Received: 13 March 2023 | Revised: 17 July 2023 | Accepted: 26 July 2023

DOI: 10.1111/bcp.15874

REVIEW ARTICLE

Unintended impact of pharmacovigilance regulatory interventions: A systematic review

Tomas Lasys[1] | Yared Santa-Ana-Tellez[1] | Satu J. Siiskonen[1] | Rolf H. H. Groenwold[2] | Helga Gardarsdottir[1,3,4]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands

[2]Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands

[3]Department of Pharmaceutical Sciences, School of Health Sciences, University of Iceland, Reykjavik, Iceland

[4]Department of Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, The Netherlands

Correspondence
Helga Gardarsdottir, Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, The Netherlands.
Email: h.gardarsdottir@uu.nl

Aims: Studies assessing the impact of pharmacovigilance regulatory interventions often focus on the expected (or intended) outcomes, while any possible unintended impact may be overlooked. The update of the Good Pharmacovigilance Practice guideline in 2017 elaborated on impact assessment, emphasizing the need also to assess possible unintended impact. This systematic literature review investigated how often the unintended impact of regulatory interventions was considered in publications of studies investigating pharmacovigilance regulatory interventions in Europe.

Methods: We conducted a systematic review of the literature on MEDLINE and EMBASE from 1 January 2012 to 28 February 2022 to identify publications that investigated the impact of regulatory interventions in Europe. The primary outcome of the study was the number of publications reporting assessments of unintended impact. In addition, we studied the characteristics of these publications, including the type of outcomes assessed, the analytical methods applied and the type of data used.

Results: In total, 96 publications were included in the analysis. The unintended impact of pharmacovigilance regulatory interventions was investigated in 23 of 96 publications (24%). The drug classes most frequently studied in the publications assessing unintended impact of regulatory interventions were oral glucose-lowering drugs ($n = 6$, 26%), opioids ($n = 4$, 17%), antidepressants ($n = 4$, 17%) and antipsychotics ($n = 3$, 13%). The reported methods to assess the unintended impact were interrupted time series ($n = 10$, 43%) and descriptive statistics with or without significance testing ($n = 2$ [9%] and $n = 9$ [39%], respectively). The outcomes selected for unintended impact assessments included the use of other drugs ($n = 16$, 70%), health outcomes ($n = 8$, 35%) and behavioural changes ($n = 4$, 17%). Most of the publications reported on the use of electronic health record databases ($n = 13$, 57%) or claims databases ($n = 13$, 57%), while registries were used in 4 publications (17%).

Conclusion: The unintended impact of pharmacovigilance regulatory interventions was reported in only a quarter of identified publications. There was no apparent increase in attention to unintended impact assessments after the update of the Good Pharmacovigilance Practice guidelines.

KEYWORDS
impact evaluation, pharmacovigilance, postauthorization studies, real-world evidence, regulatory intervention, systematic literature review, unintended impact

1 | INTRODUCTION

In Europe, medicinal products undergo a rigorous assessment process before market authorization. Still, the medicinal product assessment does not end with the authorization approval. Each authorized medicine continues to be assessed via various postauthorization activities to ensure that its benefit–risk balance remains positive.[1,2] These processes are essential to guarantee that patients receive the best care based on the most recent information. Due to the importance of this postapproval process, in 2012, the EU-wide Pharmacovigilance legislation was implemented, and a set of supporting guidelines called Good Pharmacovigilance Practices (GVP) was developed. GVP includes guidance on implementing pharmacovigilance regulatory interventions called risk minimization measures (RMMs) that are meant to support risk minimization when prescribing, dispensing and/or using a medicinal product, including considerations on how to assess the impact of these pharmacovigilance regulatory interventions.[1,2] Examples of such pharmacovigilance regulatory interventions include Direct Healthcare Professional Communications (DHPCs), national drug safety alerts and safety warnings.

Studies that assess the impact of pharmacovigilance regulatory interventions often focus on the expected (or intended) outcome. Nevertheless, even when pharmacovigilance regulatory interventions seem effective, they might also have unintended effects.[3–6] For example, the withdrawal of oral fusafungine from the market in Germany led to an increase in prescribing nasal or throat preparations of fusafungine.[7] Similarly, pharmacovigilance regulatory interventions regarding atypical antipsychotics for treating behavioural and psychological symptoms of dementia were issued due to the increased risk of stroke and all-cause mortality. However, these interventions were followed by increased use of conventional antipsychotics (although none of the conventional antipsychotics has this indication on its label).[8]

Previously conducted systematic reviews of the impact of pharmacovigilance regulatory interventions showed that unintended impact is rarely assessed. A review by Goedecke *et al*. mentioned that unintended impact is assessed in only a small number of studies.[4] Georgi *et al*. showed that unintended impact was assessed in only 6 out of 72 identified studies (8%).[3] While the review by DeFrank *et al*. examined types of unintended impact, their review did not focus on the methods used for conducting such studies.[5] In 2017, GVP was updated with an expanded discussion on the impact assessments of RMMs, which emphasized the need to assess their possible unintended impact.[9] Likewise, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, since the 2018 revision, includes a chapter on measuring the impact of RMMs and, specifically, the unintended impact of RMMs.[10] Even with the increasing attention to the possible unintended impact of regulatory interventions, it is unknown to what extent studies measuring the impact of pharmacovigilance regulatory interventions include an analysis of the potential unintended impact. In addition, it is unclear whether the updated European guidelines have led to an increased attention to the unintended impact of pharmacovigilance regulatory interventions in scientific research. We conducted a systematic literature review of studies investigating the impact of regulatory pharmacovigilance regulatory interventions in Europe, focusing on the methods and data used to assess the unintended impact.

2 | METHODS

2.1 | A systematic review of the literature

A systematic review of the literature was conducted in MEDLINE and EMBASE to identify publications that investigated the impact of regulatory interventions in the European Economic Area (EEA), focusing on identifying unintended impact of pharmacovigilance regulatory interventions and highlighting the methodology and data used. We focused on studies conducted in the EU Member States and EEA countries because we expected them to be directly influenced by the new guidelines and legislations published by the European Medicines Agency (EMA) since 2012.

The search strategy was developed a priori and described in the protocol available in the European Union Electronic Register of Post-Authorization Studies (EU PAS Register) under study number EUPAS47825.[11] The complete list of keywords for both databases is presented in the supplementary material. The literature search was supplemented by references from relevant systematic reviews identified by our search and by using the online tool connectedpapers.com that identifies related publications based on a given reference.[12]

Two reviewers independently screened all the identified publications by title and abstract. In case of conflicting opinions, the publication was reviewed by a third reviewer, and the final decision was made by a majority vote. After the initial screening, 2 reviewers individually assessed the eligibility of publications based on a full-text assessment. In the event of conflicting opinions, the same procedure as in the first stage was followed: the publication was reviewed by a third reviewer, and the final decision was made by a majority vote.

2.2 | Inclusion and exclusion criteria

We included English language publications published in PubMed and EMBASE from 1 January 2012 to 28 February 2022 that assessed the impact of regulatory interventions in the EEA for medicines for human use. Since the UK was part of the EU for most of the study period, we

included publications studying the UK population if the study period covered the time before 1 February 2020 (the date of official withdrawal from the EU). We included original research publications, excluding duplicates, conference abstracts, case series, case reports, letters to editors, commentaries, editorials, lecture notes, guidelines and systematic reviews. We included studies using quantitative methods, except for publications based on data from surveys and questionnaires. We also excluded publications from which the relevant information could not be retrieved for the descriptive analysis, publications assessing interventions that were not implemented at least on a national level (e.g., hospital centres, regional guidelines), and publications assessing other than pharmacovigilance regulatory interventions (e.g., reimbursement policy changes). Studies assessing regulatory interventions on vaccines and interventions due to quality issues of generic medicines or biologicals were also excluded to avoid heterogeneity in methods used in impact studies.

2.3 | Data extraction

We extracted data using a standardized data extraction form created a priori using the following process: the data extraction form used by Goedecke *et al*. was updated by adding questions about the unintended impact of regulatory interventions.[4] The focus of our study is pharmacovigilance regulatory interventions in the EEA, so the categorization of interventions was adjusted to the definitions of RMMs as defined in GVP.[9]

To assess the quality of our data extraction form, we tested it before the formal review process. Four publications found by a manual search that met the inclusion and exclusion criteria were independently reviewed by 2 reviewers each (in total, 4 reviewers participated in the process) who filled out the data extraction forms and discussed the results afterwards. Based on this discussion, new questions were added. The final set of items to be included was selected by consensus of all 4 reviewers.

The extracted information included the outcome of interest as well as basic information on the identified publications, including the article title, publication year, main studied drugs, study period, data source characteristics, type of regulatory intervention, outcomes of interest, a summary of key findings and disclosed limitations. The complete list of items is presented in the final extraction form (see supplementary material). One reviewer performed the data extraction, and a second reviewer extracted the data for a random 10% of the publications for quality assurance purposes.

2.4 | Outcome

The study's primary outcome was the frequency of unintended impact assessments included among all publications assessing impact of pharmacovigilance regulatory interventions. We assessed the methodology of these studies based on study design (before and after cross-sectional, before and after time series, cohort study, other), used analytical methods (descriptive statistics with or without significance testing, Poisson regression, logistic regression, interrupted time series regression, joinpoint regression, other), outcome measures as classified in GVP (behavioural change, drug use, health outcomes, other) and types of databases used (electronic healthcare records database, administrative database, spontaneous reporting database, registry, other).

2.5 | Definition and classification of regulatory intervention

The focus of our study was on pharmacovigilance regulatory interventions in Europe. Therefore, the categorization of interventions followed the definitions of RMMs defined in GVP. A pharmacovigilance regulatory intervention was defined as any routine or additional risk minimization measure described in the GVP modules V and XVI.[9,13] Furthermore, we included any withdrawal or suspension of marketing authorization or any other pharmacovigilance regulatory intervention implemented at least at the national level by the competent authority of an EU or an EEA Member State to safeguard public health.

Regulatory interventions were defined as routine RMMs or additional RMMs. The routine RMMs are: (i) updates to the summary of product characteristics; (ii) updates to the package leaflet; (iii) changes to the pack size; and (iv) changes to the legal status. The additional RMMs are: (i) educational programmes; (ii) controlled access programmes; (iii) controlled distribution systems; (iv) pregnancy prevention programmes; and (v) DHPCs.[9,13]

2.6 | Definition of unintended impact study publications

We defined publications regarding unintended impact as any impact publications that aimed to assess outcomes that were not the primary goal of the regulatory intervention, regardless of whether they could be considered positive or negative. We classified decreased use of the medicine targeted by the regulatory intervention as an intended impact unless the publication explicitly stated that decreased use is an unintended impact or decreased use is detected in a subpopulation of medicine users that was not targeted by the intervention. Also, publications assessing overall medicine use, even if the regulatory intervention targeted a subgroup of the overall users, were considered as intended impact analyses if no data confirming unintended impact were provided. Furthermore, we did not consider paradoxical effects (increased use of the medicine after the implementation of pharmacovigilance regulatory intervention) as an unintended impact since the observed effect may be due to factors other than the regulatory intervention.

Market access withdrawals may cause shifts to other available treatments, but the treatment selection guidelines are usually not part of pharmacovigilance regulatory interventions. Therefore, we considered studies assessing treatment switches aftermarket withdrawals intended impact studies unless the study explicitly describes medicine switching as an unintended impact.

We used the categorization of unintended impact proposed by DeFrank *et al.* These include decreased use or discontinuation, use of drug substitutes, changes in knowledge, attitudes or beliefs, spill-over effects, shifts in diagnoses, changes in clinical practice, changes in health behaviour or health outcomes.[5]

2.7 | Data analysis

Data were analysed using descriptive analysis methods, presenting totals and percentages for the extracted variables.

3 | RESULTS

3.1 | Overview of all impact publications identified

Our search identified 3232 unique publications, of which 131 were included for full-text review, and 92 met our in- and exclusion criteria. Four related publications were identified using the tool Connected Papers[12]; these publications were also included in the analysis. The complete selection process is presented in Figure 1.

Out of the 96 included publications, 2 used the EudraVigilance database covering all the EEA countries (including the UK). The rest of

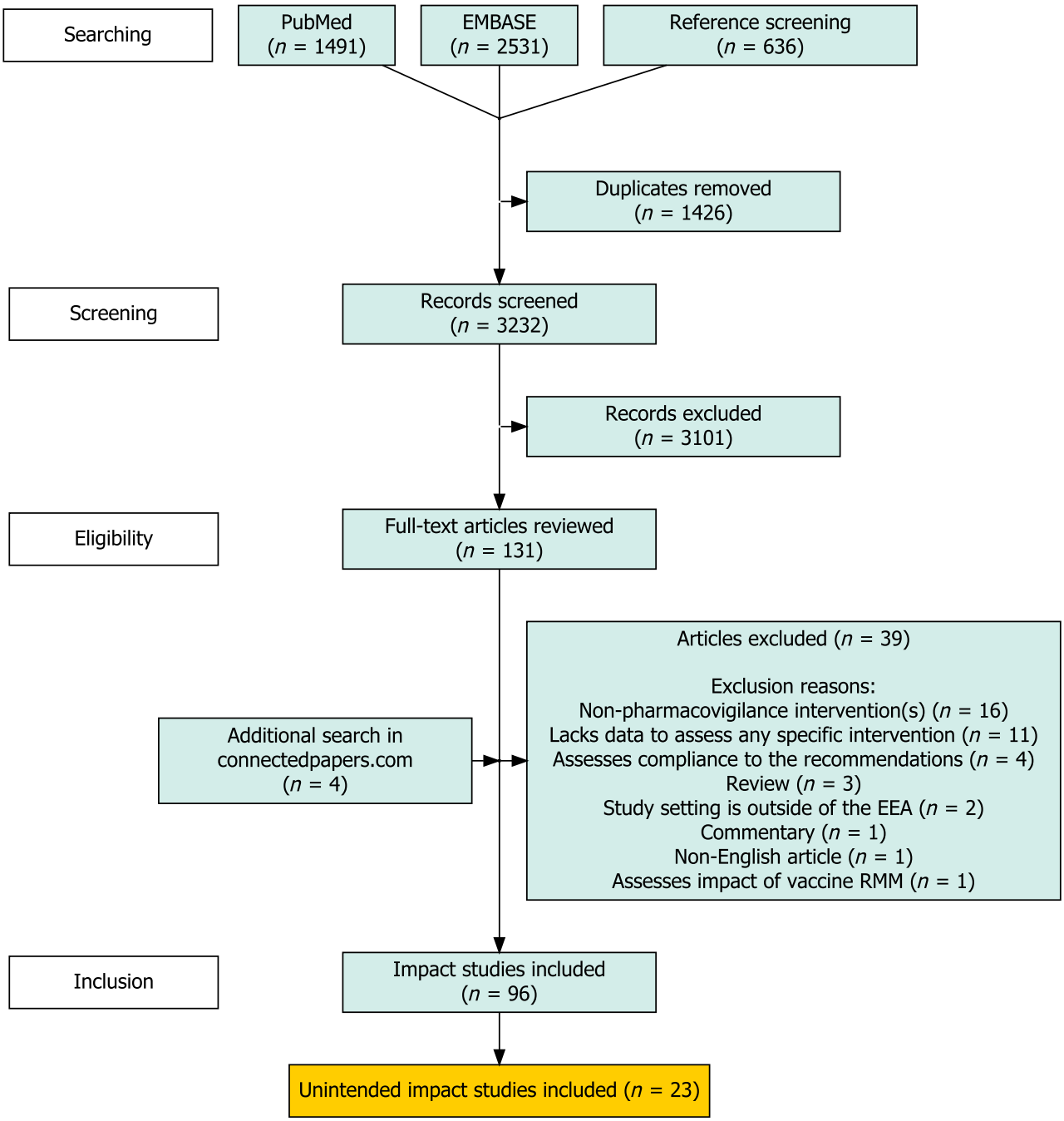


FIGURE 1 Systematic literature review process flowchart.

the publications studied the impact in 15 out of 31 EEA countries, of which 24 publications (25%) used data from at least 2 countries. Most included publications analysed data from the UK ($n = 42$, 44%), Germany ($n = 18$, 19%) and France ($n = 16$, 17%). More detailed information about countries is presented in Figure 2.

The most frequently assessed pharmacovigilance regulatory interventions were DHPCs ($n = 31$, 32%) and other communications regarding the safety of medicines (national or EU-wide drug safety communications, drug safety alerts and safety warnings, $n = 37$, 39%). The most frequently assessed drug classes were antipsychotics ($n = 13$, 14%), oral glucose-lowering drugs ($n = 12$, 13%) and antidepressants ($n = 12$, 13%). Six publications (6%) included impact assessments for multiple drug classes. More information on included studies is presented in Table 1.

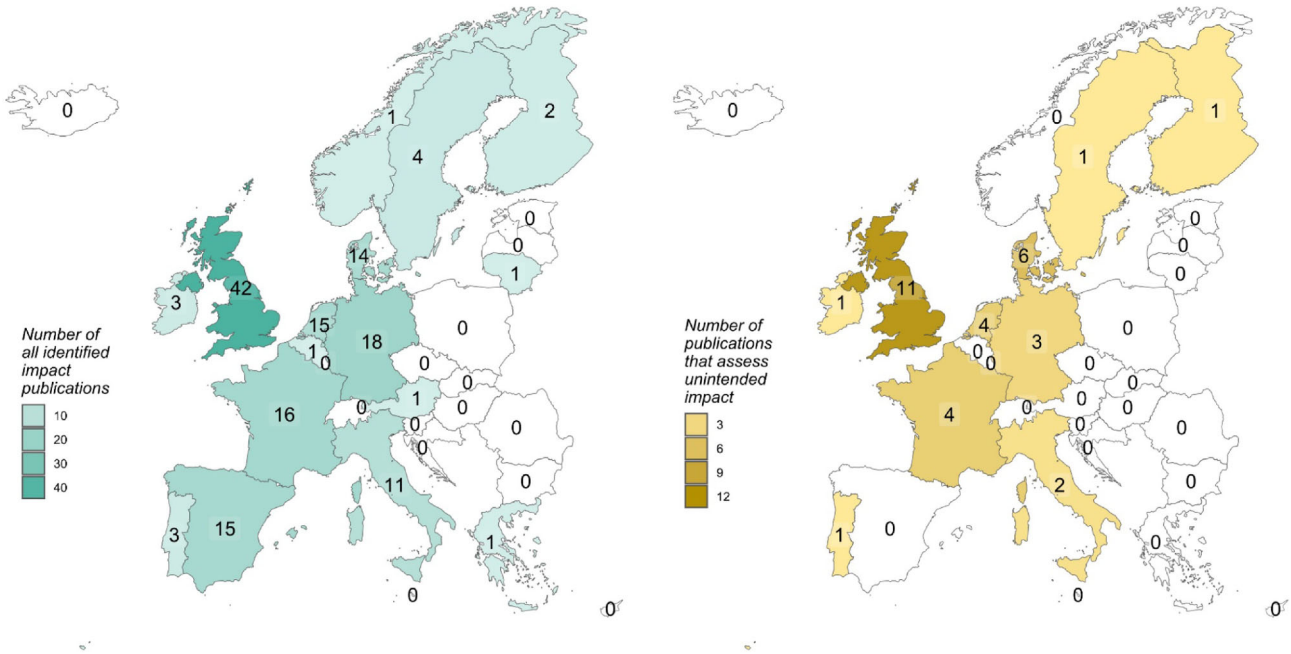
3.2 | Overview of publications that report on the assessment of the unintended impact of regulatory interventions

Of the 96 publications, 23 (24%) included an assessment of the unintended impact of regulatory interventions. The proportion of publications reporting unintended impact ranged from 0 to 50% during the study period, and the number of publications ranged from 0 to 5 per year. Over time, there was no substantial increase in the proportion or number of publications addressing unintended impact during our study period. Furthermore, no clear change was detected after the 2017 GVP updates. Detailed information is presented in Figure 3.

Publications on unintended impact ($n = 23$) most often assessed oral glucose-lowering drugs ($n = 6$, 26%), opioids ($n = 4$, 17%), antidepressants ($n = 4$, 17%) and antipsychotics ($n = 3$, 13%). One publication described separate assessments of medicines of 3 different classes, and 3 publications reported 2 outcomes in their assessments. These publications were counted for each relevant category in the analysis. The characteristics of the publications that report on unintended impact are presented in Tables 2 and 3.

The outcome most frequently reported in the unintended impact assessment was the use of other drugs, that is, substitutes ($n = 16$, 52%). This outcome was used to assess the use of drug substitutes ($n = 14$, 61%) and spill-over effects ($n = 3$, 13%). Two of the publications that assessed the use of substitutes interpreted the patterns of drug substitute use as undesirable.[14,20] Other publications describing the use of substitutes described changes after interventions without commenting on whether the results were desirable or not. The publications suggesting spill-over effects reported on the use of drugs of the same class as those targeted by the regulatory interventions. Two out of 3 of these publications detected decreased use of those drugs suggesting spill-over effects: regulatory interventions targeting rosiglitazone were associated with a decreased use of pioglitazone, and interventions targeting rofecoxib were associated with a decreased use of other coxibs.[21,22] One publication explicitly mentioned the intention to assess a spill-over effect of intervention in its methods section.[23]

Health outcomes were assessed in 8 (35%) publications. The changes in the glycaemic control indicators after rosiglitazone withdrawal were assessed in 2 publications.[15,32] Two studies investigated



The left panel shows the number of publications assessing pharmacovigilance regulatory interventions; the right panel shows the number of publications assessing unintended impact of pharmacovigilance regulatory interventions. Publications that included data from multiple countries were counted for each country.

FIGURE 2 Number of publications assessing pharmacovigilance regulatory interventions by studied country.

TABLE 1 Characteristics of publications assessing the impact of pharmacovigilance regulatory interventions.

Regulatory intervention assessed[a]	All publications ($N = 96$), *n* (%)	Publications that address unintended impact ($N = 23$), *n* (%)
Routine risk minimisation measures		
Provision of information and recommendations in the summary of product characteristics and the package leaflet	29 (30%)	5 (22%)
The labelling on the immediate or outer packaging of the medicine	5 (5%)	3 (13%)
Changes to pack size	0 (0%)	0 (0%)
Changes to legal status	15 (16%)	9 (39%)
Additional risk minimisation measures		
Educational material	11 (11%)	2 (9%)
Controlled access programme	5 (5%)	2 (9%)
Pregnancy prevention programme	4 (4%)	0 (0%)
Direct healthcare professional communication	31 (32%)	3 (13%)
Other communications about medicine's safety	37 (39%)	7 (30%)
Multiple interventions throughout the study period[a]	34 (35%)	9 (39%)
Most frequently studied medicines (ATC classification)[a]: The complete list is available in the supplementary material		
Antipsychotics (N05A)	13 (14%)	3 (13%)
Blood glucose lowering drugs, excl. insulins (A10B)[b]	12 (13%)	6 (26%)
Antidepressants (N06A)	12 (13%)	4 (17%)
Antiepileptics (N03A)	11 (11%)	0 (0%)
Opioids (N02A)	8 (8%)	4 (17%)
Anti-inflammatory and antirheumatic products, nonsteroids (M01A)	8 (8%)	2 (9%)
Propulsives (A03F)	6 (6%)	0 (0%)
Antithrombotic agents (B01A)	6 (6%)	0 (0%)
Hypnotics and sedatives (N05C)	5 (5%)	2 (9%)
Hormonal contraceptives for systemic use (G03A)	4 (4%)	0 (0%)
Immunosuppressants (L04A)	4 (4%)	0 (0%)
Drugs affecting bone structure and mineralisation (M05B)	4 (4%)	0 (0%)
Multiple drug classes assessed in a single publication[a]	6 (6%)	1 (4%)
Number of countries studied in the publication		
1	72 (75%)	17 (74%)
2	6 (6%)	2 (9%)
3	6 (6%)	3 (13%)
4	5 (5%)	0 (0%)
5	5 (5%)	1 (4%)
All the EEA countries (including the UK)	2 (2%)	0 (0%)
Data source type[a]		
Claims database	49 (51%)	13 (57%)
Electronic health records database	45 (47%)	13 (57%)
Registry database	9 (9%)	4 (17%)
Other	14 (15%)	4 (17%)
Multiple types of data sources[a]	18 (19%)	8 (35%)

Abbreviations: ATC, Anatomical Therapeutic Chemical; EEA, European Economic Area.

[a]If publications included assessments of multiple drug classes, were conducted in multiple countries or used several data sources, they were counted for each relevant category.

[b]All the studies assessing blood glucose-lowering drugs assessed thiazolidinediones (ATC code: A10BG).

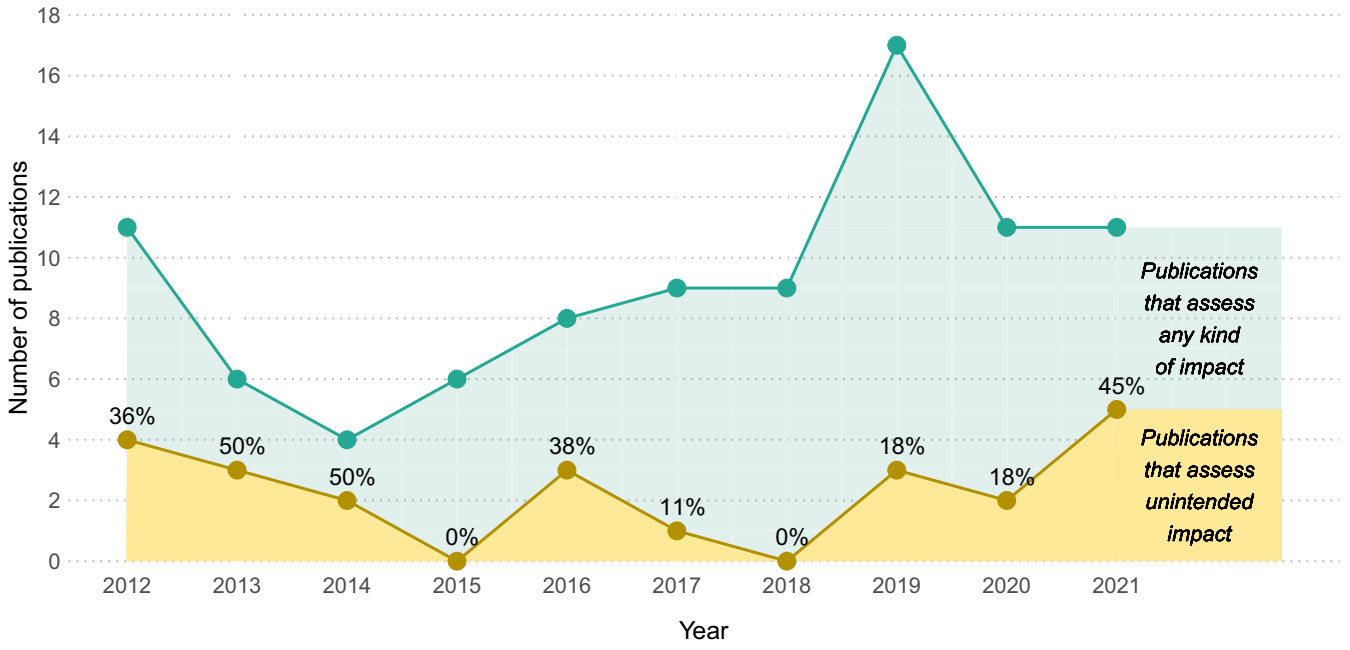


FIGURE 3 Number of publications assessing pharmacovigilance regulatory interventions conducted in the European Economic Area and published between 2012 and 2021.

changes in hospitalization rates due to psychosis after the withdrawal of thioridazine and pipotiazine palmitate.[33,34] One study used 3 health outcomes to assess the impact of aprotinin withdrawal. Selected outcomes were the rate of blood transfusions during surgery, the volume of blood lost during surgery and postoperative morbidity.[35] One publication simultaneously assessed the impact of market withdrawals of dextropropoxyphene, pioglitazone and tetrazepam by assessing the number of spontaneous adverse event reports for alternative treatment options considering the change of reimbursements of other medicines.[16] The publication assessing the impact of the guidance on codeine use used case reports of poisonings related to codeine substitutes considering the change in prescriptions following the regulatory intervention.[24]

Behavioural change was reported as an outcome in 4 publications. A publication by Valkhoff *et al.* assessed the impact of rofecoxib withdrawal on the use of other coxibs or nonsteroidal anti-inflammatory drugs and concomitant gastroprotective agents.[21] Wijlaars *et al.* focused on physician prescription and diagnosis protocol following DHPCs regarding the use of selective serotonin reuptake inhibitors (SSRIs) in children and adolescents.[25] A previously mentioned publication by Sheldon *et al.* assessed the discontinuation of replacement treatment after pipotiazine palmitate market withdrawal alongside hospitalization rates.[34] One publication described a discrete choice model for assessing the impact of regulatory interventions on SSRIs use in children and adolescents. The behavioural change outcome was defined as the probability of being prescribed antidepressant medications based on the patient's and physician's characteristics. The authors concluded that there is a lower probability for adults to be prescribed SSRIs medications after the intervention, thus indicating a spill-over effect.[36]

Most of the publications used a before–after time series design ($n = 13$, 57%), followed by a before-after cross-sectional study design ($n = 5$, 22%) and cohort study design ($n = 3$, 13%). The most common analytic method applied to assess the unintended impact of pharmacovigilance regulatory interventions was interrupted time series ($n = 10$, 43%), followed by descriptive statistics with or without significance testing ($n = 2$ [9%] and $n = 9$ [39%], respectively). Other analytical approaches identified were Poisson regression and the discrete choice model (for both $n = 1$, 4%).

Six publications (26%) assessed the unintended impact of regulations in at least 2 different countries. Data were analysed separately for each database. Most of the publications used electronic health records databases ($n = 13$, 57%) or claims databases ($n = 13$, 57%), while registries were used in 4 publications (17%). In 4 publications (17%), the data were collected only in a limited part of the country, including hospital centres or databases from separate regions.[14,15,26,34] Also, 3 publications used spontaneous reporting databases.[16,24,27]

4 | DISCUSSION

This systematic literature review provides a comprehensive assessment of the publications on the unintended impact of pharmacovigilance regulatory interventions in Europe. Our results show that, despite the increasing attention to the unintended impact of these interventions, only a quarter of the publications assessing the impact of regulatory interventions reported on the unintended impact. Furthermore, there was no marked change in the number of publications that addressed the unintended impact of pharmacovigilance regulatory interventions after the 2017 updates of the GVP guidelines.

TABLE 2 Characteristics of publications addressing unintended impact assessments of pharmacovigilance regulatory interventions.

	Publications included $N = 23$, n (%)	References of the studies
Study design		
Before and after cross-sectional study	5 (22%)	15–19
Before and after time series study	13 (57%)	14,20–31
Cohort study	3 (13%)	32–34
Case–control study	1 (4%)	35
Discrete choice model	1 (4%)	36
Analytical method		
Descriptive statistics	9 (39%)	15,17–19,25,30,32–34
Descriptive statistics with significance testing	2 (9%)	16,35
Interrupted Time Series regression analysis	10 (43%)	14,20–24,26,28,29,31
Poisson *R*	1 (4%)	27
Discrete choice model	1 (4%)	36
Outcomes used for assessing impact [a]		
Behavioural change	4 (17%)	21,25,34,36
Health outcomes	8 (35%)	15,16,24,27,32–35
Use of other drugs	16 (70%)	14,15,17–26,28–31
Multiple outcomes[a]	5 (22%)	15,21,24,25,34
Type of anticipated or reported unintended impact[a]		
Changes in health behaviour/outcomes	9 (39%)	15,16,21,24,27,32–35
Spill-over effects	4 (17%)	21–23,36
Use of drug substitutes	14 (61%)	14,15,17–20,22,24–26,28–31
Shifts in diagnoses	1 (4%)	25
Multiple types[a]	5 (22%)	15,21,22,24,25

[a]Studies that used multiple outcomes or assessed multiple types of unintended impact were counted more than once for each applicable category.

TABLE 3 Characteristics of publications addressing unintended impact assessments of pharmacovigilance regulatory interventions.

Outcome measure (n of unintended impact publications, %)	Unintended impact assessed (n of unintended impact publications, %)
Use of other drugs, 16 (70%)	Use of drug substitutes ($n = 14$)
	Spill-over effects ($n = 3$)
Health outcomes, 8 (35%)	Glycaemic control indicators ($n = 2$)
	The proportion of hospitalized patients ($n = 2$)
	Blood transfusions during surgery, the volume of blood lost during surgery and postoperative morbidity ($n = 1$)
	Adverse events reports ($n = 1$)
	Suicide rates ($n = 1$)
	Case reports on poisonings ($n = 1$)
Behavioural change, 4 (17%)	Concomitant use of drugs ($n = 1$)
	Shifts in diagnoses ($n = 1$)
	Discontinuation of replacement therapy ($n = 1$)
	Spill-over effects ($n = 1$)

Our study extends previous work regarding the unintended impact of pharmacovigilance regulatory interventions. We focused specifically on publications aiming to assess the unintended impact of regulatory interventions in the EEA countries, while previous reviews applied no geographical restrictions.[3–5] Furthermore, we used a longer study period after the 2017 GVP changes: Georgi *et al.* review included interventions up to 12 January 2019, while our period extended to 28 February 2022.[3] Our assumption is that a longer follow-up period is

needed to cover the lags in implementing the guidelines. However, as mentioned previously, we did not find a marked change in the number of publications assessing unintended impact.

We classified publications as unintended impact publications if, based on the information provided in the methods section, the selected outcomes were outside the scope of the described pharmacovigilance regulatory intervention. This approach differed from the review done by DeFrank *et al*., where the studies were selected if the authors conveyed that their study findings could be the unintended impact of regulatory actions.[5] The difference was based on our aim to assess the methodology of studies that aim to assess unintended impact, and DeFrank's approach would exclude all the studies that assessed but did not find unintended impact. Since the same outcome can be used to assess both intended and unintended impact, relying only on study findings might also include unintended impact that was anticipated when planning the study. For example, in 2 publications that assessed interventions targeting only females, male subjects were also included in the analysis, and the results were stratified by sex.[37,38] Since the authors did not clarify why male subjects were included in the study, it is unclear whether this subgroup was selected as a control group assuming only secular change or as a group to check possible spill-over effects. Based on this lack of clarity about methodological considerations, we classified these studies as assessing only the intended impact.

We considered the inclusion of other medicines not targeted by the intervention as a method to assess unintended impact. Of note, only in 1 study was the choice to include additional medicines to check for spill-over effects explicitly mentioned.[23] Nevertheless, we did not consider publications that assessed only drug switches after a market withdrawal as unintended impact publications because they did not specify whether the included drugs in the study were desirable alternatives after the withdrawal or not. If market withdrawals of medicines are implemented as a regulatory intervention due to an unfavourable benefit–risk ratio, the need to treat the condition remains. Therefore, the withdrawal of a drug might lead to the use of other therapies. If publications do not state which drug switches are preferred, it is unclear if other drugs are used to assess unintended impact or only to describe the clinical decision-making after the market withdrawal.

Most publications assessed the impact of DHPCs or other communication strategies to disseminate information about drug safety ($n = 67$, 70%) that are meant to remind or update healthcare provider knowledge about the safe use of medicines. These results concur with previous reviews assessing the effectiveness of various pharmacovigilance regulatory interventions.[39–42] However, in many cases, the purpose of DHPC was to inform healthcare professionals about new restrictions, contraindications or other routine measures to minimize risk. In fact, 26 publications (27%) assessed the impact of several pharmacovigilance regulatory interventions implemented simultaneously or following each other in quick succession. Furthermore, while 36 publications mentioned that the study aimed to assess pharmacovigilance regulatory interventions of national authorities, some mentioned EMA referral procedures and other actions in the introduction, indicating that EU-wide and national interventions might overlap. Besides pharmacovigilance regulatory interventions, other factors could also contribute to drug use. For example, 5 studies mentioned increased media attention to the drug's safety, of which 3 studies considered this in the analysis.[25,43,44] Although the dates of the communications issued offer certainty about the start of the intervention, these overlapping decisions and additional factors surrounding the implementation of pharmacovigilance regulatory interventions can lead to biased estimates of the impact of pharmacovigilance regulatory interventions, including their unintended impact. A possible solution to this could be a more thorough communication about all pharmacovigilance regulatory interventions and additional actions related to the safety of the medicines, as presented by Pinto *et al*., who assessed the impact of pharmacovigilance regulatory interventions targeting nimesulide.[45] This study included the description of a search strategy to identify regulatory interventions targeting nimesulide, including media attention and Google search patterns, and based on search results, constructed and visually depicted periods of regulatory actions instead of focusing on the specific date of the intervention.[45]

While regulatory interventions issued by EMA are mandatory for all Member States, most regulatory interventions are implemented by national authorities, which can lead to differences in outcomes between the Member States. Different impact assessments between countries might affect the generalizability of results which could be even more aggravated because some studies only use data from a single country or even from parts of countries. Among included publications, multinational studies examining the impact of pharmacovigilance regulatory interventions for diclofenac and hydroxyzine initiation and discontinuation reported that the possible impact of interventions differed between countries based on trend and step changes.[28,29] This could be due to different implementation strategies used by competent authorities and different levels of drug use in the preintervention periods.

In addition to the possible differences between national implementation of pharmacovigilance regulatory interventions, not all countries are equally involved in conducting impact assessments. Even though the regulatory interventions are mandatory for all EU Member states and usually implemented by all EEA countries, we did not identify a single impact study for 16 out of the current 30 EEA countries. Although the discrepancies might be explained by different infrastructures for pharmacoepidemiological research, the same could apply to the frameworks of information dissemination to healthcare providers and their involvement. Thus, the current coverage raises generalizability issues and suggests a need for a broader selection of countries for future impact studies.

Most of the publications reported drug use as the primary outcome. While aggregated dispensing or prescribing data of a specific medicine can be used as a proxy for drug use, it does not provide information on the impact on individual medicine users. The change in medication use in the general population may overlook the unintended impact that the spill-over effect could cause a decrease in use in other populations, as demonstrated by Dubois *et al*. The authors reported a change in the use of SSRIs in the general population

following a regulatory intervention targeting only children and adolescents.[36] In addition to the outcome selection, the data source is also important. Three studies assessing possible health outcomes of unintended impact used spontaneous reporting registries.[16,24,27] While health outcomes seem more direct to check the impact on a patient, they might lack the sensitivity to detect possible impact, as discussed by Dal Pan.[39]

Our study has some limitations. First, not all the research on impact assessments may have been published in scientific journals. Since most impact assessments are communicated within regulatory procedure reports, our systematic review might not have captured all relevant studies. Second, publications might also be missed with the search strategy due to a lack of standardized reporting of study designs, analytical methods and outcomes. To minimize the impact of this heterogeneity of the reporting, we supplemented the search strategy with references identified in reviews and publications found by applying snowballing technique via an online tool connected papers.[12] Also, the assessment of publications was challenged by the heterogeneity of methods and data sources and the lack of standardized reporting. These issues could be improved by adding a comprehensive framework of methodological suggestions for these studies in guidelines for pharmacoepidemiological studies.[46] Current guidelines only offer examples of previously conducted impact studies as possible considerations.[9,10] In addition, tools that aim for more transparent and clear reporting of postauthorization safety publications could be applied in the context of impact publications. These include the structure of the postauthorization safety publication study protocol template suggested in GVP, the ENCePP checklist for protocol guidelines and making the protocols publicly available by registering them at the ENCePP register.[10,47] Of all included unintended impact publications, only 2 had their study protocols registered in the EU PAS register, and 1 was registered at ClinicalTrials.gov website.[28–30]

Our study highlights that assessments of the unintended impact of risk minimization measures are still lacking. Different terms used to describe outcomes when addressing unintended impact suggest the need to clarify the definitions used to describe unintended impact. Additionally, the high variability of the methods and their description used in unintended impact assessments makes it difficult to set an example of how these assessments should be performed. Harmonizing the tools used for impact assessments is necessary to help researchers standardize impact assessments of risk minimization measures. Lastly, there is a need for continuous attention to unintended impact when conducting pharmacovigilance regulatory intervention assessments. Possible solutions include more elaborate guidelines supporting impact assessments and more transparent reporting of the methodology used in these assessments, for example, by publishing the study protocols in open-access registries.

5 | CONCLUSION

Our systematic review shows that despite growing attention to unintended impact assessments of pharmacovigilance regulatory interventions in related guidelines and recommendations, unintended impact is assessed in only a minority of such studies. These results underline the need for further incentives for conducting unintended impact assessments of pharmacovigilance regulatory interventions and a more standardized way of performing and reporting these studies.

AUTHOR CONTRIBUTIONS

Tomas Lasys, Yared Santa-Ana-Tellez, Satu J. Siiskonen, Rolf H.H. Groenwold and Helga Gardarsdottir contributed to the conceptualization of the study, formed the study design and had key contributions to the research protocol. Tomas Lasys took responsibility for gathering all the required data. Tomas Lasys, Yared Santa-Ana-Tellez and Satu J. Siiskonen performed data analysis, quality checks and interpretation. Helga Gardarsdottir was the principal investigator of the study. Drafting the manuscript was a shared responsibility of all authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

After the publication, data and other material related to our systematic review will be uploaded to the osf.io portal (DOI: 10.17605/OSF.IO/RDM3E).[48]

ORCID

Tomas Lasys https://orcid.org/0000-0002-8892-9820
Yared Santa-Ana-Tellez https://orcid.org/0000-0003-3086-446X
Satu J. Siiskonen https://orcid.org/0000-0003-3095-9530
Rolf H. H. Groenwold https://orcid.org/0000-0001-9238-6999
Helga Gardarsdottir https://orcid.org/0000-0001-5623-9684

REFERENCES

1. Commission Implementing Regulation (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council. *Official Journal of the European Union*. 2012; L159/5.
2. European Medicines Agency. Good pharmacovigilance practices. Published online 17 September 2018. Accessed June 30, 2022. https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices
3. Georgi U, Lämmel J, Datzmann T, Schmitt J, Deckert S. Do drug-related safety warnings have the expected impact on drug therapy? A systematic review. *Pharmacoepidemiol Drug Saf*. 2020;29(3):229-251. doi:10.1002/pds.4968
4. Goedecke T, Morales DR, Pacurariu A, Kurz X. Measuring the impact of medicines regulatory interventions – systematic review and methodological considerations. *Br J Clin Pharmacol*. 2018;84(3):419-433. doi:10.1111/bcp.13469
5. DeFrank JT, McCormack L, West SL, Lefebvre C, Burrus O. Unintended effects of communicating about drug safety issues: a critical review of the literature. *Drug Saf*. 2019;42(10):1125-1134. doi:10.1007/s40264-019-00840-3
6. van Hunsel F, Gardarsdottir H, de Boer A, Kant A. Measuring the impact of pharmacovigilance activities, challenging but

important. *Br J Clin Pharmacol*. 2019;85(10):2235-2237. doi:10.1111/bcp.14042

7. Hedenmalm K, Kurz X, Morales D. Effect of withdrawal of fusafungine from the market on prescribing of antibiotics and other alternative treatments in Germany: a pharmacovigilance impact study. *Eur J Clin Pharmacol*. 2019;75(7):979-984. doi:10.1007/s00228-019-02650-z
8. Sultana J, Fontana A, Giorgianni F, et al. The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study. *CNS Drugs*. 2016;30(11):1097-1109. doi:10.1007/s40263-016-0366-z
9. European Medicines Agency. Guideline on good pharmacovigilance Practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (EMA/204715/2012 rev 2). Published Online 28 March 2017. Accessed June 12, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf
10. ENCePP. Guide on Methodological Standards in Pharmacoepidemiology Rev. 10. Accessed March 6, 2023. https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml
11. Study protocol: impact of medicines regulatory interventions in Europe: a systematic review focusing on unintended consequences, data used and methodology. Accessed March 6, 2023. https://www.encepp.eu/encepp/viewResource.htm?id=47826
12. Connected Papers|Find and explore academic papers. Accessed January 9, 2023. https://www.connectedpapers.com/
13. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (EMA/838713/2011 Rev 2). Published Online 28 March 2017. Accessed August 20, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
14. Georgi U, Tesch F, Schmitt J, de With K. Impact of safety warnings for fluoroquinolones on prescribing behaviour. Results of a cohort study with outpatient routine data. *Infection*. 2021;49(3):447-455. doi:10.1007/s15010-020-01549-7
15. Ehrenstein V, Hernandez RK, Ulrichsen SP, et al. Rosiglitazone use and post-discontinuation glycaemic control in two European countries, 2000–2010. *BMJ Open*. 2013;3(9):e003424. doi:10.1136/bmjopen-2013-003424
16. The French Network of Pharmacovigilance Centres, Pageot C, Bezin J, et al. Impact of medicine withdrawal on reporting of adverse events involving therapeutic alternatives: a study from the French spontaneous reporting database. *Drug Saf*. 2017;40(11):1099-1107. doi:10.1007/s40264-017-0561-y
17. Leal I, Romio SA, Schuemie M, Oteri A, Sturkenboom M, Trifirò G. Prescribing pattern of glucose lowering drugs in the United Kingdom in the last decade: a focus on the effects of safety warnings about rosiglitazone. *Br J Clin Pharmacol*. 2012;75(3):861-868. doi:10.1111/j.1365-2125.2012.04401.x
18. Bachmann CJ, Aagaard L, Burcu M, et al. Trends and patterns of antidepressant use in children and adolescents from five western countries, 2005–2012. *Eur Neuropsychopharmacol*. 2016;26(3):411-419. doi:10.1016/j.euroneuro.2016.02.001
19. Sørensen AMS, Rasmussen L, Ernst MT, et al. Use of tramadol and other analgesics following media attention and risk minimization actions from regulators: a Danish nationwide drug utilization study. *Eur J Clin Pharmacol*. 2021;77(4):617-624. doi:10.1007/s00228-020-03016-6
20. Lombardi N, Vannacci A, Bettiol A, et al. Prescribing trends of codeine-containing medications and other opioids in primary care after a regulatory decision: an interrupted time series analysis. *Clin Drug Investig*. 2019;39(5):455-462. doi:10.1007/s40261-019-00767-8
21. Valkhoff VE, van Soest EM, Masclee GMC, et al. Prescription of non-selective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal - a 617 400-patient study. *Aliment Pharmacol Ther*. 2012;36(8):790-799. doi:10.1111/apt.12028
22. Herdeiro MT, Soares S, Silva T, Roque F, Figueiras A. Impact of rosiglitazone safety alerts on oral antidiabetic sales trends: a countrywide study in Portugal. *Fundam Clin Pharmacol*. 2016;30(5):440-449. doi:10.1111/fcp.12207
23. Hostenkamp G, Fischer KE, Borch-Johnsen K. Drug safety and the impact of drug warnings: an interrupted time series analysis of diabetes drug prescriptions in Germany and Denmark. *Health Policy*. 2016;120(12):1404-1411. doi:10.1016/j.healthpol.2016.09.020
24. Kennedy C, Duggan E, Bennett K, Williams DJ. Rates of reported codeine-related poisonings and codeine prescribing following new national guidance in Ireland - Kennedy - 2019 - Pharmacoepidemiology and Drug Safety - Wiley Online Library. Published Online 2019. Accessed February 7, 2022. https://onlinelibrary.wiley.com/doi/10.1002/pds.4725
25. Wijlaars LPMM, Nazareth I, Petersen I. Trends in depression and antidepressant prescribing in children and adolescents: a cohort study in The Health Improvement Network (THIN). *PLoS ONE*. 2012;7(3):e33181. doi:10.1371/journal.pone.0033181
26. Guthrie B, Clark SA, Reynish EL, McCowan C, Morales DR. Differential impact of two risk communications on antipsychotic prescribing to people with dementia in Scotland: segmented regression time series analysis 2001–2011. *PLoS ONE*. 2013;8(7):e68976. doi:10.1371/journal.pone.0068976
27. Isacsson G, Ahlner J. Antidepressants and the risk of suicide in young persons – prescription trends and toxicological analyses. *Acta Psychiatr Scand*. 2014;129(4):296-302. doi:10.1111/acps.12160
28. Morales DR, Macfarlane T, MacDonald TM, et al. Impact of EMA regulatory label changes on hydroxyzine initiation, discontinuation and switching to other medicines in Denmark, Scotland, England and the Netherlands: an interrupted time series regression analysis. *Pharmacoepidemiol Drug Saf*. 2021;30(4):482-491. doi:10.1002/pds.5191
29. Morales DR, Morant SV, MacDonald TM, et al. Impact of EMA regulatory label changes on systemic diclofenac initiation, discontinuation, and switching to other pain medicines in Scotland, England, Denmark, and the Netherlands. *Pharmacoepidemiol Drug Saf*. 2020;29(3):296-305. doi:10.1002/pds.4955
30. Istvan M, Caillet P, Rousselet M, et al. Change in the regulatory framework for zolpidem: what is the impact on the landscape of the prescription of sedative medications? The French national ZORRO study. *Br J Clin Pharmacol*. 2021;87(8):3310-3319. doi:10.1111/bcp.14753
31. Rousselot N, Pariente A, Mansiaux Y, Victorri-Vigneau C. Impact of secured prescription implementation for zolpidem on hypnotics use in France: a time-series analysis on national data. *Ann Family Med*. 2020;18(4):345-348. doi:10.1370/afm.2556
32. Morgan CL, Puelles J, Poole CD, Currie CJ. The effect of withdrawal of rosiglitazone on treatment pathways, diabetes control and patient outcomes: a retrospective cohort study. *J Diabetes Complications*. 2014;28(3):360-364. doi:10.1016/j.jdiacomp.2014.01.007
33. Purhonen M, Koponen H, Tiihonen J, Tanskanen A. Outcome of patients after market withdrawal of thioridazine: a retrospective analysis in a nationwide cohort. *Pharmacoepidemiol Drug Saf*. 2012;21(11):1227-1231. doi:10.1002/pds.3346
34. Sheldon RJG, Pereira M, Aldersley G, et al. Clinical outcomes following switching antipsychotic treatment due to market withdrawal: a retrospective naturalistic cohort study of pipotiazine palmitate injection (Piportil Depot) discontinuation, subsequent acute care

use and effectiveness of medication to which patients switched. *Ther Adv Psychopharmacol*. 2022;12:20451253211067040. doi:10.1177/20451253211067042

35. Walkden GJ, Verheyden V, Goudie R, Murphy GJ. Increased perioperative mortality following aprotinin withdrawal: a real-world analysis of blood management strategies in adult cardiac surgery. *Intensive Care Med*. 2013;39(10):1808-1817. doi:10.1007/s00134-013-3020-y
36. Dubois P, Tunçel T. Identifying the effects of scientific information and recommendations on physicians' prescribing behavior. *J Health Econ*. 2021;78:102461. doi:10.1016/j.jhealeco.2021.102461
37. Vázquez Mourelle R, Carracedo-Martínez E, Figueiras A. Impact of a health alert and its implementation on flutamide prescriptions for women: an interrupted time series analysis. *BMC Health Serv Res*. 2020;20(1):597. doi:10.1186/s12913-020-05453-6
38. Polard E, Degremont A, Rault C, et al. Trends in sodium valproate prescriptions among children aged 0 to 14 years between 2010 and 2016: a study based on the French National Health Insurance Database. *Seizure*. 2019;70:71-76. doi:10.1016/j.seizure.2019.07.007
39. Dal Pan GJ. The use of real-world data to assess the impact of safety-related regulatory interventions. *Clin Pharm Ther*. 2022;111(1):98-107. doi:10.1002/cpt.2464
40. Vora P, Artime E, Soriano-Gabarró M, Qizilbash N, Singh V, Asiimwe A. A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic register of post-authorization studies. *Pharmacoepidemiol Drug Saf*. 2018;27(7):695-706. doi:10.1002/pds.4434
41. Artime E, Qizilbash N, Garrido-Estepa M, et al. Are risk minimization measures for approved drugs in Europe effective? A systematic review. *Expert Opin Drug Saf*. 2019;18(5):443-454. doi:10.1080/14740338.2019.1612875
42. Artime E, Qizilbash N, Herruzo R, Garrido-Estepa M. Risk minimisation evaluation with process indicators and behavioural or health outcomes in Europe: systematic review. *Pharm Med*. 2020;34(6):387-400. doi:10.1007/s40290-020-00361-w
43. Berger F, Saâïd S, van Gelder T, Stricker B, Becker M, van den Bemt P. Media attention regarding sudden cardiac death associated with domperidone use does not affect in hospital ECG recording. *Pharmacoepidemiol Drug Saf*. 2017;26(11):1418-1424. doi:10.1002/pds.4321
44. Hernandez JF, Mantel-Teeuwisse AK, van Thiel GJMW, et al. A 10 year analysis of the effects of media coverage of regulatory warnings on antidepressant use in the Netherlands and UK. Alessi-Severini S, ed. *PLoS ONE*. 2012;7(9):e45515. doi:10.1371/journal.pone.0045515
45. Pinto D, Silva A, Heleno B, Rodrigues DS, Santos I, Caetano PA. Effect of European medicines agency's regulatory measures on nimesulide utilization in Portugal. *Pharmacoepidemiol Drug Saf*. 2018;27(6):630-637. doi:10.1002/pds.4424
46. Arlett P. Measuring the impact of risk communications: robust analytical approaches are key. *Br J Clin Pharmacol*. 2020;86(4):635-636. doi:10.1111/bcp.14222
47. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII – Post-authorisation safety studies (EMA/813938/2011 rev 3). Published Online 9 October 2017. Accessed June 12, 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf
48. Lasys T, Santa-Ana-Tellez Y, Siiskonen SJ, Groenwold RHH, Gardarsdottir H. Unintended impact of pharmacovigilance regulatory interventions: a systematic review. Additional Material Published Online 11 July 2023. doi:10.17605/OSF.IO/RDM3E

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Lasys T, Santa-Ana-Tellez Y, Siiskonen SJ, Groenwold RHH, Gardarsdottir H. Unintended impact of pharmacovigilance regulatory interventions: A systematic review. *Br J Clin Pharmacol*. 2023;89(12):3491-3502. doi:10.1111/bcp.15874