

# Repurposing Drugs: An Empowering Approach to Drug Discovery and Development

## Drug repurposing for drug development

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### ABSTRACT

Drug discovery and development is a time-consuming and costly procedure that necessitates a substantial effort. Drug repurposing has been suggested as a method for developing medicines that takes less time than developing brand new medications and will be less expensive. Also known as drug repositioning or re-profiling, this strategy has been in use from the time of serendipitous drug discoveries to the modern computer aided drug designing and use of computational chemistry. In the light of the COVID-19 pandemic too, drug repurposing emerged as a ray of hope in the dearth of available medicines. Data availability by electronic recording, libraries, and improvements in computational techniques offer a vital substrate for systemic evaluation of repurposing candidates. In the not-too-distant future, it could be possible to create a global research archive for us to access, thus accelerating the process of drug development and repurposing. This review aims to present the evolution, benefits and drawbacks including current approaches, key players and the legal and regulatory hurdles in the field of drug repurposing. The vast quantities of available data secured in multiple drug databases, assisting in drug repurposing is also discussed.

## Introduction

Drug development is a laborious and lengthy process requiring galactic investment. Bringing a medicine from an abstract notion to a commercial medication can take around 15 years of development and 0.8–1.5 billion dollars [1]. The normal process of drug discovery and development involves preclinical testing followed by clinical evaluations in four phases. It is estimated that annually, 9 out of 10 medications fail during Food and Drug Administration (FDA) assessment, preventing them from being used in a real world scenario [2]. Due to these challenges, it is lucrative to seek alternative approaches such as drug repurposing or repositioning to find solu-

tions for illnesses for which no treatments are available. Some such situations could be rare diseases or a rapidly spreading pandemic for which there is no cure. To enable resourceful drug repurposing, availability of drug databases would be an essential requirement.

Systematic ‘drug repurposing’ (or ‘drug repositioning’/‘drug re-profiling’) is the re-assessment of established pharmaceutically suitable substances in novel indications that have been uncovered [3]. It is the technique of discovering new indications for already authorized medications in technical terms [4].

The recent COVID -19 (Coronavirus Disease 2019) pandemic brought to light the need for ways to discover drugs quickly. This

review attempts to present the evolution, process and role of drug repurposing in drug discovery and development. The role of drug databases in aiding the process of drug repurposing is also highlighted.

## Historical evolution of drug development process

Historically, drug development has evolved over the centuries in tandem with the progress in science and technology.

- a) *Serendipity*: Originally, actions of drugs were discovered by serendipity – a chance observation, as with penicillin [5]. ► **Table 1** summarizes several examples of plant products discovered by serendipity for their medical uses. In all these examples the original plant product was initially used for some other purpose, cosmetic or recreational but with time the importance of the plant was realized for its medical value. These serendipitously discovered drugs serve as early examples of drug repurposing.
- b) *Natural to synthetic*: With the further development in the field of chemistry the active principle was isolated. Without knowing the biological target, substances were screened for biological activity, whether crude extracts or purified chemicals. Small molecules were later developed to address a particular physiological/pathological pathway [6]. There was a transition from the use of natural products to synthetic or semi-synthetic products. Subsequently congeners with better efficacy and safety profiles started

to be developed. For example, morphine extraction from *Papaver somniferum* and subsequent synthesis of congeners.

- c) *Off-label use*: Some of the drugs started to be used for “off-label” use i.e. use of drugs for indications other than for what they had been originally approved [14]. This again demonstrates an attempt to repurpose drug use by physicians in clinical practice. Propranolol, for example, was first authorized in the US in 1968 for the therapy of arrhythmias, but it was later authorized for the antihypertensive therapy and treatment of angina pectoris ten years later. Much more surprisingly, propranolol was found to prevent migraine attacks in people suffering from cardiac arrhythmias or angina who were previously suffering from migraines. Migraine was added as an authorized indication for the use of this drug in 1979, subsequent to several years of off-label use [15]. A few examples of off-label medicine use have been listed in ► **Table 2**.
- d) *Classical pharmacology*: In classical pharmacology, to differentiate substances that had a desirable therapeutic impact, chemical libraries comprising of synthesized small molecules, natural ingredients, or isolates were tested in intact cells or complete organisms. Compounds which showed promising activity were then taken ahead for further evaluation [6].
- e) *Reverse Pharmacology*: Since human genome sequencing made it possible to clone and synthesize huge quantities of purified proteins quickly, screening vast chemical repositories against disease-modifying biological targets is another popular method

► **Table 1** Serendipitous discovery of medical uses of plant products.

Plant product	Originally discovered use	Current repurposed medical use
Caffeine	The realization of the effects of coffee (caffeine) by the prior of an Arabian convent who noted the behavior of goats that gambled and frisked through the night after eating the berries of the coffee plant [6].	Cognitive and physical performance enhancement particularly in shift workers and athletes [7, 8].
Atropine	(i) Use of mushrooms or the deadly nightshade plant (containing the belladonna alkaloids atropine and scopolamine) by professional poisoners [6]. (ii) A rather different use of belladonna (“beautiful lady”) to dilate pupils [6].	(i) Treatment of symptomatic bradycardia [9]. (ii) Mydriasis and cycloplegia for ophthalmic examination or therapeutic purposes (eg. in iridocyclitis) [10].
Ephedrine	Chinese herb <i>ma huang</i> (containing ephedrine) used for thousands of years as stimulant and as an antiasthmatic and traditionally used to treat cold like symptoms and allergic manifestations [11].	Treatment of clinically significant hypotension perioperatively [12].
Curare (d-Tubocurarine)	Curare containing arrow poisons used for centuries by South American Indians to paralyze and kill animals hunted for food [6].	Non-depolarizing muscle relaxation during anesthesia for surgical procedures. Now rarely used as an adjunct for clinical anesthesia because safer alternatives [13].

► **Table 2** Off-label uses of some medicines.

Drug	Approved indication	Off-label use	Reference
Gabapentin	Focal seizures, Neuropathic pain	Bipolar disorder, diabetes, fibromyalgia, neuropathic pain symptoms, headache, hiccups, hot flashes, restless leg syndrome	[14]
Sertraline	Anti-depressant	Premature ejaculation	[16]
Atypical antipsychotics (eg, risperidone, olanzapine, quetiapine)	Schizophrenia, Bipolar disorder	Anxiety, dementia, eating disorders, obsessive-compulsive disorder, personality disorders, posttraumatic stress disorder, substance abuse	[14]
Methotrexate	Neoplastic diseases (like Choriocarcinoma, Osteosarcoma, Acute lymphocytic leukemia) Rheumatoid arthritis, Psoriasis	Ectopic pregnancy	[17]
Bupropion	Depression, seasonal affective disorder, and smoking cessation	Sexual dysfunction caused by antidepressants, Attention deficit hyperactivity disorder (ADHD) in adults and children, Depression associated with bipolar disorder	[18]

► **Table 3** Repurposed drugs and their original indications.

Drug	Original Indication	Approved Repurposed Use	Reference
Sildenafil	Pulmonary arterial hypertension	Erectile dysfunction	[20]
Thalidomide	Morning Sickness	Leprosy (Erythema Nodosum Leprosum)	[20]
Azidothymidine (Zidovudine)	Chemotherapy	Acquired Immunodeficiency Syndrome	[21]
Mycophenolate Mofetil	Prevention of organ transplant rejection	Lupus Nephritis	[22]
Infliximab	Crohn's Disease	Rheumatoid arthritis, Ulcerative colitis	[23]
Amphotericin B	Antifungal	Antiparasitic	[24]
Doxycycline	Antibiotic	Antimalarial	[25]
Eflornithine	Antitumour	Antiparasitic	[26]
Miltefosine	Antitumour	Antiparasitic	[27]
Paromomycin	Antibiotic	Antiparasitic	[28]
Remdesivir	Hepatitis – C	Ebola virus, COVID-19 *	[29]
Tocilizumab	Rheumatoid arthritis, other autoimmune rheumatic diseases	COVID-19	[30]
Baracitinib	Rheumatoid arthritis	COVID-19	[30]
Molnupiravir	Influenza viruses and encephalitic alphaviruses	COVID-19	[30]

\* In view of the COVID-19 pandemic, Remdesivir was given emergency use authorization to treat COVID-19 in nearly fifty countries.

– what is called reverse pharmacology [19]. Reverse pharmacology is also used to denote the process in which several traditional medicines that have been used as age old remedies (thereby proving that they are safe and effective in humans) are taken to the laboratory to better understand the mechanism of action and generate their pharmacological profile ('bedside to bench' approach).

In the conventional approaches listed above, drug repositioning emerged as another method of identifying new uses of old drugs. A multitude of examples exist for the successful and approved repositioning of old drugs (► **Table 3**), perhaps the most well-known example is that of sildenafil which was initially developed as a drug for pulmonary artery hypertension but was later repurposed to erectile dysfunction.

## Advantages

Repurposing compounds has certain benefits compared to the conventional drug discovery and development methods:

- (i) *Hastens drug development*: There is significant reduction of research and development time. For a repurposed medication, the development period is shortened to 3–12 years [31]. It alleviates the slowdown due to a reported sharp drop in active therapeutic agent entries in different phases of drug development [32].
- (ii) *Reduction in costs and risks*: This is due to the fact that repurposed medicines have well-established pharmacokinetic characteristics [33]. With a 45 percent failure rate linked to safety or toxicity concerns, both developers and patients are interested in lowering the risk of side effects. The latter stand to gain a major edge in terms of gaining faster access to medications that would otherwise be unavailable and have established safety characteristics [34].
- (iii) *Personalized medicine*: It also opens up new possibilities for tailored medications [35] as it aids in the development of subtype-

specific medicines [36], reducing medication failure owing to ineffectiveness.

## Disadvantages

A number of downsides may also be associated with repurposing:

- (i) *Dosage*: When the dosing regimen used to treat a new disease varies from that needed to treat the initial target disease, the research team would have to start with Phase I clinical trials, essentially stripping repurposing of its benefits over novel drug development.
- (ii) *Potential pharmaceutical and toxicological issues*: The contributions of "pharmaceutical and toxicological" experts are hardly ever involved in the development of novel formulations for current treatments in new disease-affected areas.
- (iii) *Issues related to patent rights*: Owing to a shortage of expertise in the regulatory aspect of repurposing, and the extent of the uniqueness of the new drug indication, patent rights concerns for drug repurposing can be extremely complicated [37].

## Major stakeholders

In the field of repurposing there are three major stakeholders, namely – (i) academic research institutes, (ii) repurposing firms and (iii) pharmaceutical firms

- (i) *Academic institutes* are less limited by the necessity of a success for profit but rely on technological innovations that attract talent, government financing and collaborations with profit oriented enterprises.
- (ii) *Repurposing technology firms*, instead, are constrained by their business strategy, which may include technical consultancy, compound assessment, drug repositories and/or framework for drug repositories and screening interface. They often make use of emerging technology, experience, targeted investigation, and flexibility, but they can lack the tools required to undertake preclinical and clinical drug discovery in a regulatory-oriented setting quickly and effectively.

(iii) *Big pharmaceutical firms* may be more focused on a single medication or compound, which is commonly done during the product's final stages of research or after it has been launched [38].

## Ideal Candidates

Leads that have progressed through Phase III of a clinical trial are worthy candidates for repurposing as they have been shown to be effective in bigger populations and to be safe [39]. They may generally be divided into two categories: unforeseen discoveries and targeted mechanism of action (MoA) research activities. Generic medications are, for the most part, a shared platform for major stakeholders in drug repositioning such as academic research institutes, biotechnology, and pharmaceutical companies. Such drugs have been on the market for a long time, have well-established side effect profiles, and are easy to get for preclinical and clinical development research. Pharmaceutical firms, on the other hand, have an edge of accessing drug-related details about their respective substances when it comes to medicines that fall under the two other groups, namely failed drugs or those that are already under patent. As a result, access to data is often skewed towards pharmaceutical firms, making them an important participant in the attempt to routinely find novel indications for existing molecules [38].

Potential candidates for repositioning can be categorized on the basis of the level of evidence known as drug repositioning evidence level (DREL). The DREL increases based on the quality of evidence available. The range of evidence in increasing order of quality is as follows – no proof or *in silico* projections (lowest quality), *in vitro* research, animal studies hypothetically projected to humans, insufficient human studies such as evidence from medical records or observed clinical effects and well-documented clinical end point studies in humans (highest quality) [40].

To produce meaningful and pragmatic investigational techniques, repurposing necessitates a close collaboration between basic experimental and computational researchers. Many analytical resources that entail extensive data processing, installation, and running bundled applications would be difficult for life scientists to use. Similarly, experimental verifications of predictions will be impossible for computer scientists to conduct. Fortunately, drug databases are complex computational tools that assist establish a link between basic laboratory researchers and the numerous *in silico* methods for repurposing pharmaceuticals [3].

## Repurposing Approaches

There are two types of systematic repurposing methods: (1) Experimental or exploratory screening methods and (2) *In silico* methods that use current information to detect possible new drug–disease relationships. (► Fig. 1).

### Experimental or exploratory screening methods

With substantial differences in their usage and functionality, these methods are used as a source of hits for both medication development and drug repurposing. Investigations for new candidate hits are often fueled by a ‘High Throughput Screening’ or HTS approach, which necessitates highly specialized screening equipment and compound libraries holding millions of compounds [38].

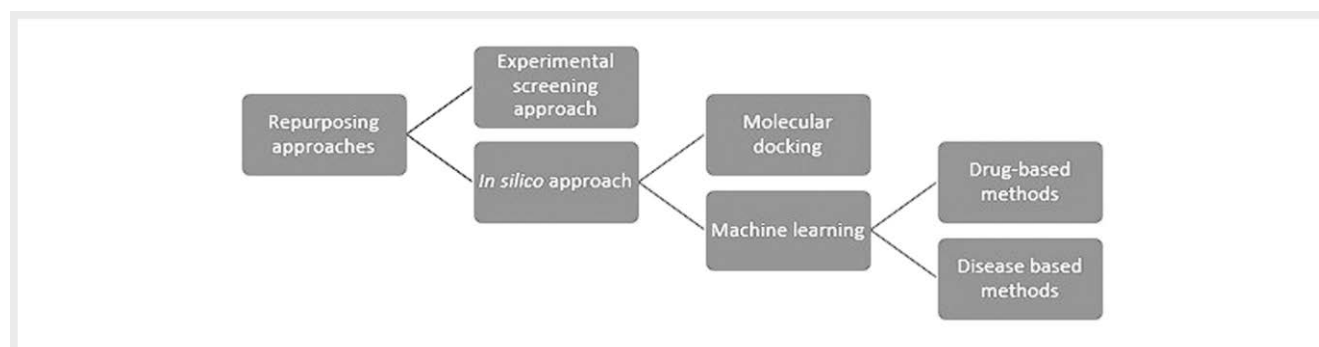
Repositioning activities concentrate on known compounds that have been authorized for marketing or unsuccessful, for which there is some information of their toxicity or molecular mechanism, and are guided by in-depth screening. Typically, authorized compound repositories of around 2000 compounds are available [38].

The congruent results that have arisen from multiple laboratories that were working separately in search of molecules that promote myelin recovery, represent a successful example of repurposing potential through screening methodologies. Increasing the oligodendrocyte precursor cells (OPCs) differentiation into oligodendrocytes as well as promoting axon remyelination are also part of myelin repair [41]. The anti-parkinsonian agent benztropine was reported as a possible repurposing hit using optic nerve OPCs in rat [42]. Benztropine also crossed the bloodbrain barrier, which is essential for myelin repair. Some investigators also discovered clemastine, an anti-histaminic with anti-muscarinic property, as another potential hit [43]. Experiments with OPCs produced from stem cells verified benztropine as a hit and two additional hits that were previously unrecorded – miconazole and clobetasol [44]. Quetiapine, an atypical antipsychotic with anti-muscarinic properties was also identified as a hit for remyelination [45]. Clemastine and quetiapine have also entered clinical trials in multiple sclerosis to see if they can help with myelin recovery [38].

### In silico approaches

Two major *in silico* repositioning methods are molecular docking and machine learning [46].

(i) Molecular docking methods are utilized in structural molecular biology and computer-assisted drug development to mimic and predict physical interactions between medicines and targets



► Fig. 1 Classification of Repurposing Approaches.

[31]. Using a scoring system, successful docking algorithms may effectively explore high-dimensional configuration spaces and properly grade potential dockings [47]. However, some drawbacks exist – because the configurations of several specific proteins are not completely established, docking is greatly constrained by the necessity of known three-dimensional configuration of chemical ligands and protein targets [31]. Furthermore, molecular docking approaches necessitate a considerable amount of computing power, resulting in lengthy runtimes [48]. Besides this, molecular docking findings have a high false-positive rate because of mistakes in the calculated protein structure and insufficient simulation of molecular interactions [31]. As one of the first examples of this strategy, sirolimus, an immunomodulator, was demonstrated to reverse resistance to dexamethasone in acute lymphoblastic leukaemia [49]. The *in silico* results were supported by a substantial decrease in viability of cells exposed to sirolimus plus dexamethasone relative to dexamethasone alone. Additionally, the combination of sirolimus and dexamethasone resulted in long-term remission in xenografted acute lymphoblastic leukaemia [50], demonstrating the efficacy of the transcriptomic-based repurposing method. However, clinical proof of the hypothesis of using sirolimus or similar medications to combat glucocorticoid resistance is also awaited [51].

- (ii) Machine learning approaches tend to be more advantageous than docking simulation because they can analyze a greater number of potential candidates for experimental screening in the future [48].

Methods of machine learning can be characterized as either "drug-based" or "disease/illness-based". Drug-based strategies look for repurposing possibilities from a chemical or pharmacological standpoint, whereas illness-based strategies concentrate on illness management, symptoms, and pathophysiology. Where more precise characterization of pharmacological features is required, drug-based approaches, which contain pharmaceutical or chemical data on medications, may be preferred. Where there is a lack of understanding of pharmacological information of the drug, disease-based strategies are favored. This is also true if we concentrate on a specific illness [46].

As an example, in a study, researchers used a combination of Electronic Medical Records (EMR) and data from insurance claims to see whether the anti-parkinsonian drug Levodopa has the ability to protect against age-related macular degeneration (AMD). They showed that AMD happened considerably later in patients receiving Levodopa prescriptions than in those who did not receive them, and that the odds ratio of developing AMD was significantly lower in those with Levodopa prescriptions [52].

### Deep Learning in the COVID-19 pandemic

Deep learning is a branch of machine learning which relates to a systematic approach to information exploration using layers of linear and non-linear transformations [53]. Artificial neural networks are the most extensively employed deep learning method, with an artificial neuron as the fundamental unit that changes the weighted sum of input data values nonlinearly.

Convolutional Neural Network (CNN) is particularly suitable neural network for image processing. Chemical imagery has been analyzed using CNN to provide understanding into medication therapeutic actions [54]. Biological sequences are another sort of data that has been extensively studied for medication repurposing. However, neither FNN nor CNN take into account the data's sequential existence. Recurrent neural networks (RNNs) are built primarily for sequences, with a recurrent cell emerging at each sequence position to keep past knowledge while acquiring new information in a sequential order [55].

Beck and colleagues [56] created the Molecule Transformer-Drug Target Interaction model, which is a hybrid CNN and RNN model that predicts whether any currently available antiviral medications would function in SARS-CoV-2. Several recognised antiviral medications, including atazanavir, remdesivir, efavirenz, ritonavir, and dolutegravir, were analytically detected as viable treatments for SARS-CoV-2 disease. Another study using machine learning and statistical analysis approaches discovered that mefuparib (CVL218), a poly-ADP-ribose polymerase 1 inhibitor, blocked SARS-CoV-2 replication without obvious toxic effects *in vitro* [57]. When compared to remdesivir, mefuparib has more potent antiviral activity during the entry of the virus and comparable antiviral activity after the entry of the virus, meaning that the drug may be a promising candidate against SARS-CoV-2.

Recently, a repurposing strategy involving a mix of methodologies and datasets was recorded. Similarity ratings for illness and medication pairs were calculated independently in genomic data and lab test data taken from Electronic Medical Records, based on the concept that similar medications can be utilized to treat similar conditions. The outcome was the recognition of terbutaline sulphate, an anti-asthmatic agent, as a potential treatment for amyotrophic lateral sclerosis (ALS), based on similarities between terbutaline sulphate and ursodeoxycholic acid (which has previously been shown to slow the progression of ALS) on the one hand, and Kawasaki syndrome and ALS on the other. The possible therapeutic advantage of terbutaline sulphate for ALS was then shown and tested in a zebrafish model of ALS by preventing axon defects and neuromuscular junction degeneration, but no clinical trial has shown a comparable clinical benefit to date [58].

Repurposing approaches can also be categorized into data-driven and hypothesis-driven methods. Statistical modelling methods are used to explore large-scale '-omics' data sets in data-driven approaches. Network simulation is one of the most widely used data-driven techniques. A network-based technique recreates a biological network and then mimics its interactions to find a therapeutic target. Potential drug targets may be discovered as a function of the association relationships between drug targets. For example, if a possible drug target participates in several biological processes, it could be ruled out because any changes to its activity may disrupt its other behaviours, possibly resulting in side effects [59].

Hypothesis-driven methods, on the other hand, are used to study relatively small processes with small number of molecular components. The need for quantitative information of interactions is a fundamental problem for hypothesis-driven techniques. It is necessary to hypothesize the necessary versions of the numerical parameters in the interactions. Dynamical modelling is one of the most popular hypothesis-driven methods, and it aims to discover

and explain the interactions between various parts of an entity and their behavior [60].

## Role of databases in drug repurposing

Drug data may be found in a variety of biomedical data repositories which can help in searching drugs for repurposing. There is no standard way of classifying such databases but they can be classified according to the drug repurposing activity they help in (► Fig. 2) [61].

The development of drug databases has two basic objectives: meticulous archiving of current information and effective acquisition of new information. Since (1) new information is usually found on the basis of current knowledge, and (2) novel information can be archived and reinserted into current databases after it has been confirmed, these two elements are interconnected. The drug databases will begin to expand and become even more extensive as these two elements alternate. Large amounts of drug-related information, such as medications, illnesses, genes, and proteins, have indeed been created in recent years as a result of the fast growth of computer technology. Drug-related studies, such as pharmacogenomics and precision medicine, have tremendously benefited from the existence of such information [62]. These drug databases can be a powerful tool for drug repurposing.

► **Table 4** describes the salient features of a few repurposing databases that provide target and drug profiles. The information has been derived from individual websites and previous reviews [62, 63].

### Limitations/Challenges of drug databases [62]

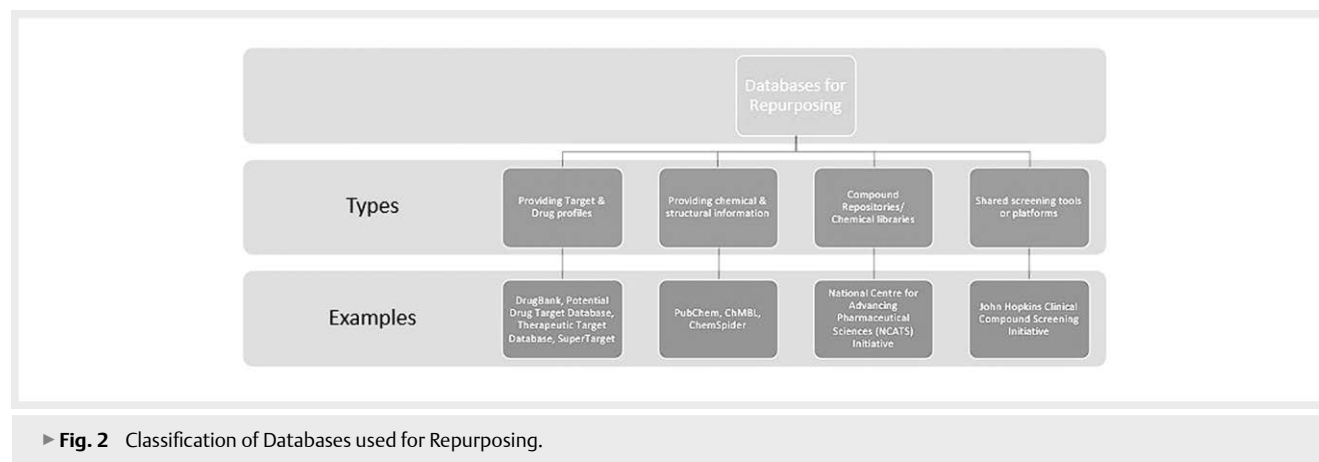
- *Semi automation of data extraction* – Building a database takes a lot of time and necessitates a large amount of manual work. Basic automated tools are used for retrieving documents on specific subjects or collecting sentences containing specific drug names. Despite the fact that these computational tools are really helpful, human curators also have to put in a lot of work to collect information.
- *Integration of databases* – These databases were built keeping into focus various purposes, as well as distinct priorities and scope. One of the obstacles is entity matching (or mapping) between databases. Some databases give crosslinks to other

databases for entity matching, but not all entities have crosslinks, and many databases do not give this service at all.

- *Integrating entity relationships* is another problem. If there is only one form of relationship between two entities, it is not a concern. If there are several types of relationships between two entities, we must first identify all conceivable relationships and analyse how these relationships are represented in various pharmacological databases. When interactions are displayed as textual data with no standardized version, integration becomes more complicated.
- *Maintaining up-to-date drug databases* – The management of pharmacological databases faces two issues as the medical research grows. For one, further human intervention is expected as the amount of literature that needs to be checked grows. Second, corrections are needed in the event that later experiments uncover new information that contradicts previous findings. Several current drug databases haven't been revised since their initial publication, or are only revised on a regular basis. It's a challenging job to keep drug databases up-to-date with the new research.
- *Databases as training sets*. Numerous researches have used artificial intelligence to handle a variety of drug-related issues. The use of information drawn from drug databases as positive training sets while considering those that are not archived in the databases as negative training sets is a recurring theme in these researches. Approaches that are more competent for utilizing drug databases as training sets are required.

### Regulatory and legal issues in drug repurposing

In contrast to a patent, which is typically obtained at the beginning of the development process, lasts much longer, and is based on intellectual property rights rather than proof of safety and efficacy, marketing exclusivity is only given after a drug has been approved by the regulatory authority and only when statutory requirements are satisfied [69]. Marketing of drugs already approved for other indications involves certain regulatory issues such as patents. So because the subsequent new use is neither novel nor unique under current patent law, and proof of new usage has previously been shown in scientific publications, ensuring economic returns by pat-



► **Table 4** Repurposing databases providing drug target and drug profiles.

Name of the database	Date since when	Details of information available	Data extracted from	Free	Last updated	Additional remarks
Therapeutic Target Database (TTD) [64]	2002	<ul style="list-style-type: none"> <li>▪ 37316 Drugs</li> <li>▪ 3419 Targets</li> <li>▪ Information about the known and explored therapeutic protein and nucleic acid targets, the targeted disease, details of the pathophysiological targets, as well as the medications that are intended against them. All of the data presented is thoroughly cited.</li> <li>▪ Web-accessible protein database for in silico target identification.</li> <li>▪ Currently contains 1207 protein entries with 3D structures present in the Protein Data Bank.</li> <li>▪ 841 known or potential drug targets.</li> </ul>	Textbooks, Journal articles, Catalogs of FDA approved drugs, Reports from pharmaceutical companies and US patent databases	Yes	2020	
Potential Drug Target Database (PDTD) [63]	Not clear (After 2000)	<ul style="list-style-type: none"> <li>▪ Contains gene–drug relations</li> <li>▪ Information on diseases, genetic variants, guidelines for drug dosage</li> <li>▪ Information on interactions between drug and gene, drug and drug and drug and disease</li> </ul>	Literature and several online databases such as TTD, DrugBank and Thomson Pharma	Yes	Unknown	
Pharmacogenomics Knowledge Base (PharmGKB) [65]	2000	<ul style="list-style-type: none"> <li>▪ Systems information</li> <li>▪ Genomic information</li> <li>▪ Chemical information</li> <li>▪ Health information</li> <li>▪ Currently &gt; 11,000 KEGG DRUG entries</li> </ul>	Literature, and information from other gene and drug databases such as dbSNP and DrugBank.	Yes	Unknown	
Kyoto Encyclopedia of Genes and Genomes (KEGG) Drug [66]	1995	<ul style="list-style-type: none"> <li>▪ Information on approved, vet approved, nutraceutical, illicit, withdrawn, investigational and experimental drugs.</li> </ul>	Drug labels (package inserts), only includes information on approved drugs.	Yes	2021	KEGG DRUG is a database for approved drugs in Japan, the United States and Europe.
Drug Bank [67]	2006	<ul style="list-style-type: none"> <li>▪ 2037 FDA-approved small molecule medications, 241 FDA-approved biotech pharmaceuticals, 96 nutraceuticals, and almost 6000 experimental medications are among the 9591 drug listings. These drug listings are connected to 4270 non-redundant protein sequences.</li> </ul>	Textbooks and journal articles	Yes	DrugBank is updated daily, downloads are released quarterly.	
SuperTarget [68]	2008	<ul style="list-style-type: none"> <li>▪ &gt; 300000 drug-target interactions, contains information on drugs, targets and side effects.</li> </ul>	Other knowledge bases (such as DrugBank, TTD) and the PubMed indexed evidence. Adverse drug reactions were extracted from Canadian Adverse Reaction Monitoring Program.	Yes	Unknown	
Drug Interaction Knowledge Base (DIKB) [62]	2005	<ul style="list-style-type: none"> <li>▪ Drug-mechanism evidence with the goal to associate assertions about drugs' mechanistic properties with supporting and refuting evidences.</li> </ul>	Journal articles, drug labels and authoritative statements were used to collect evidences.		Fall 2017	Based on the provided evidences, individuals can make their own judgements.
Drug-Gene Interaction database (DGidb) [62]	2013	<ul style="list-style-type: none"> <li>▪ Drug-gene interaction with more than 40,000 genes and 10,000 drugs found in more than 100,000 interactions between drugs and genes, or belonging to one of 42 druggable gene groups.</li> </ul>	Literature and over 20 publically available sources such as PharmGKB, TTD, DrugBank, PubChem, Gene Ontology.	Yes		

\* In view of the COVID-19 pandemic, Remdesivir was given emergency use authorization to treat COVID-19 in nearly fifty countries.

ent protection or marketing of the drug by other companies for the repurposed conditions has raised the following issues:

### Extension of Patent Term

It is understandable that a company seeking approval to market its drug (already under a patent) for a new indication will desire extension of the patent or a new patent. Some countries have evolved a mechanism to handle such issues. In Europe, the legal patent protection timespan, throughout which no generics firm can utilize the innovator's data, is eight years starting from the marketing approval, as well as two years of marketing exclusivity, within which the generics firms can utilize the data to support their approval process but cannot sell a product based on the data. If the innovator develops a new use within the eight-year exclusivity term, the innovator will be allowed to claim an extra year of exclusivity if the novel use provides considerable advantage over current medicines [70].

In the United States, a novel molecule's original exclusivity term is five years (for new biological entities this is 12 years of guaranteed exclusivity against subsequent biosimilars), although medications using a previously authorized active component can get an extra three years if their application includes findings of fresh clinical trials for a novel indication [70].

Although the extension of patent term gives an opportunity to get a satisfactory level of profit, sometimes the period of extension may not be sufficient for the same [70].

A patent for the novel use can be sought for off-patent medications, but enforcement may be a concern if the novel use utilizes currently existing strengths and dosage forms. While it is possible to take advantage of a few of the benefits of medication repositioning by employing the same strengths that were sold for the primary use, an optimal solution would be for the novel use to need non-marketed strengths or a distinct, new formulation [71].

### 'Skinny labeling'

Skinny labeling refers to the practice of seeking approval for some but not all approved indications of a branded drug by the generic drug manufacturers [72]. Normally for an Abbreviated New Drug Application (ANDA) the whole innovator label must be replicated; However, if a particular drug product is authorized for two or more purposes, but just one of them is patent-protected, ANDAs may be authorized with labelling for only one (non-patent-protected) indication, assuming no adverse safety problems. This 'skinny-labeling' strategy is performed by including a statement in the ANDA declaring that the ANDA is not labelling for the patent-protected indication [73].

A pharmaceutical firm files two kinds of patents in the US – a compound patent (which prevents other companies to manufacture that compound) and an indication patent (which prevents other companies to use the patented indication on the label). Sometimes, it may so happen, that the compound patent may expire before the indication patent. In such a scenario, the other companies can legally manufacture the compound but cannot market it for the patented indication as that patent has not expired yet. Instead they may market it for another approved indication which is not yet patent protected (by skinny labeling). The innovator company may suffer a loss due to this, especially if the non-patented

use may boost the business for the product that outweighs the business due to the patented indication by a great deal. [72–73]

### Conclusion and future prospects

Repurposing drugs is a valuable approach empowering drug discovery and development. Data accessibility via electronic capture, databases and advances in associated analytical approaches provide a vital framework for evaluating repurposing candidates in a structured way. Advances in the field of drug repurposing are likely to drastically reduce the time span and economic investment in drug development. Additionally, from a clinical perspective, the physicians usually have a long-term experience with drugs that are already being utilized (in terms of mechanisms, efficacy and adverse events). This could increase their comfort level with such drugs, getting approved for a new indication with or without the change in dose or route. For example, a number of established drugs like hydroxychloroquine, ivermectin, azithromycin, dexamethasone, tocilizumab were all repurposed for COVID-19 in the dearth of effective medicines and rapidly evolving situation. Having a past experience with these medications helped the healthcare providers to use them and be vigilant of the possible adverse events.

Due to patent issues the pharmaceutical industry may not be very keen to adopt the repurposing strategy on a large scale. A possible solution to this could be regulatory incentivization of repurposing research to the innovating pharmaceutical firm. Another issue is lack of involvement of the toxicological and pharmaceutical scientists for the new indication, which can easily be solved by their participation in the repurposing process. Further improvements in databases and their increased integration may lead to better opportunities in the field of repurposing. Currently, skilled manpower is required to extract and curate data. With the exponential improvement in computational technology and artificial intelligence with each passing year, several shortcomings with respect to databases such as tedious data extraction, integration and updating, may present fewer difficulties.

The drug repurposing strategy could help meet the unfulfilled health needs. A predictable end-point of research in repurposing ultimately could be drugs for all indications. Drug repurposing is a futuristic approach. Currently drug development is a time consuming and expensive affair. Very few new drugs are present in the pipeline. Drug repurposing offers an alternative model for the same. Further development of drug databases, methods of computational chemistry and use of artificial intelligence offers possibilities of hastening the process. A decade back or so, the ideas of machine learning were still in their infancy. In this day and age, machine learning and deep learning are specific areas where rapid development is being observed not only in repurposing but in health economics and outcomes research, pharmacovigilance and epidemiological research. If we project this trend in the future, more progress in these fields seems very much plausible.

In the near future, it may be possible to manifest a global scientific database for use by all kinds of scientists – from those working in basic sciences to those involved in clinical trial processes – providing impetus to the process of drug discovery and repurposing. An international consortium may be formed to look into the eco-



nomic, specifically, patent aspects and regulatory issues for the same. The standard process in existence will definitely evolve and gain from the current norm in the next five to ten years.

## Conflicts of Interest

The authors declare that there are no conflicts of interest.

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