SYSTEMATIC REVIEW

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Impact of Safety-Related Regulatory Action on Clinical Practice

A Systematic Review

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Abstract

Background: After market approval, new serious safety issues are regularly identified for drugs that lead to regulatory action to inform healthcare professionals. However, the effectiveness of these safety-related regulatory actions is under question. We currently lack a comprehensive overview of the effects of these drug safety warnings on clinical practice to resolve the debate about their effectiveness.

Objective: The aim of this systematic review is to provide an overview of studies that assessed the impact of safety warnings.

Study Selection: A systematic search was performed for articles assessing the impact of Direct Healthcare Professional Communications or 'Dear Doctor' letters, Black Box Warnings and Public Health Advisories on clinical behaviour published between January 1996 and January 2010. The following variables were extracted: publication year, country, name of the drug, safety issue, specific safety warning (Direct Healthcare Professional Communication/Black Box Warning/Public Health Advisory), effect (intended/unintended) of the safety warning, outcome measure and study design. Papers were checked for several quality aspects. Study data were summarized using descriptive analyses.

Results: A total of 50 articles were identified. Two articles assessed two different drugs and were therefore counted twice (n = 52). Thirty-three articles described the impact of safety warnings issued for three drugs and drug groups, i.e. third-generation oral contraceptives, cisapride and selective serotonin reuptake inhibitors. The remaining 19 articles described a broad variety of 14 drugs and drug groups. Twenty-five studies applied an interrupted time series design, 23 a controlled or uncontrolled before/after design, and four articles applied both. None of the articles could rule out the influence of confounding factors. The intended effects were reported in 18 (72%) of the 25 before/after analyses, whereas only 11 (41%) of the 27 interrupted time series analyses reported an impact. Only two (8%) of the before/after analyses against

11 (41%) of the interrupted time series analyses reported mixed impacts. When unintended effects were assessed in case of selective serotonin reuptake inhibitors and third-generation oral contraceptives, these were almost always present: in 19 of 22 and 4 of 5 articles, respectively. Our review shows that safety-related regulatory action can have some impact on clinical practice but firm conclusions are difficult to draw. Evidence is primarily based on three drugs and drug groups. Almost half of the studies had inadequate before/after designs and the heterogeneity in analyses and outcome measures hampered the reporting of overall effect sizes. Studies with adequate interrupted time series design reported a more mixed impact of safety warnings than before/after studies. Furthermore, this review shows the relevance of considering not only the intended but also the unintended effects of safety warnings.

Conclusions: There is a clear need for further research with appropriate study designs and statistical analyses, with more attention to confounding factors such as media coverage, to understand the impact of safety-related regulatory action.

1. Background

Knowledge of the full benefit-risk profile of a drug at the time of market approval is incomplete. Pre-registration trials are limited in establishing the full safety profile of new drugs due to, for example, small sample size, short duration and a homogeneous study population.[1,2] In approximately 10% of all marketed drugs, safety-related regulatory action is required for new and serious safety issues[3-5] leading to hospitalization, disability or even death.[6,7] With these safety warnings, healthcare professionals and patients are informed of these safety issues or even of the possible withdrawal of the drug from the market.

Regulatory authorities and the pharmaceutical industry employ several safety warnings to inform healthcare providers of serious safety issues of drugs.[8] The summary of product characteristics can be updated with new safety information. Public Health Advisories (US only) permit the notification of patients and physicians of a serious safety issue to improve selection of medication. A Black Box Warning (US only) highlights a drug's potential safety issues in a framed box on the label and the patient package inserts. A Direct Healthcare Professional Communication (DHPC) [in the EU] and Dear Healthcare Professional letter (in the US) or 'Dear Doctor' letter (further referred to as a DHPC) is a paper-based personalized mailing to healthcare professionals. Finally, a drug can be withdrawn from the market due to a safety issue when the benefits of a drug no longer outweigh its risks.

The effectiveness of safety warnings has been criticized.[9,10] Previous research concluded that safety warnings can be effective, albeit not always and not always sufficiently.[10] Additionally, safety warnings have resulted not only in *intended*, but also in *unintended* effects. The safety warnings for selective serotonin reuptake inhibitors resulted in *intended* reduced prescription in the population at risk after the identification of an increased risk of suicidality and suicidal thoughts in children and adolescents.[11] Unfortunately, some *unintended* effects were also reported. The prescription of selective serotonin reuptake inhibitors decreased in adults as well,[12-14] possibly associated with a temporal increase in suicidality in the general population,[12] although these results have been contradicted.[15]

The experience with selective serotonin reuptake inhibitors indicates that several inventories of effectiveness of safety warnings have been performed, but with various results. The overall effect of safety warnings is unclear. Since the monitoring of the outcome of risk minimization measures will become mandatory in the near

future, such an overview is required.[16,17] To that end, we performed a systematic review of the effects – both intended and unintended – of safety warnings on clinical practice. In this review, we specifically targeted DHPCs, Black Box Warnings and Public Health Advisories when referring to safety warnings.

2. Literature Search

2.1 Search Strategy

A systematic search for articles published between January 1996 and January 2010 evaluating the impact of DHPCs, Black Box Warnings and Public Health Advisories safety-related regulatory actions was performed in three steps. First, index terms and free text words were identified from an initial set of papers retrieved by random search. Based on the terms used in these articles, we systematically searched the online literature databases MEDLINE and EMBASE for relevant papers without any language restrictions (table I). A second search in MEDLINE and EMBASE was performed based on drugs with a DHPC in the Netherlands. We added this step because the initial analyses indicated that we were missing relevant publications. As a third step, the included papers' references were checked (snowballing) and a first author search was performed to search for additional relevant papers.

Two reviewers (SP/JV and PM) independently evaluated all the papers identified for eligibility. A first selection was based on titles and abstracts and a second and final selection was based on examination of each full paper. Any disagreements were resolved during consensus meetings with a third reviewer (SS).

2.2 Inclusion and Exclusion Criteria

Only randomized trials, quasi experiments (interrupted time series and controlled or uncontrolled before/after studies) evaluating the impact of DHPCs, Black Box Warnings and/or Public Health Advisories on clinical practice were included. In randomized trials the impact of an intervention is assessed by comparing an intervention group to a randomly assigned control group. Both groups are exposed to the same biases and therefore considered alike, permitting the assessment of the causal effect of an intervention. Before/after studies are used to measure the impact of safety warnings at three or fewer timepoints both before and after the intervention. Interrupted time series designs have data collected at multiple instances (preferably >20 datapoints) before and after an intervention, with the

Table I. Search strategy[a]

		And	And	And
Step 1: systematic literature search	((Drug information* OR drug information) OR (drug labelling* OR drug labelling) OR (drug surveillance program* OR drug surveillance program) OR (drug monitoring* OR drug monitoring) OR (drug contraindication* OR drug contraindication))	(Letter* OR communicat* OR dear doctor OR warning*)	((Clinical study* OR clinical study) OR (time series analysis* OR time series analysis) OR (controlled study* OR controlled study))	Year [1996–2009]
Step 2: DHPC search	(*Active substance* OR *brand name*)	*Safety issue*	(Clinical study* OR time series analysis* OR controlled study*)	[*Year DHPC publication*]
Step 3: snowballing and first author check	References of included papers were hand searched			
	'1st Authors' last name initial(s).'/au			Year [1996–2009]

a Italicized terms were adjusted according to specific drug/safety issue for which the DHPC was issued, or the author.

DHPC = Direct Healthcare Professional Communication.

advantage that they can detect whether an intervention has an effect significantly greater than underlying secular trends.[18]

Cross-sectional articles evaluating only the situation after a safety warning were excluded since no comparative impact could be estimated. For example, articles only evaluating a safety warning in cases of a withdrawal of a drug were excluded, since clinical behaviour will change by definition and the article would therefore cause bias. Opinion articles, surveys, reviews, duplicates in different languages and publications of non-original data were excluded to avoid publication bias.[19]

2.3 Data Extraction

Five reviewers (SP, JV, ME, FT and PM working in varying pairs) systematically extracted the following variables: publication year, country, drug name, safety issue, effect (intended/unintended), study design, safety warning type (DHPC/Black Box Warning/Public Health Advisory) and outcome measure. The Cochrane Effective Practice and Organisation of Care Review Group (EPOC) quality criteria for interrupted time series studies score list was used to check the quality aspects of the studies.[20] The same quality aspects were scored for before/after papers, except for items that were only applicable to interrupted time series design studies. Again, any disagreements were resolved by consensus or, if necessary, by a third reviewer.

The main goal of a safety warning, i.e. to minimize occurrence of the issue, was defined as its intended effect – for instance, to prevent prescription to specific patient groups (e.g. selective serotonin reuptake inhibitors to adolescents/children), to prevent co-prescription in case of a drug-drug interaction (e.g. cisapride and macrolides increasing the risk of QT prolongation), or to promote baseline/follow-up laboratory tests (e.g. liver function testing with troglitazone use).

Unintended effects were defined as unforeseen or unintended – for instance, an increase in suicides after the issuance of warnings restricting the use of selective serotonin reuptake inhibitors in children and adolescents.

The effect of a safety warning was scored on the authors' reports – i.e. a safety warning had an effect, no effect or mixed effects. Mixed effects were defined as an effect for one outcome measure but no effect for another.

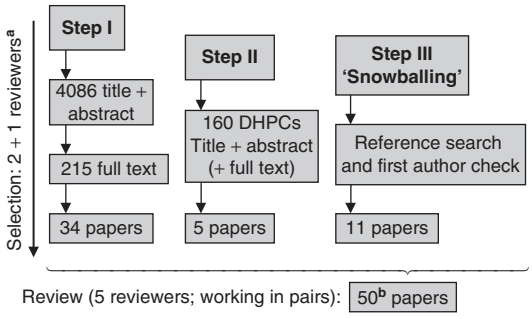
2.4 Data Analysis

Data were summarized according to the following variables: drug group, assessed impact, study design, safety warnings type and outcome measure, using descriptive analyses. The quality of the included studies was scored by adding up each quality aspect that was met. The studies were counted in different ways for each variable:

- Drug group: if an article assessed a safety warning for more than one drug, the article was assigned to all relevant drugs and drug groups. In that case the study was counted more than once.
- Assessed impact: the impact of a safety warning was split into intended and unintended impacts.
- Study design: if one study assessed several outcome measures with different study designs, the result of each individual outcome measure was attributed to the related study design. In such cases a study design was counted more than once.
- Type of safety warning: in papers assessing more than one safety warning, the effect of each safety warning was assessed separately. If more than one safety warning was evaluated, but only one overall effect was presented, the overall effect was attributed to each individual safety warning.
- Outcome measure: if one study assessed several outcome measures, the impact of a safety warning was counted for each individual outcome measure. Consequently, when an impact was observed on drug use but not on a more specific outcome measure such as conducted laboratory tests, the effect of that safety warning was categorized as a mixed effect.

3. Findings

A total of 4086 papers were identified using the first search strategy, of which 215 papers were selected for full-text examination resulting in the inclusion of 34 papers for detailed analysis (figure 1). The second step, based on the safety issues mentioned in 160 DHPCs issued in the Netherlands, yielded a further five eligible papers. Snowballing



a Two reviewers independently evaluated the papers, with a third reviewer adjudicating in a consensus meeting when there was disagreement regarding the eligibility of a study.

b Two of 50 papers evaluated safety-related regulatory action for two different drugs and drug groups.

Fig. 1. Search results. **DHPC** = Direct Healthcare Professional Communication.

yielded another eleven papers. In total 50 papers were included. In two papers[21,22] two different drugs and drug groups were assessed, therefore each paper was counted twice in further analyses (n = 52).

The main results of the data extraction are shown in table II and the key variables of the individual studies are shown in the Appendix table S1 (see Supplemental Digital Content, http://links.adisonline.com/DSZ/A64).

3.1 Drug Group

Three different drugs and drug groups, i.e. third-generation oral contraceptives (increased risk of thrombosis, published 1996–9);[43-51] cisapride (risk of serious cardiac arrhythmias, published 2000–5);[21,23-26,52-54,60] and selective serotonin reuptake inhibitors (risk of suicide in adolescents and children, published 2005–9)[11-15,27-31,55,61-63,66] accounted for 33 articles in our review (table II). The remaining 19 papers described a broad variety of 14 different drugs and drug groups.[21,22,32-41,56-59,64,65]

3.2 Assessed Impact

An *intended* effect was observed in 9 of 14 articles[11-15,27,28,30,31,42,55,61-63] in which the intended effect of safety warnings for selective serotonin reuptake inhibitors was assessed (figure 2). These intended effects primarily concerned (large) decreases of the volume of drug use in children and adolescents, but also improved psychiatric care (Appendix table S1). *Intended* effects of a safety warning issued for third-generation oral contraceptives were assessed in six articles.[44-46,48,49,51] In four of these six articles[44,46,49,51] strong reductions in the use of third-generation oral contraceptives were reported and/or a shift in use towards second-generation oral contraceptives. The remaining two articles[45,48] reported mixed impact; a reduction in drug use was observed but no changes in venous thromboembolism cases and discontinuation rates/switches were reported. In the case of cisapride, 7 of 17 assessed DHPCs[21,23,26,54,60] presented intended effects, and 9[23-26,52,53] showed no intended effects (reduced drug use volume or contraindicated drug use). One DHPC showed mixed results. While no effect was observed for overall use of the DHPC, an effect was observed for new users of cisapride.[21] The early US DHPCs (1995 and 1996) and the Italian 1998 DHPC lacked impact, whereas subsequent US DHPCs (1998 onwards) and the Dutch and New Zealand DHPCs did achieve their intended effects (Appendix table S1).

Articles published on safety warnings issued for the remaining drugs and drug groups reported effects as intended to a varying degree. The three papers assessing terfenadine safety warnings[32-34] reported intended effects on contraindicated drug use, except for contraindicated concomitant use of ketaconazole, which did not decrease.[32] Two of three troglitazone papers reported intended increases in laboratory testing after the safety warnings.[35,36] In the remaining publications a decrease in filled prescriptions was observed only for new drug users and not for all drug users, explained by a higher sensitivity to detect changes in prescriptions for new users.[21] The warning for tramadol failed to achieve the intended decrease in contraindicated drug use.[37,41]

Unintended effects were evaluated for safety warnings issued for selective serotonin reuptake inhibitors and third-generation oral contraceptives. In the 12 publications addressing possible unintended effects, of which four only assessed unintended and no intended effects,[29,43,47,50] nearly all warnings for selective serotonin reuptake inhibitors

(19 of 22 warnings)[12-14,29,55,61] and all four warnings for third-generation oral contraceptives[43,47,49,50] showed unintended effects.

3.3 Study Design

No randomized controlled trials, or controlled before/after studies were identified that assessed the *intended* or *unintended* impact of safety warnings.

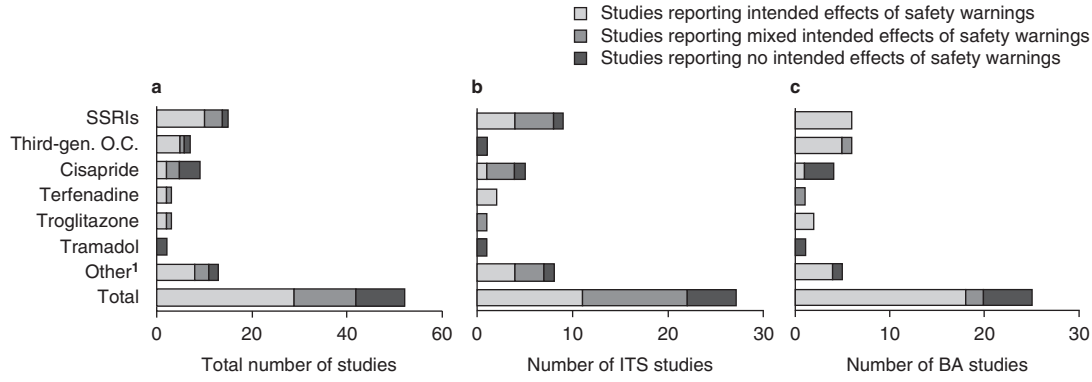
Of those studies evaluating the intended effects, 23 papers applied an interrupted time series design and 21 a before/after design (table II). Four papers applied both interrupted time series and before/after designs for different outcome measures.[22,42,48] These articles are counted twice with respect to our study design analysis, leading to a total of 25 before/after and 27 interrupted time series analyses.

Table II. Study characteristics

Key study characteristics	Number of studies (N = 52) [n (%)]	References
Country		
USA	26 (50)	13,14,21-42
EU	19 (37)	11,15,43-59
Other	7 (13)	12,60-65
Drug or drug group		
SSRIs	15 (29)	11-15,27-31,42,55,61-63
Third-gen. O.C.	9 (17)	43-51
Cisapride	9 (17)	21,23-26,52-54,60
Terfenadine	3 (6)	32-34
Troglitazone	3 (6)	21,35,36
Tramadol	2 (4)	37,41
Other	11 (21)	22,38-40,56-59,64,65
Assessed impact		
Intended effect	40 (77)	11,21-28,30-41,44-46,48,51-54,56-60,62-65
Unintended effect	4 (8)	29,43,47,50
Both intended and unintended effect	8 (15)	12-15,42,49,55,61
Study design		
ITS	25 (48)	13,14,21,23,25-30,33,34,37,39,40,50,55,56,58,60,62-65
BA	23 (44)	11,12,15,24,31,32,35,36,38,41,43-47,49,51-54,61
ITS and BA	4 (8)	22,42,48
Safety warning (n = 97)[a]		
DHPC	65 (67)	11,12,15,21,23-27,29,32-39,41,43-60,62-65
BBW	15 (15)	12,14,22,27-29,31-33,38-40,62
PHA	17 (18)	12-14,28-30,42,56,61,62
Outcome measure (n = 77)[a]		
Drug use (volume)	35 (45)	11,12,12-14,21,22,28,39,40,42,44-46,48-52,55,56,60-65
CI/DDI	17 (22)	22-26,32-34,37,40,41,52-54,59
Laboratory testing	4 (5)	35,36,38,39
Spontaneous ADE reporting	2 (3)	57,58
Care	7 (9)	13,15,28,30,42,56,61
Other	12 (16)	12,15,29,31,43,45,47-49,55,56,61

a The numbers of evaluated safety warnings and outcome measures are larger than the number of included studies as several studies evaluated more than one safety warning and/or outcome measure.

ADE = adverse drug event; **BA** = before/after study or ITS with less than three datapoints before or after an intervention; **BBW** = Black Box Warning; **CI**/**DDI** = contraindicated use/drug-drug interaction; **DHPC** = Direct Healthcare Professional Communication; **ITS** = Interrupted Time Series; **PHA** = public health advisory; **SSRIs** = selective serotonin reuptake inhibitors; **Third-gen. O.C.** = third-generation oral contraceptives.



1 'Other' includes antipsychotics, infliximab, isotretinoin, nimesulide, pemoline, pioglitazone, rosiglitazone, statins, telithromycin, ticlopidine.

Fig. 2. Study design and intended effects per drug and drug group. Panel (**a**) reports the effects of all included studies (n = 52); panel (**b**) of ITS studies only (n = 27); and (**c**) BA studies alone (n = 25). Two papers evaluated safety-related regulatory action for two drugs and drug groups (Wilkinson et al.,[21] Starner et al.[22]) and four papers used both ITS and BA analyses for different outcome measures (Libby et al.,[66] Farmer et al.,[48] Starner et al. [×2][22]) and are therefore represented twice. Four articles assessed only unintended effects of safety warnings and are therefore not reflected in this figure (Forrester.,[29] Child et al.,[43] Williams et al.,[50] Wood et al.[47]). **BA** = before/after study or ITS with less than three datapoints before or after an intervention; **ITS** = Interrupted Time Series; **SSRIs** = selective serotonin reuptake inhibitors; **Third-gen. O.C.** = third-generation oral contraceptives.

Overall, *intended* effects were reported in 29 (56%) of 52 analyses (figure 2). While only 11 (41%) of 27 interrupted time series analyses reported an impact, such intended effects were reported in 18 (72%) of 25 before/after analyses. Eleven (41%) interrupted time series and two (8%) before/after analyses reported mixed impact.

All six papers assessing the *intended* effects of safety warnings on third-generation oral contraceptives had a before/after design (figure 2), one paper also included an interrupted time series analysis where no impact of the warning on venous thromboembolism cases was reported (Appendix table S1).[48] Seventeen interrupted time series and 13 before/after designs were used in the remaining studies. The nine interrupted time series analyses for safety warnings on selective serotonin reuptake inhibitors, mainly reported effects (four articles)[13,42,55,63] and mixed effects (four articles).[14,27,28,62] The five interrupted time series analyses assessing cisapride warnings primarily reported mixed effects (three articles)[21,23,26] for the different warnings that were evaluated.

Unintended effects of the evaluated safety warnings were reported in five of six analyses for both interrupted time series and before/after analyses.

Regarding the quality assessment of the papers, interrupted time series papers scored on average 6.7 out of 8 quality aspects, ranging from 3 to 7 of 8 (Appendix table S1). Before/after papers had a similar average score of 4.6 of 6 quality aspects, ranging from 3 to 5 of 6. All papers used a reliable outcome measure. However, none of the papers could rule out the influence of confounding factors such as media attention. Of the 29 analyses applying the stronger interrupted time series design, 21 used appropriate statistics.

3.4 The Type of Safety Warning

Ninety-seven safety warnings were assessed in the 52 articles, ranging from 1 to 8 warnings per paper and 1 to 13 warnings per drug or drug group (Appendix table S1). Twenty-one papers evaluated more than one safety warning.[12,14,15,21-23,25-29,32,33,35,36,38,39,56,59,62,64] The DHPC was the most frequently evaluated warnings (65 of 97 warnings), with similar numbers of Black Box Warnings (15) and Public Health Advisories (16) evaluated (table II).

Intended effects were evaluated in 91 cases: 52 (57%) showed an impact, 24 (26%) did not and 15 (16%) had mixed effects (figure 3). In our study, DHPCs, Black Box Warnings and Public

Health Advisories had similar patterns of impact as intended by the warnings, showing an effect in 56%, 57% and 61%, respectively, with no effect in 27%, 21% and 31%, respectively, or a mixed effect in 17%, 21% and 8%, respectively.

Effects were reported for nearly all (86%) safety warnings evaluating *unintended* effects but assessment was limited to selective serotonin reuptake inhibitors and third-generation oral contraceptives (Appendix table S1). Only DHPCs were issued for third-generation oral contraceptives, while selective serotonin reuptake inhibitors received DHPCs, Black Box Warnings and Public Health Advisories. No variation in impact was observed across the different safety warnings.

3.5 Outcome Measures

The 52 articles in our study assessed the impact of safety warnings for 77 outcome measures. The majority (28) of articles assessed the intended impact of warnings on clinical behaviour by evaluating overall drug use volume (Appendix table S1).[11,12,14,15,21,22,27,28,39,40,42,44-46,48,49,51,52,55,56,60-65] In some articles more specific drug use measures were assessed: drug-drug interaction/contraindicated use (16 articles),[22-26,32-34,37,40,41,52-54,59] drug use in defined populations (adults, children, etc.) [16 articles],[11,12,14,15,27,28,31,45,48,49,51,55,61-63,66] new users of a drug (1 article),[21] refusal of antidepressant prescription (1 article),[31] or discontinuation rates/switches (1 article).[45] Nine studies assessed care-related outcomes such as the type of healthcare provider (e.g. general practitioner, psychiatrist), diagnosing patterns (5 articles),[13,28,30,42,56] and adherence to performing warning-dictated laboratory tests (4 articles).[35,36,38,39] These papers specifically intended to evaluate the non-drug-treatment recommendations of a warning. Additionally, in five papers clinical outcome measures were assessed, e.g. venous thromboembolism cases (1 article),[48] mortality (1 article),[56] hospital admissions (1 article)[56] and spontaneous adverse drug event reports (2 articles).[57,58]

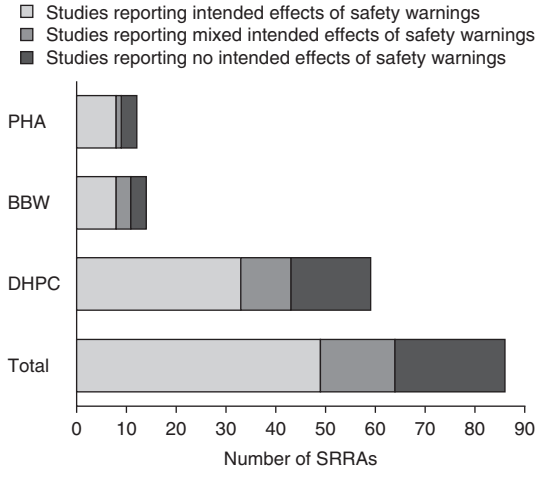


Fig. 3. Safety warnings and intended effects (n = 86). Two papers evaluated warnings for two drugs and drug groups (Wilkinson et al.,[21] Starner et al.[22]) and four papers used both ITS and BA analyses for different outcome measures (Libby et al.,[66] Farmer et al.,[48] Starner et al. (×2)[22]), therefore represented twice. The number of evaluated warnings is larger than the number of included studies, as several studies evaluated more than one safety warning (see Appendix table S1). **BA** = before/after study or ITS with less than three datapoints before or after an intervention; **BBW** = Black Box Warning; **DHPC** = Direct Healthcare Professional Communication; **ITS** = Interrupted Time Series; **PHA** = Public Health Advisory; **SRRAs** = safety-related regulatory actions.

In eight studies the use of multiple outcome measures led to mixed intended effects (Appendix table S1).[21,28,32,39,40,45,48,56] For six of these eight articles, impact was observed on the volume of drug use in general but not for more specific outcome measures such as drug use outcomes, e.g. only new users of troglitazone,[21,40,45] healthcare outcomes such as laboratory tests because of hepatoxicity risks,[39,56] and clinical outcomes such as venous thromboembolism cases in third-generation oral contraceptives.[48,56] The remaining two articles only reported the impact of safety warnings on one of two contraindicated concomitantly used drugs,[32] and the impact of two of the three assessed warnings on the volume of drug use.[56]

The outcome measures for the *unintended* effects of safety warnings were matched with the specific message of a warning (Appendix table S1). All three publications assessing spillover effects (decreased drug use by the non-targeted adult population) of the selective serotonin reuptake inhibitor warnings reported effects.[12-14] The outcome measures related to suicide and suicidal thoughts (self-poisoning, suicide rates and hospital admissions) showed more varied results.

Two articles reported increases in self-poisoning cases;[29,55] but of three articles assessing suicide rates,[12,15,61] one[15] reported no increase. The latter study also found no increase in hospital admissions for self-harm.[15] Lastly, impact was found on health services use, as shown by a decrease in the rate of physician visits after the safety warning.[61]

Both articles assessing abortions after a safety warning for third-generation oral contraceptives reported increases in the number of abortions.[43,49] In addition, an increase in conceptions was observed.[47] Moreover, a decrease in third-generation oral contraceptive use was observed in Ireland, although this was not in line with recommendations by national authorities.[50]

4. Discussion

This systematic review provides the first overview of articles published on the effect of safety warnings. We identified 52 studies that assessed the impact of safety warnings on clinical practice. Intended effects were found in the majority of cases but varied between drugs and drug groups. Unintended effects were also reported. No firm conclusions on effect size can be drawn due to a number of factors, including the small number of drug groups evaluated, deficiencies in the study design and inconsistency in outcome measures.

The available studies mainly assessed three drug groups: selective serotonin reuptake inhibitors, third-generation oral contraceptives and cisapride. The focus on these drug groups is in line with the extensive media attention that two of these safety-related issues received. The studies included indicated that the so-called 'pill scare' had a very large impact, specifically in the UK[43-48] after the UK Committee of Safety of Medicine advised discontinuation of third-generation oral contraceptive use. Consequently, the warnings resulted in a similar impact in adjacent countries that had taken a less rigorous approach.[50] A BBC broadcast[67] in the UK about self-harm and suicide related to the selective serotonin reuptake inhibitor paroxetine caused further media attention in several countries, which was followed by an extensive reassessment of the benefits and risks associated with the product group and a number of successive regulatory actions, especially in the US.[68] The debate about cisapride seems to have been triggered by the potential preventability of prescribing concomitant contraindicated drugs, but did not generate as much public interest.

Data related to selective serotonin reuptake inhibitors and third-generation oral contraceptives also shows that the observed impact was not always as intended, which highlights the relevance of taking not only the intended but also the unintended effects into account. Of eight selective serotonin reuptake inhibitor papers evaluating the unintended effects of the warnings, six identified unintended effects such as increases in suicide rates and unintended spillover effects, in particular decreased use of antidepressants in adults. Unintended effects of the warnings were also found for third-generation oral contraceptives: increases in conceptions and abortion rates were observed. The concerns surrounding this specific safety issue caused many women to switch to other oral contraceptives or to cease using oral contraceptives all together.

How to present risk to the general public was extensively discussed as a result of the 'pill scare'. The risk of venous thromboembolism with third-generation oral contraceptive use was presented as doubling. This implied a large increase in risk, although the absolute risk of venous thromboembolism was still smaller than that of venous thromboembolism during pregnancy. Afterwards, restrictions on third-generation oral contraceptive use were withdrawn in the UK and the wording of the warning was adjusted.[69]

Almost half of the studies applied a before/after design, which coupled with heterogeneity in the analyses and outcome measures hampered reporting of overall effect sizes of safety warnings. Inclusion of before/after studies could be considered a limitation due to their inherent methodological flaws.[70] For example, with a before/after study design it is not possible to control for seasonal changes in drug use. However, it is suggested that using a before/after design could be valid where a comparable control group is used to assess any differences between the groups that could be attributed to the intervention.[71] Notwithstanding that, all papers with before/after

design were included in the systematic review to provide a comprehensive overview of what had been evaluated to date. Interrupted time series design is the best available study design to evaluate the impact of policy changes where it is almost impossible to employ a control group, and it is regarded as the 'strongest' quasi-experimental study design.[72] When considering the interrupted time series studies alone, the most apparent intended effects of safety warnings were observed in the case of terfenadine through a decrease in contraindicated drug use. In cases of the selective serotonin reuptake inhibitors and cisapride, the majority of interrupted time series studies reported mixed effects, mainly regarding the volume of drug use.

The interpretation of results is further complicated because of the assessment of different outcome measures (e.g. drug use/contraindicated drug use/laboratory tests/spontaneous adverse drug event reports), different interventions (DHPCs/Black Box Warnings/Public Health Advisories), and the heterogeneity of analyses. However, since the warnings can have different intentions, assessing specific outcome measures regarding the safety issue in question is a more accurate method to detect the intended impact of a warning. For example, where a DHPC is issued to address an increased hepatoxicity risk, with a recommendation for testing the liver function of patients, assessing the impact on laboratory tests could be more appropriate than simply assessing drug use.

In addition, the majority of the papers included did not assess every safety warning that was issued for the drugs and drug groups. Sometimes, warnings were preceded by or coincided with other warnings regarding the same safety issue, and which were not analysed in the study. This was the case in the study by Gibbons et al.[12] in which several warnings issued between October 2003 and December 2006 were evaluated, although three other warnings issued within that period (between September and December 2005), were not assessed. These other warnings may have strengthened the safety message, the impact of which was assessed, and therefore have biased the results. Similarly, several articles reported an overall effect only, and lacked assessment of the effect by individual warnings. Therefore, our data do not allow the drawing of conclusions about which safety warning strategy is more effective, especially since two-thirds of the warnings evaluated concerned DHPCs.

A limitation of the outcome in all studies was that none of the papers could rule out the influence of confounding factors such as media attention, which could have strengthened the effect of the safety warnings. For example, in the case of the increased risk of suicide and suicidal thoughts in selective serotonin reuptake inhibitor use, the media hype that occurred could have been an influential factor on the effect of the safety warnings on drug use.[14,27,55]

The strength of this research was that it was extensive and comprehensive. Various search methods were used to minimize selection bias – searches were performed without any language restrictions and only the first or most relevant paper published on the same dataset was included.[19] Furthermore, we evaluated different safety warnings; papers assessing the effects of Black Box Warnings and Public Health Advisories, which were also commonly used to communicate safety problems of drugs in the US, were also included as well as DHPCs.

5. Conclusions

Our review highlights the gap in the current knowledge on effectiveness of safety warnings and also shows the relevance of taking not only the intended effects but also the unintended affects into account. There is a clear need for more research to understand the impact of safety warnings, using appropriate study designs and statistical analyses. Both the intended and the anticipated unintended effects of safety warnings should be assessed. Not only should the impact on drug use be evaluated, but also the impact on outcome measures that specifically evaluate the intention of the warning. Moreover, all individual warnings issued for the drug in question should be assessed instead of only a selection. The impact should be reported per warning instead of an overall effect. The interrupted time series study is the preferred study design as it allows for greater reliability in

assessing the impact of safety warnings in comparison to before/after designs. When conducting a study with one drug or a limited selection of drugs, confounding factors should be better described and included in the analysis, which is possible with advanced interrupted time series analysis methods.

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