Drug Reprofiling: Approaches, Benefits And Challenges

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Abstract

Drug reprofiling also known as drug repositioning or repurposing is an method for finding new uses of already existing drugs which is cost effective and less time consuming method as compared to new drug discovery.

 There is bunch of drugs which are initially developed for particular disease and later reprofiled with new uses for different types of disease with the help of various reprofiling approaches. Reprofiling a drug also has its problems but are less in comparison to new drug discovery. Over the years new methods have also discovered to reprofile drug with more complex computational approaches which is making drug reprofiling more effective.

Keyword

Drug Reprofiling, Drug repurposing, Computational approach, Intellectual Property Rights, Data availability.

Introduction :-

It includes chancing new medical uses for being medicines which consists medicine which are still in use, medicines which are now not in use or remitted drugs.
Taking in use of any medicine which is approved by the Food and Drug Administration[FDA] making in use of existing drugs to cure another complaint or illness rather than its firstly designed for[1], discovering a new drug will takes lot of time and hard work and still it gives no guarantee of blessing and results which are anticipated rather of going through the time consuming trials processes for launching a new medicine[2], medicine reprofiling can be a way to save the hard work and time because a formerly being drug has passed the trials so there will be veritably little of examinations for a known medicines and plus discovering a new medicine requires invincible quantum of plutocrat which can be saved with medicine

reprofiling. It can be a better option for conditions which don't have any particular remedial treatment procedure in that case reprofiled medicines can be used for that complaint for which we formerly know the reprofiling or responses of medicine / drugs. For case when epidemic of covid 19 approached in 2019 and there were no medicines or drug for a new type of contagion medicines like Remdesivir, Favipiravir which was fate for the treatment of Ebola outbreak in 2014 and to treat influenza are used for treatment of procedures of nimbus contagion which actually saved lives of millions of people.[5]

Establishing a new medicine will take billions of dollar and around some 1 decade or more than 1 and half decade to show its success rates fully.   Numerous medicines have certain properties which aren't just limited to a certain use but have other uses for colourful types of infections, conditions, illness, medicines reprofiling is surely not a new fashion but it has results which has saved lot of sweats, plutocrat and lives. With medicine reprofiling we can prognosticate the results of drugs which isn't inescapably possible with a new medicine.

Reprofiling of medicine can include change in formulation or the change in expression although a little change but a conspicuous and a new system of use medicine reprofiling includes the improvement of motes used for timber of drugs.[7]   Failure rate in new medicine discovery is veritably high and that can loose the plutocrat up to half of the total investment or occasionally the whole investment can be ruined.

Reprofiling of medicine is grounded on substantially two generalities:

1) Some conditions includes same natural targets.
2) Knowing all other medicines conditioning rather than only for which it specifically designed for.

Regularly new drug discovery would include following steps:

1) Preclinical studies:

Which can take upto half of decade or more than it and testing on laboratory animals.[2]

2) Safety review:

To confirm the total safety of laboratory animals.

3) Clinical research step 1:

It takes one and half years and includes pharmacokinetic behaviour of drug in humans for first time.

4) Clinical research step 2:

 Testing on the patients with targeted disease on large scale which can take around 2 years.

5) Clinical research step 3:

It includes large scale trials on patients of selected disease and it takes 3 and half years.

6) research step 4:

Reassuring the drug effects after the market launch of drug , And takes about one and half years.

While as reprofiling of drug will include:

1) Compound identification:
   Selection of an appropriate drug for a particular disease, And can take usually 1.2 years.
   2) Compound acquisition:
   Taking licence for the selected drug which can require zero to two years.
2) Development step:
   It can usually take one to five years with collecting and reassuring all the preclinical data
3) 4) FDA survey after marketing:

Food drug administration reviews the drug after its Market launch.[3]

Table showing drugs their original indications and uses

Drug, pharmacological category	Original indication	New indication
Amantidine, Anti-viral	Influenza	PD
Aspirin, NSAID	Pain and inflammation	Prostate cancer
Bromocriptine, Dopamine receptor antagonist	PD	DM (type 2)
Bupropion, SSRI, Anti-depressant	Depression	Smoking cessation
Celecoxib, COX-2 inhibitor, NSAID	Inflammation	Breast and colon cancer
Digioxin, Cardiotonic	CVDs such as heart failure	Prostate Cancer
Dimethyl fumarate, Anti allergic	Psoriasis	Multiple Sclerosis (MS)
Everolimus, Immune suppressants	Immune Suppressant	Pancreatic neuroendocrine tumors
Favipiravir, Antiviral	Influenza	COVID - 19
Fluoxetine, Anti-depressant	Depression	Premenstrual dysphoria
Gabapentin, Anti-epileptic	Epilepsy	Neuropathic pain
Imatinib, TKI (Anti-cancer)	CML, ALL	GIST

Approaches:

Drug repurposing involves primarily two approaches: the experimental approach and the theoretical approach.

    I.   Experimental Approaches:

The experimental approach, also known as the activity-based approach, utilizes existing drugs for their pharmaceutical effects through animal-based experimental biological assays. This approach encompasses target-based and all-based experiments in both in-vivo and in-vitro methods. Unlike the theoretical approach, the experimental approach does not require specific structural information about the protein target. However, it is generally more time-consuming due to experiments conducted on living animals, adding complexity to the process.[8]

Binding Assay to Identify Specific Targets:

A study by Branchmar et al. used HeLa cells to identify the protein targets of gefitinib. Various technologies, including mass spectrometry and chromatography, are commonly employed to explore all available binding targets of drug molecules. Mass spectrometry studies have revealed that the drug can interact with 20 different types of protein kinases, indicating potential targets for gefitinib.[9]

Phenotypic Screening:

In drug discovery and related fields, phenotypic screening is frequently employed to understand the biological effects of a drug, particularly those linked to a specific disease. Advances in technology and screening equipment allow this approach to screen thousands of chemical drug libraries simultaneously. Drug candidate screening may involve cell-based assays, and, in some cases, the entire living organism can be utilized. Well-known assays in phenotypic screening include cell viability assays, signalling pathway assays, and various other cell assays. Phenotypic screening can also be employed to reprofile drugs by screening libraries of existing drugs to discover new effects. Despite its physiological focus and higher likelihood of moving reprofiled drugs to clinical trials, phenotypic screening is more costly compared to theoretical methods.[9][7]

II.   Theoretical Approach:

Theoretical approaches encompass two main strategies:

1. Literature-Based Approach

2. Computational Approach

1.   Literature-Based Approach:

In the literature-based approach, hypotheses are generated by sifting through vast volumes of data and associating various scientific facts. An example of this method is Swanson's model, which suggests that if two entities 'A' and 'C' exist, they are linked through the intermediary 'B.' This approach involves drawing correlations from extensive scientific literature.[7]

2.   Computational Approach:

The computational approach heavily relies on data and systematically combines drug-target-disease relationships. With the continuous emergence of new technologies, data on drug-target-disease information is stored in databases like DrugBank, ChemBank, GeneCards, OMIM, and PubMed. These databases encompass diverse data types, including chemical structure and electronic health records, facilitating the development of novel methods for drug reprofiling by identifying potential candidates for drug-disease relationships.[10]

Computational-based approaches on drug reprofiling can be categorized into three types:

a. Profile-Based Drug Reprofiling

b. Network-Based Drug Reprofiling

c. Database Drug Reprofiling

   a. Profile based drug reprofiling

Profile based drug reprofiling uses drugs bioactive profile with other disease profile or drug profiles. These profiles are clinical profiles or chemical structure profiles and expression profiles. Expression profiles can be used to drug disease identification or drug - drug identification. The comparisons among the drugs profiles or drug - disease can find the unknown characteristics of drugs. Total information collected from these profiles can be used to identify new methods for drug reprofiling. Next type of profiles based approach is using involves molecular docking. Identical structures of chemical can trigger same reactions. Potential drugs candidate predicted by similarity with target molecular can be used to find new drug target relationships. Similarity between ligand binding site is majorly used for identifying potential drug - disease pairs.

For instance if a specific protein which is causative target of disease A has a similar local structure with that of protein B which is a therapeutic target of medicine B we can force that medicine B can be used to treat disease A. It is an effective approach in drug reprofiling. But finding drug only based on their chemical structure can be difficult because biological activity generally alters the chemical structure of target molecules.[10]

   b. Network-Based Drug Reprofiling:

Various network-based approaches enhance existing disease-associated gene networks. Algorithms like Clusternis identify biological subnetworks based on topological structure, offering potential candidates for drug-target relationships. An example includes identifying iloperidone, an antipsychotic drug for schizophrenia, as a new drug for hypertension. Network-based approaches are valuable for discovering potential drug candidates.[10]

   c. Data-Based Drug Reprofiling:

Clinical data, such as electronic health records (EHR), is crucial for drug reprofiling. Sildenafil, initially developed for pulmonary arterial hypertension, was rebranded as Viagra due to side effects and repurposed for erectile dysfunction. Systematic approaches analyze diverse clinical data, including drug prescriptions, images, and symptom descriptions, stored in EHR. Limited accessibility to EHR data exists. Text mining is another data-based approach, utilizing extensive literature on disease-gene relationships, drug-disease, and drug-target for identifying relationships in drug reprofiling.[10]

Methods:

Based on the quality and quantity of pharmacological, toxicological, and biological activity-related information, methods are classified into three categories:

   1. Drug-Based Method
   2. Target-Based Method
   3. Disease-Based Method

   1. Drug-Based Method

This method involves studies on biological activity, adverse reactions, and structural properties to identify specific molecules with precise biological effects in animal assays or care. It primarily focuses on the biological effects and pharmacology of drugs, without emphasizing biological estimation.

   2. Target-Based Method:

The target-based method includes virtual screening of drug molecules from various databases and drug libraries. It entails screening drug molecules against specific protein molecules of interest.

3. Disease-Based Method:

This method is preferable when comprehensive information about the disease is readily available. It allows for quick drug reprofiling based on the information about the drug molecule and the disease.[3]

Examples of Successfully Repurposed Drugs:

Over the past 20 to 50 years, numerous successfully repurposed drugs have emerged. One example is antidepressants that have found new applications. For instance, Wellbutrin, initially designed by GlaxoSmithKline for depression treatment, was later renamed Zyban and generates over $ 125 million annually. Another example is duloxetine, initially used as a non-selective serotonin reuptake inhibitor, repurposed to treat stress urinary incontinence, earning around $ 800 million per year.

Successfully reprofiled drugs for oncologic indications include Thalomid, originally developed for morning sickness treatment and now marketed for multiple myeloma, showcasing the versatility of drug repurposing. Countless examples exist of reprofiled drugs that are successfully rebranded, bringing in millions for companies and delivering positive outcomes for patients.[11]

Benefits of drug reprofiling:

The total valuation of reprofiling drugs was of $ 24.4 billon in year 2015 and as per industry experts it can touch $ 35 billons till year 2027, 25% of yearly revenue of pharmaceutical industry is due to reprofiled drugs.

General benefits of drugs reprofiling:

The time required for development of and drug is get reduced by 5-7 years as compared to the novel drug development. Up to 25% to 40% of yearly profits can be made from these reprofiling drugs with their sales. Important information regarding dose, toxicity, pharmacology and formulation is already present in the case of reprofiled drug. Reprofiled drugs have generally higher approval rates. The average cost of reprofiling a drug is around $ 300-400 million as compared to new drug discovery which requires at least more than $ 2 billon.

Reprofiling of drugs for rare disease:

Reprofiling drugs to treat either rare disease or common disease have the benefit of less risk as we already know its causes, effects, toxicity etc. Because of less costing and less time for development of reprofiling drugs it can be used to treat rare disease which is not the case with novel drug delivery.

Reprofiling across different therapeutic area:

Pharmaceutical industries are searching for totally new uses of approved drugs for totally new conditions.

For example- ofatumumab is a monoclonal antibody to treat leukemia but new clinical studies are showing its effectiveness in a adults.

Reprofiled drugs are most commonly used for the treatment of Alzheimer. Out of total Alzheimer treating drugs 18% drugs are taken from cardiovascular indication, 14% drugs are of psychiatric uses, 20% are hematologic and oncologic agent, 10% drugs are neurologic drugs, 12% of drugs are used in treatment of 12% of drugs are used in treatment of diabetes and remaining 26% of drugs are used for other conditions.

Shorter Path:

Now days out of total approved drugs by food and drug administration one-thirds are reprofiled drugs. In the first quarters of 2020 FDA – food and drugs administration approved 28 drugs of which 12 drugs are reprofiled drugs and 16 are novels drugs. As per national centre for advancing translation science (NCATS) reprofiling of

drugs depend on previous research and development so new therapies can be ready for clinical trials quickly. Generally drugs reprofiling involves screen libraries of approved drugs against disease-specific biological assay. By identifying biology, pathophysiology and other related topics research can select useful candidate drugs for that disease. Drugs used for reprofiling have the benefits of passing all the safety and effectiveness measurements.[12]

Others Benefits:

Benefits of market potential. Some drugs gained its success the reprofiling them. The example of this is thalomid which is reprofiled thalidomide and the derivatives of some drugs Revlimid of celgene pharma company. And these drugs collect $ 2.8 billons every year for the celgene company.[13]

Returns of investment-

 If the reprofiling of a drug requires some million dollars the returns of profits has no limits as like the case of celgene pharma company.

Benefits of safety-

 Reprofiled drugs are already proved safe for human use hence very less amount of risk is involved in reprofiling of drugs.

Out-licensing-

Pharma company of ten out licensing their drugs to make more money. With reprofiled drugs companies can out license only the new use of drugs and can keep the license for the previous therapeutic uses or vice-versa. With less risk involved and less investment but the returns of profits can be very high pharma companies are very keen reprofiling the drugs and develop a new therapeutic uses for that drug. Another benefits can be of patent securing because the first company which have "strongest" patent for original drug can inherit its for new indications.[13]
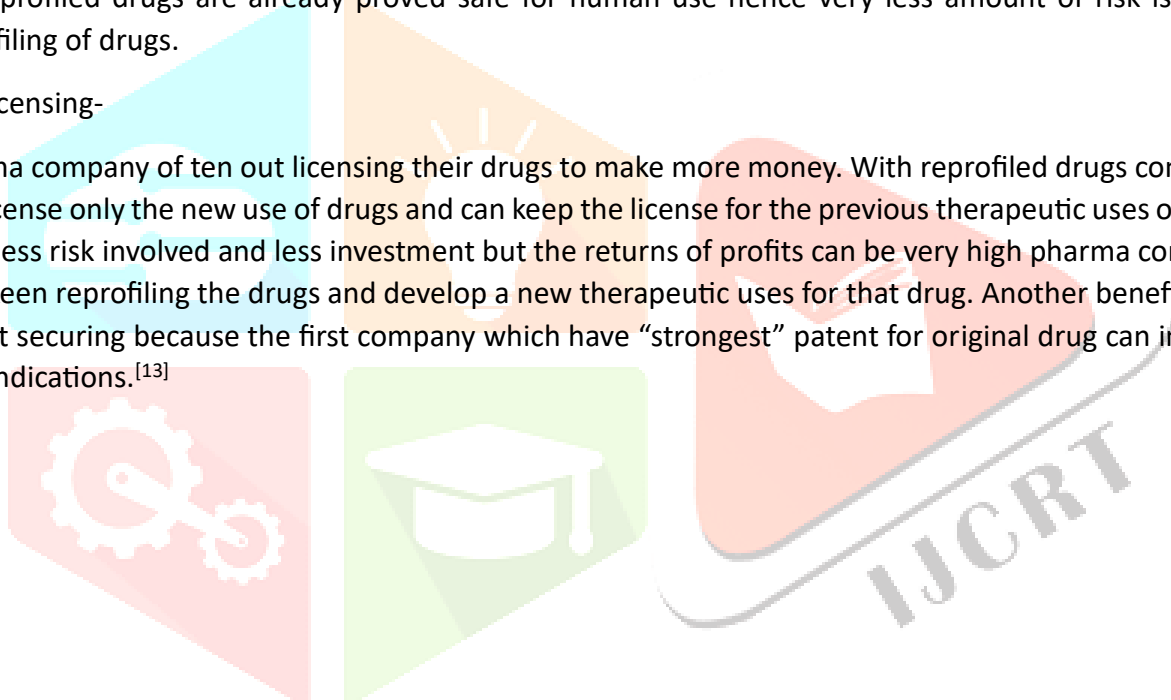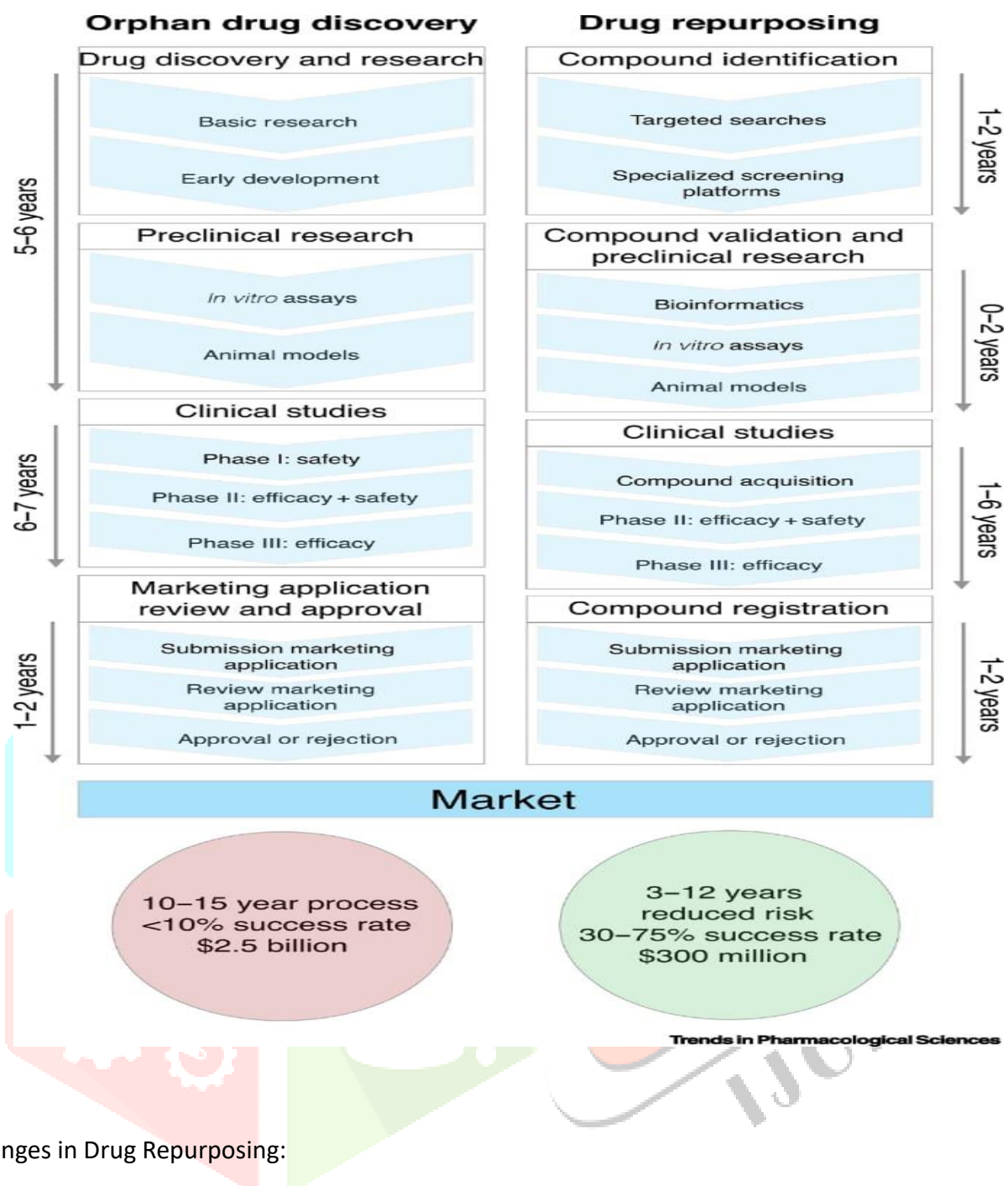
Challenges in Drug Repurposing:

The primary challenge associated with drug repurposing is the weak intellectual property rights surrounding various medicinal drugs. In some cases, registered medical practitioners may hesitate to recommend the same drug for a completely different disease.[3] The scope of treatments with repurposed drugs is limited. Additionally, the Food and Drug Administration (FDA) only allows the new application of an already existing drug for a new indication for up to 3 years, which is a relatively short period in the pharmaceutical industry to recoup investments.[14] Similar to novel drug discovery, drug repurposing may not always result in successful attempts. Organizational issues, such as the lack of a dedicated team for drug repurposing, can arise if a company's primary focus is on novel drug discovery. Funding challenges further contribute to the complexities surrounding drug repurposing.[15]

Key Challenges:

1. Intellectual Property Rights:

 - Legal complexities and challenges surround reprofiling a drug and obtaining patents for new uses of existing drugs.

 - Issues arise when all uses of a drug are already in the public domain, literary sources, or off-label, affecting the market value and novelty of repurposed drugs.

- Obtaining a patent for drugs not marketed or patented before is relatively straightforward. However, enforcing it can be challenging, especially for dosage forms or uses of already available drugs.

- The European Union provides eight years of data information protection and two years of product exclusiveness. If a discovering company identifies another use within the initial eight years, an additional year of data protection is allowed. In contrast, the US government grants a protection period of five years, extendable by three years. Despite these provisions, they may not ensure a sufficient return on investment.[1]

2. Limited Demand for Repurposed Drugs:

- Despite the multitude of diseases, there may not always be a need for repurposed drugs, especially when novel drugs are abundantly available.

- The chances of successful repurposing can increase if a shift is made from monotherapy to combinations of repurposed drugs.[1]

3. Drug and Data Availability:

- Valuable information from clinical trials may not be easily accessible and often remains outside the public domain.

- Even if informative data is obtained, integrating various types of data can pose challenges and require substantial analytical power.

- Some companies are reluctant to release chemical information of failed drugs for reprofiling opportunities, hindering the exploration of new uses.

- Collaboration between companies for agreements on market launch and profits can be intricate.

- The availability of the drug itself can be a major hurdle. Even if a new application is identified, producing it on a larger scale may be challenging if the necessary compounds are not readily available.[1]

Conclusion

While preparing this review we have concluded that drug reprofiling is an cost effective and less time consuming method for drug development, like every other method this one also has its benefits and challanges which we have included in our review along with various approaches and methods to reprofile drug

Although we believe drug reprofiling can be useful option for novel drug development

If used in good way drug reprofiling can be revolutionary method for pharmaceutical industry

"There is a lot of truth in the saying that we do not need to find new drugs rather we need to find the patients who can benefit from existing drugs"

- Christopher Lipinski

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