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The “Learning” Pharmacovigilance System
From Concept to Reality

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The “Learning” Pharmacovigilance System

“Tell me and I forget. Teach me and I remember. Involve me and I learn.” - Benjamin Franklin

While experiential learning has been true for humans, it is now increasingly becoming a reality for machines. Machines and Systems are becoming “intelligent” and “smart,” capable of learning and improving their performance with increasing exposure. Is it true in healthcare? The answer is an obvious ‘yes’ as intelligent systems of all types are developed for activities that were traditionally considered “human,” such as diagnostics using image recognition and robotic-assisted surgeries, which have already entered clinical practice. Can this evolution in technology improve the safety and efficacy of medicines? Can we build a “learning pharmacovigilance system” that becomes more efficient with real world patient safety data?

This article explores the possibility of creating a “learning pharmacovigilance system” and the impact such a system could deliver on transforming drug safety.

What is a learning system?

We live in a complex and uncertain world with new threat to public health appearing every day. In order to effectively solve these real-world problems, we need a system that learns and evolves continuously. Instead of systems handling situations based on pre-defined rules, a learning system needs to confront real-world complex problems by using the experience it gains with data and diverse scenarios over time.

Artificial intelligence (AI) technologies coupled with high performance computing have made significant advances and have potential to solve many complex problems in the real world. Typically, a continuous learning system applies 5-step iterative process. AI learning agent observes the environment, perform necessary action, receive feedback on the actions performed, make relevant changes to its next actions, and improve performance. The system ability to predict gets better with time and experience.

In medicine, advanced AI technologies have been applied for diagnosis based on medical imaging. There are examples of successful detection & classification of lung nodules into malignant or benign based on the CT images. A recent study has shown that AI learning agents were better than dermatologists in detecting skin cancer. It has been proven that machine learning based diagnosis can help medical doctors not only decrease the error rate but also increase the sensitivity and specificity of diagnosis of conditions.
A model for a learning PV system

So how can such systems be applied to pharmacovigilance (PV)? What does a learning pharmacovigilance system look like?

In pharmacovigilance, such intelligent systems should be able to identify new and previously unknown drug safety issues early enough to prevent significant damage to public health. In order to accomplish this, the PV system should be built to:

- Ingest data from a variety of sources and conduct assessment for risk identification
- Learn and improve continuously with patient level safety data
- Mitigate drug-related risks through real-time communication

Data Ingestion

In order to effectively assess the safety risk of a drug, it is important to collect and analyze health data from all possible sources. A highly scalable system should be developed to be able to analyze data across health multiple systems; clinical trials registries, various omics databases (such as genomics and proteomics), and real-world data sources such as social media, mobile health apps, and wearables (Figure 1).

For instance, when a patient experiences a suspected adverse event, the treatment options should be available through clinical decision support system, the data on concomitant medications can be obtained from electronic prescription systems, the symptomology and medical history can be obtained from the electronic health records. These data sets can be combined with the data obtained from spontaneous adverse event reporting systems, published literature, and data from past or current clinical trials. Any possible correlation with the genomic or proteomic data can be analyzed to understand the pathophysiology of the adverse event. External factors that might have an impact on the safety of the drugs can be derived from the real-world evidence data from mobile health applications, wearables, and social media monitoring. These analyses can be performed at the individual and as well as population level.
Learn and improve with safety data from each patient

Using the comprehensive pharmacovigilance data sources, intelligent systems should be able to perform extensive analyses such as classification, clustering, prediction, anomaly identification, ranking, and recommendations resulting in early detection of drug-related safety issues. After identification of the suspected drug safety issues, the relationship between the drug and event can be validated through clinical studies. These clinical studies should be designed to test if the identified risk is associated with the drug in the target population. Further, it can be verified if the environmental and physiological factors assessed during risk identification has an impact on drug action. The outcome of these clinical studies can be used for “learning” by the AI algorithms and will improve the predictions in the next iteration (Figure 2).
Real-time risk communication

Since the systems used for healthcare decision making will be interoperable with the clinical data management and pharmacovigilance systems, the drug-related risks identified by AI-based analyses can be communicated in real time to the healthcare practitioners. As the risks identified will be communicated to clinical decision support systems, the healthcare practitioners can take these risks into account while devising treatment strategies and prescription options.

Figure 2: A Continuous, Learning-and-Improving Pharmacovigilance System

Transformation of Pharmacovigilance

The continuously learning and evolving pharmacovigilance system will ensure accuracy in risk identification. With the increasing experience with data, the AI-based algorithms will be able to identify risks early, potentially before the onset of clinical symptoms. For example, if a certain drug causes adverse reactions when given to individuals with a certain genetic composition in a specific environment, the adverse events can be prevented through a different treatment option and early intervention.

Patients are increasingly playing an important role in the decision-making process for their treatment. Even regulators such as FDA in the US are considering patient’s experience and their participation in regulatory decision making through its patient-focused drug development initiative.

By incorporating data from social media, health tech apps, and wearables into the pharmacovigilance system, we can capture patient’s experience and thereby factor that into the health risk assessments.
Currently, there is also a lag in communication of drug-related risks to the healthcare practitioners, potentially leading to significant damage to public health. Interoperability of pharmacovigilance and healthcare systems will ensure a continuous flow of information from pharmacovigilance systems to healthcare practice.

Combining these data sets will lead to improved drug-related risk assessment and will open the possibility of discovering novel genetic/proteomic biomarkers associated with a specific patient response. These can further help in the development of personalized treatments.

**Need of the hour?**

Current pharmacovigilance systems have been facing some chronic issues such as:

- Under-reporting of adverse events by healthcare professionals, patients, and caregivers
- Lack of population data for a specific drug for better risk estimation
- Delayed identification of product quality issues and medication errors
- Increased background rate of events with changing environmental factors

Further, the medicinal treatment paradigm is shifting from simple and small molecular entities to more complex products such as CART therapies, gene therapies (e.g., CRISPR), and complex combination products. According to FDA, the biologic medicines are becoming a backbone of modern therapy. These advanced therapies have entered the clinical practice after a long incubation period in the laboratories. Therefore, the current pharmacovigilance methods may not be adequate to detect the risks associated with these treatments.

Moreover, regulatory authorities are moving toward precision medicine, whose primary aim is to address inter-subject variability. While the current pharmacovigilance methods assume more homogenous populations.

In order to support the changing medical treatment landscape, and to overcome the current challenges, pharmacovigilance systems should undergo a major transformation from the current static system to a more dynamic and evolving system. The end-to-end pharmacovigilance technology infrastructure, from data ingestion to analysis to risk identification and communication, should take advantage of advancement in AI-based technologies. As medical science is evolving, the pharmacovigilance system should also evolve to ensure that the new treatments continue to be safe and effective and prevent any major public health hazards.
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