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Factors influencing the implementation of medicine risk communications by healthcare professionals in clinical practice: A systematic review

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ABSTRACT

Background: Regulatory medicines risk communications aim to prevent patient harm through the dissemination of safety information to healthcare professionals (HCPs), patients, and the public. Evidence suggests that in addition to implementing the required changes, HCPs also respond to these communications through unintended and unwarranted actions and behaviours such as stopping medicine courses unnecessarily, and blanket actions spilling over to unintended patients' populations. Misunderstanding and mis-implementation of medicines risk communications could jeopardise patients' safety and clinical outcomes. Therefore, it is important to understand the determinants that affect HCPs responses to medicines risk communications. This systematic review aims to identify the factors that affect the implementation of risk communications by healthcare professionals.

Methods: Fifteen databases, including EMBASE, PubMed, Scopus, Web of science, CINAHL PLUS were searched in April–May 2018, and the search was updated again in June 2021 to identify studies reporting on factors influencing HCPs' uptake of medicine risk alerts. We used keywords such as *risk communication*, *safety update*, and *safety regulation*. Studies were excluded if they did not involve pharmacovigilance or patient safety alerts; or if they only focused on measuring HCPs' practice after alerts; or evaluating the effectiveness of risk minimisation measures without reporting on factors affecting HCPs' actions. Studies relating to occupational hazards, case reports, interventional studies, and studies not involving HCPs were also excluded. The Mixed Method Appraisal Tool (MMAT) was used to assess the quality of the included studies. A Narrative synthesis approach was undertaken using thematic analysis and concept mapping, followed by a critical reflection of the synthesis.

Results: Twenty-eight studies met our criteria and were included in the synthesis. We identified four themes summarising the factors influencing HCPs' implementation of risk communications. These include HCPs: knowledge of medicine alerts; perceptions of alerts; attitudes, and concerns regarding medicine alerts; and the self-reported impact of these alerts. Our concept mapping exercise identified key interactions between different stakeholders, and these interactions determine HCPs' implementation of medicine risk communications. These stakeholders comprise of alert developers, including the sources and senders of safety information, and the receivers of safety information including health care institutions, HCPs, patients and their carers.

Conclusions: Healthcare professionals are crucial to translating risk communication messages into clinical practice. However, if they have inadequate information about the content of the alert, and have inaccurate perceptions about the alert, they may not implement the required clinical changes as intended. Communication of medicine risk alerts does not always translate into improved patient care, due to a complex interaction between stakeholders involved in the creation and implementation of these alerts. These complex interactions should be the subject of future research efforts to understand the alert-implementation trajectory and identify the mediators for change and interventions to improve implementation.

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1. Introduction

Pharmacovigilance is defined by the World Health Organization[1,p42] as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem". The importance of this sector of clinical science arose from the fact that clinical trials, in the pre-marketing phase, test the efficacy and safety of medications for a short period of time and on a limited number of people (ranging from 500 to 5000).[2] These individuals usually underrepresent the actual population, where people from different age groups use different medications for long periods of time and have various life-styles, which might lead to the occurrence of unexpected adverse drug reactions.[2]

Pharmacovigilance involves four basic activities to minimise and manage the threats of adverse drug reactions. These included: Risk identification; assessment; mitigation; and communication.[3] Without an effective risk communication,[4] "the active dissemination of safety information for an intended audience",[5,p4], pharmacovigilance may fail to prevent patient harm.[4]

Pharmacovigilance centres have different strategies for communicating medication safety information. The European Medicine Agency (EMA) publishes safety information on their websites and requires direct health care professional communications (DHPC) to be sent through marketing authorisation holders.[5] The United States (US) Food and Drug Administration (FDA) used to communicate safety information through different methods, but this was standardised in 2010 to a single Drug Safety Communication (DSC). This is an FDA independent analysis and communication process for posting safety information on their website, aimed at healthcare professionals, the patients, and the public.[6] After the DSC is posted on the FDA website, it would then be sent out through different channels, such as listservs, MedWatch and healthcare professionals' newsletters.[6] In more serious situations, the FDA issues a black box warning [also known as box warning(BW)] on its website, medication package inserts, and the websites of the marketing authorisation holders.[7]

The success of a risk message is typically determined by the source sending it.[8] This includes the extent to which the recipient audience matches the sender's intended outcome.[8] Evaluating the impact of medication's safety communications is a way of determining the success of the communication and will also highlight the barriers for implementation.[9] Furthermore, measuring the impact of medications' safety communications on healthcare professionals' behaviours is only a surrogate for patient outcomes, and healthcare professionals' behaviour in response to these communications could compromise patient safety. Cisapride, for instance, has been linked to ventricular arrhythmia, resulting in fatalities and sudden death.[10,11] In response, the FDA issued a black box warning, a press release, and the manufacturer disseminated Dear Healthcare Professionals letters (Klausner cited by Smalley,[12] Smalley[12]). Based on an analysis of databases from three pharmacoepidemiologic sites, only minor changes were observed in contra-indicated prescribing that could lead to QT-prolongation complications.[12] Eventually, cisapride was voluntarily withdrawn from the market.[10,13,14] This led to a subsequent market shift[15] and raised concerns relating to potential safety issues associated with alternative agents.[15,16]

In another example, following the warning from EMA and the FDA related to the suicidal risk for children and adolescents taking selective serotonin reuptake inhibitors (SSRIs), Gibbons[17] reported a significant increase in the rates of suicide in children and adolescents in US and the Netherlands, which appeared to be parallel to the decrease in SSRIs prescriptions for patients within the same age group. Although this association was not found in another ecological time-series study conducted in the UK, the prescriptions of SSRI in youth younger than 18 years of age declined following the warning compared to the prescription rates before the warning.[18]

A number of systematic reviews explored the impact of regulatory related communications and actions. Piening[19] reviewed the literature published between 1996 and 2010 that measured the impact of direct healthcare professional communications, black box warnings and public health advisories on clinical behaviours. They identified a total of 50 articles more than half of which measured the impact associated with third generation oral contraceptives, SSRIs and cisapride. The intended impact on clinical practice was reported in 72% and 41% of studies using before/after analysis and interrupted time series analysis, respectively. Unintended effects were reported in 19 of the 22 studies relating to SSRIs and in 4 of the 5 studies relating to third-generation oral contraceptives.

Dusetzina[20] review focused on the impact of FDA regulatory actions on health outcomes and the utilisation of medication and healthcare services. Their search included studies published between 1990 and 2010. This search yielded a total of 49 studies relating to 16 medications or therapeutic groups. About one third of the medications covered were antidepressants. They found that advisory warnings regarding increasing laboratory or clinical warnings had a transient and modest effect on the intended actions, while mainly leading to a decreased use of medications. Spillover effects were also evident in their review. A common example was that associated with FDA communications in 2003–2004 regarding the use of antidepressants in children, where the authors also reported decreases in the utilisation of these medication in the adult population. However, while most studies evaluated databases (medical or pharmacy claims) to measure the impact of these communications, only 9 of the 49 studies explored healthcare providers' beliefs and attitudes regarding safety communications.

Three systematic reviews reported factors that could affect healthcare professionals' implementation of medicines' safety communications. The authors of one study reported communication factors that could affect the effectiveness of the dear healthcare professionals letters, including the clarity of the content and medium of delivery, as different healthcare professionals have different preferences.[21] It was also reported by Møllebæk[21] that healthcare professionals prefer safety communications from authoritative agencies rather than the pharmaceutical industry. However, this systematic review focused on including studies focusing on communication factors relating to the sender, message, the use of media, and recipient related factors.[21] However, the review did not explore environmental factors such as lack of resources.[22] The second systematic review identified reasons for the unintended impact of safety communications, including the service receivers' (patients, their parents, or guardians) refusal to use the medicine of concern, liability concerns and perceiving that there is no risk or the risk is minimal.[23] However, it only included studies that reported unintended effects of the alerts.[23] Excluding studies that reported intended effects or studies that did not involve an unintended effect could have led to missing studies that reported on factors without reporting any type of alert-related impact. Dusetzina[20] provided insights on healthcare professionals' awareness and levels of agreements with medicines safety communications. They found that healthcare providers had high awareness of general safety communication, and less awareness of more specific recommendations, like antidepressants follow-up schedules.[20] The extent to which providers agreed with the content of risk messages varied from high, with messages relating to the use of over-the counter cough medications in children, to low in other cases, such as monitoring patients taking antiepileptic medications.[20] However, this systematic review focused only on US FDA related safety communications. Thus, factors that could be identified from other regulatory areas or knowledge and attitudes of healthcare professionals from different geographical arears were not captured.

Some of the outcomes of a risk communication could be related to changing knowledge,[24] perceptions or attitudes. At the same time, knowledge and attitudes could be barriers to implementing the intended outcomes.[22] With minimal information on causational reasons that could be related to the specific type of risk communication uptake,[23] it is important to identify the range of possible factors that could influence

the uptake of medicines risk communications by the targeted audiences. Understanding the factors that influence HCPs actions and responses to regulatory agencies (RAs) medicine risk communication could improve the effectiveness of risk communication and, ultimately, could enhance patients' safety and clinical outcomes. This systematic review aims to identify the factors that could influence HCPs' implementation of medication risk communication. We used a narrative synthesis approach, including two synthesis processes, thematic analysis and concept mapping using a theoretical framework. The results of the thematic analysis will be presented in this review.

2. Methodology

2.1. Systematic review registration

This is a systematic review as per the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Guideline (Supplement 1 & 2 PRISMA checklists).[25] The protocol of this review was PROSPERO registered (CRD42018116468).

2.2. Literature search and study selection

Search terms were developed based on concepts derived from the population, intervention, and outcome strategy (Table 1).[26] These terms were reviewed independently by another researcher and an information manager. The final search terms (Supplements 3–8) were adjusted per database requirements. MESH terms and alternative terms were used in PubMed and CINAHL PLUS, respectively.

The search was conducted between April and May 2018 including the following databases: AMED; EMBASE; Embase classic; Global Health; HMIC; International Pharmaceutical Abstracts; Health and Psychosocial Instruments; PsycEXTRA; PsycINFO; MIDIRS; OpenGrey; Web of science; PubMed; Scopus and CINAHL PLUS. AB and IB independently screened the titles and abstracts of all studies retrieved against the inclusion and exclusion criteria. Disagreements were resolved through discussion and providing the justification for including or excluding a certain study based on the inclusion and exclusion criteria.

A first update was conducted by AB between May–August 2019 using the same search strategy including the following databases: Web of science, PubMed; Scopus and CINAHL PLUS. No extra studies that meet the inclusion criteria were identified at this point.

A second update was conducted by AB in June 2021 using the same search strategy and the following databases PubMed; Scopus and CINAHL PLUS. One study was identified to meet the inclusion criteria. IB reviewed the study against the inclusion criteria and agreed on its inclusion.

The references of the included studies, and the references of relevant reviews (i.e., reviews focused on the impact of post-market drug safety communications) were also manually searched by AB.

Table 1
Population, outcome, intervention[26]

PICO	Criteria
Population	Healthcare professionals; type or rank of healthcare professionals was not prespecified.
Intervention	Medicines' risk-related regulatory communication.
Comparator	Not applicable
Outcome (with variation)	Factors that could possibly affect healthcare professionals' uptake and implantations of medicines' risk-related communications.

2.3. Inclusion & exclusion criteria

Studies were included if HCPs reported any possible factor(s) influencing their uptake of alerts. English Oxford Dictionaries was used to define factor[27] and uptake[28](Supplement 9). Studies that did not have an abstract written in either English or Arabic were excluded. This was to avoid translation biases, as the research team are fluent in both languages.

Studies that did not involve pharmacovigilance or patient safety regulatory agencies (RAs) were excluded. Studies were also excluded if they only measured HCPs' practice after alerts or only evaluated the effectiveness of risk minimisation measures. Studies related to occupational hazards, case reports, interventional studies, and studies not involving HCPs were also excluded. AB contacted authors of primary studies when the published information was insufficient to decide inclusion or exclusion. Additionally, AB contacted the authors of seven eligible abstracts, including an abstract of an article in Spanish, two conferences, two meetings, and two research letters, but none of the authors contacted could provide the English full text. Thus, these abstracts were excluded.

2.4. Data extraction

A data extraction form was developed to retrieve essential information. AB conducted the data extraction. Data from seven studies was independently extracted by NS. The two sets of extracted information were compared and differences were resolved, which were mainly related to the level of details to be included. Moreover, one heading of the data to be extracted appeared to be confusing. This was "targeted patient population", and it was changed to "targeted population from the alert" to reflect the aim of this heading.

Extracted information included the author and year of publication, country, name of the authoritative agency involved, medicine of concern and type of regulatory action, targeted population from the alert, study participants and settings, objectives of the study, method of data collection, method of data analysis, factors and processes identified as impacting implementation. The data extracted were utilised to inform the table of characteristics. However, it was not utilised in the analysis process as the analysis was conducted inductively.

The Anatomical Therapeutic Chemical (ATC) classification system[29] was utilised to code medicines and the Medical Dictionary for Regulatory Activities (MedDRA)[30] to code safety concerns. This information was reported in the table of self-reported impact in the supplementary materials.

2.5. Quality assessment

Quality assessment was conducted using the Mixed Method Appraisal Tool (MMAT) version 2018.[31] AB assessed the quality of all the included studies. IB and NU independently repeated the assessment of 9 and 7 studies respectively. Initial disagreements were resolved by discussions and by agreeing on the criteria to judge the items of MMAT. More details about this step are presented in Supplement 10. Full text articles were not excluded based on their quality assessment.

2.6. Data analysis

A narrative synthesis approach, involving four setps was used, based on the Economic and Social Research Council guidance.[32,33] This is a systematic approach to qualitatively synthesise data from various types of studies when meta-analyses are deemed unsuitable.[32,33] In contrast to narrative reviews, this approach provides new insights and supports decision-making, rather than solely summarising the included studies.[32]

2.6.1. Step 1: developing a theory

The first step, developing a theory, involves thinking about how

interventions work, why they work, and for whom they work.[33] The Theoretical Domain Framework (TDF) was used at a later stage of the synthesis to identify different factors. This framework integrates 128 theoretical constructs from 33 theories.[34] TDF's first version was refined and validated in 2012, resulting in a second version[35] that was used in this review. This version includes the following 14 domains: knowledge; skills; social/professional role; assumptions; beliefs about consequences; reinforcement; intentions; goals; memory; attention; environmental contexts and resources; social influences; emotions; and behavioural regulations.[35]

2.6.2. Step 2: preliminary synthesis

In the second step, preliminary synthesis, both tabulation and thematic analysis were employed since combining tools leads to a comprehensive description of studies compared to using only one tool.[33,36] While tabulation was initially used in this review to develop an initial description that eases the process of comparing the studies,[33,36] thematic analysis was also chosen because it could be flexibly applied across different study approaches.[37] As the included studies had heterogeneous participants, outcomes, settings, regulatory actions involved, and types of medicines, it was not possible to mathematically pool the data; therefore, the quantitative data was converted to qualitative at the data stage.[38] However, percentages and significance levels were sometimes presented for illustrations.

Using thematic analysis at this stage addresses the limitations of content analysis, the alternative tool for translating the data.[33] Contrary to content analysis, recurrences of a particular theme do not necessarily reflect its vitality. Furthermore, in content analysis, un-reported evidence is considered as unimportant.[39] However, thematic approaches have been criticised for lacking transparency.[39] To mitigate this, we followed Braun and Clarke's guidance.[37] The analysis process was completed by AB, and co-authors reviewed and confirmed the final product of the thematic analysis.

To facilitate coding, MAXQDA was used. The results sections (and open-ended questions in one study's discussion section) were read line by line and inductively coded. Components that were irrelevant to the review (e.g., patient interviews) were not coded. This resulted in 456 codes that were grouped into initial common themes. Within the knowledge theme, Knowledge levels were classified as high (70% or more), fair (50 to < 70%), or poor (knowledge level <50%).[40]

2.6.3. Step 3: concept mapping

The third step is to explore relationships within and across studies.[33] Exploring relationships between empirical studies in systematic reviews is challenging, and is further complicated by the heterogeneity of the data.[41] Therefore, an analytical framework is necessary to link the pieces of evidence.[41] Thus, concept mapping was employed. This tool visually explores the relationships among the extracted data and highlights concepts related to the review's questions.[33] The codes from the preliminary analysis were reviewed to identify the range of possible factors. The factors were then matched with TDF constructs, which were presented in a table and the behaviour change wheel.[35,42–44] The results of this will be presented in a separate paper. After that, the TDF table was reviewed to extract the sources of the factors. As a result, different sources of factors have been identified, including the source and sender of the alert, the HCPs themselves, the healthcare institutions, and the patients and their carers. A figure illustrating the sources of factors is presented in this systematic review. This step was conducted by AB, and the final product was reviewed and approved by the co-authors.

2.6.4. Step 4: critical reflection

This narrative approach includes a critical reflection on the synthesis process, which is represented in the limitations section.[33] Supplement 11 includes examples of the analysis process.

3. Results

3.1. Studies' characteristics

Twenty-eight full-text articles were included in this review[45–72] (Fig. 1 PRISMA[25]). Most of these studies (n = 19) were conducted in the US.[45–47,49–52,55,57,60–62,64,67–72] Two studies were part of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE), and were conducted in nine European countries.[56,63] A correction of de Vries[63] was recently published[73] and the information was updated in the table of characteristics. Four studies were qualitative[49,57,64,65] and 24 were quantitative.[45–48,50–56,58–63,66–72]Studies were conducted in different care settings with a range of 10–3625 participants, except for one cohort study that reported the number of patients for whom medicines were reviewed, but not the HCPs involved.[60] The most studied alert was issued by the FDA regarding antidepressants-associated suicidality in children and adolescents (n = 4)[45,46,57,66]. The characteristics of the included studies are presented in Table 2. Tabulation of the result sections of the included studies are presented in supplement 12.

3.2. Quality assessment

Qualitative studies scored 80%–100%[49,57,64,65] on the MMAT, while quantitative studies scored 20%–80%.[45–48,50–56,58–63,66–72] Lack of reporting was a main reason for quantitative studies not fulfilling the MMAT criteria.[45–48,50–55,61,66–69,71] The details of the studies' quality assessment are presented in Table 3.

3.3. Healthcare professionals' knowledge of medicine alerts

In total, this theme was identified from 22 studies.[45–47,49–54,56–61,63,64,66,67,69–71] Diverse areas of knowledge were reported regarding medicine alerts. The majority of studies (n = 19) explored HCPs' awareness of an alert's release.[45–47,49–54,56–59,61,66,67,69–71] However, only five studies assessed healthcare professionals' knowledge of the content of the alert.[49,57,58,61,71] In two studies, HCPs were evaluated with regard to their knowledge of an evolving medicine risk.[70,71] In one, the knowledge of a study that led to the regulatory decision that prompted the alert was evaluated.[51] Four studies reported HCPs' familiarity with tools used in medicine safety communications,[56,59,61,63] while only two studies reported HCPs' knowledge of the existence of the regulatory agency or its website.[59,64] One study did not investigate knowledge directly, yet a lack of knowledge was provided as a reason for physicians' nonadherence to boxed warnings.[60] In this study, the area of knowledge deficiency was not specified.[60]

Studies reported on knowledge using a variety of methods. Three studies were qualitative,[49,57,64] one was a cohort observational study,[60] and the rest were quantitative surveys.[45–47,50–54,56,58,59,61,63,66,67,69–71] Most studies (n = 14) investigated HCPs' knowledge in relation to one medicine or one medicine class,[45–47,49–54,57,66,67,69,70] while five studies involved more than one medicine[56,58,59,61,71] Fourteen studies reported the knowledge across one professional group,[45,47,49,51,53,60,61,63,64,66,67,69–71] while eight studies did so among at least two professional groups.[46,50,52,54,56–59] Knowledge was reported in most studies within a single country,[45–47,49–54,57–61,64,66,67,69–71] while two articles, relating to the same project, investigated knowledge across different countries.[56,63] Only two studies used a control medicine (a medicine without specific alerts, e.g., without a BW, at the time of the study).[61,71] None of the studies specified a cut-off point or a threshold for acceptable knowledge levels.

3.3.1. Healthcare professionals' knowledge of the release of an alert

In total, 13 studies reported physicians' awareness of alerts, resulting in 64 physician–alert combinations.[45,49,51–54,56,61,66,67,69–71] As a whole,

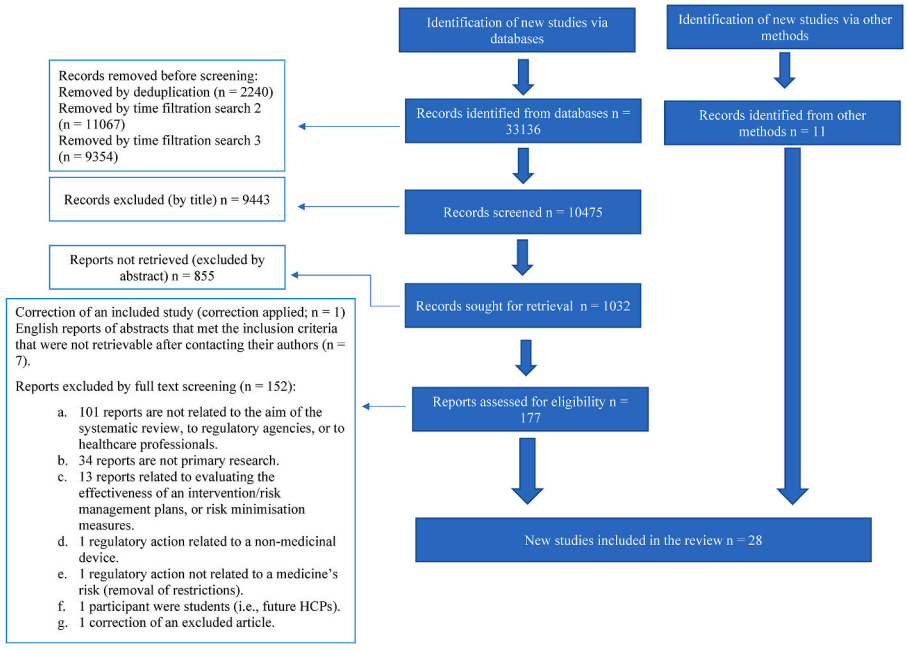

Fig. 1. PRISMA flowchart.

physicians possessed poor knowledge in 29 of the physicians–alert combinations, followed by high knowledge in 25 and fair knowledge in 10 of the combinations. In the included studies, the knowledge levels of primary care providers (PCPs), general practitioners (GPs), emergency physicians, and paediatricians were reported in at least two studies, while the rest were repeated once. Family medicine and internists were reported in two studies,[51,52] but in one study their knowledge percentage was presented collectively.[52]

Primary care providers demonstrated high levels of knowledge of alerts related to antidepressants[45] and of zolpidem and eszopiclone alerts.[49] Similarly, there was a high level of knowledge among general practitioners regarding alerts relating to OTC cough and cold medicines,[70] valproate (birth defects),[56] diclofenac,[56] contraceptives,[56] and ivabradine.[56] Interestingly, general practitioners also demonstrated a high level of knowledge regarding the FDA consideration to remove cough and cold active ingredients from medicines for children below the age of six years.[70] However, GPs possessed poor levels of knowledge of the alert related to vitamin D[54]. In addition, emergency medicine physicians possessed high levels of knowledge of two alerts, namely droperidol[67] and haloperidol,[61] and fair levels of knowledge of a metformin-related alert.[61] Among these physicians, there were poor levels of knowledge of alerts related to midazolam,[61] ciprofloxacin,[61] and naproxen.[61] Paediatricians also demonstrated high levels of knowledge regarding antidepressants alerts[66] and OTC cough and cold medicine alerts,[69] but poor knowledge regarding six alerts relating to vitamin D[54], midazolam,[61] ciprofloxacin,[61] haloperidol,[61] metformin,[61] and naproxen.[61] The details of the physicians' levels of knowledge are presented in Table 4.

Five studies described pharmacists' levels of knowledge with regard to alerts released on vitamin D[54], ceftriaxone and calcium interaction,[47] valproate (birth defects),[56] contraceptives,[56] diclofenac,[56] and ivabradine[56] (Fig. 2). Pharmacists demonstrated high levels of knowledge of five alerts relating to calcium and ceftriaxone interaction,[47] nelfinavir,[52] valproate,[56] diclofenac,[56] and contraceptives.[56] Meanwhile, fair levels of knowledge were demonstrated in the pharmacist groups with respect to alerts related to vitamin D[54] and ivabradine.[56]

One study reported the exact level of knowledge of nurse practitioners and nurse midwives in relation to the release of a nelfinavir-related alert.[52] The level of knowledge was high among this group of practitioners.[52]

There were three studies that provided the collective levels of knowledge of different health professional groups with regard to the release of an alert related to antidepressants in youth[46,57] and of an antipsychotics-related alert.[50] All three US-based studies found high levels of knowledge among the participants, with the first including paediatricians and paediatric nurses (only a minority of the sample were nurses),[57] the second involving physicians, physician assistants (also called physician associates), and nurses from different specialities,[46] and the third involving pharmacists (94% of the sample), physicians and nurses.[50] Two other studies revealed the range of knowledge levels among different groups of healthcare professionals in relation to the existence of different alerts.[58,59] One of these studies was conducted in the Netherlands and involved GPs, internists, community pharmacists, and hospital pharmacists.[59] A fair level of knowledge of etoricoxib, and a high level of knowledge of clopidogrel were reported in this study.[59] The second study was conducted in Ghana and included pharmacists, nurses, physician assistants, and doctors (the study did not specify the types of doctors). The study participants ranged in their level of knowledge from possessing poor knowledge of codeine alerts to possessing a fair knowledge of diclofenac alerts.[58]

3.3.2. *Healthcare professionals' knowledge of alerts' content*

Five studies assessed HCPs' knowledge[49,57,58,61,71] of the content of alerts. The researchers targeted physicians in most studies, but one study also examined nurses.[57] In one study, the authors reported that only a few knew about the recommendations of the alert. However, the study did not report specific percentages.[57] In the remaining studies, 40 profession–alert combinations were found. Among these combinations, one demonstrated high levels of knowledge, including of carbamazepine[71]; two showed fair levels of knowledge, including of zolpidem[49] and newer antiepileptics[71]; and 37 combinations reported poor levels of knowledge, including of valproate[71] (related to both birth defects and IQ changes), midazolam,[61] ciprofloxacin,[61] haloperidol,[61] metformin,[61] and naproxen.[61] Further details of the participants' knowledge of the content of alerts are presented in Table 5. One study (based in Ghana) reported the collective levels of knowledge of healthcare professionals in relation to the content of different alerts.[58] In this study, a high level of knowledge was observed regarding the content of alerts among those who knew about the release of the alerts.[58]

Table 2
Characteristics of the included studies.

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
Qualitative studies							
Richardson et al. (2007)[57]	US Washington state	US FDA	Black box warning. All antidepressant medicines, including all SSRIs, may cause suicidality risk.	Adolescents	Nine practices, of which five were in rural and four in urban settings. The total number of individuals participating were 35, of whom 32 were paediatricians and three paediatric nurse practitioners.	To examine the changes in depression treatment practices after the black-box warning	Focus groups' interview and an individual interview
Morrato et al. (2008)[64]	US	Not specified	Not specified	Not specified	Twenty physicians (specialty: psychiatry (n = 10) or internal medicine (n = 10))	To identify the range of drug safety information sources used most by US physicians; To explore their perceptions of the relative advantages and disadvantages of different scientific, drug company and third-party sources; To improve drug risk communications (based on physicians' recommendations)	Semi-structured interviews
Kesselheim et al. (2017)[49]	US	US FDA	Zolpidem: DSCs label changes due to impaired driving and alertness issues. Eszopiclone: FDA issued a DSC related to eszopiclone, reporting label changes because patients could experience diminished driving skills, memory and coordination.	Men and women, but women were more likely to be affected by the risks with Zolpidem.	Ten physicians who practised primary care were listed as prescribers of zolpidem or eszopiclone. sometime between July 1, 2012 and June 30, 2013.	To evaluate physicians' awareness and understanding of emerging drug safety information related to zolpidem or eszopiclone	Semi-structured interviews
Barker et al. (2019)[65]	Canada	The study included different sources of quality-related events, including recalls and safety alerts from Health Canada.	Not specified	Not specified	15 community pharmacy managers (12 females); the participants were from different community pharmacies, including nine large corporates, two small banner chains, and four independent pharmacies.	To explore the barriers that might limit the use of patient safety information sources with community pharmacies	Semi-structured interviews
Quantitative nonrandomised studies (cohort study)							
Kloet et al. (2017)[60]	US	US FDA	No prespecified medication warnings. However, in-patients medications for boxed warnings were checked.	Not reported	The study involved reviewing medications of 393 general medicine and ICU patients (18 years and older) who were cared by physicians at an urban, academic medical centre.	To determine prescriber adherence rates to BWs in adult in-patients (they also sought to assess prescriber reasons for nonadherence and detect ADRs as a result of nonadherence.)	Prospective cohort quality improvement project
Quantitative descriptive studies (surveys)							
Reed et al. (1999)[55]	US	US FDA	FDA had reported 130 deaths in the US that may be related to patients'	The patients included in this study were all male with chest	94 paramedics	To explore whether paramedics and online physicians consider the use of	Survey

(*continued on next page*)

Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
			use of sildenafil in May 1998. Pfizer Pharmaceuticals distributed a letter to all emergency physicians alerting them to potentially severe drops in systemic blood pressure that may occur when patients prescribed sildenafil are administered nitrates.	pain, for whom base-station contact was required and for whom prehospital nitroglycerin was either requested or ordered.		sildenafil prior to ordering nitrate therapy in the prehospital setting (however, the objective of the survey, which is the part included in this systematic review, was not reported.)	
Richards et al. (2003)[67]	US	US FDA	A black box warning for droperidol was released by the Canadian Health Protection Branch. Concern was raised over potential prolongation of the QT-interval, torsade de points, and sudden death after administration of droperidol.	Not specified as it occurred with patients with no known risk factors. Also, the contraindication is specified for patients with known or suspected QT prolongation, including patients with congenital long QT syndrome. The extreme caution was related to patients who may be at risk of developing prolonged QT syndrome. Other risk factors may include age over 65 years, alcohol abuse and use of agents such as benzodiazepines, volatile anaesthetics and IV opiates.	506 emergency physicians (working in private/community n = 278 (55%); academic/ county n = 187 (37%) and health maintenance organisation n = 41 (8%) hospitals. Of the total number of participants, 124 (25%) practise in the inner city, 299 (59%) in urban and 83 (16%) in rural settings.	To determine if droperidol's use by emergency physicians has changed since the FDA warning	Web-based survey
Mazor et al. (2005)[62]	US	A sample of DDLs identified through the Medwatch website or direct contact with pharmaceutical companies	Not specified; Those were issued between 2000 and 2001.	Not specified	Ten primary care physicians (internists) were recruited to serve as raters.	To describe key characteristics of recent DDLs in terms of content, organisation and format, and to examine the extent to which these characteristics influenced physicians' perceptions of the importance of the information provided and the likelihood that they would change prescribing practices as a result.	The recruited physicians served as raters. Each physician rated each letter on eight items intended to assess the presentation of the information, the perceived importance of the information and whether the information would be likely to impact their prescribing behaviour. Letters were randomly ordered for each physician.
Habib et al. (2007)[68]	US	US FDA	Black box; Droperidol; Concerns raised for serious cardiac arrhythmias, secondary to QT prolongation.	Patients with postoperative nausea and vomiting (for the study).	A total of 295 physicians completed the survey; 176 (62%) of 282 practised in a private hospital and 106 (38%) of 282 in an academic institution. Two hundred fifty-seven (93%) of 277	To determine the practice of members of the Society of Ambulatory Anesthesia (SAMBA) in the management of postoperative nausea and vomiting (PONV) before and after the	Survey posted on the website

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
					respondents were attending anesthesiologists, 9 (3%) were fellows and 11 (4%) residents in training; 176 (87%) of 203 respondents practised in a surgery centre, 44 (22%) of 203 practised in an office practice, and 48 (24%) of 203 practised in a procedure facility or other location; 233 (81%) of 287 indicated that ambulatory surgery constitutes 50%–100% of their practice.	FDA black box warning on droperidol.	
Bhatia et al. (2008)[46]	Nebraska, US	US FDA	Black box warning; All antidepressant medicines, including all SSRIs, may cause suicidality risk.	Children and adolescents	605 family medicine clinicians with the following specialities: family medicine physicians, family medicine nurse practitioners, family medicine physician assistants, family medicine residents, general practice; 139 paediatric clinicians with the following specialities: paediatricians, paediatric nurse practitioners, paediatric physician assistants, developmental and behavioural; 122 psychiatric clinicians with the following specialities: general psychiatrists, child and adolescent psychiatrists, psychiatric nurse practitioners, psychiatric physician assistants, psychiatric residents; 739 clinicians practising in urban and 127 in rural settings	To determine the clinical implications of the FDA warning	Survey
Cheung et al. (2008)[66]	Canada	US FDA	Black box warning; All antidepressant medicines including all SSRIs may cause suicidality risk.	Children and adolescents.	670 paediatricians	To examine the impact of the FDA Black box warning on the practice of paediatricians in the management of children and adolescents with antidepressants	Mailed surveys
Cordero et al. (2008)[45]	South- West US	US FDA	Black box warning; All antidepressant medicines including all SSRIs may cause suicidality risk.	Children and adolescents less than 24 years of age	115 primary care providers working in medical centres affiliated medical schools or primary care clinics	To explore the accuracy of primary care providers' understanding of the FDA black box warning label for SSRI antidepressants for children and adolescents	Web-based survey
Fogler et al. (2009)[52]	US	US FDA	Nelfinavir mesylate; In 2007, the FDA and Pfizer Inc. announced the	Pregnant women in need of antiretroviral medicine	26 infectious disease physicians; 36 obstetrician/ gynaecologists; 29	To determine how widely the information has been disseminated and	Phone survey

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
			presence of a process-related impurity in nelfinavir mesylate, ethyl methanesulfonate, which was teratogenic, mutagenic and carcinogenic in animals.		primary care physicians (family/internal medicine); 5 other physicians; 18 nurse practitioners/certified nurse midwives; 7 pharmacists	how many clinicians had pregnant patients whose care was affected by the change in the recommendations	
Harder et al. (2009)[48]	Canada	US FDA and Health Canada	Ceftriaxone and calcium-containing solutions; Health Canada issued notice to hospitals.	Specific recommendation for patients under 10 weeks of age and another for patients older than 10 weeks of age.	152 pharmacists from nine provinces and one territory evenly divided between teaching or tertiary care and community or general hospitals where the participants commented that they represented paediatric hospitals	To assess the opinions and responses of pharmacists and their respective institutions regarding warnings of the calcium-ceftriaxone interaction	Online survey
Karpel et al. (2009)[51]	US	US FDA	Long-acting β-agonist (LABAs); Black box warning was placed by the FDA on all LABAs and products that contained the combination of inhaled-corticosteroids and LABAs, suggesting that LABAs are associated with increased mortality in asthmatic patients.	Asthmatic patients	1107, in total, consisted of the following: 429 pulmonologists, 395 allergists, 141 internists, 132 family physicians and 10 paediatricians; The setting for the entire sample was as the following: 64.4% were in private practice, 24.1% in academic practice, 4.8% in training programmes and 6.6% in other settings (i.e. clinic groups, military or hospitals).	To investigate physicians' knowledge of the black box warning for LABA	survey via e-mail
Shneker et al. (2009)[72]	US	US FDA	FDA issued an alert regarding antiepileptic drugs (AEDs) and suicidality (defined as suicidal ideation and behaviour).	Risk is higher in patients with epilepsy.	175 clinicians who treated patients with epilepsy	To understand neurology health practitioners' reaction to the FDA alert and explore how it may affect or change their clinical practices	E-mail survey
Garbutt et al. (2010)[69]	US	US FDA	Nationwide Public Health Advisory released about the use of over the counter (OTC) cough and cold medicines (including decongestants, anti-histamines and cough expectorants and suppressants) in children younger than two years of age (serious and life-threatening side effects) and older children (they only provide symptom relief and do not cure the cause of illness or reduce its duration).	Children younger than six years of age	105 community paediatricians	To determine paediatricians' attitudes towards and use of these products	Mailed survey
Saad et al. (2010)[50]	US	US FDA	Boxed warning about antipsychotic medicines and	Elderly patients with dementia	65 geriatric practitioners (pharmacists (94%)	To determine the influence of the FDA's boxed warning	Web-based survey

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
			cerebrovascular accidents.		physicians (3%) and nurses (3%) from different settings, including nursing home facilities, teaching, veterans affairs, clinical private practice, community hospital, university health care or other specialities, including neurology, psychiatry, hospice, geriatrics, internal medicine and family medicine	on the management of psychosis in elderly patients with dementia	
Yaghmai et al. (2010)[70]	US	US FDA	Nationwide Public Health Advisory released about the use of over the counter (OTC) cough and cold medicines (including decongestants, antihistamines, and cough expectorants and suppressants) in children younger than two years of age (serious and life-threatening side effects) and older children (they only provide symptom relief and do not cure the cause of illness or reduce its duration).	Children younger than six years of age	33 general paediatricians	To assess the effects of the FDA recommendations on parent counselling and prescribing practices of community paediatricians	Cross-sectional survey conducted by phone
Esterly et al. (2011)[47]	US	US FDA	Ceftriaxone and calcium containing solutions; FDA alert	In 2007: all patients. In 2009: patients older than 28 days were removed from the 2007 warning; however, the FDA mentioned their recommendation in terms of using both medicines subsequently in patients older than 28 days	Members of the Society of Infectious diseases pharmacists (SIDP) with a hospital practice site affiliation; 94 responses were included in the analysis. From those, 11% described their roles as administration, 78% as clinical and 54% reported their professional role as antibiotic stewardship pharmacists. 77% of the respondents reported a university affiliation.	To quantify the impact of the FDA warning on healthcare institutions	Survey was distributed in a paper form in a national meeting. A link to the online survey was also e-mailed to the members of the Society of Infectious Diseases Pharmacists.
Théophile et al. (2011)[54]	France	French Medicines Agency	The manufacturer, at the request of the French Medicines Agency ((DDL) the AFSSAPS, placed a press release. Also, an e-mail with a link to the press release and the DDL was sent to the subscribers of the AFSSAPS mailing list. Malaise in neonates and infants caused a safety concern related to an incorrect method of	Neonates and infants	The participants included paediatricians (n = 45), GPs (n = 255), and pharmacists (n = 92).	To assess the effectiveness of such DDL and collect the opinions of healthcare professionals on the best way to provide them with information	Mailed survey

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
			medicine administration and to a pipette not adapted for neonates. These malaises occurred immediately after the administration of two brands of an oral solution of vitamin D, the first alone and the second in combination with vitamins A, E and C.				
Piening et al. (2012)[59]	Netherlands.	Lareb = Netherlands Pharmacovigilance Centre; MEB = Dutch Medicines Evaluation Board	Rimonabant (depression risk); Moxifloxacin (hepatoxicity, skin reactions); Clopidogrel (Proton pump inhibitor interaction); etoricoxib (hypertension)	Not specified	Total 1141 healthcare professionals, including 233 general practitioners, 410 internists, 223 community pharmacists and 175 hospital pharmacists	To explore healthcare providers' experiences and their preferences for risk communication of safety issues of medicines, comparing the views of GPs, internists and community and hospital pharmacists	Mailed survey
Bell et al. (2013)[71]	US	US FDA	FDA safety warnings for antiepileptics included (1) Suicidal thoughts with 11 antiepileptics. (2) High risk of birth defects in offsprings of mothers receiving Divalproex (valproate semisodium). (3) Cognitive impairments in offspring of mothers receiving Divalproex. Only preliminary findings were reported in the drug product insert. (4) Risks of hypersensitivity reactions related to carbamazepine use were associated with the HLA-B*1502 haplotype marker, which is more common in patients of Asian descent. This study also included a control question: neurologists were asked whether they knew that lacosamide did not have 'black box' safety warnings.	Patients using antiepileptics. Two of the risks were raised for pregnant women. One of the risks was raised for patients of Asian descent.	505 neurologists	To evaluate the knowledge of the US neurologists of recent antiepileptics warnings, their sources of medicine safety information and whether they incorporate this safety information into their practices	Survey sent by e-mail
Flood et al. (2014)[53]	UK	National patient safety agency (NPSA)	A rapid response report, released by the NPSA, indicated that adult patients were being	Not specified	100 gastroenterology clinicians	To evaluate potential reductions in risks associated with midazolam injection, a sedating medicine,	Online survey

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
			overdosed with high-strength midazolam injection when used for conscious sedation.			following a UK National Patient Safety Alert	
Sabblah et al. (2016)[58]	Ghana	Ghana Food and Drugs Authority (FDA)	Azithromycin (cardiovascular risks); risks with the use of codeine for analgesia in children and adolescents; diclofenac (risk of cardiovascular events); paracetamol (risk of severe skin reactions); incidents reported of therapeutic ineffectiveness and restrictions on the use of ketoconazole due to severe liver injury, adrenal gland problems and drug interactions. All were issued in 2013 by Ghana Food and Drugs Authority (FDA).	Children and adolescents for codeine related risks; not specified for other letters	913 health workers, who included 597 (65.39%) pharmacists, 136 (14.90%) doctors, 95 (10.40%) nurses and 85 (9.31%) physician assistants	To assess the effectiveness and relevance of DHP letters as an effective risk minimisation tool and seek opinions of health workers about the most effective way of communicating safety information	Structured questionnaire
Smollin et al. (2016)[61]	California, US	US FDA	Black box warning was associated with five medicines: (1) ciprofloxacin (increased risk of tendonitis and tendon rupture; it should be avoided in patients with a history of myasthenia gravis). (2) Midazolam IV (respiratory depression and respiratory arrest, especially when used for sedation in noncritical care settings. (3) Naproxen (increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke. Increased risk of serious gastrointestinal adverse events). (4) Haloperidol (increased mortality in elderly patients with dementia-related psychosis. (5) Metformin (Lactic acidosis is a rare but serious complication.)	Ciprofloxacin to avoid in patients with a history of myasthenia gravis; haloperidol in elderly patients with dementia. Not specific for the other warnings.	81 physicians, including 50 emergency medicine physicians and 31 paediatricians; 16 of them were in their first postgraduate (PG) year, 20 in the second year, 16 in the third year, 5 in the fourth year and 24 were attending fellows.	To assess physicians' awareness and knowledge of boxed warnings (black box warnings); To gain a better understanding from where physicians obtain information regarding serious adverse medicine reactions for commonly prescribed medicines	Survey distributed via e-mail

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Table 2 (*continued*)

Author (Year)	Country	Authoritative agency (medicines/drugs regulatory agencies)	Medicine type and regulatory safety action	Subject of risk communication	Sample description	Study aim and objectives	Data collection method or methodology
de Vries et al. 2017[63]	SCOPE project: Norway, Sweden, Denmark, Ireland, UK, Spain, Italy, Netherlands and Croatia	National competent authorities	Not specified	Not specified	1766 general practitioners (25 from Denmark, 847 from Spain, 85 from Croatia, 144 from Ireland, 183 from Italy, 72 from Netherlands, 105 from Norway, 108 from Sweden and 197 from UK); Of the 1766, 1551 were community-based, 39 hospital-based and 32 practised in other settings.	To assess healthcare professionals' awareness and preferences regarding risk communications	Survey
de Vries et al. 2018[56]	SCOPE project: nine European countries (Croatia, Denmark, Ireland, Italy, Netherland, Norway, Spain, Sweden and the UK)	National competent authorities	Distribution of DHPC (direct healthcare professionals communication); Combined hormonal contraceptives (2014): Risk of VTE; Diclofenac (2013): Risk of cardiovascular events; Valproate (2014): Risk of teratogenicity; Ivabradine (2014): Risk of cardiovascular events.	Diclofenac patients with ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure.	3288 participants; of them, 54% were GPs, 40% pharmacists and 7% cardiologists. Their country-wise was as follows: (General practitioners: Croatia 85; Denmark 25; Ireland 144; Italy 183; Netherlands 72; Norway 105; Spain 847 Sweden 108; UK 197); (Cardiologists*: Croatia 4; Denmark 7; Ireland 5; Italy 63; Netherlands 17; Norway 40; Spain 56 Sweden 15; UK 15); (Pharmacists*: Croatia 104; Denmark 35; Ireland 281; Italy 104; Netherlands 64; Norway 381; Spain 13; Sweden not available; UK 318).	To assess and compare the familiarity of GPs, cardiologists, and pharmacists with DHPCs as communication tools, their awareness of specific drug safety issues and the sources through which they had become aware of the specific issues	Cross-sectional web-based survey

AFSSAPS: Agence Française de Sécurité Sanitaire des Produits de Santé (the French Medicines Agency); DDL: Dear Doctor Letter; ED: Emergency Department; FDA: Food and Drug Administration; NPSA: National Patient Safety Agency; SCOPE: Strengthening Collaboration for Operating Pharmacovigilance in Europe; SSRI: Selective Serotonin Reuptake Inhibitor; UK: United Kingdom; US: United States; * based on published correction of de Vries (2018) published in de Vries (2020).[73]

3.3.3. *Other knowledge areas*

Other knowledge areas included healthcare professionals' knowledge of the existence of the regulatory agency,[59,64] the tools that they used,[56,59,61,63] and their awareness of the research that led to the regulatory decision.[51] The majority of participants in the Netherlands-based quantitative survey were aware of the Dutch Medicines Evaluation Board (MEB).[59] However, all general internists (n = 10) participating in the qualitative US-based study were not aware of the US FDA free email alert service regarding new medicine warnings.[64] Healthcare professionals' familiarity with DHPCs was reported in three studies, two of which were related to the same project across different European countries,[56,63] and the third was conducted in the Netherlands.[59] A high level of DHPCs' familiarity was observed among the participants in the three studies.[56,59,63] Similarly, general practitioners from different European countries possessed high levels of awareness of the national competent authorities' communications, and fair levels of awareness of educational materials.[63] Only one study of those reporting HCPs' familiarity with alert communication tools was conducted in the United States.[61] In this study, physicians (emergency medicine physicians and paediatricians with different levels of training) showed a high level of awareness of the concept of US FDA BW.[61] Furthermore, a high level of knowledge of the Salmeterol Multicenter Asthma Research Trial (SMART), a study reported by the authors as leading to the US FDA LABA BW, was noted among physicians (pulmonologists, allergists, internists, family medicine, and paediatricians; a difference in sample sizes was reported, ranging from 10 paediatricians to 429 pulmonologists).[51]

3.3.4. *Demographic characteristics associated with healthcare professionals' level of knowledge*

Different studies explored demographic associations with healthcare professionals' levels of knowledge. Eight of these studies focused on healthcare professionals' knowledge of the existence of an alert. Studies investigated different demographic characteristics including professional groups,[52,58,59] settings,[50] years of training,[61] specialities,[51,61] the number of patients treated in practice,[52,71] and the sources for obtaining general information on the safety of medicines.[71] Professional groups that were reported to have significantly increased levels of knowledge included nurses (higher knowledge in at least one of the six alerts relating to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole),[58] pharmacists (in alerts related to rimonabant, moxifloxacin, and clopidogrel),[59] and primary care HCPs, including GPs and community pharmacists with the etoricoxib-related alert.[59] On the other hand, with regard to the nelfinavir-related alert, the lowest level of knowledge was observed among obstetricians, who demonstrated almost half of the levels of knowledge of all other groups collectively.[52]

Two studies identified a significant association between knowledge and speciality,[51,61] and one with the level of training.[61] In the first, pulmonologists and allergists possessed a greater level of knowledge related to the LABA alert than did primary care providers.[51] In the

Table 3
Quality assessment of the included studies.[31]

Qualitative studies (MMAT, 2018)								
Reference	Screening question 1: Clear research question	Screening question 2: Collected data allow to address the research question	Item 1: Qualitative approach appropriate to answer the research question	Item 2: Qualitative data collection method adequate to address the research question	Item 3: Findings adequately derived from data	Item 4: Interpretation of results sufficiently substantiated by data	Item 5: Coherence between qualitative data sources, collection, analysis and interpretation	Calculated score (%) (excluding the screening questions)
Kelsselheim 2017[49]	Yes	Yes	Yes	Could not be determined	Yes	Yes	Yes	80%
Richardson et al. 2007[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Morrato et al. (2008)[64]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Barker (2019)[65]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
Quantitative nonrandomised studies (MMAT, 2018)								
Reference	Screening question 1: Clear research question	Screening question 2: Collected data allow to address research question	Item 1: Participants representative of the target population	Item 2: Measurements appropriate regarding both outcome and intervention (or exposure)	Item 3: Complete outcome data	Item 4: Confounders accounted for in the design and analysis	Item 5: Intervention administered during the study period (or exposure occurred) as intended	Calculated score (%) (excluding the screening questions)
Kloet (2017)[60]	Yes	Yes	Could not be determined	Outcome: yes Exposure: yes	No. 26% of general medicine patients with box warning non-adherence were discharged before the pharmacists talked with physicians.	No	Yes	40%
Quantitative descriptive studies (MMAT, 2018)								
Reference	Screening question 1: Clear research question	Screening question 2: Collected data allow to address research question	Item 1: Sampling strategy relevant to address the research question	Item 2: Sample representative of the target population	Item 3: Measurements appropriateness	Item 4: Risk of nonresponse bias is low.	Item 5: Statistical analysis appropriate to answer the research question	Calculated score (%) (excluding the screening questions)
Bhatia (2008)[46]	Yes	Yes	Yes	Yes	Could not be determined; validity and reliability not reported	No; Response rate 57.5% of 1521; Difference in subpopulations	Yes; Did not mention if normally distributed or not to measure the mean	60%
Habib (2008)[68]	Yes	Yes	Yes	No	Could not be determined; Validity, reliability, pretesting of the questioner were not reported.	No; Response rate 25% of 1179	Yes	40%
Smollin (2016)[61]	Yes	Yes	Yes	Yes	Could not be determined; Validity and pretesting of the questioner were not reported.	Could not be determined; Response rate 41%; Difference in respondents' subgroups	Could not be determined; All included tests (mean, SD; T-test; ANOVA) would be appropriate if the data were normally distributed. This information was not reported.	40%
Sabblah (2016)[58]	Yes	Yes	Yes	Yes	Yes	Could not be determined; Response rate 83.15% of 1098;	Yes	80%

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Table 3 (*continued*)

						Difference in respondents' subgroups		
Yaghmai (2010)[70]	Yes	Yes	Could not be determined	Could not be determined	Could not be determined	Could not be determined; Response rate 71.7% of 46	Yes	20%
Bell (2013)[71]	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability, pretesting of the questioner were not reported.	No; Response rate 13.1% of 4627; Then, 100 were excluded because they did not meet the inclusion criteria.	Could not be determined; Not reported where ANOVA test was performed	40%
de Vries (2018)[56] Authors of this study reported that ethics approval was not considered necessary.	Yes	Yes	Yes	Yes	Yes	No. Response rate not reported; Total 3625 respondents, 377 of them were excluded because they were not from the targeted population. Excluded HCPs who were not familiar with DHPC from the assessment of awareness about safety issues, although HCPs could know the issue from another source. Difference in subpopulations	Yes	80%
Esterly (2011)[47]	Yes	Yes	No	Could not be determined	Could not be determined; Validity, reliability, and pretesting of the questioner were not reported.	Could not be determined; Response rate reflected the initial respondents before being excluded due to duplication in institutions.	Yes	20%
Fogler (2009)[52]	Yes	Yes	No	No	Could not be determined; Validity, reliability, and pretesting of the questioner were not reported.	No. All individuals approached agreed to participate; however, they only included individuals who called a hotline service within a certain year.	Yes	20%
Garbutt (2010)[69]	Yes	Yes	Yes	Yes	Could not be determined; Validity and reliability were not reported.	No; 53% of 197 (physicians, not patients); Matched respondents and non-respondents	Yes; Did not report if data were normally distributed or not to be judged for mean/median	60%
Piening (2012)[59]	Yes	Yes	Yes	Yes	Yes	No; Totally, 1141 from 3488 responded.	Could not be determined; Not clear which type of ANOVA test was performed; Not clear why Wilcoxon signed rank test was performed, although it is for paired data	60%
Richards (2003)[67]	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported.	No; Response rate 25% of 2000	No	40%
Saad (2010)[50]	Yes	Yes	Yes	No	Could not be determined; Validity, reliability and pretesting of	No; Response rate was not reported. Most respondents were pharmacists (61/65).	Yes	40%

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Table 3 (*continued*)

					the questioner were not reported.			
Shneker (2009)[72]	Yes	Yes	Yes	Yes	No; Did not assess for validity and reliability; Pretesting of the questioner was not reported.	No; Response rate 22% of 780	Yes; Correlation reported in the discussion but did not specify which test was performed . Did not report if data were normally distributed or not	60%
Mazor (2005)[62]	Yes	Yes	Could not be determined; No information about how physicians were chosen	Could not be determined	Yes	Could not be determined	Yes; Did not report if data were normally distributed or not to be judged for the mean; Average rating of the letters had classification for each result; however, the basis was not clear.	40%
de Vries (2017)[63]	Yes	Yes	Yes	Yes	Yes	Could not be determined; Differences among participants from different countries	Yes; Not reported if data were normally distributed (for the mean)	80%
Cheung (2008)[66]	Yes	Yes	Yes	Yes	Could not be determined; Validity and reliability were not reported. Variables for the reason of changes in prescribing practices were not clear.	No; Response rate 38% of 1748	Yes	60%
Reed (1999)[55]	Yes	Yes	Yes	No. The survey only included paramedics, although the observation part (not covered in this review) and the aim includes both paramedics and physicians.	Could not be determined Validity, reliability and pretesting of the questioner were not reported.	No; Response rate 47% of 200 paramedics.	Yes	20%
Theophile (2011)[54]	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported	No; Response rate for paediatricians: 31% of 145. Response rate for general practitioners 37% of 680; Response rate for pharmacists: 40% of 230	Yes	60%
Flood (2015)[53]	Yes	Yes	Yes	Could not be determined; Not clear why only gastroenterologists were targeted	Could not be determined; Overall, the study is valid as multiple different sources were used. Reliability was reported in one point in the study but not in the survey (which is the only part included in this review). Variables were clear. It was	Could not be determined; Response rate not reported; 100 gastroenterologists responded.	Yes [for the survey part only].	40%

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Table 3 (*continued*)

					not reported if the survey was pretested or not.			
Karpel (2009)[51]	Yes	Yes	Yes	Yes	Could not be determined; Validity, reliability and pretesting of the questioner were not reported.	No; Response rate was 9.9% of 11147. Difference in subgroups of population; Large differences with the paediatricians' groups, but they were not analysed independently.	Yes; For the Pearson X^2 test and the Fisher exact test, only reported that they used either test for relationships, but did not give details on where each test of the two was performed	60%
Harder (2009)[48]	Yes	Yes	Yes	Yes	Could not be determined; Reliability and pretesting of the survey were not reported.	Could not be determined; No response rate	Yes	60%
Cordero (2008)[45]	Yes	Yes	Yes. Although excluded primary care practitioners whose information were not available.	Yes.	Could not be determined. Validity, reliability, and pretesting of the questioner were not reported.	No; Response rate was 15.15% of 764. 74% of the respondents practised with medical centres affiliated with medical schools.	Yes	60%

second, attending physicians and fellows were more knowledgeable about medicines with or without BW than were residents.[61] In the same study, greater levels of knowledge were observed among the resident groups with increasing years of training.[61] One study found that most HCPs who reported being very familiar with the antipsychotics-related alert were practising in a nursing facility and in teaching hospital settings.[50] Furthermore, two studies reported that healthcare professionals' levels of knowledge increased as the number of patients treated in their practice increased.[52,71] In the case of the nelfinavir-related alert, awareness was significantly higher as the number of HIV-infected patients in participants' practice increased.[52] Similarly, being aware of antiepileptics-related alerts modestly increased as the number of epileptic patients treated each year increased.[71] In the same study, only specialist organisations as sources of obtaining general knowledge of the safety of medicines were associated with increased levels of knowledge of the release of an alert.[71] However, the type of practice, region, years of practice, and age of respondents were not associated with their knowledge of medicine safety issues.[71]

Only three studies reported significant associations or differences with HCPs' levels of knowledge of the content of alerts. One study reported that nurses were more likely to remember the content of the letters released by the Ghana FDA in 2013 (six letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole) compared to the other participating healthcare professionals.[58] As with the knowledge of the release of an alert, knowledge of the exact risk reported in five alerts related to antiepileptics increased only slightly with the increased number of epileptic patients treated each year.[71] Moreover, using specialist organisations as a general source of medicine safety information was associated with HCPs' increased knowledge of the exact risk of alerts.[71] However, the participants' type of practice, region of practice, years in practice, and age were not associated with their knowledge of the exact risk reported in the alerts related to antiepileptics.[71] The third study reported that there were no statistically significant differences between attending physicians and residents when identifying the content of a BW.[61] Furthermore, there was no statistically significant difference in residents' abilities to identify the content of the BW based on their years of training.[61]

Two studies reported significant associations or differences with healthcare professionals' familiarity with the tools used in communicating the alerts, and one study reported differences in terms of HCPs' familiarity with the regulatory agency.[59] In a study based in the Netherlands, the authors reported a significant difference when reporting the range of healthcare professionals' unfamiliarity with DHPCs, which was lowest among hospital pharmacists and highest among general practitioners.[59] In the same study, the authors reported that hospital and community pharmacists were more familiar with the Dutch Medicine Evaluation Board (knowing about it and visiting its website) than internists and general practitioners.[59]

In another survey that was distributed to HCPs in nine different European countries, pharmacists in Italy were found to be significantly more familiar with direct healthcare professional communications than were GPs from the same country.[56]

Only one study reported characteristics associated with HCPs' knowledge of a potential regulatory decision regarding the safety of medicine. In comparison with physicians who were not aware of the FDA's consideration to remove active ingredients from cough and cold products in children below the age of six years, physicians who were aware of the potential recall had significantly more years in practice.[70]

3.3.5. Possible factors affecting healthcare professionals' knowledge of medicine alerts

One factor possibly affecting healthcare professionals' knowledge is whether they took action in order to increase their knowledge, such as reading the alert. Although most HCPs in one study reported reading the antidepressants-related BW,[45] healthcare professionals reported different actions related to reading other alerts that they received, whether they read all of the alerts[59,64] or only those relevant to them.[59] Further action involved visiting the regulatory agency's website or using one of its services. Although some HCPs reported visiting the regulatory agency's website[59] or using one of its services,[64] the majority of

Table 4
Physicians' knowledge of the release of an alert.

Table 4: Physicians' knowledge of the release of an alert

First Author	Speciality	Medicine																			
		Zolpidem & Eszopiclone	Droperidol	Antidepressants	Nelfinavir Mesylate	LABA	OTC Cough & Cold	Vitamin D	Carbamazepine	Newer Antiepileptics	Valproate Birth Defects	Valproate IQ Changes[1]	Midazolam	Ciprofloxacin	Haloperidol	Metformin	Naproxen	Diclofenac	Contraceptives	Ivabradine
Kesselheim[49]	PCP	100%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Richards[67]	EP	-	91%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cheung[66]	Paediatricians	-	-	72%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Cordero[45]	PCP	-	-	96%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Fogler[52]	Infectious disease physician	-	-	-	80.8%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Obstetrician/gynae cologist	-	-	-	33.3%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Family/internal medicine	-	-	-	51.7%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Other physicians	-	-	-	60%	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Karpel[51]	Allergists	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Family physicians	-	-	-	-	93.2%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Internists	-	-	-	-	87.8%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	Pulmonologists	-	-	-	-	98.1%	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Garbutt[69]	Paediatricians	-	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-	-	-
Yaghmai[70]	GPs	-	-	-	-	-	100%	-	-	-	-	-	-	-	-	-	-	-	-	-
Théophile[54]	Paediatricians	-	-	-	-	-	-	49%	-	-	-	-	-	-	-	-	-	-	-	-
	GPs	-	-	-	-	-	-	48%	-	-	-	-	-	-	-	-	-	-	-	-
Bell[71]	Neurologists	-	-	-	-	-	-	-	81.2%	80.6%	79%	83.2%	-	-	-	-	-	-	-	-
Flood[53]	Gastroenterologists	-	-	-	-	-	-	-	-	-	-	-	63%	-	-	-	-	-	-	-
Smollin[61]	Emergency medicine	-	-	-	-	-	-	-	-	-	-	-	10%	40%	82%	50%	20%	-	-	-
	Paediatrics	-	-	-	-	-	-	-	-	-	-	-	16.1%	22.6%	38.7%	38.7%	32.2%	-	-	-
	PGY1	-	-	-	-	-	-	-	-	-	-	-	12.5%	25%	56.3%	43.8%	25%	-	-	-
	PGY2	-	-	-	-	-	-	-	-	-	-	-	10%	35%	60%	55%	30%	-	-	-
	PGY3	-	-	-	-	-	-	-	-	-	-	-	12.50%	12.5%	50%	43.8%	25%	-	-	-
	PGY4	-	-	-	-	-	-	-	-	-	-	-	20%	40%	80%	60%	0%	-	-	-
	Attending/fellow	-	-	-	-	-	-	-	-	-	-	-	12.5%	50%	83.3%	37.5%	25%	-	-	-
de Vries[56]	GPs	-	-	-	-	-	-	-	-	-	76%	-	-	-	-	-	-	96%	88%	70%
	Cardiologists	-	-	-	-	-	-	-	-	-	34%	-	-	-	-	-	-	79%	61%	91%

[1] At the time of the study the authors reported that the valproate product insert did not mention this specific risk, while it mentioned that there had been reports of developmental delay, autism, and/or autism spectrum disorders in children born to mothers who were exposed to valproate during pregnancy.

Smollin[61] classified participants in two ways, namely speciality and years of training.

PGY: Postgraduate Year.

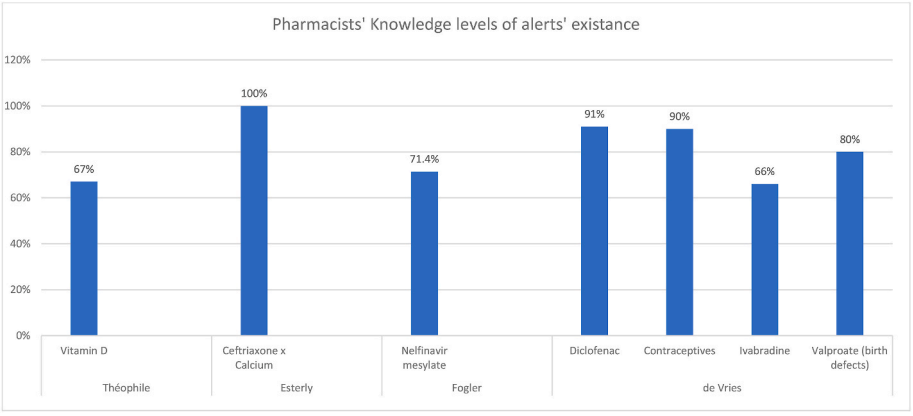

Fig. 2. Pharmacists' levels of knowledge of the release of an alert.

participants in one study had never visited the regulatory agency's website.[59] In addition, HCPs reported subscribing to journals as a means to keeping up to date about the safety of medicines.[64] However, not actively searching for information[65] and not reviewing the in-store website on a daily basis were also reported.[65] Healthcare professionals also reported using multiple sources for information confirmation[49] and for ensuring information quality (the latter reported by only one participant).[64]

The participants in the included studies reported using different sources to become aware of specific alerts, or sources they use generally to update their knowledge of the safety of medicines. The sources were divided into those related to regulatory agencies, pharmaceutical companies, medical sources, non-medical sources, and point-of-care sources. A sixth category was that of information reporting the mode of delivery without specifying the exact source. Table 6 includes details of these sources. However, some participants reported that they did not update their knowledge or did not have a method with which to update their knowledge.[61] Some HCPs also reported not using any source to obtain information about alerts.[58,64] Healthcare professionals' satisfaction with the current ways of delivering medicine safety information could also

Table 5
Healthcare professionals' knowledge of alerts' content.

Reference	Speciality /Professional Background	Medicine									
		Zolpidem	Carbamazepine	Newer Antiepileptics	Valproate Birth Defects	Valproate IQ Changes[1]	Midazolam	Ciprofloxacin	Haloperidol	Metformin	Naproxen
Kesselheim[49]	Physician	50%	-	-	-	-	-	-	-	-	-
Bell[71]	Physician	-	73.9%	60.2%	33.5%	48.9%	-	-	-	-	-
	Emergency medicine	-	-	-	-	-	6%	22%	4%	38%	12%
	Paediatrics	-	-	-	-	-	13%	10.3%	0%	13%	10.3%
	PGY1	-	-	-	-	-	0%	12.5%	0%	25%	6.3%
	PGY2	-	-	-	-	-	5%	15%	0%	30%	10%
	PGY3	-	-	-	-	-	12.5%	6.3%	0%	31.3%	12.5%
	PGY4	-	-	-	-	-	0%	0%	0%	40%	20%
Smollin[61]	Attending/fellow	-	-	-	-	-	12.5%	33.3%	8.3%	25%	12.5%

[1] At the time of the study the authors reported that the valproate product insert did not mention this specific risk, while it mentioned that there had been reports of developmental delay, autism, and/or autism spectrum disorders in children born to mothers who were exposed to valproate during pregnancy.

Smollin[61] classified participants in two ways, namely speciality and years of training.

PGY: Postgraduate Year.

influence their motivation to update their knowledge.[49,59] They also had different preferences regarding future alerts in terms of sources or senders[59,63–65] format,[54,63,65] content,[64,65,71] and mode of delivery.[49,54,58,59,63–65,71] These are presented in Supplement 13. Furthermore, different beliefs towards the sources of medicine safety information were expressed. These beliefs are presented in Table 7.

In addition to healthcare providers, healthcare institutions and managers may also play a role in ensuring that healthcare professionals receive information about the safety of medicines. Healthcare institutions and managers of community pharmacies reported providing their staff with such information.[47,48,65] Not permitting pharmaceutical company representatives in the workplace[49] and pharmacy managers filtering the information received[65] have also been reported. Only one study reported managers taking steps to ensure that staff were informed about the alert, which involved asking HCPs to sign after reading the information.[65]

Different barriers to healthcare professionals updating their information on the safety of medicines were identified. The information-seeking process was perceived to be time-consuming[49,59,65] and not enough time was available to search for and read updates related to the safety of medicines.[49,65] Workload and interruptions at work were other barriers to healthcare professionals searching for and reading medicine safety information.[65] Another barrier was that of overwhelming information, which was reported in two studies.[49,65] This included receiving information that is irrelevant to HCPs' practical setting but related to other practices,[65] as well as being overwhelmed by information related to medicines' regulatory aspects rather than specific information regarding the safety of medicines when using the website of a regulatory agency.[49] In one of these studies, a participant reported feeling inundated by the volume of emails received.[65] Healthcare professionals (community pharmacy managers) reported being overwhelmed by the number of sources and the need to combine information from different sources.[65] However, a physician in another study reported receiving excessive amounts of sources including journals, brochures and newsletters through the mail.[64] Although many of them were redundant, the participant felt that it was better to receive a large amount of information than not receive enough.[64]

In one study a participant expressed that they are either not receiving the information that they desire or they do not know how to access the information.[65] Similarly, two other studies reported difficulty in using regulatory agency websites.[49,64] Difficulty in using information systems and a need for guidance on how to access the information were also reported.[65] Time delays in receiving alerts[58,64] and the possibility that the alerts may not be seen by HCPs,[49,64] or that they might be mistakenly discarded by HCPs thinking that they are advertisements,[64] were also reported challenges.

3.4. Healthcare professionals' perceptions of alerts

HCPs' perceptions of alerts were identified in six studies.[45,47,48,55,57,72] Inaccuracies in perception were identified to be related to either the nature of the risk included in the alert[45,55,57,72] or the recommendations regarding the alert.[47,48] These inaccuracies were found at the individual level of healthcare professionals themselves or at the level of the healthcare institution in which they work (e.g. the hospital level). In all studies reporting perceptions at the level of healthcare professionals, perceptions were risk-related, while perceptions at the level of healthcare institutions were recommendation-related. Both types of perception-related inaccuracies are discussed in subsequent sections.

3.4.1. Inaccurate perceptions of risk

Inaccurate risk perceptions were identified in four studies.[45,55,57,72] Three of these studies involved physicians,[45,57,72] and one study involved paramedics.[55] Underestimation of the risk appeared in three studies. They included primary care providers who thought that there was no risk of suicidality or that the risk was low in comparison to the benefits of antidepressants.[57] The second was also related to the risk of suicidality, where physicians in open-ended survey answers indicated that suicide in epileptic patients was linked neither to antiepileptic medicines nor to epilepsy, but rather to comorbid psychiatric conditions[72]; the study also stated that suicide rates were low or not an issue in epileptic patients (although the risk involved suicidality).[72]

Table 6
Sources of specific and general knowledge of medicine alerts.

Category	Type of Source	Was a Source for Knowing about a Specific Alert	As a General Source to Obtain Information about Alerts
Related to regulatory agencies	US FDA website/MedWatch/Listserv[49,52,61,64,71]	✓	✓
	MEB website[59]	✓	✓
	Pharmacy regulatory authority website, Institute for Safe Medication Practices (ISMP) Canada sources[65]	–	✓
	Canada's Community Pharmacy Incident Reporting (CPhIR) system[65]	–	✓
	Health Canada[65]	–	✓
	Ghana FDA (letter)[58]	✓	✓
	National competent authority's information centre.[56]	✓	–
Related to pharmaceutical companies	Pharmaceutical representative[49,52,64,71]	✓	✓
	Drug company websites[49]	–	✓
	Mail from manufacturers[49]	–	✓
	Pharmacy inserts/product inserts/product labelling[49,64,71]	✓	✓
	DHCP[52,59,64]	✓	✓
	Drug advertisement[49]	–	✓
Related to medical sources	Specialist organisations/professional associations[56,58,71]	✓	✓
	Medical/health newspapers[49,64,69]	✓	✓
	Professional journals[49,56,59,64,69,71]	✓	✓
	Drug software (web-based/mobile applications)[49,52,58,61,64]	✓	✓
	CME or other educational programs[61,64,71]	–	✓
	Conferences[49]	–	✓
	Medical insurance companies[64]	–	✓
	Medical meetings[64]	–	✓
	Professional regulatory bodies/councils[58]	✓	–
	College website (no further information was provided)[65]	–	✓
Related to non-medical sources	Popular press (lay media, newsletters, news reports)[49,56,61,64,69]	✓	✓
	Social media[49]	–	✓
Point-of-care sources	Colleagues/peers[49,52,58,64,69,71]	✓	✓
	Formularies[49]	–	✓
	Clinical pharmacists[61]	–	✓
	Word of mouth[61]	–	✓
	Electronic medical records[64,49]	–	✓
	Prescribing alerts/pharmacy system alerts[64]	–	✓
	Company owning the community pharmacy[65]	–	✓
	Community pharmacy webpage/pharmacy intranet[65]	–	✓
	Database provider folder in the pharmacy's general email account[65]	–	✓
	Managers supplying the information to their staff[65]	–	✓
	Patients/parents[69]	✓	–
	Hospitals/healthcare facilities where HCPs practise[58,47]	✓	✓
Related to the mode of delivery	Internet services and internet-based resources[58,64,52,56]	✓	✓
	Email notifications/Listserv[61,52,65]	✓	✓
	Computer-aided[64]	–	✓
	Podcasts[61]	–	✓
	Journals (types of journals not specified)[61]	–	✓
	DHPCs[56]	✓	–
	Hard-copy letters[58]	✓	–
	Soft-copy letters[58]	✓	–

Paramedics in the third study stated that chest pain medicines administered to patients would not be affected by sildenafil.[55] In this study, however, it was not reported whether or not paramedics were aware of the release of the alert. Overestimation of the risk included in the alert was reported in one study, in which primary care providers inaccurately thought that patients had died from suicide in aggregated clinical trials related to antidepressants.[45]

3.4.2. *Inaccurate perceptions of recommendations*

Inaccurate perceptions of recommendations were identified in two studies, both of which were related to calcium and ceftriaxone interactions.[47,48] Both studies involved pharmacists describing their healthcare institutions' positions in relation to the alerts. One of these studies specified perceptions of the US FDA 2007 alert, which indicated that ceftriaxone and calcium IV solutions should not be administered within 48 h of each other, regardless of the patient's age.[47] This study reported the different forms of institutional interpretations of the alert, including both correct and inaccurate interpretations.[47] Examples of inaccurate interpretations included that ceftriaxone should never be used in neonates, and to avoid any form of calcium-containing products within 48 h of administering ceftriaxone to adults.[47] The second study addressed Health Canada's alert to hospitals involving the same issue but differing in the timeframe for separation depending on age (to avoid administration within five days for patients below 10 weeks of age, and to avoid administration of both products within 48 h of each other for all other ages).[48] Although both an accurate interpretation and no interpretation were reported, the alert was interpreted by most healthcare institutions as a relative contraindication, in which the benefits outweigh the risks in some situations.[48]

3.4.3. *Characteristics associated with inaccurate perceptions*

Only one of the six studies investigated characteristics associated with wrongful perceptions.[45] This study found that overestimation of the risk was associated with the participants' disagreement with the risk, in which those who were more likely to disagree with the release of the alert were more likely to perceive that death occurred within patients in aggregated clinical trials.[45] The same study reported that the length of a licence and experience was not associated with the likelihood of having a wrongful perception of the risk.[45]

3.4.4. *Facilitators of accurate perceptions of safety alerts*

Different factors that may contribute to optimising the perception of alerts were derived from four studies.[45,47,55,58] However, none of these

Table 7
Healthcare professionals' beliefs towards the sources of medicine alerts.

Source Category	Positive Beliefs	Negative Beliefs
Related to regulatory agencies	• MEB are knowledgeable about medicines[59] • Information from MEB is more trustworthy than information from pharmaceutical companies.[59] • FDA is reported to be much better than a colleague opinion.[64]	• The findings and recommendations of the FDA are controversial.[71] • FDA is biased towards the industry and it is a bought and sold group.[64]
Related to pharmaceutical companies	• Pharmaceutical companies provide trustworthy information[49] • Pharmaceutical companies are knowledgeable about medicines[59] • Believing that pharmaceutical companies would provide all of the information on safety issues associated with their products.[64] • Pharmaceutical companies' DHPCs are viewed more favourably than other pharmaceutical companies' sources[64]	• Pharmaceutical companies are not reliable due to potential bias and conflicts of interest[49] • The information from pharmaceutical companies is less trustworthy than that from MEB[59] • Perceived as being the least credible and biased.[64] • Information from pharmaceutical companies' representatives is viewed with scepticism[64] • Pharmaceutical companies may have limited targeted audiences based on medicine's indications and a physician's prescribing habits.[64]
Related to medical sources	• Online sources such as Medscape, Medline, Monthly Prescribing Reference, Epocrates, and DynaMed are considered reliable[49] • Academic sources (journals were given as an example) are considered the most trustworthy by healthcare professionals and are not directly impacted by financial interests[49]	• Physician Desk Reference was not trusted because it is developed by pharmaceutical companies[64] • Credibility of medical meetings was questioned because they are often sponsored by pharmaceutical companies[64] • Medical meetings were not perceived to be an efficient source of information because these meetings do not usually address safety-related issues[64]
Related to non-medical sources	• Medications' risk issues can be brought to the attention of HCPs through news reports[64] • News reports are believed to improve physician–patient dialogue[64]	• Information from popular press might reach the public before physicians — as the public becomes aware of risks first, there is concern that physicians will not have the time to read the resources and form an opinion on the issue before being asked by patients[64]
Point-of-care sources	–	• Pharmacy alert systems do not account for the whole clinical picture[64]
Only reported mode of delivery	• Computer-aided and online sources are considered timely and reliable.[64]	–

One study reported healthcare professionals' beliefs towards groups of sources in general, including (1) scientific sources (this included medical newsletters, medical journals, colleagues, and continuing medical education) are most credible and provide in-depth information, (2) third party sources (internet services, popular press, drug software/personal digital assistant, Physician Desk Reference, product labelling, US FDA, medical insurance companies electronic medical records/prescribing alerts) are considered to be fast, readily accessible electronically, and can be customised according to the physicians' needs; however, they have mixed credibility.[64]

studies assessed how those facilitators influenced healthcare professionals' understanding of the alerts. Facilitators were present at the level of the source of the alert (one study),[58] the level of the healthcare institution (two studies),[47,55] and the level of the healthcare professionals (one study).[45] A source-related facilitator involved writing letters in a language that would be easily understood by the healthcare provider.[58] This was demonstrated in one study in which most participants positively evaluated the language understandability of safety letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole sent by the Ghana FDA.[58] Two studies mentioned facilitators at the level of healthcare institutions. More than half of the participants in one study reported receiving a guideline on the management of chest pain in patients who take sildenafil, although the sender of this guideline was not specified.[55] The second study reported healthcare institutions' investment in employee hours to interpret the US FDA alert relating to ceftriaxone and calcium IV solution interactions, which for most participants ranged from 1 h to more than 100 employee hours.[47] Nevertheless, the nature of the activities undertaken by these healthcare institutions to interpret the alerts was not reported. One study reported the steps that were taken at the level of healthcare professionals to obtain an accurate understanding of the alert related to the risk of suicidality of antidepressants in youth.[45] These steps involved primary care providers reading, seeking information, further supervision, continuing education, and consultation.[45]

3.4.5. *Barriers to accurate perceptions of safety alerts*

Barriers to accurate perceptions of safety alerts were obtained from six studies.[50,58,62,65,71,72] Most of these barriers were source-related, specifically to alert creation (four studies).[58,62,71,72] The remaining barriers were related either to the development of guidelines (one study) or to time and workplace-related barriers (one study). Three studies included source-related barriers in terms of the formatting of alerts.[58,62,72] One of these studies reported primary care physicians' ratings of alerts issued between the years 2000 and 2001, which were identified through MedWatch (FDA) and pharmaceutical companies.[62] Some letters had deficiencies in the clarity of the writing, readability, and overall communication effectiveness.[62] Moreover, relevant information was not always apparent and it was reported that such information was obscured by less critical information.[62] In this study the use of special formatting was associated with higher ratings.[62] In the same study, the length of letters or the placement of key information was not associated with the ratings of letters. The effect of the letter content was not evaluated as the letters had similar content characteristics.[62] Similarly, a US-based study relating to suicidality associated with antiepileptics showed that physicians did not rate the clarity of the FDA alert highly.[72] In another study relating to the risk of suicidality with newer antiepileptics alerted by the US FDA, many neurologists revealed that suicidality is a vague concept.[71] In Ghana, however, only a few participants were not satisfied with the language used in the Ghana FDA's 2013 letters related to azithromycin, codeine, diclofenac, paracetamol, and ketoconazole.[58] A barrier related to the development of guidelines was identified in one study.[50] In this study, most of the geriatric practitioners indicated that there was a need to develop guidelines in response to the FDA BW regarding the use of antipsychotics in patients with dementia.[50] A lack of guidance was reported in the same study as a reason for not considering the alert in clinicians' practice.[50] One study identified multiple tasks in the workplace and time constraints as obstacles to assessing and reflecting on medicines' safety information.[65]

3.5. *Healthcare professionals' attitudes and concerns regarding medicine alerts*

The majority of studies reported healthcare professionals' attitudes towards alerts' placement (i.e. issuing of the alert)[49,51,67–70] or content.[48,57,59,62,71]

3.5.1. Mixed attitudes towards the placement of alerts

Studies that investigated the attitudes of HCPs towards placing an alert focused on the FDA's US-based alerts.[49,51,67–70] Three of these alerts were BW (two related to droperidol[67,68] and one to LABA[51]), two were nationwide public health advisories (both related to OTC cough and cold medicines[69,70]), and one was related to DSC label changes, which involved the hypnotic medicines zolpidem and eszopiclone.[49] All of these studies investigated physicians' attitudes towards the placement of the alert.[49,51,67–70]

Noticeably, studies that reported that most of their participants had positive attitudes towards the placement of an alert involved non-BW alerts. These studies were related to DSC label changes regarding hypnotic medicines,[49] as well as the nationwide public health advisory concerned with OTC cough and cold medicines.[69,70] On the other hand, nearly half of the participants of two studies reported negative attitudes towards the placement of the alert. These studies involved droperidol[67] and LABA's[51] FDA BWs. Only one study reported that the majority of its participants had negative attitudes towards the placement of the alert, which involved droperidol's BW.[68]

3.5.2. Mixed attitudes towards the content of alerts

Two studies reported healthcare professionals' attitudes towards the importance of medicine safety information.[59,62] However, individual studies reported on HCPs' attitudes towards the recommendations of an alert,[57] the importance of knowing the details of an alert,[71] and their attitudes towards following those recommendations.[48]

Healthcare professionals from the Netherlands, including physicians and pharmacists,[59] and physicians from the US[62] had positive attitudes towards the importance of medicine safety information both generally[59] and within specific letters[62] respectively. However, negative attitudes were reported among US-based healthcare professionals (mostly physicians and a few nurses) towards antidepressants' BW recommendations.[57] Similarly, negative attitudes were reported among US-based physicians regarding the importance of knowing the exact risk of both suicidality with newer antiepileptics and birth defects with valproate (Divalproex).[71] Negative attitudes towards the need to strictly adhere to Health Canada's alert regarding calcium and ceftriaxone interaction were also reported by almost half of participating pharmacists who were based in Canada.[48] In the same study, most of those who had or would have a direct role in the institution's position regarding the alert disagreed with strictly following the recommendation.[48]

3.5.3. Healthcare professionals' concerns regarding medicine safety communications

Healthcare professionals' concerns were identified in eight studies.[45,48,49,53,57,67,68,72] Six of these studies involved the US FDA,[45,49,57,67,68,72] one involved Health Canada,[48] and one involved the UK's National Patient Safety Agency.[53] Concerns were expressed in four studies involving physicians,[45,53,67,68] one including pharmacists,[48] one including clinicians who treat epilepsy,[72] and one involving both physicians (the majority) and nurses.[57]

The areas of concern included malpractice[45] and media attention[57] regarding antidepressants' BW, as well as liability with antidepressants' BW,[57] antiepileptics alerts,[72] and droperidol BW.[68] Patient-related concerns were also expressed including patient risk,[45] patient compliance,[72] poor patient experience and/or outcomes,[53] and patient dependence on the medicine of concern (although this was not the risk reported in the alert).[49] Losing the medicine from the market was another concern reported by healthcare professionals.[67] Other areas of concern were either not specified[48] or were general (such as concerns surrounding adverse events[45] and negative impacts[72]).

3.5.6. Characteristics associated with healthcare professionals' attitudes and concerns

This subtheme was only identified in two studies relating to healthcare professionals' attitudes towards the placement of the alert[51] and the content of alerts.[59] In the first study, primary care providers had significantly higher agreement with the placement of the US FDA LABA BW than did other specialists.[51] The authors of the second study found that most healthcare professionals appeared to have a positive attitude towards the importance of safety information. However, the hospital pharmacists in the study had a higher appreciation of the importance of safety information compared to GPs.[59]

3.5.7. Reported explanations for healthcare professionals' attitudes and concerns

Two studies provided explanations for healthcare professionals' attitudes towards the alerts,[49,57] and one of them clarified the nature of healthcare professionals concern in relation to the alert.[57] Having a positive attitude towards the placement of a hypnotics' alert was attributed by the authors to the participants' reluctance to prescribe these medicines, and the fact that the alerts supported their arguments against using them.[49] However, having a negative attitude towards the US FDA's antidepressants' BW was justified by different reasons including: a lack of space (the study did not specify space as being physical or temporal); the recommended frequencies not being acceptable to patients and their families; the participants feeling uncomfortable about recommending additional follow-up visits while not knowing their additional value; and concerns surrounding reimbursement as some participants suggested that they could see two to three patients with acute conditions in the time it takes to see one depressed youth (this study was conducted within the United States healthcare system).[57] Healthcare professionals in one study explained their liability-related concerns surrounding the US FDA antidepressants' BW stating that most use of antidepressants in youth is off-label, with no clear guidelines being available to treat depression in this patient group.[57]

3.6. Self-reported impact of alerts

Different forms of self-reported impact were highlighted in the included studies. These included HCPs' actions in response to the alert, whether to take no action,[45–47,50,51,54,57,58,66,68–70,72] take the intended action,[46,54,55,60,69–71] change their practice in a certain way,[45,46,50,51,57–59,66–69,71,72] or increase referrals.[45,46,57,66] Moreover, some physicians preferred to reduce the frequency of prescribing the medicine of concern[46,47,57,67,70] or stop prescribing it.[46,57,66–70] It also appeared that alerts could influence the choice of medicine to be used.[66–68] For example, about half of providers in a qualitative study stated that as a result of the alert, they now only use fluoxetine to avoid using other antidepressants off-label in young patients.[57] Spillover effects were also reported in two studies.[47,51] In one of these studies, a spillover effect was reported more with primary care providers than with specialists ($p < 0.001$) in LABA prescribing in COPD.[51] The effect of alerts upon the medicine of concern, such as its formulary availability in at least one healthcare institution,[47,48,67,68] and HCPs' opinions on its utility following the alert[67] were also reported. In studies related to the use of antipsychotics in dementia patients,[50] as well as the use of OTC cough and cold medicines in children,[69,70] the authors investigated the use of supportive or non-pharmacological measures. However, two studies did not compare the use before and after the alert.[50,70] Possible impacts on HCPs were seen in different studies, such as amongst primary care providers indicating that they might provide a follow-up in coordination with a psychologist,[57] and amongst primary care physicians (internists) stating that they would likely change their practice in response to most of the letters that they rated.[62] Interestingly, HCPs reported that alerts affected service recipients' (patients, family members, or carers) willingness to use the medicine of concern,[45,46,66] as well as affecting healthcare institutions' policies and protocols.[47,48,55,68] Details of the different types of self-reported impact, in accordance with the type of medicine and the safety concern involved that were investigated by the authors of the included studies, are presented in Supplement 14.

Reasons for never prescribing droperidol in one study included medico-legal considerations; the medicine of concern not being available; believing that other medicines are more effective; and considering that droperidol is a dangerous medicine.[68] In another study, physicians who observed activation, including aggressive behaviour or agitation, ($p < 0.001$) or any side effects reported in the FDA alert regarding antidepressants ($p < 0.001$) stopped treatment more than those who did not observe activation or any of the alert's side effects.[66] Pharmacy managers in a qualitative study reported a range of barriers, including source overload, content overload, a lack of information relevance, source system complexity, and a lack of time, which had affected their ability to access, filter, read, reflect and act on the safety information, despite their intention to use this information in their practice.[65]

3.7. Concept mapping

The narrative synthesis approach used in this systematic review involves utilising a theoretical framework to identify and characterise factors affecting HCPs' implementation. The result of this step of the synthesis is reported in a separate review. Key players identified from this step to interact and affect HCPs' implementation of risk alerts included the developers (the sources and senders) of the safety information and the receivers of safety information [healthcare institutions (e.g., hospitals), the healthcare professionals' themselves, and the patients and their carers). Fig. 3 represents the conceptual mapping of all the possible factors relating to the key players. The developers' factors relate to the senders, channels used to deliver alerts (e.g., failure or delays in alerts' delivery and patient access to information before HCPs, and the effectiveness of medium used to deliver the alert) and the messages (e.g., clarity and formatting). Healthcare professionals' factors included knowledge of alerts' existence and content, their knowledge of how to implement the recommendations, action planning and goals toward the implementation, their judgments and opinions, trust, and the influence of colleagues among each other. External factors relate to healthcare institutions (medicine of concern or alternatives availability, policies, position and interpretations of the alerts, availability of resources and staff education), and patients or carers (demands related to medicine use).

4. Discussion

4.1. Summary of the results

This systematic review explored different factors that could influence HCPs' uptake of alerts. Knowledge of alerts was the most frequently investigated factor at different levels, including HCPs' awareness of the alert release, their knowledge regarding the content of the alert, as well as their knowledge of regulatory agencies, and the tools used by them to disseminate emerging information about the safety of medicines. Possible factors that could affect HCPs' knowledge included their actions in terms of searching and reading alerts, whether they had sources to update their medicine safety information, the effectiveness of the sources in delivering such information, and HCPs' beliefs and trust in these sources.

Barriers preventing healthcare professionals from updating their medicines safety knowledge were also identified, such as lack of time, workload, and being overwhelmed with information that could be irrelevant to one's practices. Our findings suggest that some HCPs had inaccurate views/perceptions towards the information reported in the alerts. However, this was only reported in a smaller number of studies. Different facilitators were identified that could influence the perception of HCPs of the alerts, including the understandability of the alert, receiving updated clinical practice guidelines involving the alerts, the time it takes to address the alerts, and HCPs' actions to understand the alert, such as seeking supervision and continued education. Other barriers include alert formatting and clarity, and lack of guidelines to address the alerts' recommendations.

Many HCPs have mixed attitudes towards the alerts and their contents. For example, if HCP perceive many barriers towards the implementation of the alert, they are more likely to have negative attitudes towards the alerts' recommendations. Various areas of concern of the HCPs' towards the alerts were also identified, including: liability issues, and negative patients' outcomes. Our findings highlight various interactions between the different key players that could affect HCPs' implementation of the alerts. These key players include the developers (sources and senders) of the safety information, and the receivers of safety information [healthcare institutions (*e.g.,* hospitals), the healthcare professionals' themselves, and the patients and their carers].

4.2. Healthcare professional-related factors

Knowledge about the existence of an alert and familiarity with its content is essential to its implementation. This was consistent with findings by Cabana et al. who highlighted that lack of awareness hinders physicians' implementation of guidelines.[22] Familiarity with the content of an alert would at least require that HCPs' read the alerts. Barriers to HCPs' reading of alerts were also identified by Faied et al.,[74] including their busy schedules and lack of trust in alerts' sources. Although altering HCPs' knowledge might be the expected outcome of an alert, it should be viewed as a modifiable factor when it comes to implementing actionable alerts. Sending an additional email from the RA to HCPs,[75] or including the alert in continuing medical education (CME) activities[76] could improve HCPs' knowledge of medicines safety information.

A Netherland-based RCT was conducted by Piening,[75] and included ophthalmologists and hospital pharmacists, who were the targets of a DHPC related to pegaptanib. Both the control and intervention groups received a paper-based DHCP, while only the intervention group received an additional email newsletter from the MEB. A survey was sent two weeks later to both groups. The results of the RCT revealed a significant increase in awareness about the existence of the alert among the intervention group. In addition, more participants in the intervention group reported conducting a form of action in response to the alert, compared to the control group participants who reported that they did not take any action as a result of the alert. Interestingly, among those who were aware of the existence of the alert in both groups, similar knowledge levels about the recommendation presented in the alert were highlighted. The majority of the participants of this RCT worked in a general hospital, which might affect the generalisability to other settings. The findings of this study might be limited by those who prefer to receive an email from the MEB, as both the control and the intervention group reported a high preference to receiving an email from the MEB regarding drug safety information. As the response rate was 18.6%, it could be that those who answered the online questionnaire (invitation sent by email) are those who prefer to receive an additional email. Moreover, the effect was measured two weeks post the additional email. Thus, information sustainability and retaining information might not be reflected.

Kraus[76] investigated the impact of internet-based CME on clinicians' knowledge of the US FDA alerts. In this study, Medscape sent a Safe Use Alert (SUA) email to 176,988 registered members. This email included the "Dear Healthcare Provider" letter about ipilimumab at the time of its approval for the treatment of unresectable or metastatic myeloma, aligning with the FDA risk evaluation and mitigation strategies (REMS) for distributing the letters. At the same time, a CME-certified activity was posted on the Medscape website, made available on the specialty website, and sent through specialty-specific email alerts to members. This study used a pre-test/post-test learning assessment. Targeted populations included both physicians, nurses, and pharmacists required by the REMS, as well as other HCPs who might be involved in managing patients receiving ipilimumab. In these assessments, the test takers acted as their own controls. Totally, 40,842 HCPs became aware of the FDA's REMS requirements for ipilimumab. Of these individuals, 20,642

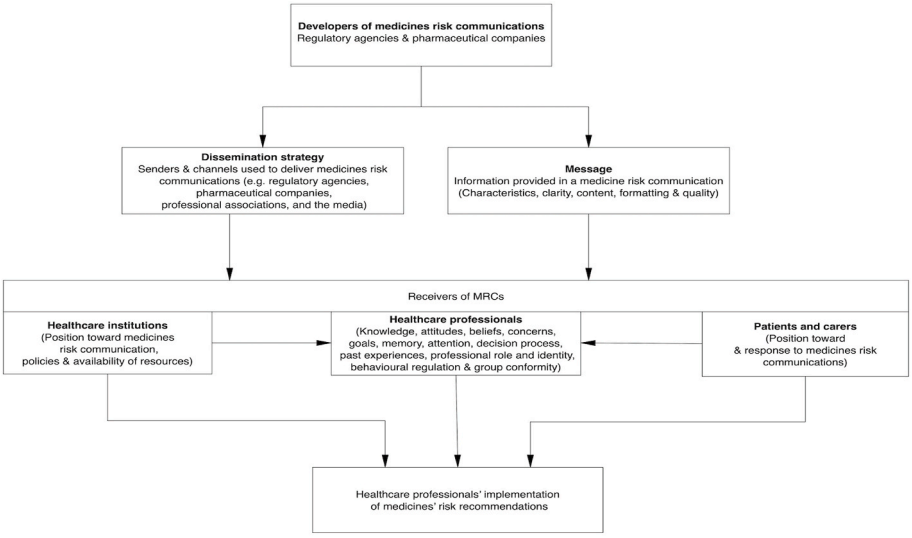

Fig. 3. Concept mapping.

learned about the REMS only through the SUA, and 20,764 individuals learned about it by undertaking the CME activity. Similar improvements in test scores were noticed among those who read the CME activity in the cohort who did not receive the SUA (47.8%), and those who both received and opened the SUA (47.6%). HCPs who read the CME materials, whether or not HCPs received and/or opened the SUA, had a similar degree of knowledge improvement. Unaffected participants (who responded incorrectly to both pre-assessment questions and post-assessment questions, or who responded correctly to pre-assessment questions but incorrectly to post-assessment questions) were lower in the cohort who read both the SUA and the CME activity (9.5%) compared to those who read the CME activity alone (14.7%). The impact of this intervention on healthcare professionals' actions in response to the safety information was not evaluated. Moreover, the safety issue communicated in this study was related to pre-market safety issues rather than emergent safety information. Thus, it is not clear whether HCPs would be more in agreement with pre-market safety information compared to post-market information; and whether their information-seeking behaviour would also be different in both situations.

Unlike knowledge, perception was less frequently reported in the included studies. In the current systematic review, the lack of a guideline to address the alert can result in inaccurate perceptions regarding the alert. Incorporating alert information into clinical practice guidelines (CPG) is already practiced. For example, the UK-based National Institute for Health and Care Excellence (NICE) acknowledges that clinically significant medicine safety updates or medicine withdrawal from MHRA are examples of events that could affect the guidelines.[77] Examples of recent NICE published guidelines incorporating information from MHRA in their clinical guidelines, included fluoroquinolone antibiotics[78] and valproate safety issues.[79] However, two potential obstacles might preclude the usefulness of incorporating post-market alert information into clinical guidelines. First, whether HCPs would adopt and adhere to these guidelines.[22,80] Second, whether guidelines are updated in a timely manner, to include emerging information about medicines alerts. Between March and July 2009, Alonso-Coello[81] carried out a survey of international institutions involved in developing clinical guidelines. Most of these institutions reported updating their guidelines. The timeframe to check the need for updates was three to five years for about 61% of the institutions, followed by less than three years for 30.6% of the participating institutions. Robin[82] published a systematic review of methodological handbooks related to guidelines updating. Only 8.6% of the handbooks recommended less than or equal to one year, 40% recommended two to three years, and 22.9% recommended four to five years. Further research is required to explore the process and evaluate the impact of incorporating emerging medicines safety information into clinical guidelines, and whether such information is incorporated in a timely manner.

Francke[80] found that guideline complexity is an influencing factor in its implementation, as guidelines that are easy to understand and do not require specific resources have a high chance of being implemented. In this meta-review of systematic reviews, the authors focused on the importance for the developers to take into account the complexity of the guidelines, and their comprehensiveness by the different targeted audiences.[80] Lack of relevance was one of the reasons reported in our review for not reading alerts. Further research could explore whether alerts that are tailored to each professional group, clearly indicating what is expected and how this could be clearly translated into their clinical practice, are effective in improving alerts uptake.

Even when being aware of an alert, HCPs did not always follow the recommendations. One possible factor was the (dis)agreement with the issuance of an alert and/or its recommendations. The extent to which HCPs agree with recommendations was also an influencing factor in clinicians' adherence to clinical practice guidelines.[22,83,84] In the RCT conducted by Piening[75] concerning the value of an additional email sent by the MEB to HCPs, there was a significant increase in the awareness about the existence of the alert among the intervention group, and a bigger proportion of participants from the intervention group agreed with the alert compared to the control group. It was noticeable that almost all respondents (93%) considered medicine safety information as important. Thus, having a positive attitude or agreeing with the alert could be different for those who do not consider medicine safety information important to their clinical practice. Further studies are required to investigate HCPs' reasons for disagreement with the importance of a safety alert and/or its recommendations.

One of the reasons for negative attitudes towards alerts' recommendations reported in the current systematic review was the lack of resources. Other reasons were unreasonable scheduling due to cost, or lack of space-related issues. Involving stakeholders, to not only assess the comprehensiveness of the alert's recommendation, but also to identify barriers that might affect their attitudes towards the recommendations, is warranted. However, having a positive attitude towards the intervention does not assure implementation by the HCPs, thus its possible effects on HCPs' implementation should also be further studied.[85]

A qualitative study examined barriers to the implementation of a

hospital-developed policy to ensure naloxone distribution to patients at risk of overdose. One reported barrier to implementation was that those staff who would be expected to implement the policy were not involved in its development.[86] However, contradictory evidence is available for the usefulness of involving end-users in guidelines development.[80]The European Medicine Agency has taken steps to involve the different stakeholders through public hearings.[87] Since 2017, the EMA has held two public hearings regarding valproate,[88,89] quinolone, and fluoroquinolone antibiotics safety issues.[89,90] Through public hearings, the EMA has considered the different stakeholder's perspectives, including how certain medicines are perceived by the public, how recommendations might affect the population, and how the public can have a greater understanding of how the EMA evaluates medicines.[87] Research is needed to understand the impact of initiatives such as the EMA's initiative on improving HCPs' attitudes towards the alerts, as well as in implementing medicines safety alerts. It was also identified in the current review that HCPs have different views towards alerts' senders. Thus, it might be important to evaluate initiatives for strengthening HCPs' trust in different senders.

In the current review, HCPs' trust of the sender was found to be possibly affected when the alert lacked the evidence supporting its recommendations, or when they anticipated the sender to be biased towards the industry. A recent retrospective study comparing post-market drug alerts on cardiac harm in Australia, Canada, the UK, and the US regulatory advisories, issued between 2010 and 2016, found that these regulators reported a range of evidence of harm, and US FDA was the only regulatory agency reporting the evidence used in decision making.[91] Among the studies included in the current review, only one study investigated HCPs' knowledge about the evidence leading to regulatory decisions. Further studies are needed to assess HCPs' awareness of evidence underpinning the regulatory decisions, and whether facilitating their access to transparent, straightforward, and scientifically based decision-making processes would improve their confidence in regulatory agencies' decisions.[92]

Møllebæk[21] reported that, in most studies, HCPs preferred non-industry and medical authority sources with no financial interests. Trusting guidelines' sources were further reported as a promotor for nurses' adherence to clinical guidelines.[83] The Centre for Regulatory Research on Tobacco Communication conducted a national telephone survey in the US, between September 2014 and June 2015, which included 5014 adults over 18, and 1215 adolescents.[93] Among the adults, 64.6% reported trusting the CDC, and 62.5% reported trusting the FDA, demonstrating moderate levels of trust for both.[93] On the other hand, adolescents had a high level of trust in the CDC (72.2%) and the FDA (78.8%).[93] Regulatory agencies and researchers should also explore trust towards alerts' senders, and identify what might cause a lack of trust, and how this impacts alert implementation by HCPs.[94–96]

Trust was one of six elements proposed by public relationship academics, Dr. Linda Childres Hon of the University of Florida, and Dr. James E. Grunig of the University of Maryland, for evaluating organizational public relationships. One contributing element of trust was transparent communication. A total of 502 participants in the US answered an online survey in April 2020. The authors investigated the role of transparent communication and trust in influencing public perception, attitude, and social distancing behaviour during the COVID-19 pandemic.[97] For this purpose, they utilised three aspects of transparent communication, including substantiality, accountability, and participation.[97] The authors explained these three components based on previous literature.[97] First, substantial information is demonstrated through the disclosure of information,[98] by acknowledging that it is the human right to be provided with comprehensive and complete information,[99] by open administrative procedures and government hearings,[100,101] and by recognizing that openness is essential to the disclosure of information. Second, participation of other parties,[97] as information sharing by itself does not ensure transparency,[102] audiences involved in addressing the interests of both sides,[103] and a mutual understanding of a message[104] could maximise transparency. Thus, organisations are responsible for ensuring that interested audiences can actively acquire, create, and provide information.[105] Third, accountability refers to organisations' acceptance of responsibility and mitigation of problems.[97,106] Accountability involves making the decision process visible, to ensure public understanding.[99] The results of this survey revealed that public trust in state government and health institutions during the COVID-19 pandemic was significantly increased by information substantiality.[97] Only trust in health institutions (the CDC) was enhanced by audiences' participation, while accountability had no effect on public trust, in either health institutions, or state government.[97] In turn, organisational trust was an important element in increasing the perceived risks, subjective norms, and behavioural control of the public, which all promoted social distancing behaviour.[97] It is noticeable that attitudes also impacted public behaviours into social distancing.[97] However, the organisational trust did not affect the public's attitudes.[97] Nevertheless, it is not clear if the same results would be obtained in non-crises medicine safety communications. Moreover, this study was based on a cross-sectional survey that targeted around 500 individuals in the US, thus it might not be generalisable to larger populations, or those living in other geographical areas. Furthermore, the survey was administrated for one week in April, 2020[97] so information on behaviour sustainability is not clear, and more longitudinal studies might be required.

4.3. *External factors: healthcare institutions and patients*

External factors might also affect HCPs' implementation, even with sufficient knowledge and attitudes.[22] Regulatory agencies should consider collaboration with healthcare institutions (*e.g.*, hospitals) in the dissemination and interpretation of the alerts. A framework might be provided to hospitals to deal with alerts, and to be aware of what is expected from healthcare organisations in terms of alerts implementations. Regulatory agencies could partner with healthcare organisations, in order to improve the uptake and implementation of medicines safety communications.

An example of such collaboration included The National Patient Safety Alerts Committee (NaPSAC). The NaPSAC was formed in 2018 at the request of the Secretary of State for Health and Social Care after evidence that safety advice and guidance issued to HCPs in the NHS was not having the intended effect.[107] The initiative was launched by the collaboration of a regulatory agency (MHRA) and healthcare organisations (Public Health England, and NHS England and NHS Improvement Patient Safety Team).[108] One of the goals of NaPSAC is to ensure the alignment of alerts produced by different bodies, by using National Patient Safety Alerts. Additionally, it aimed to ensure that the required actions were evaluated for feasibility, risk of unintended consequences, equalities impact, effectiveness, and cost-effectiveness, and that the actions were specific, measurable, achievable, realistic, and timely (SMART).[108] Evaluating the roles of such initiatives in improving HCPs' implementation of emerging medicines safety information is important to further enhance patient safety. Establishing a feedback channel from healthcare organisations and HCPs, and carefully evaluating the effectiveness of alerts could also be considered, to ensure that the targeted audiences receive and accurately interpret these alerts.[109] Such evaluation should consider the role of healthcare institutions in promoting or hindering the implementation.

As only one of the included studies in the current review reported a role of a lead person for implementing the alert,[53] further research should investigate the roles of the lead persons in ensuring implementation of the alerts by the multi-disciplinary HCPs, as well as providing such leads with evidence-based implementation strategies, and helping them with identifying barriers and facilitators to alert implementation.[110]

In the current systematic review, patients, their families, and carers' acceptance or refusal of the medicines of concern were identified as

possible external factors affecting HCPs' implementation of alerts' recommendations. Patients were also identified as a factor in an overview of systematic reviews,[80] since patients' resistance and perceptions of lack of necessity for a guideline were barriers to implementation. More research is needed in terms of determining the influence of patients-related factors on the implementation of medicines safety alerts. The utilisation of the TDF to characterise factors affecting HCPs' implementation of alerts in the current review (results reported in a separate publication) identified that HCPs' goals, priorities and implementation intentions could be affected by patient factors, such as the patients' health status.[57,72] Patient-related factors such as patients' demographics, health condition, presence of comorbidities, and use of polypharmacy have been reviewed by Medlinskiene.[111]

Further research is required to identify whether evaluating patients' related health outcomes of an alert, and providing HCPs with such information, will influence their perception of the value of the alert, and their implementation of alerts-related recommendations. However, previous systematic reviews[24,112] highlight the scarcity of studies measuring alerts' impact on patients-related health outcomes compared to other outcomes.

4.4. Other recommendations

It is important to consider the impact of alerts issued by international RAs' on HCPs' actions.[112] This is because on occasions, alerts may issue different guidance/recommendations.[91] During the "pill scare" in 1995, the UK Committee on the Safety of Medicines warned against the thromboembolic risk associated with third-generation oral contraceptives, and advised providers to only prescribe these agents for females who cannot tolerate the first and second generation contraceptives.[113,114] Although the Irish Medicines Board did not advise this, Williams and co-authors[114] found that both prescribers and users in Ireland were affected by the UK advice; with a noticeable reduction in consumption of third-generation oral contraceptives and an increase in use of second-generation ones.

Our findings support DeFrank[23] research recommendations when evaluating alerts' impact. It should focus on identifying the outcomes, reactions, and understanding of HCPs and patients, and evaluate the impact of different communication strategies on outcomes.[23] We further recommend that RAs define or map out the unintended and the spillover effects associated with alerts, and consider the factors behind HCPs undertaking unintended actions and the consequences of such actions on patient outcomes. Frameworks might aid in identifying possible barriers against their intended implementation. Development of interventions with psychological effects, and giving prescribers feedback on their performance should be considered.[63,115]

4.5. Limitation of the systematic review

Most of the studies included were quantitative in nature, and data were collected through surveys, thus limiting the insights associated with qualitative data.[116] Since the findings were based on heterogeneous studies in the type of alerts, types of medicines, and populations targeted, the mathematical pooling of the data was not possible.

The majority of the included studies were based in the US, which could affect the generalisability of the results. Excluding papers that did not report possible factors might have affected the full exploration of both impact and preferences. Our synthesis is further limited by the inclusion of studies only concerning communications issued by RAs. Studies evaluating the effectiveness of risk minimisation measures, and studies involving only pharmaceutical companies were excluded from the analysis. These studies could have provided additional insights into the factors relevant to the pharmaceutical industry.

Furthermore, the studies' inclusion was based on the author's assessment of RAs involvement. This could have possibly led to the omission of studies. However, the extensiveness of the search conducted reduced the risk of missing out papers.

Exclusion of papers without Arabic or English abstracts may have resulted in a language bias. It should also be highlighted that our search strategy was restricted by limiting the search to the titles of the study. This was done to manage the large number of citations resulting from limiting the search to abstracts. The wide range of search terms used in variable databases, as well as searching the references of the included studies helped mitigate the risk of missing papers. Moreover, the search update was limited to three of the databases searched in the first update.

4.6. Methodological limitation of the included studies

Most of the included studies used a cross-sectional survey, in which participants' answers might be affected by social desirability biases. Nearly one-half of the cross-sectional surveys were either web-based or distributed via email, which might affect the generalisability of these studies. Issues related to the sample size included one professional group being notably less represented than other professions within a single study,[50,57,61] which might have affected the results representing the underrepresented groups. Bias related to the sample frame was identified in three studies, where knowledge levels might be higher in these participants, due to their interest in the topic,[52,53] or position within their institution,[47] which might have placed them in a better position to know about the alerts. The results should be interpreted with caution, as most of the studies scored less than 80% in their quality assessment. Only seven studies scored 80% or more; fulfilling at least 4 of the 5 MMAT questions.

5. Conclusion

Pharmacovigilance medicines risk communications aim to reduce patients' harm resulting from adverse drug reactions and medicine errors. Healthcare professionals have an essential role in translating these communications into their clinical practice. Their actions, in response to these communications, may jeopardise patients' safety and health-related outcomes, and may affect patients' right to make informed decisions about their treatments. It is important to ensure that healthcare professionals have adequate information about the content of the alert, and that the alert is perceived as intended, without ambiguity or misinterpretation. These are important determinants of healthcare professionals' implementation of the clinical changes intended in these alerts.

Communication of medicine risk alerts does not always translate into their implementation, and the desired improvement in patient care. This is due to a complex interaction between stakeholders involved in the creation and implementation of these alerts. These complex interactions should be the subject of future research efforts to understand the alert-implementation trajectory and identify the mediators for change and interventions to improve alerts' implementation.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

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