A Review on Adverse Drug Reaction Detection Techniques

Ahmed A. Nafea[1,*], Manar AL-Mahdawi[2], Mohammed M AL-Ani[3] and Nazlia Omar[3]

[1]Department of Artificial Intelligence, College of Computer Science and IT, University of Anbar, Ramadi, Iraq

[2]Department of Medical Physics, College of Science, Al-Nahrain University, Jadriya, Baghdad, 10072, Iraq

[3]Center for Artificial Intelligence Technology, Faculty of Information Science and Technology, Universiti Kebangsaan Malaysia, Bangi, Selangor, Malaysia

***Abstract*—The detection of adverse drug reactions (ADRs) is an important piece of information for determining a patient's view of a single drug. This study attempts to consider and discuss this feature of drug reviews in medical opinion-mining systems. This paper discusses the literature that summarizes the background of this work. To achieve this aim, the first discusses a survey on detecting ADRs and side effects, followed by an examination of biomedical text mining that focuses on identifying the specific relationships involving ADRs. Finally, we will provide a general overview of sentiment analysis, particularly from a medical perspective. This study presents a survey on ADRs extracted from drug review sentences on social media, utilizing and comparing different techniques.**

***Index Terms*—Adverse drug reactions, Detection, Machine learning, Deep learning, Sentiment analysis, Trigger terms.**

I. Introduction

Adverse drug reactions (ADRs) are unintended negative effects that occur as a result of taking a medication. They can range from minor side effects, such as a headache, to severe and life-threatening reactions, such as anaphylaxis. ADRs are important for both patients and health-care workers, as they can be a precedent for increased disease, hospitalization, and even death. The World Health Organization (WHO) estimates that ADRs are responsible for around 6.5% of hospital charges worldwide and that about 1 in 10 hospital admissions are related to ADRs. Early detection of ADR is important in reducing its impact on patients and health-care systems (Edwards and Aronson, 2000).

Detection of ADRs is a main step in reducing the problem of these reactions in patients and health-care systems. A common method for ADR is natural reporting, in which health-care professionals and patients report ADR to supervisory groups or pharmaceutical companies. Natural reporting is known to be underreported and not fully typical of the true incidence of ADRs (Yadesa, et al., 2021).

The growth of social networks has led to a significant increase in the amount of text-based information available in recent years. This has allowed common users to freely share their thoughts and opinions on a category of topics like product reviews (Kiritchenko, Zhu and Mohammad, 2014). In these reviews, users can offer evaluations of a specific product, detailing both its positive and negative sides based on their personal experience with it (Liu, Bi and Fan, 2017).

In the last year, researchers have become interested in a novel form of product evaluation known as medical reviews. These reviews concern users sharing their personal experiences with specific medications to evaluate their efficiency. They often mention several side effects and other medically relevant information. As a result, a new task has arisen, namely, the identification of these mentions, referred to as ADR detection (Ebrahimi, et al., 2016).

Several studies in the literature have focused on detecting ADR by crawling data from social media like drug websites or Twitter (Sarker and Gonzalez, 2015; De Rosa, et al., 2021). Comments and reviews from regular users are analyzed to identify ADR mentions. The statement "It made me very dizzy" is an example of dizziness, where the user is describing a side effect of a specific medication.

In the literature, a lot of researchers have been utilizing ML techniques to detect ADR (Ebrahimi, et al., 2016; Kiritchenko, et al., 2018; Yousef, Tiun and Omar, 2019; Pain, et al., 2016; and Plachouras, Leidner and Garrow, 2016). To detect ADR, researchers use annotated medical data to train classification models. The model is trained to recognize features, such as trigger terms, that are frequently associated with ADR. These trigger terms are selected keywords that have been determined to have a high likelihood of showing the presence of ADRs. Different classification methods are utilized in combination with trigger-term features to train the

ARO-The Scientific Journal of Koya University
Vol. XII, No. 1 (2024), Article ID: ARO.11388. 11 pages
Doi: 10.14500/aro.11388
Received: 06 September 2023; Accepted: 16 May 2024
Regular review paper: Published: 07 June 2024
Corresponding author's email: ahmed.a.n@uoanbar.edu.iq
Copyright © 2024 Ahmed A. Nafea, Manar AL-Mahdawi, Mohammed M. AL-Ani and Nazlia Omar. This is an open access article distributed under the Creative Commons Attribution License.

model. However, numerous complex challenges persist in the field of ADR extraction.

This study is important because it has applications in the mining of medical opinion, a process that can be utilized to evaluate medications and gather feedback from patients. This can be beneficial to both patients, who can make other informed decisions about their medication, and doctors and drug manufacturers, who can use the feedback to make better decisions about the development, regulation, and prescribing of medications. The objectives of this work include understanding ADR detection, characterizing the key concepts of ADR, and presenting a classification of various methods used for ADR extraction.

II. Literature Review

In the past, ADR was described as major, dangerous, or bad reactions resulting from the use of a medication. These reactions required warning, immediate medical attention, dosage adjustments, or discontinuation of the product to prevent potential risks associated with its administration (Edwards and Aronson, 2000). ADR is a universal issue of importance, as it can impair patients' medical conditions and contribute to increased morbidity rates, even leading to fatalities. According to a prior investigation, there were approximately 100,000 deaths resulting from medical errors in the United States in 2000, with approximately 7,000 of those deaths attributed to drug reactions (Pouliot, Chiang and Butte, 2011).

ADR is extremely dangerous for patients around the world and is one of the leading causes of death for patients (Pirmohamed, et al., 2004). Traditional ADR surveillance systems are often ineffective in detecting ADR that occurs after long-term exposure or under specific conditions. These systems are prone to underreporting, a lack of complete data, and delayed detection. Due to these limitations, many ADRs may go undetected (Sarker, et al., 2015). Latest medical reports (Gurulingappa, Mateen-Rajpu and Toldo, 2012) and data on the social network (Ginn, et al., 2014; Nikfarjam, et al., 2015) about ADRs abound and are rapidly generated. Furthermore, machine learning (ML) and advanced natural language processing (NLP) algorithms help automatically detect large numbers of ADRs of unstructured data.

Pharmacovigilance strategies face a critical obstacle in identifying early identification of ADR in their post-approval times. Pharmacovigilance is described as the research and practices related to the identification, evaluation, awareness, and prevention of adverse effects or any other drug problem (WHO, 2002). A research has shown that ADR is a major public health concern after a drug is released. These reactions can cause hospitalizations, emergency visits, and even deaths, with numbers in the millions and resulting in costs of around $75–180 billion annually (Hacker, 2009). However, pre-approved clinical trials have various limitations; therefore, it is difficult to measure the true effects of a medication until it has been released and used by a larger population (Ahmad, 2003; Lazarou, Pomeranz and Corey, 1998). For example, through volunteer reporting systems and electronic health records (EHRs), various resources have been used to monitor ADR. The exponential development of electronically accessible health information and the ability to process vast amounts of it automatically, using ML algorithms and NLP, opened new opportunities for pharmacovigilance. Annotated companies have recently become available to identify ADR, enabling data-centric NLP algorithms and supervised ML techniques to automatically help detect ADR (Harpaz, et al., 2012).

One field in which data have grown and continue to grow tremendously in recent years is social media (Ginn, et al., 2014). Individuals share their personal health experiences in online communities each day. The strength of this study includes information about the utilization of prescription medications, side effects, and treatments discussed in social networks. Those that focus on health issues, in particular, attract significant user interest. These social networks are a valuable and credible source of information for people dealing with similar health issues. In recent years, a research on the detection of ADR has shifted to the utilization of data from these social media platforms due to the wealth of information available on them (Leaman, et al., 2010).

A. Terminology of ADRs

This study (Edwards and Aronson, 2000) proposed new terminology for ADRs by analyzing the definitions provided by the WHO and other sources. ADR was defined as a detrimental or unpleasant reaction caused by a medical product that needs prevention, specific treatment, dosage adjustment, or discontinuation of the product. The definition of "adverse event" refers to an outcome occurring during drug use but not necessarily directly linked to it. These definitions were distinguished from an "adverse event," which refers to an outcome occurring, while a patient is using a drug but may not necessarily be directly attributed to it. The terms "adverse drug reaction" and "drug side effect" were considered interchangeable, with the latter being more commonly utilized by non-health-care professionals and incorporating unintended beneficial reactions.

B. Biomedical Text Mining and Information Extraction (IE)

IE refers to the automatic extraction of structured data from semistructured or unstructured text. The purpose of a lot of biomedical text mining tasks is the extraction of some specific information from domain resources (Simpson and Demner-Fushman, 2012). To achieve this goal, the IE task falls into three subtasks: named entity recognition (NER), relation extraction, and event extraction. The following sections provide a brief overview of some of this area's tasks and their current state-of-the-art techniques and open issues (Cohen and Hersh, 2005).

Biomedical text mining resources

The main exchequer for biomedical text mining is text, either annotated or non-annotated (Simpson and Demner-Fushman, 2012). It can be divided into many different categories based on various portions, such as EHRs and published papers. Medical social media are a big group of medical texts and the topic of much biomedical text mining research.

Medical social media and drug reviews

Medical Question and Answer portals, medical reviews, medical weblogs, and Wiki are a sample of social networks in the medical domain. The basic difference between these resources and other more formal texts, such as published research articles, is that their contents usually contain both experience and medical information. Processing these sources, which can be written by patients, doctors, physicians, and nurses considering this difference, is crucial. In a good step toward taking this problem into account, the authors (Denecke and Nejdl, 2009) classified content on social networks into two groups: affective content and informative content. To do this task, they used ML. Based on this observation, the extensive use of adjectives is an effective sign of content, and medical terminology is an indicator of informative content. Then, they applied this classifier to a comprehensive comparison of existing social media on the web based on their informativeness. This approach, similar to subjectivity classification, is unable to evaluate opinionated and unelected sentences in the medical domain due to the side effects, which typically imply unfavorable opinions.

As a result, more research is needed in this direction. This study focuses on ADR detection techniques in drug reviews. There are vast numbers of social networking platforms where people can share, experience, or gain awareness of one drug. These websites may be dedicated to drugs or may overlay different types of products. From a structural point of view, most of these drug reviews, such as Drugratingz.com and Druglib.com, are semistructured.

The study by Goeuriot et al., (2011) analyzes drug reviews on three websites, analyzing user-generated information based on view terms, medical terminology frequency, article length, sentence length, and specific POS proportions. They also deduce from the linguistic observation that drug reviews are much more like spoken language than survey papers, while both are full of medical terminology. However, in spite of the existence of some drug side effects such as anxiety, insomnia, headaches, and nausea in some of the opinion lexicons as opinion words, some other side effects such as sweating and impulsiveness are typically assigned to neutral words.

In addition, it is valuable to imply another special feature of drug review and its effect on opinion mining. You can see this phenomenon in the comment section of semistructured reviews and in unstructured reviews. Many patients cover their experiences in reviews. They talk about their disease and their condition before taking the drug or even after stopping the drug. As a result, the existence of sentimental words or symptoms in a sentence cannot indicate that the sentence is opinionated.

This section includes some special characteristics of drug reviews investigated, particularly from the perspective of opinion mining. Further details on the opinion mining concepts discussed here will be given in section on Relation extraction.

NER

The word "named entity" was coined for the Sixth Message Understanding Conference (MUC-6) and is now commonly used in NLP (Grishman and Sundheim, 1996). During that period, MUC primarily focused on IE tasks that involved extracting structured information about client operations and associated security measures from unstructured text sources, such as newspaper articles. In the process of defining these tasks, it became evident that the identification of information entities, such as personal, organizational, and geographical names, as well as numerical expressions, such as time, date, monetary values, and percentages, was crucial.

The task of NER involves identifying specific entities within the text, such as individuals, locations, organizations, drugs, time expressions, clinical procedures, and biological proteins. NER systems are commonly employed as an initial step in various tasks, including question answering, information retrieval, coreference resolution, and topic modeling.

NER is the process of identifying terms in biomedical texts. It was also used in biomedical texts. This task consists of three stages: (1) term recognition, (2) term mapping, and (3) term classification (Li, 2011). For example, in the sentence "Methadone works very well for chronic pain," methadone and chronic pain should be known in the first phase. In the classification stage, they are classified into pre-defined groups, which are the name and symptoms of the drug in this case. A final step is to map these meanings to medical definitions using lexicons such as the Unified Medical Language System (UMLS) Metathesaurus.

Although this task appears simple on the surface, there are many challenging issues in the biomedical domain that should be considered, including name variation, extensive use of acronyms and abbreviations, lack of a complete dictionary, and context-dependence of language. However, NER systems exhibit high accuracy in their results, as recent community-wide evaluations have shown (Simpson and Demner-Fushman, 2012). Nevertheless, existing systems are not sufficient to address all long-term extraction problems. Therefore, it would be helpful to know the NER approaches and their limitations. The following includes discussing NER.

Dictionary-based algorithm

The dictionary-based algorithm uses exact or partially matching terms with words or phrases in a given biomedical lexicon. This algorithm is sensitive to spelling mistakes, homonymy, and morphological variants. Although some schemes are applied to resolve these problems, this method is often used in combination with the other methods.

Rule-based approach

The earliest NER systems used common rule-based methods (Zweigenbaum, et al., 2007). These systems define some rules to show the patterns of medical target terms and their contexts. Rule-based approaches outperform dictionary-based approaches in many cases due to the consideration of context and the definition of detailed rules for extraction. However, the manual generation of these rules takes time but is a one-time effort, and they are very specific and are not extensible to other entity extractions.

 http://dx.doi.org/10.14500/aro.11388

ML-based approach

With the growth of available annotated corpora, ML-based approaches have been converted into a common approach in the NER problem, either as a standalone solution or in combination with other techniques in a supervised or semisupervised manner and classification-based (using NB and SVM) or sequence-based Hidden Markov Model (HMM), Maximum Entropy (ME), and Conditional Random Fields (CRF). (Cohen and Hersh, 2005; Simpson and Demner-Fushman, 2012; Simpson and Demner-Fushman, 2012).

Side effect extraction

Defining side effect extraction is a common NER issue that is used in biomedical literature for pharmacovigilance and recently in biomedical opinion analysis for drug reviews. Some works cited by Li (2011) show the importance of patient-reported side effects in pharmacovigilance. On the basis of these observations, Li proposes a statistical algorithm to identify adverse reactions to cholesterol-lowering drugs taken from five websites in drug reports. To do so, he compares the word distributions of reviews of statin drugs with those of non-statin drugs using statistical NLP techniques such as pointwise mutual information and log likelihood. Having a distinction will assess the side effects that are more associated with statin drugs than other reducing cholesterol medications. In fact, this method also discriminates patient pre-condition from special drug side effects, since patient pre-condition is common in all cholesterol-reducing drugs and will be eliminated. For example, in the sentence 'I took Lipitor because I had high cholesterol, but it caused muscle aches', this system does not detect 'high cholesterol' as a side effect because it is often reviewed in other reviews of cholesterol-lowering drugs. However, this work has some limitations. First, it should focus on two types of drugs for one disease. Second, it omits the common side effects of one disease drug, so it is not applicable to discovering all the side effects of one particular drug. In another work, Skentzos, et al. (2011) used TextMiner to find an adverse reaction to statin drugs in the electronic medical records of patients.

In another work, Yalamanchi (2011) developed a query-based side effect extraction system from drug reviews at the site "www.askapatient.com" called Sideffective. In this system, they use a BigHugeLabs thesaurus service to recursively build a complete side effect lexicon from small training data. This system's main drawback is that it does not discriminate between drug side effects and symptoms of the disease.

Relation extraction

The objective of the extraction relationship is to determine the presence of a relationship between a couple of entities. Although the type of entity is typically very specific (that is, drugs), the relationship type can be very general (that is, any biomedical association) or very specific (that is, a regulatory relationship) (Cohen and Hersh, 2005). Most of the work in this field focuses on relational extraction between genes, proteins, and other kinds of relationships (Cohen and Hersh, 2005). Approaches to relational extraction fall into four categories: statistically based, rule-based, classification-based, and NLP-based methods.

In the first, it will include insight into some types of relations that are more related to side effect extraction in the next two sections, and then it will discuss relation extraction methods in the following sections.

Drug–symptom relation

The drug–symptom relation is an example of many associations between entities in the medical domain, such that its detection is essential for many biomedical systems such as pharmacovigilance and, in particular, for drug review sentiment analysis systems.

In a medical text, drug–symptom association is subdivided into 3 categories as follows (Wang, Tsujii and Ananiadou, 2010):

1. Treat relation: A drug is taken to cure a disease or symptom (that is, methadone and pain).
2. Cause relation: A drug causes a symptom (that is, methadone and nausea).
3. Indirect treatment relationship: A drug treats a disease (that is, rosiglitazone, diabetes, and polyuria).

In short, a drug and symptom are related to each other in a treatment or cause relationship. A side effect is a symptom that participates in a causal relationship with a particular drug, that is, nausea for methadone.

Disease–symptom relation

Similarly, this researcher can see the problem from the perspective of the disease and its relationship with the symptom (Wang, Tsujii and Ananiadou, 2010) and divide this relation into 3 groups as follows:

1. Manifestation relation: A symptom is a direct sign of disease (that is, migraine and headache).
2. Indirect manifestation relationship refers to the scenario where a symptom serves as an indication of a disease that has a strong association with the target disease. For example, chest pain can be considered a symptom that is closely linked to diseases like diabetes and heart disease.
3. Treatment-induced relationship: The sign is caused by a procedure or treatment (that is, clinical depression, imipramine, and fever).

Among these three groups, the first two groups show disease symptoms and should not be considered drug side effects. The third relationship can show drug side effects in some situations in which the drug has performed the treatment procedure. For example, in the above example, 'fever' is the side effect of 'Imipramine' (an antidepressant drug). Therefore, the symptoms in the last case should be considered a side effect.

Statistical methods

The essence of these methods is using the co-occurrence degree of two entities to detect the relationship between them. The research in Cao, Hripcsak and Markatou (2007) is an example of using co-occurrence measures to detect the association between clinical entities.

The main advantage of this technique is its simplicity. However, in most cases, it is not possible to use this method alone to detect the type and direction of the association. In fact, the high co-occurrence of two entities just shows the existence of a relationship and nothing more. An additional problem inherent in this method is the lack of equivalency between statistical and medical associations in some cases.

These two drawbacks make these methods inconvenient for detecting a special type of disease symptom or drug symptom.

Classification

These types of algorithms use supervised ML to detect the association between entities using lexical, syntactic, and semantic features. This approach can be used to detect a special relationship between a drug or disease and symptoms by defining the appropriate features for the training phase.

NLP based

Large progress in terms of extraction techniques has been made (Zweigenbaum, et al., 2007). In these techniques, the syntactic structure of the biomedical text, which can be made of a dependency analyzer, is utilized to find the grammatical relationship among two biomedical entities.

Event extraction

Event extraction is a task of text mining in the biomedical scope. It is the process of extracting interactions between biomedical entities and their consequences. Simple verbs are typically utilized to detect events. For example, in the sentence "In E. Coli, glnAP2 can be activated by NifA", the verb 'activated' is the event, and the event cases are 'In E. Coli", "glnAP2", "NifA" (Ananiadou, et al., 2010).

Knowledge of resources and tools

The main difference between the biomedical field and other areas is the broad scale of knowledge, resources, and methods. The UMLS is a set of biomedical lexicons and instruments that have been created by the US National Library of Medicine (NLM) (Li, 2011). This collection, which is extensively used by researchers, provides a Metathesaurus, a semantic network, and a lexicon that contains biomedical terms and common English words (Simpson and Demner-Fushman, 2012). The UMLS Metathesaurus, the most extensive biomedical thesaurus, contains about 1.7 million biomedical terms, and each of the 134 semantic categories is assigned to at least one. Such semantic types are grouped into 15 semantic groups (Denecke and Nejdl, 2009).

The mapping of words or phrases to UMLS concepts is very common in biomedical literature. To achieve this goal, most medical systems, such as SeReMeD, use MetaMap. MetaMap is an NLM-configurable program that automatically maps biomedical text to Metathesaurus concepts (Aronson, 2001).

Detection using a combined approach

The extraction of some meaningful, specific associations is a challenging issue in the biomedical research area. Few studies have been conducted on clinical texts, and drug reviews have remained almost unexplored in this research direction until now.

Discrimination of disease (magnetic resonance spectroscopy) and drug (adverse drug event [ADE]): Methods and applications

Recommend a combination of approaches to NLP and approaches to statistics (Wang, Tsujii and Ananiadou, 2010). For electronic health reports, they use co-occurrence to track two signs of disease and an ADE. They use the EHR structural function to resolve the limitations of statistical methods and assess the form of relationships based on the section in which they occur. Although performance improvements are demonstrated using section-by-section filtering, the unstructured narrative analysis of drugs does not apply to this method. In a different statistical way (Li, 2011), they extract non-statin and statin cholesterol side effects by reducing the drug, taking into account the difference between the pre-condition of the patient and the side effects. They filter the pre-conditions of patients by removing symptoms that occur in both statin and non-statin drug reviews. In addition, another study (Weeber, et al., 2000) developed a system called the DAD, which uses the rules of association to detect adverse reactions to drugs.

III. ADR Detection Techniques

A. ML Techniques

ML plays a vital role in accurately categorizing text through the use of supervised or unsupervised methods. The challenge lies in choosing the most suitable approach for a given sentiment analysis task. For example, when the objective is to classify opinionated documents into positive or negative categories, supervised learning is more effective as it can handle pre-defined class labels. Conversely, if the task involves analyzing text and classifying nouns, adjectives, and adverbs, unsupervised learning is more suitable. This section will explore recently proposed techniques for sentiment analysis, utilizing both supervised and unsupervised learning techniques.

Supervised learning

Supervised learning is aimed at training the data to identify specific patterns during the testing phase. In the context of sentiment analysis, this becomes highly useful as the data can be trained to identify patterns that show whether an opinion is positive or negative. Several supervised learning techniques, such as NB, SVM, and K-nearest neighbor, can be applied efficiently in sentiment analysis.

NB

This is one of the commonly used classifiers for SA (Tan, et al., 2009), which mimics statistics to build a probabilistic model (Thabtah, et al., 2009) for the individual examination of each feature. This can be represented through the identification of the presence and absence of each character in a given case (Huang, Lu and Ling, 2003). Referring to SA, this classifier searches a document for the presence or absence of words (Govindarajan, 2013).

The Naive Bayes classifier exists in two forms: multinomial model and the multivariate Bernoulli model. The aim of the multinomial model is to address the existence of opinion words with respect to their presence or absence in the considered text, while the multivariate Bernoulli model examines the frequency of occurrence of the opinion words in a text. As per Huang, Lu and Ling (2003), the multivariate Bernoulli model handles relatively small data more efficiently than the multinomial model.

The study by Yu and Hatzivassiloglou (2003) presented an NB-based subjectivity identification approach for the classification of opinionated sentences. They used the NB classifier to classify such sentences as positive or negative. Similarly, Zhang, et al. (2011) comparatively studied the performance of NB and SVM classifiers in the classification of opinions into classes (positive and negative). From the analysis, they reported better performance of the NB classifier compared to the SVM classifier. Another study by Moghaddam and Ester (2012) compared the performance of KNN, NB, and SVM classifiers for sentiment analysis and reported that the SVM classifier outperformed the NB and KNN classifiers.

SVM

The SVM is basically a classifier that relies on labels for linear data classification (Joachims, 1998). This is not an indication of the inability of SVM to handle more than two classes; rather, its training phase is based on two classes (Lee, et al., 2012). In this study, the SVM training will be based on the '1' class label, 'not-1' class label, '2' class label, and not-5 class label. Then, the testing phase will involve mapping new instances to the most similar class label (most proximal to the hyperplane). This hyperplane is a margin that divides the data into two linear groups (Zhang, Yoshida and Tang, 2008). SVM can handle a huge number of features efficiently (Huang, Lu and Ling, 2003).

A study by Somasundaran, et al. (2007) presented an SVM-based subjectivity identification approach for the classification of answers to opinion questions into subjective and objective classes. The proposed method relies on a keyword feature and question type to classify the answers into subjective and objective classes. Another study by Xu, et al. (2011) focused on the identification of comparative correlations between products based on the product's reviews. The authors succeeded in establishing a comparison between SVM and CRF, even though the performance of CRF was reported to be superior to that of SVM. Furthermore, Prabowo and Thelwall (2009) presented the approach of combining a rule-based approach and SVM for the classification of movie reviews into positive and negative classes. The study found a competitive performance of the approach compared to the performance of the baseline study.

Logistic regression (LR)

The LR model defines the linear equation for class probability (Montgomery, Peck and Vining, 2021).

Unsupervised learning

The unsupervised learning techniques show an alternative for ADR detection. These techniques do not require labeled data and instead aim to identify relationships in the data that can be utilized to detect ADRs. There are a lot of unsupervised learning techniques utilized for ADR detection, including clustering, association rule mining, and anomaly detection.

Clustering is a technique that group's similar data points together based on their characteristics. In the context of ADR detection, clustering can be utilized to identify subgroups of patients who are more likely to experience ADRs. In this study, Roitmann, Eriksson and Brunak (2014) utilized clustering to identify subgroups of patients with different patterns of ADRs caused by antibiotics. They found that the clustering approach was able to accurately identify patients who were at high risk for ADRs and that these patients could be trained for closer monitoring or preventive interventions.

Another unsupervised learning technique is association rule mining, which can be utilized for ADR detection. This technique is used to detect patterns in the data, like the association between a drug and an ADR. This study (Sangma, Anal and Pal, 2020) proposed association rule mining to identify associations between drugs and ADRs in a large EHR dataset. They found that the association rule mining method was able to identify various previously unknown drug-ADR associations, which could be used to improve the safety of drug prescribing.

Anomaly detection is utilized to detect data points that turn from the model. In the context of the detection of ADR, anomaly detection can be used to detect patients who have experienced unusual or unexpected ADRs. For example, a study by Bijlani, Nilforooshan and Kouchaki (2022) used anomaly detection to identify patients who experienced ADRs that were not listed in the package inset for a particular drug. They found that the anomaly detection method was able to identify a number of previously unknown ADRs, which could be used to improve the safety of drug prescribing.

B. Deep Learning (DL) Techniques

DL techniques are an important field in medical informatics, particularly for their ability to analyze large volumes of unstructured data, such as EHRs and social media posts, to identify ADRs. ADRs are defined as unintended and harmful effects of drugs, and they are a major public health concern, leading to hospitalization and even death.

Conventionally, ADR detection has been done through methods such as spontaneous reporting systems and clinical trials. However, these methods are often time-consuming and have low sensitivity, leading to the underreporting of ADRs. With the advent of digital health and the increasing availability of large amounts of data, there is an opportunity to use DL techniques to improve ADR detection.

One of the most popular DL techniques used in ADR detection is convolutional neural networks (CNNs). CNNs are particularly useful for analyzing text data, such as EHRs, and have been shown to be effective in identifying ADRs from free text notes. A study by Shen, et al. (2019) used CNN to identify ADRs.

Another DL technique that has been used in ADR detection is recurrent neural networks (RNNs). RNNs are particularly useful for analyzing sequential data, such as social media posts, and have been used to identify ADRs from social media data. In a study by Zhang and Geng (2019), RNNs analyzed social media posts and identified ADRs.

In addition to CNNs and RNNs, other DL techniques such as deep belief networks, deep neural networks, and long short-term memory networks have also been used in ADR detection. These techniques have been shown to be effective in identifying ADRs from various types of data, such as EHRs, social media posts, and clinical trial data.

To further improve the performance of ADR detection, some studies have used DL techniques in combination with other methods, such as NLP and feature engineering. For example, a study by Zhang, et al. (2020) used a combination of NLP and a DL model to extract ADR-related information from EHRs.

C. NLP

Clinical information is not accessible for pharmacovigilance applications in narrative reports, and it is buried either in the scientific literature or in clinical narrative studies. High-throughput technology, NLP, has been applied for decades in biomedicine. The NLP systems were developed for the identification, extraction, and encoding of biomedical literature and then clinical narratives (Davis, 1965). Some NLP techniques have also been applied to identify ADE from EHR systems (Aronson, 2001; Bates, et al., 2003; Honigman, et al., 2001; and Rindflesch and Fiszman, 2003). However, these concentrate on ADE identification and patient protection, not on information discovery and pharmacovigilance.

An increasing number of researchers are focusing on establishing links and extracting between entities from textual data, and NLP has become an essential part of the automatic extraction of relations and entities during documents (Rebholz-Schuhmann, et al., 2007). Co-occurrence statistics are most commonly used to determine entity relationships and have been shown to be effective in acquiring associations between biological and clinical entities (Cohen and Hunter, 2008; Narayanasamy, et al., 2004).

Latent semantic analysis (LSA) is a technique used to detect ADRs in EHRs. LSA is a type of NLP method that is used to analyze unstructured text data and extract useful information. It works by identifying patterns and relationships between words in a text and grouping similar words together. This allows LSA to identify ADRs by detecting patterns in patient EHRs. LSA can be used to identify ADRs that may have been missed by traditional detection methods such as spontaneous reporting or active surveillance. In addition, LSA can help identify potential ADRs that may be associated with new medications by analyzing the literature and clinical trial data (Nafea, Omar and Al-Ani, 2021).

D. Data mining

This study (Roddick, Fule and Graco, 2003) presented observations on the application of exploratory data mining techniques to scientific and clinical data. This enabled the authors to raise a number of general issues and provide indicators from a broad perspective of possible future research areas in data mining and knowledge discovery (Hanauer, 2007). This study discusses the difficulties and resolutions encountered in conducting research and providing patient care through the analysis of electronic data. The figures from the Michigan health statistics system were used for their study, but the author was concerned and focused on the challenges involved in text mining alone. The challenges the author inferred included asserting accurate diagnosis and processing EHRs in the natural language (Hanauer, 2007).

IV. Challenges in ADR Detection

ADRs are a significant concern in the health-care industry, as they often lead to patient harm, increased health-care costs, and regulatory burdens. Detecting ADR with a timely approach is important for ensuring patient safety and efficiently observing the use of drugs. The process of ADR detection comes with various challenges that require the implementation of innovative approaches and techniques. This study shows the primary challenges in ADR detection techniques.

One major problem in ADR detection is the underreporting of adverse events. Health-care professionals frequently fail to report ADRs due to reasons like a lack of awareness, time constraints, fear of liability, or the observation that ADRs are expected outcomes. Consequently, this leads to incomplete and biased data, which hampers the detection process. Addressing underreporting requires initiatives to improve reporting systems, enhance awareness among health-care professionals, and foster a culture of reporting ADRs.

Another challenge in ADR detection is the heterogeneity and integration of the data. ADRs can be reported from many sources, including spontaneous reporting systems, EHRs, social media, scientific literature, and clinical trials. Each data source has its own limitations, biases, and data formats. Effectively integrating heterogeneous data from multiple sources when considering data quality, reliability, and standardization is a significant challenge. Advanced techniques such as data integration, NLP, and ML approaches are being developed to overcome this challenge.

Signal detection and noise present a fundamental challenge in ADR detection. It is difficult to identify meaningful signals from large volumes of noisy data due to the abundance of unrelated events, confounding factors, and background noise. Distinguishing true ADRs from coincidental associations becomes challenging. To address this, various signal detection methods, such as disproportionality analysis, data mining algorithms, and statistical modeling, are employed to improve the signal-to-noise ratio and accurately identify potential ADRs.

Establishing a temporal relationship and assessing causality between drug exposure and ADR occurrence is crucial in ADR detection. However, real-world data often present complex relationships due to factors such as delayed ADR onset, multiple drug exposures, and confounding variables. Differentiating between ADRs, pre-existing conditions, and other events becomes a challenge, making causality assessment difficult. Robust methods for analyzing temporal relationships and assessing causality are essential for accurate ADR detection.

The detection of rare and long-term ADRs poses additional challenges. Many ADRs are rare or occur after prolonged drug exposure, making their detection challenging. Traditional ADR detection methods may not adequately capture these events due to limited sample sizes or short monitoring periods. Innovative techniques, such as data mining algorithms, predictive modeling, and active surveillance systems are being explored to improve the

 http://dx.doi.org/10.14500/aro.11388

detection of rare and long-term ADRs.

Ethical and privacy concerns are integral to ADR detection. ADRs involve sensitive patient health information, raising ethical and privacy considerations. Striking a balance between the need for ADR detection and patient privacy and confidentiality is a significant challenge. Strict data anonymization and de-identification techniques, secure data sharing frameworks, and adherence to regulatory guidelines are necessary to ensure patient privacy when facilitating ADR detection research.

V. Discussion

As shown in Table I, a comparison between the techniques utilized to discover the side effect of a drug through our study shows that many studies rely on ML and DL to extract the side effect of a drug (Yates and Goharian, 2013; Emadzadeh, et al., 2018; Akhtyamova, Alexandrov and Cardiff, 2017; andCocos, Fiks and Masino, 2017; and Lee, et al., 2017). This review shows that the identification of adverse drug effects relies on

TABLE I
A Comparison between ADR Techniques

Author	Year	Method	Features	Data	F-measure
Yates and Goharian (2013)	2013	Rule-based	Trigger terms	Benchmark dataset	0.78
Pain, et al. (2016)	2016	SVM	Trigger terms	Twitter data	0.94
Ebrahimi, et al. (2016)	2016	SVM	Trigger terms+Medical Concepts	Drug websites	0.55
Plachouras, Leidner and Garrow (2016)	2016	SVM	Trigger terms+Gazetteers	Twitter data	0.60
Emadzadeh, et al. (2018)	2017	SVM	HAS	Twitter data	0.62
Akhtyamova, Alexandrov and Cardiff (2017)	2017	CNN	word2vec embedding	Twitter data	0.54
Cocos, Fiks and Masino (2017)	2017	RNN	Word-embedding vectors	Twitter data	0.75
Lee, et al. (2017)	2017	CNN	word2vec	Twitter data	0.64
Wang, et al. (2018)	2018	WSVM	combination of synthetic oversampling techniques and under-sampling performs	Twitter	0.42
Kiritchenko, et al. (no date)	2018	SVM	Domain-specific trigger terms	Twitter data	0.43
Yousef, Tiun and Omar (2019)	2019	SVM, LR, NB	Syntactic trigger terms	Dataset from Yates and Goharian (2013) updated by Yousef, Tiun and Omar (2019)	0.69
Wang, et al. (2019)	2019	DNN	Word-embedding	SIDER	0.84
Dai and Wang (2019)	2019	Vote-based undersampling (VUE) and random under-sampling boosting	WESMOTE	Imbalanced social media	0.49
Odeh and Taweel (2019)	2019	CNN	domain and semantic	Twitter posts ADE data	0.60 0.76
Yousef, et al. (2020)	2020	RNN	document embedding	medical sentiments data	0.90
Zhang, et al. (2020)	2020	CNN	GICN	TwiMed- Twitter	0.83
Yousef, et al. (2020)	2020	SVM, LR, NB	Lexicon replacement	medical review	0.87
Li, et al. (2020)	2020	Adversarial transfer learning	Private CNN	TwiMed	0.67
Fan, Fan and Smith (2020)	2020	BERT	Word-embedding	WebMD and Drugs.com	0.97
Zhang, Cui and Gao (2020)	2020	SVM, LR, NB, RF	The shallow linguistic feature set and a deep linguistic feature	Twitter	0.94
Zhang, et al. (2021)	2021	Adversarial transfer learning	Bi-LSTM	Twitter	0.68
Shen, et al. (2021)	2021	GAR framework	Word-embedding	TwitterADR	0.74
Nafea, Omar and AL-Ani (2021)	2021	SVM, LR, NB	LSA	Dataset from Yates and Goharian (2013) updated by Yousef, Tiun and Omar (2019)	0.82
Nafea, Omar and Al-qfail (2023)	2023	ANN	LSA	Dataset from Yates and Goharian (2013) updated by Yousef, Tiun and Omar (2019)	0.85
Nafea, et al. (2024)		Ensemble model	Point-wise mutual information	Dataset from Yates and Goharian (2013) updated by Yousef, Tiun and Omar (2019)	0.89

ADR: Adverse drug reactions, SVM: Support vector machine, CNN: Convolutional neural networks, RNN: Recurrent neural networks, WSVM: Wavelet support vector machine, LR: Logistic regression, NB: Naive Bayes, RF: Random forest, GICN: Gated Iterative Capsule Network, BERT: Bidirectional encoder representations from transformers, GAR: Graph adversary representation, ANN: Artificial neural networks, LSA: Latent semantic analysis, WESMOTE: Word embedding-based synthetic minority oversampling technique, SIDER: Data from side effect resource, ADE: Adverse drug event, HAS: Hybrid semantic analysis, LSTM: long short-term memory, DNNs: Deep neural networks the use of ML and DL (Zhang, Cui and Gao, 2020; Wang, et al., 2018; Wang, et al., 2019; and Dai and Wang, 2019). The results varied depending on the data, and various methods were used to address them. This review particularly focused on the application of these methods to the task of extracting ADR and highlighted which methods might be suitable for this purpose. Despite the diversity, there are several common elements among the systems (Pain, et al., 2016; Ebrahimi, et al., 2016; Plachouras, Leidner and Garrow, 2016; Emadzadeh, et al., 2018; and Kiritchenko, et al., no date).

According to this study, DL techniques have shown a great approach to the detection of ADR and have been shown to improve the performance of ADR detection methods (Fan, Fan and Smith, 2020). However, more research is needed to address the challenges with DL-based ADR detection, such as the lack of labeled data and the interpretability of models (Zhang, et al., 2021; Li, et al., 2020). The DL techniques for ADR detection are still in the early stages of development, and there are various challenges that need to be addressed. One of the major challenges is the lack of labeled data, which is necessary to train DL models (Shen, et al., 2021), while another challenge is the interpretability of DL models, which is important for understanding the underlying mechanisms of ADRs and making decisions based on the results of the models (Wang, et al., 2019; Odeh and Taweel, 2019; Yousef, et al., 2020; and Zhang, et al., 2020) (Li, et al., 2020; Nafea, Omar and Al-qfail, 2023).

ML is utilized to predict ADRs with various algorithms such as SVM, NB, and LR (Yousef, Tiun and Omar, 2019; Rami Naim Mohammad Yousef, et al., 2020; and Nafea, Omar and Al-Ani, 2021). This study shows that the algorithms can be trained on large datasets of ADRs and drug information to detect patterns and relationships among drugs and ADRs. The results can be utilized to develop predictive models that can help detect patients at risk for ADRs, allowing for earlier intervention and potentially reducing the incidence of ADRs. By utilizing these techniques, ML can assist health-care professionals in detecting ADRs more effectively and efficiently, leading to improved patient outcomes. However, there are several challenges with using ML for ADR detection. The first challenge is that the quality of the data used for training and testing ML models can impact the accuracy of ADR predictions. This includes issues with data completeness, accuracy, and consistency. The second challenge is limited data availability. The availability of high-quality, comprehensive data on ADRs is limited, making it challenging to train ML models with sufficient data to accurately predict ADRs.

Unsupervised learning techniques show alternatives for ADR detection. These techniques do not require labeled data and rather aim to identify patterns and relationships in the data that can be used to detect ADRs. Clustering, association rule mining, and anomaly detection are some of the most common unsupervised learning techniques used for ADR detection. These techniques have been shown to be effective in identifying patients at high risk of ADRs and identifying previously unknown drug-ADR associations.

VI. Conclusion

This review delves into text mining and IE algorithms within the biomedical field, specifically focusing on the detection of ADRs from social media drug reviews. By examining previous research and addressing the challenges integral to ADR detection, as well as discovering biomedical sentiment analysis, this study has gained valuable insights into the complexities of this field. This study shows a comprehensive survey of ADRs extracted from drug review sentences on social networks, employing various techniques and methodologies. Looking ahead, there are promising avenues for future research. This research proposes the utilization of active learning and transfer learning methodologies to augment the performance of ADR detection models. These advanced techniques offer the potential to enhance the accuracy and reliability of ADR detection within medical opinion-mining systems. By addressing these challenges and incorporating sophisticated methodologies, we anticipate significant improvements in the accuracy and efficiency of ADR detection. This will contribute to enhancing patient safety and health-care outcomes by providing timely and reliable information on drug reactions.

References

Ahmad, S.R., 2003. Adverse drug event monitoring at the Food and Drug Administration. *Journal of General Internal Medicine*, 18(1), pp.57-60.

Akhtyamova, L., Alexandrov, M., and Cardiff, J., 2017. Adverse Drug Extraction in Twitter Data using Convolutional Neural Network. In: *2017 28th International Workshop on Database and Expert Systems Applications (DEXA)*. IEEE, pp.88-92.

Ananiadou, S., Pyysalo, S., Tsujii, J., and Kell, D.B., 2010. Event extraction for systems biology by text mining the literature. *Trends in Biotechnology*, 28(7), pp.381-390.

Aronson, A.R., 2001, Effective mapping of biomedical text to the UMLS Metathesaurus: The MetaMap program. In: *Proceedings of the AMIA Symposium*. American Medical Informatics Association, p.17.

Bates, D.W., Scott Evans, R., Murff, H., Stetson, P.D., Pizziferri, L., and Hripcsak, G., 2003. Detecting adverse events using information technology. *Journal of the American Medical Informatics Association*, 10(2), pp.115-128.

Bijlani, N., Nilforooshan, R., and Kouchaki, S., 2022. An unsupervised data-driven anomaly detection approach for adverse health conditions in people living with dementia: Cohort study. *JMIR Aging*, 5(3), p.e38211.

Cao, H., Hripcsak, G., and Markatou, M., 2007. A statistical methodology for analyzing co-occurrence data from a large sample. *Journal of Biomedical Informatics*, 40(3), pp.343-352.

Cocos, A., Fiks, A.G., and Masino, A.J., 2017. 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), pp.813-821.

Cohen, A.M., Hersh, W.R., 2005. A survey of current work in biomedical text mining. *Briefings in Bioinformatics*, 6(1), pp.57-71.

Cohen, K.B., and Hunter, L., 2008. Getting started in text mining. *PLoS Computational Biology*, 4(1), p.e20.

Dai, H.J., and Wang, C.K., 2019. Classifying adverse drug reactions from imbalanced twitter data. *International Journal of Medical Informatics*, 129, pp.122-132.

Davis, J.M., 1965. Efficacy of tranquilizing and antidepressant drugs. *Archives* *of General Psychiatry*, 13(6), pp.552-572.

De Rosa, M., Fenza, G., Gallo, A., Gallo, M., and Loia, V., 2021. Pharmacovigilance in the era of social media: discovering adverse drug events cross-relating Twitter and PubMed. *Future Generation Computer Systems*, 114, pp.394-402.

Denecke, K., and Nejdl, W., 2009. How valuable is medical social media data? Content analysis of the medical web. *Information Sciences*, 179(12), pp.1870-1880.

Ebrahimi, M., Yazdavar, A., Salim, N., and Eltyeb, S., 2016. Recognition of side effects as implicit-opinion words in drug reviews. *Online Information Review*, 40(7), pp.1018-1032.

Edwards, I.R., and Aronson, J.K., 2000. Adverse drug reactions: Definitions, diagnosis, and management. *The Lancet*, 356(9237), pp.1255-1259.

Emadzadeh, E., Sarker, A., Nikfarjam, A., and Gonzalez, G., 2018. Hybrid semantic analysis for mapping adverse drug reaction mentions in tweets to medical terminology. *The AMIA Annual Symposium*, 2017, pp.679-688.

Fan, B., Fan, W., and Smith, C., 2020. Adverse drug event detection and extraction from open data: A deep learning approach. *Information Processing and Management*, 57(1), p.102131.

Ginn, R., Pimpalkhute, P., and Nikfarjam, A., 2014. Mining Twitter for Adverse Drug Reaction Mentions: A Corpus and Classification Benchmark. In: *Proceedings of the Fourth Workshop on Building and Evaluating Resources for Health and Biomedical Text Processing*. Citeseer, pp.1-8.

Goeuriot, L., Na, J.C., Kyaing, W.Y.M., Foo, S., Khoo, C., Theng, Y.L., and Chang, Y.K., 2011. Textual and informational characteristics of health-related social media content: A study of drug review forums, p. 548-557.

Govindarajan, M., 2013. Sentiment analysis of movie reviews using hybrid method of naive bayes and genetic algorithm. *International Journal of Advanced Computer Research*, 3(4), p.139.

Grishman, R., and Sundheim, B.M., 1996. Message Understanding Conference-6: A Brief History. In: *COLING 1996 Volume 1: The 16th International Conference on Computational Linguistics*.

Gurulingappa, H., Mateen-Rajpu, A., and Toldo, L., 2012. Extraction of potential adverse drug events from medical case reports. *Journal of Biomedical Semantics*. *Journal of Biomedical Semantics*, 3(1), pp.15.

Hacker, M., 2009. Adverse drug reactions. In: *Pharmacology*. Elsevier, Netherlands, pp.327-352.

Hanauer, D., 2007. *Mining Clinical Electronic Data for Research and Patient Care: Challenges and Solutions*. Clinical Assistant Professor University of Michigan, USA.

Harpaz, R., DuMouchel, W., Shah, N.H., Madigan, D., Ryan, P., and Friedman, C., 2012. Novel data-mining methodologies for adverse drug event discovery and analysis. *Clinical Pharmacology and Therapeutics*, 91(6), pp.1010-1021.

Honigman, B., Lee, J., Rothschild, J., Light, P., Pulling, R.M., Yu, T., Bates, D.W., 2001. Using computerized data to identify adverse drug events in outpatients. *Journal of the American Medical Informatics Association*, 8(3), pp.254-266.

Huang, J., Lu, J., and Ling, C.X., 2003. Comparing Naive Bayes, Decision Trees, and SVM with AUC and Accuracy. In: *Third IEEE International Conference on Data Mining*. IEEE, pp.553-556.

Joachims, T., 1998. Text Categorization with Support Vector Machines: Learning with Many Relevant Features. In: *European Conference on Machine Learning*. Springer, Berlin, pp.137-142.

Kiritchenko, S., Mohammad, S.M., Morin, J., and de Bruijn, B., 2018. NRC-Canada at SMM4H shared task: Classifying Tweets mentioning adverse drug reactions and medication intake. *arXiv preprint arXiv:1805.04558*.

Kiritchenko, S., Zhu, X., and Mohammad, S.M., 2014. Sentiment analysis of short informal texts. *Journal of Artificial Intelligence Research*, 50, pp.723-762.

Lazarou, J., Pomeranz, B.H., and Corey, P.N., 1998. Incidence of adverse drug reactions in hospitalized patients: A meta-analysis of prospective studies. *JAMA*, 279(15), pp.1200-1205.

Leaman, R., Wojtulewicz, L., Sullivan, R., Skariah, A., Yang, J., and Gonzalez, G., 2010. Towards Internet-Age Pharmacovigilance: Extracting Adverse Drug Reactions from User Posts to Health-Related Social Networks. In: *Proceedings of the 2010 Workshop on Biomedical Natural Language Processing*, pp.117-125.

Lee, K., Qadir, A., Hasan, S.A., Datla, V., Prakash, A., Liu, J., and Farri, D., 2017. Adverse Drug Event Detection in Tweets with Semi-Supervised Convolutional Neural Networks. In: *Proceedings of the 26th International Conference on World Wide Web*, pp.705-714.

Lee, L.H., Wan, C.H., Rajkumar, R., and Isa, D., 2012. An enhanced support vector machine classification framework by using Euclidean distance function for text document categorization. *Applied Intelligence*, 37(1), pp.80-99.

Li, Y.A., 2011. *Medical Data Mining: Improving Information Accessibility Using Online Patient Drug Reviews*. Massachusetts Institute of Technology, Cambridge.

Li, Z., Yang, Z., Luo, L., Xiang, Y., and Lin, H., 2020. Exploiting adversarial transfer learning for adverse drug reaction detection from texts. *Journal of Biomedical Informatics*, 106, p.103431.

Liu, Y., Bi, J.W., and Fan, Z.P., 2017. Ranking products through online reviews: A method based on sentiment analysis technique and intuitionistic fuzzy set theory. *Information Fusion*, 36, pp. 149-161.

Moghaddam, S., and Ester, M., 2012. Aspect-Based Opinion Mining from Online Reviews. In: *Tutorial at SIGIR Conference*.

Montgomery, D.C., Peck, E.A., and Vining, G.G., 2021. *Introduction to Linear Regression Analysis*. John Wiley & Sons, United States.

Nafea, A.A., Ibrahim, M.S., Mukhlif, A.A., AL-Ani, M.M., and Omar, N., 2024. An ensemble model for detection of adverse drug reactions. *ARO-The Scientific Journal of Koya University*, 12(1), pp.41-47.

Nafea, A.A., Omar, N., and AL-Ani, M.M., 2021. Adverse drug reaction detection using latent semantic analysis. *Journal of Computer Science*, 17(10), pp.960-970.

Nafea, A.A., Omar, N., and Al-Qfail, Z.M., 2024. Artificial neural network and latent semantic analysis for adverse drug reaction detection. *Baghdad Science Journal*, 21, pp.226-233.

Narayanasamy, V., Mukhopadhyay, S., Palakal, M., and Potter, D.A., 2004. TransMiner: Mining transitive associations among biological objects from text. *Journal of Biomedical Science*, 11(6), pp.864-873.

Nikfarjam, A., Sarker, A., O'Connor, K., Ginn, R., and Gonzalez, G., 2015. 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), pp.671-681.

Odeh, F., and Taweel, A., 2019. A Deep Learning Approach to Extracting Adverse Drug Reactions. In: *2019 IEEE/ACS 16th International Conference on Computer Systems and Applications (AICCSA)*. IEEE, pp.1-6.

Pain, J., Levacher, J., Quinquenel, A., and Belz, A., 2016. Analysis of Twitter Data for Postmarketing Surveillance in Pharmacovigilanc. In: *Proceedings of the 2nd Workshop on Noisy User-generated Text (WNUT)*, pp.94-101.

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A.K., Walley, T.J., Farrar, K., Park, B.K., and Breckenridge, A.M., 2004. Adverse drug reactions as cause of admission to hospital: Prospective analysis of 18 820 patients. *BMJ*, 329(7456), pp.15-19.

Plachouras, V., Leidner, J.L., and Garrow, A.G., 2016. Quantifying Self-Reported Adverse Drug Events on Twitter: Signal and Topic Analysis. In: *Proceedings of the 7th 2016 International Conference on Social Media and Society*, pp.1-10.

Pouliot, Y., Chiang, A.P., and Butte, A.J., 2011. Predicting adverse drug reactions using publicly available PubChem BioAssay data. *Clinical Pharmacology and Therapeutics*, 90(1), pp.90-99.

Prabowo, R., and Thelwall, M., 2009. Sentiment analysis: A combined approach. *Journal of Informetrics*, 3(2), pp.143-157.

Rebholz-Schuhmann, D., Kirsch, H., Arregui, M., Gaudan, S., Riethoven, M., and Stoehr, P., 2007. EBIMed-text crunching to gather facts for proteins from Medline. *Bioinformatics*, 23(2), pp.e237-e244.

Rindflesch, T.C., and Fiszman, M., 2003. The interaction of domain knowledge and linguistic structure in natural language processing: Interpreting hypernymic propositions in biomedical text. *Journal of Biomedical Informatics*, 36(6), pp.462-477.

Roddick, J.F., Fule, P., and Graco, W.J., 2003. Exploratory medical knowledge discovery: Experiences and issues. *ACM SIGKDD Explorations Newsletter*, 5(1), pp.94-99.

Roitmann, E., Eriksson, R., and Brunak, S., 2014. Patient stratification and identification of adverse event correlations in the space of 1190 drug related adverse events. *Frontiers in Physiology*, 5, p.332.

Sangma, J.W., Anal, S.R.N., and Pal, V., 2020. Clustering-based hybrid approach for identifying quantitative multidimensional associations between patient Attributes, drugs and adverse drug reactions. *Interdisciplinary Sciences: Computational Life Sciences*, 12, pp.237-251.

Sarker, A., and Gonzalez, G., 2015. Portable automatic text classification for adverse drug reaction detection via multi-corpus training. *Journal of Biomedical Informatics*, 53, pp.196-207.

Sarker, A., Ginn, R., Nikfarjam, A., O'Connor, K., Smith, K., Jayaraman, S., Upadhaya, T., and Gonzalez, G., 2015. Utilizing social media data for pharmacovigilance: A review. *Journal of Biomedical Informatics*, 54, pp.202-212.

Shen, C., Li, Z., Chu, Y., and Zhao, Z., 2021. GAR: Graph adversarial representation for adverse drug event detection on Twitter. *Applied Soft Computing*, 106, p.107324.

Shen, C., Lin, H., Guo, K., Xu, K., Yang, Z., and Wang, J., 2019. Detecting adverse drug reactions from social media based on multi-channel convolutional neural networks. *Neural Computing and Applications*, 31, pp.4799-4808.

Simpson, M.S., and Demner-Fushman, D., 2012. Biomedical text mining: A survey of recent progress. In: *Mining Text Data*. Springer, Berlin, pp.465-517.

Skentzos, S., Shubina, M., Plutzky, J., and Turchin, A., 2011. Structured vs. unstructured: Factors affecting adverse drug reaction documentation in an EMR repository. *AMIA Annual Symposium Proceedings*, 2011, p.1270.

Somasundaran, S., Wilson, T., Wiebe, J., and Stoyanov, V., 2007. QA with Attitude: Exploiting Opinion Type Analysis for Improving Question Answering in On-line Discussions and the News. In: *The International AAAI Conference on Web and Social Media*.

Tan, S., Cheng, X., Wang, Y., and Xu, H., 2009. Adapting Naive Bayes to Domain Adaptation for Sentiment Analysis. In: *European Conference on Information Retrieval*. Springer, Berlin, pp.337-349.

Thabtah, F., Eljinini, M.A.H., and Hadi, W.M., 2009. Naïve Bayesian Based on Chi SQUARE to Categorize Arabic Data. In: *Proceedings of the 11th International Business Information Management Association Conference (IBIMA) Conference on Innovation and Knowledge Management in Twin Track Economies, Cairo, Egypt*, pp.4-6.

Wang, C.K., Dai, H., Su, E.C.Y., and Wang, F.D., 2018. Adverse Drug Reaction Post Classification with Imbalanced Classification Techniques. In: *2018 Conference on Technologies and Applications of Artificial Intelligence (TAAI)*. IEEE, pp.5-9.

Wang, C.S., Lin, P.F., Cheng, C.L., Tai, S.H., Yang, Y.H.K., and Chiang, J.H., 2019. Detecting potential adverse drug reactions using a deep neural network model. *Journal of Medical Internet Research*, 21(2), p.e11016.

Wang, X., Tsujii, J., and Ananiadou, S., 2010. Disambiguating the species of biomedical named entities using natural language parsers. *Bioinformatics*, 26(5), pp.661-667.

Weeber, M., Klein, H., Aronson, A.R., Mork, J.G., de Jong-van den Berg, L.T., and Vos, R., 2000. Text-Based Discovery in Biomedicine: The Architecture of the DAD-System. In: *Proceedings of the AMIA Symposium*. American Medical Informatics Association, p. 903.

WHO., 2002. *The Importance of Pharmacovigilance*. WHO, Geneva.

Xu, K., Liao, S.S., Li, J., and Song, Y., 2011. Mining comparative opinions from customer reviews for competitive intelligence. *Decision Support Systems*, 50(4), pp.743-754.

Yadesa, T.M., Kitutu, F.E., Deyno, S., Ogwang, P.E., Tamukong, R., and Alele, P.E., 2021. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: A systematic review and meta-analysis. *SAGE Open Medicine*, 9, p. 20503121211039100.

Yalamanchi, D., 2011. *Sideffective-System to Mine Patient Reviews: Sentiment Analysis*. Rutgers University-Graduate School-New Brunswick, New Jersey.

Yates, A., and Goharian, N., 2013. ADRTrace: Detecting Expected and Unexpected Adverse Drug Reactions from User Reviews on Social Media Sites. In: *Advances in Information Retrieval: 35th European Conference on IR Research, ECIR 2013, Moscow, Russia. Proceedings 35.* Springer Berlin Heidelberg, pp.816-819.

Yousef, R.N.M., Tiun, S., and Omar, N., 2019. Extended trigger terms for extracting adverse drug reactions in social media texts. *Journal of Computer Science*, 15(6), pp.873-879.

Yousef, R.N.M., Tiun, S., Omar, N., and Alshari, E.M., 2020. Enhance medical sentiment vectors through document embedding using recurrent neural network. *International Journal of Advanced Computer Science and Applications*, 11(4).

Yousef, R.N.M., Tiun, S., Omar, N., and Alshari, E.M., 2020. Lexicon replacement method using word embedding technique for extracting adverse drug reaction. *International Journal of Technology Management and Information System*, 2(1), pp.113-122.

Yu, H., and Hatzivassiloglou, V., 2003. Towards Answering Opinion Questions: Separating Facts from Opinions and Identifying the Polarity of Opinion Sentences. In: *Proceedings of the 2003 Conference on Empirical Methods in Natural Language Processing*, pp.129-136.

Zhang, M., and Geng, G., 2019. Adverse drug event detection using a weakly supervised convolutional neural network and recurrent neural network model. *Information*, 10(9), p.276.

Zhang, T., Lin, H., Ren, Y., Yang, Z., Wang, J., Duan, X., and Xu, B., 2021. Identifying adverse drug reaction entities from social media with adversarial transfer learning model. *Neurocomputing*, 453, pp.254-262.

Zhang, T., Lin, H., Xu, B., Ren, Y., Yang, Z., Wang, J., and Duan, X., 2020. Gated Iterative Capsule Network for Adverse Drug Reaction Detection from Social Media. In: *2020 IEEE International Conference on Bioinformatics and Biomedicine (BIBM)*. IEEE, pp.387-390.

Zhang, W., Peissig, P., Kuang, Z., and Page, D., 2020. Adverse Drug Reaction Discovery from Electronic Health Records with Deep Neural Networks. In: *Proceedings of the ACM Conference on Health, Inference, and Learning*, pp.30-39.

Zhang, W., Yoshida, T., and Tang, X., 2008. Text classification based on multi-word with support vector machine. *Knowledge-Based Systems*, 21(8), pp.879-886.

Zhang, Y., Cui, S., and Gao, H., 2020. Adverse drug reaction detection on social media with deep linguistic features. *Journal of Biomedical Informatics*, 106, p.103437.

Zhang, Z., Ye, Q., Zhang, Z., and Li, Y., 2011. Sentiment classification of Internet restaurant reviews written in Cantonese. *Expert Systems with Applications*, 38(6), pp.7674-7682.

Zweigenbaum, P., Demner-Fushman, D., Yu, H., and Cohen, K.B., 2007. Frontiers of biomedical text mining: Current progress. *Briefings in Bioinformatics*, 8(5), pp.358-375.