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The effectiveness of direct to healthcare professional communication – A systematic review of communication factor studies

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ABSTRACT

Background: Direct to healthcare professional communication (DHPC) is the prevalent regulatory measure to inform about and potentially mitigate newly identified drug risks in EU and USA. According to multiple studies and reviews, however, the effectiveness of DHPC to reduce risk is less than optimal. Prior systematic reviews have indicated that contextual, qualitative knowledge of communication factors related to the clinical setting is needed to further explain and supplement findings in quantitative effectiveness studies.
Objectives: This article systematically reviews studies of DHPC and, on that basis, describes the communication factors that influence the effectiveness of DHPC in order to discuss future research trajectories.
Methods: PubMed, Scopus (including Embase) and Web of Science databases were searched for studies on communication about emergent drug risk to healthcare professionals, excluding studies limited to the quantifiable effect of communication. The search results were deductively categorized using the Communication Sequence Model. Then, prevalent themes within categories were identified and described using thematic analysis.
Results: A total of 16 studies published between 1993 and 2017 were included; 12 based on surveys, 2 on document analysis, and 2 primarily on interviews. The prevalent themes included "Health Care Professionals (HCPs) have less trust in communication from industry than authorities and medical associations", "HCPs have diverse preferences for how to receive drug risk information" and "Clinical usability of the presented information is less than optimal."
Conclusion: Communication factors in DHPCs are multiple, multi-facetted and are examined primarily by surveys. Future research would benefit from identifying nationally dependent factors and employing methods that better provide knowledge on the qualitative reception and handling of drug risk communication.

1. Background

Written communication to healthcare professionals (HCPs) about emerging drug risks is an integral part of the regulatory risk management. Direct healthcare professional communication (DHPC; also named "Drug Safety Communication", "Dear doctor letter", "Safety Advisory") is a central measure to manage post-marketing drug risks in the EU and USA.[1–3] Despite its wide use, numerous case-based studies and reports on the effectiveness of DHPCs have indicated that they perform less than optimally, as they have not been found to have a measurable effect on prescribing practices.[4–7] Recent reviews of DHPC effectiveness studies[3,8–10] also concluded that the general impact of DHPCs is less than optimal. But more importantly, the reviews concluded that the methods to assess DHPCs effectiveness at a general level are limited, even though recent and more general frameworks for evaluating the quality of studies in risk minimization may improve the methods.[11] At least three factors inhibit effectiveness assessment of DHPCs. First, studies on DHPC effectiveness are heterogeneous in study design, therapeutic area, communication type and intended recipient. Multiple methods ranging from time series analysis of drug utilization

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patterns to awareness surveys are applied; and the objects of study range from drug-based communication to drug class-based communication. The nature of the communication evaluated and its intended recipient vary from specialist practitioners to a wide range of healthcare professionals. This variation inhibits quantitative comparison and evaluation.[3,9]

Second, many studies on DHPC effectiveness examine drug utilization patterns to determine the success of a given safety communication.[3] However, in cases where the drug risk communication is found ineffective, such pharmacoepidemiological methods do not provide explanatory insights into the situated reception of the communication, the clinical decision-making process it seeks to inform, or the individual context of clinical drug risk management, including the role of media reports and professional peers.[12] Qualitative knowledge may supplement existing quantitative methods by shedding light on the contextual factors which influence DHPC effectiveness.[13]

Third, the success criteria by which the DHPCs effectiveness is measured are not firmly established. The EMA[14] along with numerous studies recommend applying both process indicators (e.g. information distribution statistics and awareness surveys) and outcome indicators (e.g. occurrence of adverse reactions) as success metrics.[15,16] But the central question of what constitutes the success of the communication intervention beyond its indications remains understudied and not sufficiently discussed.[17–20]

To address this methodological gap a number of studies and editorials have advocated a multidisciplinary approach to the assessment of DHPCs' effectiveness.[6,12,13,20–26] Calls for multidisciplinarity are based on the notion that social scientific methods may complement understanding the clinical context and physicians' preferences and behavior in regards to DHPCs. The first step is to review the existing studies that provide knowledge on these aspects of communication.

The purpose of this study is thus to produce a comprehensive review and systematic appraisal of studies of the effectiveness of DHPC which report on the communication factors. In order to produce a status of current developments in assessing the effectiveness of DHPC and discuss potential future research trajectories and eventually improve DHPC, the predominant themes and conclusions of included studies will be presented and discussed.

2. Methods

2.1. Search strategy

A systematic review was performed based on the PRISMA guidelines for systematic reviews.[27] Three article databases were searched for studies of drug-related safety communication to HCPs. PubMed was searched in full-text mode for articles in English using the search string below (Table 1). To ensure a more comprehensive list of results the PubMed search was supplemented by searches in Scopus (including Embase) and Web of Science using the same search string but limited to searching abstracts, titles and keywords. Scopus and Web of Science are two of the largest multidisciplinary research databases, which ensure interdisciplinary width in the search strategy. The time period of all searches was from inception of the database to May 3rd, 2017 and subsequently updated on January 10th, 2018. The search string consisted of four search term clusters of which number three captured specific research methods in order to increase the probability of including studies in communication factors and excluding studies on communication effect alone. Initial searches resulted in a relatively large number of studies of the effects of regulatory labeling of consumer goods, e.g. tobacco product and alcohol, which are beyond the scope of this study. These were excluded using cluster four applied to the title field only.

Table 1
Search string combined four search term clusters for research database queries.

Search string: Four search term clusters	
	1) drug information* OR drug labelling OR drug surveillance OR drug contraindication* OR risk minimi* OR drug safety*
AND	
	2) letter* OR communicat* OR dear doctor OR dear healthcare OR warning*
AND	
	3) survey* OR questionnaire* OR interview* OR focus group* OR qualitative
NOT	
	4) Title terms=consumer* OR direct-to-consumer* OR cigar* OR tobacco OR alcohol*

2.2. Eligibility criteria

Inclusion was based on three serial criteria that each article should meet. Criterion 1 "Does this article report on communication of pharmaceuticals, i.e. the purposeful transmission of information on pharmaceuticals from a sender to a recipient?" criterion 2, "Do the recipients of this communication include HCPs?", criterion 3, "Does the study provide knowledge on communication factors, including analytic, explanatory or descriptive?" The latter criterion was added to exclude studies that only reported on measurable (quantitative) effects of communication and not its factors.

The search was not limited to studies reporting on DHPCs alone. A pilot search revealed that studies of other additional risk management measures (aRMMs) like educational material or changes to package leaflets may provide useful knowledge about the communication aspects which are the focus of this review, e.g. HPCs' media preferences for drug risk alerts.

The reliability of the eligibility procedure was ensured by inter-rater selection process and assessment.[28] Three authors individually screened a subset of the 814 titles and abstracts and subsequently compared to remove any ambiguity of inclusion criteria. The minor differences in screening among authors was resolved by specifying criteria further. On that basis, minor adjustments were made to criteria 1 and 2.

The quality of the articles was assessed by their methodologies. Interview studies and focus groups studies were assessed by appropriate research design, data collection and analysis, based on the Qualitative Research check list of the Critical Appraisal Skills Programme.[29] None were excluded on this basis. As no specific quality assessment tools were found for the included survey and document analysis studies, a meta Quality Assessment Tool[30,31] was applied to assess the quality. None were excluded on this basis.

2.3. Data extraction and analysis

The data extraction from the included studies was performed in three steps. In all steps the qualitative data analysis software Nvivo (QSR International, version 11.4.0 for Mac) was utilized. First, data was identified in the included articles by coding relevant sections of records line-by-line. Following recent methodologies in qualitative systematic reviews,[32,33] the data to be extracted was defined as "key concepts" in the "Findings", "Results" or "Conclusion" sections of the included articles.

Secondly, the coded data was categorized using the communication factors from the Communication Sequence Model (Fig. 1).[34–36] The Communication Sequence model conceptualizes communication as a totality of five constitutive parts in a temporal sequence: sender, message, medium, recipient, and effect. The Communication Sequence model was selected as the methodological framework in this review because it allows communication research to focus on the features of communication and not the product or output.[37(p3)] That is, the effect of

Fig. 1. Communication Sequence Model.

Table 2
Operationalization of the Communication Sequence Model for categorization of results.

Communication factor category	Analytical mode	Analysis questions
Sender	Examines the sender's stakes in and objectives with communication, preference for media use, production and requirements for content, understanding of and attitude towards recipient.	What is the sender's objectives and success criteria with the text? How is content decided on? What are the conditions of text production? What media are preferred and why?
Message	Examines content, e.g. evidence, arguments, style, organization, formatting examples, and directives.	Is an at-risk patient group identified? Is the extent to which certainty of evidence stated? Is the document formatted appropriately? Is the information concise and instrumental to the recipient?
Medium	Examines preferences, advantages and challenges particularly in relation to recipient preferences.	Does the use of media match with the recipients' preferences? What are the attitudes associated with specific media?
Recipient	Examines the psychological and sociological dispositions of the recipient in the act of receiving, evaluation and acting upon the communication	How important is the communication to the recipient? In which situations is it more or less likely to be effective? What role does trust in the sender play?
Effect	Examines behavioral and/or opinion changes following from the communication, in the target group (not identical to recipients)	N/A

DHPC is beyond the scope of this review because they are well described in the existing literature using drug utilization research methods as noted in the introduction of the paper. The factorial focus, which the Communication Sequence model gives, allows for a clearer identification and deeper analysis of factors which influence an effect of communication. Table 2 describes the specific analytical operationalization of the categories in the Communication Sequence model (see Fig. 1).

Third, following the data extraction and the deductive categorization an inductive theme analysis of the results in each of the communication factor categories was performed. The categorized data were analyzed inductively, exploring whether results respond to similar research questions or apply different scopes within the same topic, thus highlighting salient aspects of the communication. This inductive analysis involved inference across diverse methodologies and research objectives, ultimately resulting in analytical themes of research results across the found articles.[32] The analysis proceeded over three iterations in which three authors convened to evaluate and qualify its results.

3. Results

The search string yielded 1021 articles across the three different databases that were searched. Following deduplication, screening, eligibility and quality assessment 16 studies were included (See Fig. 2 and Table 3). These studies were published between 1993 and 2017 in 13 different journals representing three different research areas: 9 articles in drug safety and clinical pharmacy (e.g. *Drug Safety*), 3 articles from specialized medical journals (e.g. *Neurology*), 3 articles from social science in medicine journals (e.g. *Journal of Health Communication*), and one article from a multidisciplinary journal (*SpringerPlus)*. Twelve studies utilized survey methods only, two studies applied document analysis methods and two studies used interview methods alone or in combination with a survey.

After categorizing the included studies using the Communication Sequence model, six themes within the categories were found (See Table 4). Multiple studies reported on more than one category, while fewer studies only reported on one of the themes.

3.1. Sender

One study reported on the sender factor of the communication, so no analytical themes emerged from this factor's category. The one article, Urushihara et al. (2014), reported on a government funded survey study with 74 anonymous representatives in the Japanese industry's pharmacovigilance departments. Even though the survey sample inhibits the identification of potential patterns beyond the specific study, four relevant results were extracted from this study. First, when asked about the relative importance of different target groups for drug risk communication respondents deemed the physicians most important. The public and the media were generally considered the least important target for the communication. Secondly, Urushihara et al. concluded that “strength of evidence” was the most important aspect of drug risk communication and “treatment option” was deemed the least important. Third, a discrepancy was reported between who was perceived as the most important stakeholder and who the respondents spent the most time on. “While physicians and pharmacists were the most prioritized communication targets, pharmacovigilance departments devoted the most resources to regulators, at more than 30%.” Fourth, senders of DHPCs regard the risk management plan beneficial for improving cooperation with HCPs and for increasing transparency: “67.3% of respondents considered that disclosure of the safety risk management plan was useful, with the expectation that this would make it easier to gain the cooperation of healthcare professionals and patients in ensuring effective implementation, and by reason of the public significance of ensuring the transparency of post-marketing activities.”

3.2. Content

Five studies reported on the content in the drug risk communication. Two themes were identified in this communication factor category: there is a moderate lack of clarity, according to American physicians, and that the clinical usability of the presented information is less than optimal.

3.2.1. A moderate lack of clarity, according to American physicians

Two studies reported on the quality of the written communication in terms of clarity, i.e. ease of comprehension and distinguishable points of information (none of the found studies, however, provided a definition of clarity). Across methods and results of these studies it was inferred that respondents, in this case American physicians, reported a moderate lack of clarity. Both studies found clarity to be an important aspect of the written communication by surveying physicians' estimation of specific DHPCs. In Mazor et al.[39] ten American physicians rated

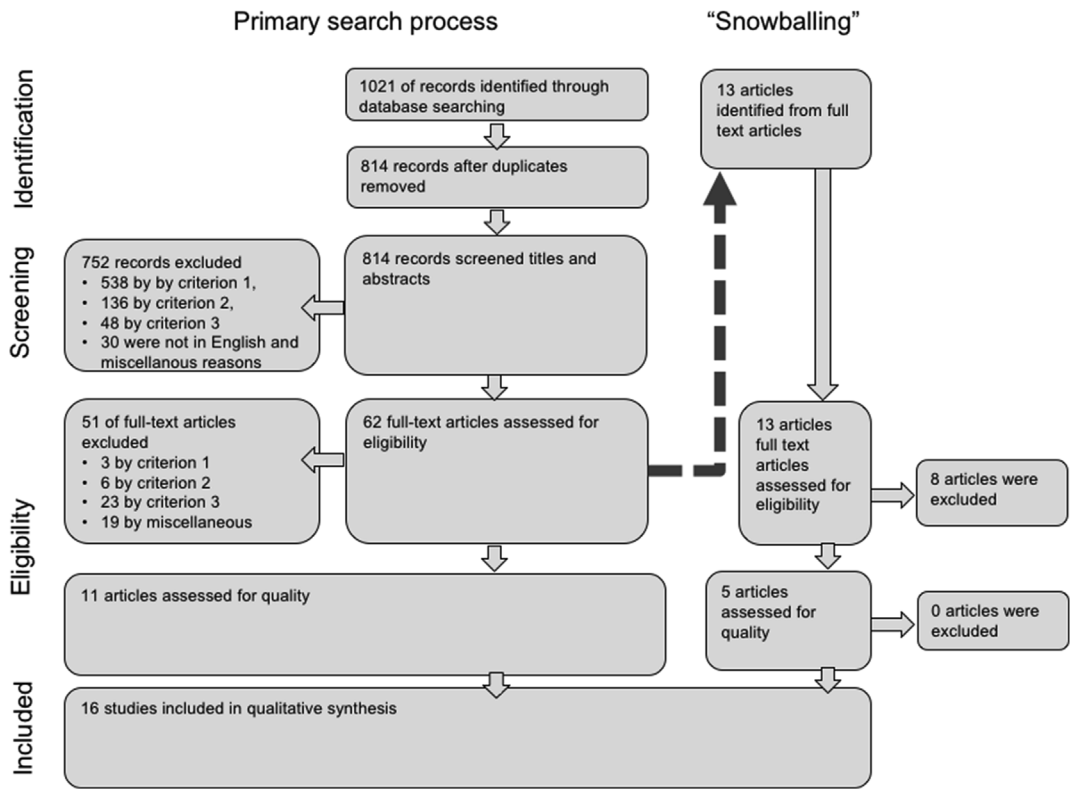

Fig. 2. Search results.

Table 3
Results and primary methods.

No	Study included	Primary method
1	Barry CL, Busch SH. News Media Coverage of FDA Warnings on Pediatric Antidepressant Use and Suicidality. *Pediatrics*. 2010; 125 (1):88–95.	Document analysis
2	Bell, S. G., Matsumoto, M., Shaw, S. J., Brandt, J., & Krauss, G. L. (2013). New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists. *Epilepsy and Behavior*, *29* (1), 36–40.	Survey
3	de Vries, S. T., van der Sar, M. J. M., Cupelli, A., Baldelli, I., Coleman, A. M., Montero, D., … 6, O. behalf of S. W. P. (2017). Communication on Safety of Medicines in Europe: Current Practices and General Practitioners' Awareness and Preferences. *Drug Safety*, 1–14.	Survey
4	Hamrosi, K. K., Raynor, D. K., & Aslani, P. (2013). Pharmacist and general practitioner ambivalence about providing written medicine information to patients-A qualitative study. *Research in Social & Administrative Pharmacy*, *9* (5), 517–530.	Survey
5	Kesselheim, A. S., McGraw, S. A., Dejene, S. Z., Rausch, P., Dal Pan, G. J., Lappin, B. M., … Campbell, E. G. (2017). Patient and Physician Perceptions of Drug Safety Information for Sleep Aids: A Qualitative Study. *Drug Safety*.	Interview
6	Lee, L. Y., Kortepeter, C. M., Willy, M. E., & Nourjah, P. (2008). Drug-risk communication to pharmacists: Assessing the impact of risk-minimization strategies on the practice of pharmacy. *Journal of the American Pharmacists Association*, *48* (4), 494–500.	Survey
7	Mazor, K. M., Andrade, S. E., Auger, J., Fish, L., & Gurwitz, J. H. (2005). Communicating safety information to physicians: An examination of dear doctor letters. Pharmacoepidemiology and Drug Safety, 14 (12), 869–875.	Survey
8	Morrato, E. H., Curbow, B., Crum, R. M., Nowels, C., & Feinleib, M. (2008). Communicating drug risk to physicians: Challenges and opportunities. International Journal of Risk & Safety in Medicine, 20 (3), 143–154.	Focus groups interviews
9	Piening, S., de Graeff, P. A., Straus, S. M. J. M., Haaijer-Ruskamp, F. M., & Mol, P. G. M. (2013). The Additional Value of an E-Mail to Inform Healthcare Professionals of a Drug Safety Issue: A Randomized Controlled Trial in the Netherlands. *Drug Safety*, *36* (9), 723–731.	Survey
10	Piening, S., Haaijer-Ruskamp, F. M., de Graeff, P. A., Straus, S. M. J. M., & Mol, P. G. M. (2012). Healthcare professionals' self-reported experiences and preferences related to direct healthcare professional communications: a survey conducted in the Netherlands. *Drug Safety*, *35* (11), 1061–72.	Survey
11	Shneker, B. F., Cios, J. S., & Elliott, J. O. (2009). Suicidality, depression screening, and antiepileptic drugs: reaction to the FDA alert. *Neurology*, 72 (11), 987–91.	Survey
12	Sturkenboom, M. C., de Jong-van den Berg, L. T., Cornel, M. C., Stricker, B. H., & Wesseling, H. (1994). Communicating a drug alert. A case study on acitretin in The Netherlands. *European Journal of Clinical Pharmacology*, *47* (2), 125–132.	Survey
13	Théophile, H., Miremont-Salamé, G., Robinson, P., Moore, N., Bégaud, B., & Haramburu, F. (2011). Relevance of a "Dear Doctor letter" to alert healthcare providers to new recommendations for vitamin D administration. European Journal of Clinical Pharmacology, 67 (7), 681–6.	Survey
14	Thomson, A. N., & Barham, P. M. (1993). The effect of a warning about putative adverse events on drug prescribing in general practice. *Social Science and Medicine*, *37* (7), 883–886.	Survey
15	Urushihara, H., Kobashi, G., Masuda, H., Taneichi, S., Yamamoto, M., Nakayama, T., … Sugimori, H. (2014). Pharmaceutical company perspectives on current safety risk communications in Japan. *SpringerPlus*, *3*, 51.	Survey
16	Woloshin, S., Schwartz, L. M., Dejene, S., Rausch, P., Dal Pan, G. J., Zhou, E. H., & Kesselheim, A. S. (2017). Media Coverage of FDA Drug Safety Communications about Zolpidem: A Quantitative and Qualitative Analysis. *Journal of Health Communication*.	Document analysis

Table 4
Results of deductive analysis and inductive analyses.

Communication factor	Number of studies	Themes found
Sender	1	*[N/A, no themes across studies, due to one study only]*
Content	5	A moderate lack of clarity, according to American physicians Clinical usability of the presented information is less than optimal
Medium	13	News media coverage perform moderately well in correctness and balancing risks and benefits HCPs have diverse preferences for how to receive drug risk information
Recipient	10	HCPs have less trust in communication from industry than authorities and medical associations News media coverage is the least preferred source but also a positive factor

specific DHPCs deficient in terms of readability. Here 25% of cases were deemed deficiently unclear and 28% deficiently unreadable. In Shneker et al.[40] 175 American neurologists rated the clarity of a FDA warning on risks of suicidality using antiepileptic drugs and reached an average value of 5.3 (1 = very confusing, 10 = very clear). Some respondents reported that they did not consult patients on the risk of suicidality due to the lack of clarity of the DHPC.

3.2.2. Clinical usability of the presented information is less than optimal

Five studies reported on the limited clinical usability of the information presented in drug risk communications. Across these studies it was found that two factors limit or even inhibit the usability of DHPC information, namely insufficient strength of evidence and difficult use of the information in clinical practice. Two studies explicitly reported on role of strength of evidence in DHPCs. Bell et al.[41] and Shneker et al.[40] both reported specialists' evaluation of the content in FDA alerts on drug risks relating to neurology and anti-epilepsy drugs, respectively. In both cases a reportedly "significant" number of respondents felt that the evidence presented in the safety warning was either "flawed" or too deficient to include in patient counseling. In two other studies respondents pointed to difficulty in using the information in clinical practice. In Moratto et al.'s focus group study[42] the participating physicians' recommendation for improving the drug safety communication emphasized the need for "facts": "State the facts clearly and succinctly … Give us the risks. Give us real data and let us and our patients make the choices".[42(p150)] The focus group also illustrated the connection between recommendations and evidence: "*Be very specific about recommendations*. Otherwise, physicians will not necessarily take direct action because they will view the warning as advice not direction."[42(p150) Italics original] The difficulty in use is corroborated by Hamrosi et al.'s focus group study[43] of Australian HCPs. Most focus group participants (especially GPs) in this study requested benefit-risk information which would help them explain the decision about medicine and the medicine's necessity to the patient. They requested a more balanced approach to benefits and risk in written drug risk communication.[43(p526)] The suboptimal status of content in DHPCs was also reported in a 1994 study by Sturkenboom et al.[44] who used structured questionnaires (n = 1038) to examine Dutch HCPs' preference among the three different direct risk communications. They compared direct drug risk communication from the health authorities, from pharmaceutical industry (i.e. DHPC) and from pharmaceutical association. When asked about the content specifically, the communication from the health authorities scored highest because the requested actions were clearly articulated for each target group. The DHPC from the pharmaceutical company, however, was rated second because it did not contain any background information about the incident.

3.3. Medium

Thirteen articles reported on the media factor in the communication. It was inferred that news media coverage performs moderately well in correctness and in balancing risks and benefits and, secondly, that HCPs have diverse preferences for how to receive drug risk information.

3.3.1. News media coverage perform moderately well in correctness and balancing risks and benefits

Two articles examined the remediation and circulation of content from regulatory drug risk communication in popular news media. It was found that these studies both concluded that news media communicate risks relatively well in terms of correctness and balancing risk and benefits. None of the studies, however, explicitly offered definitions on these parameters in support of their evaluations. Barry et al.[45] reported on the risk-benefit balance in news coverage on childrens' use of attention deficit/hyperactivity disorder (ADHD) medication vis-à-vis cardiac and psychiatric risks. They found that the overall coverage was "relatively balanced in its portrayal of the risks and benefits."[45] Taking a different approach, Woloshin et al.[46] studied which risks, from a regulatory drug risk communication, was reported in American popular news media. They found that more than half of the news media stories correctly reported three of the key risk messages in the FDA warning they investigated. However, they also found that less than one third of the news stories included a specific warning mentioned in media reports.

3.3.2. HCPs have diverse preferences for how to receive drug risk information

Six studies reported on HCP's preferences about how to receive drug risk communication. Across these studies it was found that there are inconsistent preferences about the optimal medium for communication about new drug risks, potentially due to varying clinical and cultural contexts. Lee et al.'s[47] 2008 study of pharmacists' preferences concluded that "new" types of electronic communication channels should be utilized in order to overcome the lack of awareness their results showed. In contrast, Théophile et al.'s[48] 2011 study concluded that postal mail was the preferred medium among French and Dutch physicians. [1] Third, in Piening et al.[49] HCPs were asked about four specific safety issues. Here the knowledge was mostly obtained from professional journals (59%) and DHPCs (49%). Fourth, Bell et al.[41] found that a large number of physicians endorsed systematic notification from specialty organization (n = 190, base n = 505) or an email (n = 176). De Vries et al.[50] provided perhaps the most authoritative study of medium preferences due to number of HCP respondents. A total of 1766 general practitioners (GPs) from 9 European countries responded and 63% percent preferred electronic communication and 89% found a repetition of the safety message useful.

3.4. Recipient

Ten articles reported on the recipient factor of the communication. Our inductive reading produced two themes. First, HCPs have less trust towards written drug communication from industry sources. Second, that HCPs adapt their drug communication to patient literacy. They cite colleagues as important sources on changes in prescribing.

[1] Sturkenboom et al. also concluded that HCPs prefer postal mail but in a study from 1994, when there were few feasible alternatives to postal mail.

3.4.1. HCPs have less trust in communication from industry than authorities and medical associations

Five articles reported on the influence of HCPs' trust towards the communication source. They suggested that the receiving HCPs prefer drug risk information from national medical authorities and professional medical associations over industry. Piening et al.'s[49] survey of Dutch HCPs concluded that physicians in particular (pharmacists less so) had less trust in safety communication sent by industry than by official authorities, and that physicians preferred drug risk information from professional medical associations. In de Vries et al.'s[50] survey of 1766 European HCPs the least valued senders of drug risk information were lay press and pharmaceutical companies, whereas the highest rated were national medicinal authorities and professional bodies. Based on 505 neurologists' survey responses, Bell et al.[51] concluded that the only method of safety notification that was associated with an increased knowledge of drug risks was notifications from specialty organizations.

However, two studies applying qualitative methods gave a more complex picture of trust in drug risk communication. Kesselheim et al.[21] reported that some respondents expressed that they had received trustworthy information from drug companies while others felt that such information was unreliable due to potential bias. Morrato et al.'s[42] focus group study concluded that scientific senders, i.e. sources for medical professionals, were preferred the most due to the high credibility and in-depth information, although they were narrowly distributed (a "hit-or-miss" source). Industry senders were least favored due to their commercial bias and a narrow audience. They were, however, considered legally correct and substantive. DHPC was more favored in this group, although difficult to separate from other commercial industry communication in daily practice. Official authority as a source was valued ambiguously. Some respondents perceived FDA as biased towards industry, consequently not trustworthy, while others estimated an FDA warning higher than a warning from one singular colleague.

3.4.2. News media coverage is the least preferred source but also a positive factor

Three articles reported on the influence of news media coverage on HCPs awareness and attitude. They suggested that there is a low preference for learning about drug risks in news media although a recognition that it is effective and potentially helpful. Kesselheim et al.[21] found that information about new drug risks in mass-mediated news coverage has a positive effect on HCPs' awareness of new drug risks. Although the HCPs surveyed in Piening et al.[49] rated "media" (i.e. non-medical media) as the least preferred source of new drug risk information among different sources, HCPs are not categorically dismissive of news media coverage. The HCPs interviewed in Morrato et al.[42] emphasized that news coverage may lead to a more informed patient discussion and may help flag drug risk for further research. It can, however, also catch the physician off-guard as patients may have read about drug risks in news media before the physician has consulted medical journals.

4. Discussion

Before discussing the results of each of the communication factor categories, one general comment about the results is due. This review highlights the diversity of factors influencing HCPs awareness and decision in regards to drug risk communication. As most of these insights have been provided using surveys, one methodological point should be made. While surveys are highly useful for understanding the extent and degree of already known and specified issues, they do not constitute the best method for exploring lesser known and specified issues such as contextual factors of communication in the clinical setting. The majority of survey studies provide relatively limited knowledge because explorative measures such as follow-up questions of respondent driven accounts are not possible.

The first communication factor in review – the sender – is significantly less studied than other factors. While the other three factors (i.e. "content," "media" and "recipient", as "effect" is beyond the scope of this review) were covered by multiple studies, only one study reports on the perspective of the communicative role of industry and regulators, namely Urushihara et al.[38] Even though this factor may seem less important, the absence of studies does call for more research because efforts to evaluate the effectiveness of risk minimization measures should encompass the entire communication process. While not directly relevant to other geographical areas nor representative of industry perspectives, Urushihara et al.'s study invites questions about the compatibility of industry risk minimization practices and the objectives of communicative risk minimization measures targeting HCPs. For example, to what extent does the efforts of industry representatives sending the DHPCs match the needs of receiving HCPs? Such questions about alignments are important because any change of practice regarding DHPCs will involve a change of practice for industry pharmacovigilance departments, so empirical knowledge about relevant work procedures and preferences will not only qualify a new communication procedure, it will support the implementation of it. As for regulatory organizations, any effort to improve DHPC would also require empirical knowledge on the regulatory procedures for endorsing messages and designating communication strategies, particularly in Europe where the process proceeds from a supranational level at the EMA to national authorities.

Content, the second communication factor examined, demonstrates a significant finding and a gap in knowledge. In line with recent workshop reports on drug risk communication[52] we found that HCPs request risk information that is more applicable to daily practice. Seemingly, the gap between population-level risk information and relevant risk information for individual patient is insufficiently supported by the DHPCs examined in the included studies. Furthermore, the absence specific content studies indicate a gap in the current research. Dominant methods for developing risk communication messages, such as the Mental Models Approach to Risk Communication (MMARC),[53] are based on the notion that content of risk communication should be tested on and subsequently tailored to the target audience. Following the mantra "users know best", risk communication starts and ends with its recipients. Applying this best practice of tailoring communication to recipients, communication of emergent drug risk would involve more studies on the specific content of DHPCs and on senders' efforts to customize it for the specific situation.

In terms of the medium for distributing drug risk communication, the diverging media preferences across geography and cultures suggests that there is no "one-size-fits-all" solution. The theme we called "HCPs have diverse preferences for how to receive drug risk information" emphasizes the need to adapt communications and, as de Vries et al.[50] suggest, examine the media landscape and HCPs' preferences in order to tailor communication to existing preferences and media landscape. The transition from paper-based to digital modes of communication deserves specific note. While the HCPs' flow of new information is now dominated by digital modes of communication, DHPC continues to be understood and practiced primarily as a hard copy document to be disseminated physically. For example, De Vries et al.[50] found that the majority of the surveyed European medicine authorities did not allow industry to distribute DHPCs without sending a hard copy version. As professional users become accustomed to – or are indeed "native" to – digital communication environments, hard copy documents circulated via mail may easily fall short of expectations to access, ease of use, further information and actuality. Interestingly, social media have increasingly come to dominate the media landscape, also in professional contexts such as healthcare, yet it has only been examined in one of the included studies, namely Kesselheim et al.[13] Furthermore, the practice of using commercial advertisements space in medical journals as a medium for drug risk communication has not been investigated even

though this would seem to have potential. In light of these gaps and following recent suggestions,[12,13,46] it is highly relevant to broaden the scope of media beyond the distribution of DHPC letter and popular news coverage to address how regulatory drug risk communication is re-mediated and circulated in the media landscape. This would require more specific conceptualization of the function of emergent drug risk information in decision-making situations and clinical practice. As this review indicates, HCPs pick up drug risk information from a wide range of sources and include it in their clinical judgment in ways that are still under-described.

As to the recipient category, trust in the communication is relatively well-described theme. In this respect, we found a significant difference between survey-based studies and interview- or focus group-based studies. Even though some respondents in qualitative interviews regard industry sources as generally credible and useful, the majority of studies show that HCPs prefer non-industry sources with medical authority and with no financial interests involved. Even though dissemination through partnership with NGOs and non-industry affiliated organizations has been a topic of discussion since the FDA's strategic plan in 2009,[54] none of the included studies articulate this aspect. Even though a 1994 study have found that letters sent by pharmaceutical associations was scored low by rating healthcare professionals,[44] reviews on the use risk management approaches from other disciplinary fields suggest that suggest that the inclusion of third-party organization may be beneficial.[26,55]

The absence of some themes is also notable. When compared with recent workshop reports on drug risk communication,[52] one of the main reasons for taking action in response to a communication was the severity of the risk. This factor was only discussed in one study, namely Mazor et al.'s.[39] Also, multiple comments hypothesize the existence of alert fatigue with HCPs, i.e. the risk over over-communicating risk to HCPs to the extent that it proves counterproductive. However, this issue has not been investigated systematically.

4.1. Strengths and limitations

The number of studies which were identified and reviewed here does not support substantive conclusions on the specific communication factors influencing DHPCs. Rather, this review has demonstrated a diversity of factors which influence HCPs' decision-making and consequently support suggestive conclusions about the current status of contextual communication knowledge about DHPCs. Secondly, across the included studies geographic and cultural differences implicate differences in clinical practice, media landscape and regulatory environment. This limits the applicability of the conclusions to specific national contexts.

5. Conclusion

This review has identified research articles about communication factors and inferred the prevalent themes within this research, thus supplementing recent reviews on the quantifiable effectiveness of DHPCs with a review of qualitative, contextual knowledge. It has demonstrated a diversity of factors across four different communication categories, which need to be further specified and examined. In order to gain an overview of the diversity of influential factors the Communication Sequence Model was applied. In combination with a thematic analysis method this allowed for more focused consideration of the individual factors which ideally will translate into more focused efforts in future research and regulatory practice. Finally, it was concluded that several factors are dependent on national, regulatory contexts. Consequently, future research would benefit from identifying nationally dependent factors and examining these in well described contexts.

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