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THE EVOLUTIONARY PROCESS OF DRUG RESTORATION

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ABSRACT

Drug repurposing is a technique or approach that identifies expanded uses for pre-approved pharmaceuticals or current therapies. Repurposing has the potential to discover new drugs by leveraging phenotypic advantages, without explicitly explaining the underlying mechanism. The disease-centric approach, the target-centric approach, and the drug-centric approach are the three methods of medication repositioning. Virtual screening is one of the semantic methods for conducting drug repurposing with of computational methods. A molecular docking approach and calculation of binding free energy are used to estimate binding affinity and drug-receptor interactions. Repurposing drugs helps to identify the most promising drugs for further clinical investigation. Drug repurposing suits well for the quickly nascent and reemerging infectious diseases for which no current therapeutics is available. Pharmaceutical companies are undertaking drug repurposing projects for rare diseases, oncology, infectious and autoimmune diseases and more whose drug's safety, pharmacodynamics, and pharmacokinetic qualities were previously established. Over the past 5 years, pressure on the industry caused by the 'innovation gap' of rising development costs and stagnant product output have become major reasons for the growing interest in drug repurposing. Two variables could sustain the flow of compounds into repurposing initiatives in the current economic environment. First, there is an increasing desire to add new projects to existing product

pipelines, particularly for projects where part of the risk has been eliminated. Secondly, the number of possible compounds that have been shelved for geopolitical concerns is rising. These factors may continue to provide opportunities for academia as well as a small number of successful indications discovery companies. our goal is to conduct a thorough study on drug repositioning by gathering all the relevant information on drug repurposing in a user-friendly manner and providing a concise understanding of it the information we provide id sourced from reputable platforms such as PubMed, Science Direct, Medline and Scopus.

Keywords: Drug repurposing, target-centric approach, disease-centric approach, pharmacodynamics

INTRODUCTION

Drug repurposing is gaining popularity in the pharmaceutical industry throughout the world, not only for cost, budget, time, and risk reduction, but also for better treatment and a longer life **[1]**. Drug repurposing is a technique or approach that identifies expanded uses for pre-approved pharmaceuticals or current therapies. Drug repurposing is also known as drug re-profiling, drug repositioning, drug rediscovery, drug redirection, drug reformulating, therapeutic switching, indication switching, and indications discovery **[2]**. Using a medicine for a purpose other than its original prescription is a systematic method that decreases the danger of disintegration, failure, and a shorter time frame cycle with a lower investment and a higher success rate. This procedure seeks FDA-approved pharmaceuticals or older drugs with the capacity to treat various diseases, or drugs that failed in subsequent phases of research, trials, or due to other abnormalities in the drug **[3]**.

The goal of drug repurposing is to quickly identify compounds with an established safety profile and known therapeutic advantages that may prove efficacious for other indications. Pharmaceutical companies are undertaking drug repurposing projects for rare diseases, oncology, infectious and autoimmune diseases and more. The drug's safety, pharmacodynamics, and pharmacokinetic qualities were previously established **[4]**.

The disease-centric approach, the target-centric approach, and the drug-centric approach are the three methods of medication repositioning. The disease-centric strategy focuses on uncovering strong links between an existing medicine and a new indication. The target-centric strategy, on the other hand, entails tying a known target and its existing medication to a novel indication. Finally, the drug-centric strategy links a known medicine to a new

target and indication. These three techniques differ in their potential and limits, but most crucially in the amount of start-up information and computational power required. The stages of drug repurposing are integral in uncovering novel therapeutic uses for approved drugs, encompassing various crucial steps **[5]**.

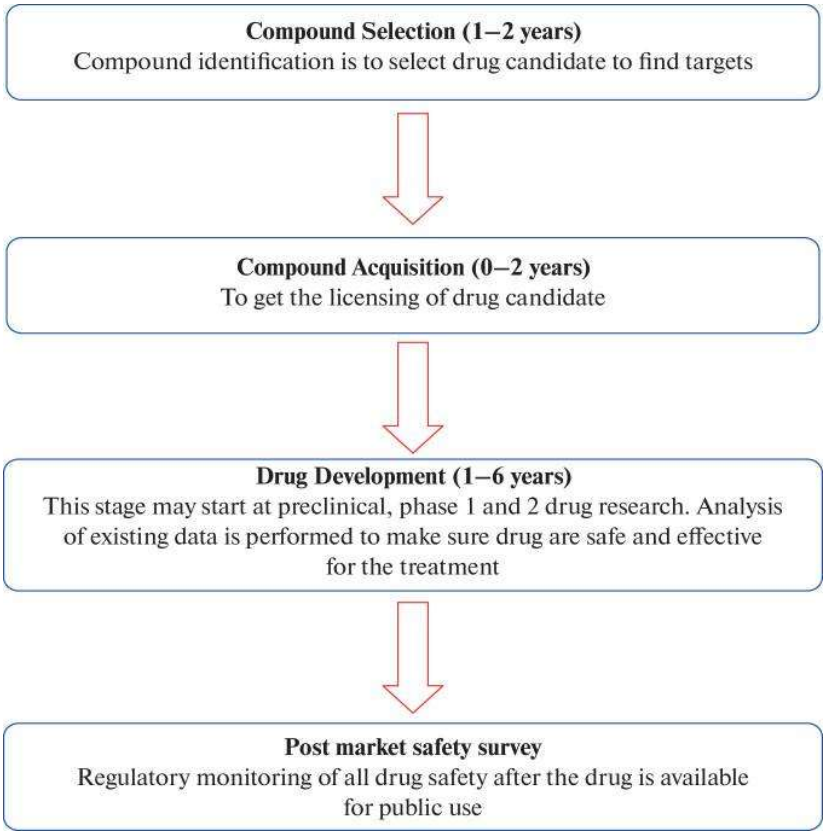


Figure 1: Stages of repurposing

The significance of repurposing drug [6]

Repurposing has the potential to discover new drugs by leveraging phenotypic advantages, without explicitly explaining the underlying mechanism. This approach allows for direct evaluation in preclinical animal models, yielding results that are highly applicable to clinical research and applications. Furthermore, repurposed medications can swiftly advance to Phase II clinical trials, minimizing the risk of failure. The main difference between traditional drug discovery system and drug repurposing is given in **Table 1**.

Table 1: Difference between traditional drug discovery system and drug repurposing

Traditional drug discovery	Drug repurposing
Include 5 stages	Include 4 stages
Discovery and preclinical	Compound identification
Safety review	Compound acquisition
Clinical research	Development
FDA review	FDA post-market safety monitoring
FDA post-market safety monitoring	

Generally, traditional drug discovery includes -more time consuming, high investment, more risk of failure, clinical efficacy and safety profile should be evaluated.

Whereas, Drug repurposing includes- Less time consuming, Lesser investment compared to traditional drug discover, less risk of failure, Clinical efficacy and safety profiles already exist.

Computational approaches have much lower cost and fewer barriers. So various computational approaches are; most used approaches are on Gene expression. Some researches grouped drug repurposing methods according to biological methods used and others divided drug repurposing methods into two types-

1. Data driven
2. Hypothesis driven **[4]**

Core methodologies for dug repurposing approaches are mainly divided into three categories

1. Network based approaches **[Table 2]**
2. Text mining approaches **[Table 3]**
3. Semantic approaches **[Figure 2] [5, 6]**

Table 2: Networks based drug repurposing

Name	Method	Network	Description	Key findings	Advantage	Disadvantage
RNSC	Cluster	PPI	A global network algorithm to identify protein clusters on PPI networks	Some complex proteins	This method considers both local and global information from networks. Overlap clusters can be detected as well.	Some information may be dropped because the cluster size is small.
RRW	Cluster	PPI	An effective network cluster approach to identify protein clusters on a PPI network	Some complex proteins	This is a general method with a high prediction accuracy.	It is a time-costly and memory-costly method that cannot detect overlap clusters.
Cluster ONE	Cluster	PPI	A global network algorithm to identify node clusters on networks.	Some complex proteins	This approach outperformed the other approaches including MCL, RRW, etc., both on weighted and unweighted PPI networks.	There is no a gold standard to evaluate clusters.
-	Cluster	Drug–protein database	A variant of Cluster ONE algorithm to cluster nodes on heterogeneous networks	(Iloperidone, schizophrenia) → Hypertension	This is an efficient cluster approach that integrates multiple databases.	It is difficult to distinguish between positive associations and negative associations on the network.
-	Cluster	Drug-target-disease	An algorithm to detect clusters on the network	(Vismodegib, Basal cell carcinoma) → Gorlin syndrome	This is a general and highly robust approach.	This approach loses weakly associate genes of diseases and drugs.
MbiRW	Cluster	Drug-disease	A bi-random walk-based algorithm to predict disease-drugs relationships.	(Levodopa, Parkinsonian disorder) → Alzheimer's (Cabergoline, Hyperprolactinemia) →Migraine	Predictions of this approach are reliable.	The approach needs to adopt more biological information to improve the confidence of the similarity metric.
-	Cluster	Drug – protein chemical	A k-means-based network cluster algorithm on heterogeneous networks.	(Canertinib, Acute lymphoblastic leukemia) → SCLC	This approach is easy to implement. Predictions of this approach are reliable.	This approach needs to integrate multiple databases.
-	Propagation	Drug-target	An algorithm that combines four network-based approaches to predict drug-target	Melanoma's target cMyc was predicted	This approach is easy to implement. Predictions of this approach are reliable.	This approach needs to integrate multiple databases.

			relationships.			
-	Propagation	Disease-protein-gene	A random walk-based network algorithm with a diffusion kernel to predict disease-gene relationships.	Some disease-gene relationships	This is a global efficient method that can be applied on other networks such disease-drug networks.	This approach can only be used for genes whose protein-protein relations are known. It does not perform well on small disease-gene family data.
PRINCE	Propagation	Disease-gene	A global propagation algorithm to predict disease-gene relationships.	Some disease-gene relationships	This is a global network approach combined with a novel normalization of protein-protein interaction weights and disease-disease similarities.	This approach relies on phenotype data, so some diseases that lack phenotype information are excluded. The performance of this approach relies on data quality.
DrugNet	Propagation	Disease-drug-protein	A comprehensive propagation method to predict different propagation strategies in different subnets.	(Methotrexate, antimetabolite and antifolate) → cancer (Gabapentin, epilepsy) →neuropathic pain	This method is robust and efficient.	The performance of this approach relies on the quality of disease data.

Table 3: Text mining approach

Name	Class	Input	Output	Description
Biovista	Static	Biological knowledge	Gene-protein relationships	A mining framework to extract gene-protein relationships.
BioWisdom	Static	Ontology	Drug-disease, drug-target relationships	A platform to discover novel biological entity relationships.
FACTA+	Static	Tekst	Abstracts and linked concepts	A system to find associated concepts based on a user query
EDGAR	Static	UMLS terms	Drug-gene relationships	A system to extract relationships between drugs and genes involved in cancer using syntactic analysis
PolySearch	Dynamic	Bio-entities	Drug-disease, Drug-gene relationships	A web service to extract links between biological terms
TextFlow	Dynamic	Document	Knowledge	A web-based text mining and natural language processing platform
EXTRACT2	Static	Bio-entities	Entity relationships	A text mining-based tool to map biological entities to ontology/taxonomy entries
Anni 2.0	Static	Bio-entities	Linked concepts	An ontology interface of a text mining tool to extract concepts relationships
DrugQuest	Static	Drugs	Drug-drug relations	A knowledge discovery tool to detect drug-drug relationships
MaNER	Dynamic	Medical Document	Relevant entities	A rule-based system to mine relevant entities in medical documents
BEST	Dynamic	Biomedical Literature	Relevant bio-entities	A knowledge discovery system to extract relevant bio-entities.
Alibaba	Dynamic	Bio-entities	Linked concepts	A tool to fit a PubMed query as a graphical network

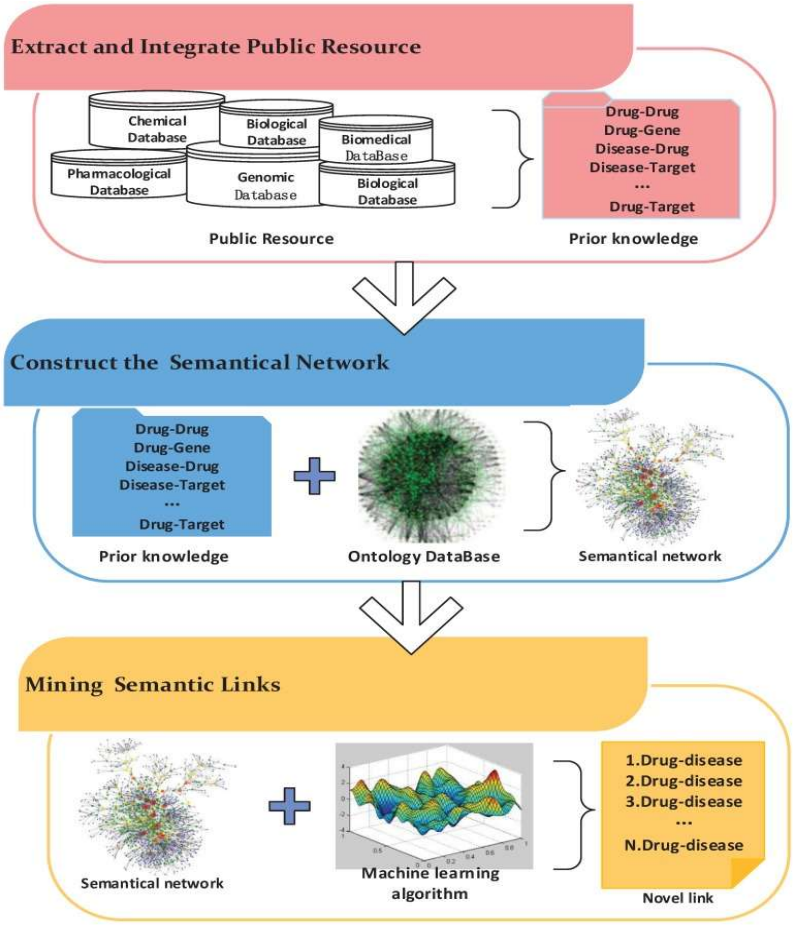


Figure 2: Semantic method approach

Virtual screening is one of the symetic methods for conducting drug repurposing with of computational methods and the MTiO open screen, which is freely accessible to non-commercial users. It can be conducted typically using molecular docking or ss mining and also data mining approaches based on literate are gaining significant strength. it must be noted that systemic approach is not 100 % accurate v/s strategies have been proposed and it remains to be best.by implementing virtual screening of drug libraries, it is possible to identify potential drugs through drug repurposing. A molecular docking approach and calculation of binding free energy are used to estimate binding affinity and drug - receptor interactions [6].

Virtual screening methods are classified as: **[Figure 3]**

1. Receptor based screening
2. Ligand based screening

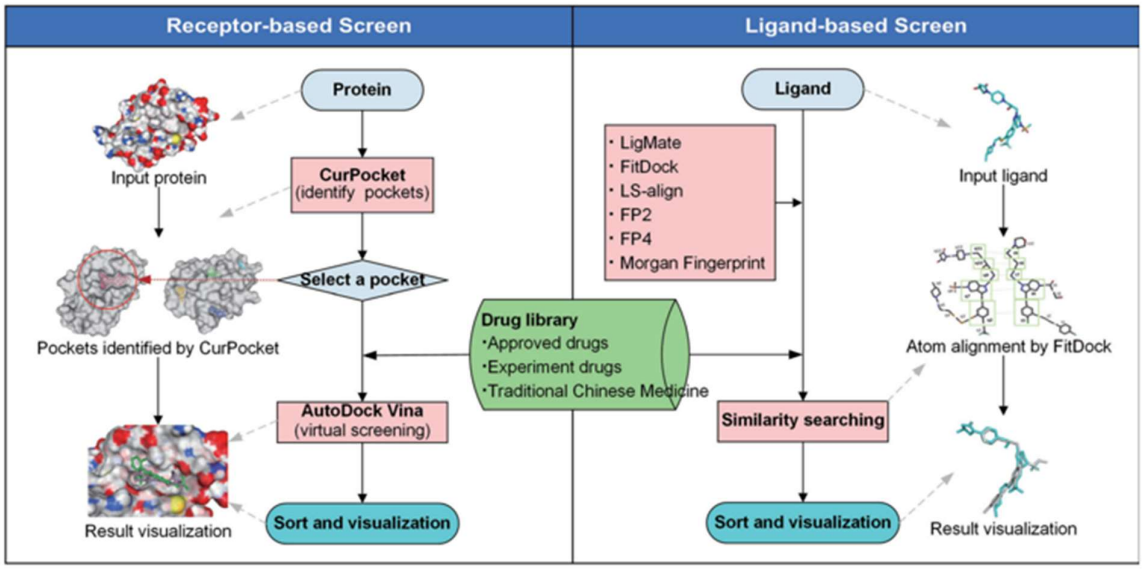


Figure 3: Receptor based and ligand-based screening

Target based Methods

Specific information of the targets, such as 3D protein structures, is required to perform this strategy **[Table 4]**. In contrast, knowledge-based techniques require information on pharmaceuticals or diseases, such as side effects, regulatory approval labels, clinical trial data, and published disease biomarkers or disease pathways. Using these tools, researchers may effectively analyze a large number of pharmacological compounds with known chemical structures, such as the Simplified Molecular Input Line-Entry System.

Table 4: Target-based medication repositioning techniques include

Activity – based approach	*In silico* – based approach
Experimental (*in vitro* and *in vivo*) screening	Computational (virtual) screening
Target based and cell/ organism-based screening assay	Protein target-based screening
Requires no structural information of target proteins and drug – induced cell/disease phenotypic information	Requires no structural information of target proteins and drug – induced cell/disease phenotypic information
Time and labour consuming	Time and labour efficient
Lower rate of false positive hits during the screening	Higher rate of false positive hits during the screening

Table 5: Summary of all repurposed drugs

Drug name	Original indication	Diseases name
Aspirin	Analgesia	Colorectal cancer
Azathioprine	Rheumatoid arthritis	Renal transplant
Cycloserine	Urinary tract infection	Tuberculosis
Duloxetine	Depression	stress urinary
Galantamine	Polio and paralysis	Alzheimer's
Gemcitabine	Antiviral	Cancer
Finasteride	Benign prostatic hyperplasia	Hair loss
Imatinib	Chronic myelogenous	GIT tumors
Topiramate	Epilepsy	Obesity
Minoxidil	Hypertension	Hair loss
Phentolamine	Dermal necrosis	Autism
Raloxifene	Osteoporosis	Breast cancer
Sildenafil	Angina	Erectile dysfunction
Sunitinib	Renal cell carcinoma	Pancreatic tumors

Thalidomide	Nausea	Leprosy and multiple myeloma
Zidovudine	Cancer	AIDS
Atomoxetine	Depression	Hyper activity disorder
Bupropion	Depression	Smoking cessation
Cimetidine	Gastric ulcer	Breast, lung, prostate cancer
Colchicine	Gout	Pericarditis and covid 19 [under development]
Favipiravir	Influenza	Covid 19 [under development]
Hydro chloroquine	Malaria	Covid 19 [under development]
Ivermectin	Scabies, river blindness, helminthiasis	Covid 19 [under development]
Fluro uracil	Cancer	Breast cancer
Gabapentin	Epilepsy	Neuropathic pain
Propranolol	Hypertension	Migraine

In case of drug repurposing, a lot of preclinical and clinical knowledge about the candidate drug exist as the drug already passed through these stages so it suits well for quickly nascent and reemerging infectious diseases for no current therapeutics is available. Drug bank, the potential drug target database, therapeutic target database, super target data base, and drugs and all related information about the drug is provided **[Table 6]**.

Table 6: Open-source models for drug repurposing studies

Compound specific database	Data obtained from
Pub chem	Resources
ChEMBL	Compounds
Chemspider	Molecules in clinical studies
USFDA electronic orange book discontinued drug product list 54	Small libraries
Online drug repurposing hub	Screening platforms in the search for new indications of old drugs or failed
Drug bank	Chemical structures
Therapeutic target data base	Chemical structure
Protopedia	Target 3D structures
Pharm GKB	drug target information
data base interacting	Protein interaction information
STRING and HPRD	Protein interaction information
Adverse reaction database (Canada)	Adverse effects and clinical trial information
NCBI-GEO and CCLE	Omics data

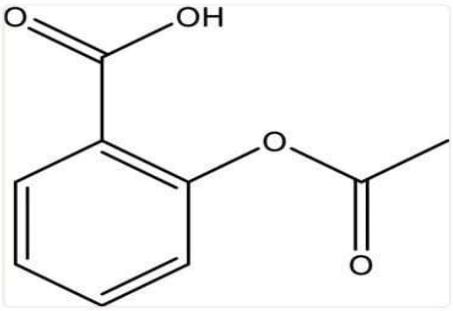
This strategy is far from new, it has gained considerable momentum in the last decade about one-third of the approvals in recent years corresponds to drug repurposing and currently generates around 25%of the annual revenue for pharmaceutical use and also it comes with high risk of failure. Only about 10% of new drug applications gain market approval **[7]**.

Different approaches used to improve drug development success include; Bio informatics, Claims data/EMR, and Natural language processing.

The oldest repurposed drug

Aspirin [acetyl salicylic acid]

Structure:



Original indication

Nonsteroidal anti-inflammatory medication with cyclooxygenase inhibitor action. All NSAIDs have the potential to lessen the effects of inflammation present in most types of arthritis and have analgesic effect. They are not connected to steroid medicines, which are other categories of well-known anti-inflammatory pharmaceuticals analogous to hormones such as cortisol.

Mechanism of action

NSAIDs prevent body molecules that produce arthritic pain and inflammation. Aspirin inhibits cyclooxygenase-2 [COX-2] and has analgesic and anti-inflammatory properties.

History of aspirin

In 1828, Johann Buchner isolated salicin, a yellow bitter crystal from willow bark. It was hydrolyzed into sugars and salicylic aldehyde, then oxidized to salicylic acid. In 1838, chemist Charles Frederich Gerhardt obtained acetyl salicylic acid by acetylation of salicylic acid. After nearly 50 years, Felix Hoffman at Bayer and Co. identified a medicine to alleviate rheumatic pain in 1897 and released it in the form of powder as NSAIDS in 1899.

Dr. Lawrence Craven of California conducted a clinical study in 1948 and discovered that patients who were given aspirin did not have a heart attack. Harvey Weiss and Louis Aledort established that aspirin has antiplatelet activity in 1967. This is the first instance of drug repurposing, and in the 1970s, prostaglandins were reported to be the primary reason for its pharmacological action, and while at low concentrations, it selectively inhibited COX-1, at high concentrations and with prolonged exposure, it acetylated COX-2 as well as other proteins and nucleic acids, and finally, in 1998, acetyl salicylic acid was validated as an anti-platelet agent.

Dosage	Pharmacological action
High dose >325 mg	Anti-inflammatory
Low-dose [75-80mg]	Reducing platelet aggregation

New indication

Aspirin in colorectal cancer [8]

Platelet COX1 generate thromboxane A_2 [TXA_2] which promotes platelet aggregation and vasoconstriction. Enhanced TXA_2 synthase promotes tumor angiogenesis and metastasis. In support of this concept Patron et al. demonstrated that in colorectal cancer Aspirin 75mg/day inhibits TXAS leading to inhibition of angiogenesis and vasoconstriction. In platelet, COX-2 availability is lower than

COX-1. During inflammation, platelet activation induces COX-2 release from the endothelial cell. COX-2 expresses marginal prostacyclin-2 (PGI2) which release α-granules from platelet and inhibit TXA_2. The α-granules release promotes angiogenesis. ASA at low-dose (75mg/kg) inhibit COX-1 and COX-2 mediated PGI2 which inhibit TXA2 as well as α granule. The decrease in PG synthesis leads to decreased inflammation and hence decreases in incidences of cancer/tumor. At relatively higher doses (>300mg/kg/day), ASA inhibits COX-2 and increase arachidonic acid concentration in rats. This enhances acid sphingomyelinase and evokes the conversion of sphingomyelin (a lipid in animal cell membrane) to waxy lipid ceramide which is a well-known mediator of apoptosis. Considering the higher dose necessary for this effect, repurposing of ASA against cancer is difficult, if it is to be mediated by COX-2 inhibition. Fortunately, COX-1 inhibitions at lower doses have been shown to contribute to its anticancer action. Accordingly, ASA has been shown to be effective clinically at lower doses against colon and breast cancer shown to be effective clinically at lower doses against colon and breast cancer.

Applications

- Repurposing drugs helps to identify the most promising drugs for further clinical investigation.
- Drug repurposing suits well for the quickly nascent and reemerging infectious diseases for which no current therapeutics is available.
- This method will accelerate the discovery of old drugs that could potentially treat new indications, either via the established mechanism of action or by identification of new ones.
- Many newly identified active compounds have low potency, which limits their immediate clinical applications because the tolerated plasma drug concentrations are lower effective ones.
- Synergistic drug combinations are an alternative approach to increase rate of drug repurposing, as they may lower the required for individual drugs, in turn reducing the risk of drug toxicity.

Current challenges and prospects for repurposing activities in pharmaceutical companies

The repurposed drug may fail to demonstrate a benefits harms balance in clinical trials. Moreover, there are legal and regulatory issues which are specific barriers to drug repurposing, and which must be carefully analyzed before any development of repurposed drug **[9]**.

Pharmaceutical businesses encounter numerous and diverse hurdles when it comes to drug repurposing. Apart from the scientific difficulties involved in locating promising and reliable candidate compounds, it's also necessary to create business plans to enable the introduction of current compounds as treatments for novel indications. Pharmaceutical companies face a challenge in trying to recover the investment needed to bring a repurposed product to market, even with the potentially shortened clinical development path for repurposed drugs. The need to demonstrate the efficacy of the molecules in new indications remains a significant commitment. For products to benefit from this exclusivity, new intellectual property (IP) must be created. Intellectual property may originate from various sources, including the repurposing concept itself, a novel formulation, or various other approaches (e.g., dosage level, drug combination, and mode of administration) that could enhance the drug and customize it to a new patient demographic. Furthermore, the new IP's underlying inventions frequently add another degree of risk to the product's development process. An almost full clinical program may be needed to characterize the new technology/formulation, beyond the efficacy for the new indication, as opposed to the shortened regulatory pathway that repurposed drugs are expected to follow, such as the FDA's 505(b) **[10-13]**. This may result in expensive and protracted development times, which would be another obstacle to getting the repurposed medication into clinical use.

Such new policies for drug repurposing might be modeled after the FDA's Qualified Infectious Disease Product designation, which grants accelerated clearance and extra years of marketing exclusivity for the approval of novel antibiotics (Woodcock, 2014). Importantly, academic institutions and nonprofit patient advocacy groups are frequently exempt from the above-mentioned business model restrictions, and creative approaches to multi-partner collaborations may help support drug repurposing efforts by integrating the requirements, needs, and expertise of the various entities **[14-16]**.

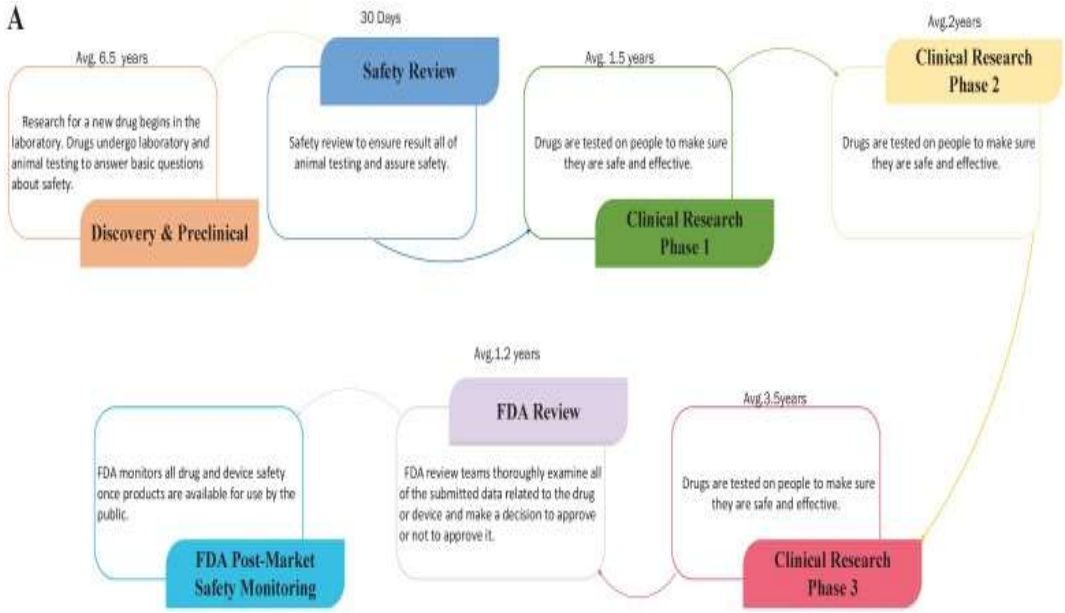


Figure 4: Challenges in drug repurposing

Intellectual property and economic considerations [10-12]

- There are some legal aspects that could impair patenting a new medical use or enforcement of patent rights, thus diminishing the incentives for drug repurposing.
- Some national legislation impedes obtaining a patent for second or further medical uses.
- For drugs that are off-patent, a patent for new indication can be obtained but enforce-ability could become an issue, if the new indication makes use of already available strengths and dosage forms. data and compound availability.
- Whereas the open-source model is progressively gaining ground within the drug discovery community, public access to certain of data is still limited.
- Some pharmaceutical companies are less inclined than others to release their chemical libraries to a branch the possible applications of their compound collections which could pose a fundamental barrier to drug repurposing prospects if a potential repurpose indications falls outside the organization's core disease area.
- Finding a reliable vendor in such circumstances might prove challenging.

Can the repurposing space be exhausted?

Many argued that systemic drug repurposing campaigns may rapidly exhaust the drug repurposing prospects for a given disease.

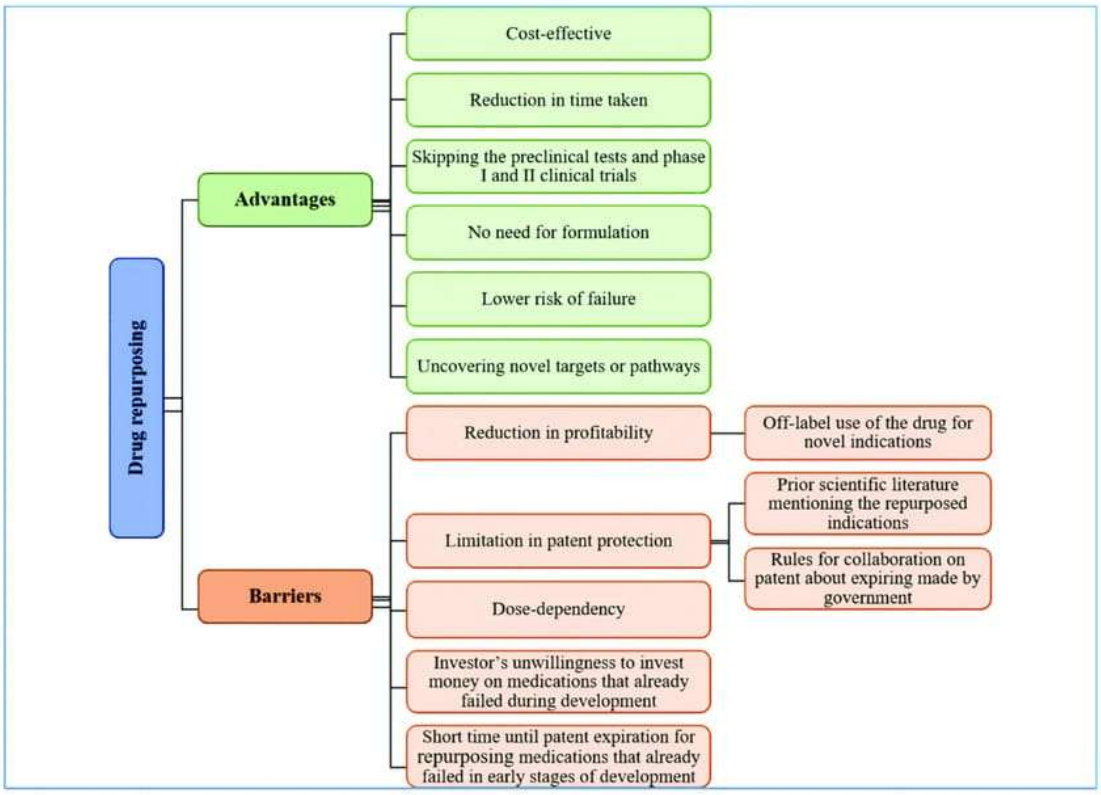


Figure 5: Advantage

Major players in repurposing field

Pharmaceutical companies, repurposing technology businesses, and academic institutions and research centers are the three main stakeholders in the repurposing space. The focus, area of expertise financial models, and incentives vary substantially, despite the fact that they all use the same general strategy for drug development-finding new uses for already-approved medications. One way to conceptualize academia is as two-fold: one is devoted to inventing a molecule or indication, while the other is more focused on methods such in silico or HTS. Although it is dependent on scientific discoveries that draw talent, government financing, and collaborations with nonprofit institutions, it is less restricted by the necessity for economic or commercial success. Conversely, organizations that repurpose technology are restricted by their choice of business strategy, which might differ based on 1.

Drug pipelines, screening platforms, databases, drug library platforms, consulting services, and compound evaluation service providers are all included in these models. It is common practice to combine models, which may improve business performance as well as the results of repurposing initiatives. Technology repurposing firms often make advantage of cutting-edge technologies, specialized knowledge, targeted research, and

flexibility, but they might not have the resources necessary to effectively conduct preclinical and clinical drug development within a regulatory framework. On the other hand, larger pharmaceutical corporations might devote more of their attention to life cycle management initiatives for particular compounds or products, usually in late-stage or post-marketing development. Successful partnerships between larger pharmaceutical companies and smaller repurposing technology companies can present a strong chance to combine in-depth product expertise with advanced repurposing capabilities **[19]**. Adamas Pharmaceuticals, a tiny biotech business, produced a novel medicine combination for the innovative commercialized memantine, which was paired with donepezil to treat Alzheimer's disease. Forrest Labs, the original owner of memantine, purchased the new therapeutic entity for exclusive rights **[17-20]**.

CONCLUSION

Traditional drug development strategies are costly, failure prone and expensive venture, therefore, drug repurposing as recently drawn attention and brings drugs out faster for clinical use. However, this is a complex process involving multiple factors such as commercial technology model patents, investment and market demands. Selecting the appropriate approach to make full use of massive amounts of medical data is still a challenge and intellectual property is also a highlighted issue and protection is limited because of the law, these issues prevent repositioned drugs from entering the market. Moreover, some repositioned projects are forced to be abandoned, which is a waste of time and money.

Conflicts of interest

None.

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