging of current admission		Leads to irreversible invalidity and is potentially life threatening
Need to take action	You should be alert for the safety issue		Additional monitoring of users (for example additional lab tests)
Life span of the drug	A drug with less than 10 years' experience		A drug with more than 10 years' experience
Type of evidence for the drug safety issue	From epidemiological research and spontaneous reports		From clinical research

DHPC Direct Healthcare Professional Communication, *SmPC* Summary of Product Characteristics, *WHO* World Health Organisation

report, and clinical research) and need to take action (i.e. be alert for the drug safety issue, and additional monitoring of users) were derived from what is commonly presented in DPHCs. Lastly, the life span of the drug was defined in levels using the definition for "well-established use of the European Medicines Agency", that is, > 10 years of clinical use in the EU [19]. General information concerning the disease, the population and potential alternative therapies were kept constant in all hypothetical DHPCs. Given the number of elements and levels, a total of 48 different hypothetical DHPCs could be composed.

2.5 Outcomes

Respondents were asked per hypothetical DHPC how important it was for them to be informed about the drug safety information (0–100 fixed-point scale), when they would like to receive this information (select all that apply: i.e. immediately; periodically; when I look for drug information; at the moment of prescribing; does not matter) and what their action would be after receiving such a DHPC (select all that apply: i.e. discontinuing drug for existing users; reconsidering drug for existing users; stop prescribing to new patients; reconsidering the drug for new patients; additionally testing users; discussing the safety issue with colleagues; nothing; other, with the option to provide free text information) (Supplementary Table 1; questions 5–7 [see ESM]).

2.5.1 Data Management and Analysis

All respondents that were hospital pharmacists (in training), polyclinic pharmacists or medical specialists (in training), and answered at least one question of the online survey were included in the study.

Descriptive statistics were used to summarize the respondents' background characteristics as well as their use of and preferences for information sources and DHPCs.

A generalized linear mixed model was used to analyse answers to the question 'How important is it to you to be informed about this safety issue', where participants could indicate a value from 0 to 100 on a fixed-point scale. Coefficients with 95% confidence intervals (CI) were reported. The questions concerning the preferred timing of the communication and the stated action were analysed using logistic mixed models per outcome option. Adjusted odds ratios (AdjOR) with 95% CI were reported. In these models, all determinants were included as fixed effects. Respondents were included as random effects to correct for answering multiple hypothetical DHPCs.

SPSS version 25 (IBM Corp.) was used for all analyses.

2.5.2 Informed Consent

Written informed consent was collected from all respondents in the survey.

3 Results

Professional associations of pulmonology, gynaecology, internal medicine, cardiology, urology, nephrology and hospital pharmacists participated in our request to invite their members to complete the survey. Of the 183 HCPs that opened the online survey, 178 answered at least one of the questions (Table 2). Of these 178 respondents, 74 were pharmacists and 104 medical specialists. In total, 129 HCPs completed the full survey, including 59 pharmacists and 70 medical specialists, resulting in more than 1000 assessments related to the 16 hypothetical DHPCs.

3.1 DHPC Familiarity and Other Sources of Information

Including those in training, most hospital pharmacists (97%) and just over half of the medical specialists (53%) were familiar with DHPCs (Table 2). The latter percentage increased to 62% when excluding the medical specialists in training. Among the HCPs familiar with DHPCs, around half (46%) always read them and 61% found them useful. The preferred channels for receiving DHPCs were by email for all professions, and for pharmacists the 'Kennisbank'—a digital compendium of the Dutch Royal Society of Pharmacy (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP), whereas specialists preferred the Pharmacotherapeutic Compass—a free digital source for drug therapies hosted by the National Health Care Institute (Zorginstituut Nederland)—and the computerized physician order entry (CPOE) system. Most HCPs preferred to receive DHPCs through multiple channels (Table 2). The preferences are in line with the sources for drug information they reported to use in general (Table 2). Over half of the HCPs (54%) would prefer drug safety issues, as presented in DHPCs, to be incorporated automatically into professional guidelines.

3.2 Importance to be Informed

For a drug safety issue with all determinants set to the reference category (base case) in the mixed model, the importance to be informed was rated 57.8 on the 0–100 fixed-point scale. This increased when the frequency of the safety issue increased (coefficients 6.8, 95% CI [4.7–8.8]

Table 2 Respondent characteristics and background information

	All respondent *N* (%) 178	Pharmacists *N* (%) 74 (42)	Specialists *N* (%) 104 (58)
Profession			
Hospital pharmacist (in training)	65 (37)		
Polyclinic pharmacist	9 (5)		
Medical specialist (in training)	104 (58)		
Missing	0 (0)		
Age[a]			
< 35 years	25 (14)	17 (23)	8 (8)
35–45 years	47 (26)	18 (24)	29 (28)
46–55 years	30 (17)	13 (17)	17 (16)
> 55 years	27 (15)	11 (15)	16 (15)
Missing	49 (28)	15 (20)	34 (33)
Hospital work experience[a]			
< 5 years	21 (12)	8 (11)	13 (13)
5–10 years	37 (21)	18 (24)	19 (18)
> 10 years	71 (40)	33 (45)	38 (37)
Missing	49 (28)	15 (20)	34 (33)
Type of hospital (select all that apply)[a]			
Academic	42 (24)	19 (26)	23 (22)
Top clinical	36 (20)	16 (22)	20 (19)
General	53 (30)	24 (32)	29 (28)
Missing	49 (28)	15 (20)	34 (33)
Familiar with DHPCs			
Yes	127 (71)	72 (97)	55 (53)
Yes, but never seen one	9 (5)	0 (0)	9 (9)
No	34 (19)	1 (1)	33 (32)
Missing	8 (5)	1 (1)	7 (7)
Reported reading of DHPCs[b]			
Always	58 (46)	35 (49)	23 (42)
Often	38 (30)	23 (32)	15 (27)
Sometimes	17 (13)	6 (8)	11 (20)
Seldom	6 (5)	2 (3)	4 (7)
Missing	8 (6)	6 (8)	2 (4)
Reported usefulness of DHPCs[b]			
Very useful	15 (12)	7 (10)	8 (15)
Useful	62 (49)	34 (47)	28 (51)
Neutral	30 (24)	20 (28)	10 (18)
Not useful	10 (8)	4 (6)	6 (11)
Not useful at all	2 (2)	1 (1)	1 (2)
Missing	8 (6)	6 (8)	2 (4)
Preferred channel to receive DHPCs (select all that apply)			
DHPC letter	41 (23)	19 (26)	22 (21)
DHPC email	93 (52)	51 (69)	42 (40)
Newsletter professional association	52 (29)	16 (22)	36 (35)
Pharmacotherapeutic Compass	66 (37)	10 (14)	56 (54)
'Kennisbank'	49 (28)	46 (62)	3 (3)
CPOE	70 (39)	23 (31)	47 (45)
App (e.g. Lareb)	33 (19)	8 (11)	25 (24)
No preference	0 (0)	0 (0)	0 (0)

Table 2 (continued)

	All respondent *N* (%) 178	Pharmacists *N* (%) 74 (42)	Specialists *N* (%) 104 (58)
Missing	21 (12)	6 (8)	15 (14)
Preference for multiple channels to receive the information?[c]			
Yes, multiple	80 (62)	31 (56)	49 (66)
No, only one	23 (18)	14 (26)	9 (12)
No preference	25 (19)	9 (16)	16 (22)
Missing	1 (1)	1 (2)	0 (0)
Preference for automatic incorporation of safety issues, as described in the DHPC, in professional guidelines			
Yes	96 (54)	36 (49)	60 (58)
No	41 (23)	24 (32)	17 (16)
I don't know/no opinion	18 (10)	6 (8)	12 (12)
Missing	23 (13)	8 (11)	15 (14)
Sources for general drug information used (select all that apply)[a]			
DHPC	37 (21)	23 (31)	14 (13)
Newsletter (MEB, Lareb)	46 (26)	22 (30)	24 (23)
Pharmacotherapeutic compass	102 (57)	33 (45)	69 (66)
'Kennisbank'	63 (35)	59 (80)	4 (4)
Lareb	62 (35)	23 (31)	39 (38)
Medical journals	101 (57)	49 (66)	52 (50)
Clinical trials	37 (21)	14 (19)	23 (22)
Conferences	68 (38)	24 (32)	44 (42)
SmPC	55 (31)	47 (64)	8 (8)
National guidelines	84 (47)	39 (53)	45 (43)
Health base	3 (2)	3 (4)	0 (0)
Colleague	65 (37)	29 (39)	36 (35)
General media	5 (3)	4 (5)	1 (1)
Other	9 (5)	5 (7)	4 (4)
Missing	49 (28)	15 (20)	34 (33)

The Pharmacotherapeutic Compass is a free digital source for drug therapies hosted by the National Health Care Institute (Zorginstituut Nederland). The 'Kennisbank' is a paid digital information source for drug therapies generated by the Royal Dutch Pharmacists Association (Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, KNMP)

App application, *CPOE* computerized physician order entry, *DHPC* Direct Healthcare Professional Communications, *Lareb* the Netherlands Pharmacovigilance Centre Lareb, *MEB* Medicines Evaluation Board, *SmPC* Summary of Product Characteristics

[a]These questions were placed at the end of the survey, resulting in more missing answers

[b]Only respondents familiar with DHCPs (yes) received this question

[c]Only respondents that chose multiple channels through which they liked to receive DHPCs received this question

and 11.6 [9.6–13.7]). Similarly, the importance was higher for more serious safety issues (12.7 [11.0–14.4]) and for safety issues for which additional monitoring was recommended (5.2 [3.5–6.9]) (Table 3). Less than 20% of the ratings were <50 and around 40% of the ratings were ≥80 (Supplementary Table 2, see ESM).

3.3 Timing of Communication

In 56% of the DHPCs concerning drug safety issues that occurred in more than 1/1000 patients, the HCPs preferred immediate communication, whereas this percentage was 35% for issues that occurred in less than 1/10,000 patients (Supplementary Table 3, see ESM). Similarly, immediate communication was preferred in 58% of the DHPCs for irreversible and life-threatening safety issues, whereas this was only 28% for safety issues leading to hospitalisation. Furthermore, immediate communication was preferred in 48% of the DHPCs where direct action was needed, whereas this was 38% when one should be aware of the safety issue only.

In the mixed models, the frequency and seriousness of the safety issue as well as the need to take action were all

Table 3 Influence of content elements of a drug safety issue on the importance to be informed

Determinant	Level	Coefficient	95% CI
Intercept		57.8	54.38–61.21
Frequency of the safety issue	Very rare	Ref	
	Rare	**6.8**	**4.7–8.8**
	Uncommon	**11.6**	**9.6–13.7**
Seriousness of the safety issue	Hospitalisation	Ref	
	Life threatening and irreversible	**12.7**	**11.0–14.4**
Need to take action	Be alert	Ref	
	Additional monitoring	**5.2**	**3.5–6.9**
Life span of the drug	<10 years	Ref	
	>10 years	−1.4	−3.1–0.3
Type of evidence	Epidemiological studies and spontaneous reports	Ref	
	Clinical research	0.5	−1.2–2.2

In bold the siginificant ($p \leq 0.05$) content element levels shown

CI confidence interval, *Ref* reference category

Table 4 Influence of content elements of a drug safety issue on the preferred timing of the communication

Determinant	Level	Immediate (e.g. through a DHPC)	Periodically (e.g. through a newsletter of professional association)	When I look for drug information (e.g. integrated in the Pharmacotherapeutic Compass or 'Kennisbank')	At the moment of prescribing (e.g. integrated in the CPOE)
Frequency of the safety issue	Very rare	Ref	Ref	Ref	Ref
	Rare	**2.0 (1.4–3.0)**	0.8 (0.6–1.2)	1.0 (0.6–1.5)	**1.8 (1.1–2.8)**
	Uncommon	**3.5 (2.3–5.2)**	**0.6 (0.4–0.9)**	0.9 (0.6–1.4)	**2.1 (1.4–3.4)**
Seriousness of the safety issue	Hospitalisation	Ref	Ref	Ref	Ref
	Life threatening and irreversible	**6.6 (4.7–9.2)**	**0.5 (0.3–0.6)**	1.1 (0.8–1.6)	1.3 (0.9–1.9)
Need to take action	Be alert	Ref	Ref	Ref	Ref
	Additional monitoring	**2.0 (1.4–2.8)**	**0.6 (0.5–0.9)**	1.1 (0.7–1.5)	**2.1 (1.5–3.2)**
Life span of the drug	<10 years	Ref	Ref	Ref	Ref
	>10 years	0.9 (0.7–1.3)	1.1 (0.8–1.5)	0.9 (0.6–1.2)	0.7 (0.5–1.1)
Type of evidence	Epidemiological studies and spontaneous reports	Ref	Ref	Ref	Ref
	Clinical research	1.0 (0.7–1.4)	1.1 (0.8–1.5)	1.1 (0.7–1.6)	1.0 (0.7–1.4)

Data shown as adjusted odds ratio (95% confidence interval), in bold significant ($p \leq 0.05$) content element levels shown

CPOE computerized physician order entry, *DHPC* Direct Healthcare Professional Communications, *Ref* reference category

significant determinants for the preferred moment of communication (Table 4). Higher frequencies resulted in a higher preference for immediate communication (adjOR 2.0, 95% CI [1.4–3.0] for rare, 3.5 [2.3–5.2] for uncommon, compared with very rare), as did irreversible and life-threatening drug safety issues (6.6 [4.7–9.2]) and drug safety issues with the recommendation of additional monitoring (2.0 [1.4–2.8]). These same determinants were negatively associated with a preference for periodical communication. Preference to receive the information at the moment of prescribing was associated with more frequent safety issues and safety issues with the recommendation of additional monitoring (1.8 [1.1–2.8], 2.1 [1.4–3.4] and 2.1 [1.5–3.2]). The preference for receiving information about safety issues when actively searching for information on that specific drug in general drug information sources was not affected by any of the content elements.

3.4 Stated Actions

When asked what kind of actions the HCPs would take following the DHPCs, discussing the drug safety issue with colleagues and reconsidering the drug for new users as well as for existing users were the most common actions, stated in at least 52%, 40% and 33%, respectively (43%, 45% and 40% for specialists; 62%, 31% and 25% for pharmacists) (Supplementary Table 4, see ESM). Carrying out extra tests was stated in at least 17% of the cases but increased to 59% when such action was recommended in the DHPC (19–58% for specialists; 14–61% for pharmacists). Discontinuing the drug in existing users was uncommon, stated in 1–12% of the cases depending on the frequency, seriousness and need to take action (2–18% for specialists; 0–3% for pharmacists). Stop prescribing the drug to new users was stated in 7–25% depending on the same content elements (10–32% for specialists; 2–16% for pharmacists).

In the mixed models, the frequency, seriousness and need to take action influenced the indicated actions significantly (Table 5). The DHPCs with safety issues at the highest frequency and the highest level of seriousness were associated with an increased likelihood to discontinue the drug among existing users (adjOR 3.2, 95% CI [1.2–9.1] and 16.0 [5.8–44.1], respectively). Similarly, these were also associated with an increased likelihood to stop using the drug for new patients (3.4 [2.0–5.9] and 6.88 [4.1–11.4], respectively). Such safety issues were also more likely to be discussed with other colleagues (2.0 [1.4–3.1] and 1.4 [1.0–2.0], respectively). The drug safety issues for which it was recommended to perform additional monitoring were strongly associated with the action to perform such additional tests (15.4 [10.6–22.4]). None of the determinants were strongly associated with the intention to reconsider the drug for new patients, although this action was somewhat more likely for safety issues related to drugs older than 10 years (1.4 [1.0–1.9]).

4 Discussion

Drug safety issues that are more frequently occurring, more serious and for which action is recommended are considered more important by HCPs to be informed about, and are more often preferred to be received immediately (i.e. through a DHPC). Similarly, when drug safety issues are more frequently occurring or when action is recommended, HCPs preferred to receive information on this safety issue at the moment of prescribing this drug to a patient (e.g. through a CPOE system). Discussing the safety issue with colleagues was the most common stated action. Most of the stated actions were affected by the frequency and seriousness of the safety issue. HCPs were more likely to stop prescribing the drug to new patients and to discontinue or reconsider the drug in patients already taking the drug in case of safety issues that occurred in at least 1 out of 1000 patients and/

Table 5 Influence of content elements of drug safety issue on intended actions

Determinant	Level	Discontinue existing users	Reconsider existing users	Stop prescribing new patients	Reconsider new patients	Additional testing for users	Discuss issue with colleagues
Frequency of the safety issue	Very rare	Ref	Ref	Ref	Ref	Ref	Ref
	Rare	1.1 (0.3–3.9)	**1.6 (1.1–2.3)**	1.6 (0.9–3.0)	1.0 (0.7–1.5)	1.5 (1.0–2.2)	1.0 (0.7–1.5)
	Uncommon	**3.2 (1.2–9.1)**	**2.1 (1.4–3.0)**	**3.4 (2.0–5.9)**	1.3 (0.9–1.9)	1.3 (0.9–1.9)	**2.0 (1.4–3.1)**
Seriousness of the safety issue	Hospitalisation	Ref	Ref	Ref	Ref	Ref	Ref
	Life threatening and irreversible	**16.0 (5.8–44.1)**	**3.0 (2.2–4.1)**	**6.9 (4.1–11.4)**	1.2 (0.9–1.6)	1.1 (0.8–1.5)	**1.4 (1.0–2.0)**
Need to take action	Be alert	Ref	Ref	Ref	Ref	Ref	Ref
	Additional monitoring	1.2 (0.5–2.9)	1.0 (0.8–1.4)	1.4 (0.9–2.2)	0.9 (0.6–1.2)	**15.4 (10.6–22.4)**	0.8 (0.6–1.1)
Life span of the drug	<10 years	Ref	Ref	Ref	Ref	Ref	Ref
	>10 years	0.8 (0.3–2.2)	1.2 (0.9–1.7)	0.8 (0.5–1.3)	**1.4 (1.0–1.9)**	1.2 (0.9–1.7)	1.0 (0.8–1.5)
Type of evidence	Epidemiological studies and spontaneous reports	Ref	Ref	Ref	Ref	Ref	Ref
	Clinical research	0.8 (0.4–1.5)	1.2 (0.9–1.6)	1.2 (0.8–1.8)	0.9 (0.7–1.3)	0.9 (0.7–1.3)	1.0 (0.7–1.3)

Data shown as adjusted odds ratio (95% confidence interval), in bold significant ($p \leq 0.05$) content element levels shown

Ref reference category

or for issues that could be irreversible and potentially life threatening. The type of evidence for the safety issue (i.e. whether it was based on clinical research or on epidemiological research and spontaneous reporting) had no impact on the preferences and responses towards the drug safety communications. Our study showed a surprisingly low familiarity with DHPCs among medical specialists, especially among those in training, who had a higher preference for receiving such information through other information channels.

Our results provide a deeper understanding on the influence of the content of safety messages on whether and when HCPs prefer to be informed about drug safety issues. Their perceived importance of being informed and being informed immediately depended evidently on three elements of the safety issue, that is, the frequency, the seriousness and the need for action. Although this may seem apparent, it underscores the value of providing direct communications for these types of safety issues. HCPs use multiple sources to obtain drug safety information, which differ in being distributed directly to them, such as DHPCs or bulletins, or are accessible on demand [12]. The majority of hospital-based HCPs in our study indicated they prefer to be informed about important drug safety issues immediately (i.e. through a DHPC), whereas less important safety issues could be communicated through periodic information sources, such as newsletters. This wish to be informed rapidly has been expressed before [12]. The optimal way of disseminating this information is still unclear, since information overload is a previously identified problem [4, 12]. In our study, HCPs preferred communication about more frequently occurring safety issues and safety issues with the recommendation of additional monitoring at the moment of prescribing, such as through a CPOE system. Other studies showed that pop-up warnings in the CPOE can be effective [20], although again it is advised to use such warnings in moderation in order to prevent 'alert fatigue' [21, 22].

Furthermore, our study illustrates that DHPCs concerning more frequently occurring and more serious drug safety issues are more likely to impact drug utilization, whereas the impact for less frequent or serious issues is likely to be limited. Regarding the seriousness, this is in line with earlier studies showing a larger decrease in drug use for more serious safety issues [6]. Where other studies showed that HCPs want to be informed about the frequency of safety issues [9, 12], our study adds that the likelihood to take action will differ depending on the content of such information. DHPCs have been criticized for a lack of clinical relevance and clear recommendations [9–12]. Our study showed that DHPCs with a clear recommendation to conduct additional testing were considered more important and were more likely to result in actions compared with DHPCs asking to be alert. This confirms findings from an earlier study, where a clear recommendation showed more impact than a more complicated warning [23]. A review conducted in the UK observed that communications with a restriction or change in indication had a larger impact than communications without a recommendation for action [13]. Another study, however, did not find a significant difference between communications with or without an explicit prescribing advice [3]. This discrepancy could be explained by differences in the content of the recommendations included, of which the clarity and quality should also be taken into account [10]. When a DHPC is lengthy, some HCPs may just quickly screen it and not read the part including the relevant recommendation [4]. One of the most common stated actions following the DHPC was to discuss the safety issue with colleagues. A previous study already indicated that the opinions of other clinicians were considered important to assess the clinical utility of the safety information received [9]. Uncertainties or debate about the clinical utility of a safety issue may result in a lack of action, and, therefore, may limit the impact of the DHPC in practice. According to our study, actions following a DHPC were only minimally impacted by the life span of the drug, confirming the results from a previous study [6].

Only half of the participating medical specialists and nearly all participating hospital pharmacists indicated that they were familiar with DHPCs, as opposed to a previous study among Dutch HCPs which showed higher familiarity of 72% among general practitioners, 85% among specialists, but similar rates of 95% among hospital pharmacists [8]. A more recent study showed a familiarity of 92% among pharmacists, specialists and GPs without significant differences between the professions, except for Italy where pharmacists were more familiar with the DHPC than GPs (99% vs 90%) [24]. The low familiarity among medical specialists in our study may be explained in part by the proportion of specialists in training in our study. More generally, HCPs may find it challenging to keep up to date on drug safety issues and some disregard DHPCs because these are mistaken for biased information coming from a pharmaceutical company [4, 12]. Furthermore, HCPs expect that important messages will be repeated through various channels [9, 12]. The medical specialists in our study clearly preferred and used multiple other channels to obtain or receive drug safety information.

4.1 Implications

Currently, for all drug safety issues for which a DHPC is deemed necessary, the same strategy is used by urgently distributing the information through direct mailings. This risk communication strategy cannot easily be altered considering legal obligations of pharmaceutical companies and regulators. Several studies have already provided recommendations to improve the process, such as using multiple

channels and more trustworthy senders [5, 7, 8] and providing clear recommendations [9, 10, 12, 25]. Besides the confirmation that multiple channels are preferred, our findings support the need to adapt the current communication strategy and tailor it to the content of the message. For many hospital-based HCPs, the preferred moment of communication depends on this content. They prefer that less urgent safety issues are communicated only periodically. Thus, drug safety issues that are rare or very rare, not irreversible nor life threatening and without immediate action needed may be combined in periodical newsletters. These would typically include DHPCs that are distributed to raise awareness of the safety issue and safety issues that require 'watchful waiting'. In such cases, this strategy would generate time to assess the clinical implications of the safety issue and formulate clearer recommendations, which could improve the uptake and impact of the information [13, 25]. Furthermore, the hospital-based HCPs prefer that multiple channels are used, and many prefer that safety information currently distributed in DHPCs is automatically incorporated into clinical guidelines and the information sources they commonly use when actively searching for drug information. This is in line with previous findings of HCPs who were concerned they might miss one-off communications [9, 12]. An additional channel for receiving important safety information, preferred particularly by medical specialists, is the CPOE. This would be an appropriate channel to provide alerts when additional monitoring is needed, but also other clinically relevant recommendations; for example, restrictions of indications or new contra-indications could be incorporated in CPOE systems. This is likely to increase the uptake and impact of such recommendations. Finally, our study showed that the perceived importance of being informed and preferences for the timing of the communication did not depend on the source of the safety issue, that is, evidence from epidemiological studies or spontaneous reports or clinical trials.

4.2 Strengths and Limitations

Our exploratory study was a first to examine the impact of the content elements of drug safety information on the preferences and responses of hospital-based HCPs towards such communications. Given the explorative nature of this study, we did not correct for multiple testing. By creating hypothetical DHPCs, several content elements were systematically varied whereas other factors were kept constant. This experimental design gives insight into the impact of these elements without the influence of factors that can be difficult to control, such as personal experiences. On the other hand, elimination of such factors can also be considered a limitation, since they can play a role when validating safety information [9]. Furthermore, using hypothetical DHPCs inhibits any assessment of actual behaviour, and we were only able to evaluate the impact of the content elements on stated actions. Also, our survey design does not allow for assessing any long-term impact. All respondents were hospital-based HCPs in the Netherlands, and our findings may not be generalizable to other countries as it has been found that preferences for how to receive drug safety information may vary depending on clinical and cultural contexts [25]. In addition, our results may not be generalizable to other HCPs in the Netherlands. Our respondents were recruited indirectly and therefore a real response rate could not be calculated. However, the estimated medical specialist population of interest, including those in training, was 9780 in 2019, resulting in a response rate of 1.1% [26]. The estimated hospital pharmacist population including those in training was 675 in 2019, resulting in a response rate of 10.9% [27]. We did include a diverse group of hospital-based HCPs when looking at their disciplines, age and working experience. Of note, this information was missing for 28% of our respondents, due to HCPs not completing the full questionnaire.

5 Conclusion

Our study shows that the frequency and the seriousness of a safety issue as well as the recommended action are likely to influence the impact of DHPCs and should be clearly stated in the DHPC. Depending on the content, some DHPCs are not likely to have much impact on drug utilization. In these cases, other information channels might be more appropriate to disseminate the safety information. The current strategy for drug safety communications does not align with the preferences of hospital-based HCPs with regard to the both the channel and the timing of the communication. Both could be tailored depending on the content of the message, where less urgent safety issues without a recommendation for action can be communicated periodically.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40264-022-01230-y.

Declarations

Consent to participate Informed consent was obtained from all individual respondents included in the study.

Consent for publication Consent for publication was not required since all responses were anonymous.

Authors' contribution Study conception and design of the survey were performed by Esther de Vries, Elisabeth Bakker, Petra Denig and Peter G.M. Mol. Material preparation, data collection and analysis were performed by Esther de Vries, Taco B.M. Monster, Petra Denig and Peter G.M. Mol. The first draft of the manuscript was written by Esther de Vries and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards Prior to the commencement of this study, details of the research were entered into the University Medical Center Groningen's Research Register (UTOPIA study number 201900103) and it was determined that the study did not fall within the reach of the Dutch research involving human subjects act (WMO) and ethics approval was thus not required for the study. For this non-WMO study, the METc will not conduct any further assessment. Written informed consent was collected from all respondents in the focus groups and respondents in the survey.

Conflict of interest Petra Denig and Elisabeth Bakker have no conflicts of interest that are directly relevant to the content of this study. Esther de Vries, Taco B.M. Monster, and Peter G.M. Mol are (part-time) employees of the Dutch Medicines Evaluation Board. Any opinions, conclusions and proposals in the text are those of the authors and do not necessarily represent the views of the Dutch Medicines Evaluation Board.

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Availability of data and material The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability The code used when analyzing the data of the current study are available from the corresponding author on reasonable request.

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