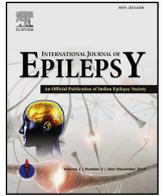




Contents lists available at ScienceDirect

International Journal of Epilepsy

journal homepage: <http://www.journals.elsevier.com/international-journal-of-epilepsy>

Review article

Drug repositioning

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ARTICLE INFO

Article history:

Received 4 July 2016

Accepted 6 September 2016

Available online 10 October 2016

Keywords:

Drug repositioning

De-novo drug discovery

Pharmacotherapy

ABSTRACT

Rapid advances in pharmacotherapy and bioinformatics has led to the discovery and growing popularity of drug repositioning which includes re-investigating or recycling of existing drugs for new indications. There are innumerable advantages as well as challenges of drug repositioning. Since de-novo drug discovery takes plenty of time, effort and money, it has proved to a preferred alternative strategy for accelerated drug discovery. Moreover it is relatively inexpensive and carries minimal risk due to availability of previous pharmacological, safety and toxicology data. The strategies used are Known drug – new target/ Drug focus/Drug-centric, Known target– new indication/ Target focus/Target-centric and Disease focus/Disease-centric. Drug repositioning is a new breakthrough strategy to benefit patients by offering safer and effective treatment using shelved drugs.

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Drug repositioning is defined as the process of finding a new indication for an approved drug or abandoned pharmacotherapies.¹ 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.² 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, re-profiling, re-tasking, therapeutic switching and indication switching.³ 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.

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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.⁴ This difference in productivity exists even though pharmaceutical companies have invested stupendous amounts in novel drug discovery technologies.⁵ 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.⁶ 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.⁷ 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.^{8,9}

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.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.^{9,11,12} 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.¹ Few studies have shown that approval of a repositioned drug can be achieved in only 4 years.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.¹⁴

List of successfully repositioned drugs^{8,9,11,15–17}:

Drug	Original indication	New indication
Amantadine	Influenza	Parkinsonism
Amphotericin	Antifungal	Leishmaniasis
Aspirin	Inflammation, pain	Anti-platelet, stroke
Amitriptyline	Anti-depressant	Neuropathic pain
Azathioprine	Rheumatoid arthritis (RA)	Multiple sclerosis (MS), inflammatory bowel disease (IBD) and organ transplants
Bupropion	Depression	Smoking cessation and weight-loss (combi-therapy)
Bimatoprost	Glaucoma	Eyelash growth
Bromocriptine	Parkinson's disease	Diabetes mellitus
Bleomycin	Antibiotic	Cancer
Bromocriptine	Parkinson's disease	Type II diabetes
Buprenorphine	Pain	Drug treatment
Colchicine	Gout	Recurrent pericarditis and familial mediterranean fever
Clofazime	Tuberculosis	Leprosy
Canakinumab	Rheumatoid arthritis	Muckle–Wells syndrome
Cyclosporine	Organ transplant rejection	Psoriasis and rheumatoid arthritis
Colesevelam	LDL-lowering	Type II diabetes
Crizotinib	Clinical trials for anaplastic large-cell lymphoma	Non-small cell lung carcinoma (NSCLC)
Cycloserine	Tuberculosis	CNS disorders
Dimethyl fumarate	Psoriasis	Multiple sclerosis
Dapoxetine	Antidepressant	Premature ejaculation
Doxepin	Antidepressant	Atopic dermatitis
Donepezil	Alzheimer's disease	Dementia
Duloxetine	Depression	Stress, fibromyalgia, urinary incontinence and chronic musculoskeletal pain
Etanercept	Rheumatoid arthritis	Plaque psoriasis
Everolimus	Immunosuppressant	Pancreatic neuroendocrine tumors
Eflornithine	Cancer	Hirsutism and sleeping sickness
Fluoxetine	Antidepressant	PMDD (premenstrual dysphoric disorder)
Finasteride	Hypertension	Benign prostatic hyperplasia and male pattern baldness
Galantamine	Chronic fatigue syndrome	Alzheimer's disease
Gabapentin	Epilepsy	Neuropathic pain
Glycopyrronium	Anti-ulcer	Chronic obstructive pulmonary disease (COPD)
Gemcitabine	Anti-viral	Various cancers
Hydroxychloroquine	Malaria	Lupus and rheumatoid
Histrelin	Prostate cancer	Precocious puberty
Imatinib	CML	Gastrointestinal stromal tumors
Ibuprofen	Inflammation, pain	Osteoarthritis (OA), rheumatoid arthritis (RA), headache and migraine
Iproniazid	Tuberculosis	Antidepressant
Imflicximab	Autoimmune diseases	Crohn's disease
Lomitapide	Hypercholesterimia	HoFH (homozygous familial hypercholesterolemia)
Methotrexate	Cancer	Psoriasis and RA
Miltefosine	Cancer	Visceral leishmaniasis
Minoxidil	Hypertension	Male pattern baldness
Milnacipran	Anti-depressant	Fibromyalgia
Naltrexone	Opioid/alcohol addiction	Weight-loss (combi-therapy)
Nelfinavir	Acquired immunodeficiency syndrome (AIDS)	In clinical trials for multiple cancers
Onabotulinumtocin	Facial spasm	Chronic migraine, cervical dystonia and facial cosmetics
Paroxetine	Antidepressant	Menopausal hot flashes
Paclitael	Various cancers	Stent re-stenosis prevention
Plerixafor	AIDS/HIV	Lymphoma and multiple myeloma
Pertuzumab	Various cancers	HER-2 + breast cancer
Pregabalin	Anticonvulsant and neuropathic pain	Fibromyalgia
Pramipexole	Parkinson's disease	Restless leg syndrome
Propranolol	Hypertension	Tremors, angina and migraine prophylaxis
Raloxifene	Osteoporosis	Breast cancer

(Continued)

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

There are two approaches of drug repositioning¹⁴:

- (i) **Known drug – new target/drug focus/drug-centric** where 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 revives 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-arrhythmic drugs (AADs). Among class I AADs, Propafenone enhanced anticonvulsant action of classical anti-epileptic drugs (AEDs)²² 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.²⁴ Mexiletine was found to be effective in the treatment of symptomatic partial epilepsy and Lennox–Gastaut syndrome^{25–27} and decreased pentylentetrazole-induced convulsions, and sound induced convulsions in DBA/2 mice.²⁸ In class II AADs, Propranolol decreased seizures in patients with chronically unstable generalized epilepsy²⁹ and it demonstrated anticonvulsant action in models for generalized tonic–clonic and complex partial seizures, but not for myoclonic convulsions,³⁰ 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.

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