Artificial Intelligence in Drug Repurposing: Revolutionizing Drug Discovery through Computational Case Studies

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Abstract

The application of artificial intelligence (AI) in drug repurposing has significantly reshaped the conventional landscape of drug discovery, allowing for the swift identification of new indications for existing medications. This review presents three notable case studies baricitinib for COVID-19, metformin in cancer therapy, and donepezil for Alzheimer's disease and related neuroinflammatory conditions to showcase the transformative impact of AI technologies in this field. Utilizing tools such as knowledge graphs, machine learning algorithms, transcriptomic profiling, and pathway analysis, AI has enabled the accurate prediction of drug-target relationships, supported clinical hypothesis generation, and, in some instances, contributed to regulatory approvals. Nevertheless, challenges remain, including issues related to data quality, bias in observational datasets, limited mechanistic interpretability, and complex regulatory pathways. Despite these barriers, the outlook for AI-enabled drug repurposing remains optimistic, driven by continuous improvements in data harmonization, model transparency, and precision medicine strategies. The review emphasizes the importance of cross-disciplinary collaboration, rigorous validation standards, and regulatory adaptation to fully capitalize on AI's potential in expediting drug development processes.Limitation of AI in drug repurposing

Keywords Artificial Intelligence, Drug Repurposing, Machine Learning, Baricitinib, Metformin, Donepezil, COVID-19, Cancer Therapy, Alzheimer's Disease.

1. Introduction

Traditional drug discovery is an expensive and time-consuming endeavor, typically requiring 10 to 17 years and investments of $2 to $3 billion per approved drug. Moreover, the success rate remains low, with only around 11% of drug candidates in Phase I trials eventually reaching the market [1]. In contrast, drug repurposing or repositioning offers a cost-effective and time- efficient alternative by identifying new therapeutic uses for already approved or

investigational drugs. This approach capitalizes on existing data related to safety and pharmacokinetics, significantly reducing development costs to approximately $300 million and shortening the timeline to 3–12 years [2].

While many early repurposing successes were discovered by chance—such as the use of minoxidil for hair loss or sildenafil for erectile dysfunction—advancements in artificial intelligence (AI) and machine learning (ML) have transformed the field into a more systematic, data-driven process. AI technologies facilitate the analysis of vast biomedical datasets, including transcriptomic and proteomic profiles, clinical trial records, electronic health data, and molecular structures, to uncover novel drug-disease associations [2–3]. Techniques like signature reversion analysis and knowledge graph modeling have proven effective in predicting repurposed therapies for a variety of diseases, including cancer and neurodegenerative disorders.

Comprehensive databases such as DrugBank, ChEMBL, and the IUPHAR/BPS Guide to Pharmacology offer curated information on drug–target interactions, while platforms like the Connectivity Map (cMap) and LINCS support transcriptomic-based comparisons (Santos et al., 2017). AI-based tools like BenevolentAI and DeepDR have emerged as leaders in the field, with notable achievements such as the rapid identification of baricitinib as a treatment candidate for COVID-19 through natural language processing and target prediction algorithms [1].

AI-powered drug repurposing shows great potential, particularly in areas like oncology and rare diseases, where traditional drug development often lacks commercial viability. By merging mechanistic understanding with advanced computational methods, this strategy not only accelerates discovery but also opens doors to personalized and precision medicine. This review highlights the methodologies, platforms, and pivotal case studies that underscore the transformative role of AI in modern drug repurposing.

2. Role of AI in Drug Repurposing

Artificial Intelligence (AI) has emerged as a powerful catalyst in drug repurposing, tackling key limitations of traditional drug development such as high costs, extended timelines, and high failure rates. Drug repurposing, which focuses on identifying new clinical applications for already approved medications, benefits from the known safety and pharmacokinetic profiles of these compounds, offering a more efficient development path. The integration of AI has dramatically accelerated this process by enabling high-throughput data analysis, target identification, and molecular modeling with improved accuracy and reduced resource expenditure.

AI-powered repurposing pipelines frequently leverage machine learning (ML), deep learning, and natural language processing (NLP) to process vast and complex datasets—ranging from gene expression patterns and clinical trial results to electronic health records, drug-target interactions, and adverse effect databases. These tools facilitate the detection of novel drug– disease associations, the prediction of off-target actions, and the strategic prioritization of candidate compounds for experimental studies [1,5].

Several AI methodologies have shown significant potential. For example, the deep learning model DeepDR has effectively linked transcriptomic data with drug-disease associations [6]. Another innovative approach is the use of phenome-wide association studies (PheWAS), which combine genomic and clinical information to uncover new applications for existing drugs, particularly for rare conditions, by correlating phenotypic patterns with established drug targets [7].

Structure-based drug repurposing (SBDR) has also been enhanced through AI. By combining molecular docking, virtual screening, and molecular dynamics simulations with machine learning algorithms, researchers have improved the accuracy of binding affinity predictions and target identification. These techniques were particularly impactful during the COVID-19 crisis, where AI helped rapidly identify potential therapeutics [8].

NLP algorithms play a key role in mining scientific literature and pharmacovigilance data to uncover hidden repurposing opportunities. For instance, BenevolentAI used AI-powered literature mining to identify baricitinib as a potential COVID-19 treatment, illustrating the capability of NLP in discovering clinical efficacy signals overlooked in formal trials [9].

However, AI-assisted drug repurposing is not without its constraints. Current models often face challenges related to data sparsity, heterogeneity, and a lack of interpretability. Moreover, algorithms alone may fall short in providing the contextual understanding that human experts bring to the table. Therefore, a hybrid approach—blending AI with domain expertise—is increasingly seen as essential for prioritizing drug candidates for clinical advancement [8].

Looking ahead, the next wave of AI applications in drug repurposing will focus on the integration of multi-omics data, enhancing algorithmic transparency, and creating tools tailored to precision medicine. The convergence of computational power and biological insight positions AI as a transformative force in next-generation pharmaceutical development [10–11].

3. Case Studies

3.1 Repurposing Donepezil for Alzheimer's Disease with AI

Donepezil, a well-known cholinesterase inhibitor used for treating mild to moderate Alzheimer's disease (AD), has traditionally been used to improve cholinergic function. However, advancements in AI-driven drug discovery have expanded its potential far beyond symptomatic treatment, revealing alternative biological mechanisms and therapeutic possibilities.

Fang et al. (2022) introduced a network-based AI framework that merged GWAS, transcriptomic data, and drug–protein interactions to pinpoint repurposing candidates for AD. Among others, Donepezil emerged near AD-associated genetic clusters, indicating its possible involvement in disease-modifying pathways. Bayesian models and network proximity scoring supported its relevance to key AD processes [12].

In a separate preclinical study by Cui et al. (2019), Donepezil was shown to facilitate remyelination in a cuprizone-induced CNS demyelination model by promoting oligodendrocyte maturation. Interestingly, these effects were not reproduced by other AChE inhibitors, suggesting that Donepezil's mechanism extends beyond cholinergic activity [13].

A systematic review by Grabowska et al. (2023), analyzing over 120 studies from the past decade, identified Donepezil as one of 573 repurposing candidates for AD. However, only a small fraction of these studies integrated real-world data, emphasizing the need for clinical validation using AI and electronic health records [14]. Joodi et al. (2025) further documented Donepezil's involvement in modulating several key pathways in AD, including NF-κB, GSK- 3β, and mitochondrial dynamics, supporting its repositioning as a neuroprotective agent rather than merely a symptom reliever [15]. Cummings et al. (2025) discussed the strategic value of repurposing drugs like Donepezil in light of their known safety and affordability but acknowledged limitations in intellectual property and regulatory incentives [16].

This multi-layered exploration showcases how AI and network-based models can uncover overlooked neuroprotective functions of Donepezil, supporting its broader application in treating complex neurodegenerative diseases.

3.2 AI-Guided Repurposing of Baricitinib for COVID-19

The COVID-19 pandemic highlighted the urgent demand for effective therapies, steering attention toward drug

repurposing. Baricitinib, originally approved for rheumatoid arthritis as a JAK1/2 inhibitor, emerged as a promising candidate for COVID-19 due to its dual ability to inhibit viral entry and modulate immune responses.

In early 2020, BenevolentAI deployed an AI-powered biomedical knowledge graph to identify drugs that could interfere with SARS-CoV-2 infection. Their system pinpointed clathrin- mediated endocytosis (CME) as a key viral entry route and identified Baricitinib as an effective inhibitor of AAK1 and GAK—kinases involved in this pathway. Its favorable pharmacological profile, compared to similar oncology drugs, made it particularly suitable for urgent clinical use [9,17].

Subsequent meta-analyses of immune modulators in COVID-19 treatment found Baricitinib to yield the most significant mortality reduction, with hazard ratios between 0.56 and 0.69. Other JAK inhibitors like ruxolitinib and tofacitinib underperformed due to insufficient AAK1 inhibition at therapeutic doses [17]. Baricitinib's successful repositioning led to inclusion in global treatment protocols and WHO recommendations, demonstrating the real-world impact of AI-enhanced discovery during a public health emergency.

3.3 Metformin as a Repositioning Agent in Oncology

Metformin, a widely used anti-diabetic drug, has attracted considerable interest as a candidate for cancer therapy. Its known safety, affordability, and broad availability make it appealing for repurposing, particularly in oncology. AI and real-world data platforms have accelerated the investigation into its anticancer potential by integrating preclinical models, epidemiological insights, and trial simulations. Mechanistically, metformin has shown promise by activating AMPK, suppressing the mTOR pathway, inhibiting insulin/IGF-1 signaling, and enhancing

antitumor immune responses, particularly through CD8+ T cell activation and reduced lymphocyte exhaustion [18].

Observational studies have linked metformin use to lower cancer incidence and mortality, with meta-analyses reporting a 20–40% risk reduction across various tumor types. However, Yu and Suissa (2023) highlighted critical flaws in many of these studies—particularly immortal time bias—which inflated metformin’s perceived benefit. When corrected, the protective effect was significantly reduced or absent [19].

The case of metformin highlights the dual nature of AI-driven drug repurposing. While early computational predictions and mechanistic insights were promising, inconsistent clinical outcomes exposed the limitations of poor study designs. This case reinforces the need for rigorously designed studies and translational validation to bridge the gap between AI predictions and clinical impact.

Together, these case studies illustrate the growing capabilities and limitations of AI-assisted drug repurposing, emphasizing the need for hybrid models that combine algorithmic innovation with human expertise and robust clinical validation.

Table 1: Comparative Overview of AI-Assisted Drug Repurposing Case Studies

Parameter	Donepezil (Alzheimer’s Disease & CNS Disorders)	Metformin (Cancer)	Baricitinib (COVID-19)
Original Indication	Alzheimer’s disease (symptomatic relief)	Type 2 diabetes mellitus	Rheumatoid arthritis

AI Approach Used	Network proximity analysis, pathway modeling, literature mining	Systems biology modeling, multi-omics integration	Biomedical knowledge graph (BenevolentAI)
Target Mechanism Identified	Beyond AChE: remyelination, anti-inflammatory, immune modulation	AMPK activation, mTOR inhibition, IGF-1/insulin suppression, T-cell modulation	AAK1/GAK (viral entry inhibition) + JAK1/2 (cytokine storm modulation)
Validation Method	In vivo remyelination models, transcriptomic studies, systematic reviews	Preclinical models, retrospective data, RCTs	Mechanistic modeling, in vitro testing, and clinical trials (e.g., ACTT-2, COV-BARRIER)
Clinical Trial Evidence	Limited to preclinical and small-scale studies; clinical validation ongoing	Mixed/negative results in RCTs despite positive preclinical and observational data	Mortality reduction in Phase III trials; WHO guideline inclusion
AI Advantage	Mechanistic expansion beyond cholinergic systems	Hypothesis generation, pathway mapping, combination therapy prediction	Rapid candidate identification in pandemic emergency
Limitations Observed	Lack of RCTs; data heterogeneity; low translational trials	Immortal time bias in observational studies; high-dose toxicity in trials	Limited to certain populations; drug-drug interactions
Outcome/Impact	Potential for future CNS repositioning; model for precision repurposing	Cautious optimism; not yet standard-of-care in oncology	Emergency use authorization; integrated into treatment protocols

3. Challenges of AI in drug repurposing

While artificial intelligence (AI) has brought substantial advancements to drug repurposing, several key obstacles still limit its reliability in clinical settings. One of the primary concerns is the inconsistency and limited accessibility of biomedical data. AI algorithms require well- structured and high-quality datasets, yet real-world data are often fragmented, incomplete, and inconsistent, which undermines model performance and reproducibility. Furthermore, many AI predictions are based on retrospective observational studies that are susceptible to biases, including immortal time bias and confounding by indication. For example, earlier claims about metformin's anticancer properties were frequently exaggerated due to misinterpretation of flawed datasets. Another critical limitation lies in

the opacity of deep learning models. These systems often operate as "black boxes," making it difficult to understand the biological mechanisms underlying their predictions. This lack of interpretability reduces clinical trust and hampers experimental verification. Additionally, a significant gap persists between computational predictions and their translation into effective therapeutic interventions. Challenges such as drug dosing, bioavailability, and unintended side effects frequently hinder the practical application of AI-identified candidates. Many promising repurposed drugs, such as donepezil for neuroinflammatory conditions, lack comprehensive clinical validation, highlighting a broader issue of insufficient follow-up. Generalizability is also a concern, as AI models trained on limited datasets may underperform when applied to different populations or disease variants. Beyond technical limitations, regulatory and economic constraints further slow progress. The deep learning models operate as “black boxes,” offering little insight into how or why a drug is predicted to work, making it challenging for clinicians and regulators to trust or validate these outcomes. This is particularly evident when AI identifies off-target effects or novel mechanisms without supportive biological data. Another limitation is the dependence on high-quality, diverse, and integrated datasets, which are often scarce. Biomedical data such as omics profiles, electronic health records, and adverse event reports are typically siloed, inconsistent, or incomplete, reducing the reliability of the models trained on them. Additionally, limited external validation of AI-generated hypotheses remains a major issue. Many repurposing suggestions remain computational and fail to transition into preclinical or clinical testing due to lack of funding, expertise, or commercial interest, especially in the case of generic drugs like metformin or donepezil. AI models also struggle with generalizability—algorithms trained on specific populations or disease subtypes often fail to perform reliably across broader or more diverse clinical contexts. Moreover, regulatory ambiguity poses a significant challenge. There iscurrently no standardized framework for approving AI-discovered repurposed drugs, particularly when existing indications are generic and off-patent. Finally, the economic disincentive for conducting large-scale clinical trials on repurposed generics limits their advancement, even when AI predictions are promising. This was observed with metformin in cancer research, where promising retrospective data were not sufficiently supported by randomized trials. Addressing these limitations will require improved transparency in AI models, robust validation frameworks, better data infrastructure, and regulatory pathways that incentivize the clinical development of AI-identified repurposed drugs.

4. Future Prospects

The future of artificial intelligence (AI) in drug repurposing holds tremendous promise, with the potential to fundamentally transform how therapeutics are discovered, developed, and deployed. As AI technologies continue to evolve, future models are expected to become more interpretable, robust, and biologically informed. Integration of multi-omics datasets including genomics, proteomics, transcriptomics, and metabolomics will enable the identification of disease-specific molecular signatures that can guide precise drug-disease matching. Additionally, the application of natural language processing (NLP) to real-world clinical notes, biomedical literature, and adverse event databases will improve the detection of hidden drug- disease relationships that may be overlooked by conventional methods. Federated learning and privacy-preserving AI frameworks are also emerging, allowing for collaborative model training across institutions without sharing sensitive patient data. Furthermore, AI is expected to play a pivotal role in personalized drug repurposing, tailoring therapeutic suggestions based on individual genetic and phenotypic profiles. This precision-medicine approach could particularly benefit patients with rare or treatment-resistant conditions. From a regulatory standpoint, increasing collaboration between AI developers, clinicians, and regulatory bodies may soon yield standardized pathways for evaluating and approving AI-predicted repurposed drugs. Moreover, public-private partnerships and open-access platforms could facilitate shared validation pipelines and streamline experimental follow-up. As demonstrated by successful cases like baricitinib for

COVID-19, the future of AI-driven drug repurposing lies in synergizing computational predictions with translational research. With continued innovation, AI has the potential to reduce development timelines, minimize costs, and rapidly expand therapeutic options across diverse medical domains.

5. Conclusion

Artificial intelligence is reshaping the landscape of drug repurposing by enabling rapid, cost- effective, and data-driven identification of novel therapeutic uses for existing drugs. Case studies such as baricitinib for COVID-19, metformin for cancer, and donepezil for neurodegenerative conditions highlight both the promise and the challenges of AI-assisted approaches. While AI excels at integrating vast biomedical datasets and uncovering hidden drug–disease relationships, limitations including data bias, lack of clinical validation, interpretability issues, and regulatory uncertainty remain significant hurdles. Nonetheless, the continued evolution of AI technologies combined with robust experimental validation and interdisciplinary collaboration will likely overcome these barriers. By aligning computational power with clinical relevance, AI has the potential to accelerate drug discovery, reduce attrition rates, and bring safe, repurposed therapies to patients faster. The future of drug repurposing lies not in replacing traditional methods, but in enhancing them through intelligent, integrative, and precise computational strategies.

Reference

1. Pinzi, L., et al. (2024). How drug repurposing can advance drug discovery: challenges and opportunities. *Frontiers in Drug Discovery*, 4, 1460100. https://doi.org/10.3389/fddsv.2024.1460100
2. Pushpakom, S., et al. (2019). Drug repurposing: progress, challenges and recommendations. Nature Reviews Drug Discovery, 18(1), 41–58. https://doi.org/10.1038/nrd.2018.168
3. Subramanian, A., et al. (2020). A machine learning approach to drug repurposing for neurodegenerative diseases. Frontiers in Neuroscience, 14, 871. https://doi.org/10.3389/fnins.2020.00871
4. Santos, R., et al. (2017). A comprehensive map of molecular drug targets. Nature Reviews Drug Discovery, 16(1), 19–34. https://doi.org/10.1038/nrd.2016.230
5. Wan, Z., et al. (2025). Applications of Artificial Intelligence in Drug Repurposing. Advanced Science, 12(14), 2411325. https://doi.org/10.1002/advs.202411325
6. Zeng, X., et al. (2020). DeepDR: a deep learning framework for drug repurposing. Bioinformatics, 36(11), 3505–3512. https://doi.org/10.1093/bioinformatics/btaa052
7. Challa, A. P., et al. (2021). Human and machine intelligence together drive drug repurposing in rare diseases. Frontiers in Genetics, 12, 707836. https://doi.org/10.3389/fgene.2021.707836
8. Choudhury, C., et al. (2022). Structure-based drug repurposing: Traditional and advanced AI/ML-aided methods. Drug Discovery Today, 27(7), 1847–1858. https://doi.org/10.1016/j.drudis.2022.03.006
9. Richardson, P., et al. (2020). Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet*, 395(10223), e30–e31. https://doi.org/10.1016/S0140- 6736(20)30304-4
10. Wan, Z., et al. (2025). Applications of Artificial Intelligence in Drug Repurposing. *Advanced Science*, 12(14), 2411325. https://doi.org/10.1002/advs.202411325
11. Quazi, S. (2021). Role of artificial intelligence and machine learning in bioinformatics: Drug discovery and drug repurposing. *Preprints*, 202105.0346. https://doi.org/10.20944/preprints202105.0346.v1
12. Fang, J. et al. (2022). Artificial intelligence framework identifies candidate targets for drug repurposing in Alzheimer's disease. *Alzheimer's Research & Therapy*, 14:7. https://doi.org/10.1186/s13195-021-00951-z
13. Cui, X. et al. (2019). Donepezil promotes oligodendrocyte generation and remyelination. *Acta Pharmacologica Sinica*, https://doi.org/10.1038/s41401-018- 0206-4

14. Grabowska, M.E. et al. (2023). Drug repurposing for Alzheimer's disease from 2012– 2022: A 10-year literature review. *Frontiers in Pharmacology*, 14:1257700. https://doi.org/10.3389/fphar.2023.1257700
15. Joodi, S.A. et al. (2025). Drugs repurposing in the experimental models of vAlzheimer's disease. Inflammopharmacology, 33:195–214. https://doi.org/10.1007/s10787-024-01608-7
16. Cummings, J.L. et al. (2025). Drug repurposing for Alzheimer's disease and other neurodegenerative disorders. Nature Communications, 16:1755. https://doi.org/10.1038/s41467-025-56690-4
17. Richardson, P. J., Robinson, B. W. S., Smith, D. P., & Stebbing, J. (2022). The AI- Assisted Identification and Clinical Efficacy of Baricitinib in the Treatment of COVID-19. *Vaccines*, 10(6), 951. https://doi.org/10.3390/vaccines10060951
18. Chae, Y. K., et al. (2016). Repurposing metformin for cancer treatment: Current clinical studies. *Oncotarget*, 7(26), 40767–40780. https://doi.org/10.18632/oncotarget.8194
19. Yu, O. H. Y., & Suissa, S. (2023). Metformin and cancer: Solutions to a real-world evidence failure. *Diabetes Care*, 46(5), 904–912. https://doi.org/10.2337/dci22-0047