Leveraging digital media data for pharmacovigilance

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Abstract

The development of novel drugs in response to changing clinical requirements is a complex and costly method with uncertain outcomes. Postmarket pharmacovigilance is essential as drugs often have under-reported side effects. This study intends to use the power of digital media to discover the under-reported side effects of marketed drugs. We have collected tweets for 11 different Drugs (Alprazolam, Adderall, Fluoxetine, Venlafaxine, Adalimumab, Lamotrigine, Quetiapine, Trazodone, Paroxetine, Metronidazole and Miconazole). We have compiled a vast adverse drug reactions (ADRs) lexicon that is used to filter health related data. We constructed machine learning models for automatically annotating the huge amount of publicly available Twitter data. Our results show that on average 43 known ADRs are shared between Twitter and FAERS datasets. Moreover, we were able to recover on average 7 known side effects from Twitter data that are not reported on FAERS. Our results on Twitter dataset show a high concordance with FAERS, Medeffect and Drugs.com. Moreover, we manually validated some of the under-reported side effect predicted by our model using literature search. Common known and under-reported side effects can be found at https://github.com/cbrl-nuces/Leveraging-digital-media-data-for-pharmacovigilance.

1 Introduction

Pharmacovigilance is the practice of monitoring effects of FDA approved drugs. It is the science and activities related to detecting, assessing, understanding and preventing the adverse effects of drugs. The study of pharmacovigilance has been recently widened to deal with herbal, traditional and complimentary medicines, blood related products, medical devices and vaccines[1].

Drugs are extensively studied (*in vitro* experiments, *in vivo* experiments and clinical trials) before they become available to the public for general use. However, it is evident that drugs in clinical trials are monitored for their side effects under controlled conditions e.g. ethnic diversity, patient age group, dosage and duration. The general and flexible use of these drugs, particularly in less regulated regions like Africa and South Asia is likely to produce previously unobserved side effects and introduce new risks. Post-market pharmacovigilance is required as clinical trials involve limited number of patients, making it difficult to cover broader patterns and trends of drugs. Patient groups such as pregnant women and children are often excluded from clinical trials due to concerns of teratogenicity and ethical issues yet these drugs are often prescribed to such patient groups once available in the market[2,3]. Moreover, these patient groups are also active web and social media users[4]. Previous studies show that it is highly likely that FDA approved drugs will show adverse reactions due to several known and yet to be discovered off-targets[5,6].

Current pharmacovigilance efforts have room for improvement as numerous approved drugs have been withdrawn from the market due to their adverse events. One famous example is of Thalidomide, which was introduced in late 1957 and was widely prescribed as a safe treatment for morning sickness and nausea. Children of pregnant women on Thalidomide prescription showed congenital abnormalities that caused severe birth defects[7]. Thalidomide was removed from the market in most countries in 1965. Nevertheless, it continued to be used for the treatment of leprosy, and in more recent years, its indications have been extended to a much wider range of medical conditions[8]. Despite being allowed only under strict supervision and specialist advice, between 1969 and 1995, 34 cases of thalidomide embryopathy were registered in leprosy endemic areas in South America by the Latin American Collaborative Study of Congenital Malformations[9].

There is an emerging trend in people to use social media and websites to reach out to doctors and pharmaceutical companies[10]. Similarly, health-care professionals and patients are discussing the adverse experiences related to medicinal products using the digital media platforms[11]. Some studies have explored the use of social media data for pharmacovigilance[12–14]. Nikfarjam *et al.* tagged mentions of drug side-effects in social media posts from Twitter and online health community DailyStrength[15]. Similarly Cocos *et al.* developed a deep learning based method for labeling ADRs

in Twitter posts[16]. These studies were helpful in identifying the mentions of ADRs, however, downstream analysis is required to perform qualitative analysis on these ADRs[15,16]. Freifeld *et al.* evaluated the level of concordance between drug side-effects from Twitter data and adverse events (AE) reported in the FAERS[17]. They provided the correlation by system organ class between adverse event (AE) in Twitter and consumer report, but did not perform any quantitative analysis for actual AEs and do not provide any mechanism to control false positives. MacKinlay *et al.* investigated the ADR surveillance by analyzing tweets and evaluated their methodology against the reports in the FAERS database[18]. Smith *et al.* presented a method to compare ADRs mentioned in social media with FAERS, drug information databases (DIDs), and systematic reviews[19]. Even though some studies have started analysing social media data for augmenting pharmacovigilance efforts, but existing studies (i) do not account for unstructured nature of the data on the social media platforms appropriately, (ii) fail to quantify the quality of data from social media, and (iii) fail to control for the high noise in such data platforms.

In this study, we try to overcome the above mentioned limitations by (i) compiling a large phrasal ADR lexicon that is specific for ADRs, descriptive in nature and wherein the phrases representing the same ADR are grouped together using semantic similarity based hierarchical clustering, ii) comparing the ADRs found from Twitter with three reporting systems: FDA's AERS (FAERS)[20], MedEffect[1] and Drugs.com[2]; iii) using a classification model followed by a statistical model to filter out possible noise and false positives.

We used our lexicon to mine the ADRs reported on Twitter for 11 drugs (Alprazolam, Adderall, Fluoxetine, Venlafaxine, Adalimumab, Lamotrigine, Quetiapine, Trazodone,Paroxetine, Metronidazole and Miconazole). We were able to recover a significant number (approximately 50 on average) of known side effects of each drug from Twitter and predict the under-reported side effect of the 11 drugs in our dataset. Our results suggest that Twitter data shows a high concordance with FAERS (approximately 43 side effects on average) and other reporting systems and can be used as an additional source for enhancing pharmacovigilance practices. Our study will help the drug regulatory agencies and pharmaceutical companies in performing post-market pharmacovigilance using publicly available digital media data.

2 Methods and Techniques

2.1 Data Collection and preprocessing

We shortlisted 11 drugs for which significant data was available on Twitter (Table 1). Drugs are marketed under different names (Fluoxetine is also marketed as Prozac, Prozac Weekly, and Sarafem), therefore we have used a list of all the alternate names by augmenting brand names from Drug.com in the list compiled by Sarkar A, et al.[21]. Moreover, data from Twitter does not follow language rules and can have spelling and grammatical errors (Xanax can be written as xanaxx and xnaax). Therefore, all alternate names of the drugs and their common misspellings were used to collect the data from Twitter using tweepy[3] and twitterscraper [4] APIs.

Apart from Twitter data, we also used the reviews data available at Drugs.com, FAERS and MedEffect. For Drugs.com we used the data compiled by Graber et al.[22]. For collecting FAERS's data, we used the openFDA[20] "drug adverse event" API to download all the available files of Drug Adverse Events data using a python scraper. Similarly we also collected the ADRs reported on MedEffect for these drugs. From both Twitter and online reviews datasets redundant records were removed, followed by the application of stemming and lemmatization. The number of unique tweets and reviews found for each drug can be seen in the Table 1.

2.2 Data Classification

We only used tweets containing at least one drug name and an ADR. Due to the unstructured nature of the Twitter data, we need to define the context of the tweets. For example:
(i) I had xanax and it caused me anxiety
(ii) Can Xanax cause anxiety?

[1] https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html
[2] https://www.drugs.com/
[3] http://www.tweepy.org/
[4] Available: http://www.tweepy.org/

Drug names	Twitter Data			MedEffect Data	Drugs.com Data	FAERS Data
	Tweets extracted on drug names	Tweets filtered on side effect	Tweets classified as "Health"	Reviews for each drug	Reviews for each drug	Reviews for each drug
Alprazolam	290,212	95,683	15,047	1,885	1,373	30,979
Adderall	604,213	119,190	31,266	1,018	358	6,423
Fluoxetine	342,010	93,537	10,526	1,355	1,500	22,927
Venlafaxine	50,053	16,144	4,836	4,661	316	5,856
Adalimumab	70,253	26,433	3,893	77,177	697	300,859
Lamotrigine	39,946	13,149	3,932	3,435	1,065	37,067
Quetiapine	77,596	22,929	8,332	13,979	1,454	26,468
Trazodone	4,064	7,478	3,414	3,141	716	1,147
Paroxetine	106,139	34,539	5,644	8,450	1,347	32,033
Metronidazole	53,254	16,032	1,923	5,084	1,262	9,450
Miconazole	33,115	8,226	326	50	1,255	6,526

Table 1: Shows the data collected from Twitter, MedEffect, Drugs.com and FAERS for 11 different drugs.

In the first tweet it is being portrayed that the user had anxiety after having Xanax, we categorized such tweets as "Health", whereas in the second tweet a question is being put. It might be possible that drug name and side effect may co-occur in the same tweet but in different context therefore we categorized such tweets as "Non-Health". In order to reduce the false positives, we removed the tweets falling in the category of "Non-Health". The manual classification of thousands of tweets is a tedious task, so we converted this into a classification problem. From the collected Twitter data set, $2,500$ random health related tweets were manually annotated as "Health" and $2,500$ non-health tweets were were manually annotated as "Non-Health".

For training the machine learning models on the manually annotated data, we extracted features that capture the semantics and contextual information. To accomplish this we used two pre-trained word2vec models. One from "Distributional Semantics Resources for Bio-medical Text Processing" by Pyysalo *et al.* (2013)[23], trained on Wikipedia, PubMed and PMC and the second by *Godin et al.* trained on over 400 million Twitter microposts[24]. We also used Term Frequency Inverse Document Frequency (tf-idf) features, that is a term weighting scheme representing the important of a word is in a corpus[25,26]. We only used the data that is classified as "health" for further analysis (as shown in Table 1).

2.3 Tanimoto Coefficient

In order to infer the value of occurrence of a particular side effect in a drug, we calculated the tanimoto coefficient "σ" of a drug with each side-effect.

$$\begin{aligned} \sigma =& \frac{D_i \cap S_j}{D_i \cup S_j} \\ D_i \cup S_j =& f(D_i) + f(s_j) - (D_i \cap S_j) \end{aligned} \tag{1}$$

where D_i represents the name of a drug and S_j represents the side effect. i is iterated over the 11 drugs in the dataset and j is iterated over the $21,550$ side effect groups. $f(D_i)$ and $f(S_j)$ represent the number of tweets that contain drug D_i and side effect S_j respectively. The tanimoto coefficient σ has a range between 0 and 1, where 0 represents lowest similarity and 1 represents highest similarity.

3 Results and Discussion

3.1 Lexicon Compilation

In our previous study, we compiled a large phrasal ADR lexicon from FAERS (containing 20,285 phrases) and automatically clustered the phrases representing the same ADRs[27]. In this study, we expanded this lexicon by adding additional phrasal ADRs from MedEffect[5] and CHV[6]. In order to compile a list of only ADRs, we filtered the CHV phrases by excluding the concepts with UMLS IDs that were not listed in SIDER[28] (following the approach of Azadeh Nikfarjam *et al.*[29]). We grouped the ADRs together that had the same UMLS IDs to obtain $4,101$ phrasal ADR groups.

[5]https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-database.html
[6]http://consumerhealthvocab.chpc.utah.edu/CHVwiki/

We added these ADR groups and $11,956$ ADRs from MedEffect to the lexicon from FAERS. We had a total of $34,392$ unique groups[7] and our goal was to iteratively merge the groups representing similar ADRs.

3.2 Lexicon Clustering

Results from our previous study showed that nine different algorithms can be used for the automatic clustering of the phrasal ADR lexicon[27]. Here, we used Silhouette Coefficient to determine the number of clusters for our lexicon[30]. Higher Silhouette Coefficient scores represent a model with better defined clusters. For all nine clustering algorithms, we computed Silhouette Coefficient for the values of k (number of clusters) ranging from 50 to $34,300$ with an increment of 50. All nine clustering algorithms have the highest Silhouette Coefficient around $21,550$ (Figure 1a), so we chose $21,550$ as the value of k (number of clutters).

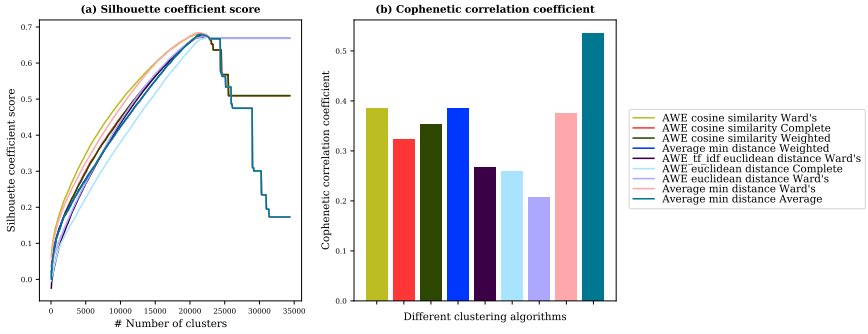

Figure 1: (a) "silhouette coefficient score" of nine clustering algorithms. All clustering algorithms have the highest silhouette coefficient around $21,550$ (b) "cophenetic correlation coefficient" of nine clustering algorithms, "Average min distance Average" algorithm has highest score of 0.54. We selected "Average min distance Average" as a clustering algorithm with k=$21,550$ (number of clusters).

We used cophenetic correlation coefficient, a measure of how good a dendrogram preserves the pairwise distances between the original data points, to select the best performing clustering algorithm[31]. A good clustering has cophenetic correlation close to 1. We computed cophenetic correlation for all nine clustering algorithms and "Average min distance Average" algorithm obtained the highest score of 0.54 (Figure 1b). Therefore, we selected "Average min distance Average" as an algorithm to cluster the phrases representing the same ADRs[8]. This clustering scheme uses the average of min distance to compute the semantic similarity between two phrases and "average" as linkage criteria[27].

3.3 Annotation and Noise Removal

In order to automate the annotation process, we constructed different models to classify the tweets/reviews into "health" or "non-health" classes based on our manually annotated dataset of $5,000$ tweets (see methods for details). We performed k-fold cross validation of different machine learning classifiers for selecting the best model using two different features: (1) tf-idf along with word2vec trained on twitter and (2) tf-idf along with word2vec trained on Wikipedia, PubMed and PMC. The MLPClassifier using tf-idf and word2vec trained on twitter outperformed other models (Table 2). Deep learning models were not used due to the limited annotated training data available in this study. Our results also suggest that as more data is fed to the classifiers, their performance increases significantly.

[7]https://github.com/cbrl-nuces/Leveraging-digital-media-data-for-pharmacovigilance/blob/master/Data/FDA-CHV-and-MedEffect-sideeffectlist.csv

[8]https://github.com/cbrl-nuces/Leveraging-digital-media-data-for-pharmacovigilance/tree/master/Data/side-effect-clusters

	Using tf-idf and word2vec trained on twitter									Using tf-idf and word2vec trained Wikipedia, PubMed and PMC								
	3-fold			5-fold			10-fold			3-fold			5-fold			10-fold		
	PPV	Recall	F1	PPV	TPR	F1	PPV	TPR	F1	PPV	TPR	F1	PPV	TPR	F1	PPV	TPR	F1
MLP	**0.62**	**0.71**	**0.66**	**0.76**	**0.75**	**0.76**	**0.80**	**0.82**	**0.80**	0.63	0.71	0.66	0.74	0.75	0.75	0.79	0.81	0.79
XGB	0.58	0.68	0.62	0.71	0.73	0.72	0.78	0.81	0.79	0.58	0.70	0.63	0.72	0.73	0.72	0.78	0.79	0.78
KNN	0.59	0.55	0.57	0.67	0.59	0.62	0.70	0.62	0.66	0.59	0.66	0.62	0.65	0.68	0.66	0.69	0.71	0.70
RF	0.62	0.63	0.62	0.72	0.64	0.66	0.74	0.67	0.70	0.61	0.62.	0.63	0.72	0.63	0.67	0.74	0.68	0.69
DT	0.54	0.64	0.59	0.64	0.68	0.65	0.69	0.70	0.69	0.56	0.64	0.60	0.63	0.66	0.65	0.67	0.71	0.68

Table 2: K-fold cross validation of different machine learning classifiers: MLPClassifier (MLP), XGBClassifier (XGB), KNeighborsClassifier (KNN), RandomForestClassifier (RF), DecisionTreeClassifier (DT) using two different types of features (1) tf-idf and word2vec trained on twitter and (2) tf-idf and word2vec trained Wikipedia, PubMed and PMC. On the basis of reported precision or positive predictive value (PPV), recall or true positive rate (TPR) and F1 score (F1), MLPClassifier turned out to be the best performing classifier using tf-idf and word2vec trained on twitter.

Drug name	# of known	Twitter	FAERS	MedEffect	Drugs.com	Tw+FA	Common	RMSE Tw+FA	RMSE Tw+Med	RMSE Tw+Drugs
Quetiapine	183	59	86	47	47	53	27	0.017	0.011	0.027
Fluoxetine	169	52	75	21	38	45	13	0.007	0.007	0.008
Metronidazole	77	26	37	18	33	19	9	0.013	0.012	0.029
Adalimumab	255	76	140	85	57	73	24	0.007	0.007	0.009
Alprazolam	223	64	79	26	45	51	13	0.010	0.013	0.009
Miconazole	13	1	6	2	4	1	1	0.042	0.016	0.646
Paroxetine	236	62	110	61	59	55	24	0.023	0.022	0.013
Adderall	127	57	56	17	27	49	10	0.006	0.006	0.014
Trazodone	125	32	30	17	30	20	12	0.006	0.004	0.012
Lamotrigine	219	66	99	42	53	60	15	0.014	0.004	0.011
Venlafaxine	187	54	65	37	32	44	16	0.009	0.011	0.009
Average	165	50	71	34	39	43	15	0.014	0.01	0.072

Table 3: Shows the number of known ADRs found from twitter and other three reporting systems (FAERS, MedEffect and Drugs.com). "# of known" represents the total number known ADRs in our compiled lists of known side effects. "Twitter", "FAERS", "MedEffect", and "Drugs.com" represent number of ADRs found from Twitter, FAERS, MedEffect and Drugs.com respectively that are also in the compiled lists of known side effects. "Tw+FA" represent number of common known ADRs found from Twitter and FAERS. "Common" represent number of common known ADRs found from Twitter, MedEffect, Drugs.com and FAERS. "RMSE Tw+FA", "RMSE Tw+Med" and "RMSE Tw+Drugs" represents Root-Mean-Squared-Error (RMSE) between the tanimoto coefficient scores (σ) of Twitter-FAERS, Twitter-MedEffect and Twitter-Drugs.com respectively.

3.4 Analysis on Cleaned Data

We compiled the lists of known side effects and indications of each drug from WebMD[9], Drugs.com[10] and Medline-Plus[11]. After filtering the "Health" tweets we calculated the tanimoto coefficient "σ" for each drug on the tweets and reviews dataset. Indications of each drug were removed from our results. While the remaining results are either known side effects, possible under reported ADRs or false positives. Table 3 shows the number of known ADRs found from twitter, FAERS, MedEffect and Drugs.com. On average 43 ADRs for each drug are shared between twitter and FAERS datasets. Root-Mean-Squared-Error (RMSE) between the tanimoto coefficient scores σ of all common ADRs between Twitter and FAERS datasets was 0.014, thus demonstrating a high level of agreement between the results from Twitter and FAERS. Similar results were found between Twitter and MedEffect dataset and between Twitter and Drugs.com dataset (Table 3). Moreover, Twitter was able to recover on average 7 known side effects that were not reported in FAERS. This supports the fact that digital media sites such as Twitter could be used to augment the current pharmacovigilance efforts.

In order to show how good twitter results are in recovering the known side effect as compared to other reporting systems, we used the known side effect list to get the top ten known side effect for each drug on the basis of tanimoto

[9]https://www.webmd.com/
[10]https://www.drugs.com/
[11]https://medlineplus.gov/

coefficient. It can be seen from the Figure 2 and Table 4 that the top 10 known side effects found from Twitter are also reported on other reporting systems (FAERS, MedEffect and Drugs.com) with high tanimoto coefficient scores σ. This shows that the data from twitter is meaningful and it can be used along with the current ADR reporting systems.

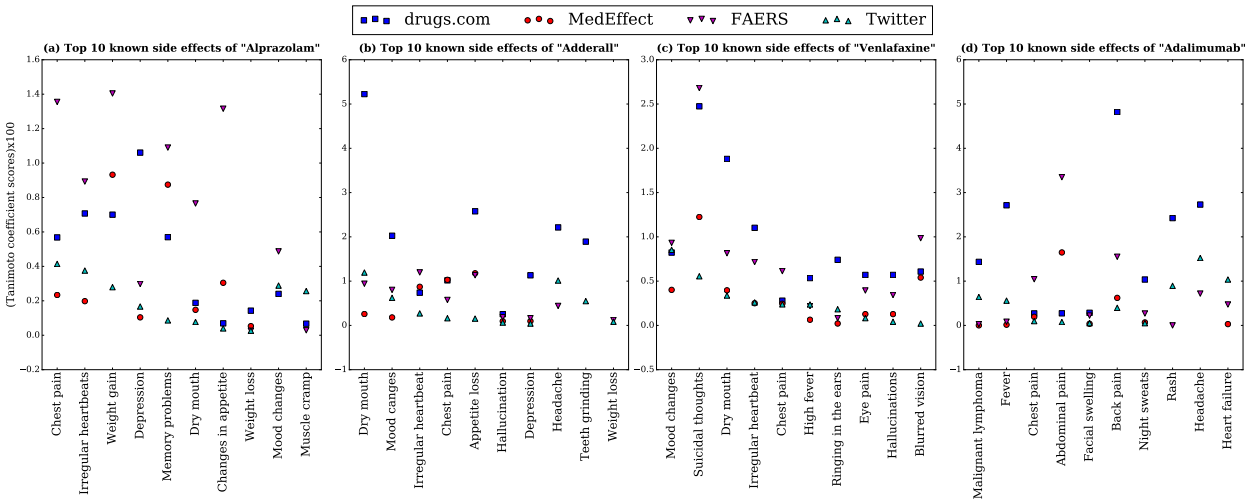

Figure 2: The tanimoto coefficient score ($\sigma \times 100$) of the top 10 known side effects found from twitter that are also reported on other reporting systems (FAERS, MedEffect and Drugs.com) for four drugs (a) "Alprazolam", (b) "Adderall", (c) "Venlafaxine" and (d) "Adalimumab"

3.5 Comparison with previous studies

Sarker *et al*[14] assessed the possibility of utilizing social media as a resource for prescription medication abuse and they reported "weight loss" as a common abuse of "Adderall". Our study finds similar results with σ of 0.0008 and 0.0012 on Twitter and FAERS dataset respectively. Smith *et al.*[19] developed a method to compare ADRs mentioned in social media with those in traditional sources and their results showed that "headache" was reported with relatively high index values on FAERS and Drug Information Databases. Our results also show that "headache" was reported on Twitter, FAERS and Drugs.com with σ of 0.0152, 0.0072 and 0.0012 respectively. Chavant *et al*[32] showed that the occurrence of "memory disorders" reported for "Alprazolam" and "Fluoxetine" in the French PharmacoVigilance Database (FPVD) are 14 and 16 respectively. Our methodology also showed "memory disorders" ADR with high σ values for "Alprazolam" (Twitter = 0.0009, FAERS = 0.0109, MedEffect = 0.0087, Drugs.com = 0.0057) and "Fluoxetine" (Twitter = 0.0001, FAERS = 0.0006, Drugs.com = 0.0013).

O'Connor *et al*[13] evaluated the viability of Twitter as a source of ADR mentions and its potential value for pharmacovigilance. They reported a list of drugs with their most common adverse reactions and the most frequent adverse effects extracted from the Twitter data using their automated system. We also reported the tanimoto coefficient "σ" score of these ADRs. It can be seen in Table 5 that our method is able to recover most of the ADRs reported by their method with significantly high scores. Our analysis showed several under-reported side effects for the drugs in our dataset. Some of the unknown side effects predicted by our methodology and previously reported by case studies have been listed in Table 6 along with a sample tweet and/or online review from our datasets.

For Prozac it has been an active debate for the past three decades whether it causes aggressive behaviour in subjects or not[33]. Our results from the Twitter ($\sigma = 0.0026$), FAERS ($\sigma = 0.0013$) and Drugs.com ($\sigma = 0.005$) suggest that certain patients do experience increase in aggressiveness after taking Prozac. Another side effect for Prozac that had a relatively high tanimoto coefficient for both Twitter ($\sigma = 0.0096$) and Drugs.com ($\sigma = 0.0164$) is having unusual dreams. Several studies have previously reported this side-effect for Prozac[34,35]. Upset stomach had a σ of 0.004 for Twitter, 0.001 for FAERS and 0.008 for Drugs.com data. This side effect has been reported in a study on preschool and high school children[36].

Drug name	Twitter score	OpenFDA score	MedEffect score	Drugs.com score
Trazodone	Headache (1.48), Serotonin syndrome (0.4), Apnea (0.4), Dry mouth (0.38), Chest pain (0.17), Suicidal thoughts (0.14), Blurred vision (0.09), Irregular heartbeat (0.08), Nasal congestion (0.06), Changes in weight (1.87)	Headache (0.14), Serotonin syndrome (0.67), Apnea (0.23), Dry mouth (0.26), Chest pain (0.39), Suicidal thoughts (0.31), Blurred vision (0.32), Irregular heartbeat (0.13), Nasal congestion (0.1), Changes in weight (0.24)	Serotonin syndrome (0.43), Apnea(0.03), Dry mouth (0.61), Chestpain (0.15), Suicidal thoughts (0.43), Blurred vision (0.18), Irregular heartbeat (0.15), Nasal congestion (0.47), Changes in weight (0.4)	Headache (5.05), Serotonin syndrome (0.14), Apnea (0.55), Dry mouth (4.43), Chest pain (0.13), Suicidal thoughts (0.11), Blurred vision (0.41), Irregular heartbeat (0.26), Nasal congestion (1.51), Changes in weight (0.6)
Paroxetine	Weight loss/gain (15.1), Chest Pain (0.31), Suicidal thoughts (0.38), Chest pain (0.31), Hallucinations (0.2), Serotonin syndrome (0.19), Dry mouth (0.1), Restless legs syndrome (0.09), Peeling/Blistering of skin(0.04), Decreased appetite (0.03)	Weight loss/gain (3.86), Chest Pain (0.93), Suicidal thoughts (5.11), Chest pain (0.91), Hallucinations (0.02), Serotonin syndrome (1.13), Dry mouth (0.73), Restless legs syndrome (0.24), Peeling/Blistering of skin (0.08), Decreased appetite (1.35)	Weight loss/gain (0.99), Chest Pain (0.18), Suicidal thoughts (1.61), Chest pain (0.18), Hallucinations (0.01), Serotonin syndrome (0.63), Dry mouth (0.31), Restless legs syndrome (0.11), Peeling/Blistering of skin (0.04), Decreased appetite (0.67)	Weight loss/gain (9.17), Chest Pain (0.43), Suicidal thoughts (1.66), Chest pain (0.43), Hallucinations (0.35), Serotonin syndrome (0.15), Dry mouth (2.08), Restless legs syndrome (0.15), Peeling/Blistering of skin (0.29), Decreased appetite (0.57)
Quetiapine	Weight gain (7.94), Restlessness (1.35), Headache (0.96), Sleep apnea (0.45), Dry mouth (0.39), Suicidal thoughts (0.3), Increased hunger (0.3), weakness (0.24), Muscle spasms (0.18), Stuffy/runny nose (0.08)	Weight gain (3.27), Restlessness (0.03), Headache (0.32), Sleep apnea (0.42), Dry mouth (0.85), Suicidal thoughts (2.28), Increased hunger (0.51), weakness (0.02), Muscle spasms (0.69), Stuffy/runnynose (0.26)	Weight gain (1.15), Sleep apnea (0.02), Dry mouth (0.32), Suicidal thoughts (0.66), Increased hunger (0.19), Muscle spasms (0.26), Stuffy/runny nose (0.09)	Weight gain (19.23), Restlessness (4.81), Headache (1.1), Sleep apnea (0.2), Dry mouth (1.2), Suicidal thoughts (2.0), Increased hunger 2.14), weakness (0.65), Muscle spasms (0.27), Stuffy/runny nose (0.34)
Miconazole	Burning (4.31)	Burning (8.96), Skin irritation (0.27), Erythema (0.43), Skin rash (0.05)	Burning (3.61)	Burning (68.95), Skin irritation (0.16)
Metronidazole	Stuffy nose (0.1), Dry mouth (0.19), Stomach pain (4.72), Metallic taste (1.29), Decreased appetite (0.22), Joint pain (0.15), Stiff neck (0.1), Peeling/Blistering skin (0.05), Vomiting (2.84), Headache (0.1	Stuffy nose (0.12), Dry mouth (0.71), Stomach pain (0.1), Joint pain (0.19), Stiff neck (0.08), Vomiting (0.06	Stuffy nose (0.08), Dry mouth (0.3)	Stuffy nose (0.7), Dry mouth (0.46), Stomach pain (4.0), Metallic taste (11.55), Decreased appetite (5.48), Joint pain (0.68), Stiff neck (0.55), Peeling/Blistering skin (0.16), Vomiting (5.7), Headache (0.08
Lamotrigine	Memory loss (0.69), Sleep disorder (0.52), Suicidal thoughts (0.34), Dry mouth (0.27), Neck pain (0.15), Back pain (0.15), Chest pain (0.14), Skin problems (0.13), Decreased appetite (0.05), Blurred vision (0.03)	Memory loss (0.06), Sleep disorder (0.59), Suicidal thoughts (1.42), Dry mouth (0.47), Neck pain (0.28), Back pain (0.52), Chest pain (0.65), Skin problems (0.98), Decreased appetite (0.85), Blurred vision (1.37)	Sleep disorder (0.14), Suicidal thoughts (0.55), Dry mouth (0.08), Neck pain (0.22), Back pain (0.05), Chest pain (0.11), Skin problems (0.17), Decreased appetite (0.24), Blurred vision (0.17)	Memory loss (1.37), Sleep disorder (0.8), Suicidal thoughts (2.55), Dry mouth (1.73), Neck pain (0.19), Back pain (0.44), Chest pain (0.45), Skin problems (0.37), Decreased appetite (0.18), Blurred vision (0.47)
Fluoxetine	Suicidal thoughts (0.86), Decreased appetite (0.09), Sleep disorder (0.07), Irregular heartbeat (0.07), Eye pain (0.04), Memory problems (0.01), weakness (0.41), Chest Pain (0.39), Dry mouth (0.39), Weight Loss (0.25)	Suicidal thoughts (3.51), Decreased appetite (1.25), Sleep disorder (0.19), Irregular heartbeat (0.69), Eye pain (0.29), Memory problems (1.15), weakness (0.04), Chest Pain (1.16), Dry mouth (0.83), Weight Loss (0.1)	Suicidal thoughts (0.46), Decreased appetite (0.06), Sleep disorder (0.21), Irregular heartbeat (0.13), Eye pain (0.07), Memory problems (0.19)	Suicidal thoughts (4.41) Decreased appetite (1.18), Sleep disorder (0.26), Irregular heartbeat (0.71), Eye pain (0.07), Memory problems (0.13), weakness (0.63), Chest Pain (0.33), Dry mouth (1.77), Weight Loss (0.13)

Table 4: The tanimoto coefficient score ($\sigma \times 100$) of top known side effect found from twitter that are also reported on other reporting systems e.g FAERS, MedEffect and Drugs.com.

Drug Brand/ Generic Name	Adverse Effects Found in Tweets (Score) by our method	Documented Adverse Effects (no order) reported by O'Connor *et al*	Adverse Effects Found in Tweets (Frequency) reported by O'Connor *et al*
Seroquel/ Quetiapine	weight gain (8.38), psychosis (1.82), dry mouth (0.40), increased appetite (0.30), restless leg syndrome (0.14), sleep paralysis (0.14), abnormal dreams (0.02)	somnolence, dry mouth, headache, dizziness, asthenia,constipation, fatigue	somnolence (22.2%), abnormal dreams (9.6%), feel like a zombie (8.1%), weight gain (6.6%), restless leg syndrome (6.6%), increased appetite (5.9%), sleep paralysis (2.9%), dizziness (2.2%), psychosis (2.2%), tremors (2.2%)
Effexor/ venlafaxine	insomnia (2.09), withdrawal syndrome (0.47), dry mouth (0.34)	nausea, headache, somnolence, dry mouth, dizziness	withdrawal syndrome (21.3%), insomnia (11.1%), headache (4.3%), malaise (4.3%), abnormal dreams (4.3%), nausea (3.4%), shaking (3.4%), fatigue (3.4%)
Paxil/ Paroxetine	weight gain (14.03), feel sick (2.27), insomnia (1.96), depression (2.18), withdrawal syndrome (0.16)	nausea, somnolence, abnormal ejaculation, asthenia,tremor, insomnia, sweating	withdrawal syndrome (27.7%), weight gain (12.8%), depression (8.5%), headache (6.4%), somnolence (6.4%), allergic (6.4%), feel sick (6.4 %), emotional (6.4%)
Prozac/ Fluoxetine	anxiety (3.14), feeling ill (2.21), insomnia (1.85), suicidal thoughts (0.86), abnormal dreams (0.0003), withdrawal syndrome (0.03)	nausea, headache, insomnia, nervousness, anxiety, somnolence	somnolence (22.2%), withdrawal syndrome (8.9%), feeling ill (8.9%), abnormal dreams (6.7%), suicidal thoughts (6.7%), tremors (6.7%), allergic reaction (4.4%)
Lamictal/ Lamotrigine	insomnia (1.62), feel sick (1.49), back pain (0.15), joint pain (0.05)	vomiting, coordination abnormality, dizziness, rhinitis, dyspepsia, nausea, headache, diplopia, ataxia, insomnia,fatigue, back pain	insomnia (17.9%), rash (12.8%), lethargy (7.7%), joint pain (5.1%), feel like a zombie (5.1%), feel sick (5.1%)
Humira	feel sick (1.83), joint pain (0.96)	upper respiratory infection, rash, headache, sinusitis, accidental injury	somnolence (24%), feel sick (8%), palpitations (8%), ache/pains (8%), joint pain (4%), headache (4%), rash (4%), respiratory disorder (4%)
Trazodone	insomnia (14.09), hangover effect (0.80), dry mouth (0.38), withdrawal syndrome (0.23)	somnolence, headache, dry mouth, dizziness, nausea	somnolence (24.3%), abnormal dreams (16.2%), hangover effect (8.1%), headache (5.4%), insomnia (5.4%), withdrawal syndrome (5.4%)

Table 5: The tanimoto coefficient score ($\sigma \times 100$) of ADRs found from twitter by our method that was previously reported by O'Connor *et al*[13].

Drug	Predicted side-effect	Literature Support	Sample Tweet(s) / review(s)
Prozac/ Fluoxetine	Aggressive Behavior	PMID: 8822529	*When I first started taking this medication I changed from Lovan, and for about 2 weeks I felt on top of the world! I was motivated, full of energy and was actually laughing after a long period of depression. It was all downhill from there... I reached the point where my brain just didn't feel right, I was more depressed than ever, feeling desperate and looking for a way out of feeling so low. I stopped taking the medication, initially to piss off my husband, and it was then that I realized this medication was the cause of my depressive moods, anxiety and anger. I would not recommend this medication to anyone without close psychiatric monitoring.*
Prozac/ Fluoxetine	Bad Dreams	PMID: 17803018, 28791566	1. *dammit my fluoxetine give me such bad vivid dream*; 2. *im having bad dream every night after i start taking fluoxetine* 3. *It's great. I get songs in my head or find myself humming, and that hasn't happened for a long time. More random positive thoughts too. And much less of the bad ones. I sometimes feel down, but it's not often and I think unavoidable. The side affect I notice is phases of vivid bad dreams. More nightmares and more stand that are stressful and occupy my mind too much, which makes me feel less rested.*
Prozac/ Fluoxetine	Upset Stomach	PMID: 24600324	1. *the side effect can be kind of sudden but yes there is a wait for the effect i spent about two week with headache getting used to prozac till it settled into my system sometimes i still have upset stomach dont take them on an empty stomach either and drink more water*; 2. *urgh prozac had it many year ago gave me epic nightmare panic attack and a constant upset stomach gave up and stopped taking it after week if it disagrees with you ask if you can have high dose citalopram instead*
Xanax/ Alprazolam	Talkativeness	PMID: 27092285	*Xanax is a miracle for me. I can't live without it. It is not addicting. I never experienced withdrawl symptoms either. I am usually tense, high strung and anxious. Xanax makes me happy, easy going, talkative, calm. It helps me sleep, I can't sleep without it. I take zoloft and seroquel but without xanax nothing seems to work or help me. I love xanax and I take it daily or else I really just can't get through the day. I have anger and a short fuse and bad temper and xanax calms my storms. Xanax is the only thing that works for me and makes me sane and able to face life head on.*
Adderall	Memory Loss	PMID: 22717254	1. *it quite obvious that adderall cause selective memory loss*; 2. *shit he looking so bad even the orange paint cant hide it adderall withdrawal symptom intense craving depression insomnia shortterm memory loss irritability and anger hunger pang panic attack anxietylethargyhallucination http ofsnortingadderall*

Table 6: Unknown side effects predicted by our methodology that have been previously reported by case studies.

For Xanax, we predicted heart burn as one of the under-reported side effects with σ of 0.002 for Twitter, and 0.0003 for FAERS. A previous clinical trial reported heart burn in more than 30% of the patients[37]. Similarly, we predicted talkativeness as another under-reported side effect for Xanax. A previous case study has reported increased talkativeness in an elderly patient with a history of anxiety, mood disorders, and hypothyroidism[38]. Similarly, a previous study supports our results on Adderall induced memory loss ($\sigma = 0.0008$ for Twitter data and $\sigma = 0.0002$ for FAERS data)[39]. A complete list of under-reported side effects that were found for the 11 drugs across all platforms can be found at https://github.com/cbrl-nuces/Leveraging-digital-media-data-for-pharmacovigilance.

4 Conclusion

Conducting clinical trials of drugs is expensive and has its own restrictions on patient groups and drug usage. Moreover, manual annotation of the data is a tedious and time consuming task. Digital data (social media and online reviews) can help in reducing the cost of pharmacovigilance efforts and can help in gathering unknown side effects of drugs. This research work provides the groundwork for augmenting current pharmacovigilance efforts. We constructed several classifiers to automatically annotate health related tweets. We were able to recover several known side effects for the 11 drugs in our dataset using social media and online reporting system. Some of the predicted side effects have already been reported by previous studies, therefore lending validity to our findings.

We filtered the tweets on a vast ADRs lexicon and then removed the possible false positives using a classifier. The data available on Twitter is without any specific medical focus and suffers from high false positives. Such false positives get very low tanimoto coefficient score due to large volume of tweets and can be removed by our methodology. Moreover, it is important to distinguish false positives from novel ADRs. This currently requires manual efforts. Our approach could highlight possible under-reported ADRs, however, subsequent manual examination by experts is required to confirm these ADRs.

The unknown side effects found by our model are the possible under reported ADRs that were not present in the list of known ADRs and need further clinical validation. In future we plan to improve the quality and quantity of data annotation and use the similar pipeline to identify the indication/symptoms of infectious diseases such as COVID-19 reported on digital media.

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References

1. W.H.O. *The Importance of Pharmacovigilance - Safety Monitoring of Medicinal Products*. World Health Organization, Geneva, Switzerland, 2002.
2. Mary C Blehar, Catherine Spong, Christine Grady, Sara F Goldkind, Leyla Sahin, and Janine A Clayton. Enrolling pregnant women: issues in clinical research. *Women's Health Issues*, 23(1):e39–e45, 2013.
3. Richard E Behrman, Marilyn J Field, et al. *Ethical conduct of clinical research involving children*. National Academies Press, 2004.
4. Maeve Duggan, Nicole B Ellison, Cliff Lampe, Amanda Lenhart, and Mary Madden. Demographics of key social networking platforms. *Pew Research Center*, 9, 2015.
5. Hammad Naveed, Xin Gao, Stefan T. Arold, Umar S. Hameed, Deborah Harrus, and William Bourguet. An integrated structure- and system-based framework to identify new targets of metabolites and known drugs. *Bioinformatics*, 31(24):3922–3929, 2015.
6. Hammad Naveed, Corinna Reglin, Thomas Schubert, Xin Gao, Stefan T. Arold, and Michael L. Maitland. Identifying novel targets by using drug-binding site signature: A case study of kinase inhibitors. *bioRxiv*, 2019.
7. J. E. Ridings. The thalidomide disaster, lessons from the past. *Methods Mol. Biol.*, 947:575–586, 2013.
8. N. Vargesson. Thalidomide-induced teratogenesis: history and mechanisms. *Birth Defects Res. C Embryo Today*, 105(2):140–156, 2015.
9. W.H.O. *Pharmacovigilance : ensuring the safe use of medicines*. World Health Organization, Geneva, Switzerland, 2004.
10. F. Gholami-Kordkheili, V. Wild, and D. Strech. The impact of social media on medical professionalism: a systematic qualitative review of challenges and opportunities. *J. Med. Internet Res.*, 15(8):e184, 2013.
11. R. Sloane, O. Osanlou, D. Lewis, D. Bollegala, S. Maskell, and M. Pirmohamed. Social media and pharmacovigilance: A review of the opportunities and challenges. *Br J Clin Pharmacol*, 80(4):910–920, 2015.

12. Abeed Sarker, Rachel Ginn, Azadeh Nikfarjam, Karen O'Connor, Karen Smith, Swetha Jayaraman, Tejaswi Upadhaya, and Graciela Gonzalez. Utilizing social media data for pharmacovigilance: a review. *Journal of biomedical informatics*, 54:202–212, 2015.
13. Karen O'Connor, Pranoti Pimpalkhute, Azadeh Nikfarjam, Rachel Ginn, Karen L Smith, and Graciela Gonzalez. Pharmacovigilance on twitter? mining tweets for adverse drug reactions. In *AMIA annual symposium proceedings*, volume 2014, page 924. American Medical Informatics Association, 2014.
14. Abeed Sarker, Karen O'Connor, Rachel Ginn, Matthew Scotch, Karen Smith, Dan Malone, and Graciela Gonzalez. Social media mining for toxicovigilance: automatic monitoring of prescription medication abuse from twitter. *Drug safety*, 39(3):231–240, 2016.
15. A. Nikfarjam, A. Sarker, K. Oconnor, R. Ginn, and G. Gonzalez. Pharmacovigilance from social media: mining adverse drug reaction mentions using sequence labeling with word embedding cluster features. *Journal of the American Medical Informatics Association*, 2015.
16. Anne Cocos, Alexander G Fiks, and Aaron J Masino. Deep learning for pharmacovigilance: recurrent neural network architectures for labeling adverse drug reactions in twitter posts. *Journal of the American Medical Informatics Association*, 24(4):813–821, 2017.
17. Clark C Freifeld, John S Brownstein, Christopher M Menone, Wenjie Bao, Ross Filice, Taha Kass-Hout, et al. Digital drug safety surveillance: monitoring pharmaceutical products in twitter. *Drug safety*, 37(5):343–350, 2014.
18. Andrew MacKinlay, Hafsah Aamer, and Antonio Jimeno Yepes. Detection of adverse drug reactions using medical named entities on twitter. In *AMIA Annual Symposium Proceedings*, volume 2017, page 1215. American Medical Informatics Association, 2017.
19. Karen Smith, Su Golder, Abeed Sarker, Yoon Loke, Karen O'Connor, and Graciela Gonzalez-Hernandez. Methods to compare adverse events in twitter to faers, drug information databases, and systematic reviews: proof of concept with adalimumab. *Drug safety*, 41(12):1397–1410, 2018.
20. Taha A Kass-Hout, Zhiheng Xu, Matthew Mohebbi, Hans Nelsen, Adam Baker, Jonathan Levine, Elaine Johanson, and Roselie A Bright. Openfda: an innovative platform providing access to a wealth of fda's publicly available data. *Journal of the American Medical Informatics Association*, 23(3):596–600, 2015.
21. A. Sarker and G. Gonzalez. A corpus for mining drug-related knowledge from Twitter chatter: Language models and their utilities. *Data Brief*, 10:122–131, 2017.
22. Felix Grasser, Surya Kallumadi, Hagen Malberg, and Sebastian Zaunseder. Aspect-based sentiment analysis of drug reviews applying cross-domain and cross-data learning. In *Proceedings of the 2018 International Conference on Digital Health*, DH '18, pages 121–125, New York, NY, USA, 2018. ACM.
23. Hans Moen Tapio Salakoski Sampo Pyysalo, Filip Ginter and Sophia Ananiadou. Distributional Semantics Resources for Biomedical Text Processing. *LBM*, 2013.
24. Fréderic Godin, Baptist Vandersmissen, Wesley De Neve, and Rik Van De Walle. Multimedia lab @ acl wnut ner shared task: Named entity recognition for twitter microposts using distributed word representations. *Proceedings of the Workshop on Noisy User-generated Text*, 2015.
25. G Salton. Automatic information organization and retrieval. *McGraw-Hill, New York*, 1968.
26. K. Spärck Jones. A statistical interpretation of term specificity and its application in retrieval. *Journal of Documentation, vol. 28, pp. 11–21*, 1972.
27. Hammad Farooq and Hammad Naveed. Gpadrlex: Grouped phrasal adverse drug reaction lexicon. In *2019 IEEE International Conference on Signal Processing, Communications and Computing (ICSPCC)*, pages 1–6. IEEE, 2019.
28. Michael Kuhn, Ivica Letunic, Lars Juhl Jensen, and Peer Bork. The sider database of drugs and side effects. *Nucleic acids research*, 44(D1):D1075–D1079, 2015.
29. Azadeh Nikfarjam, Abeed Sarker, Karen O'Connor, Rachel Ginn, and Graciela Gonzalez. Pharmacovigilance from social media: mining adverse drug reaction mentions using sequence labeling with word embedding cluster features. *Journal of the American Medical Informatics Association*, 22(3):671–681, 2015.
30. Peter J Rousseeuw. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *Journal of computational and applied mathematics*, 20:53–65, 1987.
31. Sinan Saraçli, Nurhan Doğan, and İsmet Doğan. Comparison of hierarchical cluster analysis methods by cophenetic correlation. *Journal of Inequalities and Applications*, 2013(1):203, 2013.
32. Francois Chavant, Sylvie Favrelière, Claire Lafay-Chebassier, Caroline Plazanet, and Marie-Christine Pérault-Pochat. Memory disorders associated with consumption of drugs: updating through a case/noncase study in the french pharmacovigilance database. *British journal of clinical pharmacology*, 72(6):898–904, 2011.
33. R. W. Fuller. The influence of fluoxetine on aggressive behavior. *Neuropsychopharmacology*, 14(2):77–81, 1996.
34. A. Wichniak, A. Wierzbicka, M. Wal?cka, and W. Jernajczyk. Effects of Antidepressants on Sleep. *Curr Psychiatry Rep*, 19(9):63, 2017.
35. J. M. Parish. Violent dreaming and antidepressant drugs: or how paroxetine made me dream that I was fighting Saddam Hussein. *J Clin Sleep Med*, 3(5):529–531, 2007.
36. J. A. Barterian, E. Rappuhn, E. L. Seif, G. Watson, H. Ham, and J. S. Carlson. Current state of evidence for medication treatment of preschool internalizing disorders. *ScientificWorldJournal*, 2014:286085, 2014.
37. S. Singh, R. T. Bailey, H. J. Stein, T. R. DeMeester, and J. E. Richter. Effect of alprazolam (Xanax) on esophageal motility and acid reflux. *Am. J. Gastroenterol.*, 87(4):483–488, 1992.
38. D. Kirkpatrick, T. Smith, M. Kerfeld, T. Ramsdell, H. Sadiq, and A. Sharma. Paradoxical Reaction to Alprazolam in an Elderly Woman with a History of Anxiety, Mood Disorders, and Hypothyroidism. *Case Rep Psychiatry*, 2016:6748947, 2016.
39. L. Sanday, C. L. Patti, K. A. Zanin, S. Tufik, and R. Frussa-Filho. Amphetamine-induced memory impairment in a discriminative avoidance task is state-dependent in mice. *Int. J. Neuropsychopharmacol.*, 16(3):583–592, 2013.