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Artificial Intelligence in early detection of Adverse Drug Reaction for Anti-psychotic drugs

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ABSTRACT

Impact of Adverse Drug Reactions (ADRs) is a major cause of concern with major economic and emotional consequences to different stakeholders like pharmaceutical companies, patients and even Governments. The development of new antipsychotic drugs is a long and extremely expensive process. The average development of Antipsychotic drugs is 7-10 years and costs millions of dollars to bring a new antipsychotic drug to market. One of the biggest challenges to this long and expensive frame is ADRs. Considering the conceptualization of the drug to its final delivery to patients is complex and time consuming, use of advanced technologies like Artificial Intelligence can be a game changer and a win-win situation for all stakeholders. This review article aims to highlight the use of artificial intelligence (AI) in discovery and development of antipsychotic drugs with focus on the "Pre-Clinical Research" phase.

Introduction

Antipsychotics, also known as neuroleptic drugs, are used for the treatment of various psychotic disorders like schizophrenia, acute mania, depression, personality disorder, Parkinson's disease etc. The use of antipsychotics has been linked to adverse side effects like cardiac issues, including life-threatening arrhythmias and sudden cardiac death (SCD). Side effects of Antipsychotic drugs are usually analyzed and found as part of the pre-clinical and clinical trials to understand the toxicity and dosing levels. Preclinical studies usually work on a small sample size.

World Health Organization (2022) report provides the data for 2019 that shows the following view of mental health across the world: 1 in every 8 people in the world live with a mental disorder, 301 million people were living with an anxiety disorder including 58 million children and adolescents, 280 million people were living with depression, including 23 million children and adolescents, 40 million people experienced bipolar disorder, Schizophrenia affects approximately 24 million people or 1 in 300 people worldwide, 14 million people experienced eating disorders including almost 3 million children and adolescents, 40 million people, including children and adolescents, were living with conduct-dissocial disorder. There has been a constant increase in the Adverse Event reporting cases towards FDA year on year.

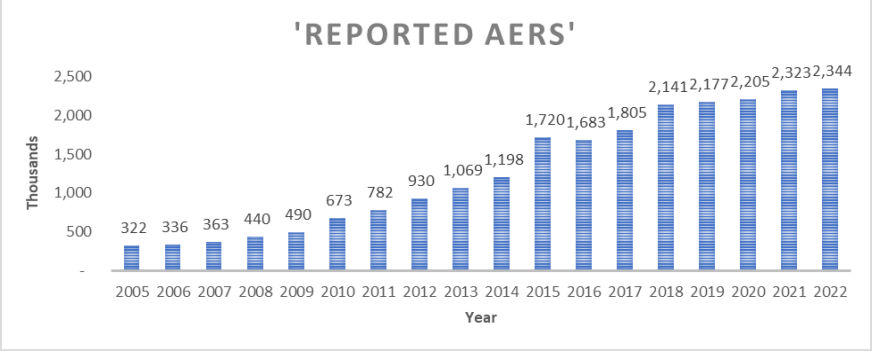

Figure 1. The report below from FDA Adverse Event reporting dashboard from the year 2005 till 2022, with newer drugs being introduced as well as reports from older drugs.

Current mechanisms to understand the efficacy of the drugs depend on measures like rodent, human trials. Disparity between the measures can lead to disparate analysis and findings; for example, an interview-based assessment will not be possible for a rodent subject. Use of technology to build and assess efficacy of drugs can be a game changer.

In this review, the aim of this research is to summarize the use of cutting-edge technology to discover new drugs for the good of humankind with use of AI in a "fail fast" approach. Studies are being undertaken to capitalize on the use of AI for design and development of Antipsychotic drugs. This research aims to complement the existing studies to mitigate drug side effects at an early stage of drug development using AI.

Drug Discovery & Development Process

Drug discovery and development process follows multiple phases. Phase 1 involves discovery and development wherein the researchers aim to discover new insights into the disease, research molecular compounds. Researchers further study methods of dosage, identification of interaction with other drugs, toxicity, Phase 2 involves vitro "within the glass" and vivo "within the living" study of toxicity before any human trials, Phase 3 involves testing the drug on a sample group of human volunteers to identify drug safety. Phase 4 involves the drug developer providing all evidence of preclinical and clinical trials to the FDA for review and approval to market the drug. Phase 5, FDA, and the drug developer monitor the efficacy and safety of the drug.

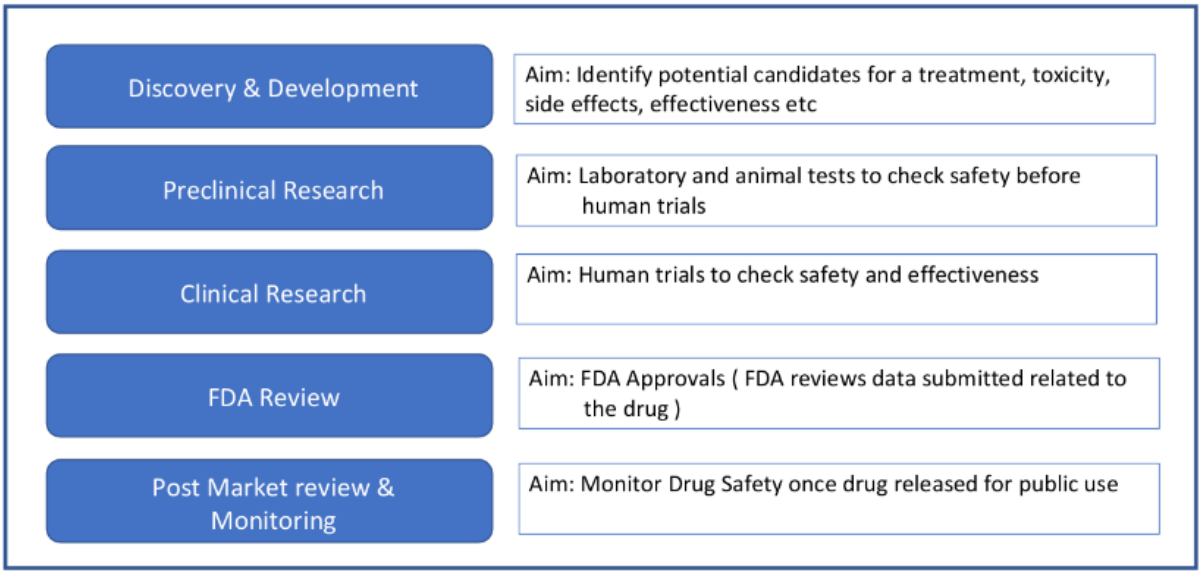

Figure 2. The review article concentrates on how AI can help reduce side effect identification at Phase 1 i.e., Discovery and Development Phase.

Antipsychotic drugs

Antipsychotic drugs are a class of medications that are used to treat psychosis, which is a condition of psychosis that causes people to experience delusions, hallucinations, and disorganized thoughts and actions. There are two main types of antipsychotic drugs: First-generation antipsychotics: These drugs were the first types of medications developed for treating psychosis. Second-generation antipsychotics: These are now the main drugs for treating psychosis. That is mostly because they have fewer side effects.

Side effects of antipsychotic drugs

Like any other medication antipsychotic drugs can also have potential side effects. The severity and occurrence of the side effects can vary depending on the specific drug, the individual's physiology, dosage, and other factors. Some of the Adverse side effects of antipsychotic drugs are presented in the table below:

Table 1. Common Adverse Side effects of antipsychotic drugs

Adverse Effects	**Description**
Blood Disorders	Blood Clotting, reduced white blood cells
Bed Wetting	Bed wetting is a common side effect of antipsychotic drugs
Movement disorders	Tremors, involuntary movements
Weight gain	Obesity
High blood sugar	Diabetes, increase in blood sugar
Sedation	difficult to stay awake and alert
Dry Mouth	Dental problems
Blurred Vision	Degeneration of the retina, glaucoma
Emotional Effects	Anxiousness, aggressiveness, depression, social withdrawal
Heart problems	Heart palpitations, increased heart rate
Neuroleptic malignant syndrome (NMS)	Rare, but a serious disorder affecting the nervous system.
Dermatological effects	Skin-related reactions, including photosensitivity or rash
Gastrointestinal Effects	Constipation, nausea
Hormonal Effects	Irregular menstrual cycles, breast enlargement, and lactation in both men and women

Artificial Intelligence

AI is a machine's ability to perceive, synthesize, and infer information and then perform cognitive functions mimicking that of a human mind.AI offers different techniques – Machine learning, supervised learning, un-supervised learning, reinforced learning, Natural language processing and Deep learning that can be used in the field of ADR identification.

Machine learning technique tries to adapt and learn from previous data in order to predict new output values, supervised learning uses labeled data "already tagged with correct data" to train a model , unsupervised learning uses Unlabeled data "similarities or differences" to train a mode, reinforced learning learns from experimenting "trial and error", Natural Language processing comprehends human language (speech to text, text to speech) , Deep learning uses neural networks – they mimic a human brain wherein the computer learns to perform a task by analyzing underlying relationships in a set of data.

In the research paper by Vatansever et al. (2020) the researchers provide a conceptual framework for an AI platform assisting drug discovery with the following steps to support the discovery process: The basic steps of building an artificial intelligence (AI) platform for drug discovery. The process for developing an AI model as follows: (1) Define the problem appropriately (objective, desired outputs, etc.), (2) prepare the data (collection, exploration and profiling, formatting, and improving the quality), (3) transform raw data into features and select meaningful features (a.k.a. feature engineering), (4) split data into training and validation sets, (5) develop a model, (6) train the model with a fraction of the data, test its performance (cross-validation) and tune its parameters with the validation set (7)

evaluate model performance on the validation set and refine the model, and (8) evaluate the model on independent data not used for method development.

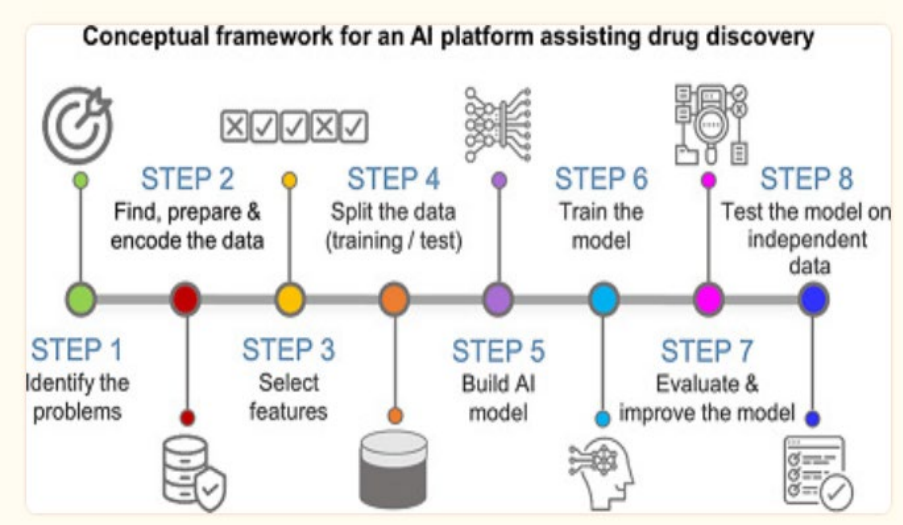

Figure 3. Source : Vatansever et al. (2020)

Bringing all together: Artificial Intelligence (AI) in drug Discovery

Vast quantities of data that are widely spread across various knowledge databases or data points need to be analyzed rapidly and with speed to identify possible ADRs as part of the drug discovery process. Artificial Intelligence platforms is the answer to crunch, analyze digitized knowledge databases to support early identification of ADRs especially for antipsychotic drugs.

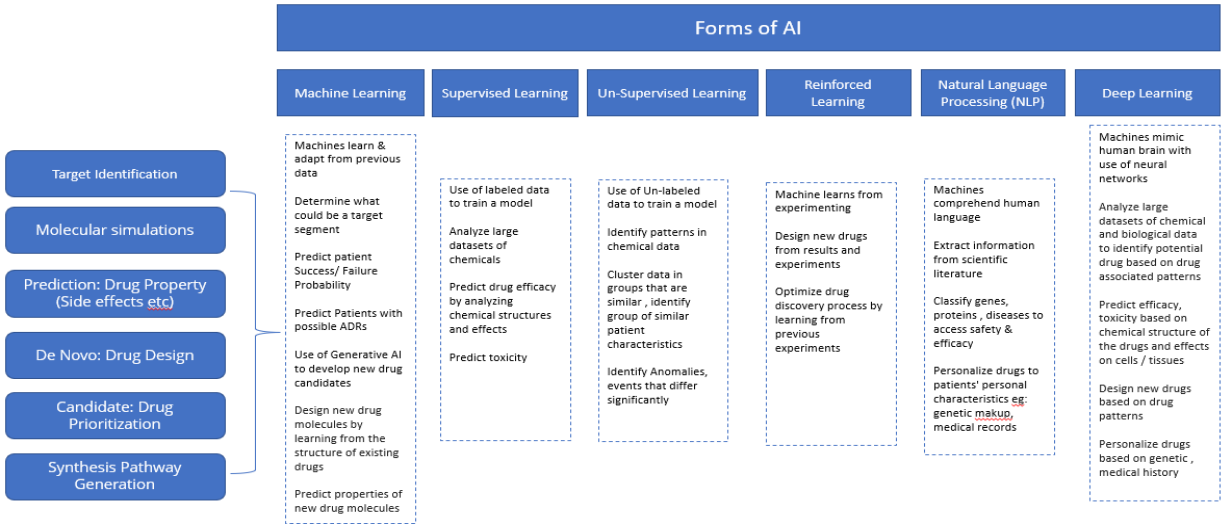

Figure 4. AI in drug discovery

AI's ability to determine a target segment, predict success/failure, possible ADRs, and predict new molecules can help in improving the antipsychotic drug discovery process. In an article published by Das and Mazumder (2023b) complied the use of supervised computational learning methods are essential to reduce time, chemical waste, design complexity, risk of failure, and cost to predict drug side effects with approaches like support vector machine, K-nearest

neighbor, Decision Tree etc. Unsupervised learning can also play an important role in analyzing chemical patterns during drug discovery. This approach has been highlighted by Polanski (2022b). Jaroslaw uses unsupervised learning to process molecular data. Vast amount of digital information available with healthcare providers can be an important source for analyzing ADRs. In a study by Iqbal et al. (2015b), Natural language processing is used to analyze Electronic Health Records (EHRs) with the use of text mining and natural language processing.

The various forms of AI (figure 4) can play a vital role in overall drug discovery at various process states e.g.: Target identification, molecular simulation, ADR detection, De Novo, identify possible drug candidates and pathway generation. There are various sources from which researchers using AI can collect data for analysis:

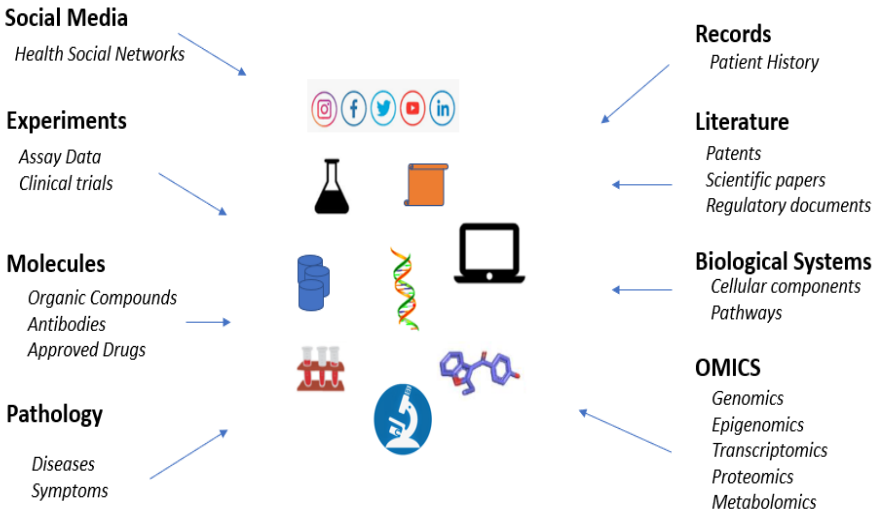

Figure 5. Various sources of data available for analysis "DATA COLLECTION"

Each set of data sources brings in different insights that can be used by AI to analyze & predict possible ADRs at each stage of the drug development process. The table below provides a view of the role AI can play to support the ADRs identification based on the data available across the sources:

Table 2. Role of AI in ADRs identification based on data available across sources.

Data Source	Insights	Role of AI
Social media	People use social forums to share their health experiences	Monitor, construct predictive models by collecting reported ADRs
Records	Use of Electronic health records available with hospitals	Use of natural language processing (NLP) tools to extract ADRs
Experiments	Use of Assay data, clinical trials	Analyze datasets, identify patterns
Molecules	Use of organic compounds, antibodies, approved drugs	Screen libraries of compounds, identify patterns, predict toxicity
Pathology	Disease symptoms	Analyze symptom datasets, predict symptoms based on patient genetics, individual symptoms
Literature	Use of insights from patents, scientific papers, regulatory documents	Analyze emerging trends, analyze scientific papers for potential drug compounds, Identify compliance risks, violations

Data Source	Insights	Role of AI
Biological Systems	Use of cellular components, pathways	Identify proteins that are involved in disease-causing pathways, identify mutations that make cells resistant to drug
OMICS	Measure and characterize different biomolecules in cell, tissues	Analyze omics data, Identify data patterns

Social Media

Today more and more personalized information is available on social media platforms. People across the globe are sharing their health experiences, these experiences can act as a great input into the analysis of ADRs for drugs, in our case antipsychotic drugs. Researchers can use AI algorithms to identify patterns & trends to identify possible ADRs during their research. The prevalence of social platforms among all age groups, and the abundance of data available through them, provides an important source that can be exploited for ADR detection. Huang et al. (2022) present use of social media posts to construct predictive models of adverse drug reactions (ADRs). The following method can be used for the extracting and analysis of social media conversations.

1. **Data collection:** Researchers can have AI tools scape social media platforms like Twitter, Facebook, Reddit, and specialized patient forums e.g., DailyStrength , MedHelp
2. **Structure Data:** Language of social media is highly informal with use of emoji's, slang, issues with logical sequence, partial information etc. AI tools would be required to structure and label data to make sense of the data.
3. **Natural Language Processing**: Use of NLP to extract and build meaningful data with word clustering and sequence labeling related to psychotic issues.
4. **Machine Learning algorithms**: Use of supervised and unsupervised AI models to classify, report and identify trends related to psychotic issues.
5. **Visualization & Validation**: Reports generated by AI tools would need validation by humans for example review samples, accuracy.
6. **Continuous loop**: Continuous feedback loop beginning from social media posts to human validation will ensure continuous training of the AI models and continuous identification of new ADRs.

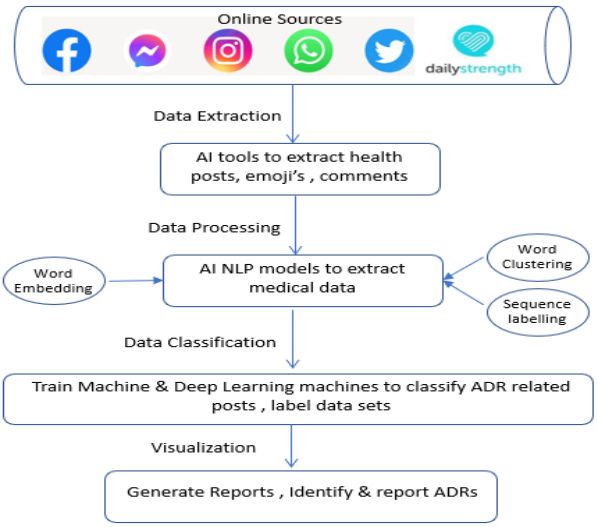

Figure 6. The flowchart below presents the possible use of AI in identifying ADRs from social media.

Electronic Health Records

Electronic health records (EHR) provide a digital snapshot of patient's medical condition, drug prescribed, medication measurements, lab results, demographic insights etc. EHR's are now replacing traditional paper-based medical records, thereby enabling researchers and health care professionals to use technology to make more informed decisions. Rajkomar et al. (2018b) present the use of EHR data for predictive modeling to drive personalized medicine and improve healthcare quality.

The availability of massive EHR databases for researchers and health care providers can redefine the ADR discovery process. EHR data can be used for disease specific analysis, in this case for psychotic scenarios.

1. **Data collection**: Obtain electronic health record (EHR) datasets from hospitals, labs, institutions, personal wearables, clinical notes/transcripts, patients medical records, patient demography etc.
2. **Data Extraction**: Use AI techniques like NLP remove inconsistencies, extract medication related information, standardize information.
3. **Data classification**: Use ML, Deep Learning techniques to learn patterns, trends, classify structured and unstructured data.
4. **Train & Validate**: Use models like logistic regression, random forests, support vector machines, recurrent neural networks (RNNs), transformer models to train AI. Validate metrics for accuracy during the training.
5. **Visualization**: Use of AI tools to predict and visualize identified ADRs.
6. **Continuous loop**: Continuous feedback loop beginning from updated EHRs to validation and visualization will ensure continuous training of the AI models and continuous identification of new ADRs.

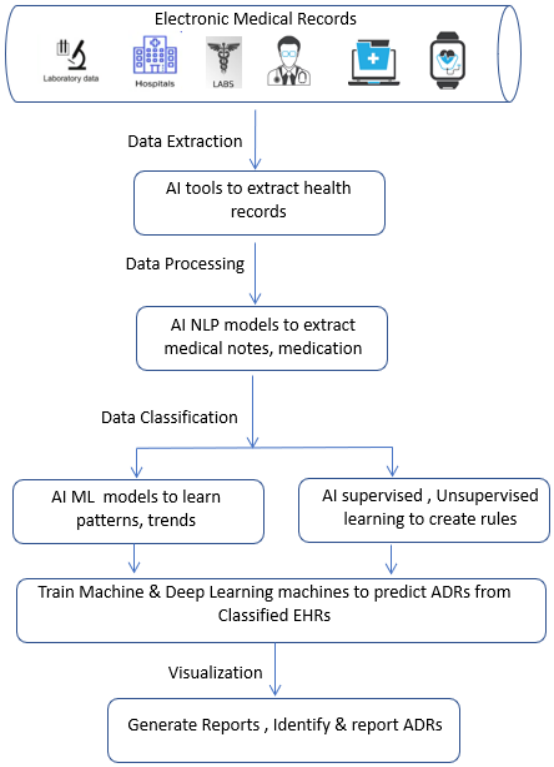

Figure 7. The call flow presents the possible use of AI in identifying ADRs from EMRs.

Preclinical Experiments

Lab research, pre-clinical tests are essential steps in drug development.AI can help consolidate and analyze findings from different stages of preclinical research including lab research, vitro-vivo studies, and importantly animal studies.

1. **Lab Research**: AI can aid researchers in experimenting and analyzing large set of data to identify potential ADRs. AI algorithms can be used to optimize experiments by analyzing and mining large datasets of preclinical assay data to identify patterns and associations that may be indicative of ADRs. Large set of genomics, proteomics, metabolomics datasets can be analyzed using AI to identify patterns and biomarkers associated with ADRs. As presented in the research paper by Qureshi et al. (2023) AI can be used to virtually screen and identify compounds, predict protein-drug interactions. AI can also be used to plan efficient routes for chemical synthesis and develop insights into the reaction mechanisms of drugs to identify potentially unwanted interactions with other molecules. The use of AI deep learning models to predict toxicity in the chemical compounds is also a valuable advantage for researchers to predict ADRs earlier.
2. **Vitro and Vivo Studies**: AI can process data from various tests and experiments to identify potential ADRs during the Vitro and Vivo studies. AI algorithms can analyze molecular and cellular effects in vitro to identify biomarkers of ADRs and their toxic effect as presented by Yang and Kar (2023b).
3. **Animal Studies**: In 2022, the US government Food and Drug Association (FDA) has approved researchers to use alternatives to animal testing, including cell-based assays. This is a landmark decision, considering traditional research has relied on animal testing. AI can support predicting drug metabolism and excretion to predict the potential of drugs to be metabolized and excreted by the body. The use of AI allows for the rapid screening of vast libraries of compounds, yielding useful insights into the compounds' potential metabolism and excretion. Using AI algorithms researchers can also bridge the gap between animal and human data by translating animal responses to potential human outcomes, enabling the prediction of ADRs.

Molecules

AI is being used to reduce the need for physical testing of candidate drug compounds by enabling high-fidelity molecular simulations that can be run entirely with computers, thereby drastically reducing both cost and time in drug discovery as presented by Noé et al. (2020b).AI-generated molecular designs using generative models and reinforcement learning can propose novel drug-like molecules as presented by Zeng et al. (2022b). Vast digital knowledge base with commonly used chemicals, bioinformatic databases providing labeled and unlabeled data can be analyzed by AI to train, validate, and test deep generative models for the drug discovery.

Pathology

A new term "digital or computational pathology" based on AI is being coined to differentiate from traditional pathology. AI forms like Deep learning, machine learning, neural networks are enabling researchers to analyze large datasets and recognizing patterns, normalizing sample data. Cui and Zhang (2021) indicate Computational pathology is burgeoning subspecialty in pathology that promises a better-integrated solution to whole-slide images, multi-omics data, and clinical informatics. Digital pathology includes the process of digitizing histopathology, immunohistochemistry or cytology slides using whole-slide scanners as well as the interpretation, management, and analysis of these digitized whole-slide images using computational approaches.

AI can be used by Pathologist in the following ways to identify ADRs for antipsychotic drugs:

1. Use of Machine learning language to analyze digitized microscopic images of tissue samples. Deep learning algorithms can help perform cell detection and classification by processing images.
2. Analyze large volumes of biomedical and pharmacological data from various sources.
3. NLP techniques can support in identification of specific ADRs, their severity, and the context in which they occur.
4. Identify potential relations and associations between drugs.
5. AI tools can continuously monitor post-market reporting, patterns, and trends to detect new ADRs and incorporate new insights for drug improvement.
6. AI can process and analyze unstructured text from medical literature, clinical notes, and adverse event reports to extract information about ADRs related to antipsychotic drugs.
7. Predict ADRs based on drug properties, patient medical history & genetics.
8. Identify biological pathways to detect ADRs.

Literature

Traditional research has involved manual processing of data available in patents, scientific research papers, regulatory documents. With AI, analysis of patents, scientific papers and regulatory documents can be undertaken much faster and economically. Some of the technique's researchers can use to identify ADRs using AI techniques is presented below:

1. Natural Language Processing (NLP): NLP algorithms like Named Entity recognition (NER) can be used to screen large datasets to extract molecule or drug in patents, experimental methods, and regulatory requirements for certain drugs. While studying for drugs, researchers can use NLP to reveal crucial ideas contained in patent literature, this can vastly reduce cases of any patent infringement. In the research presented by natural language processing (NLP) techniques He et al. (2021) have been used to extract focused on the text mining over biomedical texts (e.g., scientific literature, such as PubMed abstracts) or clinical data (e.g., clinical health records).
2. Semantic Analysis: Semantic analysis can be used to uncover hidden relationships between drugs, targets and ADRs, Wang et al. (2019) present the method to detect potential ADRs of drugs automatically using a deep neural network (DNN). They used a deep neural network (DNN) model for the detection of ADRs of drugs. The model had 2 purposes: the identification of ADRs, which entailed the discovery of potential ADRs of a drug from known ADR records, and the prediction of ADRs, which pertained to predicting the possible ADRs for a new drug. Wang et al. (2019b) used the word-embedding approach and mapping function to process new drugs that did not appear in the dataset. Furthermore, we examined the overall performance of the model with various feature combinations and the number of hidden layers in the DNN architecture.

Biological Systems

AI techniques now allow researchers to process vast amounts of data to identify genes that underly diseases. AI can be used to identify proteins that are functionally associated with a particular disease pathway. Machine learning algorithms can be used to analyze large datasets of biological data, such as gene expression data, protein-protein interaction data, and drug target data. Fang and Peltz (2022) developed a graph neural network (GNN)-based automated pipeline that could rapidly analyze mouse genetic model data and identify high probability causal genetic factors for analyzed traits.

OMICS

AI offers advanced analytical methods with predictive capabilities. The use of predictive models that understand how drugs work at a molecular level can help creation of targeted treatments. With the potential of AI to scan large database to find can be useful in repurposing existing drugs. Gao et al. (2022) present as part of their special issue: 1) AI-based models, methods, and software for the processing, analysis, visualization, and interpretation of omics data; 2) AI-based algorithms for the integrative analysis of omics, clinical, and health data, including biomedical images; 3) AI-based platforms for improving disease diagnosis, precision medicine, and patient care; and 4) AI-based approaches for protein structure prediction, gene function prediction, and drug discovery.

Conclusion and Limitations

AI can become a catalyst in revolutionizing early detection of ADRs in the drug discovery process. Although AI models are in the process of development, The possibilities offered from AI are vast right from drastic reduction in costs of drug discovery, early detection of ADRs to creation and discovery of new drugs. Each form of AI machine learning, Generative AI, Deep learning, supervised & unsupervised learning bring in value additions to researchers in their aim to find new drugs, under ADRs. This review paper tries to bring in different facets AI to support the discovery of ADRs for Antipsychotic drugs, however the concepts and thoughts can be applied to other drug discovery and diseases. The challenges and concerns of AI in healthcare e.g.: Clinical Ethics, Regulatory & Privacy concerns, Complexity will need to be kept in mind always. The review paper is intended to provide a broad overview as to how AI can be used in finding ADRs early in the drug discovery phase for antipsychotic drugs. Further detailed studies as presented in the references could be conducted per drug discovery phase and respective AI models/algorithms used in the respective phases.

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