Pharmacoepidemiology and Drug Safety

WILEY

REVIEW OPEN ACCESS

Mixed Impact of Direct Healthcare Professional Communications When Considering Proximal Outcomes and the Targeted Population: A Systematic Review

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Received: 3 December 2023 | **Revised:** 15 January 2025 | **Accepted:** 5 March 2025

Funding: The authors received no specific funding for this work.

Keywords: DHPC | drug safety | effectiveness | impact | review | risk communication

ABSTRACT

Background: Direct Healthcare Professional Communications (DHPCs) are an important risk minimisation measure. Their effect has been shown to be variable and has been measured using different outcomes and study populations. Depending on the content of the message, the optimal outcome to measure a direct effect of the DHPC can differ. This systematic review investigates whether the effects of DHPCs differ according to the use of proximal outcomes and the inclusion of the targeted population.

Methods: EMBASE and MEDLINE were searched for European DHPC effectiveness studies performed up to April 6, 2022, evaluating the impact of DHPCs issued from 2008. Outcomes and their impact were extracted, together with a classification of the message. The outcomes were categorised as knowledge/awareness, self-reported behaviour (prescribing/monitoring), prescribing of medication (including dosage changes), monitoring, or adverse events/other health outcomes, including hospitalisation. The outcomes closest to the message of the DHPC were defined as proximal. Outcomes were coded 1 when effective and 0 if not. If multiple outcomes were reported in a study, a composite outcome was created ranging from 0 to 1. Chi-square or Fisher exact tests were performed.

Results: From 7063 (scientific) publications identified in our literature search, 60 publications evaluating 31 different DHPCs were selected for our review. As publications could study multiple messages with an outcome, from the 60 scientific publications, 103 outcomes were generated for the messages, of which 30 had a high impact on the composite outcome, with the proportion of analyses with a significant association between 0.75 and 1. When taking the target population into account, some messages were studied in more than one population, resulting in 115 outcomes, of which 33 had a high impact, that is, a composite outcome between 0.75 and 1.

Conclusion: Neither the use of proximal outcomes nor the restriction of the analysis to the targeted population significantly influenced the impact observed of the DHPC. These results stress the need for improving drug safety communication.

1 | Introduction

Direct Healthcare Professional Communications (DHPCs) inform healthcare professionals (HCPs) of new important drug safety information. It is one of the risk minimisation measures regulators can take during the life cycle of a drug (Figure 1). The DHPC can be issued by, for example, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines

Summary

- DHPCs are an important tool for regulators to communicate about urgent drug safety issues. The impact of these DHPCs has reported to be variable and inadequate at times.
- Our study confirms mixed effects of DHPCs, with a high impact (with a proportion of analyses with a significant association effect and studied outcome between 0.75 and 1) observed for less than a third of the outcomes evaluated.
- The impact of DHPCs was not found not to be affected by the use of proximal outcomes for the type of DHPC message nor by the use of the targeted population of the DHPC.
- The seriousness of the drug safety issue was not associated with the DHPC impact when measured using proximal outcomes in the targeted population.
- Additional efforts to improve safety communication are required.

Agency (EMA) or by a national competent authority of an individual European country. When the DHPC is not effective, other measures should be taken to minimise the risk related to drug use.

Reviews that have reported on the impact of risk minimisation measures show that there is a large variability in findings [1–4]. This has partly been attributed to the variation in risk minimisation measures studied and the content of the messages, and to methodological issues related to the study design, selected outcomes, and study population [1–4]. Studies looking at the effects of risk minimisation measures can use various outcomes, such as the knowledge of the receivers, their prescribing behaviour, or the occurrence of related adverse drug reactions [3]. The results may differ depending on the type of outcome or study design chosen. For example, to assess the effectiveness of risk minimisation measures concerning valproate, a survey study was performed and found good knowledge of the risks and required actions, particularly among physicians who acknowledged receiving the DHPC and related educational materials [5]. The same researchers assessed in a different study the changes in valproate prescribing and concluded that the effectiveness of the risk minimisation measures was limited on this outcome [6].

What needs to be assessed to ascertain that a DPHC is effective depends on its content and intended outcomes [7]. The content may include information about new adverse reactions, indication limitations, new contraindications, changes in authorised dosage, additional monitoring, and new drug–drug interactions for a certain product [8]. This information can be related to a specific target population of patients. To link such content to intended outcomes, Dusetzina et al. classified FDA safety communications into: recommendations for increased laboratory or clinical monitoring, avoiding co-prescribing due to drug–drug interactions, avoidance of use among a subpopulation, and general caution regarding a product [9]. Weatherburn et al. made a slightly different classification in a UK review based on the type of regulatory action: withdrawal from the market, recommendations to change practice based on a change or restriction of indication, recommendations for additional monitoring, and to be aware of new information without recommending specific action [1]. Based on such a classification of messages, outcomes for assessing proximal and distal effects can be defined. With those defined as proximal for outcomes closest to the message in the DHPC. Caution or be aware messages are primarily intended to increase the HCPs' knowledge or awareness of new information, with possible distal effects on behaviour. DHPCs with recommendations for additional monitoring or with new information about contraindications, drug–drug interactions or dosing changes are intended to change the HPCs' behaviour, with possible distal effects on health outcomes.

The content of a DHPC can refer to the specific patients at risk, implying that the primary outcome to assess the effectiveness of a DHPC should reflect this population. When this is not taken into account, incorrect conclusions may be drawn. For example, the DHPC informing HCPs on the new contraindication and restricted indication of cyproterone acetate 2 mg/ethinylestradiol 35 micrograms led to decreases in the overall prescribing of this drug but the proportion of prescribing in the targeted population did not improve [10]. When looking at the content of a DHPC, there is also variation regarding the products and the seriousness of the safety issue itself. One review focusing on DHPCs issued in the Netherlands observed that the seriousness of the safety issue was associated with possible effects on prescribing [11].

To gain a better understanding of the variable outcomes observed in the effectiveness of DHPCs, we performed a systematic review extending on previous work and explored whether this variation can be explained by the choice of the study outcomes, the study population, or the safety issue itself. Our primary question is whether the effects of DHPCs differ according to the use of proximal outcomes and the inclusion of the targeted study population. Our secondary question is whether the effect of the DHPC differs across the seriousness of the drug safety issue.

2 | Methods

A systematic review was conducted including studies assessing the effects of DHPCs issued since 2008 by the European Medicines Agency (EMA) or national authorities in the European Union (EU). This year was chosen to limit variation caused by the introduction of a fixed DHPC template in 2008, since such a template may increase the impact of DHPCs [11]. Search strategies were developed for EMBASE and MEDLINE and performed on April 6, 2022 (Data S1 and S2). Finalised studies in the EU PAS register of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP [now the HMA-EMA Catalogues of real-world data sources and studies]) up to April 21, 2022 were screened for studies assessing the effectiveness of a DHPC. Snowballing, a review of all identified studies' reference lists, was applied for all publications that met our inclusion criteria. The study protocol was registered in PROSPERO (CRD42022349593).

FIGURE 1 | The drug life cycle.

2.1 | Study Selection

Original studies published in English or Dutch assessing the effects of DHPCs issued within the European Union on knowledge/awareness, self-reported behaviour, objectively measured behaviour, or health outcomes were included. Studies assessing DHPCs for suspensions, recalls, and withdrawals were excluded. Possible duplicates were marked by the screening tool Rayyan and checked by a researcher (EdV) before removal [12]. First title and abstract screening and subsequent full publication screening were conducted independently by two researchers (EdV and RU) using Rayyan. Publications were excluded in the following order: do not concern DHPC, focus is not an effectiveness study, publication type being conference abstract/letter to the editor/commentary/review, country of DHPC being non-EU, language being other than English/Dutch, concerning DHPC issued before 2008, and/or duplicate outcomes (i.e., same outcomes presented in different studies).

2.2 | Data Extraction

Using a structured data extraction form in Research Electronic Data Capture (REDCap) [13], the following data were extracted: author, title, year, journal/ENCePP, issue number/ENCePP number, DHPC, date of DHPC, drug(s) mentioned in the DHPC (including co-drug in case of interaction), study period, type of study/study design (before-after/survey/other), statistical analyses used (descriptive/before-after/interrupted time series (ITS)), population studied, country where the study was performed, and key findings. For studies with clearly defined objectives, the corresponding outcomes were extracted. For studies without

clear objectives or addressing also research questions not related to the effect of a DHPC, only the outcomes related to the DHPC were extracted. When effects of multiple DHPCs were reported in one publication, multiple data extraction forms were created. Data extraction were conducted by one researcher (EdV) and all data were checked and discussed with a senior researcher (PM).

2.3 | Additional Data Extraction and Classification

The original or Dutch DHPCs related to the included studies were retrieved and used to extract information on the drug safety issue. This was done using a previously developed archive [14] and internet sources. If the DHPC could not be identified, we searched for a DHPC addressing the safety issue studied in another language or a report of the EMA discussing the safety issue and stating a DHPC was issued. The data extracted included information about the type of message, the target population, and the seriousness of the safety issue (see below). One DHPC could include multiple messages.

The type of message was classified as:

- Recommendation related to a change or restriction of indication or a new contraindication.
- Recommendation related to a drug–drug interaction.
- Recommendation related to a change in dosing or administration.
- Recommendation for additional monitoring.
- Be aware of an adverse event or risk without recommending specific actions
- Reminder SmPC.
- Other, such as new efficacy data and off-label use.

The target population refers to specific patients at risk.

The seriousness of the drug safety issue was classified as follows: death, life-threatening/(prolonged) hospital admission, (temporary/persistent) disability or incapacity/teratogenicity, or other [15]. DHPCs mentioning fatal cases would be categorised as death. As the distinction between life-threatening and (prolonged) hospital admission can not often be made, these categories were combined.

2.4 | Data Synthesis

Outcomes were subdivided in assessing: knowledge/awareness, self-reported behaviour (prescribing/monitoring), prescribing of medication (including dosage changes), monitoring, or adverse events/other health outcomes (including hospitalisation).

First, the extracted outcomes were classified as showing supportive, unsupportive, or unknown impact of the DHPC. For pre-post designs, a significant effect on a given outcome in the desired direction was considered supportive. When no significant effect was found or was not in the desired direction, the outcome was considered unsupportive. When outcomes were presented only descriptively or only after the DHPC was issued, this was classified as having unknown impact. In studies measuring knowledge/awareness or self-reported behaviour, the outcome was considered supportive when at least 80% of the study population reached the required knowledge/awareness or recommended behaviour (Data S3). Lower percentages were considered not supportive of the intended effect [16].

Next, a conceptual approach was used to determine whether the outcomes included in the studies were optimal for assessing proximal effects given the type of message (Figure 2). Knowledge/awareness of the communicated safety issue was considered as proximal outcome when the type of message was to be aware of a safety issue without recommending specific actions. Prescribing behaviour was considered as proximal outcome for messages concerning (contra)indication, interactions, or dosing changes. Similarly, monitoring behaviour was considered as proximal outcome for messages concerning additional monitoring. Self-reported behaviour was not included as proximal outcome, given the expected self-report bias [17, 18]. Finally, health outcomes were not considered as proximal outcome since they are not directly affected by the DHPC, but can of course be the ultimate intended outcome. Of note, each extracted outcome was linked to one type of the message. For example, when a DHPC would communicate a change in dosing and a monitoring advice, an outcome related to prescribed dosages would be linked to a 'recommendation to change dosing' message.

When a study reported multiple outcomes assessing, for example, the HCPs' knowledge of a safety issue, we combined these in a composite outcome to determine the impact of the message on knowledge. Also, when a specific outcome was measured in multiple countries within one study, a composite outcome was

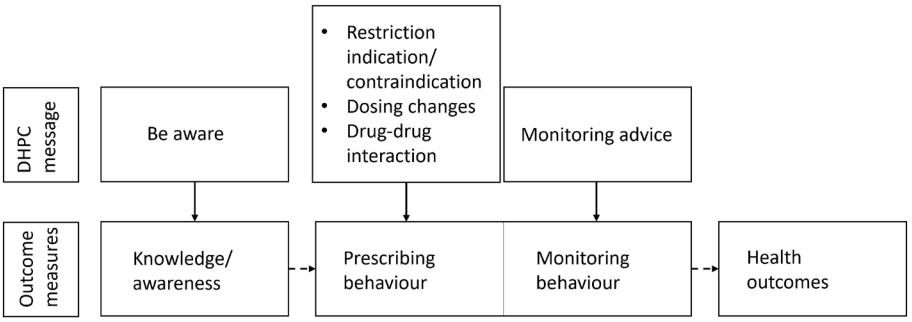

FIGURE 2 | Proximal and distal outcomes according to the type of message. Continuous arrow: Proximal outcome. Interrupted arrow: Distal outcome.

created (Data S3). For this, each reported outcome supporting the effectiveness was coded 1, and all others 0. The composite outcome was expressed as the proportion of supportive outcomes on a scale from 0 to 1.

The DHPC was used to classify the study population as being the targeted population or the non-targeted population. This usually refers to the patient population at risk. For example, when it was communicated that diclofenac was contraindicated for people with congenital heart failure, changes in diclofenac prescribing assessed in the entire patient population were classified as 'non-targeted population', whereas assessing this in people with congenital heart failure was classified as 'targeted population'. When assessing knowledge or self-reported behaviour, the target population may also refer to the HCPs. When this was assessed among all HCPs, including those that did not receive the DHPC, this was classified as 'non-targeted population'.

To determine the effect of the seriousness of the safety issue on the impact of the DHPC, the unit of analysis was the safety issue addressed. Therefore, we created an overall outcome per drug safety issue, calculating the mean (composite) outcome of all data extraction forms for the same drug safety issue. For this analysis, only studies were included that used a proximal outcome and focused on the targeted population.

2.5 | Risk of Bias

The quality of all studies, except survey studies, was assessed with the Quality Assessment Tool of the NIH for Before-After (Pre-Post) Studies With No Control Group [19]. The Cochrane Effective Practice and Organisation of Care (EPOC) standard criteria for interrupted time series were used in addition for those studies having multiple measurements before and after the intervention [20]. The first question: 'Was the intervention independent of other changes?' was not considered, since issuing a DHPC is by design not independent from other events. For the survey studies, the domain-based risk-of-bias tool for cross-sectional survey studies was used [21]. The quality of the studies was assessed independently by two researchers (E.d.V. and T.M.). Disagreements were resolved by mutual discussion and involvement of a third reviewer (P.D.) if not resolved.

2.6 | Analysis

The data were summarised showing the drug safety issue, seriousness, type of message, type of outcome, and (composite) outcomes in targeted and non-targeted populations. When similar outcomes were reported for targeted and non-targeted populations, they are presented as separate outcomes. The reported effects of the (composite) outcomes were classified as high (0.75–1), intermediate (0.74–0.25), or low (0.24–0). Chi-square tests were conducted to test whether the effect was influenced by (a) proximal outcomes or (b) the targeted populations. For these analyses, (composite) outcomes with an unknown effect were excluded. Chi-square tests were also used to test whether the effect was influenced by the seriousness of the drug safety issue. When numbers per cell were <5, Fisher exact tests were conducted.

One subgroup analysis was conducted to assess the impact of the targeted population, including only proximal outcomes. Another subgroup analysis was conducted assessing the impact of the targeted population, including only patient study populations, so excluding studies where HCPs were the study population. Also, subgroup analyses were conducted to assess the impact of the use of proximal outcomes or the targeted population, including only studies with limited or no bias. Two sensitivity analyses were performed to test the impact of using different cut-offs for the classification of the (composite) outcomes from high to low. First, using 0.80–1 (high), 0.20–0.79 (intermediate), and 0.19–0 (low) as cut-offs. Second, comparing; and 1 (full impact) to 0–0.99 (mixed/no impact). Finally, a subgroup analysis was conducted excluding studies for which it was unclear whether they studied a DHPC or other forms of national risk communication.

3 | Results

The screening of literature retrieved from Embase and Medline resulted in 58 relevant publications, and four were added due to snowballing (Figure 3).

3.1 | Data Summary—All Publications

The 81 identified publications (i.e., 60 scientific [Table 1] and 21 ENCePP [Data S4]) resulted in 86 data extraction forms linked to an individual DHPC.

The 86 data extraction forms addressed 134 messages, several of which were included in multiple studies (Table 1, Data S4, and Figure 4). Messages concerning changes or restrictions in indication or contraindication were studied most often ($n=51$), followed by be aware messages ($n=28$), drug–drug interaction ($n=17$), change in dosing ($n=15$), additional monitoring ($n=13$), SmPC reminder ($n=9$), and other ($n=1$).

Prescribing was the most common outcome measured (68 extraction forms), followed by knowledge (18 extraction forms), health outcomes (11 extraction forms), monitoring (6 extraction forms), and self-reported behaviour (4 extraction forms). For the majority of the extraction forms, outcomes were measured in the targeted population, with 19 extraction forms investigating both targeted and non-targeted populations, whereas 12 extraction forms only included a non-targeted population (Table 1, Data S4). Usually, either the study population was too broad by including HCPs in a knowledge assessment who had not received the DHPC [31] or including patients without a certain contraindication or risk factor [53, 57, 65, 80] or including drugs that were not contraindicated or recommended [40, 43].

The effects of 40 different DHPCs had been studied; 15 in both scientific and ENCePP publications, 16 in scientific only, and nine in ENCePP only. In 47 data extraction forms, the effects of 25 DHPCs were assessed in a single country, whereas in 39 data extraction forms the effects of 15 DHPCs were assessed in up to 12 countries. Often, more than one outcome was used to assess the effects of a DHPC (Table 1). The publications were published one to 11 years after the last DHPC had been sent, with a median

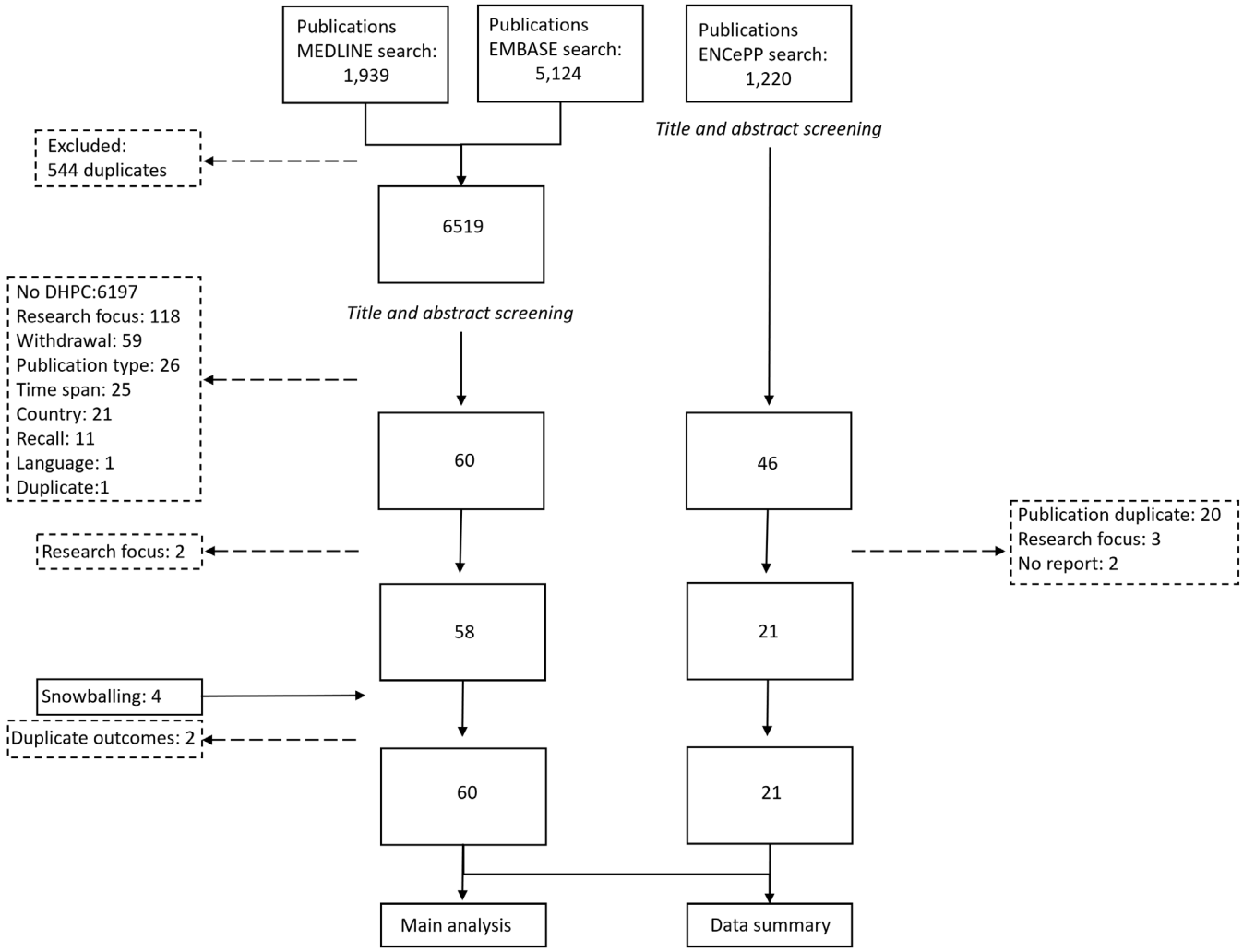

FIGURE 3 | Flowchart of the inclusion of publications. DHPC: Direct Healthcare Professional Communication; ENCePP: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

of 5 years. There was more time between the DHPC and the scientific publications than between the DHPC and the ENCePP publications; namely, a median of 6 versus 3 years.

The screening of ENCePP resulted in 21 relevant publications. However, for 13 of these, only a summary was publicly available. Therefore, the ENCePP publications were only used in the descriptive summary and not included in the main analysis.

3.2 | Outcomes—Analyses—Scientific Publications

3.2.1 | Outcome—Proximal Outcomes

The 60 scientific publications resulted in 65 data extraction forms evaluating 31 different DHPCs. Often multiple outcomes were presented, leading to a large number of composite outcomes for our main analyses. In total, 103 outcomes were linked to a specific message. Of these outcomes, 58 were classified as proximal outcomes for assessing the effect of the message. Prescribing was used 72 times, of which 53 were classified as proximal outcomes. In the other cases, outcomes were used to assess the effects of a be aware message (16 times) or a monitoring message (three times). Knowledge was used 13 times for a variety of messages and seldom to assess a be aware message (two times).

Overall, 30 of the 103 outcomes had a high impact score, 28 had an intermediate impact score, and 24 had a low impact score when looking at the proportion of the analyses in which a significant association between respectively 0.75–1, 0.25–0.74, and 0–0.24 was found. The impact was unknown for the remaining 21 outcomes. In several studies, the DHPC impact was measured in multiple countries. Some of those studies found a similar impact in all studied countries [5, 6, 31, 57, 62–67], whereas others found different impacts among the countries studied [31, 52–46]. Looking at the 82 outcomes with an impact score, there was no significant difference when comparing those with proximal versus other outcomes (Figure 5a, $p = 0.69$).

3.2.2 | Outcome—Target Population

Some studies included multiple study populations. In 12 cases, the outcome measures were studied in both the targeted and non-targeted populations, which resulted in 115 outcomes that were linked to a specific message and study population; 94 had a measurable impact, and 21 had an unknown impact. A targeted

TABLE 1 | Scientific publications overview showing the message, outcomes, and population.

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Antipsychotics: Risk of stroke and increased mortality							
Gallini [22]	f	2008	Be aware	Prescribing	0/2		France
Guthrie [23][b]	f	2009	Be aware	Prescribing	2/3		UK (Scotland)
Schulze (2013) [24]	f	2008	Be aware	Prescribing	0/2		Germany
Stocks [25][b]	f	2009, 2012	Be aware	Prescribing	1/4		United Kingdom
Sultana [26][b]	f	2009	Be aware	Prescribing	1/6		United Kingdom
Sultana [27][b]	f	2009	Be aware	Prescribing Health outcomes		3/4 2/4	United Kingdom and Italy[a]
Thomas [28]	f	2008	Be aware	Prescribing	1/1		United Kingdom
Tifratene [29]	f	2008	Be aware	Prescribing	0/1		France
McIlroy [30][b]	f	2009	Be aware	Prescribing	1/2		United Kingdom
Valproate: Risk of severe developmental disabilities (30%–40%) and/or congenital malformations (10%) during pregnancy							
De Vries [31][d]	d	2014	Indication/ contraindication	Knowledge	7/14	1/12	Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom[a]
Puig-Molto [32]	d	2014, 2018	Indication/ contraindication	Prescribing	0/2	2/2	Spain
Toussi [5]	d	2014	Indication/ contraindication	Knowledge	6/10		France, Germany, Spain, Sweden, and United Kingdom[a]
Toussi [6]	d	2014	Indication/ contraindication	**Prescribing** Health outcomes	4/42 ?/5		France, Germany GP, Germany neurologist/psychiatrist, Spain GP, Spain neurologist/ psychiatrist, Sweden, and United Kingdom[a]
Hughes [33]	d	2014, 2018	Indication/ contraindication	**Prescribing**		1/2	Ireland

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
KarlssonLind [34]	d	2014	Indication/ contraindication	**Prescribing**		1/3	Sweden
Degremont [35]	d	2014	Indication/ contraindication	**Prescribing**		3/4	France
Trimetazidine: Parkinson's disease							
Pinto [36]	d	2012	Indication/ contraindication	**Prescribing**		1/1	Portugal
Von Bredow [37]	d	2012	Indication/ contraindication	Knowledge **Prescribing**	0/3 ?/1		Bulgaria, Czech Republic, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Romania, Slovakia, and Spain
Ehlken [38]	d	2012	Indication/ contraindication	**Prescribing**	3/8		Hungary, Romania, France, and Spain[a]
(Es)citalopram: QT prolongation							
Godman [39][b]	h	2012	Be aware	Prescribing	1/1		UK (Scotland)
De Bardeci [40]	h	2011	Change in dosing Drug–drug SmPC reminder	**Prescribing** **Prescribing** **Prescribing** **Prescribing**	4/4 0/2 1/1	1/2	Germany, Switzerland, Austria, Belgium, and Hungary
Schächtele [41]	h	2011	Change in dosing Drug–drug	**Prescribing** **Prescribing**	2/2 0/4		Germany
Clopidogrel: Decreased efficacy in combination with PPIs							
Kruik-Kollöffel [42][c]	o	2009, 2010	Drug–drug	**Prescribing** **Prescribing**	2/6	0/2	The Netherlands
Thomas [28]	o	2009	Drug–drug	**Prescribing**	1/1		United Kingdom
Kruik-Kollöffel [43][c]	o	2009, 2010	Drug–drug	**Prescribing** **Prescribing**	5/6	0/2	The Netherlands

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Diclofenac: Arterial thrombosis							
De Vries [31][d]	h	2013	Indication/ contraindication	Knowledge Knowledge	17/18	4/8	Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom[a]
Morales [44][c]	h	2013	Indication/ contraindication	**Prescribing**		4/8	UK (Scotland), UK (England, Wales, and Northern-Ireland), Denmark, and the Netherlands[a]
Morales [45][c]	h	2013	Indication/ contraindication Be aware	**Prescribing** Prescribing	13/16 10/12		the Netherlands, Denmark, UK (without Scotland), and UK (Scotland)[a]
Domperidone: Cardiac risks							
Fife [46]	h	2014	Indication/ contraindication Change in dosing Drug–drug	Knowledge Knowledge Knowledge	3/15 6/15 0/5		Belgium, France, Germany, Spain, and United Kingdom[a]
Fife [46]	h	2014	Indication/ contraindication Change in dosing Drug–drug	**Prescribing** **Prescribing** **Prescribing**	11/24 5/5 4/10		Belgium, France, Germany, Spain, and United Kingdom[a]
Teeling [47]	h	2014	Indication/ contraindication Drug–drug	**Prescribing** **Prescribing**	0/3	0/1	Ireland
Aliskeren combined with ACEI and ARB; risk of hyperkalaemia, kidney damage or hypotension							
Rosich Martí [48]	d	2012	Drug–drug	**Prescribing** **Prescribing**	1/1	1/1	Spain
Angelow [49]	d	2012, 2014	Drug–drug	**Prescribing**	?/6		Germany
Sindahl [50][b]	d	2014	Drug–drug	**Prescribing**	1/1		Denmark

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Combined hormonal contraceptives: Known risk of venous thromboembolism							
De Vries [31][d]	h	2014	Be aware	**Knowledge** **Knowledge**	15/17	2/9	Croatia, Denmark, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, and United Kingdom[a]
Selke Krulichová [51]	h	2014	Be aware	Prescribing		0/4	Germany
Cyproterone acetate/ethinylestradiol (CPA/EE): Risk of venous and arterial thromboembolism							
Davis [52]	h	2013	SmPC reminder Indication/ contraindication Be aware	Knowledge Knowledge **Knowledge**	9/20 0/6 9/10		Czech Republic, the Netherlands, Spain, Austria, and France[a]
Penning-van Beest [53]	h	2013	Indication/ contraindication Drug–drug	**Prescribing** **Prescribing**	?/3	?/6	The Netherlands, United Kingdom, and Italy[a]
Flupirtine: Liver failure							
Kaplan [54]	f	2013	Change in dosing Indication/ contraindication Drug–drug	**Prescribing** **Prescribing** **Prescribing**	1/1 0/1 0/1		Germany
Kaplan [55]	f	2013	Indication/ contraindication Change in dosing Additional monitoring	**Prescribing** **Prescribing** **Monitoring**	0/4 1/1 0/1		Germany
Ivabradine: Cardiovascular risk							
De Vries [31][d]	d	2014	SmPC reminder	Knowledge Knowledge	9/20	1/3	Croatia, Denmark, Ireland, Italy, the Netherlands, Spain, Sweden, and United Kingdom[a]
Salem [56]	d	2014	SmPC reminder	**Prescribing**	3/5		France, Germany, Italy, Spain, and United Kingdom

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Mirabegron: Severe hypertension, including hypertensive crisis and cerebrovascular and cardiac events							
Heintjes [57]	h	2015	Indication/ contraindication	**Prescribing** **Prescribing**	0/4	1/4	the Netherlands, Spain, United Kingdom, and Finland[a]
Moriarty [58]	h	2015	Indication/ contraindication	**Prescribing**		1/1	UK (England)
Nimesulide: Hepatoxicity							
Pinto [59]	f	2011	Indication/ contraindication	**Prescribing** Health outcomes	1/1 0/1		Portugal
Franchi [60]	f	2012	Indication/ contraindication Change in dosing	Self-reported behaviour Self-reported behaviour	9/9 18/18		Italy, Portugal, Bulgaria, Poland, Czech Rep, Romania, Slovakia, Hungary, and Greece[a]
Pioglitazone: Bladder cancer							
Cid Ruzafa [61]	d	2011	Indication/ contraindication Be aware Additional monitoring	**Prescribing** Health outcomes Prescribing	?/2 ?/1 ?/1		Denmark
Hostenkamp [62]	d	2011	Indication/ contraindication	**Prescribing**		0/2	Denmark and Germany[a]
Rosiglitazone: Cardiovascular risk							
Leal [63][b]	h	2008	Indication/ contraindication	**Prescribing** **Prescribing**	3/5	?/2	United Kingdom
Herdeiro [64][b]	h	2008	Indication/ contraindication	**Prescribing**		1/1	Portugal

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Agomelatine: Hepatoxicity							
González-Bermejo [65]	f	2012, 2013	Additional monitoring Indication/ contraindication	Prescribing **Prescribing** **Prescribing**	0/2 0/1	0/1	Spain
Cabergoline/pergoline: Fibrotic heart valves							
Italiano [66]	h	2008	Indication/ contraindication	**Prescribing** Monitoring	?/2 ?/1		Italy
Cilostazol: Cardiovascular risk							
Castellsague [67][e]	d	2013	Indication/ contraindication Additional monitoring Drug–drug	Monitoring **Prescribing** Health outcomes **Monitoring** **Monitoring** **Prescribing**	?/4 ?/5 ?/5 ?/5 1/5 ?/13		United Kingdom, EpiChron Aragon Spain, SIDIAP Catalonia Spain, Sweden, and GePaRD Germany[a]
Codeine: Respiratory depression							
Hedenmalm [68]	f	2013	Indication/ contraindication	**Prescribing**	?/8		Spain, United Kingdom, France, and Germany[a]
Dabigatran: Risk of bleeding							
Nyeland [69]	f	2011	Additional monitoring Be aware	Prescribing Health outcomes	0/1 ?/1		Denmark
Fluoroquinolones (moxi-and levofloxacin): Liver failure and Steve Johnsons Syndrome							
Georgi [70]	f	2008, 2009, 2012	Be aware Indication/ contraindication	Prescribing **Prescribing**	3/3 3/3		Germany

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Hydrochloorthiazide: Skin cancer							
Pottegård [71]	d	2018	Be aware	Prescribing	?/3		Denmark
Hydroxyzine: Known risk of QT prolongation							
Morales [72][e]	d	2015	Indication/ contraindication	**Prescribing** **Prescribing**	5/8	3/8	UK (Scotland), UK (England), Denmark, and the Netherlands[a]
Intravenous iron-containing products Hypersensitivity reactions							
Nathell [73][e]	f	2013	Indication/ contraindication	Health outcomes		3/6	EEA countries
Midazolam injection: Overdose							
Flood [74][b]	f	2008	Change in dosing	Health outcomes Self-reported behaviour **Prescribing** Knowledge	1/1 1/1 3/5 0/1		UK (England)
NSAIDs: Narrowing artery resulting in foetal death, heart failure, kidney toxicity							
Araujo [75]	f	2008, 2009	SmPC reminder	**Prescribing**	1/1		France
Osteoporosis drugs: Jaw osteonecrosis, atypical fractures, and oesophageal cancer							
Hurtado Navarro [76][b]	d	2009	Be aware	Prescribing	1/2		Spain
PPIs: Fractures with prolonged use							
Sobel [77][b]	d	2012	Be aware	Prescribing Health outcomes	?/1 2/2		United Kingdom
Quinine: Overdose							
Acheampong [78][b]	f	2010	Change in dosing	**Prescribing** Health outcomes	1/2 ?/1		UK (England)

(Continues)

TABLE 1 | (Continued)

Author	Seriousness	Year safety communication	Type of message studied	Outcomes measured	Impact (*n*/# outcomes measured)		Countries
					Targeted population	Non-targeted population	
Strontium ranelate: Risk of myocardial infarction							
Berencsi [79][e]	h	2013/2014	Indication/ contraindication	**Prescribing**	14/32		Denmark, the Netherlands, Italy, Spain, and United Kingdom
Study summary (Outcomes—Analyses, Section 3.2)							
Total message-outcomes				*N* = 103			
Message-outcomes with impact score (Figure 5)					*N* = 69	*N* = 13	
Total outcomes with impact score for populations (Figure 5)					*N* = 69	*N* = 25	
Total proximal outcomes with impact score for populations (Figure 5)					*N* = 38	*N* = 18	
Total overall outcomes with impact score in target population (Figure 6)					*N* = 22		

Note: Seriousness: f, death; h, (prolonged) hospital admission; d, (temporary/persistent) disability or incapacity/teratogenicity; o, other. Impact: ?, unknown. Bold: Proximal outcomes.
[a]Studies measuring outcomes in different countries separately.
[b]Studies excluded from the subgroup analysis involving studies mentioning the DHPC.
[c]Studies used same data sources.
[d]Senior researcher PM involved in this study.
[e]Scientific publication also included in the ENCePP database.

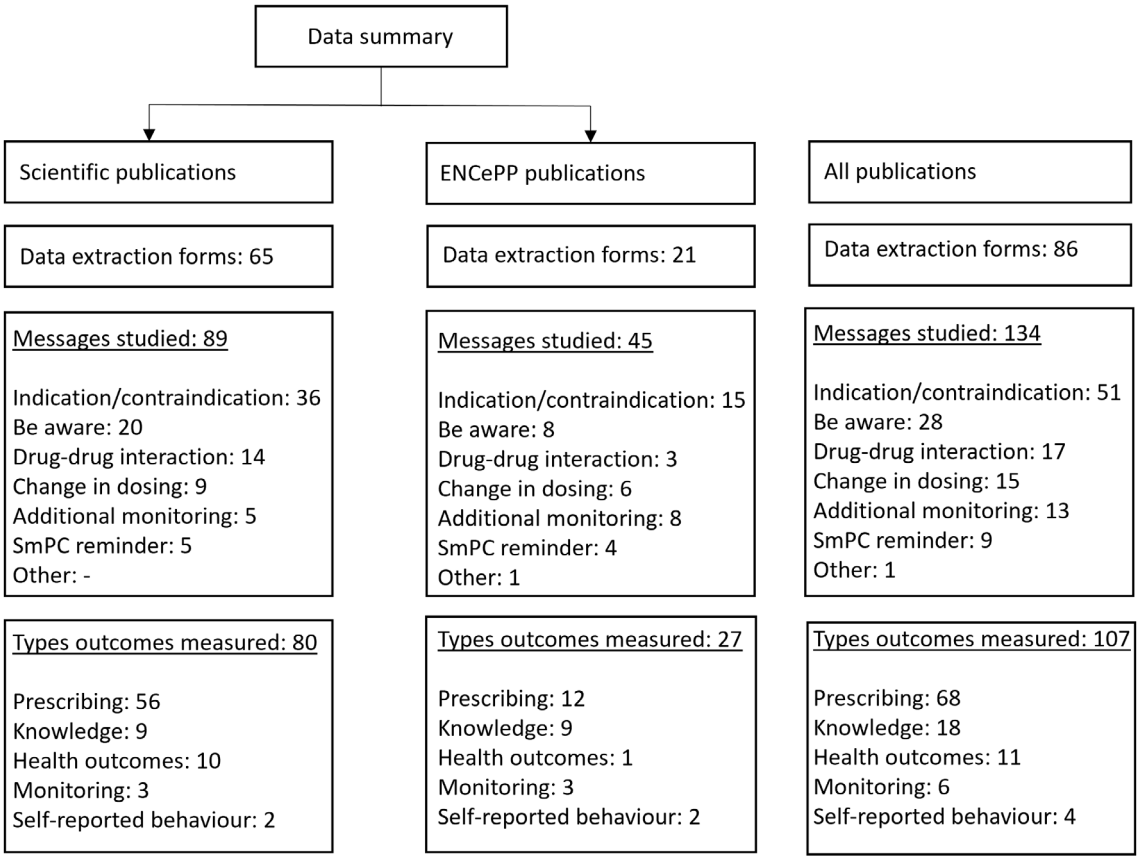

FIGURE 4 | Flowchart of data summary. ENCePP: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance.

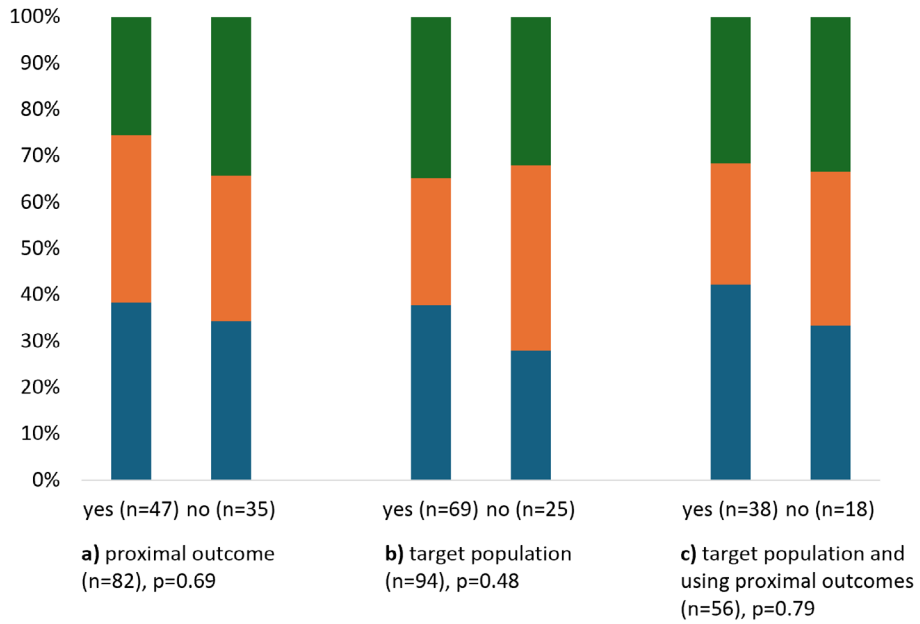

FIGURE 5 | Impact DHPC. DHPC: Direct Healthcare Professional Communication; DHPC impact high: 0.75–1 (blue); intermediate: 0.74–0.25 (orange); low: 0.24–0 (green). Statistical analysis: Chi-square test. To calculate the DHPC impact, each reported outcome supporting the effectiveness of a DHPC was coded 1, and all others 0. A composite outcome was then defined as the proportion of supportive outcomes divided by the total number of outcomes evaluating that DHPC message. Panels show Impact when analysing the effect of DHPCs on (a) proximal outcomes, in (b) target population, or when analyses are restricted to studies in (c) target population and using proximal outcomes.

population was used for 88 of these 115 outcomes (77%). Of the 94 outcomes with an impact score (i.e., 33 high, 29 intermediate, 32 low, as proportion of analyses with a significant association), 69 were measured in the targeted population. The use of the targeted population was not associated with the impact of the DHPCs, as shown in Figure 5b ($p = 0.48$). When looking only at

proximal outcomes, 56 of the 94 outcomes with an impact score remained. In the subgroup analysis including only proximal outcomes, there was also no influence of the use of the targeted population on the DHPC impact (Figure 5c, $p = 0.79$). Excluding studies where HCPs were the study population, 74 of the 94 outcomes with an impact score remained. Of those 74 outcomes, 53 outcomes were measured in the targeted population. In this subgroup analysis, the use of the targeted population also did not influence the impact of the DHPC (Data S5, $p = 0.61$).

3.2.3 | Outcome—Seriousness

Seriousness of the drug safety issues assessed at DHPC level ($n = 22$) was not associated with the overall impact, as measured by the proportion of analyses in which a significant association was found among studies using proximal outcomes in the targeted population (Figure 6, $p = 0.92$).

3.2.4 | Outcome—Sensitivity Analyses

Sensitivity analyses using categories with different cut-off values showed somewhat higher Chi-square values but again no significant differences (see Data S6 and S7). When including only the studies that specifically mentioned a DHPC, the results remained the same (Data S8).

3.3 | Quality Assessment

While (uncontrolled) before-after studies are an inherently weaker study design than interrupted time series [20, 81], the risk of bias was limited for many of the included before-after studies (Data S9). Not including a representative population, not performing statistical analysis providing p-values, and/or not measuring the outcome multiple times before and after the intervention were the main biases contributing to a higher risk of bias for these studies. The bias for most studies using interrupted time series was also limited (Data S10). Not specifying the shape/direction of the effect and/or not using appropriate interrupted time series techniques were the most commonly observed risks of bias. For survey studies, the risk of bias was introduced by not using a standard, validated, or piloted questionnaire (Data S11).

Subgroup analyses including before-after studies with a high risk of bias on no more than two criteria of the NIH assessment tool did not lead to other results (Data S12). Also, subgroup analyses including only studies with an interrupted time series design with a bias on no more than one of the EPOC criteria did not lead to other results (Data S13).

4 | Discussion

A total of 81 publications, consisting of 60 scientific publications and 21 publications from ENCePP, were identified that assessed the effects of European DHPCs issued after 2008. The distribution in low, intermediate, and high impact found for the DHPCs was similar for those studied with proximal outcomes and those who were not. The impact of DHPCs also did not differ between targeted and non-targeted populations. Finally, the seriousness of the drug safety issue was not associated with the impact of the DHPC. Overall, only 29% of the 103 outcomes evaluated in the literature showed high impact, a proportion of analyses with a significant association between 0.75 and 1, whereas 23% showed limited or no impact. Of note, for 20% the impact could not be assessed.

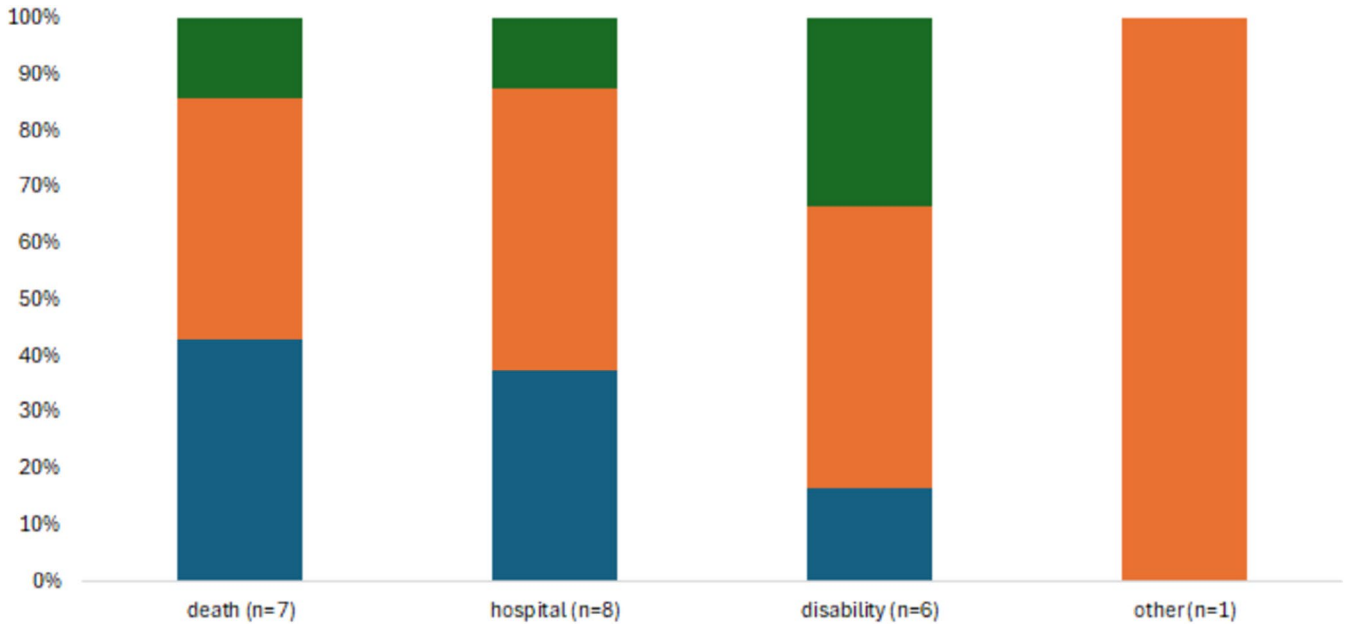

FIGURE 6 | Impact DHPC, according to the seriousness of the message in studies using proximal outcomes measured in the target population ($n = 22$, $p = 0.92$). DHPC: Direct Healthcare Professional Communication; DHPC impact high: 0.75–1 (blue); intermediate: 0.74–0.25 (orange); low: 0.24–0 (green). Statistical analysis: Fisher exact tests. To calculate the DHPC impact, each reported outcome supporting the effectiveness of a DHPC was coded 1, and all others 0. An overall outcome was made for all drug safety issues, averaging the separate composite outcomes for the same drug safety issue.

Although the majority of studies assessing DHPC effectiveness included proximal outcomes (56%) and measured those in targeted populations (70%), the impact found was mixed and not always sufficiently reported. This impact was not different for outcomes that were considered proximal to assess a certain type of message a DHPC can entail. For example, be aware messages were as likely or unlikely to lead to a change in prescribing as compared to messages regarding restricted indications or new contra-indications. In general, the lack of impact seen in many studies was not caused by the use of distal outcomes. Nonetheless, this review revealed that often a range of outcomes was included, making it difficult to draw a conclusion on whether there was an effect of the DHPC. The impact was often mixed, resulting in composite outcomes showing intermediate effects. Changing the cut-off to focus on studies showing full impact did not significantly change the findings. Furthermore, it has been mentioned that the evaluation period before and after the communication should not be too short for assessing changes in prescribing behaviour [24, 81]. A minimum number of data points, before and after interventions is not absolutely fixed, nor is the interval (e.g., monthly, quarterly or yearly) defined, but in order to include seasonality, an observation period of a year before and after is advised [20, 81]. This can lead to missing relevant changes. Some limitations of before-after studies can be addressed by an ITS design but only 33 out of the 56 (59%) before-after studies in this review used such a design. Previous reviews found a similar proportion of ITS designs: 45% and 67%, respectively, which suggests there is room for improvement still in these effectiveness studies [2, 3].

Previously, it has been noted that measuring the impact on prescribing can be difficult when drugs are not prescribed very often at baseline [62]. Sometimes the change is too small to be significant, or the change has started already before the DHPC was sent [65, 47–69]. In the latter case, one could argue that the communication was not effective, or it was redundant, but the goal of the communication was reached, namely safer prescribing. The process leading up to a DHPC already includes public information related to the agenda of the PRAC and other EMA communication, which may be picked up by other communication channels. Some drug safety issues are communicated through (social) media before they are communicated through a DHPC [14, 36]. This complicates the effect assessments and calls for ITS studies with prespecified shapes of intervention effects. This review showed that a lack of such a specification was a common bias in the ITS studies. Furthermore, other explanations for limited effect should be considered, which are related to the communication process. For a DHPC to have an impact, it should be received, understood, and accepted [8], all of which have been identified as suboptimal in previous research [31, 40, 43, 52, 46, 82–86].

Another important finding from our review was that the impact of DHPCs assessed in non-targeted populations was similar to that assessed in targeted populations. This indicates that a DHPC may have spillover effects in populations for whom it was not intended. It should be noted that this is not always a problem. For example, the use of valproate declined in a non-targeted population, being girls aged 0–14 years, which may be beneficial in preventing these girls from having to switch medication once they become of childbearing age [35]. Sometimes, however, effects are only seen in the non-targeted population [32, 40, 57]. On the other hand, there were also examples where more effects were seen in the targeted patient population [42, 43]. When knowledge was the outcome of interest, more effects were consistently seen for the targeted populations of HCPs [31].

In contrast to a previous finding, we could not confirm that the impact of a DHPC was influenced by the seriousness of the drug safety issue [11]. In the previous study, multiple interrupted time series were conducted in one country using the same methodology, whereas in this review, multiple study designs were included, conducted in a variety of settings and countries. Outcomes measured in multiple countries showed a similar impact in a few cases, but often the impact differed between countries [31, 62, 52–44]. This difference in impact could be due to differences in healthcare systems, reimbursement schemes, the availability of alternatives, but also due to different prescribing behaviour at baseline [62]. In addition, we did not take the magnitude of the effect found into account, whereas the other review did. Due to this heterogeneity and also the relatively small sample, it may become more difficult to assess whether the content of a message influenced the impact. More studies are needed, including a large number of DHPCs assessing the impact of the content of the message, including the seriousness of the safety issue, on its effects using the same methodology and setting.

4.1 | Implications

Recently, the European Guideline on good pharmacovigilance practices (GVP) Module XVI rev 3, including addendum II Methods for evaluating effectiveness of risk minimisation measures, has been published; it has been updated to provide more tools to assess effectiveness in terms of the delivery of a risk minimisation measure to the target audience, or with respect to measuring the intended knowledge and behavioural changes in the target audience and related health outcomes [7, 87]. Measurements are described for assessing the (1) dissemination coverage; (2) awareness, knowledge, and attitude; (3) behaviour changes; and (4) health outcomes. In the new GVP Module XVI, the DHPC is no longer considered a risk minimisation measure, although it can still guide how to evaluate the DHPC. We think that always assessing all outcomes is not meaningful. When a DHPC is intended to change behaviour, it is relevant to assess its impact at this level, preferably using one primary outcome. Qualitative research methods can provide additional insight, particularly when a DHPC appears ineffective and guidance is needed on additional risk minimisation measures. All studies identified in our review were of a quantitative nature. Our review illustrated that the impact of DHPCs issued since 2008 appears limited, even when this is assessed using proximal outcomes in the targeted population or in studies with low risk of bias. This implies that more effort should be put into improving the communication of new drug safety information. Currently, the DHPC is the only measure regulators can use to directly inform HCPs about new drug safety issues, and as such it cannot be dismissed. Improvements could be made to increase the applicability of the message for the target audience by providing clearer recommendations and information on clinical implications, but also by sending messages through various channels, including neutral senders and digital channels [86, 88–91]. Some

drug safety issues might be sent periodically, as was preferred by several hospital-based HCPs [90].

4.2 | Strengths and Limitations

Our systematic review provides an updated overview of European effectiveness studies of DHPCs sent from 2008 up to April 6, 2022. All steps of the literature review were performed by two researchers. Since the type of message a DHPC entails can be open for interpretation, two researchers were also involved in this classification. The included studies were assessed for bias and subgroup analyses showed that the results did not change when including only studies with limited or no bias. The impact of other bias thresholds was not assessed.

A limitation is that we did not look at the size of the impact per outcome. As pointed out by Morales et al. 'it can be challenging to determine whether a regulatory action is considered successful when no established thresholds exist' [44]. Given the large number of studies presenting multiple outcomes that were not likely to be independent (e.g., multiple outcomes assessing prescribing of related drugs), we calculated composite outcomes that average the reported effects per type of outcome. For these outcomes we applied arbitrary cut-offs to classify the impact as low, intermediate or high. The sensitivity analyses using other cut-offs did not significantly change our findings. Some DHPCs were studied multiple times by different studies. We have excluded two studies that presented data that were also included in other included studies. Regarding prescribing, the outcome of interest usually is prescribing behaviour but this was often assessed with dispensing data, which may not capture all changes in prescribing.

5 | Conclusion

Only a minority of the DHPCs issued after 2008 in Europe showed an impact in all or most (> 75%) of all assessments of DHPC effects on studied outcomes, even when proximal outcomes were used and the targeted population was included. Many studies assessed multiple outcomes instead of one primary outcome, often resulting in mixed findings. Furthermore, the impact of DHPCs was not significantly influenced by the seriousness of the drug safety issues. Efforts are needed to improve the communication of drug safety issues.

5.1 | Plain Language Summary

Direct Healthcare Professional Communications (DHPCs) are a tool used by regulators to inform healthcare professionals about new important drug safety issues and aims to minimise the risks of the issue at hand. The effect of DHPCs has shown to be variable. However, how this is measured has been variable as well. This systematic review investigates the impact of DHPCs, when this is measured in the population at risk using outcomes most optimal to measure direct effects. DHPC effectiveness studies were identified from databases EMBASE and MEDLINE. From the retrieved studies we collected; for example, the study outcomes used and their impact, and the type of drug safety message. The drug safety message was used to classify the outcomes. Similar outcomes looking at the same drug safety message within a study were combined resulting in a score ranging from 0 to 1. A total of 60 studies were included with a total of 115 outcome scores. DHPCs had a limited impact, with only 29% showing a high or full impact (i.e., a score of 0.75 to 1). The use of optimal outcomes to measure impact of DHPCs and restriction to the population at risk did not result in an improved observed impact.

Author Contributions

Study conception and design were performed by Esther de Vries, Petra Denig, and Peter G.M. Mol. 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.

Acknowledgements

R. Ultee helped with the data collection and preparation before analysis. We would also like to thank the constructive reviewers input that helped to shape our manuscript and structure our main messages.

Ethics Statement

The authors state that no ethical approval was needed.

Consent

The authors state that no patient consent was needed.

Conflicts of Interest

Petra Denig has 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.

Data Availability Statement

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

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.