IJPSR (2022), Volume 13, Issue 6 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 12 September 2021; received in revised form, 25 October 2021; accepted, 12 November 2021; published 01 June 2022

A SYSTEMATIC REVIEW ON DRUG REPOSITIONING: A NEW METHODOLOGY TO DRUG DISCOVERY

Abhilash Poudyal, Barsha Subba and Sonam Bhutia *

Government Pharmacy College Sajong, Government of Sikkim, Sikkim University, Sajong - 737135 Sikkim, India.

Keywords:

Drug repository, Repurposed, Drug Repositioning, Methods, Challenges

Correspondence to Author:
Mr. Sonam Bhutia

Assistant Professor,
Government Pharmacy College Sajong, Government of Sikkim, Sikkim University, Sajong - 737135 Sikkim, India.

E-mail: sonamkzbhutia@gmail.com

ABSTRACT: At a time where we understand that new drug discovery and development involves significant cost, expensive products and is the slow-paced process, an innovative idea called 'Drug Repositioning', which basically means repurposing of old drugs to treat diseases including both common and rare are being increasingly attractive as it provides drug development in a sustainable cost, time efficiently and the product value is also low, making it less risky for pharmaceutical investment. A drug initially marketed as an anti-anginal drug repurposed for erectile dysfunction (Sildenafil/ Viagra) is an important example of landmark evidence in history. Similarly, over the years, several drugs have been successfully repurposed into other drug uses to treat various diseases. In this systematic review article, we have focused on the wholesome idea and methodologies of drug repurposing and its approaches, methods, challenges and strategic advantages over traditional drug discovery in the present scenario.

INTRODUCTION: Drug repurposing, which can also be referred as re-profiling, drug repositioning or re-tasking is a strategy or process for identifying new indications and uses for already approved or investigational drugs which are not present within the scope of original medical indication [1]. This strategy provides various advantages for developing an entirely new drug for a given indication or uses. Firstly, the most important factor is that the risk of failure is low, as the repurposed drug has been already known to be sufficiently safe in preclinical models and humans if early-stage trials have been completed, the chances of failure is less, at least from a safety point of view in subsequent efficacy trials.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.13(6).2251-62

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.13(6).2251-62

Secondly, reduction in the time frame for drug development as most of the preclinical testing, safety assessment and, in some cases, formulation development have already have been completed. Thirdly, the investment needed is comparatively low (however, it depends greatly on the stage and development of the repurposing candidate). Lastly, drugs that are repurposed may reveal new pathways and targets that can be exploited further [2]. The idea of drug repurposing came to light because traditional drug discovery is a time-consuming, costly, laborious, and high-risk process.

Eastern Research Group (ERG) report reveals that developing a new drug usually takes about 10-15 years. Even if developed, the success rate of developing a new molecular entity is only 2.01% on an average [3]. As a result, the biopharmaceutical industry faced a serious problem of output not keeping pace with the enormous increases in pharma R&D spending [4]. Despite enhanced technology and knowledge of the human disease, therapeutic advances in relation to these benefits

have been far slower than expected [5]. Even though pharma companies have invested huge amounts in the discovery of novel technologies, like combinatorial chemistry, structure-based drug design, genomics and high-throughput screening (HTS) which promised on improving productivity (For example, many industries heavily invested in the idea that HTS technology would bring 20-fold improvements in throughput).

Till date, over US $100 million has been invested in this technology, and so far, it has yielded only a few products **Fig. 1** 6. Recent Pharma R&D Factbook obtained from CMR International reveals the number of drugs terminated in Phase III of clinical development has significantly doubled in the past 5 years, reaching 55 compounds in the period from 2008 to 2010 [7].

As a result, for every dollar spent on research and development (R&D), it has been estimated that less than a dollar of value is returned on average, which could make the pharmaceutical industry a less desirable choice for investors along with an increase in the cost and length of time required for novel drug development.

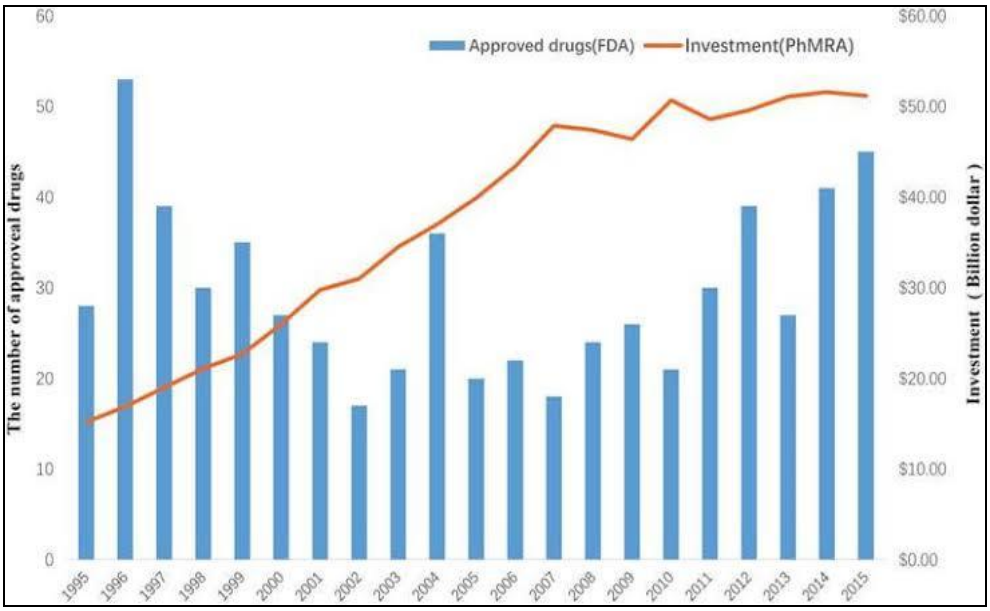

FIG. 1: BAR GRAPH BETWEEN INVESTMENTS MADE BY PHARMA INVESTOR'S VS NUMBER OF APPROVED DRUGS OVER THE YEARS

Strategies of Drug Repositioning: On-target and Off-target are the two main strategies of DR. In on-target DR, the pharmacological mechanism of a drug molecule is already known and thus can be applied for a new therapeutic indication [8].

The biological target of the drug molecule in such a strategy remains the same while the disease is not (different). An example includes repositioning of minoxidil (Rogaine), an antihypertensive vasodilator.

This drug also had the property to widen the blood vessels, thus opening the potassium channels, which allowed oxygen, blood, and nutrients to reach the hair follicles in higher concentrations. Due to this pharmacological property, this drug was repositioned and can be used to treat male pattern baldness (androgenic alopecia).

Alternately if we take a drug Aspirin which had previously been used as NSAID in the treatment of inflammatory disorders and various pain also showed to suppresses blood coagulation (clot formation) by inhibiting the normal functioning of platelets (anti-platelet drug).

It is, therefore, an effective drug used in the treatment of strokes and heart attacks. Thus, making is a good example of off-target DR where the pharmacological mechanism is not known. As a result, drugs and drugs candidates act on new targets which are out of the original scope for new therapeutic indications.

Hence, the targets and the indications both are new or unknown. Thus, dose of such drugs should be checked properly [9].

TABLE1: DRUG REPOSITIONING VS TRADITIONAL DRUG DISCOVERY

Traditional Drug Discovery	Drug Repositioning	Reference
About 13–15 years for developing any new drug in the market with a low success rate of approximately 2%	Drug repurposing Researchers only need 1-2 years to identify new drug targets and 8 years to develop a repositioned drug, on average	10
Involves six stages: (i) compound screening and identification of lead compound; (ii) preclinical study; (iii) investigational new drug (IND) application for taking approval to conduct trial in humans, only if preclinical data of the drug is found to be shows effective and safe in animals; (iv) clinical study (phase 1, 2 and 3 clinical trials); (v) new drug application (NDA) if the drug is found to be safe and effective in phase 3 clinical trials; and (vi) post-marketing surveillance (PMS) for safety monitoring.	Consists of four stages only: (i) selection of target compound; (ii) clinical trial (phase 2 and 3); (iii) NDA application and (iv) PMS. As a result, the time required for releasing a new drug in the market is reduced, along with cost-effectiveness and a low chance of failure	11, 12
Average cost billion to develop a new drug using traditional strategy is $12 billion	Average cost billion to develop a new drug using a drug repositioning strategy$1.6	13
Traditional strategy holds a higher risk of failure, costly and time-consuming	Drug repositioning holds a higher reward with a lower risk, is cost-effective and time-efficient.	4
The traditional approach to drug discovery involves de novo identification and of new molecular entities (NME)	In recent years, the use of *in-silico* techniques along with the application of structure-based drug design (SBDD) and artificial intelligence (AI) technology has further accelerated the drug purposing process	14, 15
The traditional approach to drug discovery involves a novel drug undergoing all the phages of clinical testing before it gets released into the market.	In Drug repositioning, a drug doesn't need to undergo some phages (phase 1,2 and, in some cases 3)	4
Examples of Traditional drug discovery are adalimumab, Apixaban, etanercept, ustekinumab, *etc*	Most successful examples of drug repurposing are sildenafil citrate for erectile dysfunction and repurposing of thalidomide for erythema nodosum leprosum (ENL)	2

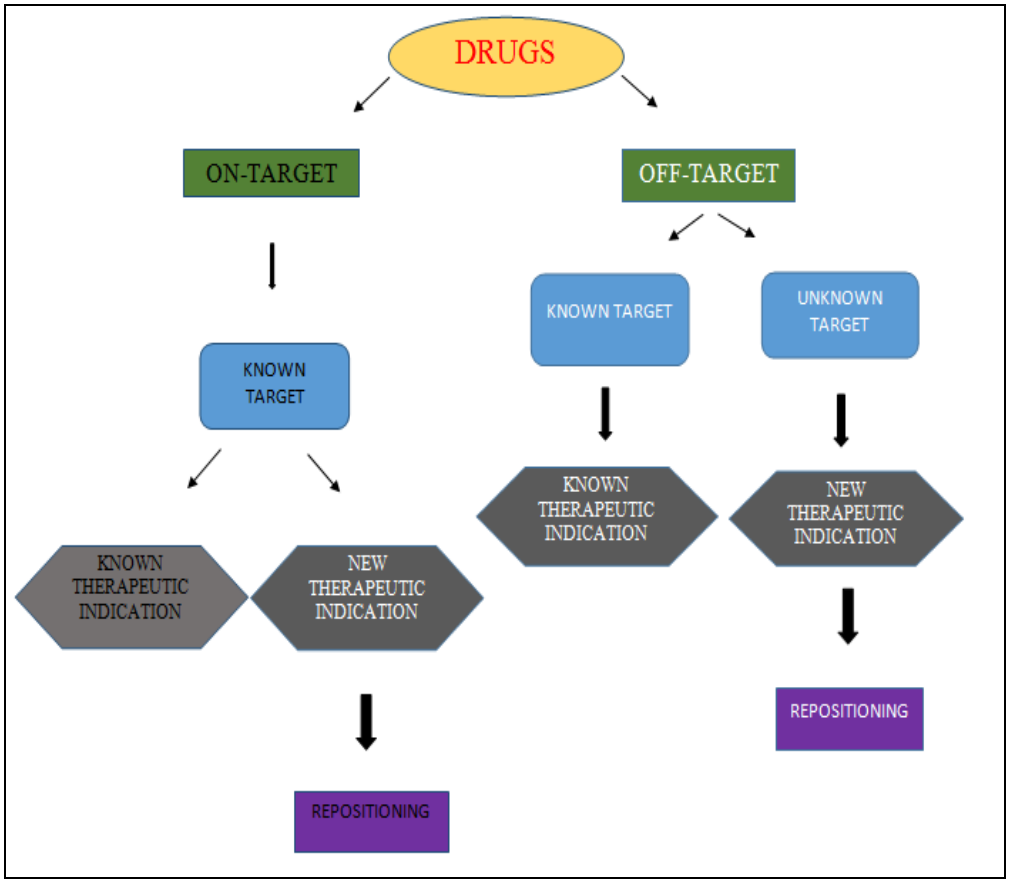

FIG. 2: STRATEGIES INVOLVED IN DRUG REPOSITIONING

TABLE 2: EXAMPLES OF SOME REPURPOSED DRUGS [16, 17]

Drug	Pharmacological Category	Original Use	Repurposed use	Development status
Amantadine	Anti-viral	Influenza	Parkinson's diseases	Already developed
Atomoxetine	Anti-depressant	Depression	Hyperactivity disorder	Already developed
Bupropion	Anti-depressant	Depression	Smoking cessation	Already developed
Bromocriptine	Dopamine receptor antagonist	Parkinson's diseases	DM (type 2)	Under development
Colchicine	Anti-inflammatory agent	Gout	COVID-19	Under development
Chloroquine	Anti-malarial	Malaria	COVID-19	Under development
Dimethyl fumarate	Anti-allergic	Psoriasis	Multiple sclerosis (MS)	Already developed
Disulfiram	Acetaldehyde dehydrogenase inhibitor	Chronic alcoholism	Cancer	Under development
Fluoxetine	Anti-depressant	Depression	Premenstrual dysphoria	Already developed
Favipiravir	Anti-viral	Influenza	COVID-19	Under development
Galantamine	AChE inhibitor	Neuromuscular paralysis	Alzheimer's disease	Already developed
Simvastatin	Hypolipidemic	cardiovascular diseases	Lung cancer	Already developed*
Ropinirole	Anti Parkinsonian drug	Parkinson's diseases	Restless leg syndrome	Already developed
Valsartan	Antihypertensive	Hypertension, Heart attack	Alzheimer's disease	Already developed

Approaches to Drug Technology: Drug repositioning comprises of two alternative yet complementary approaches, namely- the experiment-based approach and the other is the *In-silico*-based or computational approach [18-19]. Apart from these two approaches, nowadays another approach is receiving high acceptance called mixed approach, which involves approaching a drug repositioning *via* computational technology and then verifying it through a series of biological experiments (thus involving both and is called mixed approach **Fig. 3** [20].

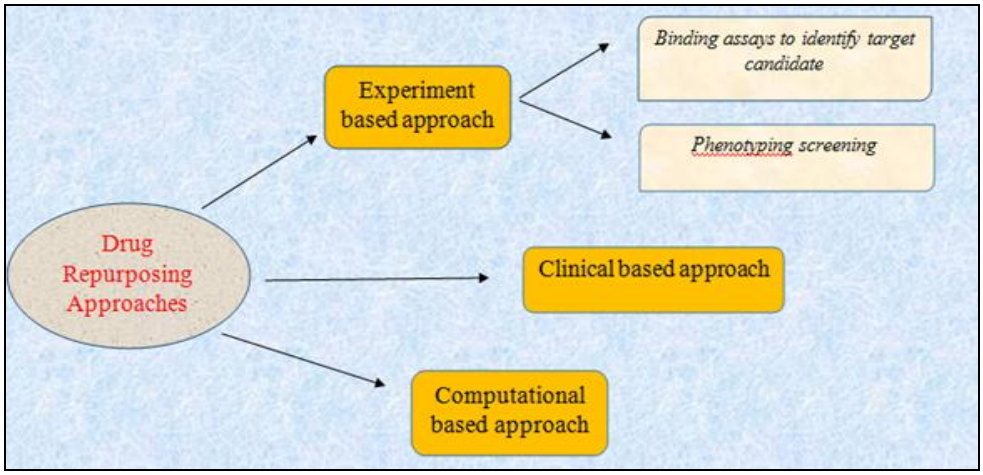

FIG. 3: APPROACHES TO DRUG DISCOVERY

Experiment-based Approach: It is also known as activity-based repositioning, which means screening of original drugs for new pharmacological indications relying on experimental assays.

It consists of protein target-based and cell/organism-based screens in *in-vitro* and/or *in-vivo* disease models without any structural information of the target proteins. They are of two types:

Binding Assays to Identify Target Candidate: Proteomic techniques including affinity chromatography and mass spectrometry are being approached to identify binding partners for an ever-increasing number of drugs. For example, Brehmer *et al.* used HeLa cell extract to study and identify possible protein targets of gefitinib (a type of targeted cancer drug called a tyrosine kinase inhibitor or TKI). Mass spectrometry revealed that the drug could interact with 20 different protein

kinases, which may be treated as possible targets of gefitinib [21]. This study shows that mistakes made during approaches to many kinase drug discovery can also be useful; also unbiased affinity approaches at an early stage are helpful in understanding the pharmacological effect of a compound in the cell, including paradoxical kinase activation by inhibitors which is a key mechanism for off-target tumour initiations in patient treatment [22]. Other examples where this technique resulted in successful include detection of quinone reductase 2 (NQO2) as cellular off-target of acetaminophen (paracetamol) and confirmation of cellular targets for the tyrosine kinase inhibitor (TKI) crizotinib [23]. It clears that the importance of protein kinase inhibitors has long been recognized and can hopefully fulfill major drug targets of the 21st century.

Phenotyping Screening: Phenotyping screening can be referred to as the methods used for identification of any biological effects of a drug, either linked directly or indirectly to a disease (without prior knowledge of the target(s) affected) [24]. Along with the development of robotic and sensitive screening tools, this approach is used for screening thousands of chemical drug libraries within a single run. It consists of a screening of target drug candidates by using either cell-based screens (high throughput screening (HTS)) or even whole organism, where cell-based assays include induced pluripotent cells lines (iPSCs) or even cell lines derived from human or animals, immortalized cell lines, *etc* [25]. For example, Iljin *et al.* [26] performed high-throughput cell-based screening (HTS) of approximately 5000 small drug-like molecules using four prostate cancer epithelial cell lines and two non-malignant prostate epithelial cell lines. After the experiment, it was observed that disulfiram (a drug used in case of alcohol abuse) possessed some selective antineoplastic property which was later validated using genome-wide gene expression studies. In drug repurposing, Whole-organism phenotypic assays are also seen to be useful. Example Cousin and colleagues [27] used a zebrafish model to evaluate 39 medications that were FDA-approved to be used in tobacco dependence. As a result, it was observed that that compounds like apomorphine and topiramate had the ability to modify nicotine and ethanol-induced behavior in this model.

Computational Based Approach: Computational approaches are mostly data-driven. It is mainly used to discover new indications for an existing drug (drug-centric) and identify effective drugs for a disease (disease-centric). It has the common strategy of similarity assessment between drugs and/or diseases [28].

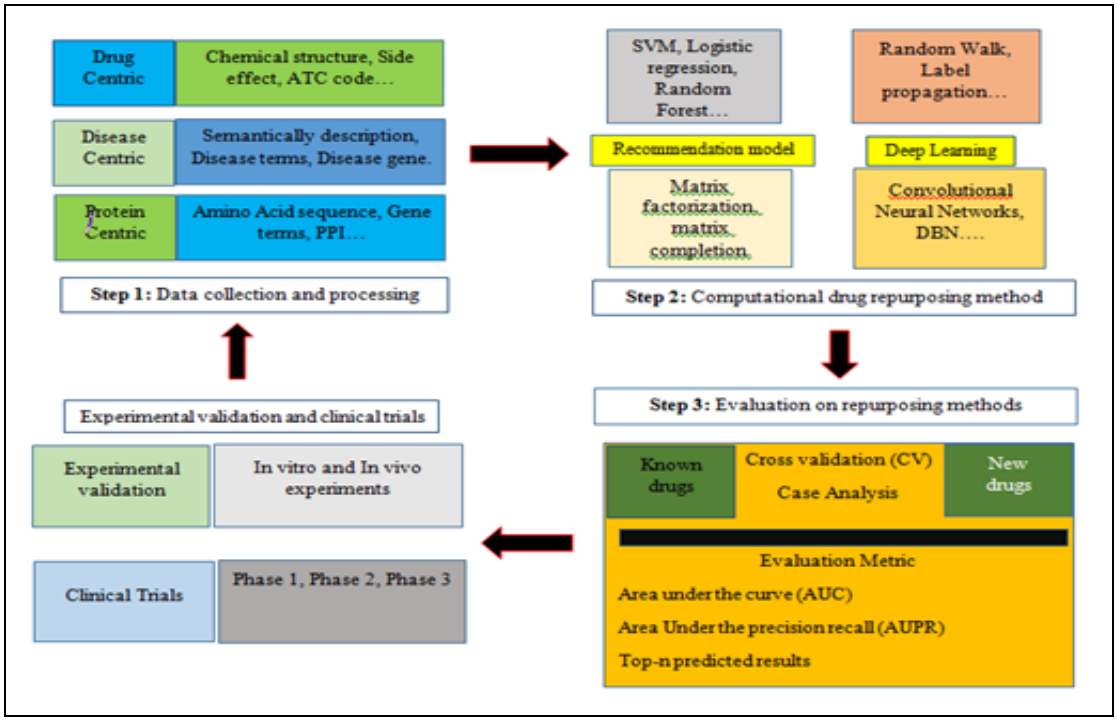

FIG. 4: COMPUTATIONAL DRUG REPOSITIONING WORKFLOW

They involve systematic analysis of data of any type including chemical structure, electronic health records (EHRs), gene expression, genotype, or proteomic data, which can further help formulate repurposing hypotheses. Due to this, data characterization of disease phenotypes and drug profiles and the entire pathway maps have become available. It can also be valuable in predicting different adverse reactions which are related to drugs, ligands targeting the different pathways, their structure-activity relationships (SAR), *etc*. also, due to the advances in computational and data sciences, it is now possible for the repurposed algorithms to develop, along with database maintenance and retrospective analysis for experimental data [29-30]. Computational approaches that are most commonly used and drug repurposing examples are discussed below **Fig. 4.**

Knowledge-Based Approach: In this approach, available data such as receptors and ligands, comes into play. It uses drug-related information's like drug targets, chemical structures, pathways, adverse effects, chemical structures, *etc*., and are used to predict unknown targets, bio-markers or mechanisms for diseases, structure-activity relationships (SAR) their adverse reaction related to drugs, ligands targeting the different pathways, *etc*. [31-32]. Thus, it could be a mechanism-based, pathway-based, receptor-based repositioning of drugs**.**

Signature Based Approach: Signature matching is a comparative technique a unique characteristic or 'signature' of a drug is compared against that of another drug, disease or clinical phenotype. In such approaches, inverse drug-disease relationships is searched by comparing gene expression profiles between drug and disease. It is basically utilized for the discovery of new off-targets or mechanisms of disease [33-34]. The characteristic (signature) of a drug interested in drug prepositioning can be obtained from three types of general data: proteomic/metabolomic data; chemical structures, proteomic/metabolomic data; or adverse event profiles. Examples include work done by Dudley *et al.* [35] where they investigated inflammatory bowel disease (IBD) using the idea of potential drug-disease pairs. They compared gene expression profiles obtained from the gene expression omnibus database with gene expression profiles comprised of approximately 170 drug compounds obtained from the connectivity map [36]. The result showed the discovery of unknown drug-disease pairs from which one pair was even validated in preclinical models. The main advantage this approach involves is the identification of novel mechanisms of action for drugs that are molecular- and/or genetic-level mechanisms.

Target/Molecular Docking Based Approach: The idea behind molecular docking is a computational structure-based strategy that helps predict binding sites that are complementarily between the ligand (a drug) and the target (a receptor). Suppose a receptor target involved in disease is known in such a case. In that case, more than one (multiple) drugs can be interrogated against that particular target, also called conventional docking (one target and multiple ligands) [37]. In this technique, drug compounds of specific interest are selected from drug libraries by either ligand-based screening or molecular docking, which uses high-throughput screening (HTS) or high-content screening (HCS) because of the number of compounds to be screened is large in this method. Several other methods, including extra precision (XP) and standard precision (SP), can also be used. As compared to screening that does not apply any biological or pharmacological information during screening or blinded search, target-based repurposing directly links targets with disease mechanisms. Thus, significantly improving the likelihood of drug discovery. When Dakshanamurthy and colleagues [38] performed molecular fit computations on over 3, 671 FDA-approved drugs across 2,335 human protein crystal structures. It was observed that mebendazole (an anti-parasitic drug) consists of a structural potential that could inhibit vascular endothelial growth factor receptor 2 (VEGFR2), a mediator of angiogenesis. It was even confirmed experimentally.

However, Target/molecular docking-based drug repurposing has some limitations, such as several questions arising on the use of docking algorithms to predict binding affinity. Other limitations include the lack of well-curated macromolecular target databases to provide accurate structural information 39. Lastly, 3D structures may not be available for some interesting protein targets because drug targets are often membrane proteins.

An example includes G protein-coupled receptors (GPCRs). Furthermore, it is seen that several advancements and improvements are made to eradicate such problems in the future.

Genetic association Based Approach: Over the past decade, there has been a huge advancement in genome-wide association studies (GWAS). It includes dwindling genotyping costs and completion of the Human Genome Project. GWAS is used to determine genetic variants in the whole genome, which gives detailed knowledge about the biology or pathophysiology of various numbers of diseases. Thus, GWAS obtains data that makes it suitable for identifying ideal novel targets for that particular disease which further helps reposition several drugs. A recent study conducted by Grover and colleagues [40-41] obtained information from three different drug–target databases: Drug Bank, Therapeutic Target Database, and Pharm GKB. It used a bioinformatics approach for matching targets identified for coronary artery disease to identify some potential repositioning opportunities. However, the exact pathophysiological mechanism is not provided from current data available in GWAS and the data's which are available data is not sufficient or appropriate due to gene variants. As a result, rational use of GWAS data is encouraged before predicting repurposing targets. Thus, even today, more than thousands of genes have not been discovered and are contributing to the pathophysiology of various diseases. Also, one should understand that current knowledge of the human genome is not absolute, and more new genes can be discovered.

Pathway Mapping / Pathway Based Approach: Potential targets found using GWAS or other techniques may be directly agreeable as drug targets; however, in some cases, such gene (genetic) may not be ideal druggable targets. In those circumstances, a pathway-based strategy could be used for obtaining information about upstream or downstream of the GWAS-associated target, which can further be used for repurposing opportunities [42-43]. Example of pathway mapping includes Pathway analysis of gene expression data, which was basically studies of a wide variety of respiratory viruses that were allowed to infect the human host model. The result showed that respiratory viral infection consisted of 67 important common biological pathways. When these pathways were crosschecked with the Drug Bank database, it was identified that several drugs had a potent effect against host-viral targets, such as, amrinone which are used in the treatment of congestive heart failure by inhibiting phosphor-diesterase, pranlukast which are used in the treatment of asthma and are a leukotriene receptor 1 antagonist. These drugs were highlighted for the treatment of viral infections because of their ability to alter the immune system. Thus these drugs can possibly be reconstructed for drugs repositioning. The advantage of these approaches is the ability to can narrow down general signaling networks from a large number of proteins to a specific network with a few proteins (or target molecules).

Targeted Mechanism-Based Approach: This method is used to describe the existing drugs whose mechanisms of action are not known with the help of available signaling pathway information, protein interaction networks, and data obtained from omics [44]. The ultimate goal is to obtain a precise medication that has gained ever-increasing recognition. This type of repurposed drug can discover the various pathophysiological mechanisms but can also aid in providing treatment to them with their respective drugs.

Clinical Based Approach: This type of approach is coincidental. Positive results are quite rare as the chances of such a drug passing Phase II/III trials are very low or negligible. However, some drugs get marketed, and only during post-marketing surveillance are different outcomes obtained. Some drugs may show different adverse reactions, while others may even treat specific kinds of disease with no labeled indication.

Thus, in such cases, clinical approaches is used to repurpose those drugs. An example includes apomorphine (dopaminergic agonist) which shows a high affinity towards D (2) within the brain known to be involved in sexual function.

Thus it was later repositioned to be used in erectile dysfunction. Other examples include drospirenone, initially used as an oral contraceptive and later repurposed for hypertension and dapoxetine used for analgesia and depression and later repurposed for hypertension.

Methodologies Involved in Drug Repositioning: Based on information available regarding the toxicological, biological, and pharmacological activity, the quality and quantity of a drug can be improved by applying three broad methods in DR. These are (a) Target-Related, (b) Drug-Related, and (c) Disease or therapy-Related.

Target-Related: The advantage of using this method is the significant success rate in drug discovery compared to the drug-oriented method. This is because most biological targets represent the disease pathways/ mechanisms directly. Virtual high-throughput screening (vHTS) or *In-silico* screening is done for drugs or compounds from compound databases or drug libraries like molecular docking or ligand-based screening. It is then followed using *in-vivo* high-throughput and/or high-content screening (HTS/HCS) and *in-vitro* of drugs against interested biomarker or selective protein molecule [45].

Drug-Related: DR of sildenafil is one of the major successes achieved using this method (either through serendipity or clinical observation). The core fundamental of this method is basically an evaluation of structural characteristics of drug molecules, adverse effects, biological activities, and toxicities. It is a type of method which emphasizes traditional pharmacology and drug discovery principles. Here studies are conducted to determine the biological efficacy of drug molecules without any knowledge of the biological targets [46].

Disease or therapy-Related: This method prevails in those cases where information of the disease model is readily available. Thus it entails specific disease network construction, genetic expression reorganization, key targets, disease identification that cause protein molecules related to cells, and metabolic pathways of interest in the disease model. In such cases, DR is directed by the disease and/or treatment based upon the availability of information given by proteomics, metabolomics, proteomics, genomics, and phenotypic data [47]. Ideal Methodologies used for Drug Repurposing are summarized below in **Table 3.**

TABLE 3: IDEAL METHODOLOGIES USED FOR DRUG REPURPOSING [48]

Method involved	Category	Method type used	Method/specific approach	Examples of drug
Disease-Related				
Disease omics/ genetics data	Bioinformatics	Signature-based	Studying gene signatures/ genomics to identify key targets	Not available
Available Pathway information	Bioinformatics	Knowledge-based	Discovery of disease mechanism and address of key targets	Vismodegib (used for skin cancer)
Disease omics data, available pathway information, and protein interaction network	Network biology	Pathway or network-based	Analysis of disease-specific pathways and networks to identify key target	Sunitinib, dasatinib (breast cancer, brain tumor)
Drug-Related				
FDA approval labels	Bioinformatics	Knowledge-based	Drug similarity studies	Not available
Phenotypic screening	Screening	Blinded/ Target-based	*In-vitro* and *in-vivo* HTS/HCS screening	Sildenafil (erectile dysfunction), rituximab (breast cancer)
Clinical trial information and adverse effects	Bioinformatics	Knowledge-based	Drug similarity studies	Not available
Drug-target information, chemical structure, information of targets and drugs	Chem-informatics/ Bioinformatics	Knowledge-based	Drug target prediction	Simvastatin, ketoconazole (breast cancer)
Target 3D structure, chemical structure, information of drugs and ligands	Cheminformatics	Target-based	*In-silico* screening, ligand-based screening and molecular docking	Fluorouracil (lung cancer), etoposide (bladder cancer)
		Disease or therapy-		

		Related		
Drug omics data	Bioinformatics and/or Network biology	Signature-based or signature- and network-based	Studying gene signatures	Sirolimus (acute lymphoblastic leukemia), Fasudil (neurodegenerative disorders)
Drug omics data, disease pathway and protein interaction network	Network biology and Systems biology	Targeted-mechanism-based	Elucidating targeted pathways	Daunorubicin, clomifene (breast cancer)
Disease omics and drug omics data	Bioinformatics	Signature-based	Similarities between drugs and diseases	Cimetidine (lung cancer), topiramate (inflammatory bowel disease)

Drug Repurposing Challenges: Even though DR is gaining utmost importance in the pharmaceutical field for the development of future drugs, as it promises reliable drugs with cost-effectiveness, low economic support and risk involved is also less. However, this idea is not well established as it does consists of several challenges that need attention for better results illustrated below.

Optimistic Investments: Finding a prominent investment has always been a major challenge in DR. Like any other project, DR also requires an upfront investment that has been notoriously difficult due to its initial failures.

The result to such organizational mentality caused repositioning of thalidomide by Celgene, even though Grunenthal Company was the inventor of that drug. This Company had one of the most famous failures in drug development history, which was majorly due to the initial use of thalidomide in the incorrect population, including women in their first trimester of pregnancy. Because of this birth defects were observed in newborns. This was a tragic effect of thalidomide that was unknown at the time of its approval [49].

Availability of Data and Compound: Different types of data integration have been computationally demanding as it requires high analysis power [50]. Furthermore, even after progressive growth in the open-source model within the drug discovery community, access to important data like clinical trials is still limited to the public [51].

Apart from that, some data types are not approachable to integration, manipulation, and data mining or are obtainable in a non-standardized manner**.** There may be issues in compound availability with generic active pharmaceutical ingredients. It occurs mostly when the compound is gone from the international market.

TABLE 4: SOME EXAMPLES OF UNSUCCESSFUL DRUG REPOSITIONING

Name of drug	Old use	New use	Approach used for repurposing	Repurposing Result	Date	Reference
Ceftriaxone	Antibiotic	Amyotrophic lateral sclerosis	High-throughput drug screening in animal models	drug screening in animal models Phase III trial failed to show efficacy	2014	[52]
Latrepirdine	Antihistamine	Huntington disease	Pharmacological analysis	Phase III trial (known as HORIZON) by Pfizer and Medivation was unsuccessful	2011	[53]
Topiramate	Epilepsy	Inflammatory bowel disease	Transcriptome based signature matching	Successful in a rodent model of inflammatory bowel disease but failed in a retrospective cohort study but no randomized clinical trial conducted to date	2014	[54]

In such cases, it creates a challenge to find a vendor that is reliable. Lastly, a prospect that poses a fundamental barrier to drug repurposing is that some pharmaceutical companies are less interested in revealing their chemical libraries like failed drugs so that it can be accessed for the repositioning of various drugs. Some examples of unsuccessful drug repositioning are discussed in **Table 4** below.

Proof of Concept (POC): Another aspect that creates a hurdle in drug repurposing is basically the

design and execution proof of concept (POC). This means developing a compound for a specific indication that is not within the company's strategic focus. It is created by the Organization of pharmaceutical R&D around specific therapeutic areas. The requirement of a considerable amount of clinical expertise is high for its clinical test. However, investigator-sponsored trials (studies initiated and conducted by interested clinicians) are very low, especially by small biotech companies or contract research organizations (CROs) as they do not risk Out-license such compounds for a particular indication or conduct such POC studies [55].

Independent Indications: Restless leg syndrome or erectile dysfunction and other such disorders/diseases pose additional complexity to repositioning projects. This is because that is medical conditions that have never been considered as independent indications before. It is considered as a challenge as such special repositioning projects require field experts that are not within the usual repertoire of a pharmaceutical company [56].

CONCLUSION: Drug repurposing has changed the pace of drug discovery as it offers time efficiency, low risk of failure, and, most importantly, makes it cheaper when it gets marketed. It has thus obtained an important recognition of all R and D sector and Major Pharma industries. However, this methodology or strategy can be used to its full potential if some of its sectors are given more focus, such as industry-sponsored phase II-IV clinical trials providing greater access to data which can create freedom for external scientists to explore the data for new findings that could expand repurposing opportunities. Data access and integration should be given more importance as it benefits repurposing opportunities, especially for clinical data, which can be achieved via technological advancement. Simplification of this process is important, especially at compound dissemination and material transfer agreement signatories' level. Academic researchers can be provided with an increased number of a compound that can be accessed. For more drug to be a promising candidate in drug repositioning requires advancement or development of a systematic and sophisticated approach. Thus, 'Drug Repositioning', if given even greater importance, can play a major role in the sector of Drug discovery in the near future in existing diseases and Orphan diseases, and Novel diseases.

ACKNOWLEDGEMENT: The authors are grateful to the host institutes-Government Pharmacy College, Sajong-Sikkim, to give such advanced facilities such as a friendly environment, internet facilities, *etc*., to collect the significant informative data for this systematic review work. Thanks to the entire colleges' team, especially to Mr. S. Bhutia, for their kind guidance, scientific instructions, formatting, and designing all the essential information to make my drafted work into a valuable review manuscript.

CONFLICTS OF INTEREST: The author declared that there are no conflicts of interest to disclose.

REFERENCE:

1. Ashburn TT and Thor KB: Drug repositioning: identifying and developing new uses for existing drugs. Nature Reviews Drug Discovery 2004; 3: 673–683.
2. Pushpakom S, Iorio F, Eyers PA, Escott KJ, Hopper S, Wells A and Pirmohamed M: Drug repurposing: progress, challenges and recommendations. Nature Reviews Drug Discovery 2019; 18(1): 41-58.
3. Xue H, Li J, Xie H and Wang Y: Review of drug repositioning approaches and resources. International Journal of Biological Sciences 2018; 14(10): 1232.
4. Ashburn TT and Thor KB: Drug repositioning: identifying and developing new uses for existing drugs. Nature Reviews Drug Discovery 2004; 3(8): 673-683.
5. Scannell JW, Blanckley A, Boldon H and Warrington B: Diagnosing the decline in pharmaceutical R&D efficiency. Nature reviews Drug discovery 2012; 11: 191–200.
6. Editorial: Colonizing therapeutic space: the overlooked science of drug husbandry. Nature Reviews Drug Discovery 2004; 3: 101.
7. Novac N: Challenges and opportunities of drug repositioning. Trends in Pharmacological Sciences 2013; 34(5): 267-272.
8. Ferreira LG and Andricopulo AD: Drug repositioning approaches to parasitic diseases: A medicinal chemistry perspective. Drug Disco Today 2016; 21(10): 1699-1710.
9. Rudrapal M, Khairnar JS and Jadhav GA: Drug repurposing (DR): an emerging approach in drug discovery. Drug Repu Hypothe Mol Asp Ther Appl 2020.
10. Sertkaya A, Birkenbach A, Berlind A and Eyraud J: Examination of clinical trial costs and barriers for drug development. US Department of Health and Human Services Office of the Assistant Secretary for Planning and Evaluation Report 2014; 1: 1-92.
11. Rudrapal M and Chetia D: Endoperoxide antimalarials: Development, structural diversity and pharmacodynamic aspects with reference to 1, 2, 4-trioxanebased structural scaffold. Drug Design, Deve and Ther 2016; 10: 3575-3590.

12. Hughes JP, Rees S, Kalindjian SB and Philpott KL: Principles of early drug discovery. British Journal of Pharmacology 2011; 162(6): 1239-1249.
13. Deotarse PP, Jain AS and Baile MB: Drug repositioning: a review. International Journal of Pharmaceutical Sciences Review and Research 2015; 4: 51-58.
14. Agrawal P: Artificial intelligence in drug discovery and development. Journal of Pharmacovigilance 2018; 6: 2.
15. Kalita J, Chetia D and Rudrapal M: Design, synthesis, antimalarial activity and docking study of 7-chloro-4-(2-(substituted benzylidene) hydrazineyl) quinolines. Medicinal Chemistry 2020; 16(7): 928-937.
16. Matthews H, Usman-Idris M, Khan F, Read M and Nirmalan N: Drug repositioning as a route to anti-malarial drug discovery: Preliminary investigation of the *in-vitro* anti-malarial efficacy of emetine dihydrochloride hydrate. Malaria Journal 2013; 12(359): 1-11.
17. Appleby BS and Cummings JL: Discovering new treatments for Alzheimer's disease by repurposing approved medications. Current Topics in Medicinal Chemistry 2013; 13: 2306-2327.
18. Oprea TI and Overington JP: Computational and practical aspects of drug repositioning. Assay and Drug Development Technologies 2015; 13: 299-306.
19. Jarada TN, Rokne JG and Alhajj RA: Review of computational drug repositioning: strategies, approaches, opportunities, challenges and directions. Journal of Cheminformatics 2020; 12(1): 1-23.
20. Turanli B, Grøtli M, Boren J, Nielsen J, Uhlen M and Arga KY: Drug repositioning for effective prostate cancer treatment. Frontiers in Physiology 2018; 9: 500.
21. Brehmer D: Cellular targets of gefitinib. Cancer Research 2005; 65: 379–382.
22. Su FRAS: Mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. New England Journal of Medicine 2012; 366: 207–215.
23. Alshareef A: The use of cellular thermal shift assay (CETSA) to study crizotinib resistance in ALKexpressing human cancers. Scientific Reports 2016; 6: 33710.
24. Moffat JG, Vincent F, Lee JA, Eder J and Prunotto M: Opportunities and challenges in phenotypic drug discovery: an industry perspective. Nature Reviews Drug Discovery 2017; 16: 531–543.
25. Aulner N, Danckaert A, Ihm J, Shum D and Shorte SL: Next-generation phenotypic screening in early drug discovery for infectious diseases. Trends in Parasitology 2019; 35(7): 559-570.
26. Iljin K, Ketola K, Vainio P, Halonen P, Kohonen P and Fey V: High-throughput cell-based screening of 4910 known drugs and drug-like small molecules identifies disulfiram as an inhibitor of prostate cancer cell growth. Clinical Cancer Research 2009; 15(19): 6070-6078.
27. Cousin MA: Larval zebrafish model for FDA approved drug repositioning for tobacco dependence treatment. PLOS ONE 2014; 9: 90467.
28. Liu Z, Fang H, Reagan K, Xu X, Mendrick DL and Slikker WJR: *In-silico* drug repositioning: What we need to know. Drug Discovery Today 2013; 18: 110-115.
29. Hift RJ and Meissner PN: An analysis of 112 acute porphyric attacks in Cape Town, South Africa: Evidence that acute intermittent porphyria and variegate porphyria differ in susceptibility and severity. Medicine 2005; 84(1): 48-60.
30. Li J, Zheng S, Chen B, Butte AJ, Swamidass SJ and Lu Z: A survey of current trends in computational drug repositioning. Briefings in Bioinformat 2016; 17(1): 2-12.
31. Brown AS and Patel CJA: review of validation strategies for computational drug repositioning. Briefings in bioinformatics 2018; 19(1): 174-177.
32. Emig D, Ivliev A, Pustovalova O, Lancashire L, Bureeva S and Nikolsky Y: Drug Target Prediction and Repositioning Using an Integrated Network-Based Approach. PLoS ONE 2013; 8:60618.
33. Lotfi SM, Ghadiri N, Mousavi SR, Varshosaz J and Green JR: A review of network-based approaches to drug repositioning. Briefings in bioinformatics 2018; 19(5): 878-892.
34. Hieronymus H: Gene expression signaturebased chemical genomic prediction identifies a novel class of HSP90 pathway modulators. Cancer Cell 2006; 10: 321–330.
35. Dudley JT, Sirota M, Shenoy M, Pai RK, Roedder S and Chiang AP: Computational repositioning of the anticonvulsant topiramate for inflammatory bowel disease. Science Translational Medicine 2011; 3: 96ra76.
36. Lamb J, Crawford ED, Peck D, Modell JW, Blat IC and Wrobel MJ: The Connectivity Map: using gene-expression signatures to connect small molecules, genes and disease. Science 2006; 313: 1929-1935.
37. Kitchen DB, Decornez H, Furr JR & Bajorath J: Docking and scoring in virtual screening for drug discovery: methods and applications. Nature Reviews Drug Discovery 2004; 3: 935–949.
38. Dakshanamurthy S: Predicting new indications for approved drugs using a proteochemometric method. Journal of Medicinal Chemistry 2012; 55: 6832–6848.
39. Kharkar PS, Warrier S and Gaud RS: Reverse docking: a powerful tool for drug repositioning and drug rescue. Future Medicinal Chemistry 2014; 6: 333–342.
40. Grover MP: Novel therapeutics for coronary artery disease from genome-wide association study data. BMC Medical Genomics 2015; 8(2): 1.
41. Greene CS and Voight BF: Pathway and networkbased strategies to translate genetic discoveries into effective therapies. Human Molecular Genetics 2016; 25: 94–98.
42. Pritchard JLE, O'Mara TA and Glubb DM: Enhancing the promise of drug repositioning through genetics. Frontiers in Pharmacology 2017; 8: 896.
43. Appleby BS and Cummings JL: Discovering new treatments for Alzheimer's disease by repurposing approved medications. Current Topics in Medicinal Chemistry 2013; 13: 2306-2327.
44. Napolitano F, Zhao Y and Moreira VM: Drug repositioning: A machine-learning approach through data integration. Journal of Cheminformatics 2013; 5(1): 30.
45. Koch U, Hamacher M and Nussbaumer P: Cheminformatics at the interface of medicinal chemistry and proteomics. Biochimica et Bioph Acta 2014; 156-161.
46. Chong CR, Chen X, Shi L, Liu JO and Sullivan DJ JR: A clinical drug library screen identifies astemizole as an antimalarial agent. Nature Chemical Bio 2006; 2: 415-416.
47. Jin G and Wong STC: Toward better drug repositioning: Prioritizing and integrating existing methods into efficient pipelines. Drug Discovery Today 2014; 19: 637-644.
48. Naylor S, Kauppi DM and Schonfeld JM: Therapeutic drug Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications 20 repurposing, repositioning and rescue. Part II: Business review. Drug Discovery World 2015; 16: 57-72.
49. Matthews JJ and McCoy C: Thalidomide: A review of approved and investigational uses. Clinical Therapeutics 2003; 25: 342-395.

50. Ritchie MD, Holzinger ER, Li R: Methods of integrating data to uncover genotype-phenotype interactions. Nature Reviews Genetics 2015; 16: 85–97.
51. Allarakhia M: Open-source approaches for the repurposing of existing or failed candidate drugs: learning from and applying the lessons across diseases. Drug Design, Development and Therapy 2013; 7: 753–766.
52. Cudkowicz, ME: Safety and efficacy of ceftriaxone for amyotrophic lateral sclerosis: a multistage, randomised, double-blind, placebo-controlled trial. Lancet Neurology 2014; 13: 1083–1091.
53. Bezprozvanny I: The rise and fall of Dimebon. Drug News Perspect 2010; 23: 518–523.
54. Crockett SD, Schectman R, Sturmer T and Kappelman MD: Topiramate use does not reduce flares of inflammatory bowel disease. Digestive Diseases and Sciences 2014; 59: 1535–1543.
55. Cappelleri JC, Siegel RL, Osterloh IH and Rosen RC: Relationship between patient self-assessment of erectile function and the erectile function domain of the international index of erectile function. Urology 2000; 56(3): 477-481.
56. Manconi M: Dissociation of periodic leg movements from arousals in restless legs syndrome. Annals of Neurology 2012; 71: 834-844.

How to cite this article:
Poudyal A, Subba B and Bhutia S: A systematic review on drug repositioning: a new methodology to drug discovery. Int J Pharm Sci & Res 2022; 13(6): 2251-62. doi: 10.13040/IJPSR.0975-8232.13(6).2251-62.