DRUG-DRUG INTERACTION PROFILES OF MEDICATION REGIMENS EXTRACTED FROM A DE-IDENTIFIED ELECTRONIC MEDICAL RECORDS SYSTEM

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Abstract

With age, the number of prescribed medications increases and subsequently raises the risk for adverse drug-drug interactions. These adverse effects lower quality of life and increase health care costs. Quantifying the potential burden of adverse effects before prescribing medications can be a valuable contribution to health care. This study evaluated medication lists extracted from a subset of the Vanderbilt de-identified electronic medical record system. Reported drugs were cross-referenced with the Kyoto Encyclopedia of Genes and Genomes DRUG database to identify known drug-drug interactions. On average, a medication regimen contained 6.58 medications and 2.68 drug-drug interactions. Here, we quantify the burden of potential adverse events from drug-drug interactions through drug-drug interaction profiles and include a number of alternative medications as provided by the Anatomical Therapeutic Chemical Classification System.

Introduction

With improvements in life expectancy and reduction in fertility rates, population ageing is driving and expanding the need for pharmaceuticals to treat and prevent chronic ailments such as hypertension, cholesterolemia, depression, and diabetes (1). Treatment of patients is crucial to ensuring their wellbeing and quality of life, yet with the addition of each new drug there is a subsequent increase in the risk for an adverse drug-drug interaction (DDI) (2). An adverse DDI refers to the undesired therapeutic outcome of the main therapeutic effect due to interactions with unintended drug targets. Use of contraindicated drugs may increase the risk of a medically adverse event leading to complications and a negative prognosis. They may also lead to non-compliance with a treatment regimen due to less severe side-effects. An increase from 94,000 deaths in 1990 to 142,000 deaths in 2013 globally was reported due to adverse events from drug treatments (3).

Although DDIs only constitute a small portion of these adverse drug reactions, they are fundamentally important in improving patient treatment and outcomes as DDIs are often predictable and thus avoidable or manageable. DDIs involve the active ingredient of one drug interfering or affecting the activity of another drug when administered to a patient at the same time (4). The resulting effect can be potentiation of compound activity or a reduction in drug efficacy. DDIs may be the result of various processes. These processes may include alterations in the pharmacokinetics of the drug, such as alterations in the absorption, distribution, metabolism, and excretion (ADME) (5). Alternatively, DDI may be the result of the pharmacodynamic properties of the drug, e.g. the co-administration of a receptor antagonist and an agonist for the same receptor. The importance of these pharmacological interactions is emphasized especially when patients are at risk of a life-threatening overdose. A prominent example is the drug warfarin (6), an anticoagulant normally used in the prevention of thrombosis and thromboembolism. Despite its therapeutic efficacy, many other medications interact with warfarin, e.g. rivaroxaban (7) and apixaban (8). When the efficacy of warfarin is increased over a certain therapeutic threshold, the consequence can be bleeding, while lowering warfarin's activity below a certain threshold can lead to an increase in blood clots or bleeding (9). Once administered, its effectiveness has to be monitored, through blood testing, to avoid blood clots or internal bleeding.

Frequency of DDI is correlated with the age of the patient, the number of drugs prescribed, and the number of physicians involved in the patient's care (10). As of 2008, nearly 90% of U.S. adults and 20% of U.S. children had reported using a prescription drug within a month of participating in a national epidemiological survey with 31% reporting the use of two or more drugs (11).

Healthcare technologies, such as electronic medical record (EMR) systems, are advancing rapidly and can better enable medical practitioners (e.g., primary care providers, specialists, pharmacists, and nurses) throughout the health care system in improving patient treatment regimens and medical outcomes (12). However, achieving quality improvement through EMRs is economically burdensome and requires a substantial time commitment. A qualitative study of physician practices after implementation of an EMR found that quality improvement depends heavily on physicians' use of the EMR—and not paper workarounds—for most of their daily tasks (13).

In an effort to improve precision medicine at the point of patient care, we leverage EAGLE BioVU, a subset of the Vanderbilt University Medical Center (VUMC) EMR system, to investigate DDI profiles for drug regimens reported at individual patient visits. We evaluated medications reported by patients at visits over a 6-year period and incorporated knowledge of validated DDIs from the Kyoto Encyclopedia of Genes and Genomes (KEGG) DRUG database (14,15) as well as the Anatomical Therapeutic Chemical (ATC) Classification System (16) to highlight potential risk of DDI for individual patients.

Significance

With a growing number of available therapeutics on the market, the risk for DDIs increases. It may be difficult for a care provider to analyze complex drug regimens for possible DDIs. Here, we propose the concept of a DDI profile which provides a tool to increase DDI awareness. These profiles can gauge the number of DDIs early in the health care chain, and can serve as a first pass filter for the prescription of therapeutics.

Methods

In modern health care systems, electronic copies of patient data are being stored at a rapid pace in EMRs. This study strived to highlight the use of external knowledge databases as an enabling source to analyze patient medication data in a data-driven capacity.

Patient data extracted from electronic medical records (EMR)

Here, we employed the Vanderbilt University Medical Center (VUMC) Synthetic Derivative (SD) as a knowledge base for our study. The SD is a de-identified version of Vanderbilt's EMR system (17,18). De-identified medical records have been scrubbed of identifying information (e.g., exact dates, names, zip-codes, etc.). The EMR system is comprised of inpatient and outpatient medical records that were recorded at VUMC and its affiliated clinics. Patient records consist of structured (e.g., laboratory tests, billing codes, procedure codes) and unstructured (e.g. clinical free text) components. Over 2.2 million records are available with an average time window of 6.5 years of medical history per patient.

The field of health care changes rapidly over time. To reflect the most recent advances and changes, we accessed EAGLE BioVU (19), a subset of the VUMC SD of 15,863 patients with at least one clinic visit resulting in a blood draw between 2007 and 2012. Actual medical records can represent many more years prior to 2007. EAGLE BioVU includes both pediatric and adult patients, and the majority of patients are female (65.35%) and African American (73.06%). Most of the patients are between the ages of 18 and 64 years (~72%), with ~16% and ~12% representing elderly and pediatric patients, respectively. The other race/ethnic groups included in EAGLE BioVU are Hispanics (10.87%) and Asians (7.12%). From among these patients, we assessed current trends in reported medications for 14,924 patients independent of racial/ethnic groups.

Ethics statement

The data in this study were de-identified in accordance with provisions of Title 45, Code of Federal Regulations, part 46 (45 CFR 46). Therefore, this study was considered non-human subjects research by the Vanderbilt University Internal Review Board (IRB). The Vanderbilt University IRB approved this research.

Drug-Drug interactions database and classification of alternative medication

The Kyoto Encyclopedia of Genes and Genomes (KEGG) project is an assortment of carefully curated databases which was initiated in Japan in 1995 (14,15). One goal of the project is to model the biological system as a computer representation. Many KEGG databases are available containing information on biological systems, genetic information, chemical reactions and compounds, and health related data.

Medication regimens can be extracted from individual patient visits with an EMR. To draw the relation between individual drugs and their mutual DDIs, we used the KEGG DRUG database. KEGG DRUG is a curated database containing information on federally approved drugs in the United States, Europe, and Japan.

Chemical structures are associated with biological targets such as signaling proteins, metabolizing enzymes, or molecular interaction networks (15). Additionally, we used the Anatomical Therapeutic Chemical (ATC)

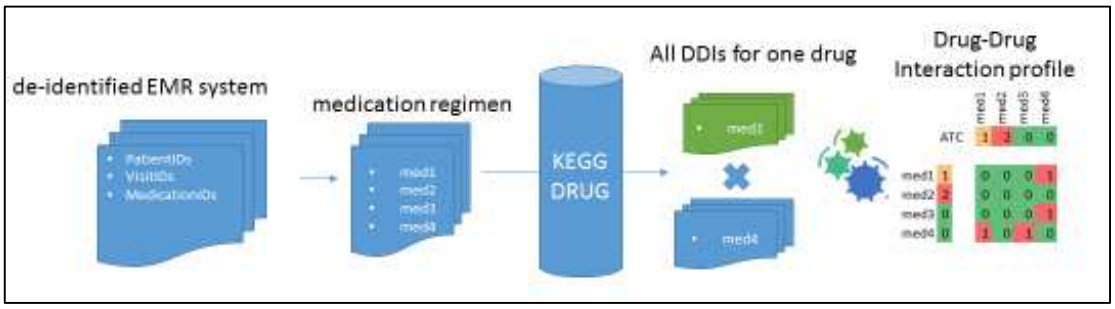

Figure 1: Flowchart representing the steps involved to construct a patient visit regimen DDI profile.

Classification System provided by the World Health Organization (WHO) (16) that allows for classification of the active compound of drugs with respect to the physiological system that the drug acts on. It is a hierarchical system based on pharmaceutical codes that group medications/drugs with similar activity with those that act on the same biological target. Identifying closely related compounds in type and application target allows for an additional layer of decision support information.

As shown in Figure 1, the complete medication regimen for a patient visit can be extracted from the local EMR and analyzed for potential DDI. In brief, medications are designated (e.g. med1 to med4) from the EMR system and then compared to each other with information curated from KEGG DRUG. Synonymous medication designations were taken into account eliminating duplication. Each medication (med1 to med4) is compared to all others. Once a validated interaction is identified (e.g. med1 with med4) the DDI profile is updated. Additionally, for each medication, a number of potential alternative treatment options according to ATC are provided. Based on the resulting data, a DDI profile can be established that quantifies or counts DDI among the medications of a particular regimen.

Results

Assessing patient exposure to medication

Medication data from the EMR and KEGG DRUG had to be synchronized or matched. We extracted 2,411 distinct medications from EAGLE BioVU. KEGG DRUG provided information for 10,250 chemicals. A total of 71% (1,714/2,411) could be match between the two data sources. We limited our study to the years 2007 to 2012. During this time frame, a total of 543,201 patient visits where recorded. On average, a medication regimen contained 6.58 medications (Table **1**). When quantifying the burden of DDIs for patients, it is important to evaluate the frequency of its occurrences. The number of reported medications is correlated with increasing age (Figure 2). Subsequently, associated DDIs follow a similar upward trend. Figure 2 shows both distributions and visualizes expected trends based on age. With increasing age, we see an uptake in the number of medications. The corresponding DDIs follow on a similar trajectory. Starting at approximately 85 years of age, we see a declining trend for both distributions. Figure 3 shows the distribution of DDIs (min, max, and average) and the number of patient visits associated with a number of drugs per regimen. The average DDI trajectory resembles a linear trend compared to a quadratic increase when considering all possible DDIs in a regimen. This suggests that in most cases only a fraction of drugs are involved in DDIs that are currently reported. On the extreme end, Figure 3 shows the maximum DDI (gray line) seen in each regimen category. While affecting only a limited number of patient visits, the trend is initially steep and begins to

Table 1: Summary statistics for medications prescribed to individual patient visits through 2007-2012.

Total #patients	Total #visits	Average #drugs in regimen per visit	Minimum regimen	Maximum regimen	Average #DDI per regimen
14,924	543,201	6.58	2	43	2.68

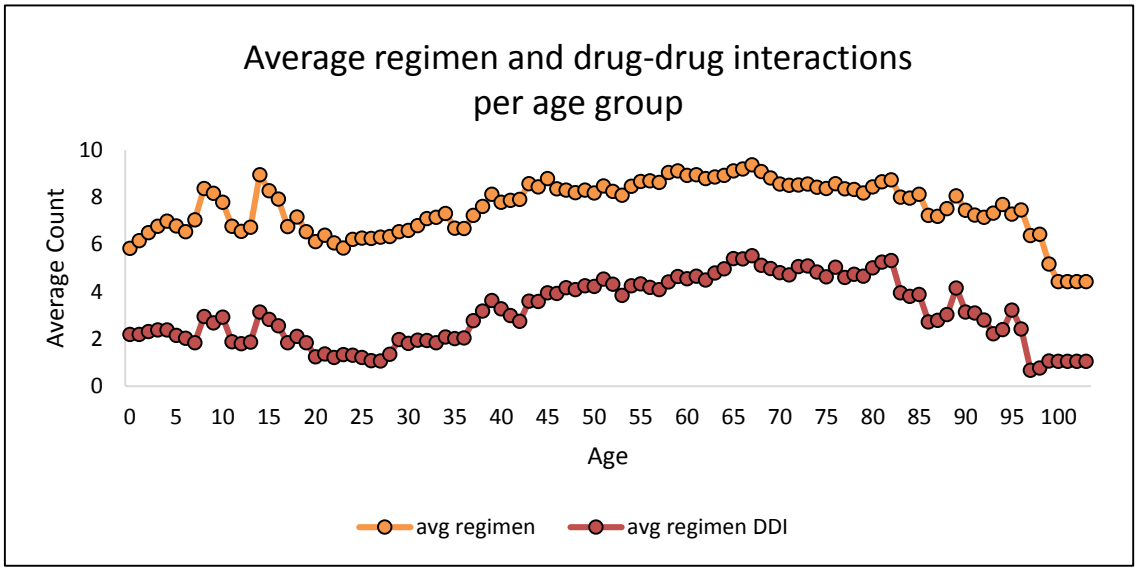

Figure 2: Distribution of average number of drugs in regimen and average drug-drug interactions related to age groups.

level out when more than 20 drugs are listed. Due to the limited number of patients are on extreme drug regimens, there is heavy fluctuation when 34 or more drugs are involved.

In this study, 46.7% of total patient visits had an average of 5 or fewer drugs with on average 1 DDI. On the extreme end, approximately 1% of patients had 20+ drugs listed in their medications lists at any given visit, exhibiting the potential for an average of 16 DDIs.

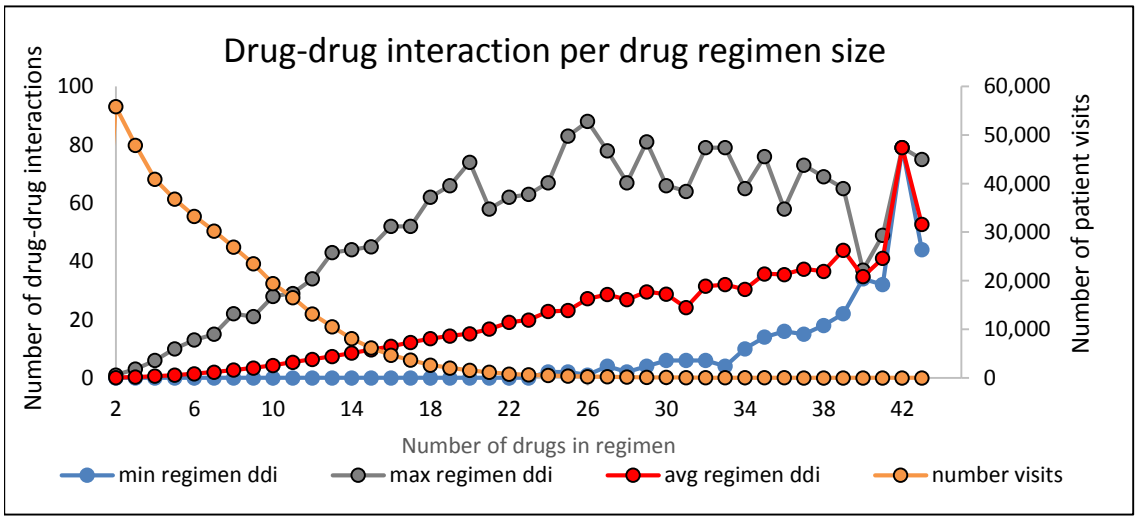

Figure 3: Distribution of drug-drug interaction related to the number of drugs in regimens showing minimum, maximum and average. Also includes the number of visits in which a specific number of medications was reported.

Drug-drug interaction profiles

In order to quantify DDIs for a medication regimen, we introduce DDI profiles. These profiles evaluate each medication pair shown as a correlation matrix (Figure 4).

DDI counts are commutative and are only counted in the upper triangular matrix. The example in Figure 4 shows a DDI profile of 6 drugs with a total of 7 DDIs. That comprises 46% of all possible DDIs considering that there are 15 total possible DDIs. Next to the medication name is the number of possible alternative medications provided by the ATC. In this example, aspirin, furosemide, revatio, and warfarin have alternative medications available.

Next, Figure 5 shows an extreme DDI profile. A 55 year old male patient has 26 drugs listed at time of his clinic visit. Given a drug regimen of 26 drugs, there is the potential for 84 known possible DDIs.

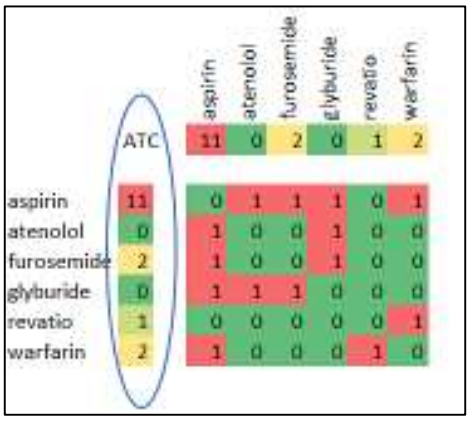

Figure 4: A DDI profile for a regimen of 6 prescription drugs. The blue ellipse indicates the number of alternative medications given by ATC, respectively.

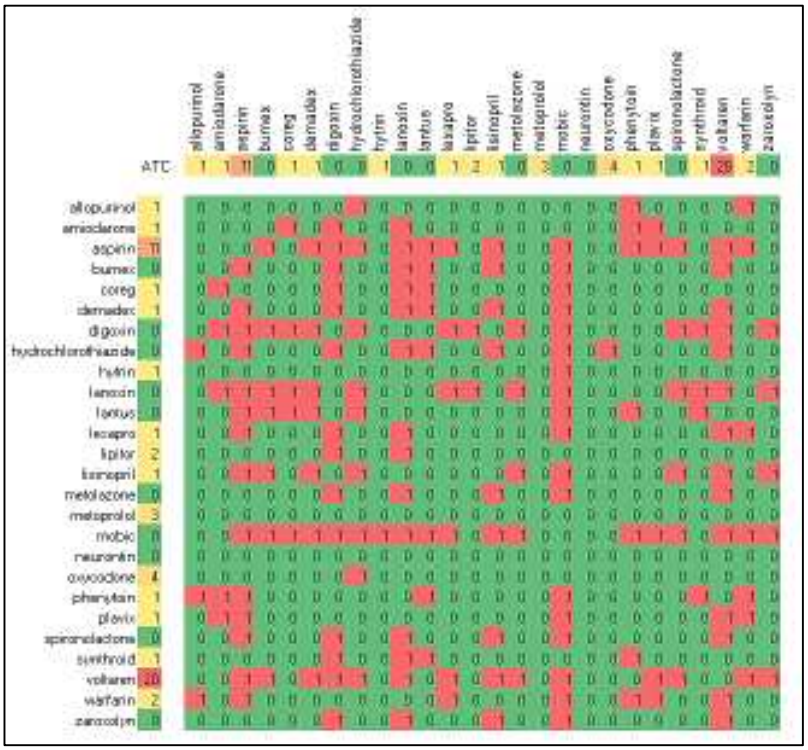

Figure 5: The DDI profile of a 55 year old male patient that consists of 26 drugs with 84 known possible DDIs.

Discussion

As the number of medications prescribed to patients increases with age (Figure 2), the risk for adverse events through DDI increases as well (Figure 3). When combining multiple drugs, the active molecules may exhibit synergistic or antagonistic influences on the intended primary therapeutic effect.

Risk of adverse drug interactions can be mitigated at the point of care, when patients visit their care provider. Providing a tool to gauge potential DDI risks at this point in the health care chain has the potential to improve quality of life for patients.

Thus, we evaluated medication regimens for patient-visits extracted from EAGLE BioVU, a subset of minority patients with de-identified electronic health records from VUMC for known DDIs available in the KEGG DRUG database. An analysis was performed to evaluate the frequencies and correlations of DDIs. DDI profiles were created to visualize and quantify individual medication regimens. In an effort to advance precision medicine, physicians could take advantage of DDI information when prescribing new medications to patients. Though, the concept of DDI profiles is not restricted to EAGLE BioVU and can be applied to other electronic health record systems with different patient population representations.

However, a unique aspect of this study is the utilization of underrepresented minority patient populations. The population represented in this study is primarily composed of African Americans. It is well known that African Americans metabolize drugs differently than populations of European descent due to differences in genetics of drug metabolizing genes (20,21). Additionally, we were able to assess DDI profiles for pediatrics. Figure 2 shows a rise of DDIs and medications in general among the pediatric patients between the ages of birth and twenty years. Most of the pediatric cases were identified as being on 6 to 9 medications. While this number appears high for what should be a fairly healthy demographic, a number of factors are likely at work. While outside the scope of this study, given the clinical nature of this population, many of the pediatrics are likely being treated for less common childhood conditions, such as type-1 diabetes which affects upwards of 200,000 youths under 20 years of age (22), and for more common ailments such as asthma with a general pediatric prevalence of 8.3% (23) and allergies (24). For the extreme elderly population (95+ years) (Figure 2), we see a decline of reported drugs and DDIs which may be due to the healthy centenarian effect. Individuals who live upwards of nine decades are typically very healthy and tend to suffer from fewer chronic diseases, and thus require fewer medications (25).

This study had a number of limitations. Medications, including over the counter drugs and supplements, utilized for this study were self-reported by the patient at the time of clinic visit. Hence, the list of medications may not be 100% accurate but these lists likely include medications that were prescribed by a physician(s) outside of the Vanderbilt healthcare system. Additionally, it is unclear whether the reported medications were taken simultaneously or during separate distinct time frames. Also, dosage of medication was not taken into account and may influence related DDIs. Future directions for this study may include extracting dosage information with tools such as MedEx (26) and assessing dosage dependent interaction information through external databases such as SIDER (27). Patients may not have taken each reported medication as intended. Furthermore, not every drug registered in the EMR was represented in the KEGG DRUG database. As a future direction, other DDI databases (e.g. SFNIX (28)) could be used to complement and validate the KEGG DRUG database. As reported in the results section, only 71% of medications could be matched between the two information systems. Pharmaceutical companies have not exhaustively assessed every drug for an interaction with all other drugs on the market. Interactions with the environment (e.g. food) and the genetic background of patients was not taken into account. A distinction between gender effects could potentially also play a role. Presumably, a future update of respective databases will provide a higher coverage and provide a more complete picture of potential DDIs.

The Anatomical Therapeutic Chemical (ATC) Classification System provided by the WHO allows for classification of the active compound of drugs in respect to the physiological system that it acts upon. It is a hierarchical system based on pharmaceutical codes that group medications/drugs based on their specific target. Identifying closely related compounds in type and application target allows for an extension of the proposed DDI profiles and gives an indication of which drugs in the medication regimen could potentially be substituted with the potential for reducing overall drug-drug interactions. This could allow for customized medication regimens. Although, it is possible that mediations/drugs in the same ATC category could contain the same active chemical compound, and thus generate the same DDIs.

With the growing number of therapeutics available on the market, physicians may not have a complete overview of the consequences that specific drug combinations could exhibit. The DDI profiles proposed here offer nascent possibilities for the development of applications that could be installed and implemented in an EMR system to increase awareness of adverse DDI. In truly leveraging today's information technology, health care organizations could make a big impact by lowering the burden of adverse DDI events and the need for additional health care treatment at point of care.

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