# Drug Side Effects Data Representation and Full Spectrum Inferencing using Knowledge Graphs in Intelligent Telehealth

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Submitted in partial fulfillment
of the requirements for the degree of
Doctor of Professional Studies
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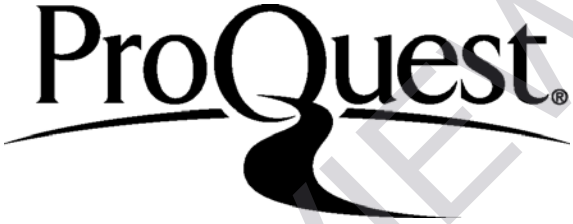

We hereby certify that this dissertation, submitted by **Saravanan Jayaraman** has successfully satisfied all the requirements for the degree of the Doctor of Professional Studies in Computing"

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# Abstract

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Drug adverse reaction data contains important constraints about side effects and conflict avoidance of component and compound drugs. We observe that many of these constraints are transitive in nature due to the relationship between drug and drug classes. Current drug side effects representations in XML does not have a proper knowledge representation mechanism to clearly specify all kinds of dependencies among the drug components and drugs. Even the recently introduced OWL based approach for medical drug side effects data representation still suffers from several shortcomings inherent to the OWL restrictions like using "is-a" relationship and usage of object property emulations.

In this research, we propose a model *Drug - Side Effects Representation And Inferencing (D -SERI)* built using Knowledge Graph (KG) and enhanced *PaceJena* to represent multiple custom relationships allowing domain experts to capture the transitive nature of the relations in an inference friendly way. The research also developed a concept demonstrator for checking out prescriptions to avoid complications. The research outcome shows that the proposed model allows the doctors and caregivers to derive

dynamic information about side-effects avoiding costly errors caused by human interpretation.

# Acknowledgements

I would like to dedicate my dissertation work to my parents whose endless love and affection gave me the power to work harder everyday with determination and perseverance to complete the research.

I would like to thank my beloved wife Viji who stood with me in every step of the way and endured countless difficulties and challenges while supporting my family during my absence. Her encouraging words and motivation throughout was a constant energy booster for me during the DPS years.

I affectionately thank my children Lakshaanya and Siddesh whose curious questions and supportive behavior gave me the zeal to strive for excellence. I wish to see them successful in life in their own way and surpass their parent's accomplishments one day.

THANK YOU to my dissertation advisor Dr. Lixin Tao for believing in me and providing constant encouragement and showing the knack to breakdown the dissertation topic and the technique to solve complex research problems. I greatly benefited from his years of guidance experience and incredible counsel. I am and will always be forever GRATEFUL!

Thanks to Dr. Frank and Dr. Qiu for all the great advice, and for being on my dissertation committee.

Special Thanks to my fellow researcher Ning Jiang who offered expert technical assistance and code review with me.

Finally, I would like to sincerely acknowledge my cohorts from the class of 2016 for supporting each other and staying together during the DPS journey.

"*Dream is not what you see in Sleep, dream is something which does not let you sleep*" – Dr A P J Abdul Kalam. Like many others before me, I definitely had many sleepless nights to accomplish my dream. During this, I also realized that the Seeking higher level of knowledge is a journey not a destination and I intend to continue this journey throughout my life.

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# Chapter 1

# Introduction

Study of Medical Drug side effects on Humans was first documented by the Greek Physician Hippocrates of Kos in 460 BC who first studied varied effects of Aspirin as a migraine to relieve pain and suffering on his patients. His followers from Hippocrates school of Medicine further continued the study of clinical study summing up the medical knowledge and wrote the everlasting drug side effect data on early human races. Along with these early studies by doctors in Graco-latino world, several similar advanced civilizations conducted studies in asymmetric manner setting up strong data spanning over centuries to be used by mankind.



## 1.1 Drug Side Effects Inference Problem

With the advent of the Web advancement with research and development, numerous domains have been remarkably driven by the emerging techniques, such as semantic web [1] [2] cloud computing [3][4][5], and big data[6]. This is even more relevant in the area of Drug development and monitoring in Telehealth [7] [8] where Domain experts depend upon these emerging technologies to encode knowledge. Recently, there is an explosion in the number of drugs approved for treatment and the effect they caused on human

population. In the US market alone, there are 2,000 medications, 94,450 health products and around 175,950 health packages with different active ingredients and these numbers are growing steadily every year. With these huge volume of drug combinations comes the challenge to have a relevant knowledge mechanism to capture the huge volume of side effects data and enable the patients and doctors a way to derive meanings about the potential outcome quickly. For example, when a doctor treats a patient with diabetic condition with any one of the drugs approved for treatment, he or she wants to make sure the benefit of prescribing the drug exceeds the side effects caused by the drug itself, in that case of side effect showing up, he or she wants to relate that to the prescribed drug and then quickly change the treatment option to suit the patient's responses to drugs. While there has been huge advances in the drug side effects data capturing globally including the nationally mandated options like MedWatch or EU drug watch and the availability of that information to public domain, the Information Technology processes behind have not been coping up due to several factors.



### *1.1.1 Side Effects Awareness*

The first is the explosion of the drug side effects data itself. Look at the growth of the side effects in the last 10 years growing exponentially. This data is extremely dynamic. Most of the Institutes and Research organizations spend enormous amount of time in just getting the data downloaded and synced periodically. As per the recent look on the MedWatch system there are 7 million data entries in the system. Figure 1 shows the continuous growth in the data. The interesting question to ask is what happens when a

new adverse event data is released and how it is synchronized with the previously stored data thereby staying relevant.

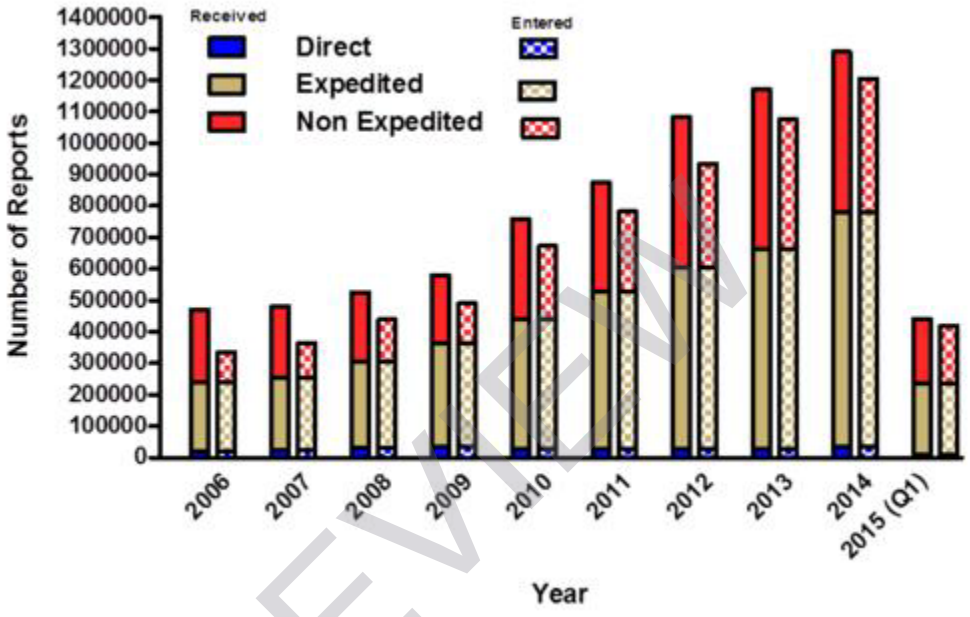



**Figure 1 Aggressive Growth of side effects data in the last decade**

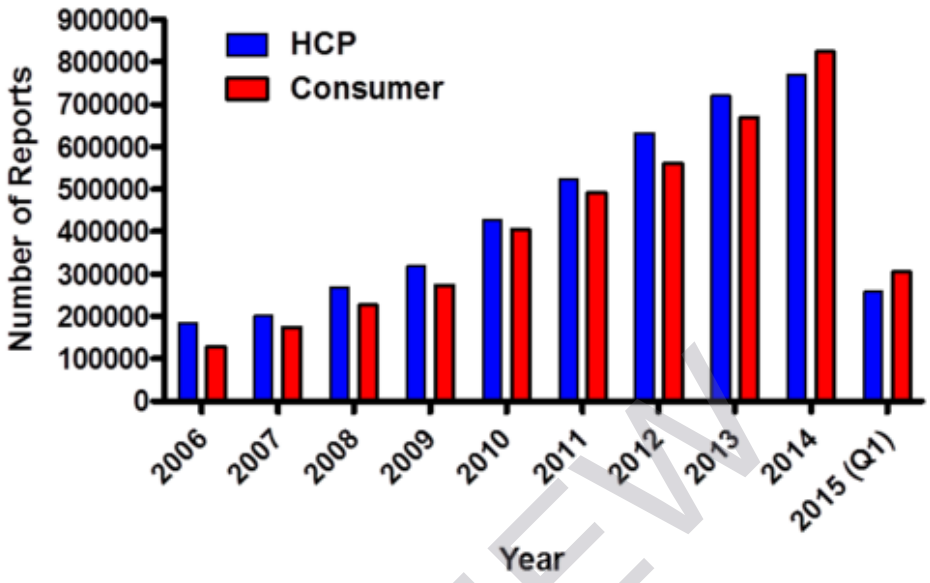



**Figure 2 Side effects data reporting by HCP vs Consumers**



A recent study by Mayo Clinic Survey [9] points that nearly 7 in 10 Americans take some form of Prescription drugs, and medication errors are surprisingly common and costly to the nation [10]. As per a study conducted by NIH.gov in a North Indian City [27], only 33% of patients knew about the side effects produced by the concerned drug, and only 15.68% knew how to recognize them. This is also confirmed by the CDC report where 70% of adults over 65 years take prescription drugs and 1 in 4 senior Americans take more than 3 prescription drugs.

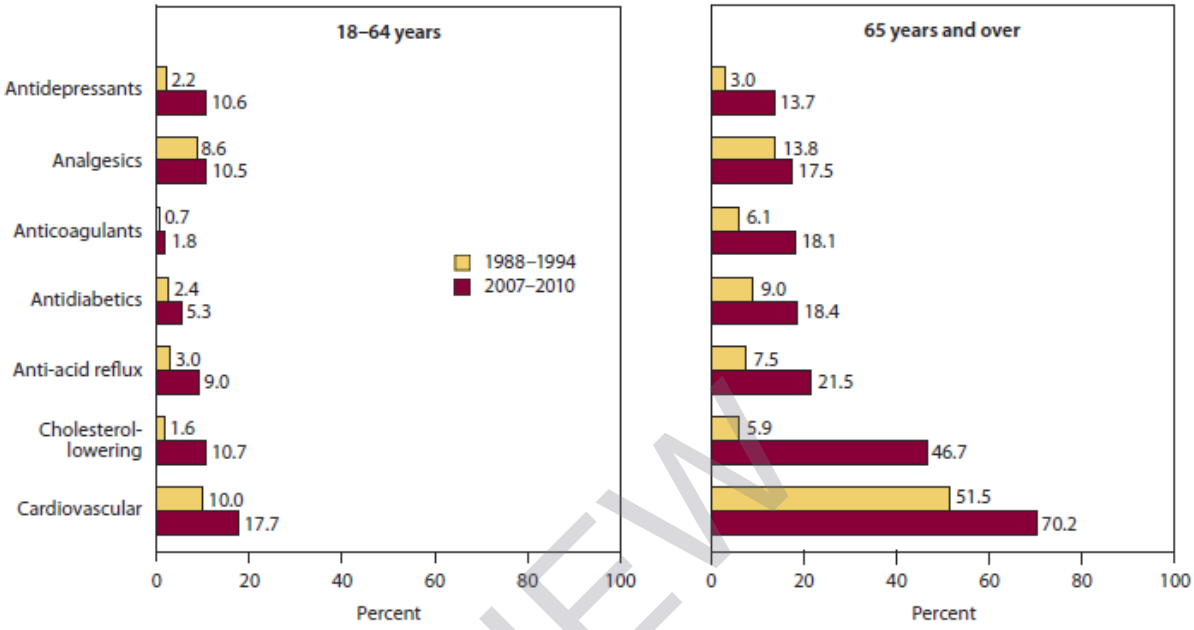
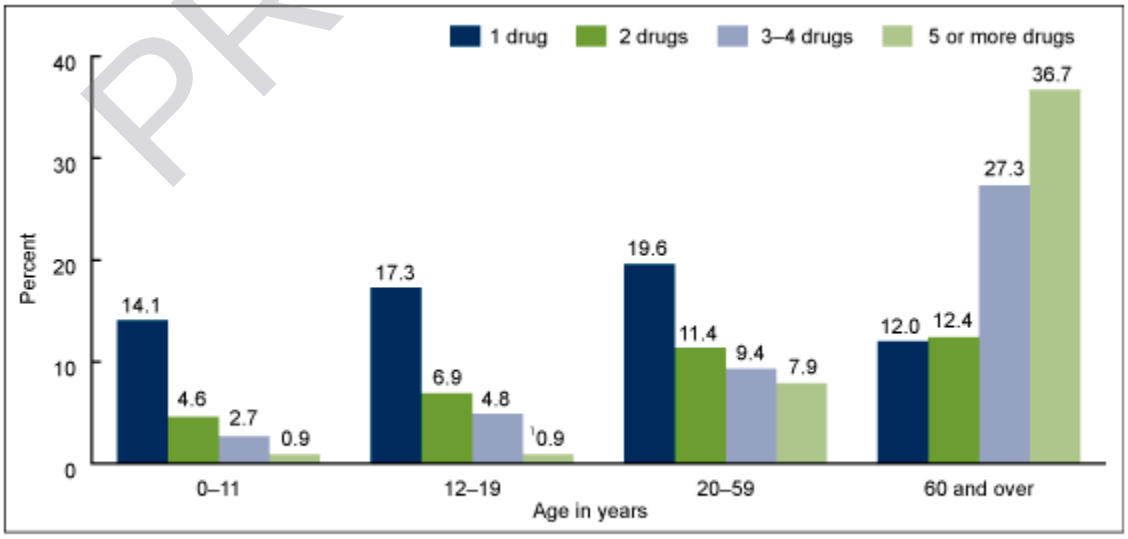



**Figure 3 Prescription drug use in the past 30 days among adults aged 18 and over, United States, 1988–1994 and 2007–2010**






!Estimate is unstable; the relative standard error is greater than 30%.
SOURCE: CDC/NCHS, National Health and Nutrition Examination Survey.

**Figure 4 Prescription drug use in combinations among adults aged 18 and over**

### *1.1.2 Growth of Drug Side Effects Data*

As per the CDC study the usage of prescription drugs increased by 10% last decade and the use of multiple prescription drugs increased by 20% and the use of 5 or more drugs increased by 70%. As pointed by the same CDC source the usage of prescription drug is directly related to availability of regular healthcare and as more and more people have access to regular healthcare the usage of prescription drugs is expected to grow linear as the necessity to treat multiple diseases at the same time especially on the senior population. This shows the problem with the data representation is not a one-time issues rather a long term issue requiring clarity and newer approaches from knowledge scientists.

### *1.1.3 Maintaining the Side Effects Data Current*

Whenever newer treatment options are available in the market, healthcare providers prefer to prescribe the advanced treatment option to their patients so they get the advanced therapeutic benefits and often doctors are looking for a better way to understand the knowledge about these new drugs to help treat the patients.

Here is one scenario. A patient suffering from uncontrolled diabetes is looking to utilize some of the newer drugs in the category. The doctor, while aware of the potential side effects of a new drug is looking forward to understand side effects of the drug better so that it does not conflict with the current treatment option for the patient. Here the doctor relies on several types of information like FDA's MedWatch data [20], or any

other data provided by the manufacturer or labelling information. While these information provide some levels of details about the drug side effects, the studies have pointed that the study of the drug side effects is one of the complex task to perform by a common man or physicians requiring enormous levels of investigation which is simply impossible due to lack of time or resources. According to the recent study by Harvard medical analytic group the knowledge mechanism of the drug data domain is not catching up with the growth pace of the data itself due to the restrictions on the current format and the lack of validation mechanisms.

### *1.1.4 Motivating Example*

This section shows a real time example where the proposed methodology can make a difference in the drug side effects data representation.

Table 1 exhibits different scenarios where the research can help doctors to avoid human interpretation errors.



**Table 1 Doctor's action during a patient visit**

| **Case** | **Patient observation for a drug** | **Doctor's action** |
|---|---|---|
| 1 | Patient does not report side effect with drug | Continue to prescribe the drug |
| 2 | Patient reports side effects but it's not known with drug | Continue to prescribe the drug while reporting new side effects. |

| | | |
|---|---|---|
| 3 | Patient reports side effects and its known with the drug | STOP the drug and look for alternatives. |

While Doctors prescribe drugs during routine visits, they always strive to make sure the benefits of prescribing the drug outweighs the risk caused by side effects. Here they always seek in-depth knowledge about the side effects keeping in mind the ultimate safety of the patient's life at the forefront of the drug prescription strategy. We take three typical scenarios often faced by doctors for this dissertation. There are several other variations of the scenarios are possible but for the case study perspective we restrict it to the three choices.



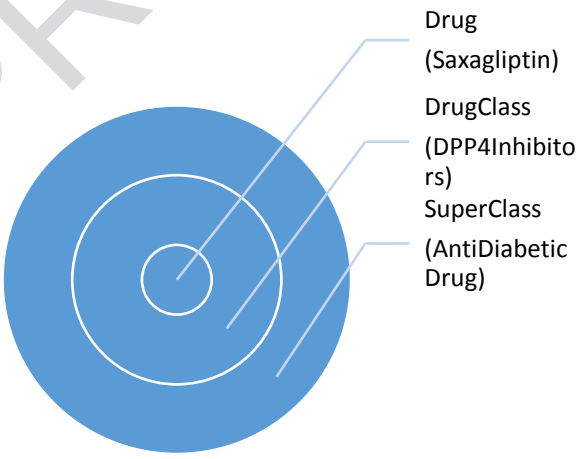



Figure 5 Saxagliptin drug class hierarchy [26] in knowledge graph

*Saxagliptin* drug is used to treat *diabetes* and they are newest treatment options for patients who are not responding well for other diabetic treatment options. While Saxagliptin----causes--- set of side effects (|A| - *Abdominal Pain, Motor Dysfunction, Hyperhidrosis, malaise, Nasal Congestion, Increased Blood Sugar, Arrhythmia, rash, Cerebro Vascular Accident* ) which is well known, doctors often find it that it does not represent the full list possible side effects. In this case, Saxagliptin's parent class DPP4Inhibitors (gliptin) causes its own set of common side effects – ( |B| - *nausea,diarrhea,stomach pain,headache,runny nose,sore throat,pancreatitis,severe join pain*).

When Doctors look for side effects caused by a drug against reported by patents, they often rely on the direct side effect list |A| as primary source as the full spectrum of the side effects is not available to them due to several reasons. This could cause them to overlook side effects like *pancreatitis* which is in |B|. Studies show that while emulations with object properties are used to capture these additional relations they often cause other problems like high cost of maintenance on data modelers.



### *1.1.5 Benefits of dynamic Side Effect Inference*

Linking the component and compound drugs using the proposed knowledge graph based approach allows the domain experts to capture the full spectrum side effects of the drug ( |A| + |B| ) by including all possible side effects while reducing syntax burden to knowledge modelers compared with any other workarounds like object properties.

Such a dynamic data representation model will also provide a full spectrum side effects to the doctors and patient helping them immensely to benefit to either adapt newer treatment models without fear or just to choose a suitable treatment model beneficial to the patient. Even when the knowledge about the drug side effects is available the current format makes it harder medical drug side effects is neither flexible nor suitable in the full spectrum nuisances of the drug side effects data drug being a chemical component.

## 1.2 Representation of Drug Side Effects Data in Knowledge Graph

A Knowledge graph describes the concepts in the domain and also the relationships that hold between those concepts. Different knowledge graph languages provide different facilities. It makes it possible for concepts to be defined as well as described. Complex concepts can therefore be built up in definitions out of simpler concepts.

### *1.2.1 Knowledge Graph Usage in Healthcare*

The usage of Knowledge Graph is well accepted especially in the semantic web [16][17] area as a primary way of disseminating the information to users or machines even though it's still evolving in the medical domain. For example, Google's knowledge vault [50] is enriched with information about 570 million objects of data and 18 billion facts making the world's largest public knowledge graph vault.

In Knowledge graph, classes are interpreted as sets that contain individuals. They are described using formal (mathematical) descriptions that state precisely the requirements for membership of the class. Unlike traditional approaches where the focus is storage of

the data with less consideration of the timely interpretation or reasoning, the primary goal of the knowledge graph is to enable timely retrieval of the knowledge in this case the use by Doctors or Patients to retrieve time sensitive data. The key once again is the modular ability of the knowledge graph to extend and grow making it an ideal option to store drug adverse data and making it highly suitable for capturing drug side effects data due to the dynamic nature of the domain.



### 1.3 Problem statement

Drug adverse reaction data contains important constraints about side-effects and conflict avoidance of component and compound drug. These are critically important in checking out prescriptions to avoid complications. Although MedWatch FAERS drug data are in XML, it doesn't have a proper knowledge representation mechanism to clearly specify all kinds of dependencies among the drug components and drugs. Therefore one has to depend on human interpretation to check prescriptions which can be error-prone. The newly introduced OWL based approach for medical drug data representation still suffers from several shortcomings inherent to the OWL restrictions like using “is-a’ relationship and usage of object property based workarounds losing the clarity and dynamic relationship building expected by domain experts to represent knowledge. It’s often difficult for the domain experts to process and derive meaningful information quickly for patients or doctors due to the following reasons.