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REVIEW ARTICLE

An Overview of Drug Repurposing

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Abstract: Drug repurposing, also known as drug repositioning or reprofiling, entails identifying new therapeutic indications for existing drugs that have already gained regulatory approval for treating other diseases or conditions. Rather than developing entirely new chemical entities, researchers explore the potential uses of approved drugs against different ailments through drug repurposing. This approach provides several advantages over traditional drug development such as lower discovery and development costs, shorter timelines to approval, and an established safety profile of the repurposed drug. A key benefit of drug repurposing stems from the extensive clinical and regulatory knowledge accumulated on the active pharmaceutical ingredient's safety, pharmacokinetics, dosing, quality characteristics, and manufacturing process during its original development. Leveraging this existing knowledge can substantially reduce the overall risks and costs associated with bringing a new drug to market. Drug repurposing also enables the rapid clinical translation of basic biological research findings. It represents a valuable strategy for addressing therapeutic gaps, particularly for rare and neglected diseases with limited research attention from the pharmaceutical industry. While drug repurposing holds promise in expediting drug development, it also faces unique scientific and technical challenges. These include identifying suitable new indications, understanding unknown mechanisms of action against new targets or pathways, establishing efficacy through clinical trials, and addressing intellectual property issues. This review aims to provide a comprehensive overview of the drug repurposing approach, analyze its key benefits and limitations, and discuss ongoing efforts to systematically advance this paradigm shift in drug discovery.

Keywords: Repurposing; Drug discovery; Clinical trials; Regulatory bodies; Safety profile

1. Introduction

Drug repurposing (repositioning) has emerged as an attractive drug development strategy to reduce the lengthy and expensive process of new drug discovery and development. The rising research and development (R&D) expenditures, declining new molecular entity approvals, and increasing generic competition have led biopharmaceutical companies to explore alternative approaches to replenish their pipelines and extract further value from approved drugs. Drug repurposing involves identifying new therapeutic uses for approved drugs outside of their original indication. This allows bypassing the early stages of drug development, thereby significantly shortening development timeline and reducing costs. Drug repurposing is especially valuable for patients with rare, complex or chronic conditions that lack adequate treatment options. By providing accelerated access to potentially effective therapies, drug repositioning complements the therapeutic stratification process. With the availability of pharmacological and toxicological profiles for approved drugs, the development cycle can be reduced by 3-12 years compared to new chemical entities. Hence, many pharmaceutical companies are now actively employing drug repurposing approaches to reinvigorate certain approved drugs as novel therapies for a wide range of diseases [1,2]. There are three main categories of drugs that hold potential for repurposing: (i) Generic drugs: These are approved drugs whose patent protection has expired, allowing wider access for research into new indications. (ii) Failed drugs: These refer to drugs that reached clinical development but failed at some stage and are no longer being actively pursued or marketed. Repurposing could rescue these assets and (iii) Patented drugs: These include both currently approved drugs still under patent protection as well as pipeline drugs in late-stage clinical development that remain proprietary. Repurposing efforts for patented drugs are typically driven by the innovator companies that have commercial interests. This review summarizes current approaches for systematic drug repurposing along with case studies demonstrating successful examples. Current drug repurposing strategies include computational and experimental methods leveraging drug-disease associations, drug similarity relationships, and biological pathway analyses [3,4]. However, drug repurposing faces several challenges such as limited in vitro and animal models, inadequate funding and resources, as well as intellectual property constraints. Further research and collaborative efforts between academia and industry can help address these limitations to fully harness the potential of drug repurposing.

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A key advantage of repurposed drugs is that they have an established safety profile based on prior clinical trials, typically Phase I or Phase II studies, that were conducted for regulatory approval of their initial indication [5]. Historically, drug repurposing originated from serendipitous or limited observations of off-target effects. For example, onabotulinumtoxinA (BOTOX®; Allergan Inc.) was incidentally found to have therapeutic benefits across eight approved indications beyond its originally approved use [6]. However, many pharmaceutical and biotechnology companies now take a more systematic approach by leveraging knowledge of mechanisms of action (MoAs) to intentionally identify potential new uses of approved drugs, often as part of life cycle management (LCM) strategies to prolong patent exclusivity. For instance, the anti-TNF agent infliximab was repurposed from Crohn's disease to rheumatoid arthritis and ulcerative colitis based on its immunomodulatory MoA [7]. In some cases, mechanistic insights have enabled repurposing into entirely new disease areas, as exemplified by the failed cancer drug zidovudine for HIV and mycophenolate mofetil for lupus nephritis [8,9]. The productivity challenges with conventional drug discovery, coupled with major repurposing successes like sildenafil, duloxetine and thalidomide, have reinvigorated interest in systematic drug repurposing (DR) to complement traditional pipelines [10-12]. Many computational strategies leveraging bioinformatics resources with drug-disease associations, drug similarity relationships and biological pathway data have emerged to enable high-throughput, evidence-based drug repurposing [13]. Advances in biomedical text mining have also been critical for extracting relationships between biomedical concepts across the scientific literature, even when not explicitly stated in the same article. By connecting information on genes, drugs, diseases and more, text mining facilitates development of drug repurposing hypotheses [14].

1.1. Advantages of drug repurposing

A key advantage of drug repurposing is that approved and many failed drugs have already undergone testing in humans, providing extensive data on pharmacology, dosing, toxicity, and formulation. Compared to conventional drug discovery, drug repurposing offers benefits including:

- Substantially lower research and development (R&D) costs by leveraging existing data.
- Shortened development timeline, often bypassing the need for Phase I trials to establish safety in humans given available clinical data.
- Potential for rescue despite previous adverse effects or failed efficacy for some indications, as risks and clinical outcomes can vary across different patient populations and diseases.

Additional benefits are faster enrollment into later-stage trials by focusing on approved drugs, higher likelihood of approval success building on existing clinical data, and reduced commercialization barriers given established manufacturing and distribution processes. By accelerating access to safe, effective therapies, drug repurposing provides value to patients, healthcare systems, as well as drug development stakeholders. However, demonstrating clinical efficacy through rigorous, indication-specific repurposing trials remains essential.

1.2. Disadvantages of drug repurposing

1.2.1. Dosing, safety and pharmacokinetics

Drugs are only approved after demonstrating clear therapeutic benefits within well-defined safety margins regarding dosing levels, formulation and route of administration. Uncertainties may arise when repurposing a drug for a new indication, as the suitable dose and delivery method targeting the focal disease region may differ. Close collaboration with toxicologists and pharmaceutical scientists is needed to establish new dosage regimens that maintain the established safety profile.

1.2.2. Engagement with other disciplines

Drug repurposing efforts require a multidisciplinary approach involving not just clinical researchers but also regulatory experts, data scientists, pharmacologists and others to fully address challenges spanning discovery, clinical development and intellectual property. Insufficient integration across disciplines can hamper progress.

1.2.3. Intellectual property considerations

The original patents covering an approved drug's use may have expired, but repurposing it for new indications raises novel intellectual property questions that need astute navigation to avoid obscuring patentability and commercialization prospects.

2. Drug repurposing for rare diseases

There is an urgent, unmet need for effective therapies for rare diseases, of which only 5% of over 8,000 identified disorders have approved treatments [14]. Most rare diseases are life-threatening, highlighting the critical urgency of this situation. Both discovering new chemical entities and repurposing existing approved drugs by elucidating novel disease pathways could help expedite treatment development for these patient populations with no other options. Notably, around 2,800 drug candidates and over 4,000 compounds

were ultimately discontinued during Phase II trials, representing a vast repertoire of potential therapeutics to rescue for rare diseases [15]. When initiating clinical trials for a repurposed drug in a new indication, development costs can be substantially reduced compared to new chemical entities. For example, a trial examining the efficacy of the unapproved drug levoketoconazole required around 90 participants, whereas repurposing the emergency contraceptive mifepristone for Cushing's syndrome needed fewer than 30 patients [16]. Such smaller trial populations are especially impactful for ultra-rare disorders. While drug repurposing offers advantages like reduced costs and shortened timelines compared to de novo drug development, it can also be expensive, time-consuming and risky with no guarantee of success [17]. Moreover, there are regulatory and intellectual property constraints that must be considered. However, with continued progress in addressing these challenges, drug repurposing remains a promising strategy to deliver effective therapies for untreated rare diseases.

2.1. Glioblastoma (GBM) therapy

Glioblastoma (GBM) is the most common and lethal primary malignant brain tumor in adults, with a median survival of approximately 15 months post-diagnosis [18]. Conventional drug development approaches are hampered by high costs and low success rates. Drug repurposing represents a faster, more affordable pathway for identifying potential new treatments. Numerous agents have shown preclinical efficacy against GBM models in human cell lines, animal models, and early phase trials, though significant testing is still needed. These preliminarily effective repurposed drugs span multiple original indications and mechanisms of action, demonstrating the promise of casting a wide net. While many repurposed candidates remain early in the pipeline, the results suggest drug repurposing could yield cost-effective therapies to incorporate into multimodal treatment strategies against this devastating cancer. Rigorously testing the most promising agents in randomized placebo-controlled GBM trials, including in specific molecular subgroups, is warranted to determine if the preclinical findings translate into meaningful clinical outcomes and survival gains. If borne out in further studies, drug repurposing may offer renewal hope for progress against this disease [19].

2.2. Rapamycin in SARS CoV-2 infection

Remdesivir is the only currently approved antiviral for treatment of COVID-19, though its efficacy remains uncertain. As a result, the World Health Organization's latest guidelines (November 2020) advise against routine use of remdesivir for COVID-19 [20]. With uncertainties around both antivirals and vaccines, drug repurposing has emerged as a strategy to identify additional effective therapies, with the mTOR inhibitor rapamycin representing one candidate. This review comprehensively summarizes the available literature on rapamycin and COVID-19 infection. Broadly, repurposed drugs under investigation for COVID-19 either directly target components of SARS-CoV-2 or modulate host immune pathways [21]. Rapamycin has been used clinically for decades since its 1999 FDA approval as an immunosuppressant to prevent organ transplant rejection. Additionally, semi-synthetic rapamycin analogs or "rapalogs" with improved pharmacology, like everolimus and temsirolimus, have been developed and used in cancer treatment based on rapamycin's anti-proliferative effects elucidated in the 1990s [22-24]. As a host-directed therapy, rapamycin may have advantages over conventional antivirals for COVID-19 treatment, including reduced susceptibility to loss of efficacy from viral mutation. Ongoing clinical trials evaluating rapamycin for COVID-19 are anticipated to determine whether it represents an effective repurposed therapeutic against this global threat

3. Examples of successful repurposed drugs

The continued discovery of new mechanisms of action and uses for existing compounds highlights the power and potential of systematic drug repurposing efforts. Following are some examples of successfully repurposed drugs

3.1. Aspirin

Aspirin was originally marketed by Bayer in 1899 as an analgesic and antipyretic. It was later repurposed in the 1980s for its antiplatelet effects at low doses to prevent cardiovascular disease. Aspirin irreversibly inhibits platelet cyclooxygenase-1 (COX-1), suppressing thromboxane A2 production and platelet aggregation [25].

3.2. Sildenafil

Sildenafil was originally developed by Pfizer for hypertension and angina pectoris. It was later repurposed to treat erectile dysfunction, driven by Pfizer's drug rescue efforts [26].

3.3. Thalidomide

Thalidomide was used as a sedative in the 1950s before being withdrawn due to teratogenicity. It was later repurposed to treat erythema nodosum leprosum and multiple myeloma [27].

3.4. Azidothymidine (AZT)

AZT failed as an anticancer agent but was successfully repurposed in the 1980s as one of the first antiretroviral drugs for HIV/AIDS.

3.5. Disulfiram

Disulfiram was used to treat alcoholism before more recent repurposing for cancers like glioblastoma, prostate cancer and melanoma.

3.6. Methotrexate

The chemotherapy drug methotrexate was repurposed for autoimmune diseases such as rheumatoid arthritis and has revolutionized treatment.

3.7. Minoxidil

Minoxidil was an antihypertensive that was repurposed as a hair growth stimulant to treat baldness.

4. Repurposing approaches

There are two main approaches for systematic drug repurposing: experimental screening and computational (in silico) methods. Integrating evidence from both experimental and computational strategies, the likelihood of discovering successful repurposing opportunities can be greatly increased

4.1. Experimental screening approaches

Experimental screening can uncover both novel drug candidates and opportunities for repurposing existing compounds. However, the application and outcomes differ significantly between these contexts. Screens for novel drug discovery involve testing large libraries with millions of compounds, requiring specialized high-throughput screening (HTS) infrastructure and substantial resource investments. In contrast, repurposing screens focus on more advanced or approved compounds with established safety and pharmacology. This enables screening of smaller, more targeted libraries typically containing 500-2,000 compounds. These include both approved drugs as well as failed agents that did not progress further in development [27]

4.2. Computational approaches

4.2.1. Molecular approaches

Leverage understanding of molecular mechanisms of disease pathophysiology and drug activity, powered by large-scale genomic, transcriptomic and other omic data. These facilitate analysis of drug targets, chemical structures and potential disease linkages.

4.2.2. Real world data (RWD) approaches

Discern unknown associations between drugs and diseases/symptoms directly from analysis of clinical, insurance claims and other real-world health data. This data-driven strategy can reveal unexpected and novel drug repurposing hypotheses [28]

5. Challenges for repurposing drugs

While interest in drug repurposing has grown, fewer repurposed therapies have emerged compared to expectations, constrained by several implementation barriers. As repurposing lacks defined regulatory guidelines, startup companies may struggle to compile necessary data for submission to authorities [29]. Additionally, intellectual property and market exclusivity protections that enable commercialization, through patents and the Orphan Drug Act, may not be readily accessible for a repurposed drug with a new indication [30-31]. On top of scientific difficulties in identifying and validating high potential repurposing candidates, creating viable commercialization strategies is key to successfully bringing a repurposed product to patients. Pharmaceutical companies need to justify investments into clinical development and approval for a new use, despite potentially shorter timelines than de novo discovery [32]. Efficacy must still be demonstrated in rigorous clinical trials in the specific repurposed indication. Other noted obstacles include limited funding and resources, inadequate predictive disease models to enable efficient candidate screening, fragmented information on drug mechanism of actions and indications, as well as alignment challenges across academia and industry [33]. Concerted efforts to address these limitations through public-private partnerships, improved data sharing, legislative initiatives and updated intellectual property policies could further unlock the promise of drug repurposing

6. Conclusion

In conclusion, drug repurposing holds much promise as a complementary approach to traditional drug development in addressing the growing healthcare needs of society. Over the past decade, there have been numerous successful examples of repurposed drugs receiving approval for new therapeutic indications. However, the field is also facing considerable challenges that require a holistic and multidisciplinary research context to overcome. While the potential advantages of leveraging existing clinical knowledge and

safety data are immense, uncertainties regarding optimal dosing and formulation for new disease contexts as well as intricate intellectual property issues threaten to impede broader realization of such initiatives. A lack of integrated efforts between clinical, regulatory and industrial stakeholders also increases the risks. Going forward, more ambitious global collaborations are needed to establish standardized drug repurposing frameworks and platforms. This includes developing unified regulatory pathways, clinical trial networks and transparent clinical databases allowing precompetitive data sharing. Artificial intelligence and systems approaches also hold potential to help systematically screen large compound libraries and identify novel indications. If these challenges are addressed diligently through holistic research and comprehensive knowledge transfer between diversified partners, drug repurposing promises to significantly enhance productivity in drug discovery. This could help lower drug development costs and times while expanding therapeutic options globally. With continued research progress and refining of best practices, repurposed drugs may play an enlarged role in bringing effective treatments to patients worldwide.

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