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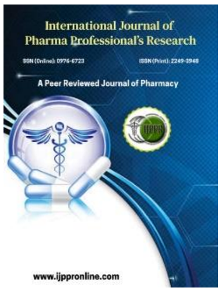

Drug Repurposing: A strategic approach to addressing unmet medical needs

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ABSTRACT: Drug repurposing, also known as drug repositioning or drug reprofiling, is gaining prominence as a strategic approach to addressing unmet medical needs. This review article explores the concept of drug repurposing, its significance in the pharmaceutical industry, and various strategies employed in identifying new therapeutic indications for existing drugs. Challenges in traditional drug discovery, such as high costs and low success rates, underscore the importance of repurposing existing drugs. Through computational and experimental approaches, along with clinical observation and serendipity, drug repurposing offers advantages including reduced time and cost of development, utilization of existing safety profiles, and potential for rapid clinical translation. Successful examples such as aspirin, thalidomide, and Viagra demonstrate the efficacy of this approach. Current trends and future directions, including integration of omics data and collaboration across sectors, highlight the evolving landscape of drug repurposing as a key strategy in addressing unmet medical needs.

1. Introduction

Drug repurposing, also known as drug repositioning, refers to the process of identifying new therapeutic uses for existing drugs that have already been approved or studied but not brought to market. This strategy involves investigating new indications for drugs that may have been shelved, abandoned, discontinued, or deprioritized for various reasons.[1] The terms used interchangeably with drug repurposing include repositioning, reprofiling, rescue, and re-tasking. It is a method that aims to find new therapeutic applications for compounds that have already undergone testing, potentially reducing the time, cost, and risk associated with traditional drug discovery processes. The concept of drug repurposing has gained traction due to its potential to repurpose existing drugs for different diseases, offering a more efficient and cost-effective approach to drug development.[2,3]

1.1 Importance in addressing unmet medical needs

Drug repurposing, or the process of identifying new therapeutic uses for existing drugs, plays a significant role in addressing unmet medical needs, particularly for rare and neglected diseases. The strategy offers several advantages over traditional drug discovery, including reduced time and cost, access to well-characterized safety profiles, and the potential for new treatments for conditions that lack licensed therapies.[4]

One of the primary benefits of drug repurposing is its ability to expedite the development of treatments for rare and neglected diseases, where there is often a lack of licensed treatments or cures. For instance, repurposing offers a viable alternative to new drug discovery when candidates that have proven safe in either preclinical or clinical phases are available.[5]

Drug repurposing can also provide new avenues of hope for patients living with untreated or difficult-to-treat conditions, particularly in the context of rare and neglected diseases. This is evident during health emergencies, where drug repurposing can quickly identify potential treatments, as demonstrated by the use of Remdesivir and Dexamethasone during the COVID-19 pandemic.[2,6,7]

Furthermore, drug repurposing can offer considerable time and cost savings compared to traditional development, with repurposed drugs generally approved sooner (3-12 years) and at reduced (50-60%) cost. [8,9]

Additionally, while approximately 10% of new drug applications gain market approval, approximately 30% of repurposed drugs are approved, giving companies a market-driven incentive to repurpose existing assets. In the context of rare diseases, repurposing holds substantial promise. For example, approximately 20% of the approved orphan drugs in Europe between 2000 and 2021 were repurposed drugs. The REMEDi4ALL initiative, an EU-funded research project, aims to create a sustainable and efficient research ecosystem that facilitates fast and cost-effective drug repurposing, with a focus on patient-centric approaches.[10,11]

2. Challenges in Drug Discovery

The challenges in drug discovery highlighted in the provided sources include

- **High cost and time-consuming process**

Drug development is a costly and lengthy enterprise, with the average time to bring a drug to market ranging from 10 to 15 years and an average cost of $2 billion. Pharmaceutical companies spend significant amounts on research and development, with costs estimated at $6 billion per new drug despite a 6% annual increase in R&D spending. The entire procedure of drug discovery is described as complicated, time-consuming, expensive, and financially risky.[9,12]

- **Low success rates in traditional drug development**
- Only a small percentage of drug development programs result in licensed drugs, with approximately 4% of programs leading to successful outcomes. For biologics, such as protein-based drugs, monoclonal antibodies, and vaccines, the success rate in clinical trials is even lower, with fewer than 10% of programs succeeding. This low success rate contributes to the high costs associated with drug development.[13,14]

Figure 1: Challenges in Drug Discovery

3. Concept of Drug Repurposing

The concept of drug repurposing involves several key aspects as outlined in the provided sources:

- **Reutilization of existing drugs for new indications**

Drug repurposing, also known as drug repositioning, refers to the process of identifying new therapeutic uses for existing drugs that have already been approved or studied but not brought to market. This strategy involves investigating new indications for drugs that may have been shelved, abandoned, discontinued, or deprioritized for various reasons.[15]

- **Exploiting known safety profiles and pharmacokinetics**

Drug repurposing leverages the established safety profiles and pharmacokinetics of existing drugs to explore new therapeutic applications. By utilizing compounds that have already undergone testing, drug repurposing can potentially reduce the time, cost, and risk associated with traditional drug discovery processes.[16]

- **Accelerating the drug development process**

Drug repurposing offers a more efficient and expedited approach to drug development by repurposing existing drugs for new indications. This strategy can lead to faster identification of potential treatments, reduced development timelines, and increased success rates compared to traditional drug discovery methods.[17,18]

4. Strategies in Drug Repurposing

Drug repurposing, or the process of identifying new therapeutic uses for existing drugs, employs various strategies to facilitate the discovery of new indications for approved or abandoned drugs. These strategies can be broadly categorized into computational approaches, genomic approaches, high-throughput screening technologies, and literature-based approaches.[19]

4.1 Computational approaches

These strategies involve the use of advanced computational techniques to identify potential drug candidates for repurposing. They can be further divided into several categories:

- **Bioinformatics and data mining**

Bioinformatics and data mining techniques are used to analyze large datasets to identify potential drug candidates. These methods can involve the use of machine learning algorithms, network analysis, and other computational tools to identify patterns and relationships in the data.[20]

- **Network pharmacology**

Network pharmacology is a computational approach that involves the use of network analysis to identify potential drug candidates. This method involves constructing networks based on the shared chemical features of drugs and then analyzing these networks to identify potential drug candidates.[21]

- **Virtual screening**

Virtual screening is a computational approach that involves the use of computer simulations to identify potential drug candidates. This method involves simulating the interactions between drugs and their targets to identify potential drug candidates that may have therapeutic potential.[22]

4.2 Experimental approaches

Experimental approaches in drug repurposing are crucial for identifying new therapeutic uses for existing drugs. These approaches include high-throughput screening, drug-target interaction studies, and phenotypic screening.

- **High-throughput screening**

This approach involves the use of automated systems to screen large libraries of compounds for potential drug candidates. High-throughput screening can be used to identify drugs with specific biological activities, such as enzyme inhibition or receptor binding.[23]

- **Drug-target interaction studies**

Drug-target interaction studies involve the examination of the interactions between drugs and their molecular targets, such as proteins or genes. These studies can be used to identify new drug candidates or to optimize existing drugs by improving their binding affinity or selectivity for their targets.[24]

- **Phenotypic screening**

Phenotypic screening involves the use of cell-based or animal-based models to identify drugs that produce specific biological effects. This approach can be used to identify drugs that have therapeutic potential for a wide range of diseases, including rare and neglected diseases.[25]

4.3 Clinical observation and serendipity

Clinical observation and serendipity are important strategies in drug repurposing, which involves the reutilization of existing drugs for new indications, exploiting known safety profiles and pharmacokinetics, and accelerating the drug development process. These strategies include case studies and anecdotal evidence, as well as observations from clinical trials and patient data.

- **Case studies** and anecdotal evidence have played a significant role in the discovery of new therapeutic uses for existing drugs. For example, the use of thalidomide for erythema leprosum nodosum was based on serendipity, while the discovery of the use of sildenafil for erectile dysfunction was based on observations of its side effects in clinical trials for hypertension.[26,27]
- **Observations from clinical trials and patient data** can also be used to identify new therapeutic uses for existing drugs. For example, a series of clinical trials of increasing size and power can be used to validate serendipitous clinical findings and underpin new uses of existing drugs for new indications. Additionally, retrospective analysis of patient data can be used to discover new uses for existing drugs, as well as to validate outputs from more systematic approaches to drug repurposing.[28]

5. Advantages of drug repurposing include

5.1 Reduced time and cost of drug development

Drug repurposing can significantly cut research and development (R&D) costs and reduce the drug development timeline. This is because approved medicines and several discarded compounds have already demonstrated safety in humans, eliminating the need for Phase 1 clinical trials. Additionally, the potential for reuse despite evidence of adverse effects and failed efficacy in some indications can further reduce costs and timelines.[29]

5.2 Utilization of existing safety and toxicity data

Existing drugs that are either approved or be safe in late-stage trials can leverage their inherently reduced development risk into potentially new indications. This is because safety accounts for approximately 30% of drug failures in clinical trials, giving repurposed drugs a significant development advantage in terms of safety.[30]

5.3 Potential for rapid clinical translation

Drug repurposing can offer new avenues of hope for patients living with untreated or difficult-to-treat conditions, especially rare and neglected diseases. It can also provide a rapid response to emerging needs, as demonstrated during the COVID-19 pandemic, where several drugs were repurposed under emergency authorization to reduce virus replication and mortality in hospitalized patients requiring ventilation.[31]

5.4 New treatments for rare diseases

Drug repurposing offers a viable alternative to new drug discovery when candidates that have proven safe in either preclinical or clinical phases are available. This is particularly important for rare and neglected diseases, where there is often a lack of licensed treatments or cures.[32]

5.5 Sales potential and lower development costs

Repurposed drugs can generate 25% to 40% of annual pharmaceutical revenues, and the overall development costs are estimated to be 50-60% lower than those for developing a novel drug. This is because approved medicines and many discarded compounds have already been tested in humans, providing comprehensive information on dose, possible toxicity, and formulation.[33]

5.6 Higher approval rates

Repurposed drugs have a higher approval rate compared to new drug applications, with approximately 30% of repurposed drugs being approved, compared to only 10% of new drug applications. This is because repurposed drugs have already demonstrated safety and efficacy in humans, reducing the risk of failure in clinical trials.[34]

5.7 Already approved medicines

Repurposed drugs are already approved medicines, which means they can be quickly and easily made available to patients. This is particularly important during health emergencies, where a rapid response is needed to treat patients.[35]

5.8 Reduced development timelines

Drug repurposing can reduce development timelines by an average of 5-7 years, allowing new treatments to be made available to patients more quickly.

5.9 Lower risk

Drug repurposing is often less risky than developing a novel drug, as the safety and efficacy of the drug have already been demonstrated in humans. This reduces the risk of failure in clinical trials and increases the likelihood of regulatory approval.[36]

5.10 Polypharmacology

Drug repurposing can identify beneficial off-target effects of existing drugs, particularly if the disease pathology is complex. Systems biology linked with polypharmacological assessments are currently being used to identify these beneficial off-target effects.[37]

Figure 2: Advantages of drug repurposing

6. Examples of Successful Drug Repurposing

- **Aspirin**

Originally developed as a pain reliever, aspirin has been repurposed for cardiovascular protection.

Studies have shown its efficacy in reducing the risk of heart attacks and strokes by inhibiting platelet aggregation and reducing inflammation.[38]

- **Thalidomide**

Initially marketed as a treatment for morning sickness in pregnant women, thalidomide was withdrawn due to its teratogenic effects. However, it has been successfully repurposed for the treatment of multiple myeloma, a type of blood cancer. Thalidomide and its derivatives have shown antiangiogenic and immunomodulatory properties, making them effective in treating this disease.[39]

- **Viagra (Sildenafil)**

Originally developed as a treatment for angina, Viagra was repurposed for the treatment of erectile dysfunction (ED). Its mechanism of action, inhibition of phosphodiesterase type 5 (PDE5), was found to enhance erectile function by increasing blood flow to the penis. Viagra revolutionized the treatment of ED and became one of the most widely prescribed medications worldwide.[40]

7. Current Trends and Future Directions

Drug repurposing, also known as drug repositioning, is an evolving strategy in contemporary drug discovery that aims to find new therapeutic uses for existing drugs. Several trends and future directions are shaping the landscape of drug repurposing, including the integration of omics data, the use of artificial intelligence and machine learning, and enhanced collaboration between academia, industry, and regulatory bodies.[41]

- **Integration of Omics Data in Drug Repurposing**

The integration of omics data, such as genomics, transcriptomics, and proteomics, plays a crucial role in identifying new drug targets and mechanisms of action. By leveraging large-scale omics datasets, researchers can uncover novel drug-disease associations and predict drug efficacy more accurately. This integration allows for a deeper understanding of drug interactions at the molecular level, leading to more precise and effective drug repurposing strategies.[42]

- **Use of Artificial Intelligence and Machine Learning**

Artificial intelligence (AI) and machine learning are revolutionizing drug repurposing by enabling the analysis of vast amounts of data to identify potential drug candidates and predict their efficacy. These technologies can analyze complex biological data, predict drug-target interactions, and optimize drug repurposing strategies. AI-driven approaches enhance the efficiency and accuracy of drug repurposing efforts, accelerating the discovery of new therapeutic uses for existing drugs.[43]

- **Collaboration between Academia, Industry, and Regulatory Bodies**

Collaboration between academia, industry, and regulatory bodies is essential for advancing drug repurposing initiatives. Academic institutions contribute expertise in basic research and data analysis, while industry partners provide resources for drug development and commercialization. Regulatory bodies play a crucial role in ensuring compliance with safety and efficacy standards. Collaborative efforts facilitate the translation of research findings into clinical applications, driving innovation and expanding the repertoire of repurposed drugs available to patients.[44]

8. Conclusion

Drug repurposing emerges as a viable and strategic approach for addressing unmet medical needs. By repurposing existing drugs for new therapeutic indications, this approach offers several advantages, including reduced development timelines, lower costs, and utilization of existing safety profiles. Successful examples such as aspirin, thalidomide, and Viagra underscore the potential of drug repurposing to transform healthcare and improve patient outcomes. However, continued research and investment in this field are essential to fully realize its potential. Collaborative efforts between academia, industry, and regulatory bodies are needed to identify new repurposing opportunities, validate findings, and navigate regulatory pathways. Integration of emerging technologies, such as omics data and artificial intelligence, can further enhance the efficiency and success of drug repurposing efforts. In summary, drug repurposing holds promise as a strategic solution to address the challenges of traditional drug discovery and meet the evolving healthcare needs of patients. Continued commitment to research and innovation in this field will be crucial for advancing medical science and improving global health outcomes.

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