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Article

Text Mining Analysis of Metoclopramide Reviews: Adverse Effects, Patients' Perspectives and Off-label Use

Lochana Menikarachchi[1], Malith Jayantha[1]

[1] Department of Pharmacy, Faculty of Allied Health Sciences, University of Peradeniya, Sri Lanka

* Correspondence: lochanac@ahs.pdn.ac.lk

Abstract: Background: User-generated online drug reviews can give insights into patients' perspectives on drug therapy and adverse reactions. This information can also be used to augment traditional pharmacovigilance systems that suffer from underreporting. The goal of this study was to analyze adverse effects, patients' perspectives and off-label uses of metoclopramide through text mining. **Methods:** User reported drug reviews on metoclopramide were obtained from two online health forums (Drugs.com and WebMD.com) through web scraping. The raw data were preprocessed and analyzed with text mining techniques such as bag-of-words analysis and sentimental analysis. Visual data analysis techniques such as word clouds and bar plots were used to draw important conclusions from the data. **Results:** Migraine and nausea were the most reported indications in Drugs.com and WebMD.com datasets, respectively. Text analytics show both FDA approved and off-label uses of metoclopramide. Anxiety and spasm were the most frequently reported adverse reactions in Drugs.com and WebMD.com datasets, respectively. Sentimental analysis showed that about 66% of the reviews on Drugs.com were negative, while 34% were positive. The analysis of the WebMD.com dataset revealed a similar finding with 64% negative reviews and 36% positive reviews. **Conclusions:** User reported adverse reactions on both health forums were consistent with known adverse reactions of metoclopramide. They included both mild (drowsiness, sleepiness, dizziness, fatigue, tiredness, bloating, diarrhea) and severe adverse reactions such as movement disorders (spasm, dyskinesia, Parkinson like symptoms) and psychiatric disorders (anxiety, confusion, panic, restlessness, depression). Patients' perspectives toward metoclopramide therapy were generally negative. Text analytics also revealed several off-label uses (migraine and hyperemesis) of metoclopramide.

Keywords: Adverse Effects; Metoclopramide; Pharmacovigilance; Text Mining; NLP

Introduction

According to World Health Organization (WHO), an adverse drug reaction (ADR) is an unintended, noxious reaction caused by a drug taken under normal conditions (1). The average per year cost for ADRs in the United States is around 30 billion dollars (2). Each year, an estimated 2 million patients in the US are affected by serious ADRs (3). These ADRs lead to approximately 100,000 fatalities making it the fourth leading cause of death in the US (3, 4). Other nations, both developed and developing face a similar burden due to ADRs (5, 6).

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects and any other drug-related problems are known as pharmacovigilance. Pharmacovigilance

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starts during clinical trials and continues after a drug is released into the market. However, due to the limitations of the clinical trials and the voluntary nature of reporting of ADRs post-marketing by healthcare professionals and the public, many noxious reactions go undetected leading to hospital admissions, emergency hospital visits and deaths (6). Thus, post-marketing surveillance of drugs remains a major concern for both drug manufacturers and regulatory bodies such as U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and WHO. Despite many developed and developing countries having national agencies for pharmacovigilance, underreporting is common. A review of 37 studies in 12 countries including the US, Canada and European countries by Hazell et al. revealed that only 6% of all ADRs are reported (7). The ADR reporting situation is much worse in developing countries. According to Uppsala Monitoring Center (UMC) and WHO, ADR reports from developing countries accounted for only 10.2% and 9% of the total reports, respectively (8). This is despite having 80% of the global population in these countries.

The use of social media for pharmacovigilance has gained increased attention over the last decade (2, 9). Social networks such as Facebook and Twitter have seen massive growth over the past 15 years. In 2018, the number of users on these platforms stood at approximately 2.2 billion and 336 million, respectively (10). According to one estimate, the total number of users on major social media will be over 3 billion by 2021 (10). The use of specialized health-related forums, message boards and social media by the public for health-related activities has also seen massive growth over the last decade. The general public tends to use these platforms for gaining medical information and sharing their experiences with disease conditions and medicines (4, 10–12).

A number of attempts have been made to extract pharmacovigilance signals from social media since 2009 (4, 13–16). The initial studies in this area focused on specialized health-related forums such as “DailyStrength”, “Yahoo Health Groups”, “MedHeath”, “AskAPatient” and “Drugs.com” (9). While the amount of data on these specialized forums is limited, they have the advantage of having more relevant adverse drug events (ADEs) data than general social media sites. Social networks such as Twitter and Facebook have a significantly high volume of data compared to health-related forums, but mining these for pharmacovigilance signals is challenging as they contain a lot of irrelevant drug-related information generated by drug manufacturers, marketers and bots (9, 11, 16).

Data mining is the process of extracting and discovering patterns in large data sets. It often involves database techniques, statistics and machine learning. Text mining is a subset of data mining that involves extracting useful information from textual data.

The goal of this study was to analyze adverse effects, patients’ perspectives and off-label uses of metoclopramide through text mining. Metoclopramide was randomly selected from the WHO’s list of essential medicines for the current study. It is among the 100 most prescribed drugs in the U.S. with more than one million prescriptions per year. Metoclopramide is an antiemetic agent and dopamine D2 antagonist prescribed for gastrointestinal disorders. It is also used to treat migraine headaches. Common side effects of metoclopramide include tiredness, diarrhea, restlessness, depression and movement disorder like tardive dyskinesia.

Materials and Methods

1. Selection of Online Health Forums

User reviews and other metadata on metoclopramide were obtained from Drugs.com (accessed on May 21, 2022, 04.30 GMT) and WebMD.com (accessed on May 27, 2022, 04.06 GMT). Drugs.com intended mainly for the U.S. market is owned and operated by the Drugsite Trust in New Zealand (17). It is the largest and most widely visited independent medicine information website on the internet. Drugs.com attracts more than 20 million visitors per month. Its peer-reviewed drug information database is powered by several independent leading medical-information suppliers such as the American Society of Health-System Pharmacists, Cerner Multum and IBM Watson Micromedex. Drugs.com also publishes health-related content from Harvard Health Publications and Mayo Clinic.

WebMD is an American corporation well known for its medical related publications such as patient directed health magazines and physician directed training materials and services such as Medscape (18). On average, WebMD attracts more than 175 million unique visitors per month. Both Drugs.com and WebMD.com have drug rankings and reviews written by patients.

2. *Web Scraping*

Web scraping or web harvesting is the process of extracting content and data from a website. Scraping a website manually is often difficult and extremely time consuming. Thus, scraping is done in an automated fashion with a piece of software called a web scraper. Since there is no uniformity among websites, the web scraper should be fed with information related to the structure of the website. This includes what HTML elements and CSS tags make up the web pages and what hyperlinks need to be traversed to collect the required information.

In this study, Webscraper's (webscraper.io) Chrome browser extension was used for scraping metoclopramide related user reviews from Drugs.com and WebMD.com. The data required for the scraping of the website is fed as a sitemap. A sitemap organizes all the information required for scraping a particular website. A sitemap is built with selectors. Selectors tell Webscraper what to do with each element on the website, including extracting a paragraph of text, clicking on a link, or scrolling down the page. Selectors act as the instruction manual for the web scraper. Webscraper's toolbar provides a visual way to create a sitemap by selecting various elements (HTML and CSS) on the website. The selector graph is the visual aid that shows the sitemap hierarchy of selectors graphically.

Two separate sitemaps were created for Drugs.com and WebMD.com. Each sitemap required a name and a start URL which acts as the initial (_root) selector of the sitemap. In order to scrape the Drugbank.com data spanned over 19 pages, the home page URL had to be appended with "/?page= [1-19]" resulting in the start URL, https://www.drugs.com/comments/metoclopramide/?page=[1-19]. A similarly modified start URL was created for scraping WebMD data spanned over 5 pages. The selector graphs for Drugs.com and WebMD.com are shown in Figure 1. The scraped data were exported to two comma separated values (CSV) files. These data files are available from the online Mendeley data repository: Menikarachchi, Lochana; Kokila, Malith (2022), "Evaluating Patients' Perspective on Metoclopramide with Text Mining", Mendeley Data, V1, doi: 10.17632/z72dbrf965.1.

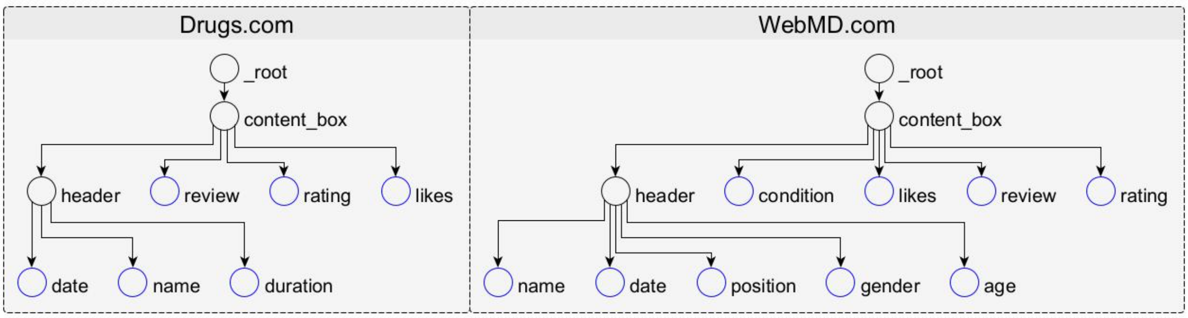

Figure 1. Selector Graphs for Drugs.com and WebMD.com

3. *Text Mining*

Text mining and analysis were done with R statistical software. R package for text mining, "tm" was used for the overall text mining process. The raw data contained in the comma separated values (csv) files were read into the R environment for further processing. The columns containing user reviews were subjected to several preprocessing steps. The raw text was transformed into an intermediate format called "corpus". Corpus is an object containing a collection of unstructured text documents.

Several transformations were applied to the corpus to cleanse input text. These included changing various delimiters to spaces, eliminating extra whitespace, removing punctuations, removing numbers, changing text to lowercase and removing common words in the English language.

The resultant corpus was then subjected to stemming. Stemming is the process of removing suffixes and other word endings in the input text. The word stemming package, "SnowballC" was used for stemming. The stemmed text was subjected to stop word removal. Stop words refer to a set of commonly used words in a language. These words carry little to no useful information for text mining applications. A custom dictionary of stop words was also created to remove unnecessary words. Several text transformations were also applied to convert various forms of the same word into a single form.

A document matrix (a table containing frequencies of words) was formed from the preprocessed corpus. A simple bag-of-words analysis was done with the document matrix. The results were analyzed and visualized with word clouds and bar graphs. R packages, GGPlot2 and GGWordCloud were used for the visual data analysis.

4. Bag-of-Words Analysis

The bag-of-words model is a simplified representation of a text used in natural language processing. In this model, the text is represented by a set of unique words disregarding their order in the text and grammar. Only the multiplicity of the words is kept. A word cloud is a quick and easy approach to analyzing textual data. A word cloud can be used to illustrate the importance of words. A typical word cloud represents more frequent words in a document in a bolder way. Such representations may include eye-catching colors, larger font sizes and bolder fonts. However, word clouds lack analytical accuracy. Other limitations of word clouds include lack of context, inability to capture complex themes and confirmation bias.

5. Sentimental Analysis

Sentiment analysis, also known as opinion mining, is a natural language processing technique used to determine whether the data conveys a positive, negative or a neutral message. A sentiment analysis was also performed on the raw data using the R package, "Syuzhet". Syuzhet is a lexicon-based sentiment analysis software that comes with four different sentiment dictionaries. In our study, the NRC Emotion Lexicon was used (19, 20). This lexicon has been used previously in health-related applications. The NRC Emotion Lexicon contains a list of English words and their associations with eight basic emotions (anger, fear, anticipation, trust, surprise, sadness, joy, and disgust) and two sentiments (negative and positive). The lexicon includes manually annotated 3338 negative records and 2317 positive records.

Results and Discussion

Figures 2 and 3 show the most frequently appeared words in the Drugs.com dataset (cut-off = 9) and WebMD dataset (cut-off = 4), respectively. They include both adverse effects and indications. Whether a word is specified as an adverse drug effect, indication or both was identified by examining the reviews manually. Words in blue indicate indications. Words colored in green indicate adverse effects. If a certain word is used interchangeably to describe both an adverse effect and an indication, it is colored in pink.

Metoclopramide is a dopamine receptor antagonist approved by the FDA to treat nausea and vomiting in patients with diabetic gastroparesis and gastroesophageal reflux disease (GERD) (21, 22). Parenteral use of metoclopramide is also FDA approved to control nausea and vomiting in chemotherapy patients (23). Metoclopramide also has several off-label uses although none of them are explicitly FDA approved. These include prophylactic use of metoclopramide to prevent nausea and vomiting in postoperative patients (24), treatment of acute migraine (25), hyperemesis gravidarum (26, 27) and Diamond Blackfan syndrome (28, 29). It is also used off-label to treat nausea in critically ill advanced liver disease patients (30).

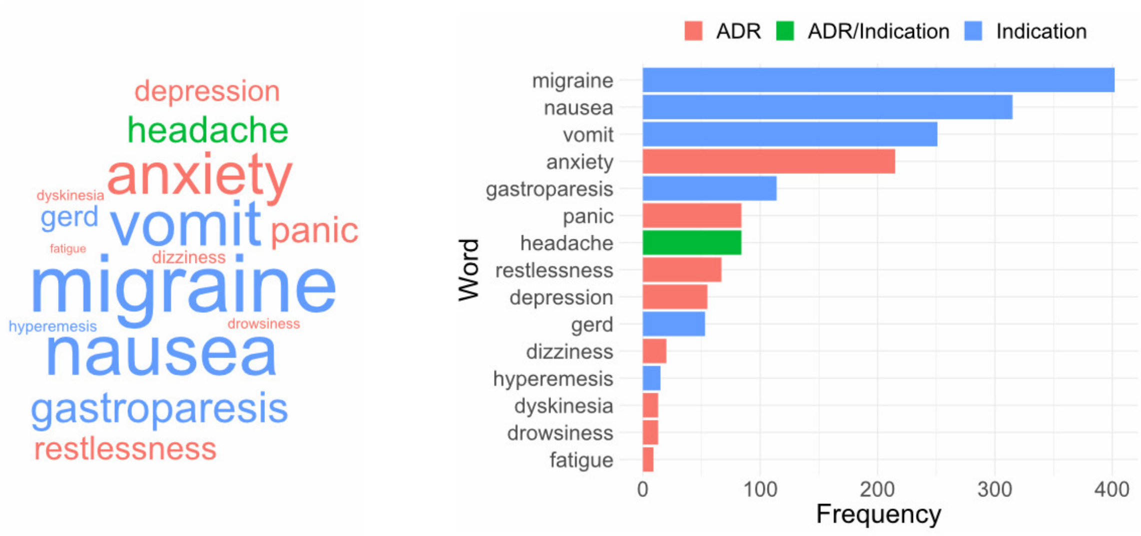

Figure 2. Most frequent words in Drugs.com dataset

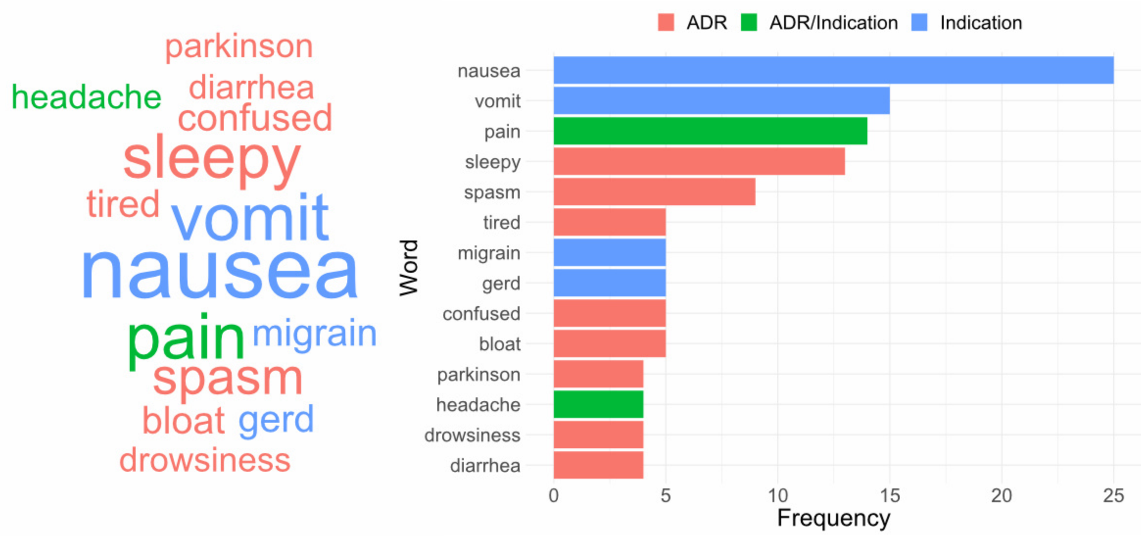

Figure 3. Most frequent words in WebMD.com dataset

Our text analytics data showed both FDA approved and off-label uses of metoclopramide. The most common indication found in the Drugs.com dataset was migraine, an off-label use of metoclopramide. It was followed by other indications such as nausea, vomiting, gastroparesis, GERD and hyperemesis (off-label). Nausea was the most frequent indication found in WebMD.com dataset. Other indications in WebMD.com dataset included vomiting, migraine and GERD. Some patients used the term headache to describe migraine.

Most commonly reported serious adverse reactions of metoclopramide included extrapyramidal movement disorders such as torticollis, trismus, opisthotonos, akathisia, dystonia, oculogyric crisis, laryngospasm, tardive dyskinesia and Parkinson like symptoms (31). Neuroleptic malignant syndrome is another serious but, rare adverse reaction associated with metoclopramide use (32). This can manifest as hyperthermia, lead pipe rigidity, leukocytosis, elevated creatine phosphokinase levels, altered consciousness, symptoms of autonomic instability, diaphoresis, tachycardia, incontinence, pallor, irregular blood pressure or pulse or cardiac arrhythmias. Less acute and generally reversible adverse reactions of metoclopramide include sedation and diarrhea (33). Rare psychiatric disorders such as panic disorder, major depressive disorder and agoraphobia have been reported with brief exposure to metoclopramide (34).

The most frequently reported adverse reaction in the Drugs.com dataset was anxiety. Other adverse reactions found in the Drugs.com dataset included panic, restlessness, depression, dizziness, dyskinesia, drowsiness and fatigue. Spasm was the most frequently reported adverse reaction in the WebMD.com dataset. Sleepiness, tiredness, confusion, bloating, Parkinson like symptoms, drowsiness and diarrhea were the other adverse reactions found in the WebMD.com dataset. All user reported adverse reactions in both datasets were consistent with the metoclopramide adverse reactions reported in the medical literature. They cover both mild (drowsiness, sleepiness, dizziness, fatigue, tiredness, bloating, diarrhea) and severe adverse reactions such as movement disorders (spasm, dyskinesia, Parkinson like symptoms) and psychiatric disorders (anxiety, confusion, panic, restlessness, depression).

Figure 4 shows sentimental analysis scores of Drugs.com and WebMD.com datasets. The analysis on the Drugs.com dataset revealed that about 66% of the reviews were negative while 34% were positive. The analysis on WebMD.com revealed a similar finding with 64% negative reviews and 36% positive reviews.

Figure 4. Sentimental analysis in Drugs.com and WebMD datasets

Conclusions

Patient reported adverse reactions on Drugs.com and WebMD.com were consistent with known adverse reactions to metoclopramide. They included both mild and severe adverse reactions such as movement disorders and psychiatric disorders. Patients' perspectives toward metoclopramide therapy were generally negative. Text analytics also revealed several off-label uses (migraine and hyperemesis) of metoclopramide.

The consistency of our findings with existing literature is quite encouraging. This shows the potential and value of these types of studies in pharmacovigilance. It remains to be seen whether these findings can be generalized across other drugs and data sources.

One drawback in studies like ours is the credibility and quality of data found on online health forums and social media. This is further compounded by missing data, patients' usage of non-medical terms, incorrect grammar, and spelling mistakes. However, these issues can be mitigated by novel text analytics algorithms and deep learning-based text processing methods.

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