Drug repositioning is defined as the process of finding a new indication for an approved drug or abandoned pharmacotherapies. It identifies new indications of existing drugs and the application of the newly identified drugs to the treatment of diseases other than the drug’s original indication. It involves analysis of drugs that have already been sanctioned for treatment of other diseases or whose targets have already been identified. Other synonyms are drug repurposing, drug rescue, redirecting, reprofiling, re-tasking, therapeutic switching and indication switching. It emerged primarily in the early 1990s as an accidental discovery but lately due to development of new advents and tools the process has become more systematic. Repurposing of older drugs can fulfill vast unmet medical needs. It is an alternative to conventional de novo drug discovery and development. Repositioning is an accelerated approach for drug discovery because existing drugs have already passed pharmacokinetic and clinical analysis.

Presently drug repositioning project plays a pivotal role in the de novo drug discovery ventures of the pharmaceutical industry. The process of new drug development is tricky, time consuming and expensive. The pharmaceutical companies have not balanced output and the tremendous increase in research and development expenditure. This difference in productivity exists even though pharmaceutical companies have invested stupendous amounts in novel drug discovery technologies. The pharmaceutical companies today are facing downhill productivity with increased research and development expenditure. The pharmaceutical industry faces multiple challenges like, higher rates of attrition, drug safety issues, high regulatory pressures, expiring patent protection, and competition from generic drugs. The pharmaceutical companies are considering drug repositioning for accelerated drug discovery as it carries minimal risk of failure and is relatively inexpensive. Moreover they are always looking for developing drugs products which are economical, and carry limited risk strategy along with protection of existing products from competition and extension of their patent protection time. Drug repositioning is a low risk, high reward strategy as compared to de novo drug discovery, which is high risk, high reward strategy. There are 2000 failed drugs sitting that have the potential to develop into successful repositioned drugs. The list of failed drugs is increasing at the rate of approximately 150–200 compounds per year.

There are innumerable advantages of drug repositioning. It helps to recoup the existing expenditure, saves time and money with better implementation of sources. The cost to re-launch repositioned drug is quite reasonable (~8.4 million USD), whereas...
cost to re-launch the new formulation is extremely expensive (~41.3 million USD). The development of new drug costs more than 2.6 billion USD.\textsuperscript{10} So to launch the repositioned drug successfully to the market is quite economical than that of new drug. In clinical trials, repositioned drugs compete with non-repositioned drugs in terms of efficacy rather than safety. Repurposed drugs escape much of the developmental cost than the traditional drug discovery due to availability of earlier pharmacokinetic, bioavailability, safety and toxicology data. Approximately 1 in 10,000 new drug that enters the clinical research and trial process, genuinely makes it to the market and roughly 30% of the drugs researched in clinical trials fail to qualify due to inefficacy.\textsuperscript{3,11,12} Thus repositioning ensures significant time and capital saving.

De novo drug discovery, right from the target identification to its development and approval takes almost 10–17 years whereas approval of an existing drug takes 3–12 years. In standard drug discovery, target discovery takes 2–3 years, screening and designing chemicals with biological activity takes 6 months to 1 year, lead optimization takes 1–3 years, 1–2 years to confirm drug ADMET (absorption distribution, metabolism, excretion and toxicity) properties using animal models, 5–6 years in clinical trial to determine drug safety and efficacy and 1–2 years for licensing. But in case of repositioning, compound identification takes 1–1.5 years, compound acquisition takes 0–1.5 years, preclinical development 0–1 year, clinical trials 1–6 years, and 1–2 years for licensing.\textsuperscript{1} Few studies have shown that approval of a repositioned drug can be achieved in only 4 years.\textsuperscript{13} Thus by reducing length of time for development and re-launch of repurposed drug we can provide accelerated treatment options to the patients. Success rates for repurposed drugs are higher as compared to de novo drug discovery. Success rate for repurposed drugs was approximately 30% in recent years and was recently approved by the US FDA.\textsuperscript{14}

\begin{table}
\centering
\begin{tabular}{|l|l|}
\hline
Drug & Original indication \hline
Amantadine & Influenza \hline
Amphotericin & Antifungal \hline
Aspirin & Inflammation, pain \hline
Amitriptyline & Anti-depressant \hline
Azathioprine & Rheumatoid arthritis (RA) \hline
Bupropion & Depression \hline
Bimatoprost & Glaucoma \hline
Bromocriptine & Parkinson’s disease \hline
Bleomycin & Antibiotic \hline
Bromocriptine & Parkinson’s disease \hline
Buprenorphine & Pain \hline
Colchicine & Gout \hline
Clofazime & Tuberculosis \hline
Canakinumab & Rheumatoid arthritis \hline
Cyclosporine & Organ transplant rejection \hline
Colesevalam & LDL-lowering \hline
Crizotinib & Clinical trials for anaplastic large-cell lymphoma \hline
Cycloserine & Tuberculosis \hline
Dimethyl fumarate & Psoriasis \hline
Dapoxetine & Antidepressant \hline
Doxepin & Antidepressant \hline
Donepezil & Alzheimer’s disease \hline
Duloxetine & Depression \hline
Etanercept & Rheumatoid arthritis \hline
Everolimus & Immunosuppressant \hline
Ellorfhane & Cancer \hline
Fluoxetine & Antidepressant \hline
Finaferverse & Hypertriglyceridaemia \hline
Galantamine & Chronic fatigue syndrome \hline
Gabapentin & Epilepsy \hline
Glycopyrrolone & Anti-ulcer \hline
Germicidine & Anti-viral \hline
Hydroxychloroquine & Malaria \hline
Histrelin & Prostate cancer \hline
Imatinib & CML \hline
Ibuprofen & Inflammation, pain \hline
Iproniazid & Tuberculosis \hline
ImiflIXimab & Autoimmune diseases \hline
Lomitapide & Hypercholesterima \hline
Methotrexate & Cancer \hline
Mitofenose & Cancer \hline
Minoxidil & Hypertension \hline
Milnacipran & Anti-depressant \hline
Naltrexone & Opioid/alcohol addiction \hline
Nelfinavir & Acquired immunodeficiency syndrome (AIDS) \hline
Onabotulinumtoxin & Facial spasm \hline
Paroxetine & Antidepressant \hline
Pacitaxel & Various cancers \hline
Perlixafar & AIDS/HIV \hline
Pertuzumab & Various cancers \hline
Pregabalin & Anticonvulsant and neuropathic pain \hline
Prampoxeole & Parkinson’s disease \hline
Propranolol & Hypertension \hline
Raloxfene & Osteoporosis \hline
\hline
& New indication \hline
Parkinsonism & & \\
Leishmaniasis & Anti-platelet, stroke \\
Neuropathic pain & & \\
Multiple sclerosis (MS), inflammatory bowel disease (IBD) and organ transplants & & \\
Smoking cessation and weight-loss (combi-therapy) & & \\
Eyelash growth & & \\
Diabetes mellitus & & \\
Cancer & & \\
Type II diabetes & & \\
Drug treatment & & \\
Recurrent pericarditis and familial mediterranean fever & & \\
Leproy & & \\
Muckle–Wells syndrome & & \\
Psoriasis and rheumatoid arthritis & & \\
Type II diabetes & & \\
Non-small cell lung carcinoma (NSCLC) & & \\
CNS disorders & & \\
Multiple sclerosis & & \\
Premature ejaculation & & \\
Atopic dermatitis & & \\
Dementia & & \\
Stress, fibromyalgia, urinary incontinence and chronic musculoskeletal pain & & \\
Plaque psoriasis & & \\
Pancreatic neuroendocrine tumors & & \\
Hirsutism and sleeping sickness & & \\
PMDD (premenstrual dysphoric disorder) & & \\
Benign prostatic hyperplasia and male pattern baldness & & \\
Alzheimer’s disease & & \\
Neuropathic pain & & \\
Chronic obstructive pulmonary disease (COPD) & & \\
Various cancers & & \\
Lupus and rheumatoid & & \\
Precocious puberty & & \\
Gastrointestinal stromal tumors & & \\
Osteoarthritis (OA), rheumatoid arthritis (RA), headache and migraine & & \\
Antidepressant & & \\
Crohn’s disease & & \\
HFOH (homozygous familial hypercholesterolemia) & & \\
Psoriasis and RA & & \\
Visceral leishmaniasis & & \\
Male pattern baldness & & \\
Fibromyalgia & & \\
Weight-loss (combi-therapy) & & \\
In clinical trials for multiple cancers & & \\
Chronic migraine, cervical dystonia and facial cosmetics & & \\
Menopausal hot flashes & & \\
Stent re-stenosis prevention & & \\
Lymphoma and multiple myeloma & & \\
HER-2 + breast cancer & & \\
Fibromyalgia & & \\
Restless leg syndrome & & \\
Tremors, angina and migraine prophylaxis & & \\
Breast cancer & & \\
\end{tabular}
\caption{List of successfully repositioned drugs\textsuperscript{8,9,11,15–17.}}
\end{table}
(Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Original indication</th>
<th>New indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinoic acid</td>
<td>Acne</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Parkinson’s disease</td>
<td>Restless leg syndrome</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Various cancers</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Angina</td>
<td>Erectile dysfunction and pulmonary arterial hypertension</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>GIST and renal cell carcinoma</td>
<td>Pancreatic neuroendocrine tumors</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>HER2-positive breast cancer</td>
<td>HER2-positive metastatic gastric cancer</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Morning sickness</td>
<td>Multiple myeloma and erythema nodosum leprous</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Cancer</td>
<td>HIV/AIDS</td>
</tr>
</tbody>
</table>

There are two approaches of drug repositioning:\(^{14}\):

(i) **Known drug – new target/drug focus/drug-centric** where the drug is already approved for specific indication and helps to identify its role in different indications. In this method single drug interacts with multiple targets.

(ii) **Known target – new indication/target focus/target-centric**

It identifies relevance between known targets of compounds and a new disease, i.e. discovers new medical potential of a new compound.

(iii) **Disease focus/disease-centric**

In this method we employ the acceptable experimental data related to disease and knowledge about how drugs modify phenotypes related to disease.

The technologies applied in drug repositioning comprises of in vivo (cell/organ/tissue/animal) phenotype model screening and in vitro, high content screening (HTC), high-throughput screening (HTS), chemoinformatics, data base driven bioinformatics information with Network and Systems Biology. These methods are used in association with available information on known target profile, pharmacokinetics of drugs, biomarkers of disease and disease pathway which will be time-saving and can lead to rapid discovery of drugs.

In spite of the entire efforts, drug repositioning still faces plenty of challenges and not all cases of drug repositioning are fruitful. Such as to test a specific drug for a considerable number of diseases or a generous number of drugs for a particular disease, it is challenging and laborious to consolidate the required computational approaches because the available information of drugs and disease may vary.\(^{14}\) In other cases drug such as bevacizumab (kinase inhibitor) was found to be ineffective in phase III trial for gastric cancer although being repositioned in other cancers.\(^{18}\) Even Sunitinib failed in clinical trials for colorectal cancer, breast cancer, prostate cancer and NSCLC, but has been successfully repositioned for treatment of renal cell carcinomas, GISTs and pancreatic neuroendocrine tumors.\(^{19}\) So looking at the ineffectiveness of Sunitinib in some cancers, we have to develop a targeted approach for some cancers. Repositioned drugs can cause adverse effect even after successfully passing the clinical safety standards. For e.g., the combination of naltrexone and bupropion was previously approved for the treatment of opioid addiction and depression respectively. It was also found to regulate energy consumption and appetite in obesity. However, due to the cardiovascular side effects of this combination, the FDA rejected this combination in 2011.\(^{20,21}\)

The most rewarding base of drug repositioning is that we can start with an old drug. It is a strategy that revolves old and dead drugs. There is still scope of research as there are still plenty of undiscovered therapeutic indications of known drugs. This approach has provided new source of income, market potential advantage, return on investment potential and money saving advantage to numerous pharmaceutical companies. Drug repositioning helps to recover the existing investment, saves time and money with better utilization of sources. It is a remunerative approach, helps to lessen the burden of diseases and accelerates productivity of pharmaceutical companies.

**Drug repositioning in epilepsy**

Due to complex nature of epilepsy and multi-target approach of anti-epileptics, drug repositioning can prove advantageous in the field of anti-epileptic drugs therapeutic armamentaria. Various studies have demonstrated anti-convulsant effects of anti-arythmic drugs (AADs). Among class I AADs, Propafenone enhanced anticonvulsant action of classical anti-epileptic drugs (AEDs)\(^ {32}\) and reduced maximal electroshock induced seizures in rats.\(^ {23}\) Lidocaine (also an anesthetic agent) demonstrated anti-epileptic activity in patients with chronically unstable generalized epilepsy.\(^ {34}\) Mexiteline was found to be effective in the treatment of symptomatic partial epilepsy and Lennox–Gastaut syndrome\(^ {23–27}\) and decreased pentylentetrazole-induced convulsions, and sound induced convulsions in DBA/2 mice.\(^ {30}\) In class II AADs, Propranolol decreased seizures in patients with chronically unstable generalized epilepsy\(^ {28}\) and it demonstrated anticonvulsant action in models for generalized tonic–clonic and complex partial seizures, but not for myoclonic convulsions.\(^ {31}\) Timolol reversed the epileptiform activity of pentylentetrazol (PTZ) in the mouse brain.\(^ {31}\) In class III AADs, Amiodarone inhibited PTZ – and caffeine-induced convulsions in mice.\(^ {32}\) In class IV AADs, Verapamil protected mice against PTZ-induced seizures and inhibited epileptogenesis in amygdala-kindled rats\(^ {33,34}\) and was found to be effective in the treatment of recurrent status epilepticus in human.\(^ {35–37}\)

Repositioning is going to gain much more importance in future as it can act as filler for ailing drug companies which are facing patent problems. In future, it can provide treatment options for rare diseases whose existing treatment options are very limited. Repositioned drugs have the same market potential as that of new drugs in the market and can also get the good market returns on the investment. Repurposing drugs can effectively lower the costs related to new drug development. It will be valuable for the patients because treatment options will be reasonable as compared to new drug discovery costs, which may not receive reasonable return on investment. Moreover, it is also important to develop both, as novel drug discovery can prevent exhaustion of supply and continuous screening of repositioned drugs can ensure full potential usage.

**Conflicts of interest**

The authors have none to declare.

**References**