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| Name | Date | What | How | Why |
| [Prediction of Putative Adverse Drug Reaction-Related Proteins from Primary Sequence by Support Vector Machines](https://link.springer.com/article/10.2165/00124363-200519050-00009) | August 2012 | First case I can find where they apply machine learning for ADR research. They classify protein structures related to ADR’s. | Using SVM classification. 93.9% of the ADR-related proteins and 98.2% of non-ADR-related proteins were correctly classified. | Identifying ADR-related proteins facilitates the design of drugs with fewer adverse effects by avoiding unwanted interaction with these proteins. |
| [Large-scale prediction of adverse drug reactions using chemical, biological, and phenotypic properties of drugs](https://academic.oup.com/jamia/article/19/e1/e28/2909247) | June 2012 | Proposes a data fusion approach to ADR prediction, common machine learning methods, and introduces some evaluation methods. Also discusses feature importance of chemical properties for prediction. | The approach they propose uses phenotypic characteristics, known ADRs, chemical structures and biological properties (protein targets and pathway information). They compared 5 machine learning algorithms with fivefold cross-validation, when predicting 1385 known ADRs of 832 approved drugs. Found that phenotypic data was the most useful for predictions. | Aim to increase accuracy of prediction models for ADR’s. |
| [Factors affecting the development of adverse drug reactions (Review article)](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3950535/#:~:text=Pharmacological%2C%20immunological%2C%20and%20genetic%20factors,pharmacodynamic%20abnormalities%2C%20and%20drug%20interactions) | February 2013 | Gives an overview of what factors can cause an ADR, and how important each one is. Also discusses polypharmacy as a factor. | Reviewed literature between 1991 and 2012 from PubMed, the Cochrane database of systematic reviews, EMBASE and IDIS to determine the main factors influencing ADR’s. Categorised factors into patient/social/drug/disease related. | To collate information around ADR’s, to aid future research. The chosen literature sources were the commonly used sources for ADR’s at the time. |
| [The SIDER database of drugs and side effects](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4702794/) | January 2016 | Paper detailing when the SIDER database was created, and an overview of everything it contains. | Released an update to SIDER, which had over 40% more drugs, ADRs and drug–ADR pairs compared to the previous version and more than 2-fold as many drug–ADR pairs. | To continue providing up to date information on ADRs, SIDER is a heavily used ADR dataset. |
| [Modelling polypharmacy side effects with graph convolutional networks](https://academic.oup.com/bioinformatics/article/34/13/i457/5045770?login=false) | July 2018 | Introduces the Decagon model, which is the GNN model that was used to gather the BioSNAP dataset that I’ll be using. Applied it to polypharmacy ADR prediction. | Pulled data from SIDER, OFFSIDES and TWOSIDES. Created a non-linear, multi-layer convolutional graph neural network model. Decagon accurately predicts polypharmacy side effects, outperforming baselines by up to 69%. | Decagon is developed specifically to handle multimodal graphs with a large number of edge types.  Polypharmacy gives a significant increased risk of ADRs. Knowledge of drug interactions is often limited because the relationships are rare, and often go unnoticed in small clinical testing. |
| [Predicting adverse drug reactions through interpretable deep learning framework](https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-018-2544-0) | December 2018 | Tested multiple machine learning models, as well as an interpretable deep learning approach. | Used chemical structures to predict. Compared 10 different state-of-the-art fingerprint models and found that neural fingerprints from the convolutional deep learning model outperformed all other methods. | The main challenge in representing the molecular graphs of drugs into features is how to represent the varying sizes of each drug molecule into a fixed-size feature representation. The proposes model can simultaneously construct chemical fingerprint features and assess their associations with ADRs. |
| [Applications of machine learning in drug discovery and development](https://www.nature.com/articles/s41573-019-0024-5) | June 2019 | Covers how machine learning is used during the drug discovery pipeline. Identifies the issue of a lack of interpretability and repeatability in deep learning prediction methods for ADR’s. | Provides a breakdown of each part of the drug discovery pipeline, and how ML algorithms are used. Gives detailed diagrams that show how each type of algorithm can be applied. | Aim to improve drug discovery pipelines, to save costs and reduce risk. |
| [Machine learning on adverse drug reactions for pharmacovigilance](https://www.sciencedirect.com/science/article/pii/S1359644618303672) | July 2019 | Discusses the issue of interpretability, and proposes a two stage deep learning framework to try and tackle that issue. | Reviews traditional machine learning methods for pharmacovigilance, and proposes a new two-stage LSTM deep learning framework. The first stage is used to predict the association between drugs and their adverse reactions by using deep learning methods running on big data. The second stage integrates an individual’s biological data into the system. To increase interpretability m SMILES was used. | Aim to increase accuracy of prediction models for ADR’s. |
| [The development of a scoring and ranking strategy for a patient-tailored adverse drug reaction prediction in polypharmacy](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7293306/) | June 2020 | Introduces a patient-tailored polypharmacy ADR prediction model. | Trained on 734 drugs from SIDER, designed in Python. Produces an overall severity profile (hospitalization and mortality risk), risk on specific ADR groups and a sorted list of the most important ADRs depending on frequency and severity. Uses a Neural Network (Multi-Layer Perceptron, MLP) machine learning classifier. | Far fewer applications deal with personalized adverse drug reactions (ADRs) prediction in the case of polypharmacy, which is important because patient specific factors do influence ADRs. |
| [A survey on adverse drug reaction studies: data, tasks and machine learning methods](https://academic.oup.com/bib/article/22/1/164/5678053) | January 2021 | Provides a summary of popular ADR datasets, factors involved in ADR’s, common machine learning methods for prediction, and suggests further improvements to the field. Improvements such as polypharmacy prediction (DDI). | Summarized ADR data sources and review ADR studies in three tasks: drug-ADR benchmark data creation, drug–ADR prediction and ADR mechanism analysis. | Attempting to identify current gaps in the field of ADR prediction, and future work. |
| [Prediction of drug adverse events using deep learning in pharmaceutical discovery](https://academic.oup.com/bib/article/22/2/1884/5826453) | March 2021 | Discusses why we need ADR prediction with machine learning. Gives an overview of current methods. Discusses DDI and methods used. Discusses future improvements, such as increasing black box model interpretability with explainable AI. | Doesn’t specify how it selected its literature for review. | Attempting to identify current gaps in the field of ADR prediction, and future work. |
| [Descriptive prediction of drug side-effects using a hybrid deep learning model](https://onlinelibrary.wiley.com/doi/full/10.1002/int.22389?casa_token=wFyukhmhKR8AAAAA%3AaUR1UKic6M0-KVysyeR4GLpuOiXFWigvZcZqZj7NjjfEAqrPDx_a2ACmI1_2PfPC-Ux2tuEtRdScx6rU) | March 2021 | Introduces a new hybrid model for ADR prediction, shows a higher accuracy than baseline methods, despite a small dataset. Future suggestions include work with larger datasets, and incorporating drug information other than chemical structure. | They use a hybrid GCNN-BiLSTM model. Its predictions provide word descriptions of the ADRs, which I’ve not seen in other models so far. | CNNs are good at reducing frequency variations; LSTMs are good at temporal modelling. It has been proven that the performance of LSTM could be improved by augmenting it with CNNs. |
| [Machine Learning in Drug Discovery: A Review](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8356896/) | August 2021 | Provides a review of tools for machine learning in drug discovery, and talks about interpretability issues. | Doesn’t specify how it selected its literature for review. | Attempting to identify current tools for ADR prediction, and future work that needs to be done. |
| [On the road to explainable AI in drug-drug interactions prediction: A systematic review](https://pubmed.ncbi.nlm.nih.gov/35832629/#:~:text=In%20this%20review%2C%20a%20comprehensive,prediction%2C%20the%20modeling%20methods%2C%20is) | April 2022 | Overview of DDI prediction, data sources, and methods. Also discusses current promising methods of XAI. | Searched five databases up to December 2021: Cochrane Library, PubMed, EMBASE, IEEE, and Scopus. The eligibility criteria consisted of DDI predictive models that were built up using ML - and/or DL-based algorithms. The articles were screened and selected independently by two reviewers, and disagreements were resolved by the third reviewer. Ended up reviewing 94 different research studies. | Attempting to identify data sources and current methods, as well as current gaps in the field of ADR prediction, and future work. |
| [Analysing adverse drug reaction using statistical and machine learning methods](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9276413/) | June 2022 | Overview of various drug databases, machine learning models, visualisation tools and evaluation tools. | Literature review was conducted based on articles published between 2015 and 2020. The keywords used were statistical, machine learning, and deep learning methods for detecting ADR signals. Reviewed 72 articles, of which 51 and 21 addressed statistical and machine learning methods, respectively. | Attempting to identify data sources and existing models, to aid future work. |
| [XSMILES: interactive visualization for molecules, SMILES and XAI attribution scores](https://jcheminf.biomedcentral.com/articles/10.1186/s13321-022-00673-w) | January 2023 | Proposes XSMILES, an interactive visualization technique, to explore explainable artificial intelligence attributions scores and support the interpretation of SMILES. | Has a visual representation of feature importance from each of the SMILES strings.  Users can input any type of score attributed to atom and non-atom tokens and visualize them on top of a 2D molecule diagram coordinated with a bar chart that represents a SMILES string. | Made to support data scientists to develop, improve, and communicate their models by making it easier to identify patterns and compare attributions through interactive exploratory visualization. |
| [Recent development of machine learning models for the prediction of drug-drug interactions](https://pubmed.ncbi.nlm.nih.gov/36748027/) | February 2023 | Covers recent developments in DDI prediction, including the best models that have been made, and new data sources. Mentions Decagon.Discusses further improvements in the field. | Doesn’t specify how it selected its literature for review, but it reviews models that have been created since 2018. | Attempting to identify gaps in current research, specifically for polypharmacy. |
| [An Attentive LSTM based approach for adverse drug reactions prediction](https://link.springer.com/article/10.1007/s10489-022-03721-y) | March 2023 | Introduces a novel approach for ADR prediction, focused on association between ADR’s, and not relying on chemical property data. Also introduces more methods of evaluation model accuracy. For future work, it suggests combining the LSTM model that evaluates ADR data, with a model that evaluates structure data. | Proposes an encoder-decoder framework based on attention mechanism and the long short-term memory (LSTM) model to predict potential ADRs. | To learn better embeddings, they optimize the traditional decoder structure so that the LSTM can receive more information from the attention layer. They were the first to consider ADR prediction as a sequence-to-sequence problem. The model is also based solely on ADR data, which are independent of other classical methods utilizing molecular drug structures. It is therefore easily combined with other methods to provide even more accurate predictions with unknown ADRs. |
| [HyGNN: Drug-Drug Interaction Prediction via Hypergraph Neural Network](https://arxiv.org/abs/2206.12747) | April 2023 | Demonstrates a model that analyses SMILES strings. High accuracy, good to consider hypergraph for mine? | Uses a hypergraph GNN model. | Wanted to analyse specifically just structures because not all datasets have extensive information, and most only have structure. GNN has shown promising performance, as well as using SMILES string for prediction. |
| [Deep learning in drug discovery: an integrative review and future challenges](https://link.springer.com/article/10.1007/s10462-022-10306-1) | July 2023 | Gives a review of recent articles and deep learning methods for DDI and DTI, as well as the datasets available. Also discusses the importance of explain-ability in drug discovery, types of XAI, and techniques for it. | Reviews more than 300 articles between 2000 and 2022. The benchmark data sets, the databases, and the evaluation measures are also presented. | Drug discovery has received a lot of attention since it significantly shortens the time and cost of developing new drugs. Deep learning approaches are increasingly being used in all stages of drug development as DL technology advances, and drug-related data grows. |
| [DDI-GCN: Drug-drug interaction prediction via explainable graph convolutional networks](https://www.sciencedirect.com/science/article/abs/pii/S0933365723001549) | October 2023 | [Does almost exactly what I want to do with explainable GNN for chemical structure](http://wengzq-lab.cn/ddi/) |  |  |
| [An objective metric for Explainable AI: How and why to estimate the degree of explain ability](https://www.sciencedirect.com/science/article/pii/S0950705123006160) | October 2023 | Presents a model agnostic measure of explain ability in machine learning models. Useful for my evaluation. | Introduces a metric called Degree of Explain-ability (DoX). It assumes that the degree of explain-ability is directly proportional to the number of relevant questions that a piece of information can correctly answer. They operationalized this concept by formalizing the DoX metric through a mathematical formula. | Aims to fill the gaps that many of the previous review papers in this table highlighted. By giving a measure of explain-ability it’s now easier to asses an interpretable deep learning model. |
| [Application of artificial intelligence and machine learning in early detection of adverse drug reactions (ADRs) and drug-induced toxicity](https://www.sciencedirect.com/science/article/pii/S2949747723000118) | December 2023 | Provides a more recent review of the current state of ADR prediction as a field. Goes into detail about types of ADR’s. Also provides a useful history of ADR’s, talking about major ADR events that began the field. Mentions a lack of interpretability in deep learning methods. Discuses future improvements, including improved accuracy with deep learning methods, and interpretability of black box models. | Doesn’t specify how it selected its literature for review. | Attempting to identify gaps in current research, specifically for polypharmacy. |

**Gap: I’ve seen hybrid models, polypharmacy and explainable AI. But not a hybrid model, for polypharmacy prediction, which is explainable.**