

Drug Repositioning: A Review

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Abstract

Drug repositioning is one of the common strategies of new indications and therapeutic targets for already known drugs. Drug repositioning is known by various names in textbooks such as drug re-proposing, re-profiling, re-tasking and therapeutic switching. Drugs may act through multiple molecular targets. Although perhaps designed for specificity, modulate several targets. This “Poly-pharmacology” may also be essential for efficacy. This “off-targets” may also lead to side-effect. Repositioning vs traditional drug discovery reduces time, reduces risk, and reduces cost. Bleeding disorder observation of aspirin (a wonder drug) over the years (1891) was made repeatedly leading to the suggestion by Craven (1953) that aspirin might be used for the prevention of thrombosis. The historically unintentional, serendipitous, or constrained research effort is now being replaced by systematic, high-throughput and rational pursuit of new therapeutic uses for marketed drugs, drugs in development, or as a drug salvaging strategy.

Keywords: Drug repositioning; Drug discovery; Polypharmacology

Introduction

Drug repositioning is defined as finding new indications and therapeutic targets for already known drugs. Recently, new indications have been found for many known drugs, therefore as a result we now have drugs that possess more than one indication. However there are other known drugs that have lost their old indications and are used for different aims ¹.

51 known drugs and vaccines with new indications and formulations consisted 30% of all sold drugs in 2009 which showed the importance of what we call drug repositioning ^{2,3}.

Drug repositioning is known by various names in textbooks and articles such as drug re-proposing, re-profiling, re-tasking and therapeutic switching.

The main reason of which scientists approach the strategy of drug repositioning is that, a drug can hit different targets and receptors in the same time or even it may activate different signaling pathways. The more the

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targets are identified, the more therapeutic aims and side effects are attributed to the old drugs.

History

In 1942 during the 2nd world war, many people suffered from typhoid disease in France. Marcell Johnson was the person who treated these patients with sulfonamide antibiotics, however the surprising side effect that he noticed was some of the patients who experienced a blood sugar drop and even few of them died after a hypoglycemic coma. Accordingly, following some complementary researches about this phenomenon in 1946, the sulfonamides were introduced as anti-diabetic medicine. Four years later in 1950, chlorpropamide and acetohexamide, the first ever anti-diabetic drugs from this family, were released to the markets ^{4,5}.

Advantages and Properties

Drug repositioning is one of the common strategies since the discovery of new indications for known drugs. This strategy has many benefits such as saving time. It is believed that a new drug needs approximately 4-9 years to be studied and synthesized while drug repositioning takes only 1 to 3.5 years to be reintroduced for new therapeutic purposes ⁶.

Another advantage is that we already know about old drugs' interactions and side effects which again help saving time when offering them for new therapeutic goals.

One of the most important advantages of drug repositioning is to cut down the cost of scientific and legal approval of a new drug from 1.8 to 0.3 billion dollars. So when a drug is patent to a pharmaceutical company, then there is no need to spend a lot of money for discovering and introducing a new medicine with similarities in therapeutic effect ⁷.

Orphan diseases involve a small group of people (less than 200,000 people nationwide) and usually there is a low demand for the medications used for them. Accordingly, drug companies do not give priority to spend money on researches for these kinds of drug. As a consequence, the microbial resistance against orphan infections is on increase which needs new forms of medication to overcome. In such a situation, new indications for known drugs through repositioning strategies can solve the problems. For example, recent studies have

discovered some anti-protozoa effects for tamoxifen, which is an estrogen receptor modulator so it can be used to cure *Leishmaniasis amazonensis* ^{2,8}.

Classification

Drug repositioning can be classified by its targets:

- 1) On target repositioning: Finding new indications for a known mechanism of a drug.
- 2) Off target repositioning: Finding new indications for a drug by studying its chemical structure, its target's structure (for example an antituberculosis effect of entacapone, which is an anti-parkinson drug) and molecular docking like finding anti-HIV effect for haloperidol.

There is another classification on the basis of the type of approaches used for drug repositioning including accidental and systemic approach.

Accidental approach: this is where a new indication is accidentally discovered for an old drug while it was being studied for a different purpose.

There are four ways which a drug can be repositioned by accident:

- 1) Serendipitously it can be found that a drug is effective for a different disease. This, for example happened for thalidomide.
- 2) Target dependent: just imagine that a protein's role in a disease is under investigation, but it is accidentally realized that a known drug additionally to its own indication, can affect this protein like everolimus.
- 3) Sometimes when a new pathway is found to play a role in development of a disease, researchers realize that there is a drug which is able to make an influence on that pathway like duloxetine.
- 4) Last but not least, a drug can be repurposed by its adverse effects like when we use the adverse effect of it as a way of treatment a different disease like sildenafil.

Important Examples for Drug Repositioning

1) Aspirin: In 1891 bleeding was a well known side effect of aspirin. Then studies on aspirin were continued until 1953 when it was suggested aspirin could be an effective medication against thrombosis. From 1973 to 1975 the complementary researches about the mechanism of action of aspirin on arachidonic acid were carried out, which introduced aspirin as one of the safest

and commonest drug for treatment or prevention of thrombosis⁹.

2) Sildenafil: Since the PhosphoDi Esterase (PDE) was discovered, sildenafil had been known as an inhibitor of PDE for treatment of angina and coronary artery diseases, however it failed to pass the second phase of its clinical trial. In 1980 studies which were being conducted on this drug suddenly shown its effects on erection, which finally in 1988 came up with sildenafil being approved by FDA for the treatment of erection problems in men.

3) Thalidomide: in 1975 thalidomide was introduced as a tranquilizer and sedative agent but soon after a teratogenic disaster (phocomelia in more than 10000 child in 46 country) happened that caused to recall it from the market. Then studies started to investigate the teratogenic side effects of thalidomide, however by accident researchers found some anti-cancer effect for it due to its anti-angiogenic impact on cancerous tissues. So thalidomide is now used for prostate cancer and multiple myeloma¹⁰.

4) Cyclosporine: cyclosporine was isolated from a fungus in 1957 and had been used as an anti-fungal drug for long time. However in 1976, Borel and his team discovered an immunosuppressive effect for it, which revolutionarily turned cyclosporine into a selective immune-regulatory drug which acts on lymphocytes¹¹.

5) Lithium: Lithium was first discovered by Weston when he was working on the petalite. Later in 1895 other studies revealed that lithium could dissolve urate stones in gout disease. Also William Homond observed an improvement in behaviors of mental patients when lithium was used for their gout condition. He first thought that it was a result of treating the gout encephalopathy, although later in 1950, the anti-maniac effect of lithium was registered by John Kidd who was an Australian psychologist¹².

6) Warfarin: this drug was first used as a pesticide agent however studies have shown that warfarin could be an anticoagulant drug if is used in a defined dosages.

Systematic Approach

Although repositioning was first seen within accidental approaches and during clinical observations, recently a

systemic strategy has been suggested for repositioning. There are two main screening policies in systemic approaches including experimental screening and insilico approach¹³.

Experimental Screening

Experimental studies are aimed to discover a novel drug or to repurpose a known drug for a new indication. As above mentioned, the adverse effects and safety of such drugs had already been measured, which is economically a substantial advantage. Experimental screening can be carried out in context of an evaluating study on a specific drug and its mechanism of action which in this case is called Target -Focused Screening Approach. Experimental screening may be a consequence of a screening study on a disease and its physiopathology that is called Phenotype Screening Approach. Usually the phenotype screening approach is more successful than the other one, as the signaling pathways are not considered in the study; however phenotype screening includes all part of the signaling pathways and cell behaviors.

Insilico Approach

Insilico approach means using different strategies to collect and analyse systemic data from various sources. For this purpose, bioinformatic and chemo-informatic analysis are hired to reach a precise and targeted drug repositioning.

In general, insilico repositioning process is consisted of three main steps which are connected to each other:

- 1) The aim: It is drug centric which means finding a new mechanism for a known drug and disease. This is all about finding a new drug for a known disease.
- 2) Common strategies: Using bioinformatics and chemo-informatic processes like molecular docking and studying the Structure-Activity Relationship (SAR)
- 3) Maintaining resources: Having a reliable information resource which renders capability of running all kinds of insilico repositioning processes¹³.

There are successful drug repositioning from Experimental Medical Research center of Tehran University of Medical Sciences. This centre carried out a study on Sumatriptan which is known for its controlling effect on migraine and cluster headaches. Complementary

studies by Dehpour *et al* on mechanism of action of Sumatriptan and its signaling pathways resulted in a new indication for the drug in treatment of pruritus¹⁴.

Drug Repositioning Challenges

Drug repositioning requires a deep understanding of biological mechanisms of drugs and also an organized and well targeted process which maintains this aim. Usually most articles related to drug repositioning are introducing successful repositioned drugs, but in reality this process faces loads of problems. For example administration of a new drug for a known disease may not have an economic benefit or the known adverse effects of a reformed drug may not let us use it in a new case of disease. On the other hand, this process should be done under legal conditions. Last

but not least, making the market ready for accepting an already known drug with a new indication is another challenge for drug repositioning.

Conclusion

We can conclude that reevaluation of old drugs has many advantages in educational, research and clinical fields. Furthermore it is cost effective to repurpose a drug for new indications. Although there are many ways for drug repositioning, we believe that insilico approach is the most useful one. We also suggest that research centers, universities and pharmaceutical companies must define encouraging policies for drug repositioning studies; as there are definitely a vast spectrum of new indications for the known drugs being in the market.

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