Drug Repurposing in NCDs: Benefits and Challenges

By

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Declaration

It is hereby declared that

1. The project submitted is my own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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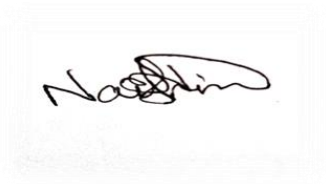

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Approval

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Ethics Statement

The study does not involve any kind of animal and human trials.

Abstract

This review focuses on repurposing of drugs for the treatment of noncommunicable diseases. Drug repurposing is the development of new indications for existing drugs. Noncommunicable diseases are causing large number of deaths every year. Therefore, drug repurposing is an effective strategy for the treatment of noncommunicable diseases. This review discusses the methods, benefits and challenges of drug repurposing as well as all the approved repurposed drugs for NCDs and the repurposed drugs that are awaiting approval by the FDA. Considering the challenges faced due to repurposing of drugs, some recommendations are put forward to improve the future of drug repurposing.

Keywords: Drug repurposing; Noncommunicable disease; Market and data exclusivity; Benefits and challenges.

Dedication

Dedicated to my parents and grandparents

Acknowledgement

First of all, I would like to thank Almighty Allah, our creator, for all the blessings and mercy that He has showered upon me. I would like to thank Him for blessing me with patience, strength, knowledge and assistance necessary for completing this project.

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List of Acronyms

NCD	Noncommunicable disease
CVD	Cardiovascular disease
COPD	Chronic obstructive pulmonary disease
RA	Rheumatoid arthritis
ADHD	Attention deficit hyperactivity disorder
PAD	Peripheral artery disease
CTE	Chronic traumatic encephalopathy
ASD	Autism spectrum disorder
FXS	Fragile X syndrome
TMJ	Temporomandibular joint disorder
ME/CFS	Myalgic encephalomyelitis/chronic fatigue syndrome
IBD	Inflammatory bowel disease
TS	Tourette syndrome
MS	Multiple sclerosis
VWD	Von Willebrand disease
TBI	Traumatic Brain Injury
HTS/HCS	High-throughput screening/High-content screening
EHR	Electronic health record

IR	Information retrieval
BNER	Biological name entity recognition
BIE	Biological information extraction
BKD	Biological knowledge discovery
CTD	Comparative Toxicogenomics Database
FDA	Food and Drug Administration
SNP	Single nucleotide polymorphism
ML	Machine learning
SVM	Support vector machine
NN	Neural network
DL	Deep learning
IC_{50}	Hal-maximal inhibitory concentration
EU/EEA	Europian Union/Europian Economic Area
PIP	Paediatric Investigation Plan
CFS	Chronic fatigue syndrome
APL	Acute promyelocytic leukemia
NMDA	N-methyl-D-aspartate
DS	Down syndrome
AD	Alzheimer’s dementia

DMF	Dimethyl fumarate
TRAPS	Tumor Necrosis Factor Receptor Associated Periodic Syndrome
HIDS	Hyperimmunoglobulin D Syndrome
MKD	Mevalonate Kinase Deficiency
FMF	Familial Mediterranean Fever
PKC	Protein kinase C
CRC	Colorectal cancer
IMPase	Innositol-phosphate phosphatase

Chapter 1 Introduction

Noncommunicable diseases are those diseases which are not infectious and they are not transmitted from person to person (HC & SM, 2013). These conditions comprise of diseases of the cardiovascular and respiratory systems, cancers, diabetes, and psychological illnesses. In 2016, it was found out that NCDs caused 71% of the 57 million deaths that occurred globally (Skolnik, 2018). As the incidence of NCDs is increasing, newer drugs are needed that are financially effective, inexpensive, achievable and versatile in all settings. As the attrition rates and costs are high, the rate of discovery and development of new drugs is slow; repositioning (aka repurposing) old drugs is of great significance to address the growing incidence of NCDs. As drug repurposing uses old drugs, these compounds are safer and do not need much time for their development and also their costs for development are low. Drug repurposing identifies new uses for drugs that are originally developed for another indication. There are several benefits to this strategy. First, it has a lower risk of failure as the safety profile of the drug has already been discovered in preclinical models and humans (Pushpakom et al., 2018). Second, in the initial preclinical and phase I trials, the pharmacokinetic, pharmacodynamic, and toxicity profiles of drugs have already been developed to minimize the time needed for drug production. Consequently, these drugs could be advanced quickly into clinical phase II and phase III trials and the associated development costs could be greatly reduced (Clohessy & Pandolfi, 2015; Nosengo, 2016). Last but not the least, the investment needed to repurpose the drug is less, however this relies upon the stage and technique of advancement of the medication. The costs of regulatory and phase III stages may be nearly same for a repurposed drug compared to a new drug with the same therapeutic use, however the costs of preclinical, phase I and phase II trials can be saved (Pushpakom et al., 2018).

1.1 Aim

The aim of this review is to outline how drug repurposing helps in the treatment of noncommunicable diseases, as well as the benefits and challenges of repurposing drugs, and the strategies by which drug repurposing can be done.

1.2 Objective

The objective of this review is to identify and compile the drugs that have been repurposed for NCDs, to present the approaches used for drug repurposing, discuss the benefits and challenges of drug repurposing and suggest ways by which these challenges could be reduced for repurposing drugs appropriately.

1.3 Rationale

Drug repurposing (aka drug repositioning) is a strategy by which old drugs that are already approved for a particular therapeutic indication are repurposed for new therapeutic indications. Noncommunicable diseases are affecting people globally and causing premature deaths. To address this growing burden, drug repurposing can be done since it has many benefits over de novo drug development. It is a cost-effective strategy, as it reduces the cost of preclinical, phase I and phase II trials. It is also less time-consuming than de novo drug developments since the trials are already completed. It has a lower risk of failure due to safety and inefficacy issues as the drugs are already tested for safety and efficacy during they were developed for their original indication (Pushpakom et al., 2018).

Chapter 2 Noncommunicable diseases

NCDs (Noncommunicable diseases) are chronic, noninfectious diseases, which are not transmitted from one person to another. Cardiovascular diseases (CVDs), diabetes, cancers, chronic respiratory diseases and mental disorders are all noncommunicable diseases. Most of the NCDs are caused by tobacco use, alcohol consumption, unhealthy diet and sedentary lifestyle. They are also caused by genetic factors and injuries. In 2018, 71% of the 57 million global deaths were caused by NCDs. Among the NCDs, cardiovascular diseases caused the highest number of deaths (17.9 million deaths, which is 31% of total worldwide deaths), cancerous conditions (9 million deaths, which is 16% of total deaths worldwide), chronic respiratory diseases (3.8 million deaths, which is 7% of all global deaths), and diabetes (1.6 million deaths, which is 3% of all global deaths). NCDs caused 75% of premature adult deaths (which occurred in people aged between 30 to 69 years) indicating that NCDs not only affect older populations but also younger populations. In 2016, there was 18% global probability of death caused by one of the four main NCDs. There is also evidence that males had a slightly higher risk of developing NCDs (22%) than that of females (15%). These numbers indicate that the burden of NCDs is growing rapidly and needs to be addressed. Therefore, drug repurposing can be used to address this growing burden (Mahabalaraju, 2017).

2.1 Names of NCDs

Table 1 lists the names of all the NCDs.

Table 1 : Names of all the non-communicable diseases

Name of Non-Communicable Disease		
Type I diabetes	Heart attack	Chronic pancreatitis
Type II diabetes	Stroke	Chronic hearing loss

Gestational diabetes	Coronary artery disease	Clotting/bleeding disorders
Chronic obstructive pulmonary disease (COPD)	Peripheral artery disease (PAD)	Attention deficit hyperactivity disorder (ADHD)
Asthma	Cerebrovascular disease	Depression
Pulmonary hypertension	Deep vein thrombosis and pulmonary embolism	Cooley's anemia (beta thalassaemia)
Cystic fibrosis	Congenital heart disease	Crohn's disease
Lung cancer	Alzheimer's disease	Down syndrome
Liver cancer	Autism spectrum disorder (ASD)	Chronic traumatic encephalopathy (CTE)
Stomach cancer	Bipolar disorder	Eczema
Colorectal cancer	Bell's palsy	Epilepsy
Prostate cancer	Cerebral palsy	Fetal alcohol syndrome
Breast cancer	Birth defects	Fragile X syndrome (FXS)
Cervical cancer	Chronic kidney disease	Fibromyalgia
Blood cancer	Chronic pain	Hemophilia
Temporomandibular joint (TMJ) disorder	Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)	Inflammatory bowel disease (IBD)
Kidney disease	Liver disease	Hemochromatosis
Muscular dystrophy	Muckle-Wells syndrome	Insomnia
Myelomeningocele	Primary thrombocythemia	Obesity
Sickle cell anemia	Sleep disorders	Psoriasis
Stress	Multiple sclerosis	Tourette syndrome (TS)
Systematic lupus erythmatosus (lupus)	Systemic sclerosis (scleroderma)	Traumatic brain injury (TBI)
Ulcerative colitis	Vision impairment	Von Willebrand disease (VWD)

Chapter 3 Drug Repurposing

Drug repurposing (aka drug repositioning) is a technique in which new therapeutic indications are found out by repurposing old drugs that are already approved for a specific therapeutic indication. When a new drug is about to be developed, an average of $2 to $3 billion and duration of 13 to 15 years is required. With the development of de novo drugs, there are many downsides. Just 10% of the drugs and 5% of the oncology drugs that have reached the phase I trial are approved. The majority of them are either incredibly poisonous or inefficient. There are currently 8000 orphan diseases that require medicines that are difficult to produce due to tremendous R&D costs (Park, 2019). This is where the drug repurposing feature comes in.

It is an economical process since the cost of preclinical, phase I and phase II trials are reduced. Since the trials have already been done, it is therefore less time-consuming than de novo drug development. As the drugs are already tested for safety and efficacy during the development of the original medication, the risk of failure is lower (Pushpakom et al., 2018). Drug repurposing is an important technique that should be proposed for the development of more successful medicines for noncommunicable diseases, as these diseases impact individuals worldwide and cause premature deaths. There are a range of methods and techniques aimed at reusing current, approved drugs for new medical uses, mostly for diseases with very different profiles than those for which the medicine was originally developed. These approaches are listed below.

3.1 Knowledge-based repurposing

In order to predict mechanisms of diseases, unknown targets or biomarkers of diseases, models are built using data like potential targets of drugs, structures, pathways, side effects and so forth (Emig et al., 2013). This strategy includes:

- Target-based drug repurposing
- Pathway-based drug repurposing
- Target mechanism-based drug repurposing

3.2 Target-based drug repurposing

Target-based drug repurposing allows HTS/HCS (high-throughput and/or high-content screening) of drug compounds when the proteins or biomarkers of interest are known(Joshua Swamidass, 2011) and also computer modeling techniques like docking or ligand-based screening are used to screen drugs from drug libraries (Doman et al., 2002). The function of target-based repurposing is to specifically connect targets with disease pathways similar to blinded search or screening that does not use information like pharmacology or biology of the disease or drug while screening, thus greatly improving the chances of drug development. The benefit of the target-based method is that it is capable of screening all drug substances with a defined chemical structure. However, these methods are not capable of identifying unknown mechanisms past the targets already known (Park, 2019).

3.3 Pathway-based drug repurposing

In this method, data such as metabolic pathways, signaling pathways, and networks of interaction between proteins are used to predict the similarity or relationship between disease and drug. For instance, for providing new targets for repositioned drugs, omics data are processed from human patients or animals which are then used to reconstruct pathways specific to a disease (Jadamba & Shin, 2016).

3.4 Target mechanism-based drug repurposing

This method discovers new uses of drugs using treatment omics data, signaling pathway information, and networks of protein-interaction (Jin et al., 2012). These approaches are advantageous to discover drugs for specific diseases (Park, 2019).

3.5 Signature-based repurposing

Disease omics data provide information about gene signatures, which are used for identifying new pathways for diseases other than the original disease pathway (Haeberle et al., 2012). Profiles of gene expression connecting a disease and a drug are compared in this method to find out if there is an inverse drug-disease relationship. For example, Dudley et al. tested drug-disease pairs which had the potential in inflammatory bowel disease (IBD) by obtaining description of gene expression from the gene expression omnibus database (Barrett et al., 2005; Dudley et al., 2011)and were correlated with gene expression profiles of 164 drug compounds derived from the connectivity map (Lamb et al., 2006). As a consequence, unknown pairs of drug-disease were identified, causing a pair to move into preclinical models. The value of these methods is that they describe novel drug modes of action. These approaches include more genetic-level and/or molecular processes (Park, 2019).

3.6 Phenotype-based repurposing

Phenotypic knowledge serves as a new way of repositioning drugs. Lately, systems methods have gradually used this type of information to detect genetic traits causing a specific human disease (Hebbring, 2014). In this method natural language processing skills are applied to electronic health records (EHRs) to identify undesirable effects of drugs that were not revealed when the drug was developed (Luo et al., 2017). For instance, mining of EHRs revealed that metformin had the potential to be repurposed for treating cancer (Xu et al., 2015).

3.7 Computational methods of drug repurposing

3.7.1 Based on transcriptional signatures

The genes in a biological system can be over- or under-expressed when treated by a pharmacologically active compound. A systematic list of these over- and under-expressed genes can be provided by transcriptomic data. The drug alters the biological system's functions and this can be measured from genome-wide transcriptional responses and the signature of the compound that causes the alteration is characterized by these responses. Comparing these signatures can lead to the discovery of new therapeutic uses of existing drugs (March-Vila et al., 2017).

3.7.2 Network-based drug repurposing

The relationships between biological molecules are arranged as networks in network-based drug repurposing, so that new properties can be found at the network level and also to find out how different biological phenotypes are produced under distinct conditions by cellular systems. In this method, a connected graph can represent a network, where each node can either act as an individual drug, a modifier molecule within a biological process, its biological target or a target pathway, whereas the interaction between two connected nodes are illustrated by an edge (March-Vila et al., 2017).

3.7.3 Ligand-based drug repurposing

It is based on the concept that there is a similarity between the biological properties of similar compounds. It analyzes the activity of ligands for new targets and predicts them. Public databases such as PubChem, CheMBL, and DrugBank consist of data of bioactive molecules, which are recovered and manually arranged from literature data. Information like cellular

activity, functional data, binding affinity and ADMET data can be found from these databases (March-Vila et al., 2017).

3.7.4 Molecular docking

The orientation of a protein to form stable complexes with a small-molecule ligand is predicted in molecular docking, and the interaction is scored. To find out how a potential drug will bind to its target, this tool can be used, as it is a flexible one. Therefore, it can be successfully used to repurpose drugs. Virtual screenings can be done in two ways:

- A known drug can be docked into a big set of various targets.
- A database of approved drugs can be docked into one intended specific target (March-Vila et al., 2017).

As an example, drugs taken from the DrugBank database were successfully repurposed by docking them into 35 crystal structures of the Protein Coding gene MAPK14. In the current review, nilotinib, which is approved for use in chronic myeloid leukemia, was discovered that it had the potential to be repurposed as an anti-inflammatory drug using an in vitro IC_{50} of 40nM.

3.7.5 Text mining

Marti Hearst defines text mining as the revelation by computer of new, previously unknown information, by automatically extricating data from various written resources. There are four steps of text mining

- Information retrieval (IR)
- Biological name entity recognition (BNER)
- Biological information extraction (BIE)
- Biological knowledge discovery (BKD)

Information retrieval is the first step of text mining, where extraction of significant documents is done from the literature. Then the documents are filtered to remove all unnecessary concepts. Then identification of important biological concepts with controlled vocabularies is done in the BNER step. The BIE and BKD stages extract necessary data for biological concepts to be understood and accordingly a knowledge graph be developed. These steps are also used for detection of the interrelationships between drug-disease and drug-target relationships. Text mining methods have originated from the Swanson 'ABC' model. In accordance with this model if there is a connection between concept A and concept B, and a connection between concept B and C, it can be said that there may a novel connection between concept A and C (Weeber et al., 2001). The 'ABC' model-based text mining methods have been developed for finding probable relationships between disease and drug in the literature (Xue et al., 2018). An approach was developed to build drug-protein connectivity maps for specific disease by combining mining techniques like network mining and text mining. At first network mining was used to extract disease-protein relationships from molecular interaction networks. The medication terms, which in a roundabout way associated with specific sicknesses like Alzheimer's disease, were then looked in PubMed abstracts by using text mining methods. Ultimately, drugs and proteins could be connected through relationships between drugs, diseases and proteins. Therefore, the drugs diltiazem and quinidine, which are antihypertensive and antiarrhythmic drugs respectively, were found that they could treat AD too, which have been confirmed by clinical evidence (J. Li et al., 2009). Another approach was proposed which was about creating networks of sentence graph using techniques like text mining. Application of this network can lead to the discovery of the relationship between any drug and any disease. These relationships are specific paths among the biomedical entities in the graph network. This methodology recognized a novel disease target of sarcoidosis (Gramatica et al., 2014). Drug-disease relationships were obtained using

a rank score by using drug-gene and gene disease relationships given in the medical abstracts (Rastegar-Mojarad et al., 2016). In order to assess whether the proposed approach is effective, the drug-disease relationships that were obtained previously were validated in the Comparative Toxicogenomics Database (CTD). The discovered relationships were confirmed by the experimental results to be highly confident (Xue et al., 2018).

3.7.6 Semantic inference

Semantic inference uses methods, which include topic modeling that speed up the process of discovering new drug uses by combining data from a variety of sources. For example, Bisgen et al. proposed a drug repositioning technique based on Latent Dirichlet Allocation that uses a topic model to process the phenome information for adverse effects of drugs (Bisgin et al., 2014). Zhu et al., on the other hand, established an ontology-based information method to guess possible pairs of drugs and diseases in breast cancer by modeling relationships between FDA-approved breast cancer drugs and associated genes, pathways, SNPs and diseases (Zhu et al., 2014). A proposal from Chen et al. considered using a network-based approach linked to semantics to analyze drug-target interactions, including chemical compounds, drugs, protein targets, mechanisms, diseases, side effects, and their relationships (Chen et al., 2012). In this model, the subgraph represented the topology and semantics between a drug and its target, where drug–target pairs situated in various areas of diseases in the model showed the resemblances were due to the opportunity of repositioning.

3.7.7 Machine learning

The applications of machine learning (ML) techniques in drug repurposing include

- Support vector machine (SVM)
- Logistic regression
- Random forest

- Deep learning (DL)
- Neural network (NN)

Logistic regression uses PREDICT, which is a similarity-based machine learning (ML) framework to combine similarities between drugs and diseases and those combined values were then used as properties in figuring out similar drugs for similar classes of diseases (Gottlieb et al., 2011).

For SVM, Napolitano et al. (Napolitano et al., 2013)used an SVM approach, which was based on similarities between drug target, chemical structure of drug, and expression of genes, to predict therapeutic class of drugs. Then these similarities were then combined into a single matrix of matrix so that it could be used as the most important part for SVM classification.

In case of NN, a model was established by Menden et al. which was based on NN to predict response of cell lines derived from cancer cells to treatment by drug, by using parameters like IC_{50}(Menden et al., 2013). In their model, genomic (e.g. status of microsatellite and alteration of 77 genes of cancer) and chemical features (e.g., structural fingerprint) of cancer cell lines were investigated to build a perceptron NN and random forest regression.

Contrasted with shallow learning, DL has the capability to discover unexpressed and complicated structures in large datasets and also allows the adjustment of connecting weights by using back propagation algorithms, allowing the determination of representation of each layer which is dependent on the representation of the previous layer (Lecun et al., 2015).

Chapter 4 Software and tools used in drug repurposing

Drug repurposing is the development of new indications that are different from the indication for which it was previously developed, pharmacological effects or binding specificities of a drug. Repurposing drugs has increased as one of the effective solutions to the chances of drug failure with the rising rates of termination of drugs in clinical trials (Sam & Athri, 2019). There are many software which can be used to repurpose drugs to find out new indications for them. Some examples of the software are given below:

Table 2 : Some software and online tools used for drug repurposing

Homology Modelling	**Structure validation**	**Binding affinity/ energy determination**	**Superimposition**	**Drug-protein interaction**	**ADMET property determination**	**Miscellaneous (e.g molecule drawing, energy optimization, structure conversion etc)**	**Molecular simulation**
SWISS-MODEL(Waterhouse et al., 2018)	ERRAT (Sehgal et al., 2018)	AutoDock(Forli et al., 2016)	PyMOL (DeLano, 2002)	BIOVIA-Discovery Studio(Raman et al., 2020)	Volsurf(Ako et al., 2012)	ChemDraw(Z. Li et al., 2004)	Desmond(Liao et al., 2011)

MODELLER(Webb & Sali, 2016)	Verify3D(Sehgal et al., 2018)	Glide(Repasky et al., 2007)	SuperPose(Maiti et al., 2004)	GOLD (Liao et al., 2011)	ChemTreeMap (Lu & Carlson, 2016)	Avogadro(Hanwell et al., 2012)	CHARMM(Liao et al., 2011)
ExPASy(Gasteiger et al., 2003)	Ramachandran Plot(Sehgal et al., 2018)	PyRx(Dallakyan & Olson, 2015)	BioSuper(Rueda et al., 2013)	Epocrates(Kheshti et al., 2016)	GRID(Carosati et al., 2004)	Open Babel GUI(Liao et al., 2011)	GROMACS(Liao et al., 2011)
BLAST (Liao et al., 2011)	PROCHECK(Ostopovici-Halip et al., 2010)	HADDOCK(Dominguez et al., 2003)	BioBlender(Andrei et al., 2012)	FRED (Liao et al., 2011)	MoKa(Milletti et al., 2010)	Jmol(Liao et al., 2011)	Amber (Liao et al., 2011)

Chapter 5 Benefits and Challenges of Drug Repurposing

Drug repositioning is a revolutionary pharmaceutical growth stream that poses both advantages and challenges. The benefits of drug repurposing include saving cost and time, as well as reducing the risk of failure due to issues of safety and inefficiency. Despite these advantages of drug repurposing, only 2% of new molecules entering clinical trials were subsequently introduced in a field different from the one in which they were originally studied. Drug firms sought to extend the use of 31% of FDA-approved drugs in the same therapeutic area (for example, testing a breast cancer drug for ovarian cancer) and those extensions were highly effective. In trying to repurpose successful drugs in different therapeutic areas, these percentages drop significantly: 18% of products have been tried in another area, with a success rate of 33 percent. The success rate was just 9%, irrespective of the therapeutic area (Neuberger et al., 2019).

5.1. Benefits

- It is a cost-effective strategy, as it reduces the cost of preclinical, phase I and phase II trials.
- It is also less time-consuming than de novo drug developments since the trials are already completed.
- It has a lower risk of failure due to safety and inefficacy issues as the drugs are already tested for safety and efficacy during they were developed for their original indication (Pushpakom et al., 2018).

5.2. Challenges

- **Patent considerations**

  There are a variety of challenges to drug repurposing, in terms of both legal and intellectual property (Ashburn & Thor, 2004; Breckenridge & Jacob, 2018). The

critical barriers to incentivizing drug repurposing are problems dealing with licensing a new indication of a drug and enforcing patent rights, since they have a significant effect on the future benefit expected from the repurposed product. In the pharmaceutical market, the repositioned medicinal use of a drug molecule will be protected, given that the new therapeutic use is unknown and innovative. Most of the indications, which have the potential to be discovered, are already given in the scientific literature or investigated in clinical practice. Even if clinical trials have been unsuccessful, presence of information of the repositioned use may not allow the right to gain patent rights unless the holder of the patent is able to distinguish his or her claims of the patent from the information already present in the public domain in some way. Also, in order to secure a patent, the patentee would be expected to provide evidence in the patent application indicating that the medication is a successful option for the new indication being considered (Pushpakom et al., 2018).

- **Regulatory considerations**

  Regulatory factors play an important role during the development of repurposed drugs. The market exclusivity provided in the Europian Union/Europian Economic Area (EU/EEA) protects from competitive market with similar drug products with similar indications for 10 years and if they comply with the agreed Paediatric Investigation Plan (PIP), then an additional 2 years are given. The submission for the applications for orphan drugs must be through a centralized process. Repositioned drugs, not having an orphan designation, have data exclusivity extending to 10 years. Applications submitted under Article 10(5) for new indications of popular substances may be allowed a data exclusivity of 1 year. In the US, the FDA is providing data exclusivity for a time span of 3 years for developing a new indication of an old drug. However, 3 years is not enough to recover the money a corporation has spent on

repurposing a specific medication (Pushpakom et al., 2018). In Europe, manufacturers of original drugs get a data exclusivity of 8 years and a market exclusivity of 2 years beginning from the date of approval of their medicine (Boulet Pascale, 2018). In Australia, there is a 5-year data exclusivity period for new drugs. The data exclusivity period begins on the date of marketing approval (*An Update on Data Exclusivity Protection in Australia - Wrays IP - Leveraging Innovation*, 2020).

- **Organizational hurdles in industry**

  Some organizational challenges can be met with repurposing in the pharmaceutical industry, especially when the new therapeutic use is not part of the main disease area of the company or if its production has been stopped, with no project in the R&D sector to provide support for the repurposed indication. This would mean that there is a shortage of workers who can work on a new project to repurpose drugs, as well as insufficient funds and means to advance the option within the organization (Pushpakom et al., 2018).

Chapter 6 Drugs Successfully Repurposed for Use in NCDs

Drug repurposing has been used for a long time to address the rapid increase in the number of people suffering from noncommunicable diseases. Some examples of drugs that have been repurposed are given in Table 3 below (Park, 2019; Pushpakom et al., 2018; Raj & Wyawahare, 2020).

Table 3 : Approved repurposed drugs

Drug name	Original indication	New indication
Raloxifene	Osteoporosis	Breast cancer
Thalidomide	Morning sickness	Multiple myeloma
Bromocriptine	Parkinson's disease	Diabetes mellitus
Gemcitabine	Antiviral	Pancreatic cancer
Propranolol	Hypertension	Migraine, tremors, angina
Dapagliflozin	Type 2 diabetes mellitus	Heart failure
Rituximab	Various cancers	RA
Amantadine	Antiviral	Parkinson's disease
Colesevelam	Low Density Lipoprotein-lowering agent	Type 2 diabetes
Galantamine	CFS (Chronic fatigue syndrome)	Alzheimer's disease
Gabapentin	Epilepsy	Partial seizures, postherpetic neuralgia
Milnacipran	Depression	Fibromyalgia
Pregabalin	Neuropathic pain	Fibromyalgia, partial onset of seizures
Cyclosporine	Immunosuppressant	Psoriasis, rheumatoid arthritis

Etanercept	RA	Psoriatic arthritis, plaque psoriasis, Polyarticular juvenile idiopathic arthritis, pediatric plaque psoriasis, ankylosing spondylitis
Glycopyrronium	Peptic ulcers	COPD
Allopurinol	Cancer	Gout, tumor lysis syndrome, hyperuricosuria
Azathioprine	Kidney transplant rejection	Rheumatoid arthritis
Dimethyl fumarate	Psoriasis	Relapsing multiple sclerosis
Duloxetine	Diabetic neuropathy, depression	Fibromyalgia, chronic musculoskeletal pain, generalized anxiety disorder
Everolimus	Immunosuppressant	Pancreatic neuroendocrine tumors, non-cancerous kidney tumors, advanced breast cancer, rare brain tumor
Methotrexate	Various cancers	Psoriasis, rheumatoid arthritis
Retinoic acid	Acne	Acute promyelocytic leukemia
Fingolimod	Transplant rejection	Multiple sclerosis
Arsenic	Syphilis	Acute promyelocytic leukemia
Hydroxyurea	Cancer	Sickle cell disease
Canakinumab	RA	Active systemic juvenile idiopathic arthritis, Cryopyrin-Associated Periodic

		Syndromes, Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), Familial Mediterranean Fever (FMF).
Relugolix	Uterine fibroids	Prostate cancer

6.1 Raloxifene

The FDA approved raloxifene for preventing postmenopausal osteoporosis in 1997 and for treating postmenopausal osteoporosis in 1999 (Messalli & Scaffa, 2009). In 2007, after successful repurposing, raloxifene was approved by the FDA for lowering the risk of invasive breast cancer in postmenopausal women with osteoporosis and in postmenopausal women at high risk for invasive breast cancer (*The Study of Tamoxifen and Raloxifene (STAR): Questions and Answers - National Cancer Institute*, 2010).

6.2 Thalidomide

In 1957, thalidomide was first sold in West Germany for overcoming the symptoms of morning sickness (Fintel et al., 2009). In 2006, it was officially approved for treating multiple myeloma (Hitti, 2006).

6.3 Bromocriptine

FDA approved bromocriptine in 2009 for its therapeutic use in parkinson's disease. However, in 2009 it was also found that it could be used to treat type II diabetes mellitus (Mahajan, 2009).

6.4 Gemcitabine

Gemcitabine is an antiviral drug, which was successfully repurposed and got approval from the FDA in 1996 for treating pancreatic cancers (*FDA Approval: Nab-Paclitaxel in Combination with Gemcitabine for Pancreatic Cancer – Pancreatica.Org*, 2013).

6.5 Propranolol

Propranolol was first developed in the 1967 as a beta-blocker to treat hypertension. After successful repositioning, it is now also used in the treatment of angina, tremors and migraine prophylaxis (Ogbru, 2019).

6.6 Dapagliflozin

In 2014, the FDA approved dapagliflozin for treating type II diabetes (T2D). In 2019, it got FDA approval to reduce the risk of hospitalization for heart failure (HF) in adult patients with Type 2 Diabetes and established cardiovascular disease or multiple CV risk factors (Stewart, 2020).

6.7 Rituximab

It was approved by the US FDA in 1997, for the treatment of relapsed or refractory, CD-20 positive, B-cell, and low-grade or follicular non-Hodgkin's lymphoma. After nine years in 2006, it got FDA approval for its therapeutic use in rheumatoid arthritis (Stewart, 2019).

6.8 Amantadine

Amantadine is an antiviral, which is also approved for use in the treatment of Parkinson's disease (PD). By August 2017, the FDA approved amantadine for reducing symptoms of PD (*Gocovri (Amantadine Hydrochloride) FDA Approval History - Drugs.Com*, 2021)

6.9 Colesevelam

Colesevelam is a bile acid sequesterant and was initially found to be an LDL-lowering agent. However, in January 2008, it was approved for the treatment of type II diabetes (Sonnett et al., 2009).

6.10 Galantamine

Galantamine was isolated for the first time from bulbs of *Galanthus nivalis*, commonly known as snowdrop, in the 1950s. It was initially used to treat chronic fatigue syndrome. Later, in 2000, it was discovered that it could also be used to treat Alzheimer's disease (*Galantamine | ALZFORUM*, 2004).

6.11 Gabapentin

Gabapentin was first approved in May 1993 in the United Kingdom for the treatment of epilepsy. Then in December 1993, U.S FDA approved it as an adjuvant drug to control partial seizures in adults and the use was extended to children in 2000. It is now approved in the USA for the treatment of postherpetic neuralgia (Gelman & Hsu, 2010).

6.12 Milnacipran

Milnacipran was first approved in France to treat major depressive episodes in December 1996. Milnacipran is a mixed serotonin and norepinephrine reuptake inhibitor (SNRI). In 2009, it was approved for the treatment of fibromyalgia (Jeffrey, 2009).

6.13 Pregabalin

Pregabalin was approved in 2004 as for the treatment of neuropathic pain. Later, in 2007, after successful repurposing, it was approved for the treatment of fibromyalgia and as an adjunctive therapy for partial onset seizures (Sinha, 2010).

6.14 Cyclosporine

Cyclosporine is a calcineurin inhibitor, used to suppress the immune system for preventing organ rejection in transplant patients. The drug was approved in 1997 for use in psoriasis and rheumatoid arthritis (Dodd-Butera & Broderick, 2014).

6.15 Etanercept

Etanercept was first approved in 1998 treating rheumatoid arthritis. It was approved for polyarticular juvenile idiopathic arthritis in 1999, psoriatic arthritis in 2002, ankylosing spondylitis in 2003, moderate to severe plaque psoriasis in 2004 and pediatric plaque psoriasis in 2016 (*Enbrel (Etanercept) FDA Approval History - Drugs.Com*, 2016).

6.16 Glycopyrronium

Glycopyrronium was first used in 1961 to treat peptic ulcers. Later in 2016, it was found out that, in its inhalable form it can be used in the treatment of COPD (chronic obstructive pulmonary disease) (Kerwin et al., 2016).

6.17 Allopurinol

Allopurinol was initially used for the treatment of cancer in 1956. After successful repurposing, it was approved in 1966 for use in the treatment of gout. It is also used for the prevention of tumor lysis syndrome and of recurrent calcium nephrolithiasis in patients with hyperuricosuria (Qurie et al., 2020).

6.18 Azathioprine

Azathioprine was approved by the FDA in 1968 as an adjunctive therapy for the prevention of kidney transplant rejection. Then in 1981, it got approval for the symptomatic treatment of active rheumatoid arthritis (Mohammadi & Kassim, 2020).

6.19 Dimethyl fumarate

Dimethyl fumarate (DMF) was licensed in 1994 in Europe as a topical formulation for the treatment of psoriasis. In 2013, the FDA approved dimethyl fumarate for treating relapsing multiple sclerosis (Ehsan & Xixis, 2020).

6.20 Duloxetine

In 2004, FDA approved duloxetine for the treatment of depression and diabetic neuropathy. In 2007, it was got FDA approval for treating generalized anxiety disorder. In 2008, it was approved for the treatment of fibromyalgia. In 2010, it was approved for the management of chronic musculoskeletal pain (Dhaliwal et al., 2020).

6.21 Everolimus

In 2010, everolimus was approved by FDA as an immunosuppressant. After one year, in 2011, FDA approved everolimus for use in the treatment of pancreatic neuroendocrine tumors. In 2012, it got approval for the treatment of non-cancerous kidney tumors, advanced breast cancer and rare brain tumor (Hasskarl, 2018).

6.22 Methotrexate

Methotrexate was first approved by FDA in 1959 for the treatment of various cancers. Then in the 1970s it was approved for the treatment of severe psoriasis. Later, in 1988, it was approved for use in treating rheumatoid arthritis (Hannoodee & Mittal, 2021).

6.23 Retinoic acid

In 1971, retinoic acid was first approved for use in the treatment of acne. In 2018, the FDA approved it for using in combination with arsenic trioxide as a medication for acute promyelocytic leukemia (APL) (Yoham & Casadesus, 2020).

6.24 Fingolimod

Fingolimod was first approved for transplant rejection. In 2010, it was approved for the treatment of multiple sclerosis (Jeffrey, 2010).

6.25 Arsenic

Arsenic was originally used to treat syphilis, however, in 2000, arsenic trioxide got FDA approval for use in the treatment of relapsed or refractory acute promyelocytic leukemia (Cingam & Koshy, 2019).

6.26 Hydroxyurea

Hydroxyurea was originally approved in 1967 as an antineoplastic drug for use in multiple cancers. In 1998, it got FDA approval for treating adults with sickle cell disease (Mercado, 2017).

6.27 Canakinumab

Canakinumab was first approved in the treatment of rheumatoid arthritis. In 2009, after successful repositioning, the FDA approved it for the treatment of Cryoprin-Associated periodic syndrome and for active systemic juvenile idiopathic arthritis. In 2016, it was approved for the treatment of Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS), Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency (MKD), and Familial Mediterranean Fever (FMF) (*FDA Approves Expanded*

Indications for Canakinumab for Three Rare Diseases | American Pharmacists Association, 2016).

6.28 Relugolix

Relugolix was approved for the treatment of uterine fibroids in Japan in 2019. In 2020, it was approved in the United States for the treatment of prostate cancer (*FDA Approves Relugolix for Advanced Prostate Cancer | FDA*, 2020).

Chapter 7 Repurposed Drugs Awaiting Approval

The table below (Table 4) lists the repurposed drugs awaiting approval

Table 4 : Repurposed Drugs Awaiting Approval

Drug name	Original indication	New indication
Ebselen	Antioxidant	Bipolar disorder
Nelfinavir	HIV protease inhibitor	Solid tumors
Loxapine	Antischizophrenia and Antipsychotic	Irritability linked to autism
Minocycline	Antibiotic	Ischemic stroke
Tamoxifen	Breast cancer	Bipolar disorder
Memantine	Alzheimer's disease	Dementia in down syndrome
Atorvastatin	Hypercholesterolemia	Cavernous angioma
Statins	Hypercholesterolemia	Oncology
Losartan	Antihypertensive	Alzheimer's disease
Amiloride	Diuretic	MS
Fluoxetine	Serotonin selective reuptake inhibitor (SSRI)	MS
Riluzol	Glutamate antagonist	MS
Ozanimod	MS	Crohn's disease
Aspirin	Analgesic, antipyretic, antiinflammatory	Colorectal cancer

7.1 Ebselen

Ebselen is an antioxidant and now it is being repurposed for bipolar disorder. Ebselen mimics the action of lithium, which causes changes in enzymatic reactions, inositol recycling and

animal behavior. It is reported to be the best lithium-mimetic (Quiroz et al., 2004). Ebselen acts on multiple targets (polypharmacology) which makes it beneficial to mimic the action of lithium as it causes direct blockage of the biological targets of lithium which include both protein kinase C and IMPase (Zarate et al., 2007).It also acts as an antioxidant and a cyclooxygenase inhibitor that is responsible for promoting survival of neurons (Schewe, 1995).

7.2 Nelfinavir

Nelfinavir is an HIV protease inhibitor, which is being repurposed for treating solid tumors. The activation of Akt (also known as protein kinase B), a nodal regulator of cellular survival pathways, is a significant step in phenotype of cancer and plays a significant role in development and maintenance of features of cancer (Blumenthal et al., 2014).

7.3 Loxapine

Loxapine is an antipsychotic and antischizophrenic drug, which is now being repurposed for use in autism (Hellings et al., 2017).

7.4 Minocycline

Minocycline is a tetracycline antibiotic and it is being investigated for use in the treatment of ischemic stroke (Amantea & Bagetta, 2016).

7.5 Tamoxifen

Tamoxifen is a medication that is used in breast cancer care. It is an oral drug that has been proposed for bipolar disorder as a possible cure. Tamoxifen works to suppress protein kinase C (PKC) intracellular activity, which is also the effect of well-established therapies such as lithium and valproate (Palacios et al., 2019). PKC is a group of enzymes, which play an important role in cell signaling.

7.6 Memantine

Memantine is a drug used to treat the symptoms of Alzheimer's disease, but it is being investigated for the treatment of Down syndrome-associated dementia. The most common form of dementia in individuals with Down Syndrome (DS) is Alzheimer's dementia (AD). There is an understanding that an increase in L-glutamate contributes to cerebral ischemia and AD pathogenesis. Memantine functions as an N-methyl-D-aspartate (NMDA) type receptor antagonist, which is thought to decrease abnormal stimulation of neurotransmission of glutamate. It binds to the NMDA receptor with a low affinity, so it does not inhibit learning and memory formation (Mohan et al., 2009).

7.7 Atorvastatin

The original indication of atorvastatin is hypercholesterolemia. It is now being repurposed for use in the treatment of cavernous angioma (Di Bello et al., 2020; Ishida et al., 2016).

7.8 Statins

Statins have been used to treat hyperlipidemia and to reduce cholesterol levels in the blood as these are lipid-lowering drugs, and are now being repurposed for treatment of cancerous conditions (Di Bello et al., 2020; Ishida et al., 2016).

7.9 Losartan

Angiotensin II receptor blockers like losartan are compounds that are widely used and therapeutically effective in cardiovascular diseases, renal diseases, the metabolic syndrome, and diabetes. Lately, ARBs have been recognized as neuroprotective agents and have the potential for therapeutic use in many brain disorders (Villapol & Saavedra, 2015).

7.10 Amiloride

Amiloride is a potassium-sparing diuretic which is widely used and is an acid-sensing ion channel blocker (Friese et al., 2007; Vergo et al., 2011). It is being repurposed for multiple sclerosis (MS).

7.11 Fluoxetine

Fluoxetine is a selective serotonin reuptake inhibitor (SSRI), which is tested for its indication in multiple sclerosis (MS) (Sijens et al., 2008).

7.12 Riluzole

Riluzole is used to treat diseases of motor neurons, reduces release of glutamate and antagonises voltage-dependent sodium channels (Bellingham, 2011). It is now being repurposed for multiple sclerosis (MS).

7.13 Ozanimod

Ozanimod was approved by the FDA in 2020 for the treatment of multiple sclerosis, however, it is also being studied for Crohn's disease. Crohn's disease is a chronic relapsing inflammatory bowel disease characterized by impaired regulation of immune responses (Mayer, 2010).

7.14 Aspirin

Aspirin, also known as acetylsalicylic acid, is an analgesic, antipyretic and anti-inflammatory drug. There are more than 600,000 global deaths due to colorectal cancer (CRC) annually, making it important to develop effective strategies for prevention. Aspirin have been shown to decrease the occurrence of colorectal neoplasia in many epidemiological studies, four controlled trials of colorectal polyp recurrence which were performed randomly, and

randomized controlled trials in patients with hereditary colorectal cancer syndromes (Garcia-Albeniz & Chan, 2011).

Chapter 8 Conclusion

There are a number of therapeutic indications of existing drugs that are yet to be discovered. Drug repositioning provides the opportunity of reviving those old drugs with new indications. Several pharmaceutical companies have benefited from this strategy by gaining a new source of sales, gaining a competitive edge in the industry, increasing their return on investment, and saving money by using sources efficiently (Mehndiratta et al., 2016). There are risks of using this technique, especially in the industrial sector, even though it has gained increased recognition at the National Institutes of Health (Collins, 2011). Considering all the relevant factors involved in drug repositioning, it is likely to increase the costs which may cause further reduction in the existing diminishing resources of the pharmaceutical industry (Oprea & Mestres, 2012). Taking the opportunities and challenges into consideration, following are four recommendations that we have conceived so that there can be a promising future for drug repurposing.

First, more data of phase II–IV clinical trials are needed from industries. External scientists might be able to mine the data for new results that could lead to repurposing opportunities, especially for programs that have been discontinued. Second, newer threats associated with repurposed medications should be investigated. Any new safety risks due to repurposed medications must be determined on a continuing basis. These may occur due to new associations between the medicine in question and the disease for which it has been repurposed, using a different population, or variations in dosage regimen (for example, chronic instead of an intermittent dosing). Third, further opportunities of funding for drug repurposing initiatives are necessary to incentivize drug repurposing. Appropriate technology should be funded, access to compounds should be supported and drug repurposing libraries should be shared. Last but not the least, steps must be taken to overcome the patent and regulatory obstacles listed previously. Data exclusivity periods should be improved for

repurposed uses, royalty agreements with generic firms, or other regulatory reforms should be introduced to ensure that expenditure in drug repurposing projects can be recovered (Pushpakom et al., 2018).

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