Received: 4 September 2019 | Revised: 25 March 2020 | Accepted: 2 June 2020

DOI: 10.1002/pds.5073

ORIGINAL REPORT

WILEY

FDA postmarketing safety labeling changes: What have we learned since 2010 about impacts on prescribing rates, drug utilization, and treatment outcomes

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Funding information
U.S. Food and Drug Administration, Grant/Award Number: 7U19FD004971-04

Abstract

Purpose: Prior literature reviews have identified gaps in understanding of how postmarketing safety labeling changes and related FDA communications impact key clinical and behavioral outcomes. We conducted a review of newly published studies on this topic to determine what new evidence exists and to identify which gaps may still remain. We believe that this information can support FDA as it develops and implements future risk communication approaches.

Methods: We searched PubMed and Embase for studies published between January 1, 2010, and August 7, 2017 that examined the impact of labeling changes or associated FDA safety-related communications. For each study, we extracted information on research design and findings for key clinical outcomes and behaviors. We also conducted a ROBINS-I review to identify potential for bias in the research design of each study.

Results: We found that the estimated impacts of FDA labeling changes on several key outcomes—including adverse events—varied. Labeling changes also yielded unintended consequences on drug prescribing in some cases, despite low provider adherence. Finally, some studies we reviewed exhibited potential for bias due to confounding, among other factors.

Conclusions: The new studies we reviewed contain many of the same limitations identified in previously published reviews. While there are several challenges to conducting this research there is substantial room for improvement in the quality of the evidence base. More information, particularly with respect to the types of populations and medications affected by labeling changes, is needed to support the development of more effective and targeted safety communications.

KEYWORDS

drug safety, labeling change, postmarketing

1 | INTRODUCTION

FDA uses safety-related labeling changes to communicate new safety information about an approved prescription drug.[1] These communications are intended to promote safer use behaviors that may mitigate a specific risk in patients who are using the drug or provide more information about a drug's risks that can facilitate informed decision-making by patients and health care providers about whether to use a drug. However, the impact of safety-related labeling changes and related risk communications on key outcomes (eg, drug utilization, safe-use behaviors, and health outcomes) is not well understood.

A small number of reviews have been conducted to evaluate the existing evidence on the public health impacts of postmarketing safety labeling changes and other, related FDA safety communications. In 2012, Dusetzina et al conducted a systematic review of the literature, finding varied results across studies, general weaknesses in study designs, and many key gaps in the overall body of knowledge.[2] Another review by Briesacher et al identified similar problems with the existing evidence base, finding few studies that used rigorous analytical methods or valid research designs to evaluate FDA regulatory actions.[3]

Our review aims to build upon and update the findings of previous reviews by identifying research published on this topic since 2010. In addition, we use a published assessment tool to evaluate the risk of potential bias in these new studies. We believe that a full appraisal of the strengths and weakness of the evidence base can support improved decision-making by FDA as it works to ensure the safety and efficacy of medical products, and can also guide researchers in developing studies that provide actionable information to the Agency.

KEY POINTS

- The impact of FDA labeling changes on studied outcomes—including drug utilization and prescribing rates, monitoring of patients, and the incidence and reporting of adverse events—is varied.
- There are several challenges to conducting high-quality studies on the impact of labeling changes, including data access and difficulties disentangling the potential impact of the communications from that of other sources of information that can influence behavior.
- Health care providers appear to have relatively low adherence to labeling changes related to dosing and monitoring.
- Spillover effects, such as decreased prescribing in patient populations not targeted by the labeling change, were observed for a few labeling changes, indicating that changes have the potential to yield unintended consequences.
- The existing literature still exhibits several important limitations in terms of the types of drug classes studied and methodological rigor. In addition, several studies exhibit high or moderate risk of bias due to deficiencies in study design, such as confounding or issues with participant selection.

2 | METHODS

2.1 | Data sources and study selection

We searched PubMed and Embase for studies published between January 1, 2010 and August 7, 2017. For each database, we required studies to meet each of three separate search strings covering (1) changes in physician practice patterns, drug utilization, and prescribing; (2) FDA; and (3) drug labeling and related safety communications (the search strings were adapted slightly from those of Dusetzina et al. 2012 and are reproduced in full in Figure 1). We then compiled results in Endnote and excluded duplicate studies. We also acquired five records from other sources, three of which were added following feedback from an expert meeting that we hosted on this topic.[4]

We selected studies for inclusion in the final review if they: (1) were drawn from peer-reviewed publications and examined empirical data, (2) focused on US populations and contexts, and (3) examined the impact of either stand-alone labeling changes or other FDA communications that contained information regarding a labeling change as either a primary or secondary analysis.

The most common reasons for excluding studies from our review included lack of evaluation of the potential impact of a labeling change, examination of a population outside the United States, or analysis of the potential impact of a labeling change for a food product or medical device. We acquired the 88 studies that met our pre-selection criteria, reviewed the complete text, and selected 52 for final inclusion in the review. See Figure 2 for more information about the study selection process.

2.2 | Study quality

We used the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool to determine if there was a potential risk of bias in study design due to (1) the randomization process or confounding, (2) participant selection, (3) misclassified interventions, (4) departures from intended interventions, (5) missing data, (6) mismeasurement of outcomes, or (7) selective reporting of results.[5] We formulated an overall risk of bias judgment for each study by weighing the severity of potential bias in each domain and considering the implications of each type of potential bias observed for study design, data collection, and the validity, reliability, and generalizability of a study's results (see Table 2). The overall risk of bias judgment for a study accounts for the characteristics of each type of potential bias observed and the totality

PubMed:

Search Number	Search Term Strings	Number of Results
#1	"Practice Patterns, Physicians'"[Mesh] OR "Drug Prescriptions"[Mesh] OR "Drug Utilization"[Mesh] OR "Product Surveillance, Postmarketing"[Mesh] OR "Health Knowledge, Attitudes, Practice"[Mesh] OR "drug use"[tiab] OR "drug dispensing"[tiab] OR "physician perception"[tiab] OR "physician perceptions"[tiab] OR "physician attitude"[tiab] OR "physician attitudes"[tiab] OR "safe use"[tiab] OR "safety"[tiab] OR "insurance"[tiab] OR "impact"[tiab] OR "impacts"[tiab] OR "change"[tiab] OR "changes"[tiab] OR "decrease"[tiab] OR "decreases"[tiab] OR "increase"[tiab] OR "increases"[tiab] OR "effect"[tiab] OR "effects"[tiab] OR "results"[tiab] OR "outcome"[tiab] OR "outcomes"[tiab] OR "decline"[tiab] OR "declines"[tiab]	12,098,180
#2	"United States Food and Drug Administration"[mesh] OR "Food and drug Administration"[tiab] OR "fda"[tiab] OR ("regulatory"[tiab] AND ("US"[tiab] OR "United States" [tiab])) OR USFDA[tiab]	72,516
#3	"Drug Labeling"[Mesh] OR "advisory"[tiab] OR "advisories"[tiab] OR "warning"[tiab] OR "warnings"[tiab] OR "precaution"[tiab] OR precautions[tiab] OR "black box"[tiab] OR "alert"[tiab] OR "alerts"[tiab] OR "boxed warning"[tiab] OR "boxed warnings"[tiab] OR "precaution"[tiab] OR "precautions"[tiab] OR "drug label"[tiab] OR "drug labels"[tiab] OR "drug labeling"[tiab] OR "drug product label"[tiab] OR "drug product labels"[tiab] OR "drug product labeling"[tiab] OR "drug labelling"[tiab] OR "drug product labelling"[tiab]	81,190
#4	#1 AND #2 AND #3	3,414
#5	#4 AND English[lang]	3,373
#6	#5 AND ("2010/01/01"[Date - Publication] : "3000"[Date - Publication])	1,717
#7	#6 NOT ("Editorial" [Publication Type] OR "Comment" [Publication Type] OR "Newspaper Article" [Publication Type])	1,671

Embase:

Search Number	Search Term Strings	Number of Results
#1	'clinical practice'/exp OR 'prescription'/exp OR 'drug utilization'/exp OR 'postmarketing surveillance'/exp OR 'physician attitude'/exp OR 'drug use':ti,ab OR 'drug dispensing':ti,ab OR 'physician perception':ti,ab OR 'physician perceptions':ti,ab OR 'physician attitude':ti,ab OR 'physician attitudes':ti,ab OR 'safe use':ti,ab OR 'safety':ti,ab OR 'insurance':ti,ab OR 'impact':ti,ab OR 'impacts':ti,ab OR 'change':ti,ab OR 'changes':ti,ab OR 'decrease':ti,ab OR 'decreases':ti,ab OR 'increase':ti,ab OR 'increases':ti,ab OR 'effect':ti,ab OR 'effects':ti,ab OR 'results':ti,ab OR 'outcome':ti,ab OR 'outcomes':ti,ab OR 'decline':ti,ab OR 'declines':ti,ab OR 'prescription':ti,ab OR 'prescriptions':ti,ab	15,912,008
#2	'food and drug administration'/exp OR 'Food and Drug Administration':ti,ab OR 'fda':ti,ab OR ('regulatory' NEXT/3 ('US' OR 'United States')):ti,ab OR USFDA:ti,ab	112,149
#3	'drug labeling'/exp OR 'advisory':ti,ab OR 'advisories':ti,ab OR 'warning':ti,ab OR 'warnings':ti,ab OR 'precaution':ti,ab OR precautions:ti,ab OR 'black box':ti,ab OR 'alert':ti,ab OR 'alerts':ti,ab OR 'boxed warning':ti,ab OR 'boxed warnings':ti,ab OR 'precaution':ti,ab OR 'precautions':ti,ab OR 'drug label':ti,ab OR 'drug labels':ti,ab OR 'drug labeling':ti,ab OR 'drug product label':ti,ab OR 'drug product labels':ti,ab OR 'drug product labeling':ti,ab OR 'drug labelling':ti,ab OR 'drug product labelling':ti,ab	118,152
#4	#1 AND #2 AND #3	5,468
#5	#4 AND [humans]/lim AND [english]/lim AND [2010-2017]/py	2,682
#6	#5 NOT ([editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	1,626

FIGURE 1 Summary of search term strings

of their impact on the study and is not simply the quantification of the number of categories in which risk for bias was observed. Studies were considered to be at risk from a source of potential bias if that source of bias could not be ruled out definitively.

3 | RESULTS

3.1 | Characteristics of included studies

3.1.1 | Types of drugs and labeling changes studied

More than 15 drug classes were examined across the 52 studies included in this review, although nearly half of the studies we reviewed examined the same three drug classes (antidepressants, erythropoietin-stimulating agents (ESAs), and antipsychotics (see Table 1). In addition, although changes to *Boxed Warnings* represent a small minority of total labeling changes,[6] more than two-thirds (37) of the studies included in our sample examined the impact of a *Boxed Warning*, while only eight of the 52 studies looked at changes made to other labeling sections, such as changes to dosing recommendations or addition of new contraindications. The disproportionately high number of impact studies on the *Boxed Warning* section, as well as the lack of research on the most frequently changed labeling sections, may prevent decision-makers from achieving a full understanding of the impacts of FDA safety labeling practices.

3.1.2 | Study objectives and outcome measures used

Almost all (45) of the 52 included studies investigated the impact of a labeling change on prescribing trends or drug utilization associated with a particular drug or class of drugs. Seventeen of the studies that measured prescribing and utilization rates also measured the impacts of the changes on additional outcomes such as drug substitution. Notably, only eight of the 52 studies we reviewed examined the impact of a safety-related labeling change on health outcomes for patients, which may impact the utility of postmarket labeling changes as tools to protect patient safety. See Figure 3 for an overview of all outcomes assessed.

3.1.3 | Data sources and covariates used

The 52 studies we reviewed relied on a number of different data sources. The most common source was prescription drug claims data (16 studies), 11 studies relied on national surveys such as the National Ambulatory and National Hospital Ambulatory Medical Care Surveys, and another 10 used electronic health record data (see Table 1).

While most studies included several covariates (most commonly age, race and/or ethnicity, gender, and various comorbid conditions), 14 studies listed no covariates. Thirty-six studies included additional covariates related to the patient population (such as marital, insurance, or employment status, income, geographic location, and health care utilization

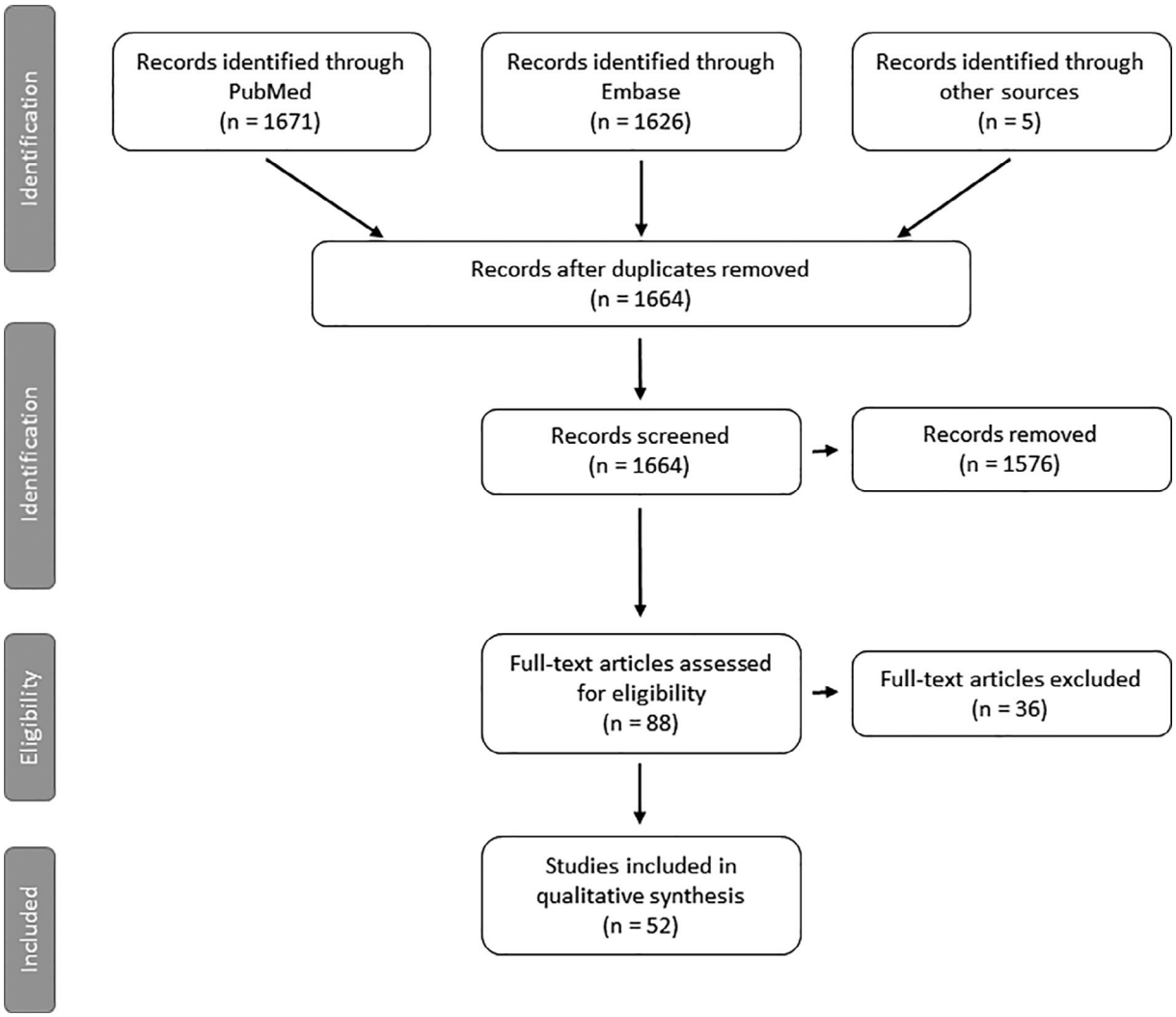

FIGURE 2 Summary of study selection process

pre-diagnosis), and 15 listed covariates specific to the health care providers or facilities (such as physician specialty or facility profit status). See Appendix I for a full listing of the data sources, measures, populations, covariates, and analytical approaches used in each study.

3.2 | Findings of included studies

Due to the wide variety of medications and labeling changes examined, as well as the heterogeneity of data sources and methods used to study those changes, we provide below some general observations about the body of evidence included in our review.

3.2.1 | Drug prescribing and utilization

The impacts of FDA labeling changes on drug utilization and prescribing varied, indicating the need for additional research on approaches to ensure that the intended impact of a labeling change is achieved and sustained. For example, 11 of the of the 37 studies that examined the potential impact of *Boxed Warnings* found an overall decrease in prescribing rates, while 19 found mixed or no effects on prescribing despite recommendations to alter prescribing practices. Two studies demonstrated that overall prescribing rates of the drug were already declining prior to the *Boxed Warning*,[7,8] and another found that while a *Boxed Warning* did appear to decrease prescribing, the effect was not sustained.[9] In addition, one study on tiagabine found that a more specific warning tailored to the drug led to a significant decline in prescribing, while another, less specific drug warning about multiple drugs did not have any effect on prescriptions.[10]

Finally and notably, in some cases, different studies of the same labeling change came to different conclusions about the effect of the examined change or communication on key outcomes (such as prescribing and utilization of ESAs[7,11-13] and antidepressants).[14,15]

TABLE 1 Characteristics of studies examining FDA labeling changes (*N* = 52)

	N[a]
Drug or therapeutic class	
Multiple drug classes	12
Antidepressants	10
Erythropoietin-stimulating agents (ESAs)	8
Antipsychotics	6
Thiazolidinediones	2
Antibiotics	2
NSAIDs	2
Long-acting β-agonists	2
Acetaminophen	1
Anti-D immunoglobulin	1
Antiepileptics	1
Dronedarone	1
Leukotriene inhibitors	1
Metoclopramide	1
Statins	1
Tiagabine	1
Data source	
Claims data	16
Both medical and pharmacy claims	12
Pharmacy claims only	3
Medical claims only	1[b]
National surveys	11
Health records[c]	10
Study-specific surveys	5
Registry	5
Other	4
FDA's Adverse Event Reporting System (FAERS) database	3
Other databases	3
Study populations	
Single patient population (with specific subtype, diagnosis, prescription treatment, or membership in health system or plan)	22
Medicare patients	4
Medicaid patients	2
Veterans affairs patients	6
Pediatric or adolescent patients	2
Elderly	1
Health care providers	7
Neither patients nor providers	8
Communications	
Boxed warning	37
Other labeling change	8
Risk comm. about labeling change	7

[a]Totals may not add to 52 as some studies may have included more than one drug, data source, or type of communication.
[b]This study included Medicare Part B billing data on physician-administered drugs.
[c]This includes both electronic health records and medical chart reviews.

3.2.2 | Incidence and reporting of adverse events

Several studies evaluated the impacts of safety-related labeling changes on the incidence and reporting of adverse events. For example, one study evaluated the impacts of more than 100 different FDA alerts and risk communications, including labeling changes, on reporting of adverse events to the FAERS database.[16] It found that while increased reporting occurred for a few drugs, the majority of risk communications did not affect reporting rates.

Another study reviewed the impacts of a labeling change on the incidence of adverse events for patients taking ESAs, using Medicare claims data from 2008 through 2013, and found mixed effects. The study observed that while the risk of experiencing some adverse events, including death, did not change, the risks of others, such as stroke, were reduced. When broken down by racial subgroups, black patients had reduced risk of adverse reactions after the labeling change.[17]

3.2.3 | Spillover effects

Spillover effects were observed for some labeling changes,[14,18,19] such as decreased prescribing for patient populations not targeted by the change, indicating that labeling changes can potentially have unintended consequences. However, the exact causes of these effects and how best to mitigate them are not well understood. For example, one study found that the *Boxed Warning* for atomoxetine for attention-deficit/hyperactivity disorder (ADHD) treatment resulted in a temporary decrease in prescribing rates for adults, even though the *Boxed Warning* was only concerned with adolescent users.[20] Another study of the *Boxed Warning* on antipsychotic psychotropic drugs, for example, found that as post-warning prescribing rates of antipsychotics decreased, prescribing rates for nonantipsychotic psychotropic drugs increased.[18] Finally, one study that evaluated the impact of a *Boxed Warning* for ESAs on health care costs for cancer patients needing treatment for anemia, found that while anemia treatment costs decreased after the *Boxed Warning* was issued, costs of other aspects of cancer care for those patients increased, resulting in no net savings.[19]

3.2.4 | Adherence issues

Health care providers appeared to have relatively low adherence to labeling changes related to dosing and patient monitoring. However, the extent to which these types of labeling changes may have prompted providers to select alternative therapies is unclear.[21-25] Two studies found that guidelines that addressed the use of drug that was the subject of a *Boxed Warning*—such as dosing recommendations or calls for increased patient monitoring—did not receive full adherence, despite providers having knowledge of the guidelines.[21,24]

3.3 | Quality of included studies

We found a high risk of potential bias in eight of the 52 studies we reviewed as well as a moderate risk of potential bias in 25 of the

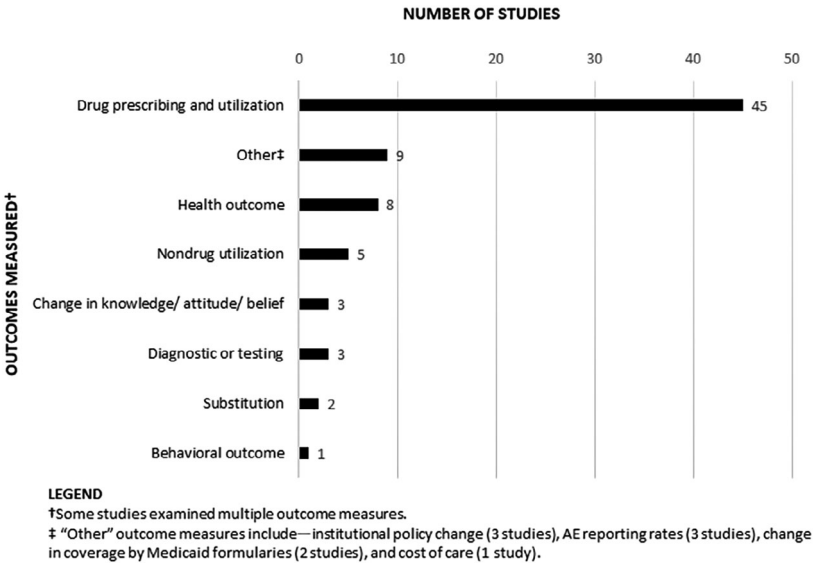

FIGURE 3 Outcomes measures examined. †Some studies examined multiple outcome measures. ‡"Other" outcome measures include—institutional policy change (three studies), AE reporting rates (three studies), change in coverage by Medicaid formularies (two studies), and cost of care (one study)

TABLE 2 Number of studies with each source of potential bias, by overall risk of potential bias

	Overall risk of potential bias		
Source of potential bias	**High (total studies = 8)**	**Moderate (total studies = 25)**	**Low (total studies = 19)**
Confounding	5	20	1
Participant selection	4	0	0
Classifying interventions	2	6	0
Departure from interventions	1	2	0
Missing data	4	4	0
Outcome measurement	6	7	0
Selectively reporting results	1	1	0

52 included studies. In studies that exhibited high risk for potential bias, this risk was commonly derived from weaknesses in participant selection, such as small sample sizes, as well as issues with confounding and outcome measurement. Many of the studies that exhibited high risk for potential bias collected data by designing and administering surveys to a small population of office-based providers or pharmacists, reducing their generalizability.

Twenty of the 25 studies that exhibited moderate risk for potential bias had baseline or time-varying confounding issues. These studies generally lacked controls for patient characteristics or behaviors, such as patient medical history or prescription drug utilization. Confounding also occurred in studies that did not properly adjust for the impacts of other factors on studied outcomes, including media coverage, provider education, and other risk communications issued for the product. A summary table of the ROBINS-I results is produced below in Table 2.

4 | DISCUSSION

Key themes from this review are generally consistent with the findings of previous reviews. While many studies in our review found that the examined labeling change had at least some statistically significant impact on the outcome of interest (typically, a decrease in prescribing rates), other studies showed no discernible effect on prescribing, rates of adverse reactions, or other studied outcomes. Studies also found that labeling changes can have unintended consequences, including decreased prescribing in populations not targeted by the change, unintended treatment outcomes as a result of patients not using a drug from which they might benefit, and unintended changes to health care costs. Several studies noted that some health care providers have not fully adhered to the labeling change guidance on dosing, use, or monitoring patients for adverse reactions, and in some cases have not changed their practices after a labeling change despite knowledge of the change.

Overall the new studies that we reviewed represent little progress forward in addressing key gaps and limitations in the existing body of evidence. Several critical evidence gaps remain, such as the fact that the bulk of the literature is concentrated on a few drugs or drug classes (eg, antidepressants, antipsychotics, ESAs). FDA has instituted postmarketing safety labeling changes for a large number of drugs, the vast majority of which have not been studied.[3] In addition, our results indicate that some studies exhibited important methodological problems—particularly with respect to potential bias arising due to participant selection, confounding, and outcome measurement. These issues impact study validity, limit the generalizability of study results, and ultimately may compromise the utility of these studies as

tools for understanding the impacts of postmarket safety labeling changes on key health and behavioral outcomes. Finally, more research is needed on the impacts of labeling changes on additional outcomes that are important to patients, as well as on the unintended consequences of labeling changes, such as impacts on health care costs and utilization of non-drug aspects of health care.

To build off the findings of our review, we collaborated with the authors of previous reviews and other subject matter experts to publish a white paper containing recommendations for addressing existing gaps in the evidence base and increasing study quality.[26] One of these recommendations is to follow a standard research framework for designing and implementing high quality studies based on best practices from social science research. As part of this effort, we identified several research areas where well-designed studies would add value, including studies that evaluate other types of labeling changes beyond *Boxed Warnings* and those that evaluate the unintended consequences of postmarket labeling changes. For a list of recommended research areas see Table 1 in the white paper.[26] We have also recommended the establishment of a consortium involving FDA and the research community to identify priority research topics and broaden the evidence base on safety labeling changes.

Despite the clear need for rigorous, high-quality studies on the impacts of FDA's safety-related labeling changes, there are several challenges to conducting this type of research. Accessing and then aggregating fit-for-purpose data can be difficult, as data may be located across several different, incompatible systems.[27] Post-marketing studies typically rely on pharmacy or medical claims data, which have several advantages (including validity, ready availability, and the ability to be linked to external datasets) but also important limitations, such as inconsistent coding across care facilities and a lack of complete clinical information.

Furthermore, disentangling the potential impacts of these labeling changes from those of other sources of information that can influence patient and health care provider behavior is a complex and difficult undertaking.[2] While there are a number of rigorous statistical methods and study designs that can be applied to these research questions, FDA cannot communicate a labeling change to some patients or providers and not others, which may preclude identifying a control group to measure impact.[3] It can also be difficult to identify the patient population for which the safety-related labeling change or communication was intended, which may make it difficult to identify an appropriate outcome measure.[4] Finally, securing adequate and timely funding for these types of studies (particularly for qualitative studies that rely on patient or health care provider interviews conducted in real time) can also pose a barrier to conducting and publishing research on labeling changes and risk communications.[28]

This review has important limitations. The heterogeneity of drugs, labeling changes, populations, and outcomes studied, along with the variable quality and strength of the statistical methods employed by the included studies, preclude anything more than a qualitative analysis of the overall impacts of safety-related labeling changes. In addition, although we made a concerted effort to identify all peer-reviewed studies that met our inclusion criteria, it is possible that we may not have found all research on this topic due to differences between our search strings and how studies were tagged in the databases.

5 | CONCLUSIONS

The gaps and limitations that we highlight in the existing evidence base make it difficult to draw firm conclusions about the impacts of safety-related labeling changes, and similarly about how to modify labeling practices to improve key outcomes. Additional research is needed to more fully characterize the impacts of safety-related labeling changes on prescribing rates, drug utilization, and treatment outcomes and to identify ways for FDA to enhance its approach to communicating the risks of pharmaceuticals. Possible approaches for enhancing this evidence base include developing a standard research framework, as well as a coordinated research agenda that highlights important topics for further evaluation. The white paper developed as part of a cooperative agreement between FDA and Duke-Margolis can help spur the generation of additional evidence on this topic. The white paper provides recommendations and outlines next steps to help FDA advance its understanding of the impacts of its post-marketing safety activities.[26]

ETHICS STATEMENT

The authors state that no ethical approval was needed.

ACKNOWLEDGMENTS

The authors would like to thank Stacie Dusetzina for her guidance and advice on this manuscript. This review was supported by the U.S. Food and Drug Administration (7U19FD004971-04). The authors would also like to thank members of Duke Evidence Synthesis Group for their assessment of the literature using the ROBINS-I tool: Evan Myers MD, MPH, Ranee Chatterjee, MD, MPH, Adam Goode, DPT, PhD, and Gillian Sanders Schmidler, PhD. This review reflects the views of the authors and not necessarily those of the U.S. Food and Drug Administration.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

U.S. Food and Drug Administration authors contributed to study design, the collection, analysis and interpretation of data, the writing of the report, and the decision to submit the report for publication.

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SUPPORTING INFORMATION

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

How to cite this article: Rosenberg M, Sheehan S, Zhou E, et al. FDA postmarketing safety labeling changes: What have we learned since 2010 about impacts on prescribing rates, drug utilization, and treatment outcomes. *Pharmacoepidemiol Drug Saf*. 2020;29:1022–1029. https://doi.org/10.1002/pds.5073