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STUDY DESIGN

Methodological Approaches to Evaluate the Impact of FDA Drug Safety Communications

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Abstract

Background When the US FDA approves a new prescription drug there is still a great deal remaining to be learned about the safe and proper use of that product. When new information addressing these topics emerges post-approval, the FDA may issue a Drug Safety Communication (DSC) to alert patients and physicians. The effectiveness of the communication—how drug safety messaging conveyed in FDA DSCs changes patient or prescriber behavior—may depend on multiple factors, including the way physicians and patients learn about the information, their understanding of the issues conveyed, and their perception of the importance of the information. In 2013, the FDA issued two DSCs addressing critical new warnings related to products containing the sedative/hypnotic zolpidem.

Objective In this article, we describe a core set of research initiatives that can be used to study how zolpidem-

Key Points

Evaluating the impact of the FDA's Drug Safety Communications (DSCs) is an essential part of drug safety oversight, and certain empirical approaches can be broadly applied to optimizing the effectiveness of regulatory risk communications.

One approach, to be used in the study of DSCs related to zolpidem-containing products, involves analysis of prescribing and related health outcome trends, direct interviews of patients and physicians, a national survey of patients, and quantitative and qualitative reviews of descriptions of the risk communications in social and traditional media.

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related DSCs affected subsequent physician and patient decision making.

Methods These research initiatives include analyzing drug utilization patterns and related health outcomes; comparing zolpidem-containing products against a comparator with similar indications [eszopiclone (Lunesta)] not covered by the 2013 DSCs; and surveying patients and qualitatively evaluating the dissemination of information regarding these drugs in traditional and social-media channels.

Conclusions Using an integrated, multidisciplinary approach, we can obtain information that can be used to optimize regulatory communications by seeking to understand the impact of the information contained in FDA risk communications.

1 Introduction

When a new prescription drug is approved by the US FDA there is still a great deal remaining to be learned about the safety and proper use of that product [1]. Pre-approval studies conducted by manufacturers generally test experimental drugs in a few hundred to a few thousand patients [2]. These studies provide important initial insights into the adverse effects and benefit/risk balance of the drug, but new information can emerge regarding the safety of prescription drugs after their approval and use in hundreds of thousands—or even millions—of patients [3]. Such safety information may provide insight into rare but deadly side effects [4], or variable activity of the product in different subgroups of patients [5]. Evolving knowledge about a prescription drug after approval can lead to new warnings being added to a drug's label [6], changes to the recommended dosing regimen [7], or recognition of harmful drug–drug interactions [8].

When reliable new safety-related risk information regarding an approved prescription drug comes to light, patients and physicians should be made aware of the information through clear and timely updates so that they can continue to use the drug optimally [9]. One of the primary mechanisms that the FDA uses to alert physicians and patients about new safety data related to approved prescription drugs is the Drug Safety Communication (DSC) [10]. DSCs are developed and released by the FDA to communicate important and serious drug safety information regarding marketed drugs to the public. A DSC is released in standardized format on the FDA website [11] and the safety messages are disseminated and diffused through other channels, including MedWatch, Medwatcher Social, Safety Alerts, blogs, targeted stakeholder emails, FDA Updates for Health Professionals list-serve, Drug Information list-serve, FDA Drug Information Twitter account, drug safety podcasts, and National Alliance for Hispanic Health (Spanish version). Each DSC message may contain a single or several pieces of information related to a particular medication or class of medications and the safety issues involved. DSCs target both healthcare providers and patients and are written plainly for a lay audience. Their goal is to protect and promote public health.

A total of 166 DSCs were issued in the years 2010–2013 (39 in 2010, 66 in 2011, 29 in 2012, and 32 in 2013), conveying numerous messages [11]. The FDA has studied trends in uptake and comments on DSCs through social media, but it has not collected comprehensive data on how patients respond to DSC messages and why they respond in the ways that they do. A recent non-FDA study suggests that safety warnings can lead to changes in patient behavior [12]. More needs to be learned on how DSC messages perform in influencing the actions of people prescribing or using a given medicine once they are aware of the new drug safety message. It is reasonable to expect that changes in drug utilization behavior among patients prompted by such drug safety messages would manifest in measurable ways, such as a decrease in average dose dispensed by a pharmacy following the release of a safety message recommending a lower dose.

Multiple factors might impact the effectiveness of the drug safety messaging conveyed in DSCs on patient or prescriber behavior, including perception, intent, and decision making. These regulatory risk communications might be improved by the application of a multidisciplinary evidence-based approach, integrating quantitative analyses of pharmacoepidemiologic outcomes such as patterns of utilization, occurrence of specific health events, and qualitative and quantitative social science analyses of awareness, perception, intent and action within the same population. Such an approach would benefit from the social and traditional media context, to provide a comprehensive view of the impact of FDA-issued risk communications and their messaging in settings of routine patient care. In this article, we describe a core set of research initiatives that can be used to study how zolpidem-related DSCs affected subsequent physician and patient decision making.

2 Selecting Study Drugs for Evaluation of Drug Safety Communication Messaging

Each DSC represents a tailored communication specific to some new set of data, but to make the discussion more concrete we chose the example of the commonly-prescribed sedative/hypnotic drug, zolpidem, which was first

approved by the FDA in 1992 under the brand-name Ambien [13]. It was originally approved for use in the short-term treatment of insomnia in adults at doses of 10 mg, with suggestions for a starting dose of 5 mg for patients who are elderly, debilitated, or who have hepatic insufficiency or use other central nervous system-active drugs [14]. Ambien quickly became the most prescribed sleep aid for US patients, reaching over $2 billion in peak annual sales in the US before a generic version was introduced in 2007. It spawned numerous follow-on formulations, including an extended release version (Ambien CR), a sublingual tablet (Intermezzo), and an oral spray (Zolpimist). In 2012, two-thirds of all prescriptions for sleeping pills provided to US patients were for some version of zolpidem [15].

Accumulating data regarding the safety of zolpidem-containing products [16, 17] led the FDA to issue a DSC about the product on 10 January 2013 [18]. In that DSC, the FDA reminded consumers about the risk of persistent drowsiness occurring the day after taking the medication, which could impair activities (such as driving) that require elevated alertness. The FDA reported that the day-after drowsiness risk was highest for controlled-release versions of the product and warned that women were at higher risk for this effect than men because women eliminated the drug more slowly from their bodies. The DSC concluded with the FDA advising women to take half the dose that had been previously recommended in labeling, that all patients should be prescribed the lowest dose that treats their symptoms, and that all patients should be aware that they are at risk from impairment related to zolpidem the day after taking the drug, even if they feel fully awake. The initial zolpidem DSC was followed by the release of a second zolpidem DSC on 14 May 2013 which noted that the FDA had formally reduced the recommended dosage in labeling of most zolpidem-containing medications by half for all patients—the first major dosage-related change to the formal label of the product since its approval over 20 years prior [19].

The pair of 2013 zolpidem DSCs have a number of features that invite an integrated, multidisciplinary, quantitative and qualitative analysis of their societal impact, therefore they are a good test case to develop a new method to study the impact of FDA risk communications. The drug involved is widely prescribed [20], and the safety communication imparts a fundamental change in the drug's routine use (i.e. cutting the recommended dosage in half) with substantial patient safety implications. Indeed, well-controlled observational studies show that taking zolpidem for insomnia at its prior recommended dose levels was associated with an increased risk for a wide range of injuries plausibly related to excessive drowsiness [21], including a 67 % increase in the risk of major injuries—head injuries or fracture requiring hospitalization—versus age-adjusted comparison groups not taking the drugs [22]. Zolpidem is routinely prescribed for outpatient use and is available from community pharmacies, which would allow use of a large commercial insurance database to track pharmacy dispensings of the product and determine whether changes occurred after the DSC messaging had been communicated. Zolpidem is not subject to any additional communication requirements or restricted distribution. That is, a Communication Plan or Elements to Assure Safe Use (ETASU) Risk Evaluation and Mitigation Strategy (REMS) are not required [23], which may interact with evaluation of the effect of DSC risk messaging.

Finally, a comparator medication exists that has a similar indication and for which a DSC had not been issued at the time the DSCs were issued for Ambien in 2013—eszopiclone (Lunesta), a sleep aid that works via a similar mechanism of action [24]. We believe that eszopiclone is a suitable comparison medication because it is a non-zolpidem-containing sedative/hypnotic used in generally similar circumstances with similar clinical effects. While certain market features (exclusivity expiration, etc.) may affect zolpidem and eszopiclone use differently, a comparison between the two around the time of the zolpidem DSCs should be able to isolate the effect of the DSCs on sedative/hypnotic prescribing. By comparing trends, and changes in trends, in zolpidem outcome measures with trends in eszopiclone outcome measures, we will differentiate the effects of the DSC from underlying temporal trends such as changes in co-payments, seasonality, or increases or decreases in the prevalence of insomnia. Of note, a DSC related to eszopiclone was released in May 2014 but our study period will end before the eszopiclone DSC, therefore its presence will not affect our results. Thus, the availability of a comparator product will allow us to more precisely investigate why people who are aware of the messaging make the decisions and take the actions that they do.

For the implementation and test of the pilot integrated method, we therefore selected the zolpidem DSCs as a case example for a pilot study to develop a new framework, bringing together a series of different methodologies to integrate an innovative evaluation of the impact of risk communication messaging, the first test of the method found in the evaluation of FDA-issued DSCs. Using this approach, we plan to test the impact of the messaging in the zolpidem DSCs, comparing these results with those of a similarly-situated drug (eszopiclone) that was not the subject of DSCs during the same period. Finally, since the zolpidem DSCs were recently issued, our analysis will allow critical evaluation of the FDA's current communication strategy and, importantly, will account for the media context by allowing us to test the uptake of the key

messages within the DSC in the contemporary social environment. This includes widespread use of modern social and traditional media tools, as well as peers, family, and healthcare providers as sources of information.

3 Overall Study Design

This study was developed through a collaboration of the FDA with investigators at the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital; the Mongan Institute for Health Policy Research, Massachusetts General Hospital; Dartmouth Institute for Health Policy and Clinical Practice; and the Computational Epidemiology Group, Boston Children's Hospital. The evaluation methods derive from linking pharmacoepidemiology and social science approaches in the same population, combined with assessment of the media milieu, to correlate the messaging associated with the FDA's DSCs with specific relevant outcomes. These include changes in new and ongoing use of the target drug, health outcomes of interest germane to use of the drug, patient and physician awareness, knowledge regarding the safety information contained in the DSC, perceptions, reported intent, and actions regarding the same safety information. The analysis employs data derived from drug utilization claims from the database of a major national insurer coupled with direct interviews of randomly sampled patients and physicians as the basis for development of a quantitative survey assessment of patients while taking the context of traditional and social-media analyses into consideration. In this way, the project will evaluate the impact of DSC messaging across several dimensions within this single population of patients covered by a single, large, national insurer.

The proposed evaluation of DSCs is founded on a logic model depicted in Fig. 1. Its phase III is of central interest as it relates safety messaging in DSCs to awareness, perception, reported intent, and actions of patients or physicians. In the first stage of information dissemination (stage 0), the messages conveyed by the DSC may be preceded by some level of awareness regarding the safety issue that may have come from counseling by the physician or pharmacist when first prescribed the drug, and prior publications or safety announcements, or may be deduced by some from knowledge of pharmacology or physiology. This background awareness, which, at minimum, comprises peers and relatives as well as social and traditional media channels, may modify the response to the message presented in the DSC. The event of interest occurs when the FDA releases the DSC (stage 1). This stage occurs at a specific calendar time but each DSC occurs in the context of varying levels of prior knowledge gained in stage 0. The DSC release itself may vary in duration or scope of dissemination.

After FDA release of the DSC, the messages within it may be picked up by a combination of traditional media and social media (stage 2). This stage will further modify existing knowledge expressed in stages 0 and 1 by adding to the background awareness and initial release. Secondary pickup will be measured through a combination of traditional and social-media metrics (including both quantitative and qualitative assessments). Through these and other channels in their social environment, prescribers and patients become aware of the messages conveyed by the DSC (stage 3). However, how the message is perceived and whether these parties may or may not fully comprehend the drug safety message, as well as this awareness, perception, and intent, may drive further knowledge-seeking and may affect continued use of the medication or determine how the DSC messaging alters future prescribing. This third stage is of greatest interest to this study and will be explored through a combination of qualitative targeted semi-structured interviews and a quantitative survey in a random sample drawn from the same population as the interviews. The targeted interviews will seek to elucidate the effectiveness of the messaging on patients and providers. This will provide a framework, given the myriad of sources of drug safety information, to evaluate patient perceptions, intent, and their actions in response to risk communication messages received from those and other sources. A patient survey will quantify the rates of factors related to awareness, perception, and intent once patients are aware of specific DSC messages, as well as the actions taken in response to the messages based on material elicited from the direct patient and physician interviews.

The impact of the DSC and its messages may also manifest as a change in use as measured through prescriptions of the target drug filled at pharmacies (i.e. either through numbers of patients receiving a new dispensing or the number of total/repeat dispensings) after a DSC was issued (stage 4). These metrics may be stratified by demographic or clinical characteristics since the DSC message may target a select subgroup of medication users, and the DSC effect may be more apparent in the target subset. Relative changes in drug use or prescribing may be measured directly through changes in health insurer claims for pharmacy dispensings, patients filling a first prescription for the drug, and correlates of dispensing along with analyses based on drug user populations (with stratification for new vs. prevalent use) before and after the selected DSCs. Differences in the variations in the rates of health outcomes of interest pre-DSC issuance compared with post-DSC issuance, such as accidents, in new zolpidem users versus new eszopiclone users, integrated with the social science

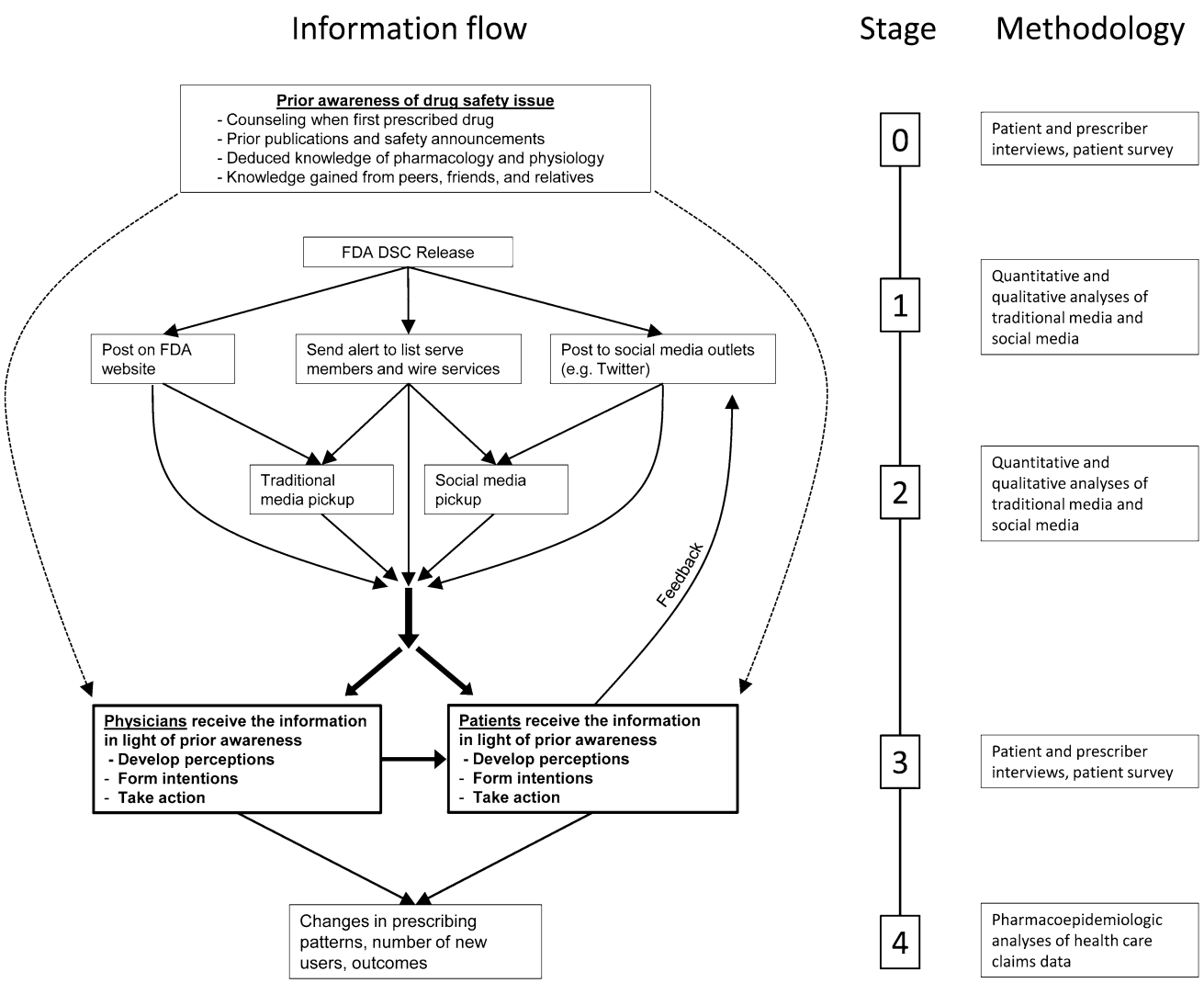

Fig. 1 Logic model demonstrating the stages of a DSC and the methodology used to assess its effects. This flowchart describes the progress of knowledge regarding drug safety through the DSC pathway and the anticipated physician and patient responses to drug safety messaging. *Dotted arrows* (one on each edge side of the information flow section of the figure) represent informal influence; *solid arrows* represent formal message transmission. Physicians also rarely post to social media but, as data show, to a much less extent than patients; as such, we did not include this feedback mechanism in the model (source: authors' analysis). *DSC* Drug Safety Communication

analyses and the media context, will be one innovative aspect of the new method being piloted in this study.

4 Integrated Analyses

The conduct of the three integrated approaches in this study (analyses of the traditional and social-media coverage of the DSC, interviews with patients, as well as surveys, along with interviews of physicians, and observational studies of the medication use and health outcomes) are described to illustrate how the DSC message is taken up by patients and prescribers and translates into measurable clinical outcomes.

4.1 Traditional and Social-Media Analyses

When the FDA releases a DSC, the essential safety messaging is conveyed through a host of media channels represented by traditional and social-media outlets. Traditional media includes newspapers, broadcast media, medical journals, and professional and lay magazines. These sources have a powerful influence on public perceptions regarding health and healthcare; much of what patients and physicians know and believe about medicine comes from these forms of media [25–27]. When the FDA releases a new DSC, journalists, medical journal editors, and other traditional media authors translate the research report into a news story for the public and physicians;

however, this process may result in partial or incorrect transmission of DSC messages because some of these authors have little training in interpreting and communicating medical data [28]. Not surprisingly, news stories regarding healthcare topics, particularly regarding the appropriate use of prescription drugs, are often incomplete or misleading [29–31]. Studying these media reports is important because these news stories and reports strongly influence the attitudes, decisions, and behaviors of their intended audiences [32–36].

The uptake of the FDA's drug safety messaging in traditional media will be measured, in part, through a quantitative compilation of news stories available through aggregating data sources such as LexisNexis (which includes Newstex, an aggregator of news blogs such as the Huffington Post, Slate, and ProPublica) and ProQuest/Factiva (to fully capture the Wall Street Journal). The quantitative metrics used to investigate these data sources include the number of news stories that mention the messages contained in the DSC, the source of the news story, and the timing of the news story relative to the release of the DSC. These services include compilation of news stories from scientific journals, as well as press releases transmitted on the health wires that might have been released.

These quantitative metrics will be complemented by qualitative metrics that assess how well the DSC message is conveyed by the news stories related to the medications. We will assess three major areas of interest in the drug communication: the specificity of the information, the terms used to describe the risks of zolpidem, and how the news media balances reports of benefits and harms. Prior research on the impact of Dear Doctor letters [37] suggests that greater specificity in warnings about prescribing (e.g. explicit listing of interacting medications) has a greater impact on prescribing, therefore the specificity of each message will be reviewed in particular. Description of drug risks and benefits in the media have often been shown to be inadequate in prior studies of health communication, with the language used sometimes being characterized as too technical, and at other times too abstract [38].

Since DSC messages are also routinely conveyed through social-media channels, we will conduct a detailed evaluation of the social-media coverage of the drug safety messaging in the time leading up to the DSC(s) and in the time following. Analyses of social media will also allow us to more fully account for the communications environment within which patients receive the messages. The Internet is the world's most relied-on health resource [39, 40], with approximately 5 % of all Internet searches being health related [41]. As an illustration of the volume of social media related to zolpidem, between October 2012 and August 2013 there were 174,704 tweets related to zolpidem/Ambien.

Our analysis will use a widely studied and previously validated platform called MedWatcher to access archived social-media data, program search queries, identify online communities, and weed out unrelated and spam-like content to arrive at a core of data that can then be interpreted and put into context for this study [42]. MedWatcher serves as a comprehensive social-media analysis tool to identify drug safety information on sources such as Facebook and Twitter [43]. The environmental effects of social and traditional media communications have not been studied in relation to differences between comparison groups matched on indication in rates of new prescriptions, healthcare utilization, or serious adverse experiences before and after the risk communication issue in users of the drug of interest in comparison to users of a drug with the same indication in the same population. We therefore seek to examine three main areas of investigation. First, how many relevant social media mentions did the FDA's safety messages initially engender? How did the reach expand after the original messages were shared? What effect did the DSC releases and subsequent messaging have on numerical references to the drug (zolpidem or eszopiclone), condition (insomnia), or safety issue (e.g. reduced alertness the next day even if feeling awake)? What was the time course of social-media communications regarding the DSC messaging, in relation to the initial DSC, and traditional media uptake and rates of health outcomes of interest?

Second, we will use content analysis of the social media we identify to address the qualitative content of DSC-related messaging in these social-media outlets. To do this, we will collect social-media conversations in English, analyze this content, and provide summary analytics, including metrics such as volume of conversation by geography, time, and topic; trends in positive, neutral, and negative sentiment; hubs of influence; and network maps visualizing the conversations happening in the online space. We may be able to assess the messaging tone of the social media mentions of the FDA DSCs and related messaging concerning zolpidem, including whether the message is being reported with credulity or with criticism/skepticism.

Finally, we will evaluate the sources referenced in social media related to the DSC messaging. Do social-media authors cite the FDA or secondary sources? For the two zolpidem DSCs, the DSC messaging and secondary uptake characteristics will be analytically related to insurance claims measures to quantify associations with changes in rates and patterns of drug product utilization, health outcomes such as serious adverse experiences, and numerous other measures of healthcare utilization coupled with subjective data on DSC messaging impact elicited directly from patients and physicians. This evaluation will reveal

the effectiveness of the message across several patient dimensions in the same target population.

4.2 Interviews and Survey

The ways in which patients and physicians receive FDA risk communications and other types of drug safety information, and their response to specific messaging covered by the DSCs, will be explored both qualitatively through direct interviews and quantitatively through a survey based on information gathered from the same random sampling frame for the pair of DSCs in this pilot. The semi-structured interviews will seek to determine unknown or unexpected factors that relate to the impact of the DSC messaging. The interviews will inform the quantitative survey of patients drawn from the random sampling frame. The novel data arising from these direct patient-focused social science analyses will provide quantitative measures of cognitive factors that can be used in conjunction with the results of the health insurance claims analyses. The goal of these evaluation methods will be to find out directly what the perceived impact of DSC message pickup through dissemination, diffusion, and duration of the risk communication messaging will be on the patient or prescriber.

We will use the same source population for the integration of the results of the interviews, survey, and the database analyses pre- and post-DSC risk communication. These patients will be drawn from the Optum Research Database, which contains fully adjudicated insurance claims from UnitedHealthcare plans. The source population of approximately 65 million people over the years 2005–2014 (approximately 14 million cross-sectionally) with comprehensive medical and pharmacy benefits is a geographically diverse sample and fairly representative of the US population for age groups under 65 years. The Institutional Review Boards and regulatory boards of the respective institutions (Brigham and Women's Hospital, FDA, Optum) have reviewed and approved all arms of this study. For the interviews and studies specifically, recruitment is opt-in (in response to direct mailers or online ads), and informed consent for participation is obtained by study staff prior to interview or survey initiation with participants.

We will first conduct semi-structured interviews with a random sample of patients from this database who represent both established users and new users of zolpidem and eszopiclone, and analyze the semi-structured interview data using qualitative methods. We will interview a randomly selected sample of patients who have prior experience with zolpidem or eszopiclone (at least 20 participants for each drug), as well as at least 10 physicians who treat patients using these prescription drugs. This qualitative approach will provide a rigorous way of investigating personal knowledge, experiences, perceptions, reflections, and outcomes among a small cohort of subjects who share a common experience [44]. Qualitative methods will be useful for exploratory research and hypothesis generation, given the paucity of published data regarding the impact of messaging involved in FDA DSC communications [45]. The interviews will be analyzed consistent with grounded theory [46], proceeding in a series of iterative steps employing the constant comparative approach [47, 48]. Investigators will first read the transcripts independently, each identifying domains or topic areas. Then, based on a joint review of the domains and their corresponding text, the investigators will create an initial set of codes, which will be further refined through successive reviews of the coded text, by adding codes as new insights are gained and combining codes to reflect higher-level themes. The interviews will concentrate on the awareness, perception, intent, and actions of patients or prescribers in response to new drug safety risk communication messages issued by the FDA. The interviews will be designed to initiate and pursue a conversation with interviewees that probes perceptions, behaviors, and beliefs about drug safety. The results will then be presented graphically and textually to highlight the lessons that emerge providing insights into dimensions and factors that drive the impact of DSC messaging on patients, leading to actions.

We will use the interview results to develop a quantitative assessment of factors that relate to impact in a survey of 2000 randomly sampled patients in the same population who have filled prescriptions for either zolpidem or eszopiclone to answer the following questions. (1) From what sources do patients receive FDA drug safety risk information? (2) Do they have knowledge of specific safety information about their sleeping pills described in the FDA DSC messaging? (3) If patients are aware of the messaging, what are their perceptions of the information? (4) What are patients' intended actions in light of these messages? The survey will be conducted using a modified Dillman method [49] to promote response rate, including a mailed initial survey packet including cover letter, survey, consent forms/health information release, and a $5 pre-incentive (by first-class mail). The quantitative survey assessing factors and themes derived from the interviews will be 8–10 pages, mostly closed-ended questions, taking patients no more than 15–30 min to complete. Two weeks following the initial mailing, participants will receive a reminder packet including a different cover letter and another copy of the survey; 2 weeks following that another replacement packet will be sent by first-class mail to all non-respondents. Patients will be offered an additional $25 incentive for completing the survey. The survey development literature supports providing pre- and post-incentives to survey participants [50, 51], although there is controversy

over whether post-incentives provide an additional boost [52]. We anticipate a 20–35 % response rate based on previous surveys in the same population that have conducted similar surveys using less rigorous methods [53]. Survey responses will be linked to claims measures of effect and differences in health outcomes of interest before and after the DSC issue developed to describe observed changes in the use of the DSC medication in response to the dissemination, diffusion, and duration of the risk communication messaging in the media environment. This pre-specified linkage will permit direct assessments of patients' behavior (represented by dispensing patterns) in response to a DSC, with stratification according to survey responses.

The interviews and surveys are needed in light of the claims data analysis because they can provide direct insights into patient perceptions of the safety of their sedative/hypnotic drugs and methods for obtaining drug safety information. While prescribing trends and other health resource utilization might be observable from claims data, the interviews and surveys will help us formulate hypotheses regarding motivations for any changes we observe. One limitation of the interviews and surveys is that they will be collected after the DSCs have been issued, and the information contained in the DSC disseminated. To address this limitation, our questions will focus on how patients obtained drug safety information in general and related to their sedative/hypnotics, as well as testing their knowledge of the information contained in the DSC to see whether the messaging has been accurately transmitted.

4.3 Claims Data Analysis of Utilization Patterns and Health Outcomes

Finally, we will tie together the results from the interviews, survey, and traditional and social-media analyses by conducting a pharmacoepidemiologic analysis of trends in the use of zolpidem and eszopiclone, and subsequent patient-related outcomes around the time of the zolpidem DSCs. This detailed evaluation will use longitudinal health insurance claims analyses that will reveal the time course of utilization for zolpidem-containing products in three distinct periods: (1) leading up to the messages in the first DSC; (2) in the time between the two DSCs; and (3) in the time after the second DSC. The goal of this analysis will be to reveal the effect of the DSCs in the context of an evolving knowledge base that includes awareness of the safety message conveyed by the DSC, while accounting for potential confounders and other factors that may modify the effect of the DSC on prescribing of the medication. Health insurance claims analyses that include detailed records of prescriptions actually filled will quantify the effect of the selected DSCs across a range of measures that include both pharmacy and medical claims. A drug safety message (included in a DSC) may lead to actions by physicians or patients, such as discontinuing a medication, switching a medication, changing to a different dose, choosing to not prescribe or take a medication, or additional physician office visits or additional diagnostic tests. These will manifest in patterns of discontinuation, switching, and other metrics that can be captured by healthcare utilization, as reflected in health insurance claims. As a comparison that will provide insight into secular changes in the healthcare utilization metrics that are unrelated to DSC messaging, the same metrics will be used for eszopiclone, a prescription drug with a similar indication that was not mentioned in any DSC during the period of the zolpidem DSCs.

The primary methodology will be an interrupted time-series analysis with a concurrent-control time trend [54]. Conducting a time-series analysis will require segmenting calendar time into sequential non-overlapping time periods of 30-day in length. In each time segment, populations will be defined on the basis of the dispensing of either a zolpidem product or eszopiclone, and will stratify new users versus continuing users. Changes in response to messages conveyed in a DSC may differently affect people already using a medication from those contemplating the initiation of a new medication. In the Optum Health Insurance database approximately 100,000 patients per month were receiving a dispensing of zolpidem in 2013. These numbers of patients should permit robust identification of DSC effects.

This study will go beyond the process measures represented by the zolpidem and eszopiclone use patterns over time, and will involve cohort analyses that will identify a number of patient-specific outcomes that might represent adverse effects of zolpidem or eszopiclone. Since the messages contained in a DSC aim to enhance public health, their impact will not be fully reflected in utilization patterns, therefore the inclusion of patient health outcomes in these analyses comes closer to a complete representation.

The cohort formed from UnitedHealth claims data through the Optum Research database will be broadly representative of patients with commercial health insurance who use zolpidem or eszopiclone, and will reflect a range of health characteristics and outcomes manifested by such a population. The patients selected for the interviews and survey will derive from the same source so that they will reflect responses among patients who received these medications within the same healthcare environment as the cohort patients. This commonality of source populations permits more direct inference between the qualitative interview/quantitative survey results and any observed utilization changes or health outcomes among the cohort. Differences that might arise between interview/survey

results to assess cognitive factors related to impact and drug utilization/health outcomes in the interrupted time trends analysis that would be attributed to differences in the source population can be ruled out (or at least will be greatly attenuated) in this study. Within the proposed data source over the relevant time period, neither zolpidem nor eszopiclone were subject to a prior authorization to obtain reimbursement for a prescription. This is an important consideration since prior authorization has demonstrated a stronger impact on utilization than safety warnings [55, 56].

We will use the method of interrupted time-series analysis to evaluate the effects of new drug safety risk communication information being released [57, 58]. This method will allow us to assess whether there were significant changes in outcomes associated with the effectiveness of the DSC risk communication messaging and to quantify the size of any observed changes. We will divide the time series into segments at change points corresponding to the dates when the DSCs were issued. We will begin by using 10 January 2013 and 14 May 2013 as change points, corresponding to the dates of issue for the two zolpidem DSCs. Using these change points, we will create an analysis file for each outcome. By examining the values of the parameters describing changes in zolpidem use relative to changes in eszopiclone use following the DSC issuances, as well as their *p* values, we can assess the contribution of the drug safety messaging to any observed changes. We will present the results from both the full models including all parameters, and the parsimonious models where non-significant parameters are omitted using stepwise selection. In addition, if a significant effect is observed, we can model both weekly and cumulative divergences from the baseline trend.

5 Conclusions

Our goal is to develop a new, integrated method to determine the factors related to the impact of FDA risk communications. The pilot development of this new, integrated method to evaluate FDA safety messages contained in the two sequential 2013 zolpidem DSCs also takes into account the context of traditional and social-media messaging to integrate with analyses of factors related to the impact obtained from semi-structured qualitative interviews of patients and providers, as well as a quantitative survey of 2000 randomly sampled patients from the same population. Our innovative approach will also feature a linked assessment of quantitative prescribing and patient outcomes in the same population in which the qualitative and quantitative social science assessments were conducted. We will also provide a comparative analysis with a similar drug with the same indication, eszopiclone, that was not the subject of the safety messaging evaluated through this integrated approach. This methodology combines rigorous analyses of DSCs via modern pathways to provide an integrated detailed case assessment of the uptake of safety information contained in FDA DSC messages. Once the new set of integrated methods described in this review are tested in the zolpidem/eszopiclone comparison pilot, further study on the cultural and language issues can be conducted to further broaden the population impact of our results. It is possible that the new, integrated method piloted in this study could be developed and tailored to the study of other risk communications, such as those included in REMS, to provide an empirical approach to optimizing effectiveness.

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Conflicts of interest Sebastian Schneeweiss is a consultant to WHISCON LLC, a consulting company specializing in the conduct of drug safety database studies. He is also a consultant to, and owns some equities in, Aetion, Inc., a software company specializing in the analyses of healthcare databases. Paula Rausch, Brian M. Lappin, Esther H. Zhou, and Gerald J. Dal Pan are employed by the FDA, which commissioned this study. John D. Seeger is a consultant to both WHISCON LLC and Optum. John S. Brownstein owns shares in, and is employed as consultant to, Epidemico, Inc., a technology company that develops social-media mining tools for drug safety. Steven Woloshin and Lisa M. Schwartz were paid under a subcontract for work on this project and are co-founders of Informulary, Inc., a company that provides data regarding the benefit, harms, and uncertainties of prescription drugs. Aaron S. Kesselheim, Eric G. Campbell, Timothy Toomey, and Jerry Avorn have no conflicts of interest that are directly relevant to the content of this study.

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