Do drug-related safety warnings have the expected impact on drug therapy? A systematic review

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Abstract

Purpose: The need for drug-related safety warnings is undisputed, and their impact should also be evaluated. This systematic review investigates and assesses the impact of safety warnings on drug therapy.

Methods: Studies published in English between January 1998 and December 2018 were searched in EMBASE and MEDLINE, complemented by manual search. Randomised controlled trials, cohort studies with a before/after component, and case-control studies were included, selected to predefined criteria, and assessed for their reporting and methodological quality.

Results: Out of 7454 references identified, 72 studies were included. A total of 28/72 (39%) studies described the impact of safety warnings on drug therapy as being effective, whereas 12/72 (17%) studies did not. Further, 26/72 (36%) studies described a partial implementation of the warnings (one part of the warning had an impact on drug therapy and another did not). Unintended effects were investigated in 6/72 (8%) studies.

While 34 (47%) studies examined safety warnings on psychotropic drugs using an interrupted time series (ITS) design (53%), a before/after (26%), and a time series design (21%), 38 (53%) studied other substances using an ITS design (34%), a before/after (40%), and a time series design (26%). The proportion of an effective impact on drug therapy was lower in the "psychotropic drugs" group (23%) than in the "others" group (53%).

Conclusion: Drug-related safety warnings induce intended and unintended effects. The included studies are of broadly varying methodological quality. To better compare their effectiveness, studies should be conducted using standardised procedures.
KEYWORDS
contraindications, drug interactions, drug-related side effects and adverse reactions, pharmacoepidemiology, pharmacovigilance, risk assessment

1 | INTRODUCTION

Written safety warnings on human drugs addressed to health care professionals (e.g., physicians and pharmacists) are intended to minimise the risks associated with drugs. Examples are reducing adverse effects by using drugs according to the respective indication, minimising drug interactions by avoiding certain combinations of active substances, conducting chemical laboratory tests for monitoring a drug therapy, and no prescription of active substances in case of existing contraindications. Drug-related safety warnings serve as a basis for safe drug therapy, for example, by informing about new side effects or drug interactions, new contraindications, or a negative assessment of the benefit-risk ratio of drugs. However, the formats of safety warnings and the responsibilities for communicating them differ worldwide. In Europe, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) is responsible for initiating risk assessment procedures and recommends pertinent safety information for human drugs.1 EMA closely cooperates with the national competent authorities responsible for human drugs.2 “Guidelines on good pharmacovigilance practices” (GVP)3 of the EMA specify processes of pharmacovigilance, for example, Module V (Risk management systems) or Module XV (Safety communication). In the United States, these procedures are defined, for example, in the Code of Federal Regulations of the Food and Drug Administration (FDA).4

The need for safety warnings as a part of pharmacovigilance processes is undisputed. Safety warnings should contribute to minimising risks in drug therapy. Assessing their effectiveness is essential to establish whether warnings have been effective or not, and if not, why and which further interventions are required.5 The impact/effectiveness can be assessed for example, based on changes in drug use or drug monitoring. As mentioned in Module XVI of the GVP “The evaluation of effectiveness should facilitate early corrective actions if needed and may require modifications over time. It is recognised that this is an evolving area of medical sciences with no universally agreed standards and approaches.”6

To date, the impact of drug-related safety warnings has been examined by three systematic reviews.5-7 A comparison of the most important aspects of these three systematic reviews is presented in Data S4. In summary, the search period for the review by Piening et al5 was defined from January 1996 to January 2010 and for Dusetzina et al6 from January 1996 to November 2010. Additionally, the systematic review by Dusetzina et al only examined the impact of safety warnings issued by the FDA; safety warnings issued by the EMA were not taken into account. While the systematic review published by Goedecke et al7 provided a descriptive presentation of the included studies, the effectiveness of the investigated safety warnings was not part of this review’s scope. A comprehensive and updated review of the current evidence on the impact of drug-related safety warnings is therefore necessary.

Our systematic review aims to investigate if safety warnings on prescription drugs lead, do not lead, or partially lead to an intended or unintended change in drug therapy in outpatients and inpatients of all ages. The effectiveness of the respective safety warning is to be assessed based on a possible change in drug therapy.

2 | METHODS

In order to answer the question “Do drug-related safety warnings have the expected impact on drug therapy?” a systematic literature search and an assessment of the included studies have been carried out. Our review includes studies investigating the impacts of drug-related safety warnings on drug therapy. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA)8 were followed.

The study protocol was registered in Prospero under record number CRD42018084154 and is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=84154

2.1 | Eligibility criteria

The inclusion and exclusion criteria defined a priori were based on Participant, Intervention, Comparison, Outcome, and Study type (PICOS scheme) and were as follows.

2.1.1 | Participants

Outpatients and/or inpatients (of all ages) undergoing drug therapy using prescription substances or substance groups worldwide. Animal studies were excluded.

2.1.2 | Interventions

Information letters with safety warnings on prescription substances or substance groups addressed to health care professionals, for example, Direct Healthcare Professional Communications (DHPC), Dear Healthcare Professional letters, Dear Doctor letters, Boxed Warnings or Black Box Warnings (BBW), Public Health Advisories, Drug Safety
warnings, and Drug Safety alerts. The following contents of safety warnings were considered: new adverse reactions, indication limitations, new contraindications, change in the previously authorised dosage, additional monitoring of laboratory values, and newly found interactions. Supplementary requirements concerning the dissemination of safety warnings imposed on the marketing authorisation holders by the competent authorities were also defined as eligible interventions.

Because of potential bias, studies were excluded that defined as intervention the marketing suspension or the withdrawal of the marketing authorisation, or additional demands in a safety warning, such as a patient’s declaration of consent or the mandatory use of checklists prior to prescription.

### 2.1.3 | Comparison

Possible comparison groups were similar regions, or comparable substances or substance groups. For randomised controlled trials (RCTs), a comparison group is essential by definition. However, the existence of comparative groups was not defined as an inclusion criterion for the included case-control studies and cohort studies with a before/after design.

### 2.1.4 | Outcome

Outcome was defined as change, partial change, or unchanged continuation of the drug therapy following the safety warning on the concerned human drug or following a supplementary requirement by the competent authority concerning the dissemination of the safety warning information. "Change" meaning the safety warning led to the expected impact following the investigated safety warning. "Partial change" was defined as only a part of the safety warning was realised, and "unchanged" means that the safety warning did not lead to a change in drug therapy. These results were categorised in terms of effectiveness in, firstly, effectiveness of intervention according to the author of the study, yes (1), ie, the safety warning led to a change in drug therapy. The impact of the investigated safety warning on drug therapy was being effective. Secondly, effectiveness of intervention, no (0), ie, no change in drug therapy after the safety warning (no impact). Thirdly, effectiveness of intervention, partial (2), means that not all contents of the investigated safety warning were implemented, but only parts of it (partially implementation). If multiple safety warnings on the same topic were examined in one study and the contents of one safety warning were implemented, but not the contents of another, these results were also grouped as partially.

The changes in drug therapy may be intended or unintended. In line with GVP modules XV and XVI,2 “intended” means that the possible changes occurring in correspondence with the safety warnings are usually drug-related and otherwise without negative consequences for the patient. As described above, their effectiveness can be derived from the change in drug therapy. “Unintended” means that the changes do not represent the contents of the safety warnings but are affected by them. The effects are not drug-related and associated with negative consequences for the patients. Therefore, studies investigating unintended effects cannot be grouped according to the effectiveness of the intervention. Figure 1 demonstrates a possible approach to systematically assess the impact/efficacy of drug-related safety warnings. An example for an unintended change is the increase in attempted suicides linked with the safety warnings on antidepressants in adolescents and young adults.9 The safety warnings investigated informed about the increased risk of suicide in young people taking antidepressants. The authors hypothesised “decreasing rates of overall antidepressant treatment after the warnings would be associated with a net increase in suicide attempts among young people.” The study results confirmed the hypothesis for adolescents and young adults. Another example, the “pill scare,” caused an increase in abortions in young women in Norway.10 The use of oral contraceptives dropped massively after a warning informed about an increased risk for adverse vascular events in users of special third-generation oral contraceptives. Subsequently, the rate of abortions increased.

Whether a safety warning led, did not lead, or partially led to an intended or unintended change in drug therapy was derived from the results presented by the authors.

### 2.1.5 | Study types

Study types are RCTs, case-control studies, and cohort studies with a before/after component and at least one data assessment or resource before and after the introduction of the safety warning. The study protocol (registered in Prospero January 2018) included interventional studies instead of actually defined case-control studies and cohort studies with a before/after component. A subsequent amendment was made at this point. Case reports, case series, and surveys were excluded.

Additionally, we only included studies published in English from January 1, 1998, to December 31, 2018, with available full text.

**KEY POINTS**

- Drug-related safety warnings influence drug therapy; their impact can be intended or unintended.
- Safety warnings regarding psychotropic drugs seem to influence drug therapy less than safety warnings on other substance groups.
- The included studies are of broadly varying methodological quality. Standardised reporting and assessment procedure are desirable in order to investigate the effectiveness of drug-related safety warnings more specifically.
2.2 | Information sources and search

We carried out a systematic electronic literature search using the databases MEDLINE and EMBASE (via the Ovid interface) for the period from January 1, 1998, to December 12, 2017. This search was updated on January 12, 2019. For this purpose, a search string with keywords corresponding to the research questions and related to the above mentioned PICOS criteria to find studies published since 1998, MESH terms and free-text search were used. The search strategy for MEDLINE is available as Data S1. During manual search, references of included studies (backward citation tracking) and relevant reviews were screened to identify further relevant studies. In addition, the Federal Institute for Drugs and Medical Devices (BfArM), the EMA, and the FDA websites were searched for relevant studies.

2.3 | Study selection and data extraction

Taking into account the eligibility criteria of this systematic review, two researchers (UG and JL) independently selected relevant articles based on titles and abstracts. Following this, two researchers (UG and JL) independently assessed the full-text articles of the preselected potentially relevant articles for their inclusion with disagreements being discussed between both reviewers. Where disagreements could not be resolved, a third reviewer (JS) was consulted to enable a decision.

Data extraction was conducted by one reviewer (UG) with its accuracy and completeness verified by a second reviewer (JL). The following characteristics were extracted from the included studies: author, country, study type (if routine data were used: database, source, design, and analytical methods), patient characteristics, type and time of the examined intervention, content of the safety warning, substance and/or substance class, comparative group (if applicable), outcome variable(s), and results. The study design was categorised as follows: interrupted time series (ITS), before/after design, and time series. The analytical methods were categorised as follows: segmented time series regression, other type of regression, descriptive statistics, and others, and the outcome variable(s) were categorised as follows: eg, number of prescriptions or prescription density, respectively, the frequency of comedication, or the monitoring of laboratory values.

Furthermore, all included studies were checked on reporting quality as well as on methodological quality. The reporting quality of non-RCT studies was assessed according to “The Strengthening the reporting of observational studies in epidemiology (STROBE) explanation and elaboration” and, where required, additionally to “The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD).” RCTs are to be assessed according to “CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials.”

The assessment of reporting quality was conducted by one reviewer (UG).

The methodological quality of non-RCTs was assessed using an adapted variant of the “Downs and Black Checklist.” The checklist is basically divided into the sections: reporting (items 1 to 10); external validity (items 11 to 13); internal validity, bias (items 14 to 20); internal validity, selection bias (items 21 to 26); and power (item 27). The results of the assessment of items 14 to 26 were summarised in tabular form. Items 9, 10, and 27 of the checklist were adapted by consensus (UG, JL, and TD). Because of the characteristics of the studies, item 9 (“Have the characteristics of patients lost to follow-up been described?”) of the checklist was extended by the reply option "not applicable." Item 10 (“Have actual probability values been reported
(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? was answered with "yes" in case confidence intervals were specified. Item 27 ("Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?") was supplemented by the question whether a priory sample size planning had been carried out. The items of this checklist were answered either with "yes," "no," "unable to determine," or "not applicable." A numerical evaluation of these items was not performed, because the rating of individual items would not or not sufficiently be represented in the overall assessment of the study.15 "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials"16 is to be used to assess RCTs. Two researchers (UG and JL) independently assessed the methodological quality of the studies using the described instruments. Divergent assessments were discussed until consensus could be reached or mediated by a third reviewer (TD).

Besides that, a qualitative synthesis based on results of the included studies was performed as follows:

- The implementation of a safety warning (effectiveness) was grouped based on the authors' findings into a safety warning to prescription drugs "lead," "do not lead," or "partially lead" to an "intended or unintended" change in drug therapy.
- Based on the contents of investigated safety warnings, the safety warnings were categorised into new reactions, indication limitations, new contraindications, dosage changes, additional laboratory monitoring, and new interactions. Potential patterns are to be deduced from the clustering.
- Based on the investigated substances or substance groups, the substances or substance groups were clustered into "psychotropic drugs" and "others." Potential patterns are to be deduced from the clustering.

In the presentation of possible patterns, the designs as well as the risk of a bias evaluation (items 14 to 26 of the checklist by Downs and Black) of the included studies are to be incorporated. An assessment of the risk of bias across studies was not planned. In order to minimise the selection of bias, a broad search is conducted as described under Section 2.2, including backward citations tracking and the search in grey literature. The following extracted characteristics are defined for the presentation of the results: author, substance or substance group, summary of content of the safety warning, outcome variable(s), objective of investigation, summary of the results (related to the content of the safety warning), study design, analytical methods, comparative group, and effectiveness. Based on the extracted study information, a descriptive analysis of the included studies is to be performed.

3 | RESULTS

3.1 | Study selection

After removing all duplicates, electronic searches resulted in the screening of 6423 titles and abstracts and 146 full texts. Additionally, 28 relevant papers were identified by manual search. A flow chart illustrating the entire study selection process is given in Figure 1. While 70 publications met our inclusion criteria, 76 studies were excluded mainly because of a lack of examined impact on the drug therapy and missing analysis of safety warnings or nonapplicable study types. A list of the studies excluded after full-text screening with reasons for their exclusion is available from the corresponding author (Figure 2).

All of the 70 publications included9,17-85 are observational studies based on routinely collected health data, which included health insurance or hospital records. Thus, no RCTs were found for the defined search period.

Two publications25,33 examined safety warnings for two mutually independent substances each, that is, 70 publications reported 72 studies. If a study contained multiple characteristics, the characteristics of these studies were counted multiple times in the following analyses, for example, studies examining more than one safety warning on one substance or substance group9,17,21,24,26,27,29,31,32,34-38,41-43,45-53,57,58,63,69,70,76,77,80-82,84,85 (multiple counts for safety warnings per study) or where a safety warning included multiple recommendations, for example, indication limitations and new adverse reactions17,18,25-27,30,36,40,42,49,50,53,55,57-59,70,72,74,76,80,82,83,85 (multiple counts for the content of the safety warning) were also subject to multiple counting.

3.2 | Study characteristics

General study characteristics are presented in Table 1. At 60% (n = 44), most of the studies examined safety warnings issued in the United States, followed by 23% (n = 17) in European countries, 8.5% (n = 6) in Canada, and 8.5% (n = 6) examined drug-related safety warnings in other countries.

The most frequently examined safety warnings concerned psychotropic drugs. Out of 72 studies, 47% (34) examined safety warnings concerning psychotropic drugs and 53% (38) studied other substances and substance groups. Further details are listed under Section 3.2.1 below.

The included studies covered different types of safety warnings. The various types of written information to communicate safety warnings are most frequently represented by Drug Safety Communications or Drug Safety alerts or Drug Safety warnings at 41% (49), followed by Dear Doctor letters or Dear Healthcare Professional letters or DHPC at 29% (35). Less frequently investigated safety warnings were BBW at 16% (19), Public Health Advisories 12% (15), or Label Change information at 2% (3).

Frequently used analytical methods for the evaluation of outcomes were segmented time series regression, followed by other types of regression, descriptive statistics, and others that could not be categorised.

A total of 31 studies used an ITS design, 24 studies used a before/after design, and 17 studies used a time series design. Out of included 72 studies, 29% (21) used comparative groups (CG), eg, two age groups, with the safety warning of interest addressing only
one age group.9,63,72 Most of the studies (71% (51)) did not use comparative groups. In summary, a total of 53% (18/34) of the studies in the “psychotropic drugs” group used an ITS design (23% with CG), 26% (9/34) a before/after (12% with CG), and 21% (7/34) a time series design (all without CG). In contrast, just 34% (13/38) of the studies in the “others” group used an ITS design (11% with CG), 40% (15/38) a before/after (8% with CG), and 26% (10/38) a time series design (5% with CG).

### 3.2.1 Contents of intervention

The contents of the safety warnings were divided into six categories: new adverse reactions, indication limitations, new contraindications, dosage changes, additional laboratory monitoring, and new interactions. Most of the studies examined mutually dependent combinations of these categories (as stated above), such as indication limitations and new side effects, as the new side effects required indication limitations. The most frequent contents of safety warnings were new adverse reactions at 53% (59), followed by indication limitations at 23% (26) and new contraindications at 11% (12). Safety warnings regarding dosage changes at 7% (8), additional laboratory monitoring at 4% (5), and new interactions at 2% (2) were less frequent. Patterns between these content-related categories and the impact of a safety warning on drug therapy could not be found.

### 3.3 Effectiveness of intervention

Whether a safety warning led, did not lead, or partially led to an intended or unintended change in drug therapy was derived from the results presented by the authors. In 66 out of 72 studies, intended changes in drug therapy were investigated with different results regarding their effectiveness. Contents of the safety warnings were described as effective in 28 out of 72 studies.17-20,23,25,26,29,31,39-44,48,50-52,54,58,64,67,68,71,73,76,81 In 12 studies, the authors concluded that the content of the safety warnings investigated did not lead to a change in drug therapy.21,22,24,25,33,34,56,61,65,78,79,82 In 26 studies, a partial change in drug therapy was shown.27,30,32,33,35-38,45-47,49,53,55,57,59,62,63,66,69,70,74,77,83-85

Unintended effects of a safety warning were examined in six out of 72 studies.9,28,60,72,75,80 These six studies could not be analysed regarding the effectiveness of safety warnings, because an unintended effect occurred in connection with a safety warning, but not as a direct consequence of the content. One example of this was the increased rate of hospitalisations due to depression after the recommended dosage limit (content of the safety warning) of citalopram in adults was implemented.60

After clustering the substances into a “psychotropic drugs” group and “others” group, a pattern was derived between the investigated substance and the effectiveness of a safety warning. As mentioned above, 47% (34) of the 72 studies examined safety warnings...
TABLE 1  General study characteristics

| Study characteristics                        | Number of studies (n = 72) |
|---------------------------------------------|-----------------------------|
| Countrya                                     |                             |
| USA                                         | 44                          |
| UK                                          | 7                           |
| Other EU countries                          | 10                          |
| Canada                                      | 6                           |
| Other                                        | 6                           |
| Substance or substance group                |                             |
| Psychotropic drugs                          |                             |
| Antidepressants                             | 19                          |
| Antipsychotic drugs                         | 10                          |
| Zolpidem                                    | 2                           |
| Antiepileptic drugs                         | 2                           |
| Promethazine                                | 1                           |
| Others                                      |                             |
| Thiazolidinediones                          | 6                           |
| (Antidiabetic agents)                       |                             |
| Cisapride                                   | 5                           |
| Long-acting beta-2-agonists (LABA)          | 5                           |
| Erythropoiesis-stimulating agent (ESA)      | 4                           |
| Clopidogrel                                 | 2                           |
| Other substancesb                           | 16                          |
| Contents of the safety warningsa            |                             |
| New adverse reactions                       | 59                          |
| Indication limitations                      | 26                          |
| New contraindications                       | 12                          |
| Changes in the previously authorised dosage| 8                           |
| Additional laboratory monitoring            | 5                           |
| Newly found interactions                    | 2                           |
| Kind of the safety warningsa                |                             |
| Black box warning (BBW)                     | 19                          |
| Dear Doctor Letter or Dear Healthcare       | 35                          |
| Professional Letter or Direct Healthcare    |                             |
| Professional Communication                 |                             |
| Drug safety communication or Drug safety    |                             |
| alert or Safety warning                     |                             |
| Public Health Advisory (PHA)                | 15                          |
| Label Change Information                    | 3                           |
| Nature of the effects                       |                             |
| Intended                                    | 66                          |
| Unintended                                  | 6                           |
| Analytical approaches                       |                             |
| Segmented time series regression            | 36                          |
| Other type of regression                    | 19                          |
| Descriptive statistics                      | 10                          |
| Other                                        | 7                           |
| Comparison group available                  |                             |
| Yes                                         | 21                          |
| No                                          | 51                          |

*aMultiple counts possible.

bAzithromycin, antihyperuricemic agents, bisphosphonates, depotmedroxyprogesterone (DMPA), desmopressin, dronedarone, droperidol, fentanyl, gadolinium, infliximab, ketorolac, leukotriene inhibitors (LTI), oseltamivir, propofol, simvastatin, tramadol.
concerning psychotropic drugs, and 53% (38) studied other substances and substance groups.

### 3.3.1 Results for the “psychotropic drugs” group

Table 2 summarises the results of 34 studies regarding “psychotropic drugs.” A total of 62% (21/34) described ineffective or partially effective, that is, the investigated safety warning showed no or only a partial impact on drug therapy. Only 23% (8/34) of the studies in the “psychotropic drugs” group described an effective impact on drug therapy as a result of the safety warning. Unintended effects were examined in 15% (9/34) of these 34 studies. For space constraints, only the group of “psychotropic drugs” is shown in Table 2.

### 3.3.2 Results for the “others” group

In contrast, just 45% (17/38) of the studies in the “others” group were presented as ineffective or partially effective. But 53% (20/38) described an effective impact, and only 2% (1/38) examined an unintended effect. Details of this group are shown in Data S2.

### 3.4 Study quality

The reporting quality of the included intervention studies was assessed on the basis of “The Strengthening the reporting of observational studies in epidemiology (STROBE) explanation and elaboration” and “The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD).” None of the studies describe all the criteria defined by STROBE or RECORD. In 43% (31) of the included studies, potential sources of bias were only inadequately described. That means, the study with its inclusion criteria and interventions as well as any outcomes of interest, or the reporting regarding patient characteristics, intervention, and outcome, respectively, were not reported transparently. 61% (44) of the studies failed to describe their potential generalisability (external validity). The criterion of data cleaning of the underlying routinely collected health data was not described in any of the studies. Apart from the lack of data cleaning, some of the studies described the remaining items of the STROBE and RECORD checklists extensively and transparently.

The methodological quality was checked according to the checklist by Downs and Black as described in Section 2.3. None of the 72 studies fulfilled all the criteria. In 13% (9) of the included studies, the analysed intervention was described inadequately (item 4 of the checklist). For example, the contents of the assessed safety warnings were not specified in a transparent way. Confounding factors (item 5) were specified in 28% (20). The main aspects for the risk of bias assessment can be summarised as follows: for all of the 72 studies, items 14, 15, 19, 24, and 26 could not be determined, items 21, 22, and 23 were answered either consistently with yes or no, and the most differences between the studies were found in items 20 and 25. In 29% (21) of the studies, the correct presentation of the most important outcome measurements (valid and reliable, item 20) was not provided. This means, 26% (9/34) of the “psychotropic drugs” group and 32% (12/38) of the “others” group of the studies included did not correctly present the most important outcome measurements. An adjustment for confounding factors (item 25) was specified in 14% (10) of the included studies. In 9% (3/34) of the studies, the risk of bias assessment can be summarised as follows: for all of the 72 studies, items 14 to 26 of the checklist by Downs and Black for the “psychotropic drugs” group and the “others” group, there was an adequate adjustment for confounding in the analyses from which the main findings were drawn. The influence of the media on the implementation of the safety warnings failed to be examined in all the studies. Only one study described the planning of the sample size (item 27 of the checklist). Table 3 and Data S3 show the risk of bias assessment (items 14 to 26 of the checklist by Downs and Black) for the “psychotropic drugs” group and the “others” group. An overview of the reporting quality as well as the complete checklist by “Downs and Black” is available from the corresponding author.

### 4 DISCUSSION

This comprehensive review of 72 studies assessing the impact of drug-related safety warnings focusses on their effectiveness. The included studies were based on routinely collected health data mainly using drug utilisation or drug monitoring as outcome variables. The quality assessment showed that the studies included were very heterogeneous. For example, 43% (31) of the studies used an ITS design as the strongest, quasi-experimental approach for evaluating longitudinal effects of interventions. With a time series or a before/after design other studies used a less strong study design. Only 29% (21) used a comparative group. Both the data basis (routinely collected health data) and the various study designs limit the validity of our review.

Besides this heterogeneity, our review has highly relevant implications for clinical care and prescription drug regulation: Firstly, the impact of drug-related safety warnings on drug therapy was demonstrated by a large part of the studies. Nevertheless, 53% (38) of the included studies described no (12) or only a partial (26) implementation of the recommendations given in the safety warning. An example for nonimplementation of a safety warning is the study of Du et al. The use of atomoxetine already decreased before the publication of the Black Box Warnings (BBW); the BBW failed to demonstrate a significant impact on atomoxetine use. The study by Kurdyak et al is to be mentioned as an example for a described partial implementation. It described a significant reduction in the use of paroxetine following a clearly written safety warning, whereas subsequent safety warnings recommending the cautious use of all antidepressants in children, or
| First author | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Designh | Analytical methods | Comparative groups | Effectivenessc |
|--------------|-----------------------------|---------------------------------------------|-------------------|--------------------------|------------------------|----------|-------------------|------------------|-----------------|
| Bergen, 2009 | Selective serotonin reuptake inhibitors (SSRI) | Advised against use of all SSRI antidepressants, except fluoxetine for the treatment of major depressive disorder in under-18-year-olds | Rates of prescribing of and self-poisoning with SSRIs (with and except fluoxetine) calculated per 100,000 population | Changes in prescribing trends of and self-poisoning | Change in prescribing of SSRIs (per 100,000) was −52.4 (95% CI −46.1 to −58.8) per quarter, which equated to a decrease of approx. 51%. Fluoxetine equated to a decrease of 20%. Rates of nonfatal self-harm did not change significantly. | Interrupted time seriesb | Segmented time series regression | Yes | 1 |
| Busch, 2010  | Paroxetine, fluoxetine | Increased risk of suicidality among pediatric patients | Receipt of paroxetine or fluoxetine within 30 days of diagnosis of major depressive disorder (MDD), medication management visits | Impact on receipt of paroxetine or fluoxetine within 30 days of diagnosis of MDD and medication management visits | After the first warning, paroxetine use declined from 20% to 8% (P < .01), use of fluoxetine increased from 12% to 16% (not significant). No significant change in the use of monitoring as a result of filling a prescription for an antidepressant. | Time seriesa | Other types of regression | No | 2 |
| Bushnell, 2016 | SSRI | Risk of suicidality in children (2003, paroxetine; 2004 all SSRI), and adolescents (2007 all SSRI) | Dose per day | Proportion of patients initiating on low dose SSRI before and after the 2004 FDA black-box warning (BBW) and the percentage-point change | Low dose after the BBW compared with prior to the BBW was prominent in children 13-17 years (37% vs 17%), relative increase 116% across all age groups: children (18% vs 14%), young adults (7% vs 5%), second prescription, 20% of children 5-9 years (9/40/4972; 21% of children 10-12 years (1530/7158), 25% of children 13-17 years (6538/26190), 21% of young adults (6809/32431), augmented dose. | Before/aftera | Descriptive statistics | Yes | 1 |
| Du, 2012     | Atomoxetine | Warning for suicidal thinking in children and adolescents | Incidence of atomoxetine use rate | Impact on incidence of atomoxetine use | Rate of atomoxetine use in children dropped from 2004 to the BBW to 6.45% (95% CI, 5.75%-7.15%), rate of initial attention deficit hyperactivity disorder (ADHD) medication for the post warning period | Interrupted time seriesb | Segmented time series regression | No | 0 |

(Continues)
| First author | Substance or substance group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design | Analytical methods | Comparative groups | Effectiveness |
|--------------|-------------------------------|-----------------------------------------------|-------------------|---------------------------|------------------------|--------|---------------------|------------------|--------------|
| Fabo, 2015   | Citalopram                    | Risks of dose-related QT interval prolongation | Percentage of daily dose citalopram greater than 20 mg | Impact on prescribing daily dose citalopram greater than 20 mg | Percentage of patients prescribed citalopram at a daily dose greater than 20 mg (not significant) | Before/after? | Descriptive statistics | No               | 0            |
| Franchi, 2012| Antipsychotic (AP) drugs      | Increased risk of mortality in patients with dementia and serious adverse cerebrovascular events (atypical AP 2004, AP without specification 2006) | Prevalence of AP use | Impact on prevalence of AP use | Significant drop in the prevalence of patients who received a prescription of AP (23.1% vs 28.0%; OR 0.79; 95% CI, 0.73-0.86; P < .001) and 2007 compared with 2006 (19.4% vs 23.0%; OR 0.79; 95% CI, 0.73-0.86; P < .001). Prevalence of prescription of quetiapine and haloperidol increased over the years. | Before/after? | Descriptive statistics | No               | 2            |
| Friesen, 2015| Citalopram                    | Risks of dose-related or drug interaction-related QT interval prolongation | Percentage of high dose citalopram prescription, number of interacting medications per citalopram prescription | Impact on prescribing high dose citalopram and the number of interacting medications | Prescribing of high doses 64.8% decline in those <65 years and 33.6% in those ≥65 years (P < .0001), number of interacting medications increased in the postwarning period (<65 years, 0.78-0.81 interactions per citalopram prescription; ≥65, 0.93-0.94, P < .001). | Interrupted time series? | Segmented time series regression | No               | 2            |
| Gallini, 2014| Risperidone, olanzapine, aripiprazole and all AP | Increased risk of mortality in patients with dementia | Monthly rates of AP use | Impact on monthly rates of AP use | Decreasing trend in overall AP before 2004, 03/2004: use of second-generation antipsychotics (SGA [risperidone, not olanzapine]) | Interrupted time series? | Segmented time series regression | Yes              | 0            |
| First author | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design$^a$ | Analytical methods | Comparative groups | Effectiveness$^a$ |
|--------------|-----------------------------|---------------------------------------------|------------------|-----------------------------|------------------------|-----------|------------------|------------------|------------------|
| Grefach, 2018 | Citalopram | Risk of QT prolongation (>40 mg/d, dose restriction <20 mg/d) (age over 60) | Proportion of patients with citalopram use and proportion of patients with high dose citalopram use | Change-in proportion of patients prescribed each of the antidepressants of interest for each month | Between the first and second FDA warnings, among patients aged 18-60, high-dose citalopram use decreased by 2.0% per month ($P < .001$) and by 1.9% per month ($P < .001$) for older adult (>60). | Interrupted time series$^a$ | Segmented time series regression | Yes | 1 |
| Guthrie, 2013 | Risperidone, olanzapine | Clear evidence of an increased risk of stroke in elderly patients with dementia | Percentage of patients prescribed antipsychotics in elderly patient with dementia each quarter | Impact on prescribing AP rate | 03/2004: absolute reduction in AP prescribing of −5.94% (95% CI, −6.64 to −5.23) and a change to a stable level of prescribing subsequently. 03/2009: no immediate reduction in total AP. | Time series$^a$ | Segmented time series regression | No | 2 |
| Karlsson, 2018 | Valproic acid | Valproic acid use in pregnancy has been associated with a higher risk of adverse drug effects (ADE), eg, malformations, impaired cognitive development of children exposed in foetal life | Number of new users of Valproic acid | Change-in Number of new users of Valproic acid (female ≤ 45 years) | No significant immediate changes in valproic acid initiations (men or women) at the time of the EMA warning; after 2 years: change (significant) in trend for females ≤45 years of age (−8.57, $P = .01$), epilepsy: no significant changes in valproic acid initiations (men or women), psychiatric disorders: significant decrease in trend was observed in females ≤45 years of age (−1.85, $P = .05$). | Interrupted time series$^a$ | Segmented time series regression | Yes | 2 |
| Katz, 2008 | SSRI and selective norepinephrine reuptake inhibitors (SNRI) | Risk of suicidal behaviour in children and adolescents | Prevalence rates of AD, rates of completions suicides | Change-in prevalence rates of AD, rates of completed suicides | AD prescriptions decreased among children and adolescents (relative risk [RR] 0.86, 95% CI 0.81-0.91), rate of completed suicides (children, adolescents) rose significantly after the warning (RR 1.25, 95% CI 1.08-1.44; annual rate per 1000 = 0.04 | Before/after$^a$ | Other types of regression | Yes | 3 |

(Continues)
| First author         | Substance or substance Group | Summary of the content of the safety warning                                                                 | Outcome variables                                                                 | Objective of investigation                                                                 | Summary of the results                                                                                                                                          | Design<sup>ab</sup> | Analytical methods | Comparative groups | Effectiveness<sup>c</sup> |
|---------------------|------------------------------|----------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Kesselheim, 2017    | Zolpidem                     | Risk of next-morning impairment and recommending lower starting doses particularly for women                     | Number of users, mean milligrams of zolpidem dispensed                           | Change in number of users (low-dose or high-dose zolpidem)                                 | 20% immediate increase (low-dose zolpidem) with the first Drug Safety Communication (DSC) ($P < .001$) and another 10% with the second, for a total increase of 30% ($P < .001$) during the study period. high-dose posted a 7% decrease with the first DSC and another 6% with the second, for total decrease of 13% ($P = .03$). | Interrupted time series<sup>b</sup> | Segmented time series | Regression        | Yes               |
| Kessler, 2010       | Promethazine                 | Respiratory depression in children younger than 2 years                                                        | Orders for promethazine                                                          | Impact on orders for promethazine                                                          | Significant decrease in promethazine use occurred between 2005 and 2006 ($P = .017$).                                                                                       | Before/after<sup>a</sup> | Other methods     | No                | 1                 |
| Kudryk, 2007        | SSRI                         | Increased risk of suicidal behaviour during AD therapy in children and adolescents                              | New SSRI prescriptions per 10 000 Ontario residents every month                   | Impact on number of new SSRI prescription per 10 000 Ontario residents                      | 06/2003 warnings resulted in a statistically significant 54% decrease ($P = .03$) in new prescriptions to patients <20 years; 10/2003; 03, 06, 10/2004 warnings had no effect on the rate of new prescriptions for paroxetine to patients <20 years, none of the five warnings had an effect on new prescriptions for SSRIs. | Time series<sup>a</sup> | Segmented time series | Regression        | No                |
| Kurian, 2007        | AD                           | Risk of suicidal behaviour in children and adolescents                                                         | Prevalence rates of antidepressant (new and current users)                        | Change in prevalence rates of antidepressant                                                | New users: decrease of 33% (95% CI, 23%-41%; $P < .001$). There was no evidence that discontinuation of antidepressant therapy increased.                                                                 | Interrupted time series<sup>b</sup> | Segmented time series | Regression        | No                |
| Libby, 2007         | SSRI                         | Risk of suicidality in paediatric patients with depression who were being treated with AD                      | Percentage of cases of depression that were diagnosed by types of providers, percentage of | Patterns of diagnosis of depression, prescription of AD pharmacological alternatives   | From 1999 to 2004, paediatric diagnoses of depression increased from 0.3% to 0.5%. After the FDA advisory was                                                                 | Interrupted time series<sup>b</sup> | Segmented time series | Regression        | No                |
| First author   | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design\(^b\) | Analytical methods | Comparative groups | Effectiveness\(^c\) |
|---------------|-----------------------------|---------------------------------------------|-------------------|---------------------------|------------------------|-------------|-------------------|-------------------|-------------------|
| Lu, 2014      | AD                          | AD warning on the increased risk of suicidality (suicidal ideation and behaviour) in children and adolescents (2004), and young adults (2007) | Quarterly percentage of enrollees admitted to hospital or treated in emergency rooms for poisoning by a psychotropic drug, deaths with suicide as a cause of death | Changes in AD use and suicidality among patients taking AD | Adolescents: relative reduction of 31.0% in AD use (95% CI, −33.0% to −29.0%), significant relative increase of 21.7% in psychotropic drug poisonings (95% CI, 4.9-38.5), Young adults: relative reduction of 24.3% in AD use (−25.4% to −23.2%), relative increase of 33.7% in psychotropic drug poisonings (26.9% to 40.4%), no changes in completed suicides for any age group. | Interrupted time series\(^b\) | Segmented time series regression | Yes 3 |
| Mittal, 2014  | Antiepileptic drugs (AED)   | Increased risk of suicidality for all AED | Proportion of members with an AED prescription claim | Impact on AED prescription claims, for patients diagnosed with epilepsy and/or psychiatric disorder(s) | No significant change in trend of AED prescription claims was detected in all three diagnostic groups (epilepsy alone, psychiatric disorder alone, epilepsy and comorbid psychiatric disorder(s)) during the entire study period (\(P > .01\)). | Interrupted time series\(^b\) | Segmented time series regression | No 0 |
| Morato, 2010  | SGA                         | Glucose level monitoring in patients with an established diagnosis of diabetes, risk factors for diabetes, or symptoms of hyperglycaemia | Monthly rates of baseline serum glucose (and lipid) testing, prescribing patterns of SGA | Increased rates of baseline serum glucose and lipid testing change in prescribing patterns of SGA | Glucose testing rates did not increase (0.9% absolute change) (trend change, 0.2%/y), new prescriptions of olanzapine (higher metabolic risk) declined (annual share decline, 19.9%; \(P < .001\)). | Interrupted time series\(^b\) | Segmented time series regression | Yes 2 |

(Continues)
| First author | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design\(^{ab}\) | Analytical methods | Comparative groups | Effectiveness\(^{c}\) |
|--------------|-------------------------------|---------------------------------------------|-------------------|---------------------------|------------------------|---------------------|-------------------|---------------------|-------------------|
| Norman, 2017 | Zolpidem | Reducing initial recommended dose for zolpidem in women | Percentage of low dose zolpidem prescription | Impact on prescribing low-dose zolpidem | Low-dose zolpidem prescription increased: elderly women (60%-74%; \(P = .14\)), only significant change in young women (42%-70%; \(P = .0045\)). | Before/after \(^a\) | Other types of regression | No | 2 |
| Ofsson, 2008 | Paroxetine | “a possible increased rate” of suicidal behaviour in youth, (paroxetine 06/2003), risks of suicidality in children and adolescents (all AD 10/2004) | AD use rates per 1000 persons | Change in rate of AD use | Decrease in new use of all AD (−17.1% per year; \(P = .30\)), new use of paroxetine remained little changed during the prewarning study period (−0.6% per year; \(P = .96\)), declined during the paroxetine warning study period (−32.3% per year; \(P < .001\)), constant during the BBW period (0.2% per year; \(P = .99\)). | Interrupted time series \(^b\) | Other types of regression | No | 2 |
| Ooba, 2018   | Lithium | Serum lithium level measurement once a week (initial phase and during the dose-increase phase); every 2 to 3 months during the maintenance dose phase | Prevalence of therapeutic drug monitoring (TDM) for Lithium | Impact on prevalence of TDM for Lithium | Warning 04/2012: prevalence increased abruptly by 69% (\(P = .001\)), warning 09/2012: decreased by 1.2% (\(P = .47\), no significant). | Time series \(^a\) | Segmented time series regression | No | 2 |
| Parn, 2010   | Paroxetine | Increased risk of suicidal thinking and suicide attempts in patients <18 years, treated with paroxetine for major depressive disorder (MDD) | Use level per 100 000 population for paroxetine | Change in use level per 100 000 population for paroxetine | Paroxetine use levels decreased for all age groups (range: 5.5%-34.1%). | Interrupted time series \(^b\) | Segmented time series regression | No | 1 |
| Rector, 2016 | Citalopram | Dosages >40 mg/d citalopram—risk of dosage-dependent QT interval prolongation | Incidence of hospitalizations and mortality when higher dosages of citalopram were or were not reduced to 40 mg/d. | Rates of hospitalizations and mortality in patients taking citalopram >40 mg/d or unchanged | All-cause hospitalizations or deaths increase after dosage reductions (adjusted hazard ratio = 4.5, 95% CI: 4.1-5.0), hospitalizations for depression or all-cause death (adjusted hazard ratio = 2.2, 95% CI, 1.8-2.6). | Before/after \(^a\) | Other types of regression | Yes | 3 |

\(^{a}\) Before/after
\(^{b}\) Other types of regression
\(^{c}\) Effectiveness
| First author | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design | Analytical methods | Comparative groups | Effectiveness |
|--------------|------------------------------|---------------------------------------------|-------------------|---------------------------|------------------------|--------|-------------------|-------------------|---------------|
| Sanfélix-Gimeno, 2009 | Risperidone, olanzapine | Increased risk of mortality in patients with dementia and serious adverse cerebrovascular events | Defined daily dose (DDD) of risperidone and olanzapine dispensed monthly | Impact on DDD risperidone and olanzapine dispensed monthly | Risperidone low strength: slope post warning −1338 (P < .001), olanzapine low strength: slope post warning −664 (P < .001) | Interrupted time seriesb | Segmented time series regression | Yes | 1 |
| Schachtele, 2014 | Citalopram, escitalopram | Risks of dose-dependent or drug interaction–related QT interval prolongation | Percentages of patients receiving DDD, number of patients in whom citalopram or escitalopram was coprescribed alongside other QT interval-prolonging drugs | Impact on prescribed dosages at discharge and co-prescribing contraindicated drugs with Citalopram or Escitalopram | Prescriptions for >20 mg/d citalopram drop from 9.8% (95% CI, 8.7%-11.0%) to 4.1% (95% CI, 3.4%-4.9%), (P < .0001), prescriptions for >10 mg/d escitalopram (P < .0001), Coprescription with other QT interval-prolonging drugs remained almost unchanged (citalopram: 19.3% [95% CI, 17.9%-20.9%] vs 18.4% [95% CI, 17.0%-19.8%], escitalopram: 17.6% [95% CI, 15.8%-19.6%] vs 17.1% [95% CI, 14.5%-19.9%]). | Before/aftera | Descriptive statistics | No | 2 |
| Stocks, 2018 | Risperidone, olanzapine | Clear evidence of an increased risk of stroke in elderly patients with dementia | Proportion of patients diagnosed with dementia and without a psychosis diagnosis who were prescribed an antipsychotic drug | Prevalence of prescribed SGA in patients diagnosed with dementia (without a psychosis diagnosis) | 03/2004: prevalence ratio before/after for SGA drugs 0.66 (95% CI, 0.61-0.71), 06/2009: prevalence ratio before/after 0.84 (95% CI, 0.79-0.90), 2012 prevalence ratio before/after 0.89 (0.83-0.95) but risperidone 1.13 (95% CI, 0.99-1.29). | Interrupted time series | Segmented time series regression | No | 2 |
| Sultana, 2016 | AP drugs | All-cause mortality and cerebrovascular events in elderly persons with dementia (03/2004 atypical AP, 03/2009 all AP) | Prevalence of AP use | Impact on prevalence of AP use | 2004: United Kingdom (UK): atypical AP decreased from 7% to 6% (P < .001), Italy: no decrease of atypical AP 2009: UK: no changes of AP use within 6 months after the warning, use of atypical and conventional AP by class increased slightly within 1 year (P = .001 and .01, respectively), Italy: AP use | Before/aftera | Segmented time series regression | Yes | 2 |
| First author | Substance or substance Group | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design | Analytical methods | Comparative groups | Effectiveness |
|--------------|-------------------------------|---------------------------------------------|------------------|-----------------------------|----------------------|--------|-------------------|-------------------|--------------|
| Thomas, 2013 | AP drugs                      | Increased mortality when used conventional AP in older adults with dementia | Rate of conventional AP prescribing | Impact on rate of conventional AP prescribing in dementia | No significant step-change was detected after the warning ($P = .962$) | Interrupted time series | Segmented time series regression | No | 0 |
| Trifiro, 2010 | Atypical AP                   | Three-fold increased risk of cerebrovascular events in elderly with dementia (UK), increased all-cause mortality risk in elderly demented patients (FDA) used atypical AP | Prevalence of AP users | Changes in AP drug use | Use of atypical AP in demented patients progressed increased from 2000 (0.2 [0.05-0.7] per 10 000) until the beginning of 2004 (9.7 [8.1-11.6] per 10 000), after which a slight decrease started. | Time series | Descriptive statistics | No | 1 |
| Valliyeva, 2008 | risperidone, olanzapine, quetiapine | Increased risk of mortality in patients with dementia and serious adverse cerebrovascular events | Prescription rates of defined AP drugs | Impact on prescription rates of defined AP drugs | Decrease of atypical AP after the first warning, 4.9% (95% CI, −6.8 to −2.9) after the second and 3.2% (95% CI, −5.4 to −1.0) after the third (each $P < .05$). risperidone: after the second warning 3.3% increased (95% CI, −4.8 to 11.3), olanzapine: after the third warning 1.2% increased (95% CI, −3.5 to 6). | Interrupted time series | Segmented time series regression | No | 2 |
| Vallu, 2010 | AD                            | Risk of suicidal behaviour in children and adolescents | AD use and psychotherapy visits | Impact on AD use and psychotherapy visits | AD dispensing—new onset MDD: similar for pre to post period for children and adolescents (AOR = 0.95; 95% CI, 0.88-1.02), non-MDD: decline for children and adolescents (AOR = 0.79; 95% CI, 0.69-0.87), psychotherapy visits: among youth were greater in the post warning period for children (AOR = 1.31; 95% CI, 1.23-1.40) and adolescents (AOR = 1.19; 95% CI, 1.15-1.24). | Time series | Other methods | No | 2 |

(Continues)
Table 2 (Continued)

| First author | Substance or substance of the safety warning | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design | Analytical methods | Comparative groups | Effectiveness |
|--------------|-------------------------------------------|---------------------------------------------|------------------|---------------------------|-----------------------|--------|-------------------|-------------------|--------------|
| Wijlaars, 2012 | AD | Paroxetine was associated with a small increase in suicidal behaviour and ideation, against the initiation of all SSRIs except fluoxetine in children | Incidence rates for depression diagnoses, symptoms and AD prescriptions by the total person-years at risk (PYAR) for each year | Changes in incidence rates for depression diagnoses, symptoms and AD prescriptions by the total PYAR for each year | SSRIs prescription rates decreased from 3.2 (95% CI, 3.0-3.3) per 1000 person-years at risk (PYAR) in 2002 to 1.7 (95% CI, 1.7-1.8) per 1000 PYAR in 2005, but have since risen to 2.7 (95% CI, 2.6-2.8) per 1000 PYAR in 2009. Rates for depression diagnoses dropped from 3.0 (95% CI, 2.8-3.1) per 1000 PYAR in 2002 to 2.0 (95% CI, 1.9-2.1) per 1000 PYAR in 2005 and have been stable since. | Time series | Other types | No | 3 |

Abbreviations: AD, antidepressants; AED, antiepileptic drugs; AP, antipsychotics; BBW, Black Box Waming; DDD, defined daily dose; DSC, Drug Safety Communication; MDD, major depressive disorder; SGA, second-generation antipsychotics; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TDM, therapeutic drug monitoring.

*Design was derived by the review authors.

**Design was explicitly named in the studies.

Yes (1), no (0), partially (2), or unintended effect (3).

4.1 | Strengths and limitations

The strength of this review is that it provides a current and comprehensive overview of globally available studies examining the impacts of drug-related safety warnings on prescription drugs published since 1998. As mentioned in Section 1, Dusetzina et al have only investigated the impact of FDA safety warnings. Furthermore, the systematic reviews published until January or November 2010. The review by Gerdthä et al did not provide any information on the impact of safety warnings on drug therapy. This procedure provides a higher level of evidence than a narrative review.

Despite that, the review has a few limitations. One of them is the heterogeneity of the included studies, which does not permit a meta-analytical presentation of the results. Additionally, the study outcomes may be influenced by recommendations of medical societies, guidelines, and media coverage or by the different drug therapy safer. A risk assessment of safety warnings in terms of time and other selective serotonin reuptake inhibitors except fluoxetine.

| First author | Substance or substance of the safety warning | Summary of the content of the safety warning | Outcome variables | Objective of investigation | Summary of the results | Design | Analytical methods | Comparative groups | Effectiveness |
|--------------|-------------------------------------------|---------------------------------------------|------------------|---------------------------|-----------------------|--------|-------------------|-------------------|--------------|
| Wijlaars, 2012 | AD | Paroxetine was associated with a small increase in suicidal behaviour and ideation, against the initiation of all SSRIs except fluoxetine in children | Incidence rates for depression diagnoses, symptoms and AD prescriptions by the total person-years at risk (PYAR) for each year | Changes in incidence rates for depression diagnoses, symptoms and AD prescriptions by the total PYAR for each year | SSRIs prescription rates decreased from 3.2 (95% CI, 3.0-3.3) per 1000 person-years at risk (PYAR) in 2002 to 1.7 (95% CI, 1.7-1.8) per 1000 PYAR in 2005, but have since risen to 2.7 (95% CI, 2.6-2.8) per 1000 PYAR in 2009. Rates for depression diagnoses dropped from 3.0 (95% CI, 2.8-3.1) per 1000 PYAR in 2002 to 2.0 (95% CI, 1.9-2.1) per 1000 PYAR in 2005 and have been stable since. | Time series | Other types | No | 3 |

Abbreviations: AD, antidepressants; AED, antiepileptic drugs; AP, antipsychotics; BBW, Black Box Warning; DDD, defined daily dose; DSC, Drug Safety Communication; MDD, major depressive disorder; SGA, second-generation antipsychotics; SNRI, selective norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TDM, therapeutic drug monitoring.

*Design was derived by the review authors.

**Design was explicitly named in the studies.

Yes (1), no (0), partially (2), or unintended effect (3).
| First Author | 14) Was an attempt made to blind study subjects to the intervention if any of the results of the study were based on “data dredging.” 15) Was an attempt made to blind those measuring the main outcomes of the intervention if any of the results of the study were based on “data dredging.” | 16) If any of the results of the study were based on “data dredging,” was this made clear? | 17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the timeframe between the intervention and outcomes the same for cases and controls? | 18) Were the statistical tests used to assess the main outcomes appropriate? | 19) Was compliance with the intervention/s made clear? | 20) Were the main outcome measures used accurate (valid and reliable)? | 21) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | 22) Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time period? | 23) Were study subjects randomised to intervention groups? | 24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | 25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | 26) Were losses of patients to follow-up taken into account? |
|--------------|---------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|
| Bergen, 2009 | Utd | Yes | Yes | Yes | Utd | No | Yes | Yes | No | Utd | No | Utd |
| Busch, 2010  | Utd | Yes | Yes | Yes | Utd | No | Yes | Yes | No | Utd | No | Utd |
| Bushnell, 2016 | Utd | Yes | Yes | No | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Du, 2012    | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Fabo, 2015  | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Franchi, 2012 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Friesen, 2015 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Gallini, 2014 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Gerlach, 2018 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Guthrie, 2013 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Karlsson, 2018 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Katz, 2008   | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Kesselheim, 2017 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Kessler, 2010 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Kurdyak, 2007 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Kurian, 2007 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | Yes | Utd |
| Libby, 2007  | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Lu, 2014     | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Mittal, 2014 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | No | Utd |
| Morrato, 2010 | Utd | Yes | Yes | Yes | Utd | Yes | Yes | Yes | No | Utd | Yes | Utd |

(Continues)
| First Author         | 14) Was an attempt made to blind study subjects to the intervention they have received? | 15) Was an attempt made to blind those measuring the main outcomes of the intervention? | 16) If any of the results of the study were based on "data dredging," was this made clear? | 17) In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls? | 18) Were the statistical tests used to assess the main outcomes appropriate? | 19) Was compliance with the intervention/s reliable? | 20) Were the main outcome measures used accurate (valid and reliable)? | 21) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? | 22) Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population? | 23) Were study subjects randomized to intervention groups? | 24) Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? | 25) Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? | 26) Were losses of patients to follow-up taken into account? |
|---------------------|-------------------------------------------------|-----------------------------------|----------------------------------|-------------------------------------------------|---------------------------------|--------------------------------|--------------------------------|-------------------------------------------------|-------------------------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|
| Norman, 2017        | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Olfson, 2008        | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Ooba, 2018          | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Pamer, 2010         | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | No                              | Yes                             | Yes                                             | No                                              | Yes                             | Yes                             | No                              | Utd                             |
| Rector, 2016        | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Sanfélix-Gimeno, 2009 | Utd                                      | Yes                               | Yes                              | Yes                                             | Utd                             | No                              | Yes                             | Yes                                             | No                                              | Yes                             | Yes                             | No                              | Utd                             |
| Schaechtele, 2014   | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Stocks, 2018        | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Sultan, 2016        | Utd                                             | Yes                               | No                               | Yes                                             | Utd                             | No                              | Yes                             | Yes                                             | Yes                                             | No                              | Yes                             | No                              | Utd                             |
| Thomas, 2013 (Antipsychotic Drugs) | Utd                                      | Yes                               | Yes                              | Yes                                             | Utd                             | No                              | Yes                             | Yes                                             | No                                              | Yes                             | Yes                             | No                              | Utd                             |
| Trifiro, 2010       | Utd                                             | Yes                               | Yes                              | Utd                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Valiyeva, 2008      | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Valluri, 2010       | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | Yes                             | Yes                             | Yes                                             | Yes                                             | Yes                             | Yes                             | No                              | Utd                             |
| Wijans, 2012        | Utd                                             | Yes                               | Yes                              | Yes                                             | Utd                             | No                              | Yes                             | Yes                                             | Yes                                             | No                              | Yes                             | Yes                              | Utd                             |

Abbreviation: Utd, unable to determine.
publication timing of the safety warning in the respective countries. It seems difficult to adjust for these factors. Safety warnings on drugs represent only one of many sources of information for health care professionals so that influences from other sources cannot be ruled out. Moreover, there are indications that the credibility of a safety warning is already influenced by the sender. In addition, a study by Bjerre et al showed that safety warnings concerning one and the same substance were published at different times and in different formats in the United States, in Canada, and the United Kingdom, and that the information provided in the safety warnings failed to be consistent at all times. Furthermore, this review is limited to English publications, so a language bias cannot be ruled out. In addition, more than half of the studies included were published in the United States. Therefore, the presentation of the results has a clear focus on US American data.

In summary, our review raises a number of questions: How can the effects of safety warnings on drug therapy be investigated independently of, for example, guidelines or media influences? What causes a change, no change, or partial change in drug therapy as a result of a safety warning? What leads to unintended changes in drug therapy? Which parameters influence the implementation of safety warnings from “psychotropic drugs” or “other” drugs? Do the parameters differ depending on the group of substances studied? The importance of evaluating the effectiveness of safety warnings is undisputed. It can be assumed that answers to these questions can contribute to an optimisation of the pharmacovigilance process.

4.2 Conclusion

Out of 72 included studies, the impact of drug-related safety warnings on drug therapy was shown by a large body of evidence. Safety warnings lead, do not lead, or partially lead to an intended or unintended change in drug therapy. Furthermore, safety warnings regarding psychotropic drugs seem to influence drug therapy less than safety warnings on other substance groups. The included studies investigating the impact of safety warnings are of broadly varying methodological quality. In order to be able to investigate the effectiveness of safety warnings on drug therapy, a uniform evaluation procedure is desirable. Further research is needed to clarify which parameters influence the impact of safety warnings to what extent.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Study concept: U.G., J.S., and S.D. Draft and critical revision of study protocol: U.G., J.S., and S.D. Systematic literature search: U.G. Screening: U.G. and J.L. Data abstraction: U.G. Quality assessment: U.G. and J.L. Qualitative synthesis: U.G. and J.S. Draft and critical revision of the article: U.G., J.L., J.S., T.D., and S.D. Overall responsibility: U.G.

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**SUPPORTING INFORMATION**

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

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