Chapter 4

Drug Repurposing and Orphan Disease Therapeutics

Neha Dhir, Ashish Jain, Dhruv Mahendru, Ajay Prakash and Bikash Medhi

Abstract

Drug repurposing (or drug repositioning) is an innovative way to find out the new indications of a drug that already exists in the market with known therapeutic indications. It offers an effective way to drug developers or the pharmaceutical companies to identify new targets for FDA-approved drugs. Less time consumption, low cost and low risk of failure are some of the advantages being offered with drug repurposing. Sildenafil (*Viagra*), a landmark example of a repurposed drug, was introduced into the market as an antianginal drug. But at present, its use is repurposed as drug for erectile dysfunction. In a similar way, numerous drugs are there that have been successfully repurposed in managing the clinical conditions. The chapter would be highlighting the various drug repurposing strategies, drugs repurposed in the past and the current status of repurposed drugs in the orphan disease therapeutics along with regulatory guidelines for drug repurposing.

Keywords: drug repurposing, drug repositioning, orphan drug, orphan disease, a rare disease, regulatory guidelines

1. Introduction

Despite rapid advancement in science and technology, translating these benefits for care and management of human diseases remains a far slower process than expected. Pharmaceutical industries, research and development (R&D) sectors are facing multifold challenges for taking out any new drug in the market including higher attrition rates, long time span and regulatory restrictions [1]. It takes $2 to $3 billion money and about 13–15 years for developing any new drug in the market with a low success rate of approximately 2% only [2, 3]. Drug development process 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. However, drug repurposing consists of four stages only: (i) selection of target compound; (ii) clinical trial (phase 2 and 3); (iii) NDA application and (iv) PMS (**Figure 1**). Thereby' drug repurposing is a trending way to reduce the effort, cost and time at every step involved in drug development and thus provides an option to bring the new drugs into the market at relatively low investments (**Figure 1**) [3].

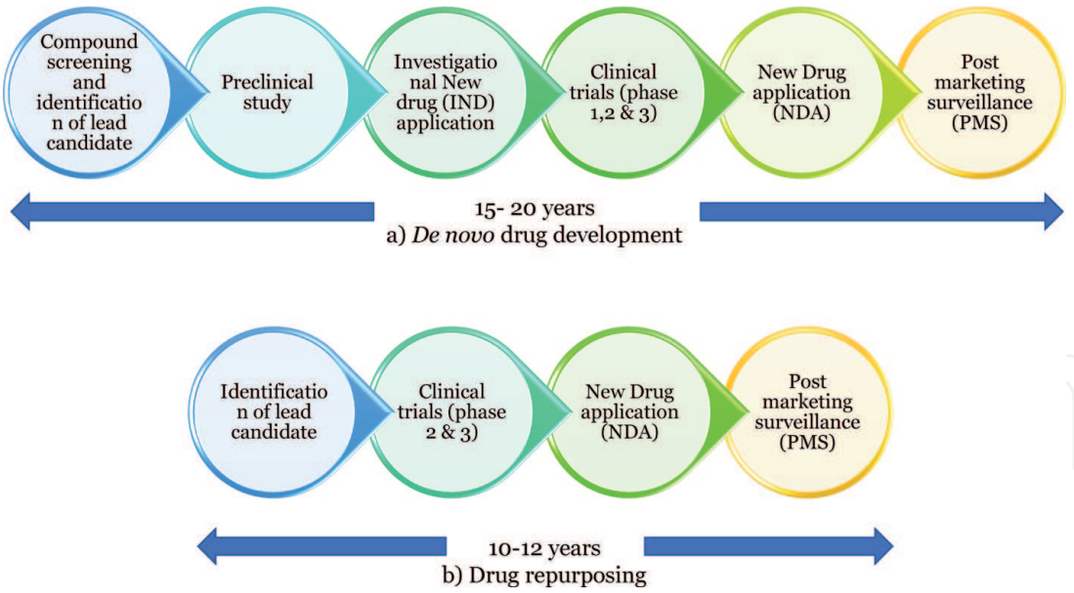

Figure 1.
Phases in drug development.

1.1 Drug repurposing

'Drug repurposing' (or 'drug repositioning') is an effective way to find new targets or new indications of any drug that is already FDA approved and existing in the market. It is an excellent alternative over the *de novo* drug development process which is relatively time consuming and money involved procedure [4]. Since the data including drug efficacy, safety, bioavailability, route and formulation of administration, pharmacokinetic and pharmacodynamic (PK-PD) profile, toxicological data and associated adverse effects, are well known with already approved drugs. Thus, the evaluation process for drug candidates gets facilitated with drug repurposing and drug enters the clinical market for new therapeutic indications. Also, drug repurposing reduces the risk of development failure into the market, thus reducing the cost of the overall drug development process. At present, in the U.S approximately 30% of newly FDA approved drugs are repurposed only [5]. History witnessed numerous drug candidates that have been repurposed either opportunistic or serendipitous. Sildenafil is one of the blockbusters in the history of drug repurposing. Sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, was introduced in the market in the 1980s by Pfizer for the treatment of coronary artery disease (CAD), hypertension and angina pectoris. During phase-1 trials of sildenafil, it was observed that the patients suffered from marked penile erection. In 1988, the drug was repurposed and approved by FDA for erectile dysfunction in the US market after the drug failed to prove its efficacy in phase-2 trials in angina patients [6]. Another big hit example is thalidomide. In 1957, the drug was developed by German pharmaceutical company named Grünentha for treatment of motion sickness in pregnant women. Soon the drug was withdrawn from the market as its use lead to serious birth defects (malformations of the limbs) and death in approximately 10,000 children in around 46 countries. Subsequently in 2006, the drug was re-approved by FDA for the treatment of multiple myeloma [4]. In the 1960s, amantadine was developed as an antiviral drug to treat influenza infections. After a few years, a patient who was suffering from Parkinson's disease (PD) had taken amantadine for her flu infection. It was seen that the patient was having improvement in her PD symptoms after taking amantadine. From there, it has been concluded that the drug can be used in treating neurological disorders. Years later, amantadine received FDA approval for treatment of PD [7].

1.2 Off-label use of drugs

"Off-label drug use (OLDU)" defines to prescribe the drug beyond the conditions for which the drug is holding the license for its market authorization. More specifically, off-label means using a drug for indications, dosage form, dose strength, route of administration or in that patient age group which are not approved by FDA [8]. FDA approves a drug to market only if it shows to be effective and safe in preclinical as well as clinical studies, refers to as "on-label drug use". However, OLDU is being extensively practiced by physicians in situations: first, when two therapeutic conditions possessing same pathophysiology; second, to treat any life-threatening condition where no treatment is available and thereby provide off-label use may be proven helpful to patient; and third, drug has not been studies in specific group or patient age (pediatrics, pregnancy or geriatric). There are many examples of drugs which have been prescribed commonly as "off-label" drugs (**Table 1**) [9].

1.3 Orphan diseases and drugs

There is no defined definition for orphan diseases (ODs). In the US it is defined as if the disease prevalence affects less than 1 in <200,000, in Japan <50,000 and in Australia <2000. WHO defines the prevalence of less than 6.5–10 in 10,000 [10]. The drug which is used in the treatment of orphan disease is referred to as an orphan drug. For example; haem arginate, is being used to treat porphyria (acute intermittent, variegate and hereditary), ibuprofen to treat patent ductus arteriosus in neonates [11] and N-acetylcysteine for paracetamol poisoning. In orphan diseases (ODs) and their management, the count for orphan diseases exists approximately 6000 but the efforts that are putting off by pharmaceutical and R&D sectors for developing new drugs in their management are negligible cause the huge amount involved in *de novo* drug development [12]. Only 5% of pharmaceutical industries are taking interest in developing new drugs in orphan disease management [12]. At present, approximately 325 drugs are available in the market, which are being used to treat only 5% of orphan diseases. Drug

Drug	Class of drug	Approved use	Off-label use
Desmopressin	Antidiuretic hormone	Central diabetes insipidus	Nocturnal enuresis
Atenolol, propranolol, metoprolol	Beta blockers	Hypertension	Migraine prophylaxis
Imipramine, amoxapine	Tricyclic antidepressant	Depression	Insomnia, Bulimia, neuropathic pain symptoms
Aspirin	NSAIDs	Analgesic	Antithrombosis in atrial fibrillation
Indomethacin	NSAIDs	Analgesic	Closure of patent ductus arteriosus
Erythromycin	Macrolide antibiotic	Haemophilus and Legionella infection, whooping cough, atypical pneumonia	Gastroparesis

Table 1.
Examples of off-label drug use (OLDU).

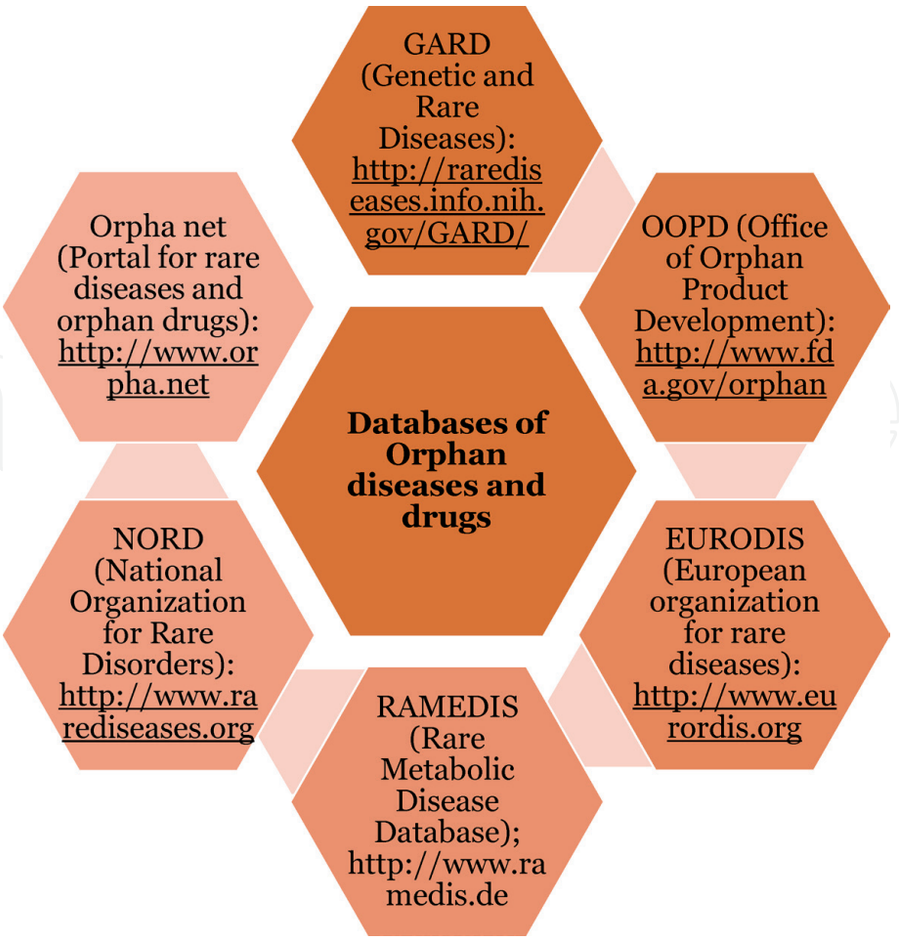

Figure 2.
Resource database for orphan diseases (ODs) and drugs.

repurposing provides one of the best faster and economical ways to find new treatment options in ODs (**Figure 2**). To facilitate drug development and treatment options in orphan disease management FDA Orphan Drug Act (ODA) 1983, has provided many of the benefits or incentives to pharmaceutical and research companies including (i) tax credits (ii) clinical research aids, (iii) fast-track marketing authorization procedures (FDA approval), and (iv) marketing exclusivity [13].

2. Approaches for drug repurposing

In drug repurposing, three major steps are involved which consist of (i) identification of target candidate for new indication (generation of new hypothesis for new indication or new target), (ii) exploration of mechanism or signaling pathway involved in drug or disease and (iii) finally proving the efficacy of drug in phase 2 and 3 clinical trials. Among all steps, identification of lead candidate is one of the most critical steps. This is the step where the most sophisticated and systematic approaches are needed to be implicated for generation of new hypothesis in drug repurposing. Drugs can be repurposed via multiple ways which may be either experimentally, clinical based or computationally (**Figure 3**). Computational approach is '*in silico*' based drug repurposing which is further subclassified as either drug-centric or disease-centric. In drug-centric, we find new indications for existing drugs while in disease-centric approach, we try new drugs for an existing disease.

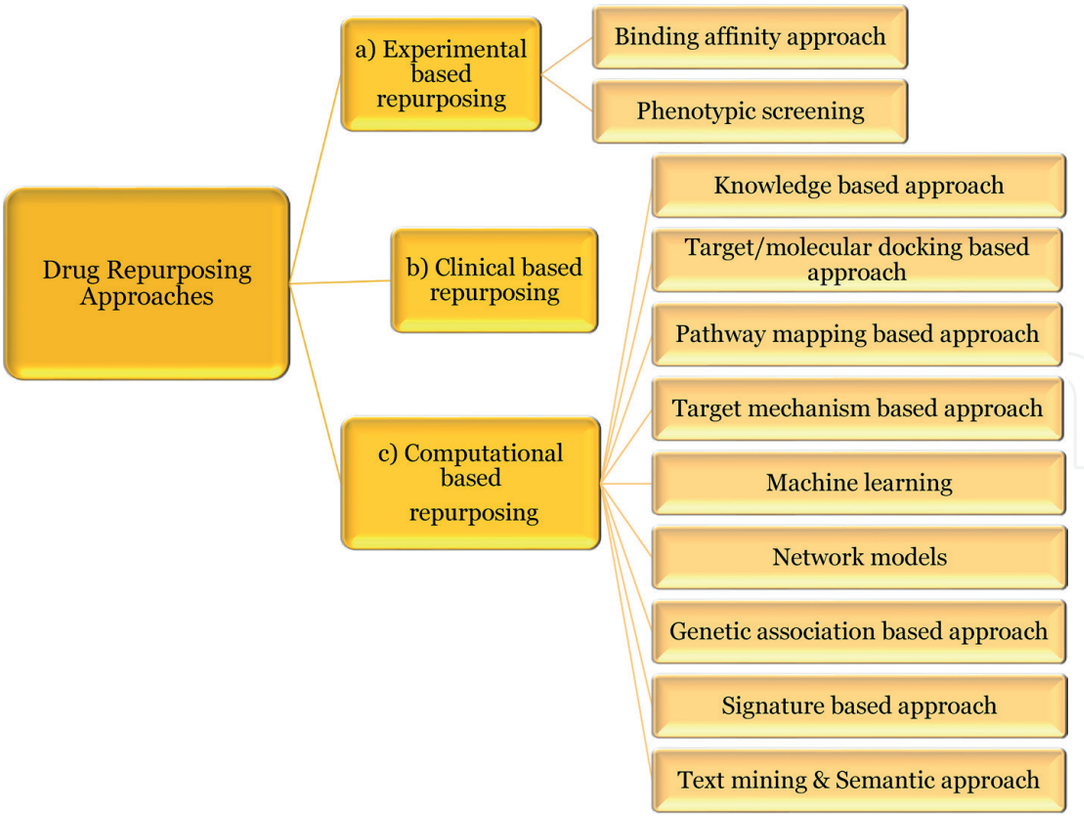

Figure 3.
Approaches for drug repurposing. (a) Experimental based, (b) clinical based and (c) computational based drug repurposing.

2.1 Experimental strategies in drug repurposing

2.1.1 Binding assays to identify target candidate

Techniques like chromatography and mass spectrometry are being used to find all possible binding targets of drug candidates. Brehmer et al. conducted a study using HeLa cell extract to identify possible protein targets of gefitinib. The results of mass spectrometry revealed that the drug can interact with 20 different protein kinases which may be treated as possible targets of gefitinib [14].

2.1.2 Phenotyping screening

In the world of drug discovery and development, the term phenotyping screening is used to describe the ways adopted to identify the biological effects of a drug which is either directly or indirectly linked to a disease. With the development of robotic and sensitive screening tools, the approach is used to screen thousands of chemical drug libraries in a single go. It involves the screening of target drug candidates either using cell-based screens (high throughput screening (HTS)) or even whole organism [15]. Cell based assays involve cell lines derived from human or animals, immortalized cell lines or induced pluripotent cells lines (iPSCs), etc. For example, Iljin et al. [16] performed HTS of approximately 5000 small molecules using prostate cancer epithelial cell lines. In this experiment, disulfiram was found to possess selective antineoplastic property which was validated later using genome wide gene expression studies [16]. Important cell-based assays that are being performed in drug discovery and repurposing include: cell viability assay, signaling pathways assay and disease related mechanistic assay. Other cell assays

that are being performed routinely in drug development include cell apoptosis, infection, cell motility, cell cycle arrest and many more [17]. Cousin et al. [18] have used zebrafish model to evaluate the efficacy of compounds against tobacco dependence. In this study the authors have found that the agents like apomorphine may be useful in modifying nicotine or ethanol induced dependence behavior [18]. Over the decades in drug discovery, these approaches are getting shifted more toward molecular targets based on phenotypic methods, which rely mainly on molecular targets of drugs and diseases and related mechanisms for hypothesis generation.

2.2 Clinical perspective

2.2.1 Clinical analysis (human experiments)

Clinical trials providing positive outcomes are quite rare as most of the drugs fail during Phase II/III trials. But many drugs which already have been marketed during post-marketing surveillance provides different outcome. Some may display different adverse events and some may treat specific kinds of disease with no labeled indication. Many drugs have been repurposed with the help of these trials. Some such examples are apomorphine was indicated for Parkinson's disease and it was repurposed for erectile dysfunction, drospirenone—oral contraceptive and repurposed for hypertension, dapoxetine—analgesia and depression and repurposed for hypertension [3]. These are very few examples of clinically repurposed drugs, there are many such drugs which have been repurposed with many new indications [1].

2.3 Computational perspective

2.3.1 Knowledge-based repurposing

This approach is based on already available data such as ligands and receptors. Specific models can be developed in order to locate the targets that have not been discovered/explored yet. These models are developed to discover the novel bio-markers, pathophysiology and receptors for various diseases. This kind of approach could also be beneficial in predicting different adverse reaction related to drugs, their structure activity relationships (SAR), ligands targeting the different pathways, etc., So, this could be mechanism based, pathway-based, receptor-based repositioning of drugs [1].

2.3.2 Target/molecular docking-based drug repurposing

In-silico screening of various compounds by generating drug library could find a lead molecule resulting targeted therapies. Drug compounds of specific interest from drug libraries can be selected by molecular docking or ligand-based screening which incorporates high-throughput screening (HTS) as large number of compounds are screened in this method [19]. The other methods include standard precision (SP), extra precision (XP).

During this screening there is no incorporation of information related to any biological or pharmacological as the screening is blinded. Target-based approach links the targets such as any receptor with the pathophysiology behind the disease and therefore the process of drug-discovery revamps. Withstanding to this target-based approach cannot predict the novel/unknown mechanism with the currently available targets of the disease [1].

2.3.3 Pathway mapping/pathway-based drug repurposing

Information such as protein-protein interaction, cell signaling and metabolic pathways can be useful for predicting the intersection between disease and drugs. The best possible example could be data available from the central database of patients can define the pathways involved in the specific disease are possibly reconstructed for drugs repositioning [19].

2.3.4 Target mechanism-based drug repurposing

Predicting the novel mechanism of action by this approach and resulting in drug repurposing for existing drugs. This is possible by gathering information from signaling pathway information, interaction networks of various proteins and also by data obtained from omics. Additionally, this will contribute to precision medicine. As, increasingly the individuals with their respective diseases have different pathophysiology among them. Precision medicine is upcoming solution for all these unique disease specific pathophysiological individuals. Advantages for drug repurposing by these approaches can discover not only different pathophysiological mechanisms but also providing treatment to them with respective drugs [19].

2.3.5 Machine learning

Machine learning (ML) techniques such as deep learning (DL), gradient boosted machine with trees (GBM), random forest (RF), support vector machine (SVM), logistic regression with elastic net regularization (EN), deep neural networks (DNN) have been usually applied for repositioning of various drugs [20, 21].

2.3.6 Network models

The various interaction patterns such as protein-protein, drug-disease, disease-gene, drug-target, drug-drug, disease-disease and transcriptomes and cell signaling networks are usually procured from different databases, which are interpreted computationally. The network models represent each and everything like drug, disease, gene and related products and their interaction patterns, for example, nodes (drug, disease and genes) and edges (interaction patterns of nodes). Network models are divided in to two types, these includes: network-based cluster approaches and network-based propagation approaches [19].

2.3.6.1 Network-based cluster approaches

These kinds of approaches have been proposed in order to determine the mechanism/relationships between the drug and the disease or the drug and the target/receptor. The biological interaction pattern in our human body has a characteristic network. The entities such as disease, drug and the protein share similar kind of interaction pattern in the network-based cluster approaches. This approach has been incorporated to develop various kinds of modules using the network topology-based cluster algorithms such as cliques/clusters/groups, subnetworks. They portray relationships or pattern of interaction between drug-drug, disease, target/receptors. The overlapping clusters cannot be detected by CLIQUE, OPTICS, DBSCAN and STING [20]. These modules are most commonly used network-based cluster approaches. Examples of repurposed drugs using network approach are atomoxetine indicated for Parkinson's disease and repurposed for attention deficit

hyperactivity disorder (ADHD), etanercept indicated for rheumatoid arthritis and repurposed for asthma [3].

2.3.6.2 Network-based propagation approaches

These approaches have been categorized as another important approach under network strategies. They can be classified in two types: local and global approach. The information under this approach circulates from node (source) to all the nodes which are networked to each other and followed by subnetwork nodes [19].

Many studies have stated that these techniques are really being helpful and providing some useful results in obtaining interaction patterns/relationships between the drug—target/receptor, gene, disease. Local propagation procures small/fewer amount of data from the database and displays improper results. In opposing to this global approach gathers all of the data from database/network and make correct predictions. Currently, researchers are working on global approach for drug repurposing/repositioning [1, 19].

2.3.7 Genetic association

Genome-wide association studies (GWAS) has been widely used to determine the genetic alterations in whole genome which contribute to specific diseases and provides the pathophysiology of various diseases. The data obtained from the GWAS helps to identify novel targets which contributes to the specific diseases can provide repositioning of several drugs. Human Genome Project has already been completed and vast amount of data is available for specific diseases. So, there is a huge opportunity for various drugs that could be repositioned and provide beneficial outcome. However, the data available from GWAS does not provide exact pathophysiological mechanism and the available data is not appropriate due to the gene variant. As, there many still thousands of genes hidden which is yet to be discovered and these hidden genes may be contributing largely behind pathophysiology of various diseases [1].

2.3.8 Signature-based repurposing

Signature inversion method is defined as the approaches which screens the inverse relationships/interaction pattern of drug and the disease by correlating the gene expression information between the drug-disease. As defined this method utilizes the expression of genes to discover off-target mechanisms as well as novel pathophysiological mechanisms related to diseases. One of the prime advantages of these approaches is that they identify unique/novel mechanisms of action for drugs. Additionally, unlike knowledge-based methods that use the databases to predict the mechanism or action of drugs, more molecular- and/or genetic-level mechanisms are involved in signature-based repurposing methods [1].

2.3.9 Text mining (data mining) and semantic approach

The data available in the literature contains large and varied amount of information/data for all the drugs in the database as well as for the diseases (including orphan/rare diseases) which are commonly occurred in individuals. Through these data one can potentially predict the new indications of existing drugs via text mining approach. Gene ontology/biological ontology allows us to correlate the available information and analyze all the biological data from different databases. One such

example of repurposed drug is Everolimus indicated for immunosuppressant and repurposed for pancreatic neuroendocrine tumors [3].

Semantic inference incorporates techniques like topic modeling which utilizes different databases for the discovery of repurposing of existing drugs. Example of repurposed drug was amphetamine which was indicated for CNS stimulant and repurposed for hyperkinesis in children (ADHD) [3].

3. Drug repurposing/repositioning for orphan diseases/disorders

Approximately 7000 rare diseases are currently present in the world and more than 95% among these lack therapeutic agents approved by US-FDA [1]. The concept behind orphan disease might be many yet they have a single key point which is common that is the disease affects a minor part of the population. The definition of orphan diseases differs in different countries. In US, orphan disease is the one affecting fewer than 2 lakh people, in Japan the disease should affect fewer than 50,000 people to be called as orphan disease and in Europe the prevalence should be 5 in 10,000 [1, 22].

It is very challenging to develop new drugs for the treatment of rare diseases because the number of patients suffering from these diseases are very limited and are distributed over a vast geographical area. Another issue is of high variability among these diseases, influenced mostly by genetic factors. Financially, the development and subsequent production of these drugs is not viable for the pharmaceutical companies therefore drug repurposing for orphan diseases is a good option [22]. The patients requiring immediate treatment also do not have the luxury of more time at their disposal therefore a new strategy is needed so that the drugs are made available faster and cheaper to these patients. The pathology and various biochemical pathways of many orphan diseases are not very well known. Computational techniques will be a helpful option in the case where the underlying mechanism of the disease is not well understood. The advancement of the huge scale genomic sequencing project may lead to the understanding of the genetic variations that may be the cause of these diseases and it may lead to possibility of repurposing the drugs which are targeting the concerned protein [1]. There are few examples of repurposed drugs described in **Table 2**.

The approved drugs have already undergone intense testing like the safety studies, bioavailability studies and PK/PD studies and therefore drug repurposing leads to significant cost cutting and faster development [22]. Hence, this is an attractive prospect for the pharmaceutical industry as well. A total of 51 new medications reaching the market in 2009, the drugs which came to the market via the strategy of drug repurposing were 30% [23].

There are particular regulations designed to promote the research into orphan diseases and these rules could give market exclusiveness in circumstances repurposed agents cannot be protected by the patent. The Orphan Drug Act (ODA; 1983) was introduced for the first time which reflected the issues regarding the economics of drug development for orphan disease and how it was unfavorable. FDA has licensed about 360 agents for rare diseases since 1983 as compared to less than 50 agents before 1983 [24]. US legislation provides for faster FDA approval, tax incentives and funding support for research in orphan diseases. Market protection is also one of the incentives in which a generic form is not allowed to come to the market for 7 years. Tax concession, waiving of the regulatory fees are also the incentives which are provided. Similar legislation has been implemented in Singapore, Japan, Europe and Australia after the success of ODA, with each jurisdiction having a little bit of difference in the definition of the indication and the incentives to be provided [1].

Drug	Original indication	New indication
Thalidomide	Morning sickness	Erythema nodosum leprosum and multiple myeloma
Sildenafil	Angina	Erectile dysfunction
Minoxidil	Hypertension	Hair loss
Zidovudine	Cancer	HIV/AIDS
Celecoxib	Pain and inflammation	Familial adenomatous polyps
Atomoxetine	Parkinson disease	ADHD
Aspirin	Analgesia	Colorectal cancer
Ketoconazole	Fungal infections	Cushing syndrome
Topiramate	Epilepsy	Obesity
Dapoxetine	Analgesia and depression	Premature ejaculation
Raloxifene	Osteoporosis	Breast cancer
Rituximab	Cancers	Rheumatoid arthritis
Duloxetine	Depression	Stress urinary incontinence.
Fingolimod	Transplant rejection	Multiple sclerosis
Bupropion	Depression	Smoking cessation
Lidocaine	Local anesthetic	Arrhythmia

Table 2.
A few examples of repurposed drugs with their new indication.

Another area of concern is the broad group of infectious diseases known to affect more than 1 billion population in tropical and subtropical areas [22]. Populations that are severely impacted are the people living below poverty line, not having appropriate sanitary conditions and in direct contact with contagious vectors or domestic animals [25]. The therapies currently present have many drawbacks like pricing and increase probability of drug resistance. Moreover, there are not much financial gains for investing money in developing drugs for these diseases as the patient population is unable to afford them [26]. Subsequently, given that the profit-making companies produce almost all the drugs, these firms will hardly be having any interest in investing in drug research and development which will not produce high financial returns. For this reason, development of therapies for these diseases becomes increasingly necessary. As discussed earlier that drug repurposing is an effective method due to various reasons, it can also be effectively used in this area where resources are limited and there is a huge need for productive therapies. Miltefosine, used for visceral leishmaniasis originally was antineoplastic agent whereas Amphotericin B used to treat fungal infections was repurposed for treating visceral leishmaniasis [22]. Other examples include Tamoxifen (agent for breast cancer) has shown to have anti-leishmanial activity, eflornithine (topical agent for hirsutism) has shown to be effective for sleeping sickness and auranofin (drug for rheumatoid arthritis) has shown to be effective against lymphatic filariasis and Onchocerca volvulus induced river blindness [27].

These days, multiple researches have demonstrated encouraging results in terms of repositioning supported by computational methods like chemical genomics screening for developing agents for such kind of diseases like schistosomiasis [28]. Some other examples where drug repurposing has shown promise for these diseases are vandetanib, trametinib and atorvastatin [29, 30].

Drug repurposing strategies have also been used in the cases of viral diseases like Zika virus where FDA approved drug for hepatitis C which is Sofosbuvir has shown promising results [22]. The target of this drug is RNA polymerase which is present in Hepatitis C and Zika virus and has shown to reduce viral load in experimental studies [31, 32]. The same is the case with prochlorperazine by targeting the binding and the entry of the virus to host cells has shown to have a strong antiviral activity against dengue virus [22].

Drug repurposing is cheaper and faster than the conventional methods and thus gives hope to the patients where the population suffering from the disease is much smaller and making the traditional model of drug discovery nonviable. A collective effort is required among all the stakeholders if already available drugs have to be repurposed. This approach helps in reducing the potential risks and the expense of developing a new agent, therefore having the ability of revolutionizing the drug market of orphan diseases.

4. Regulatory considerations for drug repurposing

In the US, to get permission for drug repurposing, research and pharma companies need to file applications under suitable sections including 505(b)(1), or 505(b)(2) or 505(j), depending upon the regulatory paths. Further, the company needs to fill NDA type 6 and sNDA (supplemental new drug application) for new indication of drug, NDA type 3 for new dosage form and NDA type 4 for drug new combination in drug repurposing [1, 33].

5. Future perspectives of drug repurposing in orphan disease therapeutics

As orphan disease affects a small percentage of the population, research and pharma companies face great challenge and burden in developing drugs for its management because of small market potential. Patients fail to get proper care, diagnosis and treatment. Even if the treatment is available, it is relatively expensive. Thus, drug repurposing can be of great help in orphan disease therapeutics. It saves both' the time and money involved in the drug development process. In October 2010, "Dr Ruxandra Draghia-Akli, the Directorate-General for Research and Innovation (DG RTD) of the European Commission (EC) and Dr Francis Collins, US National Institutes of Health (NIH)" at Reykjavík (Iceland), launched the International Rare Diseases Research Consortium (IRDiRC) to look after the drug and research development in orphan/rare diseases [34]. This consortium unites both government and private research funding societies to advance the drug development for orphan diseases at global level including task forces and drug repurposing in orphan disease therapeutics.

The research in rare diseases has already changed the global approach because earlier researchers were not much interested in repurposing the existing drug but some global breakthrough has really changed the minds of pharma companies and examples are alglucerase that was obtained from human placental tissue and was widely used for Type I Gaucher disease as a "first enzyme replacement therapy" and, it was also approved by FDA in 1991. However, it was withdrawn from the market due to adverse effect and already available drugs in the market which are prepared from recombinant DNA technology which are safe to use [35]. Fomivirsen which is an antisense oligonucleotide and was approved by FDA for

Cytomegalovirus in 1998 but it has been withdrawn from the market due to the development of highly active antiretroviral therapy (HAART) but this was the "first antisense oligonucleotide therapy" [35]. Imatinib was approved by FDA in 2001 for Philadelphia chromosome-positive chronic myelogenous leukemia (CML) as "first targeted cancer therapy" [35]. Alipogene tiparvovec was the "first targeted gene therapy" to be approved in Europe in 2012 for reversing lipoprotein lipase deficiency (LPLD) in patients with pancreatitis [35]. Strimvelis was the "First ex-vivo gene therapy" approved for patients with Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency (ADA-SCID) [35]. USFDA has approved Holoclar as orphan drug for the treatment of limbal stem cell deficiency (LSCD). Currently, this drug is in Phase IV trial and completing in mid of the year 2020 [36].

To overcome R&D-associated financial challenges and clinical trials-related failures of novel drugs, at present scenario, pharmaceutical companies are much more interested in switching to "drug repurposing" or "drug repositioning" drug development by adopting various computational approaches rather than going for de novo drug discovery, which is relatively expensive, risky and time consuming [37]. According to Southall et al. [35], the global market for drug repositioning will possibly be hiked to over $31 billion by 2020, up from about $24 billion in 2015, thus representing large commercial possibility [35].

6. Conclusion

De novo drug development is being time consuming, costly and risk-prone venture 'drug repurposing' has drawn attention of all pharma companies and R and D sectors which offers faster and cheaper ways for bringing new drugs into the market especially for targeting ODs. Based upon the benefits provided by drug repurposing, the development of more sophisticated and systematic approach is required to find more drug candidates that can be fitted into the picture of promising targets for repurposing.

Conflict of interest

There are no conflicts of interests.

Notes/thanks/other declarations

None.

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