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REVIEW ARTICLE

A Review on Repurposing of Drug

AQSA JANNAT[1], SADIA RAFIQUE[2], SANA JAVED[2,], AAMNA HABIB[3], ZUNAIRA AFZAL[4]
[1]*Synthetic and Natural product drug discovery laboratory, Department of chemistry, Government College Women University, Faisalabad, Pakistan*
[2]*Department of Pharmacy, The University of Faisalabad, Faisalabad, Pakistan*
[3]*Principal, MadinaCollege of Pharmacy, The University of Faisalabad, Faisalabad, Pakistan*
[4]*Department of Pharmacy, The University of Agriculture, Faisalabad, Pakistan*
Correspondence to Dr. SadiaRafique, Email: saadia.rfq@gmail.com, sadia.rafique@tuf.edu.pk

ABSTRACT

Background: For discovering novel drugs and to gain market acceptance process of conventional drug discovery is used in which various stages are involved.
Aim: To innovate new approaches for minimizing the cost and time of drug discovery.
Method: Several attempts were made for the building of plans based on computational tools and on bio-informatics to strengthen the repurposing method off-late. Various approaches used to invent novel signs for FDA accepted drugs are discussed in this review.
Results: The repurposing of the drugs has obtained significance in identifying novel therapeutic uses for existing drugs. It is a productive strategy for the discovery of drugs also time and cost-effective.It fills the gap for the absence of efficiency of conventional drug development.
Implications: In drug repurposing, selection and decision of suitable repurposing technique depend on previous knowledge and accessible data from particular studies. The best advantage of the drug repurposing technique is that for approved drugs all the required data is available.
Conclusion: This technique is currently appearing to overcome the restriction faced during conventional drug discovery in the form of resources, timeline, and financial support . The feasibility of repurposing technique is improved by its systematic application. Some examples of repurposed drugs are also reviewed here. This review also covers the skill of repurposing survival drugs for use against microbes.
Keywords: Conventional drug, drug repurposing, repurposing approaches, docking, proteinopathy.

INTRODUCTION

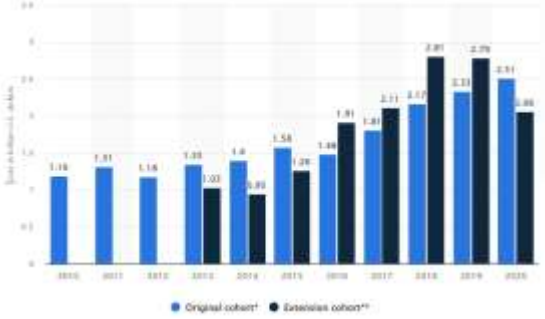
The conventional drug development process consumes resources and time vastly before a molecule is introduced into the competitive market. It is a very difficult and expensive task to develop new drugs and their approval with a great risk of failure, that's why in recent years very little progress appeared in successful projects[1]. The major causes of failure are inappropriate therapeutic theory, unexpected side effects, and acceptability being a critical matter. Modifications are required to reduce the rate of failure of drug, to enhance the effectiveness minimize the resource requirements needed for the development of drug[2]. Despite huge investment, there is a minimum chance for a lead molecule to come into the open market. Throughout the whole life cycle, the route planned for a research molecule remains uncertain. There is also a risk of safety for newly developed compounds. Due to this situation discovery of novel drugs is just like a nightmare for many newer pharmaceutical industries[3].

There is a rapid increase in the cost of manufacturing a single novel medicinal agent. In 2017, the cost of developing new cancer medicine was evaluated by Prasad and Mailankody by using data published by US Securities and Exchange Commission (SEC). The approximate cost of introducing a single cancer medicine into the market is 780 million dollars. This graph gives a year-wise explanation of the cost of developing medicinal drugs.
From 2010 to 2020, this statistic represents the mean cost of researching and developing a medicinal product from finding to commercialization by study cohort. As of 2020, the mean cost of developing a molecule in the original study cohort, which included large-cap biopharma companies, was 2.5 billion US dollars[4].

One mechanism to gain efficiency is drug repurposing. It is initiated with those drugs that have been examined in humans and have exhibited a tolerable level of protection. Such drugs are used for a novel medical state other than they initially considered. In this way, unexpected side effects are reduced[5].

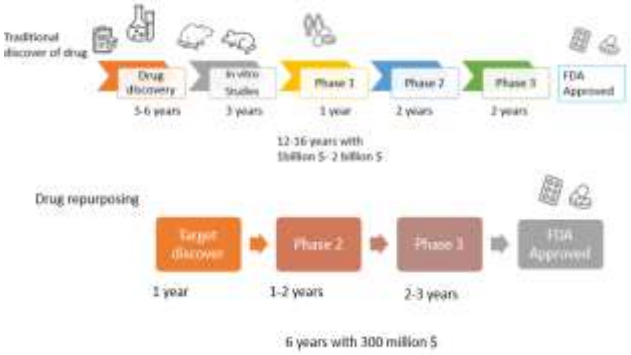
Drug repurposing is one of the feasible options for strangers in the line of novel drug research. It was first introduced by Ashburn and Thor I in the year 2004. It fills the gap for the absence of efficiency of conventional drug development. The best advantage of the drug repurposing technique is that for approved drugs all the required data is available. That's why it reduces the development hazard. It reduces the waste of time and cost[6].The figure is shown below give a brief explanation of the differences of using the conventional method to produce medicinal drug and repurposing of the drug, how it saves them time and cost

Figure 1: The mean cost of researching and developing a medicinal product.



https://www.statista.com/statistics/report-content/statistic/825727

Figure 2: Comparison of traditional drug discovery and drug repurposing.



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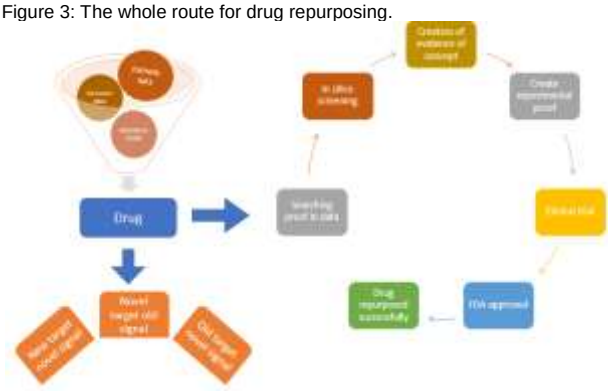
National Centre for Advancing Translational Sciences (NCATS) stated, " Repurposing of the drug is the study of drugs that are approved to cure one disease to study them against another disease as they are effective for this". In the United States of America (USA), NCATS is a component of the National Institute of Health (NIH). They inaugurate a program on " Invention of latest medicinal uses for already available molecules" in 2012 of May. This program concentrated on pinpointing new medicinal indications and therapeutic options for existing compounds and offering economic support[7].

This technique is currently appearing to overcome the restriction faced during conventional drug discovery in the form of resources, timeline, and financial support. In this way, several attempts were made for the building of plans based on computational tools and on bioinformatics to strengthen the repurposing method off-late[8].

Drug repurposing become an attractive form in discovering drug because it involves recycling old drugs, saving neglected drugs and broadening patents' lives. In the US 30% of drugs that are approved nowadays are repurposed drugs. There are two ways to perform drug repurposing either computationally or experimentally. The latter technique is called ' *insilico*screening[9]. All the steps involved in the repurposing of drug are shown in the figure below.

Figure 3: The whole route for drug repurposing.



By using the various technological trends it becomes possible to develop a repurposed drug, in which two trends are included. First thing is that a complete data have been collected and generated by using different sources, including proteomics , phenomics, genomics, and chemo-proteomics. Consequently, data identifying not only drug profile and disease phenotypes, but the whole route maps have become accessible. The second thing is that because of development in data science and computation, it has become feasible for repurposing algorithms to acquire[10].

Drug repurposing approaches: Two steps are used to do repurposing of drugs. *In silico*screening of marketed and approved drugs is done in the first step. Drugs are screened against a specific therapeutic target and shortlisted are again processed for analysis in the particular pathophysiological path of disease of concern by using *in-vivo* and *in-vitro* techniques. The second step is to go into the clinical trials for particular indications. Repurposing of the drug may be done at any step of their development just from their creation[11]. Following techniques are used in the process of drug repurposing. It may be a target base technique or docking technique.

Target base technique: Which involve the study of a specific protein ,which are involve in producing structural changes. Proteins play a vital role in a usual healthy condition and unhealthy situations. Some mutations occur in the protein then these mutated proteins trigger the development of a specific disease[12]. Diseases that are caused by the mutation in proteins come under the class proteinopathy**.** Target based techniques are directly approached protein. This process investigates a new target in the previous symptom. The superiority of the target base technique is that all drugs are screened with their well-known chemical structure[13].

Figure 4: Representation of different approaches used for drug repurposing.

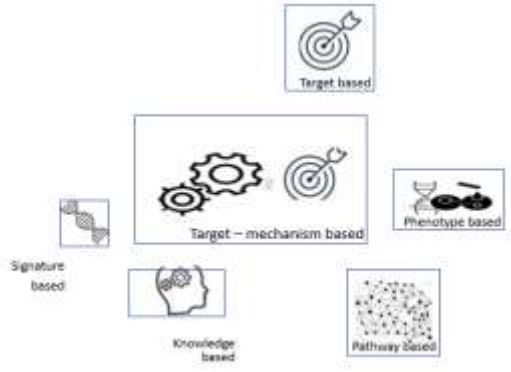
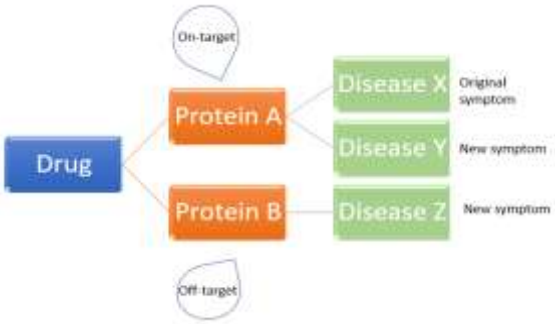


Figure 5: Graphical representation of target base technique.



Docking comes under the category of target base technique. Receptor and drug relationships are studied in docking techniques in which the potentiality of drug is predicted by using mathematical equations. Several drugs can be estimated in a very brief time against different targets. Different techniques of docking are available which are based on the variety of databases to be considered[14]. Different techniques of docking are described below:

- To check the interactions between antigen and antibody cross-docking techniques are used.
- The process of docking in which binding sites mold themselves by rotating side chains to bind the ligand is called the Induced fit docking.

Screening of a bunch of ligands against a group of target proteins is involved in Inverse virtual docking. This technique throws light on new therapeutic actions for both familiar and unfamiliar compounds. It is very beneficial in recognizing the cellular mechanism for compounds that were identified to produce possible activity against a specific disease[15].The different tools used for docking are shown in the figure.

Figure 6: Different tools used for docking.

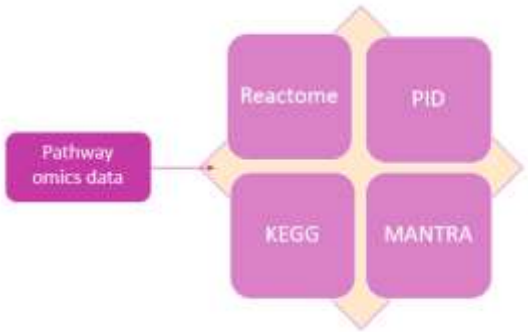
Signature-based technique: In this technique information related to gene structures is obtained from omics data on disease which is used to locate a new mechanism for infection. This technique explores inverse relationship between disease and drug by comparing disease and drug-gene expression profiles[16]. In a study prospective drug-disease combinations for inflammatory bowel sickness(IBS) were studied, using patterns of gene expression from omnibus database matched to gene expression profiles from the connectivity map, which included 164 pharmacological compounds[17].

Consequently, unrevealed drug-disease sets were detected, with one set approved in the preclinical pattern. Identifying drugs with new mechanisms of action is the advantage of using this approach. Genomics data is easily accessible by using open sources such as Connectivity Map(CMAP), Sequence Read Archive(SRA) and Cancer Cell Line Encyclopedia(CCLE). By using computational methodologies, signature-based strategies involve additional mechanisms at the molecular-level, such as dramatically altered genes[18].

Target mechanism-based technique: In this technique of drug repurposing new mechanism of operation for drugs is discovered by combining signaling pathway data, protein interaction system and treatment omics data. The need of accurate medicine is going to be important day by day, inspires such repurposing approaches for drugs[19]. For example, an unsolved topic in cancer treatment is drug resistance. Patients who initially respond favourably to medicine often develop resistance to it after one or two months of therapy. It needs additional data to derive a successful treatment for drugs, to obtain superior drug targets. The major benefit of using this approach is not to discover the mechanism of drug of and disease but also to design therapy of drug to particular diseases[20].

Pathway based technique: If the drug is repurposed by using a pathway based technique it exploits signalling pathway, pathways of metabolism to predict the connection and resemblance between drug and disease. This technique utilizes omics data for particular disease. This technique has the advantage of being able to filter down huge signalling networks to a specialized network with only a few proteins (or targets)[21].

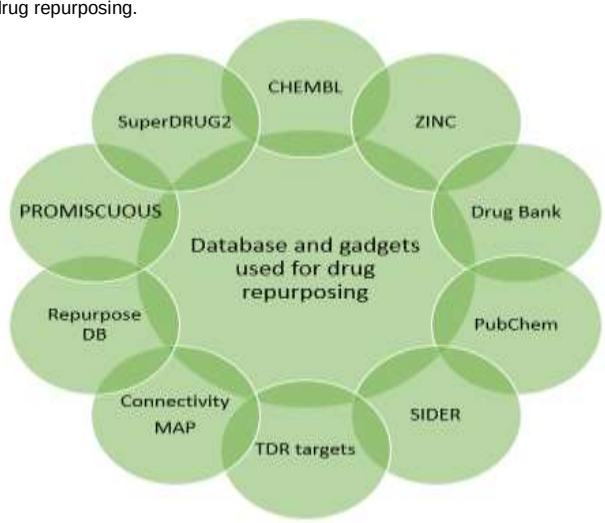
Figure 7: Figure shows the tools used for pathway based technique.



Phenotype based technique: A new method of drug repurposing is by using phenotypic information. This approach is increasingly used to discover genetic traits related with individual disease. When native language processing abilities are applied to a software that is electronic health records (EHRs), additional unfavorable drug events that were not detected during medication development can be discovered. For example, it helped in recognizing that for cancer therapy metformin can be repurposed[22]**Knowledge based technique:** This repurposing technique utilizing the information related to the drug including chemical structure, disadvantageous effect, drug target and pathways, to build unrevealed targets or mechanisms for therapy[23] .

Database and gadgets used for drug repurposing

Figure 8: Graphical representation of different tools and databases used for drug repurposing.



Examples: Some of the examples of repurposed drugs on various backgrounds are described below:

Marketed drug with a particular side effects it luckily possesses better medicinal potential towards other symptoms. For example, a drug Sildenafil has various symptoms but it is basically originated for the curing of hypertension[24].Itraconazole act as an antifungal agent primarily but after that, it is proved that it also exhibits an anti-angiogenesis characteristic. Immense literature research is required for drug repurposing, research is related to the selected disease mechanism and drug profile. Researchers are needed to be prepared with the latest authentic data which contains unexplored pathways linked to the development of disease[25].

A brief detail on some of the repurposed drugs is also describes here, with detailed mechanism, which includes metformin which is basically a antidiabetic drug but now after repurposing it is used against cancer, different drugs for Covid-19.

1.COVID-19: The WHO has designated the latest epidemic of Coronavirus illness (COVID-19) a pandemic, which began in Eastern Asia and spread throughout the world.COVID-19 is produced by the new virus SARS-CoV2, for which no vaccination exists and for which current antiviral treatments have failed.Several FDA-approved and novel antiviral medicines are being tested against COVID-19, either alone or in mixture, as they have been in the past against SARS and MERS[41]. For example:

- Sarilumab, it is formerly used against Rheumatoid arthritis but now it is repurposed for COVID-19.
- Favipiravir, is used against Influenza now it is used for COVID-19.

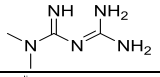
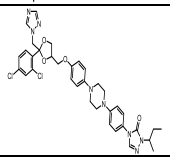
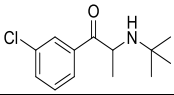
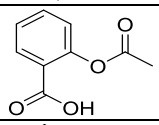
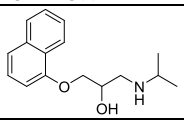
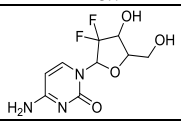
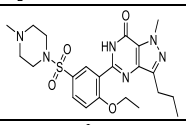
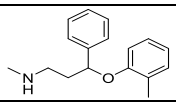
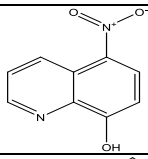
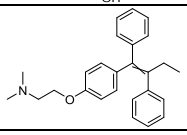
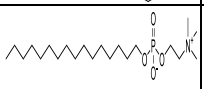
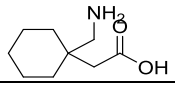
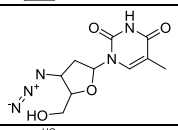
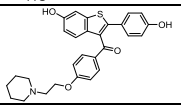
Dexamethasone, is used as a Immunosuppressant but now it is repurposed for COVID-19[42].

2.Metformin: In the 1950s phenformin was used as an antidiabetic drug but due to its huge side effects, it was banned in the 1970s. After that Metformin came into the market asanantidiabetic drug used for treating diabetes. It was approved in 1995 in the USA. It is derived from gelatine, a derivative of guanidine. Several preclinical trials have shown that both phenformin and metformin exhibit an antitumor activity so the concern is to repurpose them for cancer treatment and their prevention. Although a better consideration is required about their behavior as an antitumor activity[43].

Cancer is a destructive and uncontrollable disease. The second major cause of death in United States is cancer. During the last ten years, a considerable improvement in inherited diagnosis

has been made[44]. The whole mechanism of action of metformin to reduce cancer cell growth is described below.

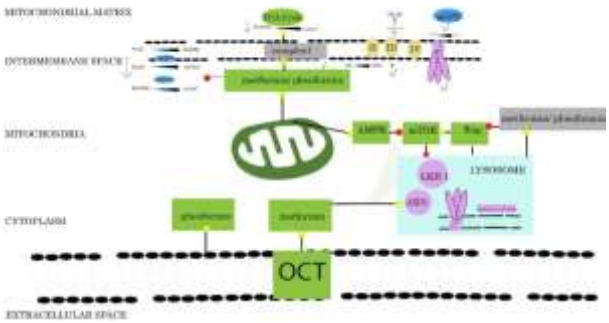
Table 1: Examples of repurposed drugs.

Drug	Old indication	New indication	Structure	Reference
Metformin	Diabetes	Cancer		(26)
Itraconazole	Anti-fungal	Prostate cancer		(27)
Bupropion	Depression	Obesity		(28)
Aspirin	Fever and pains	Melanoma		(29)
Propranolol	Reduce blood pressure, anxiety	Breast cancer		(30)
Gemcitabine	Antiviral	Cancer		(31)
Sildenafil	Angina	Erectile dysfunction		(32)
Atomoxetine	Parkinson's disease	ADHD		(33)
Benzbromarone	Treating gout	Antibacterial		(34)
Nitroxoline	Infection in urinary tract	Cancer		(35)
Tamoxifen	Breast cancer	Antibacterial activity		(36)
Miltefosine	Skin metastases	Visceral leishmaniasis		(37)
Gabapentin	Epilepsy	Neuropathic pain		(38)
Zidovudine	Cancer	AIDS		(39)
Raloxifene	Osteoporosis	Breast cancer		(40)

MECHANISM

- Metformin inhibits the mitochondrial complex I, results in decreasing synthesis of Adenosine triphosphate synthesis (ATP) leading to an increase in AMP:ATP ratio ,which results in activation of AMP-activated protein kinase (AMPK) that is involved in balancing metabolism of cells by increasing Adenosine monophosphate (AMP) into the cell. AMPK regulates the activities of different enzymes specific for metabolism and modulate the pathways that are crucial for cell division and growth, mammalian target of rapamycin (mTOR) is inhibited[45].
- Metformin makes a complex on membranes of lysosome in between v-ATPase–Ragulator–AXIN/ LKB1–AMPK c which results in activation of AMPK. Complex formation results in disconnection of controller from mTORC1, which results in inhibition of mTOR. glycerol 3-phosphate (G3P) helps the metformin to stop cell growth by inhibiting oxygen utilization and reducing ATP production[46].

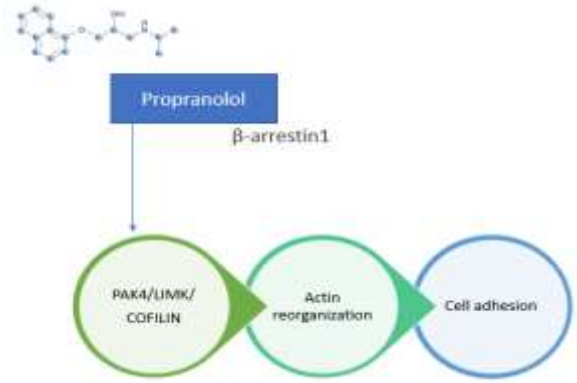
Figure 9: Mechanism of action of Metformin



3. Propranolol

- The most widespread cancer diagnosed in the world is breast cancer. In women, it is considered to be the major cause of death in developed and developing countries. In 2017 in the USA, the American Cancer Society provided a stats according to which 3.1 million women were diagnosed breast cancer . It became the major issue in the world. On the whole, women about 40,610 were diagnosed to die with the cancer of breast. Propranolol is a drug repurposed against breast cancer[47].
- Propranolol is known as beta-blockers. It works by hindering β- adrenergic receptors it works by lowering the venous and arterial pressure. Propranolol is used in the therapy of heart disease, hypertension, anxiety, essential tremor and other various diseases. It was first developed in the 1960s by James W. Black. It is available in the form of a tablet or oral suspension. It is lipophilic and rapidly absorbed in gastrointestinal tract. In 1970s experiments started to check its anticancer activity. Various studies on propranolol proposed that it may be used in different types of cancer therapies[48].
- Modern studies indicate that β-adrenergic receptors appear in breast cancer tissue. Various in-vitro researches have revealed that β- blockers can disturb the migratory activity of cancer cells and also inhibit angiogenesis(In this process new blood vessels are formed). So, propranolol has both of these properties and also inhibits metastatic activity of cancer cells[49]. In 2011, an observation by an Irish study stated that patients using propranolol have 80% coverage of breast cancer. Barron and colleagues, took investigation of women with breast cancer of stage I-IV, found that at the time of investigation women getting propranolol have a minimized occurrence of T4 tumor or metastatic (N2/N3/M1) tumor[1].

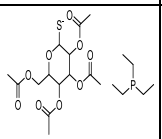
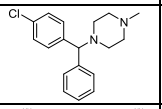
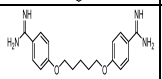
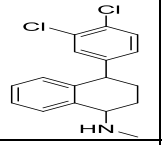
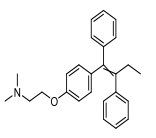
Figure 10: Mechanism of action of propranolol: Inhibit G-mediated signaling and activate β-arrestin1 which regulate cell proliferation and ERK ½ pathway.



4.Discovery of Antimicrobial drugs: Today antimicrobial resistance is one of the biggest challenges to world public health. Per year seven lacs(700,000) deaths are reported because of antimicrobial resistance all over the world. Recently, epidemics of acute contagious disease have been very common , for example, fungal disease, viral disease[50]. Globally in the history of medicine need to discover antimicrobial drug is undeniable and attempts to discover novel antimicrobial medicine should be increased. The modern discovery of drugs is a long and difficult process and most of the time it leads to failure. So, the latest approach to discover novel drugs is the repurposing of the drug[51].

Different drugs have been shown in table that is repurposed for antimicrobial uses. For example,Chlorcyclizine is initially used to reduce allergic reactions but now it is repurposed for antiviral indication.

Table 2: Examples of drugs repurposed for antimicrobial uses.

Drug	Old indication	New indication	Structure	Reference
Auranofin	Rheumatoid arthritis	Amebiasis		(45)
Chlo-rcyclizine	Minimize allergic reactions	Antiviral		(52)
Pentamidine	Antiprotozoa l effects	Antibacteri al		(53)
Sertraline	Depression	Antifungal		(54)
Tamoxifen	Anticancer	Antifungal		(24)

Challenges in drug repurposing

- Repurposing requires careful examination of every outcome, because the variety of patients have a variety of diseases and unexpected side effects may be expected in them. Repurposing requires all the essential data on drug-drug relation, on the pharmacodynamics of drugs with special importance on harmful profiles[55].
- To get the significant advantages of the repurposed drug for a new symptom requires a lot of understanding about the drug like its path of administration.
- Because of no certain criteria for repurposing of a drug candidate , it is hard for a new organization to provide necessary details to regulatory authorities[56].

Advantages and disadvantages of drug repurposing

Table 3: Advantages and disadvantages of drug repurposing.

Advantages	Disadvantages
➢ For FDA approved not only preclinical details are available but also pharmacokinetic properties toxicity and pharmacodynamic are also available so that, it reducing the development risk. This is the key advantage of using drug-repurposing techniques. ➢ Drug can readily enter the phase I and phase II clinical trials, decreasing development time and cost.	➢ Significant literature study is mandatory to gain a chartbuster. ➢ Inaccurate computational analysis may deceive the discovery.

To estimate the required response of drug, selection of target group is the leading task and is the main challenge of drug repurposing. Otherwise it produces disaster effects. For example, when Thalidomide was given to a pregnant women for managing morning sickness at the start of their pregnancy it produces side effects in women[57].

CONCLUSION

The methods of repurposing of the drug have various advantages over conventional method because of cost-effectiveness and shortness of time require for the development of drug. The feasibility of repurposing technique is improved by its systematic application. In drug repurposing, selection and decision of suitable repurposing technique depend on previous knowledge and accessible data from particular studies. It provides us a chance to widen our knowledge. These flowsheets are very helpful for a better understanding of the whole process. Hence, this technique is very helpful for industrial researchers as well as for academic researchers. Still, there are various challenges for the implementation of drug repurposing; anyway, these challenges can be solved with latest technologies.

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