Identifying Adverse Drug Events from Health Social Media Using Distant Supervision

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Abstract

Adverse drug events (ADEs) have been recognized as a significant healthcare problem worldwide. Prior studies have shown that health social media can be used to generate medical hypotheses and identify adverse drug events. Most studies adopted supervised learning approach for ADE detection in health social media, which requires human annotated data and is not scalable to large datasets. In this study, we develop an information extraction framework to identify novel adverse drug events using distant supervised learning, which leverages existing knowledge of adverse drug events and requires no labeled text. Our proposed framework achieves competent performance in identifying adverse drug events without expensive human annotation.
Introduction

Adverse drug events (ADEs) have been recognized as a significant health problem worldwide. An adverse drug event (ADE) refers to any injury occurring at the time a drug is used, whether or not it is identified as a cause of the injury. According to prior studies, about 5% of hospital admissions, 28% of emergency visits, and 5% of hospital deaths are attributed to adverse drug events (Yang et al. 2014). Post-marketing drug safety surveillance is the practice of having drug regulatory authorities monitor the safety of a pharmaceutical drug after it has been released on the market, and is an important part of the science of pharmacovigilance. It aims to detect adverse drug reactions (ADRs), a special type of ADEs in which a causative relationship can be confirmed.

Post-marketing drug safety surveillance has caught worldwide attention. In the United States, Food and Drug Administration (FDA) operates a system called MedWatch, which enables doctors, pharmaceutical companies, and the general public to report adverse drug events. The World Health Organization (WHO) operates the Uppsala Monitoring Center (UMC) for international drug monitoring. Post-marketing drug safety surveillance relies heavily on spontaneous reporting systems and electronic health records. However, this process has its shortcomings. There usually is a time delay between an adverse drug event and the report filed. Further, a significant amount of adverse drug events are unreported. The median underreporting rate of adverse events from health consumers from 37 studies across 12 countries was 94% (Yang et al. 2014). Due to these shortcomings, there is a need to gather timely adverse drug event reports for early detection of risky drugs from other sources.

In the past decade, a large number of online health communities have emerged such as PatientLikeMe, DailyStrength, and MedHelp. These online health communities are available for
health consumers to discuss any health related issues, including adverse drug events they encounter. Their discussions may provide early clues about adverse drug events (White et al 2013). In this study, we aim to develop an information extraction framework for identifying adverse drug events from health social media using distant supervision. Distant supervision leverages existing knowledge of adverse drug events and requires no manually labeled text for training. We are the first to incorporate this novel research paradigm into adverse drug event detection from health social media.

Related Work

Drug Safety Surveillance

In the past, drug safety surveillance has primarily relied on spontaneous reporting systems such as FDA’s Adverse Drug Event Reporting System (FAERS) and WHO’s VigiBase. However, these platforms suffer from under-reporting of serious adverse drug events (ADEs) and over-reporting of known ADEs (Chee et al. 2011). In recent years, research focus has broadened to include utilization of other data sources. Various studies have explored Electronic Health Records (EHRs) for documentation of adverse drug events (Wang et al. 2009; Friedman et al. 2009; Harpaz et al. 2012). However, EHRs are usually not publicly available due to privacy concerns. Additionally, they are not originally designed for recording adverse drug events thus contain redundant information. Biomedical literatures (e.g., case reports, observational studies, clinical studies) have been examined for use in adverse drug event detection. (Xu et al. 2014; Gurulingappa et al. 2013). Search logs of major search engines have been used to identify associations between adverse events and drugs (White et al. 2014). Lastly, due to the recent surge of online health communities and platforms, adverse drug event detection with health social media has also caught attention (Nikarjam et al. 2012; Yang et al. 2012; Liu et al. 2014).
Many studies have been developed in the area of extracting adverse drug events from social media.

*Adverse Drug Event Detection in Health Social Media*

Adverse drug event detection studies often utilize data collected from forums and micro-blogs. General health discussion forums, such as DailyStrength, (Leaman et al. 2010), MedHelp (Yang et al. 2012; Liu et al. 2014), and Yahoo! Groups (Nikfarjam et al. 2011; Chee et al. 2011), have been adopted as test beds for adverse drug event detection. Others have found success in detecting adverse drug events for disease-specific treatments by utilizing data from disease support forums, such as breast cancer forums (Benton et al. 2011; Mao et al. 2013) and diabetes forums (Liu et al. 2013). More recently, techniques have been developed to identify adverse event related discussions from Twitter (Bian et al. 2012; Sarker et al. 2014).

To extract adverse drug events from health social media, researchers have proposed a variety of research methods. Lexicon-based named entity recognition is often developed to identify adverse events and drug names from text (Leaman et al. 2010; Benton et al. 2011; Yang et al. 2012). Machine learning techniques are also widely adopted in the prior studies. For example, Nikfarjam et al. (2011) extract adverse events using association rule mining based on lexical and syntax features. Kernel based classification methods are also often used for adverse drug event relation extraction (Liu et al. 2013; Liu et al. 2014). Further, ensemble classifiers are developed to identify risky drugs that cause serious negative outcomes based on patient discussions (Chee et al. 2011). Sarker et al. (2014) trained a classifier with lexical and syntactic features to identify ADE assertive text.

Most prior studies adopted supervised machine learning approaches in health social media ADE research (Chee et al. 2011; Sarker et al. 2014; Liu et al. 2013; Liu et al. 2014). A
major obstacle to applying supervised learning approaches is the lack of annotated data (Mintz et al. 2009). Annotation for adverse drug events is expensive and requires medical domain knowledge. The amount of available annotated data is usually disproportional to the volume of health social media data, which can cause learning bias in supervised learning. In drug safety surveillance research, there are a large number of databases bases regarding known ADEs available. Spontaneous reporting systems have thousands of adverse drug event reports. However, this existing knowledge hasn’t been used in prior studies for detection of adverse drug events in health social media. This motivates us to investigate an alternative paradigm, distant supervision.

Distant Supervision

Distant supervision is a class of machine learning methods supervised by existing knowledge bases instead of manually labeled data (Mintz et al. 2009; Riedel et al. 2010). It generates training data automatically by aligning a knowledge base with text and predicts labels for unseen data in knowledge base. This approach avoids problems of learning bias in supervised learning, and domain dependence. It scales very well in large data sets. Distant supervision models are trained in the presence of incomplete and incorrect labels. They can predict class labels with competitive accuracy compared to supervised learning. Distant supervision was originally developed to extract binary relations between proteins and cells/tissues/diseases with the Yeast Protein Database as a source for supervision (Craven et al. 1999). The technique grew in popularity for relation extraction in large datasets. Bunescu & Mooney (2007) developed a distant supervised relation extraction model to conduct citation extraction from BibTex databases. New York Times corpus has been used as test bed to identify multiple relations among person, organizations, and locations (Hoffman et al. 2011; Riedel et al. 2010; Surdeanu et
Distant supervision models for relation extraction can be categorized by their underlying assumptions of the data and the relations of interest. Bunescu and Mooney (2007) propose single-instance single-label (SISL) assumption in their study. They assume if two terms participate in a relation, all sentences that mention these two terms express the same relation (Bunescu and Mooney 2007; Mintz et al. 2009). Thus, they aggregate features in sentences of the same pair of terms into one instance during training and prediction. Riedel et al. (2010) developed distant supervision on multi-instance single-label (MISL) assumption. That is, if two terms participate in a relation, at least one sentence that mentions two terms might express that relation (Riedel et al. 2010). In this study, they model both relations and relation mentions with undirected graphical model. The model allows for multiple instances of the same entity pair, but disallows more than one label per term pair. The most recent developments on distant supervision propose models based on multi-instance multi-label (MIML) assumption (Surdeanu et al. 2012; Hoffmann 2011; Angeli et al. 2014). These models assume each relation mention involving a pair of terms has exactly one label, but allows pairs to exhibit multiple labels across different mentions. These models learn from multiple instances and multiple labels at the same time with directed graphical model. Model performances vary on datasets depending on the fitness between the data and assumptions. No model outperforms others consistently (Surdeanu et al. 2012).

Based on the review of related work, we can observe that most prior studies adopted a supervised learning approach to identify adverse drug events and related information from health social media. However, this approach has several limitations. Annotation is usually time
consuming and expensive. Given the large volume of noisy health social media data, human annotation usually causes learning bias. As a promising alternative, distant supervision can leverage known ADEs and potentially identify novel ADEs unobserved in existing knowledge bases. We are motivated to develop a distant supervision approach to advance our identification of novel adverse drug events in health social media. We propose the following research questions:

1. How can we develop an information extraction framework for identifying adverse drug events in health social media?

2. How can we leverage existing knowledge of adverse drug events and supervise the learning of unseen relation mentions in health social media?

**Research Design**

The figure 1 shows the research framework we propose for identifying novel adverse drug events from health social media using distant supervision. Components of the research framework will be elaborated in the following section.

**Data Collection**

The data for this study comes from three sources: health social media discussion forums, Twitter, and the FDA’s adverse drug event reports from FAERS. To collect health discussion forum data, we utilize a web crawler to download forum pages from the online community of the American Diabetes Association. We store post contents, post ID numbers, author usernames, post dates, and post URLs to our data repository. To collect real-time discussions about adverse drug events from Twitter, we deploy Twitter Streaming API to track specific treatment names and store tweets containing these keywords in a database (MongoDB). Finally, adverse drug event reports
from FDA’s AERS (FAERS) database are used as a knowledge base for distant supervision. These reports are publicly available from FDA’s website. We retrieve these reports and store their contents within our database. The key information we concern is the recorded drug indications and adverse drug events.

We choose diabetes treatments as a research case to test the efficacy of our framework in this study. According to the 2014 National Diabetes Statistics Report from CDC, diabetes affects 29.1 million people in United States or 9.3% of the population. Direct medical cost of diabetes in 2012 is 176 billion US dollars. Adverse drug events of diabetes treatments can have serious consequences such as seizures, unconsciousness, or death. There have been a large amount of discussions in health social media about diabetes. A list of 41 diabetes treatments (currently on the US market) are identified based on diabetes guideline from American Diabetes Association and used to extract tweets and FDA reports related to diabetes. The Table 1 summarizes our research test bed. The American Diabetes Association online community was established in February 2009. We collect 234,874 posts from this community from 2009 to 2015. Further, we obtain 70,295 tweets related to the 41 diabetes treatments. These tweets are just a sample of all the tweets related to these treatments. Lastly, we collect 102,358 adverse event reports whose primary suspected drugs are diabetes treatments.

Data Preprocessing

To prepare the health social media discussion for further analysis, we conduct data preprocessing with the following steps: medical entity extraction, co-reference resolution, and syntactic parsing. Medical entity extraction mainly aims to identify medical condition entities (i.e., nausea, vomiting) and drug entities in health social media. To achieve this, we utilize our lexicon-based
approach designed in previous work, which combines CHV\(^1\), FAERS\(^2\) and MetaMap\(^3\) to identify medication mentions and medical event mentions (Liu et al. 2014).

In this study, relation extraction is conducted on the sentence level. For forum discussions, we perform sentence boundary detection, tokenize the text, generate part-of-speech (POS) tags, and produce syntactic parsing of each sentence with the Stanford CoreNLP\(^4\) tool. For tweets gathered from Twitter, we tokenize the tweets and generate part-of-speech (POS) tags with TweetNLP\(^5\), machine learning based text-processing tool dedicated for Twitter dataset. We also utilize the Stanford Lexical Parser for syntactic parsing with the tokenization and POS tags generated by TweetNLP.

We incorporate co-reference resolution to link medical entities across sentences within the same document. If pronouns and other referring expressions are detected, they are replaced with the original entities they are referring to. With co-reference resolution, we can identify potentially related medical events and medications mentioned across sentences.

*Distant Supervision for Adverse Drug Event Extraction*

In this study, we focus on distant supervised learning for binary relation extraction between medications and medical conditions. We define a relation as the construct \(r(e_1, e_2)\), where \(r\) is the relation name, \(e_1\) is the medication entity and \(e_2\) is the medical condition entity. The relation types we concern in this study and example entity pairs are listed in the table below.

Health social media medication-related discussions are usually based on patient experience, news, and research. Co-occurrence of an entity pair may express different relations or no relation.

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\(^1\) http://www.consumerhealthvocab.org/
\(^2\) http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/
\(^3\) http://metamap.nlm.nih.gov/
\(^4\) http://nlp.stanford.edu/software/corenlp.shtml
\(^5\) http://www.ark.cs.cmu.edu/TweetNLP/
based on context. To solve this noise issue with social media data, we develop our distant supervised learning for adverse drug event detection model based on the multi-instance multi-label assumption. We assume that each relation mention involving an entity pair has exactly one label, but allows pair to exhibit multiple labels across different mentions.

Distant supervision for adverse drug event detection can be defined as a function that takes health social media data collection (C), a set of entity medical entity mentions extracted from C (e), and an extraction model, and outputs a set of relations (R) such that any relation extracted has at least one positive instance in C. To train the model, we use FAERS as a knowledge base for drug indication and adverse drug event relations (D). If a pair of entities has been reported as an adverse event and the suspected drug causing the event, we label all mentions of this entity pair as an adverse drug event. If the entity pair is recorded as drug and its indication, we label all of its mentions as drug indications. If a pair of entities never appears in the knowledge base, we label its mentions as no relation. If the dependency path between two entities in one sentence contains negation patterns such as “n’t” and “not”, we label this sentence as no relation. Relations in D have to at least appear once in C. Using distant supervision, D is aligned with sentences in C, producing relation mentions in C based on all the relation definitions in D.

Figure 2 shows our distant supervision relation extraction model. Our proposed model consists of one multi-class classifier (Z) and three binary classifiers (y) for adverse drug event relation, drug indication relation and no relation. The Z classifier assigns relation labels from {“treat”, “cause”, “nil”}. Each binary classifier decides if its corresponding relation (“treat”, “cause” or “nil”) holds for the given sentence. X is a sentence and Z is the latent relation classification for that sentence. Wz is the weight vector for multi-class mention level classifier. yc
$y_n$ and $y_t$ are the top level classification decision for entity pair as to whether the relation holds. $W_c$, $W_t$, and $W_n$ are the weight vectors for binary classifiers.

For multi-class mention level classification, we develop three types of features: lexical features, syntactic features, and entity features. Lexical features capture the window of words between two entities, part-of-speech tags of the extracted window, and a flag indicating which entity comes first in the sentence. Syntactic features contain the shortest dependency path from medication entity to medical condition entity. Entity features capture head words and tail words of two medical entities.

For relation-level binary classification, we develop two feature groups. The first group uses a single feature to track the at-least-one heuristic. The feature is set to true if at least one instance expresses this relation. The second feature group models the dependencies between relation labels with two features. These two features learn whether the current relation can be jointly generated. For instance, if $r_c$ (cause) and $r_n$ (none) tend to be generated jointly for a given pair of medical condition and drug, the features for corresponding dependency receive a positive weight in models for “cause” and “nil”. If $r_c$ (cause) and $r_t$ (treat) cannot be generated jointly for a given entity pair, the features for corresponding dependency receive a negative weight in models for “cause” and “treat”.

We train the proposed model using Expectation Maximization (EM). In the Expectation step, we assign mention labels using the mention and relation level classifier. In the Maximization step, we train the model to maximize the log likelihood of the data using the current latent assignments. During the prediction, given an entity pair, we first classify its mentions and then decide on the final relation labels using the top-level classifiers. Thus, we can get both relation level labels and sentence level labels.
Evaluation

We evaluate our framework in two ways: hold out evaluation and manual evaluation. Hold out evaluation is conducted automatically by holding out half of the FAERS relation knowledge during training and comparing newly discovered relation instances against the held-out data. We choose the single-instance single-label (SISL) model (Mintz et al. 2009), and the multi-instance single-label model (MISL) (Riedel et al. 2010) as baselines for this automatic evaluation. This evaluation focuses on accuracy relation labels of each entity pair instead of accuracy of relation labels for each instance.

For human evaluation, we evaluate the accuracy of relation labels on mention level. Among the 41 diabetes treatments we are monitoring, three of them were approved in the past two years: Afrezza released to market in June 2014, Farxiga in January 2014, and Invokana in January 2013. Drug safety information about these three treatments mainly comes from clinical trial results. Patients have started to discuss these new diabetes treatments on social media. We retrieve top 100 relation labels on instance level for these three drugs based on the classification confidence and manually evaluate the performance using precision at K metrics.

Results and Discussions

Data preprocessing

The Table 3 shows a summary of the data after preprocessing. Overall, we retrieve about 17,000 sentences with at least one drug entity and one medical condition. These sentences contain 37 unique drug names and 476 unique medical conditions. Discussions on health social media are concentrated on particular medical conditions, while reports in FAERS have large coverage of medical conditions but low frequency.
Hold Out Evaluation

To construct baseline for automatic evaluation, we adopt single-instance single-label model using multiple logistic regression with their original implementation (Mintz et al. 2009). The model is trained with the same features as our mention-level classifier, but all mentions for each entity pair are collapsed into one instance in training. For multi-instance single-label model, we adopt Hoffmann’s (2011) implementation and train on the same feature set as our mention-level classifier. We align the entity pairs in social media data and FAERS data. There are 1,137 pairs of entities in health social media data. Half of the pairs are selected as training data, while the other half are used as the test set.

We adopted precision-recall curve measures for this study (Riedel et al. 2010; Hoffman et al. 2011; Mintz et al. 2009). To compute precision-recall curve for MIML model, we ranked the relation labels for each pair of entities with noisy-or score (Surdeanu et al. 2012):

\[
noisy-or_{<e_1,e_2>}(r) = 1 - \prod_{m \in M} (1 - S_m^{<e_1,e_2>}(r))
\]

where \( S_m^{<e_1,e_2>}(r) = p(r \mid x_m, w_z) \) if \( Z \) classifier (Figure 2) predicts the label for sentence \( x_m \) is \( r \) or 0 otherwise. \( M \) presents all the sentences containing the same pair of entities. This formula performs well for ranking because it integrates model confidence (the higher the probabilities, the higher the score) and redundancy (the more mentions are predicted with a label, the higher the score). The relation label with the highest noisy-or score is used to determine the final label for that entity pair in evaluation. Relation labels of baseline models are ranked based on their confidence score. The Figure 3 shows the precision-recall curve on three different models. According to precision recall curve, we can see that MIML model has a larger area under precision-recall curve than MISL model and SISL model which indicates MIML model can
predict relation labels with higher performance. This evaluation may under estimate the accuracy. If a true positive adverse drug event doesn’t exist in knowledge base, it will be considered as “no relation” in evaluation. Besides, some medical condition and medication pairs may have been reported to FDA but their mentions in health social media more often present “no relation”. The distant supervision based relation extraction performs well when fetching top ranked relation labels (around 70% precision).

Manual Evaluation

Figure 4 shows the precisions for values of K between 0 and 100 on manually evaluated predictions on instance level for three diabetes treatments. We first note that the precision is much higher for manual evaluation on instance level compared to automatic evaluation. This shows the false negatives in FAERS knowledge base are an issue when doing hold out evaluation. Some are in fact true relation instances.

Table 4 shows the top ranked relations we found for Afrezza, Farxiga, and Invokana. Most of them are adverse drug events. These medications are released to the market recently. Most discussions are about their adverse drug events. The diagnosis-derived events such as breast cancer and bladder cancer usually come from news and research. Patients usually report symptom-derived descriptions such as oral bleeding, irritation, pain, tiredness, hypoglycemia, weight changes, running nose, and weakness. These adverse events of medications new to the market can contribute to understand and assess the risk of new medications for both patients and clinical practitioners.

Conclusion
In this research, we develop an information extraction framework to identify adverse drug events from health social media using distant supervision. This is the first study that incorporates distant supervision in health social media ADE detection. Health social media data provide great opportunities for researchers to explore patient intelligence from user-generated social media contents. However, obtaining adequate amounts of annotated data for training a supervised learning model can be problematic. In particular, annotation of data from the medical domain is expensive and time consuming. Further, if annotated data is too sparse compared to unlabeled data, it could result in bias in learning and poor performance on unlabeled data. Distant supervision relies on existing knowledge of known adverse drug events and requires no manually labeled text. By aligning knowledge base data with health social media data, we are able to generate a large number of data for training at low cost and alleviate the learning bias issue for supervised learning. We developed ADE detection model based on multi-instance multi-label assumption. It performs better than baseline models with different assumptions. It shows that the multi-instance multi-label assumption performs best for adverse drug event detection. Based on the evaluation results, our approach can predict medication and medical condition relations with high accuracy. This approach can identify new adverse drug event relations, particularly for newly marketed drugs.
Acknowledgement

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Figures

**Figure 1.** Research Framework for Identifying Novel Adverse Drug Events from Health Social Media

**Figure 2.** Distant Supervised Learning model for Adverse Drug Event Detection from Health Social Media
Figure 3. Precision recall curve for distant supervision

Figure 4. Precision at K for manually evaluated predictions

Tables

Table 1. Summary of Research Test bed

<table>
<thead>
<tr>
<th>Data Source</th>
<th>Number of records</th>
<th>Time Span</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Diabetes Association</td>
<td>234,874</td>
<td>2009.2-2015.1</td>
</tr>
<tr>
<td>Tweets</td>
<td>70,295</td>
<td>2007.6-2015.01</td>
</tr>
<tr>
<td>FAERS (Diabetes)</td>
<td>102,358</td>
<td>2004.1-2014.06</td>
</tr>
</tbody>
</table>

Table 2. Relation types we concern in this study and example entity pairs

<table>
<thead>
<tr>
<th>Relation (/e1/e2/label)</th>
<th>Entity pair</th>
<th>Relation name</th>
</tr>
</thead>
<tbody>
<tr>
<td>/medication/medical condition/cause</td>
<td>&lt;Lantus, hypoglycemia&gt;</td>
<td>Adverse drug event</td>
</tr>
<tr>
<td>/medication/medical condition/treat</td>
<td>&lt;Actos, diabetes&gt;</td>
<td>Drug indication</td>
</tr>
<tr>
<td>/medication/medical condition/none</td>
<td>&lt;Metformin, weight gain&gt;</td>
<td>No relation</td>
</tr>
</tbody>
</table>
Table 3. Summary of mediation and medical condition mentions in data

<table>
<thead>
<tr>
<th>Count</th>
<th>ADA online community</th>
<th>Twitter</th>
<th>FAERS (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentences</td>
<td>1,456,968</td>
<td>112,107</td>
<td>NA</td>
</tr>
<tr>
<td>Sentences with at least one entity pair</td>
<td>11,794</td>
<td>5314</td>
<td>NA</td>
</tr>
<tr>
<td>Unique medication entities</td>
<td>37</td>
<td>34</td>
<td>41</td>
</tr>
<tr>
<td>Unique medical condition entities</td>
<td>476</td>
<td>145</td>
<td>12,867</td>
</tr>
<tr>
<td>Unique entity pairs medications and conditions</td>
<td>981</td>
<td>617</td>
<td>60,824</td>
</tr>
</tbody>
</table>

Table 4. Top ranked relation predictions for Afrezza, Farxiga, and Invokana

<table>
<thead>
<tr>
<th>Mediation</th>
<th>&lt;Relation label&gt;: medical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afrezza</td>
<td>&lt;cause&gt; oral bleeding; &lt;cause&gt;hypoglycemia; &lt;cause&gt;cough; &lt;cause&gt;lung problem; &lt;cause&gt;overdose; &lt;cause&gt;irritation; &lt;cause&gt;pain</td>
</tr>
<tr>
<td>Farxiga</td>
<td>&lt;cause&gt;weight loss; &lt;treat&gt; diabetes; &lt;cause&gt;bladder cancer; &lt;cause&gt;breast cancer; &lt;cause&gt;hypotension; &lt;cause&gt;genital yeast infections; &lt;cause&gt;tiredness; &lt;cause&gt;running nose</td>
</tr>
<tr>
<td>Invokana</td>
<td>&lt;cause&gt;bladder cancer; &lt;cause&gt;hypotension; &lt;treat&gt;diabetes; &lt;cause&gt;kidney disease; &lt;treat&gt;urinary tract infections; &lt;cause&gt;weakness; &lt;cause&gt;hypoglycemia; &lt;cause&gt;weight gain</td>
</tr>
</tbody>
</table>

References


