

DRUG REPURPOSING

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Abstract: Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, repurposing of 'old' drugs to treat both common and rare diseases is increasingly becoming an attractive proposition because it involves the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines. Various data-driven and experimental approaches have been suggested for the identification of repurposable drug candidates; however, there are also major technological and regulatory challenges that need to be addressed. Drug repositioning utilizes the combined efforts of activity-based or experimental and in silico-based or computational approaches to develop/identify the new uses of drug molecules on a rational basis. It is, therefore, believed to be an emerging strategy where existing medicines, having already been tested safe in humans, are redirected based on a valid target molecule to combat particularly, rare, difficult-to-treat diseases and neglected diseases. In this Review, we present approaches used for drug repurposing (also known as drug repositioning), discuss the challenges faced by the repurposing community and recommend innovative ways by which these challenges could be addressed to help realize the full potential of drug repurposing.

Keywords: Approaches, repurposed drugs, challenges, expensive, time consuming.

Introduction:

Drug repurposing (also called drug repositioning, profiling or re-tasking) is a strategy for identifying new uses for approved or investigational drugs that are outside the scope of the original medical indication⁸. Drug repurposing follows mainly two concepts. One is that a single drug interacts with multiple targets, which paves the way for searching new target sites of action for the known compound. The other concept is that targets associated with a disease are often relevant to a number of biological processes of pathogenesis which paves the way for designation of a new indication for the known target.

This strategy offers various advantages over developing an entirely new drug for a given indication.

First, and perhaps most importantly, the risk of failure is lower; because the repurposed drug has already been found to be sufficiently safe in preclinical models and humans if early-stage trials have been completed, it is less likely to fail at least from a safety point of view in subsequent efficacy trials.

Second, the time frame for drug development can be reduced, because most of the preclinical testing, safety assessment and, in some cases, formulation development will already have been completed.

Third, less investment is needed, although this will vary greatly depending on the stage and process of development of the repurposing candidate⁹.

Identification of novel indications for existing compounds through drug repurposing holds the potential to complement traditional drug discovery by mitigating the high monetary- and time- related costs and risks associated with the latter. For the purpose of this review, existing compounds refers to those that have a proven safety and tolerability profile based on successful phase I or phase II clinical trials. Examples of successful repurposed drugs, together with the ever-expanding high costs and failures of traditional drug discovery and the advent of new data and technologies, has led to the emergence of a new field of drug repurposing. Traditional drug discovery is a time-consuming, laborious, highly expensive and high risk process.

It confers reduced risk of failure where a failure rate of ~45% is associated due to safety or toxicity issues in traditional drug discovery program with additional benefit of saving up to 5–7 years in average drug development time.

Approaches used for drug repurposing:

With the advent of technologies such as genomics, proteomics, transcriptomics, metabolomics, etc., and availability of huge databases resources including drug omics data, disease omics data, etc., there are a plenty of opportunities to discover drugs by drug repositioning in a collective and integrated effort of all the above methods/approaches mentioned above. Researchers are currently equipped with the latest reliable tools and data to explore the novel unknown mechanism of actions/ pathways based upon disease-specific target proteins/genes and/or specific biomarkers associated with the progression of the disease^{34,35}. Drug repurposing based on clinical data is encompassed within these two broad areas.

Table no.1.Computer approaches and Experimental approaches

Computational approaches	Experimental approaches
<p>Computational approaches are largely data-driven; they involve systematic analysis of data of any type (such as gene expression, chemical structure, genotype or proteomic data or electronic health records (EHRs)), which can then lead to the formulation of repurposing hypotheses</p> <p>Signature matching : Signature matching is based on the comparison of the unique characteristics or 'signature' of a drug against that of another drug, disease or clinical phenotype ^{12,13}.</p> <p>Drug-centric approaches : Drug-centric repurposing approaches revolve around predicting new indications for previously approved drug molecules. Most of the molecules involved in this approach follow a common theme of potentially interacting with multiple targets (i.e., poly pharmacological agents). Although poly pharmacological agents are known to produce unwanted side effects, their actions can be exploited because they present potentially new indications for a particular drug.</p>	<p>Binding assays to identify target interactions. Proteomic techniques such as affinity chromatography and mass spectrometry have been used as approaches to identify binding partners for an increasing number of drugs.</p> <p>In an era of chemical biology for target validation, analyses of the targets and off- targets of drugs and drug repurposing have become natural bedfellows. For example, the Cellular Thermo-Stability Assay (CETSA) technique has been introduced as a way of mapping target engagement in cells using biophysical principles that predict thermal stabilization of target proteins by drug-like ligands that possess the appropriate cellular affinity.</p> <p>Phenotypic approaches : Phenotypic drug-screening methods often discover drug candidate's accidentally³⁰. New drugs can be identified based on changes in <i>invitro–invivo</i> models or even clinical observations¹⁴. For instance, it can involve screening a compound library against cell lines to measure cellular response; and finding the compounds that alter the phenotype followed by identification of disease state and mechanism of action²⁶.</p>

Drug repurposing approach puts the drug discovery process in fast track, and has been gaining attention from the researchers in wide range of scientific fields^{37, 38}. In addition, there is no need of larger investments and repurposed drugs are proven to be safe in preclinical models thus lowering the attrition rates as well³⁹. Hence, the main advantages of drug repurposing are associated with established safety of the known candidate compounds, substantially reduced development time frames and costs associated with advancing a candidate into clinical trials ⁴⁰.

In-silico repurposing approaches: *In-silico* repurposing approaches apply sophisticated analytical methods to existing data identifying new potential associations between drug and disease³².

Approaches can be broadly divided into two categories:

- Molecular approaches
- Real-World-Data (RWD) approaches

Table no.2. Molecular approaches and Real-World-Data (RWD) approaches

Molecular approaches :	Real-World-Data (RWD) approaches:
<p>Understanding the MoA of a drug, and matching it with a disease indication different than that for which it was originally approved or developed, are at the heart of molecular approaches to drug repurposing. Molecular approaches, which are based on understanding of drug activity and disease pathophysiology, and are often powered by large-scale molecular data (i.e. "omic data"), such as genomic, transcriptomic, or proteomic data, as well as data on drug targets and chemical structure. Of the various types of omic data available, transcriptomics and genomics are the two data types most widely used to support drug repurposing, due to the combination of availability of data sets on drugs and diseases, and the robustness and reproducibility of the data.²</p>	<p>It focusing on identification of unknown, at times unexpected, relationships between drugs and diseases or their symptoms, based on RWD – data on individual's health, habits, and behavior that is captured without intervention from the environment or biases introduced through data collection methodologies. RWD, non-interventional data on individual's activities and health, are characterized by large, complex, intricately structured datasets often containing several years of data on millions of patients.³</p>

Recent case studies of repurposed drugs in clinical trials:

Because many of the molecules chosen for repurposing are already approved, chances of failure are considerably reduced when

identifying new indications. In addition to lowering the drug development costs, repurposing provides an opportunity for rare disease therapy. Many studies have reported new indications for already-approved drugs using repurposing approaches. For example, amyloid- β plays a crucial part in pathogenesis of Alzheimer's disease. AstraZeneca's shelved cancer drug saracatinib, a dual kinase inhibitor, was recently found to target amyloid- β signaling in the brain and to rescue synapse loss in mice.

Table no. 3 .Successful drug repurposing examples and the repurposing approach employed:

Drug name	Original indication	New indication	Repurposing approach used
Zidovudine	Cancer	HIV/AIDS	In vitro screening of compound libraries
Minoxidil	Hypertension	Hair loss	Retrospective clinical analysis (identification of hair growth as an adverse effect)
Sildenafil	Angina	Erectile dysfunction	Retrospective clinical analysis
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma	Off-label usage and pharmacological analysis
Celecoxib	Pain and inflammation	Familial adenomatous polyps	Pharmacological analysis
Aspirin	Analgesia	Colorectal cancer	Retrospective clinical and pharmacological analysis
Ketoconazole	Fungal infections	Cushing syndrome	Pharmacological analysis

Challenges associated with delivery of repurposed drugs and prospects in pharmaceutical driven repurposing activities:

- Benefits of repurposed drug could only be achieved through utilization of suitable drug delivery systems and optimal route of delivery. Hence, success in drug repurposing is compounded by the fact that not only several basic and clinical disciplines have to congregate, but formulation and delivery route aspects are also to be considered^{15,16}.
- In certain cases, repurposed drugs may be required to be delivered through delivery systems and routes of administration, different from approved dosage regimen, thus demanding their reformulation.¹⁷
- Thus, reformulation or necessity to couple the formulation with right drug delivery device are challenges that may need to be confronted when developing suitable formulations.
- Along with scientific challenges in identifying favorable and robust candidate compounds, there is a need to business models to support bringing existing molecules as therapies for new indications.
- Despite the potentially abbreviated clinical development path for repurposed drugs, there remains a significant commitment in the need to demonstrate the efficacy of the molecules to new indications, and pharmaceuticals are faced with a challenge in trying to recoup the investment needed to bring a repurposed product to market.

Barriers to drug repurposing:

- Patent considerations,
- Regulatory considerations and
- Organizational hurdles.

Patent considerations:

There are a number of legal and intellectual property barriers to drug repurposing^{27, 26}. Difficulties associated with patenting a new repurposed indication and enforcing patent rights are the critical hurdles in incentivizing drug repurposing, as they have a great impact on the potential profit expected from the repurposed product. It is possible to protect a new repurposed medical use of a known drug molecule in most of the major pharmaceutical markets, provided the new medical use is new and inventive (that is, non-obvious). However, many of the potential repurposing uses are already known in the scientific literature or in clinical practice. Even though they may not have been proved to work through clinical testing, prior scientific knowledge of the repurposed use may limit the ability to obtain patent protection unless the patentee can somehow differentiate their patent claims over the information that is already available in the public domain. In order to obtain granted patents for a new repurposed medical use, the patentee will also be required to present data in the patent application demonstrating that the drug is a credible treatment for the new indication concerned.

Regulatory considerations:

Regulatory considerations are critical determinants for the development of repurposed drugs. A study by Murteira and colleagues¹⁰⁰ evaluating the regulatory path associated with repurposed and reformulated drugs observed that within the EU (the UK, France and Germany were studied), the centralized procedure was the most important route for the submission of repurposed drugs for approval. In the US, according to the classification of Murteira and colleagues¹⁰⁰, 'new drug application (NDA) chemical types' type 1 (new molecular entity), NDA type 6 (new indication) and supplemental new drug application (sNDA) (new indication)

were used solely for drug-repurposing submissions, while NDA type 3 (new dosage form) and NDA type 4 (new combination) were used for either drug repurposing or drug reformulation. The study also found that in both the EU (France: 83.3%; Germany: 88.9% and UK: 93.8%) and the US (69.6%), the majority of repurposing cases were approved before patent expiry of the original product

Organizational hurdles in industry:

Pharmaceutical companies are realizing the potential in drug repurposing outside their primary disease area of focus and opening up collaborations with smaller biotech firms and academic communities. The AstraZeneca Open Innovation Platform is one such example to promote external collaborations to synergize research in drug repurposing with access to well-characterized compounds suitable for repurposing through translational, preclinical experiments and clinical phase II studies. However, repurposing in the pharmaceutical industry can be met with some organizational hurdles, particularly if the repurposed indication is not within the organization's core disease area or the compound has been discontinued in development and thus there is no longer a 'live' project within the R&D division to provide dedicated support for the new indication¹.

Advantages:

Translational focus:

Aligned with, and benefiting from academic freedom, translational research in academia offers incentives by fostering novel collaborations and pairing up basic scientists with clinicians across multiple disciplines. Immediate access to hospitals and healthcare practitioners is a tremendous advantage, one that often short-cuts the communication gap between two (otherwise separate) cultures.

Disease focus:

Activities specific to clinical education and clinical research affords in-depth expertise in particular disease areas, removing 'activation barriers' and enabling projects to rapidly advance past the early (basic science) stages. Conversely, clinical observations can lead to immediate pathway links and studies at the cellular and molecular level. In this manner, diseases that lack effective therapies can rapidly be subjected to drug repurposing efforts.

Target focus:

Those targets that are nodal points in general mechanisms such as cell division, autophagy, apoptosis and metabolism can be subjected to therapeutic manipulation for various, sometimes clinically different endpoints. The complete understanding of pathway inter-dependencies and shunts, and the clinical consequences of modulated therapeutic perturbations for such targets can only be accomplished by close, effective communication between basic scientists, clinicians and pharmaceutical scientists. For a new drug to enter the market, it needs to abide by stringent regulations.

Recommendations for drug repurposing:

Bearing in mind the opportunities and challenges for drug repurposing discussed above, we conclude by putting forward six recommendations to help realize the full potential of drug repurposing.

First, there is a need for better integrative platforms for data analysis. The benefits of big data and how it can aid identification of repurposing opportunities are clear. However, data access and integration remain a bottleneck, particularly for clinical data (including clinician notes in patient case records). There is a need for advanced technological solutions that can reduce the need for manual curation and help integrate different types of omics data (BOX 5) such that subsequent analyses can be more refined and analyzed in user-friendly formats by more 'non-experts'.

Second, improved access to industry-generated preclinical and clinical compounds is needed. The MRC and NIH-NCATS initiatives are a step in the right direction, but there needs to be an increase in the number of compounds that can be accessed by academic researchers, ideally in large libraries. The processes involve also need simplification, especially at the level of material transfer agreement signatories and compound dissemination.

Third, there is a need for greater access to data from industry-sponsored phase II–IV clinical trials. This could allow external scientists to mine for new findings in the data that could open repurposing opportunities, in particular for discontinued programmes.

Fourth, newer safety liabilities of repurposed drugs should be studied. There is a continuing need to ascertain any new safety implications associated with repurposed drugs. These may arise as a result of new interactions between the drug and the disease for which it is repurposed, use in new populations or differences in the dosing schedule (for example, chronic rather than intermittent dosing).

Fifth, there is a need for further funding opportunities for drug repurposing initiatives in general, including funding of appropriate technology, supporting compound access and sharing of drug repurposing libraries. There is also a need for innovative sources of funding for drug repurposing initiatives in rare diseases in particular (BOX 1), such as crowd sourcing and parent entrepreneurs.

Conclusion:

The emerging sector of academic drug discovery is gradually replacing its early period enthusiasm with the informed realism of clinically meaningful therapeutics practice. There are significant advantages of conducting research in an integrated environment.

Risks also exist, pertaining to lack of experience with, for example, dosage and IP, which hamper the output of such projects. Perhaps more ambitious changes could assist with the development of global strategies for drug approval, as well as databases and systems that enable the transfer of precompetitive knowledge to reduce the risk of failure. Due to expensive and time-consuming traditional drug discovery process with higher failure rates, drug repurposing is becoming a promising tool in drug discovery. Drug repurposing facilitates identification of new uses of old drugs in shorter timeframes, while being cost-effective with reduced attrition rates, thus ultimately benefitting patients and the healthcare system overall. With increasing number of emerging viral infections day by day, discovery of therapeutics is required to be in tandem.

Repurposing FDA-approved drugs is a highly efficient way to leverage drugs with known safety profiles to fight the coronavirus outbreak. Proper delivery system and route of delivery has to be selected for dose reduction and to deliver repurposed drugs locally to the target site. With therapeutic delivery intervention, repurposing could be a perfect opportunity. Integration of pharmaceutical sciences and toxicology is essential to tackle issues related to dosing and safety. To treat infections caused by several viruses such as SARS-CoV-2, a quick focus on collaborative research on drug repurposing along with an optimal drug delivery strategies and inhaler devices is essential. The strategic drug repositioning in a more systematic and rational way has brought innovation with the discovery of drug molecules with unknown therapeutic indications. As drug repositioning approach offers significant reduction in R&D costs, greater chances of success, shorter research time and lower investment risk, it has gained increasing market demands. Because these advantages are beneficial for discovery scientists, drug researchers, consumers and pharmaceutical companies, enabling the application of novel approaches of repositioning strategy in the drug discovery program for almost all human diseases.

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