Translating Data into Drugs: Artificial Intelligence in Repurposing Treatments for Complex Neurological Diseases

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Abstract:

Drug repurposing has become a viable substitute for conventional drug development, providing a quick and affordable way to find novel therapeutic applications for already-approved medications. This process has been further expedited by the incorporation of artificial intelligence (AI), which has made it possible to analyse transcriptome profiles, electronic health records, and huge biological databases. Simvastatin, Zileuton, and Efavirenz are the three case studies presented in this review that illustrate how AI enables medication repurposing for complex conditions like, neuropsychiatric, neurodegenerative disorders and cancer. The original mechanisms of action of the medications are discussed in each case, along with how drug repurposing has aided in tailoring the drug's activity to the specific ailment. The integration of AI into drug repurposing holds immense promise for accelerating the discovery of novel therapies, especially for complex and rare diseases. As computational models grow more sophisticated, they will be capable of uncovering deeper biological patterns, enabling precision medicine tailored to individual patient profiles. Advancements in multi-omics data integration, natural language processing, and generative AI could further refine drug-disease matching and mechanism prediction. However, several challenges remain. The quality and standardization of biomedical data, model interpretability, and validation of AI predictions in preclinical and clinical settings are significant hurdles. Additionally, ethical concerns regarding data privacy and the regulatory framework for AI-driven drug development must be addressed. Overcoming these challenges will be crucial for fully realizing the potential of AI in revolutionizing drug repurposing and clinical outcomes.

Keywords: Artificial Intelligence, Drug repurposing, Simvastatin, Zileuton, Efavirenz

Introduction:

The practice of discovering new applications for medications that fall outside of their original medical indications is known as drug repurposing. Drug Repurposing is a good substitute (or addition) to the time-consuming, expensive, and frequently unsuccessful classic de novo drug discovery method (Pinzi et al., 2024). Using *in silico* methods to describe the components of the intricate interactions between diseases, medications, and targets is essential for drug repurposing.

Some classic examples of drug repurposing are; Aspirin, or acetylsalicylic acid, was first used as a pain reliever but has now been shown to have cardiovascular advantages, especially in lowering the incidence of heart

attacks. Since the cardiovascular consequences were first unknown, its repurposing was mainly coincidental.

When patients reported enhanced sexual performance as a side effect, Sildenafil, which was first created for hypertension and angina, was repurposed for erectile dysfunction. Its successful marketing for this new indication was a result of this surprising discovery (Jourdan et al., 2020). Due of its dual therapeutic effects on the same target, minoxidil was repositioned utilizing an on-target approach. From an antihypertensive vasodilator, it evolved into a medication to treat hair loss. It opens potassium channels and widens blood vessels to increase the amount of blood, oxygen, and nutrients that reach hair follicles (Vemula et al., 2024).

Numerous Artificial Intelligence (AI) techniques greatly improve drug repurposing, the process of discovering novel therapeutic applications for already-approved medications. AI uses supervised learning methods such as support vector machines (SVM), and logistic and linear regression to analyse labelled data, identify trends in drug properties, and forecast new target associations to connect therapeutic molecules with possible targets. Potential targets can be inferred based on drug similarities thanks to unsupervised learning techniques like principle component analysis (PCA) and K-means clustering, which extract important characteristics and hidden patterns from unlabelled drug properties.

By combining clinical trial outcomes, patient records, and genetic data, AI goes beyond target prediction and uses empirical data to provide strong validation and verification for repurposing predictions and revealing surprising drug-disease connections. Clustering and dimensionality reduction are effectively handled by regularized optimization models in conjunction with deterministic techniques such as nonnegative matrix factorization, which balance prediction accuracy and processing needs. GNINA and CLUE are AI frameworks that integrate multi-modal data for accurate therapeutic predictions, combining Natural Language Processing for unstructured text analysis, and democratizing drug repurposing through web-based platforms (Wan et al., 2025).

In this paper we discuss 3 case studies of recent times, Simvastatin, an HMG-CoA reductase inhibitor which was repurposed for Alzheimer's Disease. Repurposing simvastatin to treat Alzheimer's disease (AD) was made possible by generative artificial intelligence (AI), notably ChatGPT, which suggested different medications based on current scientific understanding. The effects of simvastatin, which was one of the top 10 medications recommended by ChatGPT, were examined in a study employing information from two sizable clinical datasets. Simvastatin was linked to a 16% lower incidence of AD in older persons, according to the data, suggesting that it may be used as a repurposing therapeutic option (Wei et al., 2023).

Efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTIs) used in combination to treat HIV was repurposed to in treatment of Parkinson’s Disease. Using drug-perturbed gene expression data, the study identified efavirenz as a possible treatment for Parkinson's disease (PD) using Standigm InsightTM, an AI-based platform. Alpha-synuclein (a-syn), a crucial protein implicated in Parkinson's disease pathology, was discovered to be inhibited in both release and absorption by efavirenz. Additionally, it assisted in reestablishing the brain's faulty metabolism of cholesterol. In a number of in vivo studies, such as those involving mice and C. elegans, the effectiveness of efavirenz in reducing a-syn propagation was shown (Kim et al., 2024).

Zileuton, a LOX-inhibitor was repurposed in depression. To find Zileuton as a potential depression treatment, researchers used text mining with deep neural networks and RNA-seq data. Sentence embeddings were produced using a Google semantic AI universal encoder, which made it possible to calculate sentence similarity and find pertinent medicinal molecules. The NRF2 pathway was identified in the study as a key target for

reprogramming M1 macrophages to have an anti-inflammatory profile, which is advantageous in cases ofdepression. The concept was validated in vitro, and additional in vivo research is planned to see whether Zileuton is suitable for antidepressant clinical trials (Kubick et al., 2020).

Case Studies:

Case Study I: Simvastatin repurposed for Alzheimer's and Cancer

Simvastatin, a statin that is frequently given for hyperlipidemia, has drawn interest because of its pleiotropic effects, which include immunomodulatory and anti-inflammatory qualities, and its potential for use in the treatment of complicated disorders including cancer and Alzheimer's disease (AD). Finding and validating these repurposing prospects has been greatly sped up by recent developments in artificial intelligence (AI).

Drug Repurposing for Alzheimer's:

Tau-neurofibrillary tangles (TNTs) and amyloid beta (Aβ) plaque buildup in the brain are hallmarks of AD. Amyloid plaques, and neurofibrillary tangles, neuroinflammation, neural mitochondrial dysfunction, autophagy disorder, and cholinergic synaptic dysfunction are all linked to the neuropathological alterations in AD. Regardless of the presence or absence of dyslipidemia, statins remain one of the primary cornerstone medications for the treatment of cardiovascular diseases. Cognitive capabilities may be impacted by the increased use of statins, particularly in older populations, for both the primary and secondary avoidance of cardiovascular illnesses. Long-term, heavy statin usage may impair cognitive abilities in both dementia sufferers and healthy individuals. The post-marketing survey revealed that statins have been linked to cognitive deficits in patients as well as medical personnel (Alsubaie et al., 2022).

In 1907, Alois Alzheimer made the first description of AD in women who had neuropsychiatric problems and memory deficits (Castellani et al., 2010). AD accounts for 70% of all forms of dementia and doubles every ten years as people age. According to reports, the prevalence of AD ranges from 3% in those 65 to 74 to almost 50% in patients 85 and beyond (Kern et al., 2018).

Drug repurposing is a compelling substitute for the costly and laborious method of developing new drugs, especially for severe, common diseases like Alzheimer's disease (AD) that have few effective therapies.

ChatGPT used as AI Tool:

The assessment and summarization of scientific knowledge might be accelerated by new generative artificial intelligence (GAI) technology like ChatGPT. evaluated top ten medications for incident AD risk in exposed and unexposed adults over 65 in two sizable clinical records:
(1) Vanderbilt University Medical Center and (2) the All of Us Research Program. ChatGPT was also charged with suggesting the twenty most promising medications for repurposing in AD. In a meta-analysis, losartan, simvastatin, and metformin were linked to a decreased risk of AD among the candidates recommended by ChatGPT. These results imply that GAI technologies may absorb scientific knowledge from a vast online search field, aiding in the prioritization of medication repurposing options and facilitating treatment of illnesses.

Three of the 10 medications most recommended by ChatGPT—metformin, simvastatin, and losartan—showed protective benefits against AD in a meta-analysis that included data from two extensive EHRs. Simvastatin was linked to a 16% lower risk of AD in a meta-analysis. In contrast VUMC and All of Us, simvastatin was reported to have consistent therapeutic effects (HR < 1) (HR > 1 using All of Us data, and statistically relevant HR < 1

using VUMC data) (Yan et al., 2024).

Widely used cardiovascular medications called statins, which reduce cholesterol by blocking HMG-CoA reductase, are becoming more and more known for their possible anticancer effects (Buccioli et al., 2024).

Drug Repurposing for Cancer:

Simvastatin's complex anticancer characteristics have been uncovered thanks in large part to AI-driven approaches. AI models have discovered simvastatin's potential to disrupt important carcinogenic pathways by examining enormous datasets that include pharmacological, proteomic, and genomic data. Simvastatin, for example, has been shown in studies to have antiproliferative effects on cancer cells by blocking the mevalonate pathway, which is essential for the post-translational modifications of proteins that govern cell proliferation and survival.

Furthermore, the investigation of simvastatin's beneficial properties in combination with other treatment drugs has been made easier by AI. For instance, studies have demonstrated that simvastatin increases the effectiveness of chemotherapy medications such as doxorubicin and cisplatin, which causes cancer cells to undergo more apoptosis. These results highlight simvastatin's potential as an adjuvant cancer treatment.

Furthermore, simvastatin's function in modifying the tumor microenvironment has been brought to light by AI-driven research. Simvastatin helps to create an environment that is less conducive to tumor development and spread by affecting angiogenesis and immunological responses. These realizations have been essential to comprehending simvastatin's wider effects in cancer treatment (Ara et al., 2024).

Using AI in repurposing drugs has several benefits, including accelerating the creation of hypotheses, cutting down on the time and expense involved in conventional drug research, and using the safety profiles of already-approved medications. There are still issues, though, such as the requirement for high-quality data, the necessity for clinical trials to validate AI predictions, and how to handle ethical issues in AI-driven research.

Case Study II: Zileuton repurposed for Depression

Mechanism and Current Use:

Zileuton is a strong and specific inhibitor of 5-Lipoxygenase. This enzyme is necessary to produce LTs, which play a significant role in the pathogenesis of asthma, allergic and inflammatory diseases. Following oral treatment, zileuton becomes active and directly inhibits 5-lipoxygenase, just like most other 5-lipoxygenase inhibitors. It doesn't attach to the protein that activates 5-lipoxygenase. For aspirin-sensitive asthmatics, zileuton has shown protection against bronchoconstriction after aspirin administration, cold, dry air, and exercise-induced asthmatic reactions (Wenzel & Kamada, 1996).

The idea that the immune system has a complicated and potent impact on the brain is supported by research on cytokines. Depression is suggested to be caused by the overproduction of the macrophage monokines IL-I, interferon alpha (INF-a), and tumor necrosis factor (TNP) in this research (Smith, 1991).

Drug repurposing and the role of AI:

The hallmarks of an inflammatory response are all present in patients with major depressive disorder, including elevated levels of soluble adhesion molecules, acute-phase reactants, and chemokines in peripheral blood and

cerebrospinal fluid (CSF), as well as increased expression of pro-inflammatory cytokines and their receptors. Gene expression profiles in peripheral blood have also been reported that are consistent with a pro-inflammatory 'M1' macrophage phenotype and an overrepresentation of IL-6, IL-8, and type I IFN-induced signalling pathways.

Inflammatory cytokines can cause decreased synaptic availability of monoamines which is a key mechanism in the pathophysiology of depression. For instance, it has been demonstrated that IL-1β and TNF activation of p38 mitogen-activated protein kinase (MAPK) increases the expression and function of serotonin reuptake pumps, decreases synaptic availability of serotonin, and causes depressive-like behaviour in experimental animals. It has been demonstrated that in stress-induced animal models of depression, IL-1β, TNF, and their downstream signaling pathways, including NF-κB, decrease brain-derived neurotrophic factor (BDNF), which promotes neurogenesis, a crucial precondition for an antidepressant response. Thus, cytokines like TNF and IL- 1β work against these actions by reducing the synaptic availability of monoamines, lowering BDNF, and raising extracellular glutamate—all of which are not targets of traditional antidepressant treatment. The findings that treatment-resistant individuals had higher inflammatory markers and that heightened inflammation is linked to less effective antidepressant treatment responses may be explained by these cytokine-driven effects (Miller & Raison, 2016).

New medication development takes a long time and costs a lot of money—an average of 15 years and $800 million per drug. To drastically cut expenses and time, the authors support screening current medications for novel therapeutic applications. Because the safety characteristics of existing medications are well-established, clinical trials may be evaluated more quickly. Existing medications are increasingly being repurposed, and several are presently undergoing clinical research for novel uses (Chong & Sullivan, 2007).

Artificial intelligence (AI)-powered biological question-answer systems may cut down on the resources required for the compound identification stage. Text mining in the context of question-answer systems has been transformed by AI. Data extraction by hand is laborious and biased (Mickael et al., 2019a).

By inhibiting the transcription of pro-inflammatory cytokines such as IL-6 and IL-1b, NRF2 is a crucial regulator that reduces inflammatory responses in macrophages (Kubick et al., 2020).

An artificial intelligence (QAAI) system that can repurpose medicinal molecules was reported in the paper. To determine the sentence embedding of an enforced text query in connection to publications kept in our RedBrain JSON database, the system uses a Google semantic AI universal encoder. To find pharmacological molecules, a sorting function is used to calculate the similarity of sentences.

Pharmacological activation of NRF2 may be essential for controlling ROS in macrophages during neurodegenerative illnesses. ROS can destroy membranes, alter the structure and function of internal proteins, denaturize lipids, and cause structural damage to the brain's DNA in neurodegenerative illnesses. Additionally, ROS contribute significantly to the progressive decline in macrophages' functional traits in neurodegenerative illnesses. Numerous endogenous antioxidant enzymes are present in the central nervous system (CNS) and are controlled by the transcription factor NRF2.

Numerous neurodegenerative illnesses and maybe depression is associated with oxidative stress, which is reduced by the transcription factor NRF2, which also controls antioxidant responses. Ziteuton can lower

inflammation and oxidative stress, two things that are frequently linked to depression, by activating NRF2. The method used aided in the discovery of zileuton as a potential substance to address neuroinflammation in neurodegenerative illnesses. Through an *in silico* approach, it also forecasted its capacity to penetrate the blood-brain barrier. Its capacity to raise the levels of NRF2 and its target HMOX1 in a macrophage cell line was also confirmed (Mickael et al., 2019).

To examine the transcriptome alterations linked to the repurposing of zileuton as a possible depression treatment, the researchers used RNA-seq analysis. To forecast possible novel zileuton indications, they fed their AI models the transcriptome data. The researchers analysed the RNA-seq data using common bioinformatics techniques and tools, such as differential expression analysis, read alignment, and gene quantification. This demonstrated notable alterations in the expression of genes related to immunological response, inflammation, and neurological functions. Using the transcriptome data, the researchers developed an AI model that was able to learn semantic embeddings of biomedical concepts. Because of this, they were able to find parallels between zileuton's transcriptome signature and those of other medications, which may indicate novel indications for conditions like depression (Kubick et al., 2020).

Validation process:

To examine zileuton's impact on neuroinflammation and depressive-like behaviours, the researchers used in vitro tests. To evaluate zileuton's anti-inflammatory properties, they employed primary microglial cell cultures and measurements of pro-inflammatory cytokine production. To assess the neuroprotective effects, they also employed measures of synaptic protein expression, neurite outgrowth, and hippocampus neuron cultures. *In vitro* and in animal models, M1 macrophages stimulated by pathogen-associated molecules such as flagellin, lipopolysaccharide (LPS), or peptidoglycans release inflammatory cytokines such TNFα, IL- 1β, and IL-12. Combining these findings points to a key pharmacological target avenue for major depression: modifying the M1 response. By using a deep averaging network (DAN), 25 chemicals were identified. To eliminate less pertinent medications, the findings were filtered using a differential convolution network (DCN). Using this method, zileuton, a lipoxygenase inhibitor, was identified as a NRF2 function regulator.

Together with earlier computer projections, these results lend credence to zileuton's potential as a modern depression treatment. The researchers were able to immediately evaluate zileuton's pertinent pharmacological characteristics and evaluate the findings in light of zileuton's potential as a therapy for depression due to the thorough in vitro validation trials (Kubick et al., 2020).

Case Study III: Efavirenz repurposing for Parkinson's

Introduction:

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily affecting the motor system due to the degeneration of dopaminergic neurons in the substantia nigra pars compacta. This leads to a deficiency in dopamine, a neurotransmitter crucial for coordinating muscle movements. The disease is characterized by motor and non-motor symptoms (Sachin Hodgar, 2023).

Pathophysiology of Parkinson's disease:

Alpha synucleinopathy can be regarded as the hallmark of PD. The pathological mechanisms by which α-syn

contributes to PD involve its interactions with cellular components, leading to disruptions in cellular homeostasis and promoting neuroinflammation. Mechanisms of α- Synuclein include:

1. Aggregation and Lewy body formation: Alpha-syn aggregates into insoluble fibrils that form Lewy bodies which are associated with neuronal death in PD.
2. Disruption of cellular processes: Pathological α-syn disrupts mRNA stability and processing by interacting with processing bodies (P-bodies), affecting mRNA turnover and storage, which is crucial for neuronal function (Chen et al., 2023; Hallacli et al., 2022).
3. Neuroinflammation: α-syn aggregates microglial cells and the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines like IL-1β, which contribute to neurodegeneration (Fu et al., 2025).

Use of artificial intelligence for drug repositioning:

Since millions of individuals worldwide suffer from Parkinson's disease, the economic burden of developing new treatments makes them more expensive and time-consuming. As a result,

the process is made more straightforward and thorough by repurposing already-existing medicines and incorporating artificial intelligence. The discovery of Efavirenz as a drug for PD can be attributed to the artificial intelligence-based prediction models employed in the study conducted by Kim et al.

Efavirenz is originally a widely used non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV-1 infection. Since its approval by the FDA in 1998 it has been the cornerstone of retroviral treatment because of its effectiveness and dose regimen. Its main mechanism of action is to block the reverse transcriptase enzyme which is essential for HIV replication (Pawar et al., 2024). Specifically, efavirenz has been identified as a modulator of α- synuclein propagation, a critical factor in PD progression, suggesting its therapeutic potential in this neurodegenerative disorder.

AI applications have been utilized for identifying potential candidates for Parkinson treatment. In the study conducted by Kim et al, a machine learning based drug discovery approach was used. The workflow consisted of employing the XGBoost algorithm trained on gene expression profiles from drug treated samples (LINCS Dataset). To enable supervised learning the model was trained to learn associations between expression features and therapeutic categories particularly focusing on the central nervous system-related indications. Based on these features potential parkinsons disease drug candidates were identified. Following a refinement process the list of predicted PD drugs was finalised. To further analyse the link of the drugs to PD related pathways, drug candidates were screened independently (Standigm DB, Hetionet database etc.). Selection of Efavirenz was based on a prediction score which determined the CNS activity as well as its role in lipid metabolism (Kim et al., 2024b).

Validation:

Efavirenz showed promising activity through experimentation. Efavirenz showed a reduction in the astrocyte/microglia. In vivo experimentation suggests that efavirenz shows improved outcomes concerning pharmacokinetic profiles, dosing regimen and adverse reactions. *In vitro* experiments showed a stark reduction in alpha-synuclein propagation.

Conclusion:

The repurposing of existing drugs offers a cost-effective, time-efficient, and clinically grounded alternative to traditional drug development, especially in the context of complex and multifactorial disorders. As highlighted through the case studies of simvastatin, zileuton, and efavirenz, artificial intelligence (AI) has become a powerful tool in uncovering new therapeutic applications for well-characterized drugs. By leveraging vast datasets— ranging from transcriptomic signatures and electronic health records to biomedical knowledge graphs—AI models have demonstrated the capacity to not only accelerate drug discovery but also elucidate plausible mechanisms of action at a systems biology level.

Simvastatin, through AI-guided analysis, was identified for its neuroprotective and anticancer properties, indicating potential beyond lipid regulation. Zileuton was uncovered as a modulator of neuroinflammation via NRF2 activation, showing promise in the treatment of inflammation- linked depression. Meanwhile, efavirenz, an antiretroviral originally used for HIV, has shown efficacy in reducing α-synuclein propagation and neuroinflammatory responses in Parkinson's models—an insight that emerged from integrative AI-driven screening and validation processes. The use of AI in medication repurposing is not without its difficulties, despite its potential. Ethical supervision, thorough experimental validation, and high-quality, objective data are still essential. However, a new paradigm in therapeutic innovation has been brought about by the combination of human expertise and computer intelligence. As AI tools continue to evolve, they are poised to transform drug repurposing from a speculative endeavour into a systematic, data-driven enterprise, offering renewed hope for patients affected by debilitating disorders.

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