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An Overview of Artificial Intelligence and Explainability in Pharmacovigilance

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Abstract **–** Artificial intelligence (AI) technologies have recently played an essential role in the health sector. One of the most important uses of these technologies is determining drug side effects. The purpose of side-effect studies is to increase the safety and effectiveness of drugs. Early detection of side effects can provide patients with a better treatment option and a better roadmap for healthcare providers. Therefore, side-effect studies are an essential tool for the healthcare industry. Drug side effects can be a serious problem for patients, and in some cases, even life-saving drugs can become unusable due to their side effects. Therefore, early detection and prevention of side effects are vital. Artificial intelligence and explainable artificial intelligence (XAI) technologies provide faster, more accurate, transparent, and explainable results compared to traditional methods of determining the side effects of drugs. These technologies can detect the side effects of drugs by analyzing large amounts of data and can also be used in developing new drugs. With the use of these technologies, the determination of drug side effects can be performed more quickly and effectively. These technologies also eliminate the limitations encountered in traditional methods used to detect the side effects of drugs.

Keywords –Pharmacovigilance, Artificial Intelligence, Explainability, Data Mining, Machine Learning

I. INTRODUCTION

Artificial Intelligence (AI) is among the technologies that can be used to help detect the side effects of drugs more quickly and accurately [1]. Pharmacovigilance is the process of monitoring, evaluating, and reporting the side effects of drugs. After the drugs are put on the market, side effects reported by patients and healthcare professionals are collected through the pharmacovigilance system, and the possible risks of these side effects are evaluated. This process plays a vital role in the safety of drugs and helps protect public health [1]. AI technologies enable rapid analysis of large data sets. This can help analyze data collected during the pharmacovigilance process faster and more accurately. AI technologies have the potential to discover new relationships by analyzing data to detect side effects. This can help to understand better and report the side effects of drugs. It can also assist in automatically processing data in the pharmacovigilance process. This saves time for pharmacovigilance professionals and can speed up the process of collecting more data for detection of side effects [2].

As a result, in this study, it is detailed that AI and explainability can help detect side effects more quickly and accurately and play an essential role in the safety of drugs.

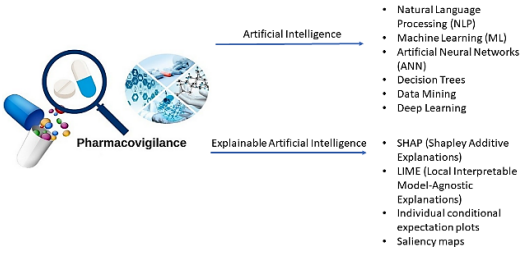

Fig. 1. Explainable artificial intelligence and artificial intelligence methods used on pharmacovigilance.

A. SIDE EFFECTS OF DRUGS

Ensuring patient safety is an indispensable principle of health services. Since every stage of healthcare has the potential to trigger an error. Some problems may arise in healthcare services' delivery, products, or procedures. The most common problem with drugs is the occurrence of side effects [3].

The therapeutic effects of drugs often bring side effects. The therapeutic range of a drug can be defined as the dosage range or serum concentration in which it is expected to achieve the desired therapeutic effect. The therapeutic range does not mean the drug cannot provide benefits at concentrations below the minimum threshold or produce adverse effects when kept within the range [4].

Side effect: It is defined by the World Health Organization (WHO) as "an unintended harmful response to a drug used at normal doses for the prophylaxis, diagnosis, treatment of a disease or for modifying physiological function". Side effects can range from mild dizziness to death in the most severe form. There are two types of side effects:

1. Type A reactions are dose-dependent reactions that can be predicted based on the pharmacology of the drug.

2. Type B reactions are idiosyncratic and unpredictable based on pharmacology [5].

Factors that predispose to the side effects of drugs; include dose, the chemical structure of the drug, patient-related factors, pregnancy, polypharmacy, and drug interactions. Different factors influence the development of side effects to varying degrees. These factors should be considered to prevent or reduce undesirable drug effects. In addition, information technology should be part of the decision-making process for drug therapy. This way, healthcare professionals stay up-to-date on drug dosing, drug interactions, side effects, and other important information needed to use the drug optimally [6].

Dosage and time of administration

Drug dosing affects the development of side effects in many ways. The side effects of some drugs develop in a dose-dependent manner [5]. The drug's administration time may also cause the effect and side effects of the drug to change. Some medications must be given in the morning, some in the evening, and some before bed [6].

Chemical structure of the drug

The dynamics governing the drug's reaction largely depend on the structural arrangement of functional groups. The drug's chemical structure determines its physicochemical properties, absorption, distribution, metabolism, excretion and toxicity (ADME/TOX) properties. Finally, the pharmacological activity of the drug molecule and the side effects it may cause largely depends on the drug's chemical structure. Therefore, it is crucial to investigate the impact of functional groups on side effects to synthesize drugs with few side effects [6-8].

Patient-related factors
Age

All drugs can cause side effects, but not all patients develop the same level and type of side effects. The elderly and pediatric patients are particularly susceptible to adverse impacts because the absorption and metabolism of drugs are more variable and less predictable in both groups.

Gender

Anatomical and physiological differences depending on gender may cause the effect of drugs to change. Women have lower body weight, more body fat, different gastric motility, and a lower glomerular filtration rate than men. These differences can change the pharmacokinetics and pharmacodynamics of drugs.

Pregnancy

Physiological changes in the body during pregnancy affect the pharmacokinetic and pharmacodynamic properties of the drug. The change in the distribution and elimination properties of the drug causes the side effect to change as well.

Creatinine clearance
Creatinine clearance reflects the function of the kidneys, which are responsible for the excretion of

many drugs. Any change in kidney profile may increase drug toxicity or reduce the therapeutic effect.

Drug-related factors
Polypharmacy

Taking more than one drug simultaneously increases the risk of side effects by causing drug interactions. The severity of the side effect increases disproportionately as the number of drugs taken increases [8].

B. IMPORTANCE OF SIDE EFFECTS

Drug safety is one of the most critical issues in medical practice, especially regarding approving new drugs or questioning the possibility of a drug being withdrawn from the market [9]. It guides pharmacological treatment and effectively decides which drug should be given to a patient.

The fact that there are many drugs on the market and the misuse of drugs that can cause serious side effects has made the issue of drug safety one of the most critical health problems of the age. The drug safety problem referred to as the 'thalidomide disaster' in the literature is related to the use of this contraindicated drug for morning sickness by many pregnant women in Europe in the late 1950s. The fact that the side effects it may cause have not been adequately investigated has led to the congenital disease known as phocomelia [10].

Drug side effects are an essential parameter in evaluating the safety of drugs. The most critical factor in the emergence of drug safety problems; The reason for this is that the understanding of possible side effects is insufficient due to the long-term and complex clinical studies. For this reason, drugs may enter the market without all their side effects being detected [11].

Pharmacovigilance studies include systematic monitoring of adverse drug reactions and determination of the safety and efficacy of drugs. The WHO defines pharmacovigilance as "the science and activities concerned with the detection, assessment, understanding and prevention of adverse effects or other drug-related problems" and plays a crucial role in ensuring that patients take safe drugs [12].

It enables monitoring the drug's effect in various patient types with comorbid diseases. The potential user population of a drug is very different from the population studied during clinical trials prior to the drug's approval. For example, significantly few clinical trials will involve very elderly patients or patients with comorbidities or breastfeeding women [13].

All drugs have side effects, but their efficacy and severity range from mild (such as mild itching or mild headache) to severe (severe rash, damage to vital organs, particularly the liver and kidneys, and even death). Most of the side effects are predictable. However, the side effects of some drugs and the effects that may occur as a result of their use in special populations cannot be predicted [9]. Today, many studies are carried out to determine the side effects of drugs.

C. CONTEMPORARY SIDE EFFECT STUDIES

Identification of drug side effects is considered an important step in drug design. Because these studies not only save time but also reduce the cost of drug development [14].

Side effect studies on a drug can be divided into the design phase of the drug, the clinical research phase before it is put on the market, and the studies after it is made available [13-15].

Studies of identifying drug side effects with traditional approaches are divided into ligand-based and docking approaches. However, the quantitative structure-activity relationship performs poorly in predicting candidate ligand binding using machine learning methods when reducing the number of ligands for target proteins. The docking approach cannot be applied to proteins with unknown 3D structures [14, 15].

The clinical research phase of drug development studies investigates drug safety, effects and side effects clinically. At this stage, drugs are administered to people with the disease intended to be treated, and side effects are tried to be detected. However, these studies are not comprehensive

enough to identify all the side effects that the drug may cause. Therefore, studies to determine side effects continue after the drug is released on the market [15].

Postmarketing surveillance of drugs involves identifying and collecting drug-related information after the drug has been approved for use in a population. It is a method of systematically monitoring the safety and efficacy of new drugs in the real world using a variety of patient types with many different comorbid diseases [13]. No single method is used in the surveillance of adverse drug reactions.

Individual case reports include reports submitted to national regulatory authorities and anecdotal reports in medical journals.

Cohort-event monitoring allows the quantification of adverse event rates. Cohort sizes typically range from a few thousand to tens of thousands of patients. Allows estimation and comparison of incidence rates among medicinal products.

Analysis of longitudinal patient records can detect a wide variety of temporal patterns between medical diagnoses and drug prescriptions [16].

D. AI AND SIDE EFFECT STUDIES

Traditionally, side effects of drugs are monitored by humans during clinical trials and postmarketing monitoring processes. However, these methods may be insufficient in detecting and reporting side effects. Therefore, using AI technologies can help detect the side effects of drugs more accurately [1, 17-19].

AI can detect and report side effects based on large amounts of data [20]. This data may include patients' health records, drug manufacturers' reports, results of clinical trials, side effect reports, and other health records. By analyzing this data, AI can identify possible causes and mechanisms of drug side effects [17, 21].

However, there are also some difficulties with the use of AI technologies. For example, data collection and analysis can take a lot of time, and it is important to use the right data to get accurate results. It should also be noted that AI technologies may not accurately detect side effects. Therefore, using AI to detect the side effects of drugs may give a more effective result when combined with other methods [1, 22, 23].

Several studies exist on using AI technologies to detect the side effects of drugs [24].

Data mining studies: These studies use artificial intelligence technologies to explore relationships between drug use and adverse effects in large existing datasets [25-27].

Natural language processing studies (NLP): These studies use artificial intelligence technologies to analyze natural language data such as reviews, health records, and other documents written by drug users [28, 29].

AI-assisted clinical trials: These studies use artificial intelligence technologies in clinical trials to detect the side effects of drugs. These studies can increase the efficiency of experiments and speed up the detection of side effects [30].

Machine learning studies use machine learning techniques to learn complex relationships between drug use and side effects [31].

Classification studies use artificial intelligence technologies to classify drug use and side effects associations. These classifications can help accurately report drug side effects [32].

There are many review articles on the use of artificial intelligence in pharmacovigilance. Only a few of these articles have focused on explainability. The difference in this study is that it focuses on both AI and XAI and their use in the field of pharmacovigilance.

E. ADVANTAGES AND DISADVANTAGES OF USE OF AI IN DRUG SIDE EFFECT STUDIES

The use of AI technologies and studies to detect drug side effects have advantages and disadvantages [33].

ADVANTAGES:

Faster results: AI technologies can analyze large amounts of data quickly, allowing for more rapid detection of side effects.

More accurate results: It can obtain more accurate results by analyzing large datasets to detect side effects.

Discovery of new associations: AI has the potential to explore new associations between drug use and its side effects. These discoveries may help better understand and report drug side effects.

Less human error: AI technologies can reduce human error in detecting side effects, contributing to more accurate results.

DISADVANTAGES:

Lack of data: If missing data is used to detect side effects, it may not give accurate results.

Data illusion: AI technologies can be misleading or misleading in data used to detect side effects.

Bias: AI may not be able to provide accurate results if the data used for detecting side effects are biased.

In some cases, AI technologies may still not be able to perform complex thinking processes as humans do and may not be able to detect all of the side effects. In conclusion, while AI technologies can provide many advantages when used to detect the side effects of drugs, they also have some disadvantages. Therefore, using these technologies may yield the best results with other methods.

F. REQUIREMENT OF EXPLANATION ON PHARMACOVIGILANCE

Explainable artificial intelligence (XAI) can be used in the field of pharmacovigilance, making the monitoring and reporting of drug side effects more efficacious [34-37]. By processing pharmacovigilance data, XAI can predict potential side effects and risks. These systems can analyze large amounts of data to detect possible side effects of drugs. In addition, XAI systems can more accurately predict side effects by considering other factors related to a drug's interactions or use. This technology can assist in developing medicinal products and vital research to ensure patients' safety and make the pharmacovigilance process more accurate, faster and more efficient.

XAI is an approach that aims to provide transparency and an explanation of how artificial intelligence, its algorithms, or other automated decision-making systems work. This is extremely important for people to understand and increase the reliability of decisions and forecasts [38].

SHAP (Shapley Additive Explanations) and LIME (Local Interpretable Model-Agnostic Explanations) methods can be used in pharmacovigilance assessments of drug safety and to understand the causes of side effects.

SHAP is used to identify the importance of features that contribute to the operation of machine learning models. In pharmacovigilance, the SHAP method can analyze drug efficacy and side effects on several characteristics (age, gender, disease status, drug dosage, etc.).

LIME is a method that reduces the complexity of machine learning models. In pharmacovigilance studies, the LIME method can reveal causes related to a particular side effect of a drug. Specifically, the LIME can identify why a drug causes different side effects for a specific patient population or disease state.

The SHAP and LIME methods are valuable tools for obtaining information about drug efficacy and side effects in pharmacovigilance. These methods can provide more efficient and informative results than traditional drug safety assessment methods [17].

Table 1. Compilation studies on artificial intelligence and pharmacovigilance in recent years.

Title of Review	Ref
Artificial Intelligence and Data Mining for the Pharmacovigilance of Drug-Drug Interactions	[39]
Artificial Intelligence in Pharmacovigilance and COVID-19	[40]

Artificial Intelligence Based on Machine Learning in Pharmacovigilance: A Scoping Review	[41]
Exploratory pharmacovigilance with machine learning in big patient data: A focused scoping review	[42]
Artificial Intelligence-Based Pharmacovigilance in the Setting of Limited Resources	[43]
Artificial intelligence in pharmacovigilance: Do we need explainability?	[17]
The Use of Artificial Intelligence in Pharmacovigilance: A Systematic Review of the Literature	[2]
Intelligent Telehealth in Pharmacovigilance: A Future Perspective	[44]
Machine Learning in Causal Inference: Application in Pharmacovigilance	[45]
Clinical pharmacology: Current innovations and future challenges	[46]
Applying Machine Learning in Distributed Data Networks for Pharmacoepidemiologic and Pharmacovigilance Studies: Opportunities, Challenges, and Considerations	[47]

II. DISCUSSION

Research in AI and pharmacovigilance shows that it can help detect the side effects of drugs more quickly and accurately. These technologies are highly effective in analyzing large datasets so that possible risks of side effects can be detected at an earlier stage. In addition, AI technologies offer higher accuracy in analyzing side effects, helping to understand side effects better. Studies in the field of pharmacovigilance have demonstrated the potential advantages of these technologies. However, there are also some disadvantages associated with using AI. These include issues such as data security and privacy, the accuracy of algorithms, and whether they can replace human expertise in recognizing side effects.

In addition, the use of AI in the field of pharmacovigilance also opens up ethical issues in the pharmaceutical industry. For example, there is a concern that pharmaceutical companies might use these technologies to hide the side effects of drugs. Therefore, it is necessary to establish clear and transparent regulations on utilizing AI technologies in pharmacovigilance.

Consequently, the use of AI in the field of pharmacovigilance may play an essential role in the safety of drugs. However, the disadvantages of its use, such as ethical and safety issues, should also be considered, and steps should be taken to resolve these issues.

III. CONCLUSION

AI can help identify the side effects of drugs more accurately, leading to a better understanding of the safety and effectiveness of drugs.

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