Journal of Biomedical Informatics 60 (2016) 132–144

Contents lists available at ScienceDirect

Journal of Biomedical Informatics

journal homepage: www.elsevier.com/locate/yjbin

Prediction of black box warning by mining patterns of Convergent Focus Shift in clinical trial study populations using linked public data

Handong Ma, Chunhua Weng *

Department of Biomedical Informatics, Columbia University, New York, NY, USA

ARTICLE INFO

Article history:
Received 29 July 2015
Revised 22 January 2016
Accepted 27 January 2016
Available online 3 February 2016

Keywords:
Black box warning
Clinical trial
Patient selection
Convergent Focus Shift
Random forest

ABSTRACT

Objective: To link public data resources for predicting post-marketing drug safety label changes by analyzing the Convergent Focus Shift patterns among drug testing trials.
Methods: We identified 256 top-selling prescription drugs between 2003 and 2013 and divided them into 83 BBW drugs (drugs with at least one black box warning label) and 173 ROBUST drugs (drugs without any black box warning label) based on their FDA black box warning (BBW) records. We retrieved 7499 clinical trials that each had at least one of these drugs for intervention from the *ClinicalTrials.gov*. We stratified all the trials by pre-marketing or post-marketing status, study phase, and study start date. For each trial, we retrieved drug and disease concepts from clinical trial summaries to model its study population using medParser and SNOMED-CT. Convergent Focus Shift (CFS) pattern was calculated and used to assess the temporal changes in study populations from pre-marketing to post-marketing trials for each drug. Then we selected 68 candidate drugs, 18 with BBW warning and 50 without, that each had at least nine pre-marketing trials and nine post-marketing trials for predictive modeling. A random forest predictive model was developed to predict BBW acquisition incidents based on CFS patterns among these drugs. Pre- and post-marketing trials of BBW and ROBUST drugs were compared to look for their differences in CFS patterns.
Results: Among the 18 BBW drugs, we consistently observed that the post-marketing trials focused more on recruiting patients with medical conditions previously unconsidered in the pre-marketing trials. In contrast, among the 50 ROBUST drugs, the post-marketing trials involved a variety of medications for testing their associations with target intervention(s). We found it feasible to predict BBW acquisitions using different CFS patterns between the two groups of drugs. Our random forest predictor achieved an AUC of 0.77. We also demonstrated the feasibility of the predictor for identifying long-term BBW acquisition events without compromising prediction accuracy.
Conclusions: This study contributes a method for post-marketing pharmacovigilance using Convergent Focus Shift (CFS) patterns in clinical trial study populations mined from linked public data resources. These signals are otherwise unavailable from individual data resources. We demonstrated the added value of linked public data and the feasibility of integrating *ClinicalTrials.gov* summaries and drug safety labels for post-marketing surveillance. Future research is needed to ensure better accessibility and linkage of heterogeneous drug safety data for efficient pharmacovigilance.

1. Introduction

Clinical trials are the gold standard for generating high-quality medical evidence. Pre-marketing clinical trials, ranging from phase I to III (sometimes also phase 0), validate the safety and efficacy of novel prescription drugs. Phase IV clinical trials, often called post-marketing surveillance trials, are designed to collect post-marketing drug information, including risks, benefits, and optimal use. Phase IV studies are crucial for clinical decision-making. The Food and Drug Administration (FDA) is responsible for regulating most medicines in order to ensure the safety of the medications. Black box warnings (BBWs) are the most severe medication-related safety warnings that can be placed on a drug label by FDA to indicate major drug-related risks [1]. If the post-marketing trials find too many adverse events, the Food and Drug Administration will restrict the use of the drug or even mandate that it be withdrawn from the market. About 20% of approved chemical entities are later found to cause severe adverse events

* Corresponding author at: Department of Biomedical Informatics, Columbia University, 622 W 168th Street, PH-20, New York, NY 10032, USA.
E-mail address: chunhua@columbia.edu (C. Weng).

http://dx.doi.org/10.1016/j.jbi.2016.01.015
1532-0464/

and hence either receive a black box warning label or are withdrawn from the market [2]. Within biomedical informatics domain, BBWs are frequently used as important predictors or gold standards in predicting adverse drug reactions (ADRs) or drug–drug combination safety [3,4]. Unfortunately, studies have shown a significant lag between the drug approval and its acquisition of BBW, ranging from 2 to 170 months [1]. This delay can cause remarkable unnecessary loss to patients and the healthcare industry. Therefore, it is crucial to accurately and timely predict human drug toxicity and future FDA actions.

Although facing challenges, many attempts have been made to tackle this problem. Previous studies utilized FDA's Adverse Event Reporting System (AERS) [5], medical literatures [6], online health forums [7] or other data sources [8] to predict adverse effects or even FDA safety actions. Hochberg et al. found that by using AERS data 2–3 years following the approval, more than half of FDA actions that occurred in the next 2–4 years were predictable [5]. Natural language processing (NLP) and machine learning methods have been developed to tackle this problem. A recent study used ensemble classifier (bagging) to identify drugs that are most similar to other watch lists and withdrawn drugs [7]. Despite those studies, rarely do researchers consider using clinical trial study population description to predict future FDA actions.

The specification of the study population of a trial reflects the focus of the trial when testing a drug. A recently published study reviewed the importance of streamlining eligibility criteria, which play an essential role in clinical and translational research for study population specification [9]. In practice, a study may only focus on a particular population subgroup, for example, those with a certain medical condition. The study population specification is important for excluding factors that introduce confounders to an experiment. Often, researchers design the eligibility criteria to generate a "pure" but not "typical" trial population as their focus on certain subgroup of patients [10]. This study population focus can shift over time, especially after a drug is launched. However, the phenomenon of study population focus shift has not received adequate attention or been utilized, partly because of the lack of data in the past.

With the massive public clinical trial information and drug safety reports available nowadays, we have an opportunity to forecast potential future BBW acquisitions before the completion of Phase IV trials. From *ClinicalTrials.gov*, which requires timely status update for all clinical trials, we can get a complete picture of the past and present study population focuses of existing trials of varying phases and gain insights to inform BBW forecast [11]. A couple of related studies have been conducted to retrieve useful information from eligibility criteria section on *ClinicalTrials.gov* [12–14]; however, the relationship between study population focus and future drug outcome remains unknown. A deeper insight into clinical trial patient selection may enable us to predict which drugs are harmful based on their study population descriptions.

In this study, we investigated the correlation between drug safety label changes and study population focus shift patterns for existing interventional drug trials. We defined the Convergent Focus Shift (CFS) pattern for each prescription drug as the converged focus in post-marketing trials compared to that in pre-marketing trials. We hypothesized that drugs with potential safety warnings have different CFS patterns compared to those without warnings. For example, studies recruit mainly smokers without cardiovascular disease for smoking cessation drug *Chantix* before its approval by FDA (pre-marketing trials). However, many studies shifted their focuses to depressed patients after the drug was approved for sale, which was followed by serious side effects in depressive patients [15]. Since monitoring CFS pattern does not require trial outcome, it has little time lag for post-marketing pharmacovigilance compared to traditional outcome-based warning systems. Understanding of the study population CFS patterns and their correlation with adverse events may help researchers assess a drug's potential safety issues and predict future black box warning acquisitions.

2. Materials and methods

2.1. Candidate drug selection

We evaluated FDA-approved prescription drugs for human beings that were among the top sellers in the United States between 2003 and 2013 based on drug type information from the *drugs@fda* database [16]. We assessed the popularity of a drug based on its retail sales in US by obtaining this information from *drugs.com* [17]. We identified 402 drugs that appeared at least once in the top-selling lists during these 11 years, including 200 drugs hitting the list between 2003 and 2013 and 100 drugs between 2011 and 2013. Those drugs were common in daily uses and might affect a large patient population, which makes it crucial to predict their safety-related issues.

2.2. Black box warning label extraction

At present, there exists no satisfactory FDA black box warning label database that contained both the label text and BBW acquisition date. Many of the previous studies manually checked the Physicians' Desk Reference (PDR) [2,18] Network (http://www.pdr.net) for drug labeling information. This manual method could only roughly identify the year of BBW acquisition date and was thus too imprecise for this study. Instead, we gathered the BBW information in a two-step semi-automatic manner. First, we automatically extracted all drug labeling information from PDR websites and created a drug database with FDA boxed warning text. This database contained 3068 drugs along with their black box warning label (if any). Second, we obtained each drug's first BBW acquisition date via manual web search to make the BBW data to be precise at the month level based on the dates specified in news and FDA safety communications. If no specific day was provided for BBW acquisition, we used the first day of that month in calculation. For example, if the resource states that "In January 2014, the FDA issued a black box warning for *losartan*" (http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm169666.htm), we set the acquisition date to 01/01/2014. We excluded those drugs without month information from this study.

In order to tag the popular drugs with black box warning information, we mapped different drug names from *drug.com* to *Physicians' Desk Reference* (PDR). In addition to the exact matches of drug names, we did a manual mapping to retrieve drug names with different semantic representations. We grouped trials for each drug regardless of dosages (50 mg, 100 mg, etc.) or product types (spray, tablets, scalp-solution, oral-solution, etc.) For example, we mapped *Lamisil-tablets* to *Lamisil-oral*, *Exelon-patch* to *Exelon* and *Children's-Zyrtec-syrup* to *Zyrtec-syrup*. We separated the drugs into two groups, one labeled with a black box warning of unexpected adverse events. We refer to the drugs with BBW label as the "BBW" group and those without a warning as the "ROBUST" group. Only the "BBW" drugs with both label content and acquisition date information were included as candidate drugs in future analysis.

2.3. Clinical trial information processing

We retrieved all interventional trial lists for all candidate drugs using the *ClinicalTrials.gov* search API. Each trial can be mapped to different drugs if it uses multiple-drug interventions. All trial contents were then downloaded from the *ClinicalTrials.gov* database