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Dissertation

DIGITAL PHARMACOVIGILANCE: THE MEDWATCHER SYSTEM FOR MONITORING ADVERSE EVENTS THROUGH AUTOMATED PROCESSING OF INTERNET SOCIAL MEDIA AND CROWDSOURCING

by

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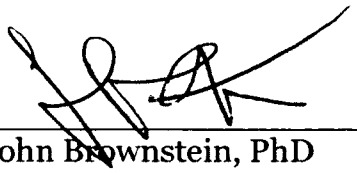

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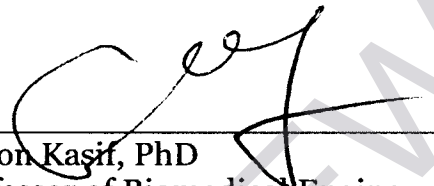

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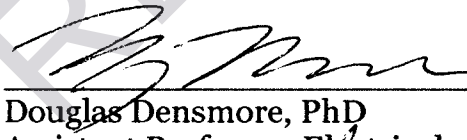

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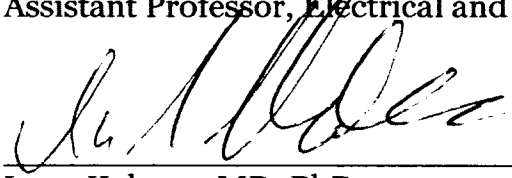

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DIGITAL PHARMACOVIGILANCE:

THE MEDWATCHER SYSTEM FOR MONITORING ADVERSE EVENTS THROUGH AUTOMATED PROCESSING OF INTERNET SOCIAL MEDIA AND CROWDSOURCING

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ABSTRACT

Half of Americans take a prescription drug, medical devices are in broad use, and population coverage for many vaccines is over 90%. Nearly all medical products carry risk of adverse events (AEs), sometimes severe. However, pre-approval trials use small populations and exclude participants by specific criteria, making them insufficient to determine the risks of a product as used in the population. Existing post-marketing reporting systems are critical, but suffer from underreporting. Meanwhile, recent years have seen an explosion in adoption of Internet services and smartphones. MedWatcher is a new system that harnesses emerging technologies for pharmacovigilance in the general population. MedWatcher consists of two components, a text-processing module, MedWatcher Social, and a crowdsourcing module, MedWatcher Personal. With the natural language processing component, we acquire public data from the Internet, apply classification algorithms, and extract AE signals. With the

crowdsourcing application, we provide software allowing consumers to submit AE reports directly.

Our MedWatcher Social algorithm for identifying symptoms performs with 77% precision and 88% recall on a sample of Twitter posts. Our machine learning algorithm for identifying AE-related posts performs with 68% precision and 89% recall on a labeled Twitter corpus. For zolpidem tartrate, certolizumab pegol, and dimethyl fumarate, we compared AE profiles from Twitter with reports from the FDA spontaneous reporting system. We find some concordance (Spearman's rho = 0.85, 0.77, 0.82, respectively, for symptoms at MedDRA System Organ Class level). Where the sources differ, milder effects are overrepresented in Twitter. We also compared post-marketing profiles with trial results and found little concordance.

MedWatcher Personal saw substantial user adoption, receiving 550 AE reports in a one-year period, including over 400 for one device, Essure. We categorized 400 Essure reports by symptom, compared them to 129 reports from the FDA spontaneous reporting system, and found high concordance (rho = 0.65) using MedDRA Preferred Term granularity. We also compared Essure Twitter posts with MedWatcher and FDA reports, and found rho = 0.25 and 0.31 respectively.

MedWatcher represents a novel pharmacoepidemiology surveillance informatics system; our analysis is the first to compare AEs across social media, direct reporting, FDA spontaneous reports, and pre-approval trials.

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List of Abbreviations

AE ..... adverse event

API ..... Application Programming Interface

CDC ..... Centers for Disease Control and Prevention

COD ..... cause of death

DHS ..... Department of Homeland Security

EMA ..... European Medicines Association

FAERS ..... FDA Adverse Event Reporting System

FDA ..... Food and Drug Administration

HHS ..... Health and Human Services

HLGT ..... High-Level Group Term

HLT ..... High-Level Term

HSG ..... hysterosalpingram

IMI ..... Innovative Medicines Initiative

LLT ..... Lower-Level Term

MAUDE ..... Manufacturer and User Facility Device Experience

MedDRA ..... Medical Dictionary for Regulatory Activities

MRI ..... Magnetic Resonance Imaging

MS ..... multiple sclerosis

NIH ..... National Institutes of Health

NME ..... new molecular entity

PDF ..... Portable Document Format

PET ..... polyethylene terphthalate

PT..... Preferred Term

ROC ..... Receiver Operating Characteristic

SAMHSA .....Substance Abuse and Mental Health Services Administration

SNRI ..... serotonin and norepinephrine reuptake inhibitor

SOC..... System Organ Class

SSRI ..... selective serotonin reuptake inhibitor

STD..... sexually transmitted disease

UK..... United Kingdom

URL .....Uniform Resource Locator

US ..... United States

USAID ..... United States Agency for International Development

VAERS ..... Vaccine Adverse Event Reporting System

WHO.....World Health Organization

XML..... Extensible Markup Language

Introduction

Half of Americans take a prescription drug [1]; many others make use of regulated medical devices both at home and in the clinical setting, and vaccination coverage for many vaccines is over 90% [2]. Together, drugs, devices and vaccines have extended our lives and transformed our health. At the same time, nearly all medical products carry a risk of adverse events—harmful impacts caused by the treatment itself. Though in many cases these effects are mild or extremely rare, for some products in some contexts, adverse events can be severe.

The process of clinical trials that precedes government approval is critical for evaluating both safety and efficacy of new medical products. However, clinical trials often exclude participants with multiple health conditions, who are taking other medications, or who don't fit specific clinical criteria [3, 4]. Further, due to inherently smaller sample sizes, clinical trials typically do not detect rare or extremely rare effects [5]. Meanwhile, once a product is approved, it is often prescribed to a much larger population of patients, many of whom don't fit the trial criteria. Further, approximately 20% of prescriptions are for "off label" usage, situations in which clinical trial outcomes have limited applicability [6, 7, 8]. The result is that clinical trials are often insufficient to determine the true risks of a product as it is used in the population. In fact, over half of approved drugs have serious side effects not detected before approval [9]. Moreover, with increased use of opioids and certain new biologics, the incidence of serious adverse events in the US has increased in recent years, even after accounting for

the increase in prescriptions [10].

Agencies such as the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) are charged with protecting population health by carefully evaluating and managing the risks and benefits of each product on the market. Because of the clear need to monitor risks beyond clinical trials, the government has established a range of reporting mechanisms for industry, consumers, and clinicians, most notably FDA MedWatch and CDC Vaccine Adverse Event Reporting System (VAERS). For drugs, biologics, and devices FDA MedWatch [11, 12, 13], in particular, the 3500 Form [14], has long been the established channel for clinicians and pharmaceutical companies to report on post-marketing adverse events. For vaccines, VAERS [15, 16] is the preferred reporting mechanism. However, these systems are often cumbersome and oriented to expert clinicians (Figure 1). Even for clinicians, who are under professional obligation report, these forms represent another paperwork burden in an already overburdened workflow. Given these barriers for both patients and clinicians, the result is that adverse events often go unreported [17, 18]. A 2012 study of hospitals by the Department of Health and Human Services Office of Inspector General found that 86% of reportable adverse events went unreported [19]. While not all of these adverse events were related to medical products (some resulted from improper procedure, highly complex cases, or other factors), clearly we face significant underreporting across our health care infrastructure. Of the reports that are collected through existing channels, 80% of drug-related

reports [20], 35% of vaccine reports [21], and 98% of device reports [22] come from manufacturers, who are under legal obligation to report all events they are aware of. While manufacturer reporting is essential, without the direct engagement of patients and clinicians, we are missing a key piece of the picture.

Figure 1. The FDA "consumer-friendly" voluntary MedWatcher reporting form (3500B). This simplified version was introduced in 2013.

Another limitation of existing reporting systems such as FDA MedWatch and VAERS is that they are often slow to publish the data they collect. FDA Adverse Event Reporting System (FAERS), the mechanism by which the FDA publishes MedWatch reports, typically releases data on a quarterly basis, with a one-year delay. At the time of writing in February 2014, the data had not been

updated in over one year [23]. The data that are released come in large relational database files, with duplication and inconsistencies. The FDA's system for disseminating medical device reports, Manufacturer and User Facility Device Experience [24] (MAUDE), is better in that it is typically updated on a monthly basis, and searchable via a Web-based form, but is still challenging for non-expert users. Although public health officials and regulators in government may have ready access to these data sets, the result of the delay is that manufacturers, clinicians, and the general public have limited opportunity to gain insights from these valuable reports.

At the same time as we see both the impact of adverse events and major reporting gaps, we have an explosion in adoption of Internet services and mobile computing devices. In particular, adoption of social media tools and smartphones has surged: 160 million Americans are on Facebook [25], 140 million US-based accounts are on Twitter [26], and 46% of American adults own smartphones [27]. In the health domain specifically, as of fall 2012, 59% of US adults had looked online for health information in the past year, 35% had gone online specifically to determine a medical condition [28], while 52% of smartphone owners reported gathering health information through their phones [29]. Meanwhile, on the clinical side, fully 85% of US physicians own or use smartphones professionally [30].

In response to the challenges of adverse event reporting and the opportunities offered by emerging technologies, we present MedWatcher, a new

system for early detection and tracking of adverse events in the population at large. This new program builds on our earlier work in infectious disease outbreak tracking and in the broader field of digital disease detection. MedWatcher consists of two main components, a data-mining module, **MedWatcher Social**, and a crowdsourcing module, **MedWatcher Personal**. With the data-mining component, we acquire a broad range of data from the Internet, in the form of posts in public forums. We then apply document classification and information extraction algorithms to filter and classify the information and extract both individual and aggregate signals of adverse events. With the crowdsourcing application, we provide a mobile and Web-based application that allows users to both track safety information on their chosen products, and easily submit adverse event reports directly into the system. We then review and filter these reports and similarly look for both individual and aggregate signals of both known and previously unknown side effects.

The job of public health officials, to keep beneficial, sometimes life-changing, and sometimes life-saving therapies available while protecting us from their side effects, remains difficult. Given the noisy data available, primarily in the form of spontaneous MedWatch reports, when an apparent signal arises, there is often no clear answer on whether to change recommendations, labels, or pull a product from the market. With the work of this thesis, we can't hope to answer these thorny questions definitively. However, for the regulators, clinicians, and patients faced with these challenges, we offer a new arrow in the

quiver. We are seeing a situation of vast underreporting of adverse events, even as more and more people are equipped with easy-to-use, high-bandwidth reporting tools. With MedWatcher, we apply the power of new information technologies to provide a new window into understanding the adverse effects of medical products as they occur in the general population.

In the work of this thesis, we seek to answer the following questions: first, can we engineer a system, MedWatcher Social, with sufficient automated classification performance to derive useful data from the noise of Internet media? Second, can we engineer a system, MedWatcher Personal, with sufficient consumer adoption to derive useful data by crowdsourcing direct reports? Third, if so, how do these new sources compare with available pre-marketing and post-marketing surveillance sources? If the new sources match closely, then we have validation of the new signals, and the advantage of our new approach comes from speed and ease of access to the data. If they don't match, then two possibilities arise: one is that our new data sources are simply too noisy to be useful; the other is that our new sources offer important insights that are not available through existing channels.

As shown in our results below, we find that we are indeed able to build effective systems for generating signals, and we find that they match to some degree with existing sources. In general, when we compare social media data with traditional MedWatch reports, we find legitimate adverse event signals in social media, but they tend to be weighted toward the more common, but less severe