

Drug Repurposing as an Effective Drug Discovery Strategy: A Critical Review

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Abstract: Drug repurposing, or repositioning, has emerged as a pivotal strategy in pharmaceutical research, offering a promising approach to uncover new therapeutic uses for existing drugs. While traditional *de novo* drug discovery typically requires 10–17 years and investments exceeding \$2 billion with only 11% of Phase I candidates reaching approval, drug repurposing can reduce development timelines to 3–12 years at substantially lower costs, with approval rates reaching approximately 30% for de-risked compounds. The current review evaluates recent approaches, benefits, challenges and successful examples of drug repurposing. Relevant literature related to the advantages and obstacles associated with drug repurposing were reviewed. Additionally, the review demonstrates computational and data-driven methods, as well as traditional and novel examples of repurposed drugs across different therapeutic fields. Drug repurposing offers a faster and cost-effective approach to new therapies, particularly for critical conditions, such as rare diseases, neurodegenerative disorders and cancer. These advantages overcome the shortcomings of traditional drug development. Successful examples include the repurposing of dimethyl fumarate, chloroquine and daptomycin, which addressed a range of medical indications beyond the original drug uses. Collectively, these findings demonstrate that drug repurposing provides a viable solution for accelerating the process of drug discovery and addressing urgent medical needs. The integration of advanced computational methods and enhancing collaborative research projects would allow further expansion of treatment options and supporting timely solutions for critical and rare medical conditions.

Keywords: drug repurposing, pharmaceutical chemistry, drug discovery, strategies, clinical applications

Introduction

The escalating costs and extended timelines associated with traditional drug development have created an urgent need for more efficient therapeutic discovery strategies. In this context, the concept of drug repurposing, also known as drug repositioning, has emerged as a transformative approach that is garnering increasing attention in both industrial and academic research.^{1–3} Drug repurposing involves the process of identifying and validating new therapeutic applications outside the scope of the original medical indication for existing drugs, thereby circumventing many of the challenges inherent in *de novo* drug discovery. This strategy represents a feasible alternative to traditional *de novo* drug discovery, which is characteristically expensive, time-consuming, and frequently impeded by high rates of failure.⁴ Indeed, the average research and development cost for a new chemical entity exceeds \$2.5 billion, with development timelines spanning 10–17 years and approximately 90% of candidates failing during clinical trials.⁵ This innovative paradigm for developing drugs involves identifying novel therapeutic indications for approved drugs or natural and synthetic products in advanced pre-clinical environments.^{1,3} Rational drug repurposing takes advantage of integrated *in silico* approaches like machine learning, data mining, and computational modelling to facilitate the selection of candidates from existing drugs and discover new applications.² The term “existing drugs” encompasses medications that have been approved, drugs withdrawn or treatments that are no longer manufactured commercially, and drug candidates currently undergoing

clinical trials. A specific case of drug repurposing, commonly called drug rescue, involves drugs that failed clinical trials due to inferior efficacy in comparison to existing market alternatives.²

The concept of “new uses” in drug development extends considerably beyond the traditional paradigm of drug repurposing, where the application of a drug is linked to the pharmacological target of a pathology that differs from the one it was initially designed for.² Furthermore, “new uses” also include numerous innovative approaches that leverage existing drugs to meet varying needs. For example, targeting new patient populations such as paediatric groups that may have distinct physiological or metabolic needs compared to adults.^{2,6}

The following sections will focus on the advantages and challenges inherent in rational drug repurposing. The aim is to elucidate how this approach can both catalyze and complement traditional drug discovery processes. Moreover, contemporary examples of repurposed drugs will be presented to demonstrate the practical impact and broad applicability of this strategy across diverse therapeutic areas.

Advantages and Challenges of Drug Repurposing

Advantages of Drug Repurposing

Traditional *de novo* drug discovery is notoriously expensive, protracted, and characterized by high attrition rates. It has been estimated that approximately 90% of drug candidates fail to pass clinical trials.^{7–11} More specifically, only 13% of all drugs that enter the first phase will be submitted to regulatory authorities, with only 11% ultimately receiving approval.^{7,12,13} The attrition rate tends to be even higher in challenging therapeutic areas like neurodegenerative diseases, where nearly all drugs developed will fail.^{14,15} However, when drug repurposing is based on compounds that have successfully navigated the first phase of clinical trials, the attrition rates are substantially lower, at least with respect to safety concerns, during the subsequent clinical efficacy studies that target new indications. Specifically, for compounds that have been de-risked, the approval rate increases to approximately 30%, depending on the phase of lead optimisation, drug development, and resolution of pharmacokinetic and formulation issues.^{8,16,17}

From a regulatory standpoint, drug repurposing offers significant advantages. To compile registration dossiers, a substantial quantity of data is required. The collection of this data can be expedited if information from previous studies and literature related to the compounds in question is already available. The entity responsible for submitting an application for marketing authorisation to regulatory agencies may be granted permission to conduct only those studies required for indication switching.^{9,16}

Drug repurposing also constitutes a strategic choice for life-threatening conditions, including rare and orphan diseases or cancer, for which it is often the only feasible approach for obtaining therapeutic options in a timely and affordable manner.^{11,17,18} With regard to temporal considerations, a repositioning campaign, spanning from initial identification to market introduction, takes an average of six and a half years and requires more than \$200 million [10, 18]. In comparison, research programs aimed at discovering a new chemical entity can take between 13 and 15 years, requiring an investment of between two and more than three billion dollars.¹¹ Furthermore, it is important to recognize that repositioning encompasses not just drugs already on the market but also the identification of new therapeutic indications for molecules of pharmaceutical interest including both synthetic molecules and natural products.⁶

Challenges in Drug Repurposing

Despite its numerous advantages, drug repurposing faces several significant obstacles. Some of the main challenges center on issues relating to intellectual property, pricing strategies, and commercialization, with the lack of patentability reducing opportunities for profit, which consequently discourages pharmaceutical companies from investing in this strategy.¹⁹ While initiatives aimed at facilitating drug repurposing through streamlined marketing authorisation have been proposed, re-patenting a known drug is feasible only if the therapeutic activity identified through repurposing represents genuinely novel information.¹¹ However, many of the possible uses discovered by pharmaceutical repositioning are already documented. Additional barriers arise from confidential and commercial issues, making it challenging to access pharmacovigilance and clinical trial data in therapeutic repositioning. This limitation has been partially addressed by

making clinical trial data public. In the developed world, the challenges of high costs and other barriers are being addressed by establishing state-run programs.^{20–22}

Beyond commercial and regulatory obstacles, drug repurposing faces significant scientific challenges. A critical issue is the frequent disconnect between in vitro or computational predictions and clinical efficacy. Many computational predictions fail to translate clinically due to inadequate understanding of disease complexity, pharmacokinetic barriers preventing therapeutic concentrations at target sites, and off-target effects that negate therapeutic benefits. Notably, repurposed drugs still require Phase II and III clinical trials for new indications, where failure rates remain substantial.²³ The COVID-19 pandemic illustrated these challenges: hydroxychloroquine showed promising in vitro activity against SARS-CoV-2, but rigorous clinical trials including the RECOVERY trial demonstrated no clinical benefit, leading the FDA to revoke its emergency use authorization.²⁴ This high-profile failure underscores the importance of mechanistic validation and rigorous clinical evidence before adopting repurposed drugs. Success is more likely when there is clear mechanistic rationale, dose compatibility with established safety profiles, and adequate drug concentrations achievable at target sites.

Lessons from Failed Repurposing Attempts

Examining failed drug repurposing attempts provides invaluable insights for improving future efforts. The COVID-19 pandemic offered an unprecedented natural experiment in drug repurposing, with over 4000 clinical trials initiated within the first year of the pandemic. The outcomes of these trials, particularly the failures, offer important lessons about the limitations and pitfalls of the repurposing approach.

The Hydroxychloroquine Case Study

The hydroxychloroquine (HCQ) experience during COVID-19 represents a cautionary tale about the risks of premature enthusiasm for repurposed drugs. Initial in vitro studies demonstrated that HCQ could inhibit SARS-CoV-2 replication at micromolar concentrations, leading to widespread off-label use and emergency use authorizations.²⁵ However, subsequent rigorous clinical trials, including the RECOVERY trial, conclusively demonstrated that HCQ had no beneficial effect on COVID-19 outcomes. The FDA revoked its emergency use authorization in June 2020 after determining that the drug was unlikely to be effective.^{24,26}

Several factors contributed to this failure. First, the in vitro antiviral activity observed was likely an artifact of drug-induced phospholipidosis rather than specific antiviral action. Second, the plasma concentrations achievable with safe doses were insufficient to reach therapeutic levels at the site of infection. Third, early positive results from small, poorly controlled studies led to confirmation bias and premature clinical adoption. Fourth, the sheer number of trials (over 168 HCQ trials registered) created a multiple hypothesis testing problem, increasing the likelihood of spurious positive results.²⁷ The HCQ experience underscores the critical importance of mechanistic validation, appropriate dosing studies, and rigorous clinical trial design before adopting repurposed drugs for new indications.

Other Notable Failures and Patterns

Similar patterns of failure have been observed across therapeutic areas. In neurodegenerative diseases, attempts to repurpose antidiabetic medications for dementia treatment have consistently failed despite promising preclinical rationale, with multiple clinical trials of insulin sensitizers showing no benefit in mitigating cognitive decline.¹² In cardiovascular disease, the repurpose of anti-inflammatory agents such as canakinumab revealed unexpected safety concerns, including increased susceptibility to fatal infections that offset potential cardiovascular benefits.²⁸

Analysis of these failures reveals common contributing factors: insufficient understanding of disease pathophysiology, overreliance on single-target mechanisms in complex diseases, inadequate attention to pharmacokinetic requirements, and failure to account for drug-disease interactions that may emerge in new patient populations. Companies have increasingly drifted away from certain therapeutic areas, such as central nervous system (CNS) drug development, due to the perception of high failure risk, despite the substantial unmet need.¹²

Recent Advances in Drug Repurposing Strategies and Approaches

In the majority of cases, drug repurposing has historically occurred through serendipity or the observation of unanticipated side effects.^{3,4} For this reason, predicting and generating repositioning hypotheses in a cost-effective and rational manner is highly desirable.³ Within this context, advances in medicinal chemistry, together with “omics” sciences (ie, transcriptomics, genomics, proteomics, and metabolomics), have introduced new drug discovery opportunities. The quantity of data generated through these technologies is increasing exponentially, ushering in what has been termed the “big” data era. This data is accessible and has been receiving growing attention as a source for extracting information of interest for drug discovery, such as through data mining.²⁹ The DrugBank, with over 12,000 investigated and approved drug-like compounds, is a prime example of a valuable data source. Similarly, the Protein Data Bank contains three-dimensional structures of more than 220,000 biomolecules, both individually and in complex with their ligands, the Protein Data Bank is another example. A third example is ChEMBL, one of the largest reference databases of biological activity annotations, consisting of more than 15 million activity data points for approximately two million individual compounds.^{29,30}

The potential for employing computational approaches in the mining and analysis of vast quantities of data with limited resources is becoming progressively crucial.³¹ Numerous studies have examined practical applications of computational workflows for drug repositioning. Notably, integrating multiple approaches has been shown to be an effective strategy for addressing the intrinsic weaknesses of individual techniques.³ For instance, ligand-based approaches are predicated on the core assumption that similarity between compounds could be indicative of similarity in biological activities.¹ Thus, the capacity to quantitatively evaluate compound similarity with regard to molecules with known biological activities is extremely desirable. Such an approach enables high-throughput screening of large public databases. However, it is crucial to consider that small structural variations can sometimes lead to unexpected and different activity profiles, known as “activity cliffs”.^{1,29,32} Such approaches do not permit major deviations from the starting chemical space when employed as stand-alone methods. Structure-based approaches employ structural data for macromolecular targets, usually obtained from experiments or computationally.^{32,33} Molecular docking is extensively employed for simulating the interactions of ligands with a macromolecular target, predicting its most favorable orientation or bound conformation. Moreover, the poses obtained through docking can undergo post-docking processes leveraging free energy computations to more precisely evaluate ligand binding scores.^{32–34}

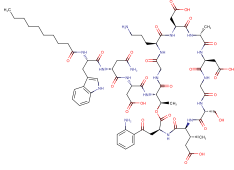
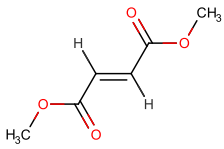
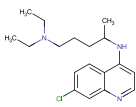
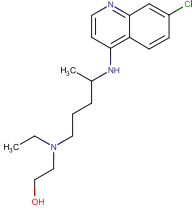
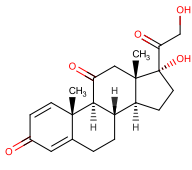
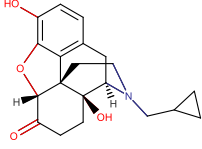
In the context of drug repurposing, molecular docking enables high-throughput virtual screening of approved drug libraries against novel therapeutic targets. The typical workflow involves screening compounds from databases such as DrugBank, ranking binding poses using scoring functions, and validating top candidates through molecular dynamics simulations.³⁵ However, *in silico* predictions require experimental validation through *in vitro* binding assays and *in vivo* models, as docking scores often correlate poorly with experimental binding affinities. Integrating multiple computational approaches has been shown to improve prediction accuracy compared to single-method approaches.

Machine learning (ML) approaches represent a subfield of artificial intelligence that relies on identifying patterns and constructing statistical models that can perform a broad array of tasks.²⁹ In the drug repurposing field, ML approaches are especially valuable due to their ability to efficiently leverage vast quantities of data while simultaneously making available non-obvious predictions.^{3,29,36} Generally, ML methods include supervised learning, characterised by the building of ML models from a “labelled” dataset (meaning that the desired outcome is already known), and unsupervised techniques, where there are no predetermined labels for the training model. With regards to drug repurposing, supervised approaches such as classification tasks predicting drug-target or drug-disease associations have been widely used.^{36,37}

Successful Examples of Drug Repurposing

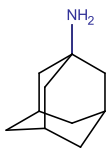
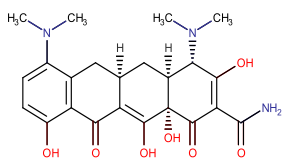
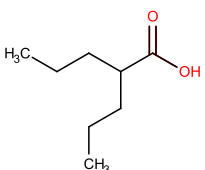
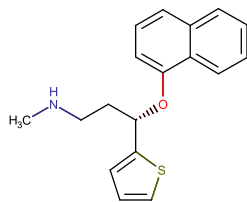
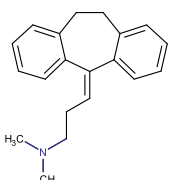
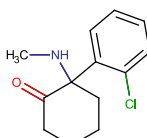
Many examples exist where drug repurposing has been successful in identifying new pharmaceutical applications for drugs already on the market. Some of these new uses have received FDA approval, while others are utilized off-label or are currently undergoing clinical trials. The following subsections of this review will discuss examples of successful drug repurpose organized by therapeutic category to illustrate the breadth and versatility of this approach. A brief overview of these examples is provided in Table 1.

Table I Successful Examples of Drug Repurposing with Drugs' Chemical Structures, Initial Uses, and New Uses

Drug	Chemical Structure	Initial Use	Repurposed Use	References
Daptomycin		Complex skin and soft tissue infections (eg, MRSA)	Bacteremia, endocarditis, chronic osteomyelitis, non-tuberculous mycobacterial infections	[38–41]
Dimethyl fumarate		Relapsing forms of MS	Psoriasis, IBD, neurodegenerative diseases (eg, Parkinson's disease)	[42–44]
Chloroquine and Hydroxychloroquine	 Chloroquine  Hydroxychloroquine	Malaria, rheumatoid arthritis, systemic lupus erythematosus (SLE)	COVID-19, Zika virus, HIV, psoriasis, IBD	[45–48]
Prednisone		Asthma, arthritis, autoimmune diseases	Organ rejection prevention in transplants, cancer treatment regimens, COVID-19-related inflammation	[49–52]
Naltrexone		Opioid addiction	Alcohol use disorder (AUD), autoimmune diseases (eg, MS, fibromyalgia), pain management	[53–56]

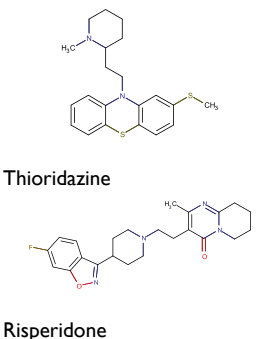
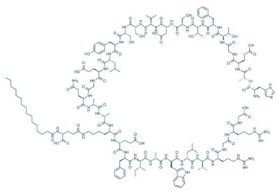
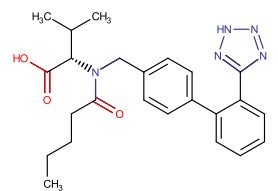
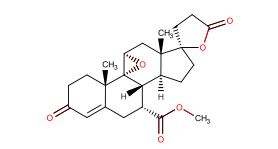
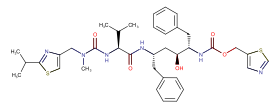
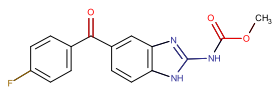
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Table 1 (Continued).

Drug	Chemical Structure	Initial Use	Repurposed Use	References
Amantadine		Influenza A and Parkinson's disease	Parkinson's disease (motor symptoms), treatment-resistant depression, MS	[57–59]
Minocycline		Acne, respiratory infections	Neurodegenerative diseases (Parkinson's disease, Alzheimer's disease), MS, traumatic brain injury	[60–64]
Valproate		Epilepsy	Bipolar disorder, migraine prophylaxis, neurodegenerative diseases (eg, Alzheimer's disease, Parkinson's disease)	[65–67]
Duloxetine		Major depressive disorder, generalized anxiety disorder	Chronic pain conditions (neuropathic pain, fibromyalgia, musculoskeletal pain), stress urinary incontinence, diabetic neuropathy, PTSD	[68–71]
Amitriptyline		Major depressive disorder	Chronic pain conditions (neuropathic pain, fibromyalgia, migraine prophylaxis), insomnia, anxiety disorders, IBS, interstitial cystitis	[72–77]
Ketamine		Anesthetic for surgical procedures	Depression, chronic pain conditions, PTSD	[78–81]

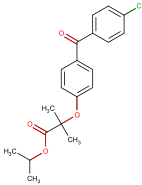
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Table I (Continued).

Drug	Chemical Structure	Initial Use	Repurposed Use	References
Thioridazine and risperidone	 Thioridazine Risperidone	Antipsychotic for acute mania, bipolar disorder, schizophrenia	Glioblastoma, lung cancer, colon malignancies, gastric cancer (GC)	[82–86]
Liraglutide		Type 2 diabetes	Obesity management, cardiovascular disease prevention	[87–90]
Valsartan		Hypertension, heart failure	CKD, diabetic nephropathy, stroke prevention, ischemic heart disease	[91–94]
Eplerenone		Hypertension, heart failure	CKD, diabetic nephropathy, stroke prevention, LVH	[95–101]
Ritonavir		HIV treatment (antiretroviral therapy)	Ovarian cancer, pancreatic cancer, breast cancer, glioma, kidney carcinoma, lymphocytic leukemia	[102–106]
Flubendazole		Antiparasitic for intestinal worms	Cancer treatment (neuroblastoma, multiple myeloma, leukemia, breast cancer, melanoma), inflammatory diseases	[107–111]

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Table 1 (Continued).

Drug	Chemical Structure	Initial Use	Repurposed Use	References
Fenofibrate		Hyperlipidemia	Cancer treatment (ovarian, pancreatic, breast cancers, glioma, lymphocytic leukemia)	[112–115]

Infectious Disease Treatments

The repurposing of antimicrobial agents demonstrates how drugs originally developed for specific infections can find utility in treating resistant or alternative bacterial pathogens. For example, Daptomycin which is a cyclic lipopeptide antibiotic used for the treatment of serious infections caused by Gram-positive bacteria. The mechanism of drug action involves calcium-dependent binding to the bacterial cell membrane, which disrupts the membrane structure and leads to cell death.³⁸ Originally developed to treat complex skin and soft tissue infections caused by resistant bacteria such as MRSA, daptomycin has been repurposed to treat bacteremia, endocarditis, and chronic osteomyelitis.^{38,39} Investigations have also explored its use in the therapy of non-tuberculous mycobacterial infections.⁴⁰ However, its versatility in treating resistant infections requires monitoring for potential muscle toxicity.⁴¹

Similarly, minocycline, which is a member of the tetracycline family of antibiotics, was originally developed for treatment of bacterial infections such as acne and respiratory infections. Its mechanism of action involves interfering with bacterial protein synthesis, thereby preventing the growth and multiplication of bacteria.⁶⁰ Beyond its antimicrobial properties, minocycline has now been repurposed for its potential neuroprotective effects, as discussed in Neurological and Psychiatric Applications.

Immunomodulatory and Anti-Inflammatory Agents

Moving from infection-targeting therapies to immune response-modulating ones, dimethyl fumarate is a drug used mainly in the treatment of multiple sclerosis (MS). This immunomodulator acts by activating the Nrf2 signaling pathway, thus offering cellular protection from oxidative stress and inflammation.⁴² Originally approved for the treatment of relapsing forms of MS,⁴² dimethyl fumarate has been investigated regarding its potential use in the therapy of psoriasis and inflammatory bowel diseases (IBD) due to its anti-inflammatory effects.¹¹⁶ More recent studies have considered its potential use in neurodegenerative diseases, specifically Parkinson's disease, for its possible neuroprotective benefits.^{43,44}

Chloroquine has shown immense versatility for varied uses. It disrupts the life cycle of the malaria parasite within the host's erythrocytes by inhibiting the hemoglobin digestion process, which leads to its inability to polymerize into hemozoin, a pathogenic biochemical reaction to the parasite.¹¹⁷ For this reason, chloroquine was initially approved for the prevention and treatment of malaria, especially for infections caused by *Plasmodium falciparum*.⁴⁵ Chloroquine also has applications in the treatment of rheumatoid arthritis and systemic lupus erythematosus (SLE) due to its immune-modulating effects.⁴⁶ In addition to the abovementioned purposes, one major disease repurposing of chloroquine has been for COVID-19 treatment, despite much debate over its efficacy for this disease.^{118,119} Simultaneously, it has been considered for Zika virus and HIV treatments, taking advantage of its antiviral properties.⁴⁷ Chloroquine possesses anti-inflammatory activity and, thus, is also used off-label for conditions such as psoriasis and IBD.⁴⁸ Hydroxychloroquine is a derivative of chloroquine utilized in the treatment of autoimmune conditions including rheumatoid arthritis, SLE and psoriasis, and is considered safe for longer administration since it has fewer adverse effects than chloroquine.⁴⁶ Nevertheless, chloroquine and hydroxychloroquine should be prescribed with caution due to their known toxicities, namely, retinopathy and cardiac problems, particularly with long-term administration.¹²⁰

Prednisone, a corticosteroid well recognized for its anti-inflammatory and immunosuppressive properties, is utilized in treating a broad spectrum of disorders such as arthritis, asthma, and autoimmune diseases.⁴⁹ Its mechanism of action involves suppressing the immune system, thus inhibiting inflammation. While it was developed for treating diseases such as asthma or allergic reactions, prednisone has also found other uses in preventing transplant organ rejection and treating various forms of cancer.⁵⁰ Prednisone has also been explored more recently as a potential therapeutic for COVID-19 inflammation and has proven effective in reducing symptom severity in severe illness.^{51,52}

Naltrexone is a drug that was originally licensed to treat opioid addiction. It works by binding to opioid receptors in the brain and preventing the euphoric sensations associated with opioids, thereby helping patients recovering from opioid addiction from relapse.⁵³ Since its approval for the treatment of opioid addiction, naltrexone has also been repurposed for the treatment of alcohol use disorder (AUD).⁵⁴ In this context, it helps decrease the craving and feelings of well-being gained from alcohol, hence assisting abstinence. Meanwhile, low-dose naltrexone is under investigation for the treatment of autoimmune conditions such as MS and fibromyalgia, wherein it is reportedly immunomodulatory and anti-inflammatory.^{55,56} Its mechanism of action as an opioid receptor antagonist makes naltrexone a candidate for the treatment of some pain conditions, thus broadening its scope from addiction treatment to pain management.

Neurological and Psychiatric Applications

The central nervous system has proven particularly amenable to drug repurposing, with several agents originally developed for one neurological or psychiatric condition finding efficacy in treating others, reflecting shared pathophysiological mechanisms across different brain disorders. For example, amantadine, which is an antiviral and dopaminergic drug used to treat influenza A and Parkinson's disease. It functions as an influenza virus replication inhibitor and increases dopamine release in the brain.⁵⁷ Though initially approved for influenza, amantadine has been repurposed for Parkinson's disease to help manage motor symptoms, especially tremors.⁵⁸ It has also been investigated in treatment-resistant depression and MS regarding its potential neuroprotective effects.⁵⁹

In addition to its antibacterial properties discussed in Infectious Disease Treatments, minocycline has emerged as a promising neuroprotective agent. The drug is still under investigation in neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease, as it has showed neuroprotective properties by reducing neuroinflammation and preventing injury to neurons.^{61,62} Further research on minocycline has examined its neuroprotective action against neuroinflammation in diseases such as MS and traumatic brain injury.^{63,64} The repositioning of this drug for neurological disorders extends a wide range of therapeutic applications beyond its antibacterial action.

Valproate was originally introduced for epilepsy but found its place later in bipolar disorder and migraine prophylaxis.⁶⁵ In general, valproate has neuroprotective effects, especially in neurodegenerative diseases such as Alzheimer's and Parkinson's disease, that extending well beyond seizure control.^{66,67} This transition from an antiepileptic drug to a treatment for neurological and mood disorders reinforces how drugs originally designed for one condition can become pivotal in managing others.

Like valproate, duloxetine is a drug with multiple therapeutic roles. Although officially classified as an SNRI (serotonin and norepinephrine reuptake inhibitor), this drug is primarily indicated in the treatment of major depressive disorder and generalized anxiety disorder. Its mechanism involves increasing the levels of both serotonin and norepinephrine in the brain to improve mood and alleviate anxiety symptoms.⁶⁸ Duloxetine, while being approved of the conditions above, is also one of the first-line pharmacological treatments.⁶⁸ Additionally, duloxetine has been repurposed for various chronic pain states, such as neuropathic pain, fibromyalgia, and musculoskeletal pain.⁶⁹ It is also used in stress urinary incontinence.⁷⁰ Furthermore, ongoing studies are investigating duloxetine's potential use in diabetic neuropathy and post-traumatic stress disorder (PTSD).⁷¹ The aforementioned repurposed applications illustrate its adaptability in tackling both mood and pain disorders, thereby rendering it a significant pharmaceutical agent in clinical practice.

Amitriptyline is a tricyclic antidepressant primarily prescribed for the treatment of major depressive disorder. Mechanistically, it functions by increasing the levels of serotonin and norepinephrine within the brain, thus promoting the elevation of mood and mitigating symptoms of depression.⁷² While originally approved for the treatment of depression, amitriptyline has subsequently been repurposed for a wide range of diseases due to its analgesic and sedative properties. Amitriptyline is commonly used for the treatment of pain syndromes, such as neuropathic pain, fibromyalgia, and migraine prophylaxis.^{73,74} More recently, because of its sedative effect, the drug is also prescribed off-label for

insomnia and anxiety disorders.⁷⁵ Contemporary studies have also tested its efficacy against irritable bowel syndrome (IBS) and interstitial cystitis where its pain-relieving effect seems encouraging in these conditions.⁷⁶ Despite its clinical efficacy, use of amitriptyline is limited by its associated side effects, which may include sedation, dry mouth, and weight gain, particularly with higher doses.⁷⁷

Ketamine is another classic example of pharmacotherapy repurposing. It is a molecule originally developed as a surgical anesthetic, exerting its action through the antagonism of NMDA receptors in the CNS, inducing anesthesia and analgesia among other pharmacological effects.⁷⁸ Nowadays, ketamine has been repurposed for the treatment of depressive disorders in patients showing inadequate response to standard antidepressant medications.⁷⁹ Recent studies have documented that ketamine has rapid benefits for symptoms of depression and self-injurious behavior.⁸⁰ Its possible use in treating chronic pain conditions and PTSD is also under investigation,⁸¹ representing one of the most important examples of the reuse of an anesthetic for the treatment of psychiatric disorders and pain-related conditions.

Thioridazine and risperidone are antipsychotic agents, developed primarily for treating acute mania, bipolar disorder, and schizophrenia in psychiatric patients.⁸² However, the anticancer properties of both drugs have prompted their clinical investigation. Thioridazine has been reported to show antitumor action against glioblastoma, lung, and colorectal cancers. It causes apoptosis through the caspase-dependent pathway and also suppresses colony formation and nuclear fragmentation in neoplastic cell lines.⁸³ On the other hand, risperidone may impede cell growth through the induction of ROS and apoptosis.⁸⁴ Inhibition of tumor growth by risperidone was also effective in the *in vivo* models.⁸⁵ Results from population-based cohort analysis revealed that the GC risk in the subjects treated with risperidone was notably lower when compared to non-users, which supports its potential use in treating cancers.⁸⁶ Because these molecules occupy a dual function in psychiatric treatment and oncology, this extends their use beyond the original indication.

Metabolic and Cardiovascular Therapies

Drugs developed for metabolic and cardiovascular conditions have demonstrated particular success in repurposing, often finding applications across multiple organ systems due to the systemic nature of these diseases and their shared pathophysiological mechanisms. For example, liraglutide, a GLP-1 receptor agonist that emulates the action of the GLP-1 hormone by inducing insulin secretion in response to meals. This, in turn, reduces glucagon secretion, which aids the reduction of excess hepatic glucose production and delays gastric emptying, promoting satiety.⁸⁷ Liraglutide was originally approved for treating type 2 diabetes, as it exerts an effect on maintaining glycemic levels within normal parameters.⁸⁷ In addition to its use in diabetes, liraglutide has been repurposed for obesity management, since it helps suppress appetite and thus contributes to weight loss.⁸⁸ Research is also underway to explore liraglutide's possible role in the prevention of cardiovascular diseases, since recent studies have indicated that it reduces the risk of cardiovascular events in patients with type 2 diabetes.^{89,90} Considering its dual role in the regulation of blood glucose and promoting weight loss, liraglutide has become an important therapeutic option for the comorbidity of diabetes and obesity.

The antihypertensive efficacy of valsartan, an angiotensin II receptor blocker (ARB) extends to repurposing in chronic kidney disease (CKD) and diabetic nephropathy, underlining the growing importance of cardiovascular pharmaceuticals in the treatment of non-cardiac diseases. Valsartan decreases blood pressure and proteinuria making it an important intervention in cardiovascular and renal diseases.^{91,92} The benefits of valsartan have also been investigated to reduce the risk of stroke in high-risk patients and to improve clinical outcomes in patients with ischemic heart disease.^{93,94} Due to its powerful RAAS inhibiting activity, this agent is one of the most important therapeutic drugs against cardiovascular and renal diseases.

Similarly, eplerenone, belonging to the class of aldosterone antagonists, is used mainly to treat hypertension and heart failure. Its mode of action includes blocking of aldosterone, a hormone responsible for water and sodium retention, hence reducing fluid retention, which in turn lowers blood pressure.^{95–97} In addition to its original indication, eplerenone has been used in CKD and diabetic nephropathy, where it has proved useful in decreasing proteinuria and preserving renal function.^{98,99} Other studies are investigating the potential use of eplerenone in stroke prevention and left ventricular hypertrophy (LVH) treatment due to its ability to block aldosterone.¹⁰⁰ Eplerenone is considered to have a better safety profile than spironolactone, another aldosterone antagonist, with fewer endocrine side effects, making it highly valuable treatment option in cardiovascular and renal conditions.¹⁰¹

Repurposed Agents with Anticancer Properties

Perhaps the most striking examples of drug repurposing involve agents originally developed for entirely different indications that have demonstrated significant anticancer activity, highlighting the potential for discovering novel therapeutic applications through systematic investigation of existing drugs. For example, ritonavir, a protease inhibitor developed for antiretroviral therapy against HIV.¹⁰² Besides impeding viral replication, ritonavir has anticancer potential by being incorporated into antineoplastic therapies. Ritonavir showed effectiveness in ovarian, pancreatic, and breast cancers by the induction of apoptosis as well as inhibition of cancer cell growth.¹⁰³ Ritonavir has been primarily studied to act synergistically with several chemotherapeutic agents such as temozolomide, enhancing its action against glioma cancerous cells, while in combination with bortezomib the drug combination acts against kidney carcinoma; hence, ritonavir may be assumed to be acting as an adjuvant agent in combination therapies.¹⁰⁴ Ritonavir further acts in lymphocytic leukemia by inhibiting key signaling pathways.¹⁰⁵ Moreover, it prevents the phosphorylation of Akt in breast cancer cells, which is a major process relating to the survival and proliferation of cancerous cells. It was considered one promising phenylpropanol prodrug for the targeted therapies against cancers.¹⁰⁶ Applications in the treatment of both HIV and cancer represent the expanded therapeutic activities of protease inhibitors from their original applications.

Flubendazole a member of the benzimidazole group of drugs, was originally created for the treatment of intestinal worm infections but recently has been repurposed due to its antineoplastic properties, which have proved efficient against neuroblastoma, multiple myeloma, leukemia, and breast cancer. The mechanisms by which flubendazole act include induction of apoptosis, production of reactive oxygen species (ROS), and caspase-3 and caspase-7 activation. This drug exhibits an antiproliferative and antiangiogenic effect on tumors, including lung, liver, and breast cancers by acting on neoplastic cells and enhancing the rate of their cell death. It has been shown to increase the expression of HER2 in breast cancer.^{107–109} A further indication for the recent repurposing of flubendazole resulted from its lethal effects against colorectal cancer, caused by its inhibiting pathways, which include the autophagy pathway and STAT3. Preclinical findings further identified that this anthelmintic drug inhibits melanoma cell proliferation and metastasis and reduces the accumulation of myeloid-derived suppressor cells, hence contributing to the anticancer immune response.^{110,111}

Fenofibrate was developed for the treatment of hyperlipidemia but exhibits anticancer activities in a range of human cancer types.¹¹² It works by inducing AMP-activated protein kinase (AMPK), with a resultant decline in cellular ATP levels and build-up of ROS leading to apoptosis and inhibition of metastasis in tumor cells.¹¹³ Furthermore, fenofibrate induces cell cycle arrest and apoptosis via the regulation of growth factor receptors and NF- κ B inhibitory activity on human breast cancer cells.¹¹⁴ It suppresses ERK signaling in lung cancer, thus contributing to its antitumor effects.^{112,115} In this respect, fenofibrate is a promising candidate for further research in oncology, expanding the scope of its therapeutic use beyond lipid management.

Conclusions

Drug repurposing has gained considerable attention in pharmaceutical research, providing an efficient and cost-effective alternative to traditional drug discovery approaches. While *de novo* drug development typically requires 10–17 years and investments exceeding \$2 billion with only 11% approval rates, drug repurposing offers a promising pathway to bypass early developmental stages, reducing timelines to 3–12 years with approval rates reaching approximately 30% for de-risked compounds. Recent computational tools, including molecular docking and machine learning, together with advances in “omics” sciences, have facilitated the systematic identification of potential therapeutic uses. Such strategies are particularly beneficial for addressing life-threatening and rare conditions, where traditional drug development methods remain unfeasible.

The successful case studies examined in this review highlight the significant versatility of repurposed drugs across diverse therapeutic areas. However, critical lessons from failed attempts, particularly the hydroxychloroquine experience during COVID-19, demonstrate that promising *in vitro* activity does not guarantee clinical efficacy. These failures reveal common pitfalls: overreliance on *in vitro* findings without mechanistic validation, inadequate pharmacokinetic considerations, and confirmation bias from early uncontrolled studies.

These observations highlight several key directions for advancing drug repurposing. The integration of computational methods with robust experimental validation is warranted to improve clinical translation. Future investments are required in collaborative research initiatives, and regulatory bodies should adapt frameworks to streamline approvals for repurposed drugs. Ultimately, drug repurposing has the potential to transform global healthcare by accelerating the development of effective therapies, provided that urgency is balanced with the scientific rigor necessary to ensure patient safety and efficacy.

Abbreviations

ARB, Angiotensin II Receptor Blocker; AUD, Alcohol Use Disorder; CKD, Chronic Kidney Disease; CNS, Central Nervous System; FDA, Food and Drug Administration; GC, Gastric Cancer; GLP-1, Glucagon-Like Peptide-1; HCQ, Hydroxychloroquine; IBD, Inflammatory Bowel Diseases; IBS, Irritable Bowel Syndrome; LVH, Left Ventricular Hypertrophy; ML, Machine Learning; MRSA, Methicillin-Resistant *Staphylococcus aureus*; MS, Multiple Sclerosis; NF- κ B, Nuclear Factor Kappa B; NMDA, N-Methyl-D-Aspartate; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; PTSD, Post-Traumatic Stress Disorder; RAAS, Renin-Angiotensin-Aldosterone System; ROS, Reactive Oxygen Species; SLE, Systemic Lupus Erythematosus; SNRI, Serotonin and Norepinephrine Reuptake Inhibitor.

Author Contributions

AA conceived and led the study, designed the research, and developed the methodology, conducted the core investigation, supervised validation, and took primary responsibility for drafting and critically revising the manuscript. SW contributed to the investigation, assisted with validation and data visualization, and supported manuscript writing and revision. AA and SW made substantial contributions to the study, participated in drafting and revising the article, gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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