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Review Article

**DRUG REPURPOSING: AN INNOVATIVE APPROACH FOR
DRUG DISCOVERY AND DEVELOPMENT****Alfiya Jakir Tamboli^{1*}, Anjali Jagannath Vargar¹, Snehal Tulshiram Vyawahare¹,
Prof. Snehal Laxman Durande²**¹Dattakala College of Pharmacy, Pune - Solapur Rd, Chincholi, Maharashtra 413130² Assistant Professor, Dattakala College of Pharmacy, Pune - Solapur Rd, Chincholi,
Maharashtra 413130**Abstract:**

Drug repurposing, also called drug repositioning, reprofiling or re-tasking, is the strategy of finding new therapeutic uses for approved, withdrawn or investigational drugs outside their original indication. Bringing a new molecule from laboratory to market usually takes more than a decade and costs well over a billion US dollars, and most candidates fail in clinical trials. Because repurposed candidates already have human safety, pharmacokinetic and manufacturing data, they can skip several early stages, which shortens timelines, lowers cost and reduces the risk of failure. This review describes the concept and history of drug repurposing, compares the main strategies (serendipitous, computational and experimental), and explains the tools that support them, including molecular docking, transcriptomic signature matching, network pharmacology, electronic health record mining and artificial intelligence. Well-known examples such as sildenafil, thalidomide, aspirin, metformin, minoxidil and dexamethasone are discussed together with repurposing efforts during the COVID-19 pandemic and in cancer, rare and neglected diseases. Regulatory pathways, intellectual property barriers and commercial incentives are also considered. Finally, the scientific, legal and economic challenges that limit the field are outlined, and future directions are suggested. Drug repurposing does not replace conventional discovery, but it is a practical and complementary route to deliver treatments faster, particularly for diseases with unmet medical need.

Keywords: drug repurposing; drug repositioning; drug discovery; computational drug design; artificial intelligence; COVID-19; rare diseases; polypharmacology.

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INTRODUCTION:

Developing a new medicine is one of the slowest and most expensive undertakings in applied science. A candidate molecule has to be discovered, optimised, tested for toxicity in animals, studied in people through three clinical phases and finally reviewed by regulators. The whole sequence commonly stretches over ten to fifteen years, and the pharmaceutical industry has struggled for decades to raise its productivity despite major investment in new screening and genomic technologies [1].

The financial burden is large and depends strongly on how it is calculated. A bottom-up model built from negotiated clinical-trial contracts estimated the mean out-of-pocket cost of a new drug at about US\$173 million, which rose to roughly US\$516 million once the cost of failed programmes was added and to about US\$879 million after capital costs were included [2]. An earlier analysis of company-reported data put the median investment per approved medicine near US\$985 million and the mean near US\$1.3 billion [3]. Whatever the exact figure, the cost of every success must also pay for many failures.

Attrition is the central problem. Only about one in ten drugs that enter phase I testing is eventually approved [4]. A recent analysis of clinical failures attributed roughly 40-50% to lack of clinical efficacy and about 30% to unmanageable toxicity, with poor drug-like properties and weak commercial or strategic planning accounting for most of the remainder [5]. Importantly, a large share of these failures happens late, after the most expensive trials have already been run.

What is drug repurposing?

Drug repurposing is the identification of new therapeutic uses for compounds that are already approved, withdrawn, shelved or still under investigation for another condition. The idea was formalised as a deliberate industrial strategy in 2004 by Ashburn and Thor, who described how existing drugs could be redirected towards new diseases to improve research productivity [6]. In the literature the same concept appears under several names, including drug repositioning, reprofiling, redirecting, re-tasking and therapeutic switching. Some authors reserve drug rescue for compounds that failed in clinical trials for their first indication and are revived for another one [7].

A repurposed drug may be used in a new disease, in a new patient population, at a different dose, by a different route of administration or in a new formulation. Strictly, the term is applied when the molecule itself is kept unchanged. Designing a new analogue of an old drug is treated as conventional medicinal chemistry rather than repurposing.

Why repurposing is attractive

The main advantage is that the molecule is already "de-risked". Most repurposing candidates have human safety data, known pharmacokinetics, established manufacturing processes and often a long post-marketing record. Early stages such as lead optimisation, preclinical toxicology and first-in-human dose finding can therefore be shortened or skipped, and development may begin directly in phase II [7]. Frequently quoted comparisons suggest that a repurposed drug can reach patients in a fraction of the time and at a fraction of the cost of a new chemical entity, although such estimates vary widely between sources and between programmes [8].

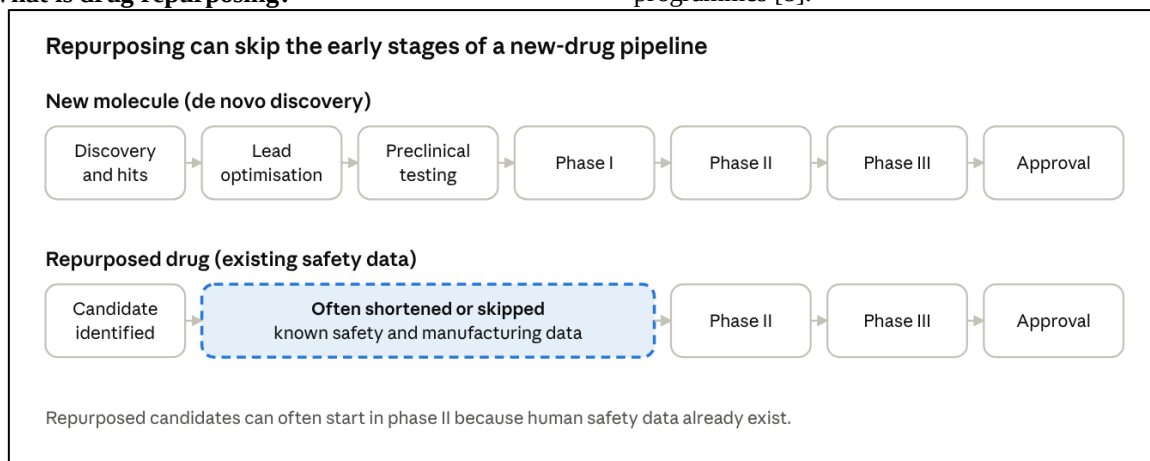


Figure 1 · de novo vs repurposing pipeline

Repurposing is also well suited to diseases that commercial developers tend to neglect. Rare disorders offer small markets, and tropical infections affect populations with limited purchasing power. In both settings the lower cost of repurposing makes development more realistic for

academic groups, non-profit organisations and public-private partnerships [7].

Aim and scope of this review

This review presents the concept, history and rationale of drug repurposing, compares serendipitous, computational and experimental strategies, and summarises representative success

stories. It then looks at repurposing in infectious diseases (with emphasis on COVID-19), cancer and rare or neglected diseases, followed by the regulatory, patent and commercial issues that shape the field. The final sections discuss limitations and future directions, including the growing role of artificial intelligence.

Historical Background and Landmark Examples

For most of the twentieth century, repurposing was a by-product of careful clinical observation rather than a planned programme. A physician or patient noticed an unexpected effect of a drug given for another reason, and that observation was later followed up. The antihistamine-derived phenothiazine chlorpromazine, whose calming action led to its use in psychiatry, is a classic example of a drug whose most important role was found outside its first intended purpose [9]. The following four stories show the pattern that repeated for decades.

Sildenafil

Sildenafil was designed as an inhibitor of phosphodiesterase type 5 (PDE5) to treat angina by relaxing vascular smooth muscle. Early human studies showed little benefit on chest pain, but volunteers reported penile erections, and the compound was redirected towards erectile dysfunction [10]. It reached the market for that indication in 1998. Because PDE5 is also abundant in the pulmonary vasculature, a lower-dose formulation was later shown to improve exercise capacity in pulmonary arterial hypertension and received a second approval in 2005 [11]. Sildenafil is therefore repurposed twice from a single mechanism.

Thalidomide

Thalidomide was marketed in the late 1950s as a sedative and as a treatment for morning sickness. It was withdrawn in the early 1960s after it was linked to severe birth defects. Soon afterwards, clinicians noticed that it relieved erythema

nodosum leprosum, an inflammatory complication of leprosy, and this use was documented in 1965 [12]. In 1999, a study of refractory multiple myeloma showed measurable anti-tumour responses [13], and the drug and its analogues became cornerstones of myeloma therapy under strict risk-management programmes. The molecular target, the protein cereblon, was identified only in 2010, decades after the clinical use began [14]. Thalidomide shows that even a drug with a tragic history can regain value once its risks are understood and controlled.

Aspirin

Aspirin was introduced as an analgesic, antipyretic and anti-inflammatory agent. Once its inhibition of cyclooxygenase was recognised, the irreversible blockade of platelet thromboxane synthesis explained why low doses prevent clotting [15]. A large randomised trial in suspected myocardial infarction later demonstrated that aspirin reduced vascular mortality [16], establishing it as a standard antiplatelet drug more than eighty years after its launch.

Minoxidil

Minoxidil was developed as an oral vasodilator for severe hypertension. Excessive hair growth in treated patients was reported in the medical literature in 1980 [17], and the company that owned the compound reformulated it as a topical solution for pattern hair loss, which was approved in 1988. The same molecule is thus used in two unrelated fields by different routes of administration.

From chance to design

The shift from chance to design began in the 2000s. Ashburn and Thor described repositioning as a business strategy [6], genomic reference databases made it possible to compare drug effects and disease states computationally, and public-private programmes began assembling libraries of clinical compounds. The table below summarises the main milestones discussed in this review.

Table 1. History of milestones

Period	Milestone	Ref.
1950s	Chlorpromazine moves from antihistamine-type pharmacology to psychiatry	[9]
1965	Thalidomide reported to relieve erythema nodosum leprosum	[12]
1980	Hair growth noted in patients taking oral minoxidil	[17]
1985	Zidovudine, first studied as an anticancer agent, shown to inhibit HIV in vitro	[18]
1988	Randomised trial confirms aspirin benefit in myocardial infarction	[16]
1998	Sildenafil approved for erectile dysfunction	[10]
1999	Thalidomide shows activity in refractory multiple myeloma	[13]
2004	Repositioning defined as a deliberate development strategy	[6]
2006	Connectivity Map links drugs, genes and diseases by expression signatures	[19]
2008	Propranolol found to shrink infantile haemangiomas	[20]
2011	Computational predictions validated experimentally (cimetidine, topiramate)	[21, 22]
2017	Drug Repurposing Hub library released	[23]
2020-2021	Dexamethasone and other repurposed agents tested at scale in COVID-19	[24]

Strategies and Approaches

A repurposing project generally moves through three stages: identifying a candidate for a new indication, testing the hypothesis in laboratory models to understand the mechanism, and evaluating efficacy in clinical studies [7]. The way the candidate is found is what distinguishes the different strategies.

Drug-centric, target-centric and disease-centric views

Repurposing questions can be framed from three starting points. In the *drug-centric* view the compound is the fixed element and the question is which other diseases it might treat. In the *target-centric* view a validated protein is the fixed element and the question is which other approved molecules modulate it. In the *disease-centric* view a condition without good therapy is the fixed element and the question is which existing drugs might work against it. Structural analyses further distinguish cases in which a drug is used in a new disease through the same target from cases in which it acts through a different target, an off-target or previously unknown one [25]. Many successful examples fall into the first group, such as sildenafil

in pulmonary hypertension, while examples such as thalidomide, whose myeloma activity depends on cereblon, illustrate the second.

Why existing drugs often have new uses

The scientific basis for repurposing is polypharmacology, the observation that most small-molecule drugs interact with several proteins and not only the one they were designed against [29]. Each additional interaction is a potential new indication, and also a potential source of side effects. Systematic comparison of ligand chemistry across large target sets has predicted unexpected targets for marketed drugs, some of which were confirmed experimentally [30]. Diseases that appear unrelated clinically may also share molecular pathways, so a drug that corrects a pathway in one disease may help in another.

Major families of approach

The literature groups repurposing methods broadly into serendipitous or observation-based, computational and experimental strategies [26, 27]. These are not mutually exclusive, and the strongest programmes combine several of them. The table compares their main features.

Table 2. Major families of approach

pproach	Core idea	Main strengths	Main limitations
Clinical observation and retrospective analysis	Notice or mine unexpected benefits in patients, records or trial subgroups	Directly relevant to humans; hypotheses are clinically grounded	Unsystematic; confounding in observational data; rare events missed
Molecular docking and structure-based screening	Predict binding of approved drugs to a target structure	Fast and cheap; needs no compound stock	Depends on structure quality; scoring is imprecise; many false positives
Signature matching	Compare drug-induced and disease-associated gene-expression patterns	Target-agnostic; links drugs and diseases directly	Cell-line models may not reflect patient tissue; noisy data
Network and systems pharmacology	Map drug, target, pathway and disease relationships as networks	Captures multi-target action and pathway effects	Incomplete interaction maps; hard to validate
Machine learning and AI	Learn drug-disease associations from large heterogeneous datasets	Integrates many data types; scales to thousands of drugs	Needs high-quality data; models can be opaque
Phenotypic and binding screens	Test approved-drug libraries in cell-based or biochemical assays	Experimental evidence from the start; finds unexpected activity	Requires physical libraries and assays; in vitro results often fail in vivo

A practical workflow

In practice, a computational or experimental screen produces a ranked list of candidates. The list is then filtered by biological plausibility, by safety in the target population and by the dose needed, since a concentration that works in vitro may be unreachable in patients. The remaining candidates are tested in disease-relevant cell and animal models and, where these support the hypothesis, in small proof-of-concept clinical studies. The aim is to reach a decision on clinical value as early as possible with minimal investment [28].

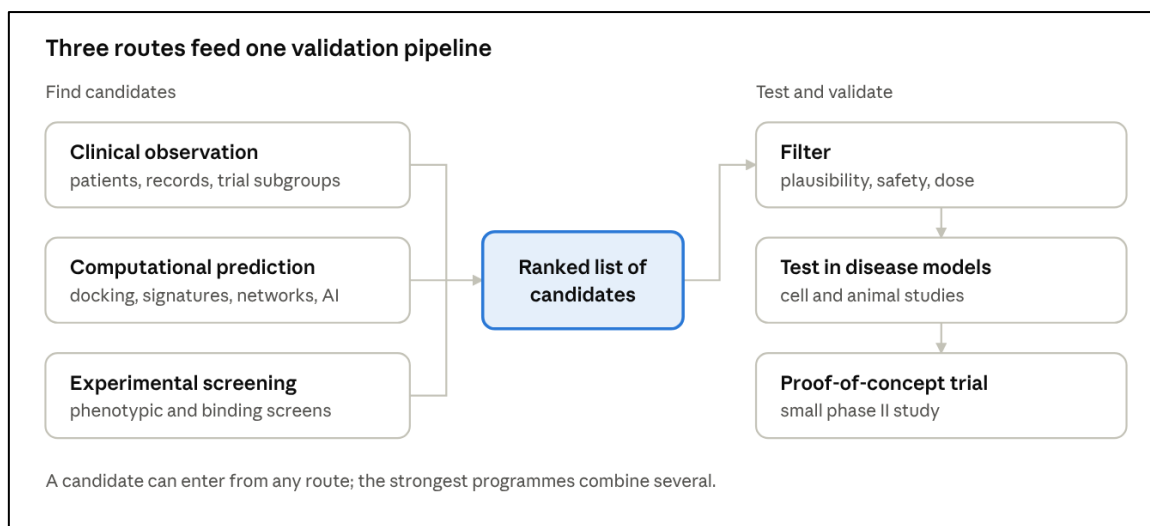


Figure 2 · routes to a repurposed candidate

Computational Approaches

Because the number of approved and clinical-stage compounds is only a few thousand, whereas the number of diseases and molecular targets is far larger, computation is the most practical way to prioritise which combinations deserve laboratory testing. Computational repurposing relies on the growing volume of public data on chemical structures, protein structures, gene expression, clinical records and published literature [27, 28].

Structure-based methods and molecular docking

Molecular docking predicts how a small molecule fits into the binding site of a protein and estimates the strength of the interaction. Docking an entire library of approved drugs against one target, or a single drug against many targets, is called reverse or inverse screening. Widely used programmes such as AutoDock Vina made these calculations accessible to academic laboratories [45], and the methods and their limits have been reviewed in detail [46]. A well-known example applied a chemical systems biology workflow to propose that entacapone, a drug for Parkinson's disease, might inhibit an enzyme of *Mycobacterium tuberculosis* [47]. The accuracy of any docking study depends on the quality of the protein structure, which has improved considerably with the arrival of highly accurate predicted structures [40]. Even so, docking scores are only approximate rankings, and they must be confirmed by biochemical assays.

Ligand-based and chemoinformatic methods

When a protein structure is not available, similarity between ligands can be used. If a drug resembles known ligands of a target, it may bind that target as well. The similarity ensemble approach compared the chemistry of marketed drugs with ligand sets of hundreds of targets and predicted off-target interactions, several of which were confirmed experimentally [30]. Quantitative structure-activity relationship models and pharmacophore searches belong to the same family.

Gene-expression signature matching

Signature matching rests on a simple idea: if a drug changes gene expression in the opposite direction to a disease, it may reverse the disease state. The Connectivity Map assembled expression profiles from cultured human cells treated with 164 small molecules and provided pattern-matching software to compare them with new signatures [19]. The later L1000 platform extended this to more than a million profiles by measuring a reduced set of about a thousand genes [31]. A related study built a network of drugs based on similar transcriptional responses to propose new modes of action [32]. Matching disease signatures from public repositories to drug signatures predicted new uses for 164 drugs, and experiments confirmed that the anti-ulcer drug cimetidine inhibited lung adenocarcinoma growth in mice [21]. The same type of analysis suggested that the anticonvulsant topiramate might help inflammatory bowel disease [22].

Network and systems pharmacology

Network pharmacology models drugs, targets, pathways and diseases as interconnected nodes, an idea developed from the recognition that many effective drugs act on several proteins at once [29]. In repurposing, the distance between a drug's targets and a disease's associated proteins within the human interactome serves as a predictor of therapeutic effect. During the COVID-19 pandemic, network-proximity methods were used to rank approved drugs against SARS-CoV-2 [33]. A later study ranked 6,340 drugs with network diffusion, network proximity and AI-based algorithms and tested the top candidates in human cells. It found that 76 of 77 drugs that reduced infection did not bind the proteins targeted by the virus, so docking alone would have missed them [34].

Literature, genetic and health-record mining

Text mining can connect facts scattered across millions of publications that no single researcher could read. Genome-wide association data can

reveal that a gene linked to a disease is already the target of an approved drug. Electronic health records offer a different route: large patient cohorts can show that people taking a drug for one condition have lower rates of another. One such analysis used hospital records to propose terbutaline, an asthma medicine, for amyotrophic lateral sclerosis [36]. Reviews of data-to-therapy pipelines emphasise that these signals need careful correction for confounding before they justify a trial [35].

Machine learning and artificial intelligence

Machine learning models can combine chemical structure, expression data, interaction networks and clinical information to predict drug-disease

associations [37]. A neural network trained on antibacterial activity screened a repurposing library and identified halicin, a compound originally studied for diabetes, as a broad-spectrum antibacterial [38]. Knowledge-graph and deep-learning models were also built from open data to propose candidates for COVID-19 [39]. The strongest limitation is that models are only as good as their training data, and published results are biased towards successful cases.

Key data resources

Repurposing studies depend heavily on curated public databases. The table lists the resources most often used by students and researchers.

Table 3. Key data resources

Resource	Type of information	Typical use in repurposing
Drug Repurposing Hub [23]	Annotated library of about 4,700 compounds, including over 3,400 drugs that have reached clinical use	Choosing screening libraries; checking known targets and indications
DrugBank [41]	Drug, target, pathway and interaction data	Finding known and possible targets
ChEMBL [42]	Bioactivity data from the medicinal chemistry literature	Ligand-based prediction; potency comparison
CLUE / L1000 [31]	Large-scale gene-expression responses to chemical and genetic perturbation	Signature matching
Protein Data Bank [43]	Experimentally determined protein structures	Docking and structure-based screening
STRING [44]	Protein-protein interaction networks	Network and pathway analysis

Experimental and Clinical Approaches

Computational predictions are hypotheses. Experimental and clinical work is needed to turn them into evidence, and some experimental approaches can also discover repurposing leads without any prediction.

Phenotypic screening

In phenotypic screening, compounds are tested for their effect on a cell, tissue or organism without assuming a specific target. This is well suited to repurposing, because the library is small enough to screen completely and the readout (killing of a pathogen, reduction of tumour cell growth, rescue of a disease phenotype) is directly relevant to the disease. An analysis of how new medicines were discovered found that phenotypic strategies contributed a disproportionately large share of first-in-class small-molecule drugs, which supports their use when the biology is incompletely understood [48]. More recently, a pooled-cell-line method screened thousands of existing drugs against hundreds of cancer cell lines and showed that many drugs developed for non-cancer conditions kill particular cancer types selectively [49].

Target-based and binding assays

Biochemical assays test whether a compound binds or inhibits a purified protein. They are fast and quantitative, and they can be run on libraries of approved drugs in plate formats. Chemical proteomics, in which a drug is used as bait to capture interacting proteins from cell extracts, widens the search to proteins that were not

anticipated. In the COVID-19 setting, a map of 332 interactions between viral and human proteins was used to select human targets and existing drugs that act on them [50], while a separate large screen of roughly twelve thousand clinical-stage or approved compounds identified several with antiviral activity in cells [51].

Retrospective clinical analysis

Observational data from patients who have already taken a drug are a practical source of repurposing hypotheses. A cohort study of people with type 2 diabetes reported lower cancer risk among those treated with metformin, an observation that triggered a large body of laboratory and clinical research on metformin in oncology [52]. These analyses are valuable but need caution. Patients who receive one drug differ from those who receive another in age, comorbidity and lifestyle, and an apparent benefit may reflect these differences. Findings therefore need to be tested in prospective trials.

Clinical validation

The final test of any repurposing hypothesis is a controlled clinical trial. Because safety data exist, small proof-of-concept phase II studies can often start early, using endpoints that show biological activity. Dose and exposure deserve special attention. The dose approved for the original indication may not reach effective concentrations in the new target tissue, and a higher dose may bring toxicity that was never seen before. Large platform trials that test several existing drugs against a

shared control group, such as the RECOVERY trial in COVID-19, have shown that repurposed treatments can be evaluated rapidly and rigorously at scale [24].

Successful Case Studies

Table 4. the drugs and their original and repurpose use

Drug	Original use	Repurposed use	How the new use emerged	Ref.
Sildenafil	Angina (PDE5 inhibitor)	Erectile dysfunction; pulmonary arterial hypertension	Side effect noticed in early human studies	[10, 11]
Thalidomide	Sedative, nausea in pregnancy	Erythema nodosum leprosum; multiple myeloma	Clinical observation, then trial in myeloma	[12, 13]
Minoxidil	Severe hypertension	Pattern hair loss	Side effect (hair growth) noticed in patients	[17]
Aspirin	Pain and fever	Prevention of myocardial infarction	Mechanism understood, then large trial	[15, 16]
Zidovudine	Experimental anticancer agent	HIV infection	Laboratory antiviral screening	[18]
Propranolol	Hypertension, arrhythmia	Infantile haemangioma	Chance observation in an infant on treatment	[20]
Miltefosine	Experimental anticancer agent	Visceral leishmaniasis	Antiparasitic activity found in laboratory studies	[53]
Dexamethasone	Anti-inflammatory, immunosuppressant	Severe COVID-19	Randomised platform trial	[24]

Cardiovascular and vascular medicine

Sildenafil, aspirin and propranolol illustrate how cardiovascular drugs have crossed into other fields. In infantile haemangioma, a French team noticed that a child receiving propranolol for another reason showed rapid shrinkage of a haemangioma, and they reported a series of eleven children in 2008 [20]. Propranolol has since become a first-line option for complicated haemangiomas of infancy, replacing corticosteroids in many centres. The case shows how a single careful bedside observation can change practice when it is followed up with systematic study.

Infectious diseases

Zidovudine was first made as a potential anticancer nucleoside. Its ability to block replication of the human immunodeficiency virus in cells was reported in 1985 [18], and it became the first drug approved for HIV infection. Miltefosine is another example with particular relevance to India. Studied initially as an anticancer compound, it proved to be an effective oral treatment for visceral leishmaniasis (kala-azar), with a cure rate of about 94% in an Indian trial [53]. An oral option was a major advance for a disease previously treated with injectable drugs.

Haematology and oncology

Thalidomide shows how a molecule can move from sedative to teratogen to anti-myeloma agent. Its repurposing led to the development of lenalidomide and pomalidomide and to the discovery of cereblon-dependent protein degradation [14], a mechanism that has itself become a new drug-

The examples in the table below were chosen because their original and new indications are well documented. They span several therapeutic areas and show different routes to the new use.

discovery platform. Metformin, originally an antidiabetic drug, is under investigation in several cancers following observational reports of reduced risk [52], but it is not yet an approved cancer therapy.

Lessons from the examples

Three general lessons emerge. First, many of the best-known successes began with chance observation, so systematic methods have the potential to find them far more efficiently. Second, understanding the mechanism often came after the clinical use, which suggests that repurposing can proceed before the target is fully defined. Third, the new indication frequently required a different dose, formulation or population, so repurposing is rarely a simple matter of prescribing the same product to different patients.

Repurposing in COVID-19 and Other Infectious Diseases

The COVID-19 pandemic was the largest real-time test of drug repurposing. No specific antiviral existed, and developing one from scratch would have taken years, so clinicians and researchers turned immediately to approved drugs. The outcome was instructive. A few repurposed agents saved lives, several widely promoted ones failed, and the difference was settled only by large randomised trials.

Dexamethasone: the clearest success

The RECOVERY trial randomly assigned 2,104 hospitalised patients to dexamethasone 6 mg daily for up to ten days and 4,321 to usual care. Death within 28 days occurred in 22.9% of the

dexamethasone group and 25.7% of the usual-care group. The benefit was concentrated in patients needing respiratory support, and it was absent in those who needed none [24]. Because dexamethasone is cheap, widely available and already known to clinicians, it could be adopted worldwide within weeks.

Drugs that did not work

Early enthusiasm surrounded hydroxychloroquine and the HIV protease inhibitor combination lopinavir-ritonavir, both of which showed activity against the virus in cell culture. In RECOVERY, neither reduced mortality in hospitalised patients [54, 55]. The WHO Solidarity trial, which enrolled patients in many countries, found that remdesivir, hydroxychloroquine, lopinavir and interferon regimens had little or no effect on overall mortality, ventilation or length of hospital stay [56]. These results are a reminder that laboratory antiviral activity does not guarantee clinical benefit, particularly when the concentration needed in cells cannot be safely reached in patients.

Antivirals and immunomodulators with positive signals

Remdesivir had been developed against other RNA viruses, including Ebola. In a placebo-controlled trial, hospitalised adults who received it recovered in a median of 10 days compared with 15 days for placebo [57]. Baricitinib, a Janus kinase inhibitor approved for rheumatoid arthritis, was proposed as a COVID-19 candidate early in 2020 through an artificial-intelligence-assisted analysis of its antiviral and anti-inflammatory properties [58]. A later trial found that adding it to remdesivir shortened recovery time compared with remdesivir alone [59]. Interleukin-6 receptor antagonists, such as tocilizumab, improved outcomes in critically ill patients in a large adaptive platform trial [60].

Other emerging infections and neglected diseases

Similar strategies have been applied to other outbreaks. Screening of approved drugs identified selective oestrogen receptor modulators as inhibitors of Ebola virus entry in cell and animal models [61]. A screen of existing compounds found several that blocked Zika virus infection and protected neural cells from virus-induced death [62]. For tuberculosis and leishmaniasis, repurposing remains attractive because the affected populations have limited purchasing power and conventional development has attracted little commercial investment.

What the pandemic taught

The pandemic showed that rapid, well-designed trials are more valuable than large numbers of small uncontrolled studies. It also showed how quickly weak evidence can drive policy, and that the infrastructure needed to test repurposed drugs, including shared protocols, rapid ethical review and

routine data collection, can be built when there is political will.

Repurposing in Cancer, Rare and Neglected Diseases

The three areas share a common problem: the conventional commercial model does not deliver treatments fast enough or cheaply enough. Repurposing offers a route that is realistic for academic groups, charities and public health programmes as well as for companies.

Cancer

Cancer drugs are expensive to develop and often expensive for health systems to buy. Repurposing non-cancer drugs is attractive because they are usually inexpensive, have established safety profiles and can be tested in combination with standard therapy [63]. The Repurposing Drugs in Oncology (ReDO) project systematically reviewed the preclinical and clinical evidence for old non-cancer drugs with anticancer potential, and published structured assessments for individual candidates [64]. Thalidomide in myeloma [13], cimetidine in lung adenocarcinoma models [21] and metformin in several tumour types [52] are examples already discussed in this review. A large-scale viability screen further showed that many non-oncology drugs have selective activity against defined cancer cell lines, which suggests that more candidates are waiting to be validated [49]. The obstacles in cancer are particular. Cell-culture activity often occurs at concentrations higher than those safely achieved in patients. Cancers are heterogeneous, so a drug that works in one molecular subtype may fail in the rest. Finally, trials of old generic drugs have no commercial sponsor, so they depend on public or charitable funding [63].

Rare diseases

There are thousands of rare diseases, and most still have no approved treatment. Small patient numbers make conventional development unattractive, and trial recruitment is difficult. Repurposing reduces both cost and risk and has become one of the main strategies in this area [65]. A well-documented example is sirolimus, first used to prevent rejection after organ transplantation, which stabilised lung function in patients with lymphangioleiomyomatosis in a randomised trial [66]. Special legislation, such as the Orphan Drug Act in the United States, grants incentives like market exclusivity to developers of orphan indications, which can also apply to a repurposed drug with a new orphan use.

Neglected tropical diseases

Diseases such as leishmaniasis, lymphatic filariasis and tuberculosis mainly affect low-income populations. Commercial returns are limited, so repurposing and collaborative models are especially important. Miltefosine for visceral leishmaniasis is a successful result of this approach

[53]. In India, the Council of Scientific and Industrial Research launched an open-source drug discovery initiative that enlisted contributors from many institutions to share data and tasks in tuberculosis research [67]. Models of this kind could be extended to repurposing, where much of the work involves data analysis that can be distributed among many laboratories and student groups.

Common neurological and metabolic disorders

Repurposing is also being investigated for complex chronic diseases such as neurodegeneration and metabolic disorders, where years of failed trials of new molecules have discouraged investment. Signature-based work found that an inhibitor of amyloid fibril formation had an expression profile opposite to that of Alzheimer's disease brain tissue, which illustrates how data-driven methods may suggest candidates in conditions with poorly understood biology [19]. Evidence in these areas is

still at an early stage, and most proposals await validation in prospective trials.

Regulatory, Intellectual Property and Commercial Aspects

Scientific promise does not guarantee that a repurposed drug reaches patients. Regulatory pathways, patent rules and funding models strongly influence which ideas are pursued, and they differ from the framework designed for new chemical entities [68].

Regulatory pathways

A new indication for an approved drug generally requires its own marketing authorisation, supported by evidence from clinical trials in that indication. Regulators have, however, created routes that let developers rely partly on existing data, which saves time and cost. The table summarises the main regulatory options relevant to students and researchers.

Table 5. The main regulatory options relevant to students and researchers

Jurisdiction	Relevant route	Practical effect
United States	Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act	Allows reliance on published literature or on the agency's earlier findings for a previously approved drug, so fewer new studies are needed
European Union	Hybrid applications and well-established-use applications	Allow partial reliance on existing data or on published evidence of long use
India	New Drugs and Clinical Trials Rules, 2019 [70]	New claims such as a new indication, dose or route for an approved drug are treated as a new drug and require approval, with waivers of some studies possible depending on the data available
Rare diseases (United States, European Union)	Orphan designation	Provides incentives such as fee reductions and a period of market exclusivity for qualifying indications

A new formulation, dose or route can also be used to adapt an old molecule to a new condition. Analyses of drug reformulation and repositioning in the industry show that such strategies can extend commercial life and improve access, but they also raise questions about the real clinical benefit of small changes [69].

Intellectual property

Intellectual property is the most frequently cited commercial barrier. If the active ingredient is off-patent, a company that proves a new use may be able to patent only the *method of use*. Such patents are weaker than composition-of-matter patents because generic manufacturers can supply the same product for the indication through off-label prescribing, and doctors cannot easily be prevented from prescribing a cheap generic once evidence is published [68]. Companies may therefore hesitate to fund expensive late-stage trials for a drug whose market they cannot protect.

Regulatory exclusivities partly compensate. In the United States, a drug approved on the basis of new clinical investigations essential to approval can obtain three years of exclusivity, and orphan products can obtain seven years. These incentives

are shorter than the protection available to a new molecule, which is why repurposing of generics is often led by academics, charities and public agencies.

Business models and public programmes

Several models have emerged to bridge the gap. Specialist repositioning companies identify indications and license them to larger firms. Large companies reposition their own failed or shelved compounds. Public funders have also created programmes that match academic researchers with industry-held compounds, such as the US National Center for Advancing Translational Sciences initiative that offers clinical-stage molecules for new uses, and public-private partnerships that pool data and libraries [7]. Open-data practice and shared screening libraries, such as the Drug Repurposing Hub, lower the entry cost for universities [23].

Safety, pharmacovigilance and ethics

A drug that is safe at one dose in one population is not automatically safe in another. New indications may involve higher doses, longer durations, children or older patients, and interactions with drugs that are common in the new disease.

Pharmacovigilance systems must therefore monitor repurposed drugs closely, and informed consent in trials must describe any risks that differ from the original use. Thalidomide remains the clearest reminder that repurposing a drug does not remove the need for strict risk management [12, 14].

Challenges and Limitations

Repurposing is not a shortcut that removes risk. It moves risk from the early stages of development to questions of efficacy in a new disease, appropriate dose and commercial viability. Reviews of the field identify technological, scientific, regulatory and financial challenges that must be addressed together [7].

Scientific and technical challenges

The most common cause of failure is that a drug acts in the laboratory but not in patients. The concentration required to affect the new target may be higher than the dose that can safely be given, as the COVID-19 experience with hydroxychloroquine showed [54, 56]. Disease models used for screening, especially cell lines, may poorly reflect human disease. Computational predictions add further uncertainty because they depend on incomplete databases and on training sets that contain more successes than failures. Efforts to build pipelines that prioritise and combine several methods aim to reduce this risk, but no single method has proved reliable on its own [71].

Data challenges

Data quality and access are persistent problems. Public databases differ in coverage, curation standards and identifiers, which makes integration difficult. Clinical-trial data from failed programmes are often held privately and are seldom published, although they would be valuable for judging the safety and efficacy of shelved compounds. Another concern is whether the supply of repurposable candidates will run out for a given disease, since the number of existing drugs is limited [7].

Clinical, legal and financial challenges

Trials are expensive, and funding is hard to find when the drug is generic and cannot be protected by a strong patent [68]. Regulatory expectations for a new indication can be as demanding as for a new drug, and developers may not receive credit for existing safety data if the data were generated under older standards. Marketing of a repurposed drug also faces competition from cheaper off-label generic use, which can reduce the incentive for a manufacturer to seek formal approval.

Hype and evidence standards

Repurposed drugs are often cheap, familiar and available, so there is strong pressure to use them as soon as a promising result is announced. The experience with hydroxychloroquine in COVID-19 shows how enthusiasm outran evidence, with large trials later finding no benefit [54, 56]. Repurposing should be judged by the same standards as any

other therapeutic claim, and a familiar safety profile should not substitute for proof of efficacy.

CONCLUSION:

Drug repurposing has moved from a matter of chance to a deliberate strategy supported by databases, computational prediction, experimental screening and modern trial design. Its central strength is that candidates already carry human safety and manufacturing information, which can shorten development and lower cost in comparison with new chemical entities [6, 7]. Examples from sildenafil and thalidomide to dexamethasone in COVID-19 show that the approach can change clinical practice, and its value is especially clear in rare and neglected diseases where conventional incentives are weak. The field is also limited by real constraints: effective dose in the new disease, weak patent protection, funding of trials for generic drugs, and unreliable evidence when enthusiasm outpaces data. The failures of hydroxychloroquine and lopinavir-ritonavir in COVID-19 are a warning that cheap and familiar drugs still need rigorous testing. For pharmacy students and early-career researchers, repurposing is an accessible area. Much of the discovery work uses open data and free software, and the interdisciplinary nature of the field draws on pharmacology, medicinal chemistry, bioinformatics and clinical science. Progress will depend on combining better prediction with transparent validation, shared data, and regulatory and funding models that reward the generation of evidence. Repurposing does not replace the discovery of new molecules, but it is a practical complement that can bring effective treatments to patients sooner.

CONFLICT OF INTEREST:

The Author declares that there is no conflict of interest.

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