Mini Review

Why Drug Repurposing (or Drug Repositioning) Fails to Live up to the Promise of Cost-Effective and Time-Effective New Drug Approvals?

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ABSTRACT

Drug Repurposing is often cited as an efficient and effective way to achieve approval of new therapeutics. There are however, many challenges with this approach. The content of this Mini Review is a summary of a recent publication entitled Drug Repurposing: Misconceptions, Challenges and Opportunities Facing Academic Researchers.

This Mini Review attempts to highlight some of the key issues that are frequently ignored or overlooked, which explains why many drugs that are proposed for repurposing fail to achieve the ultimate goal of a new regulatory label, or a data set that is sufficiently compelling to justify a drug's use in a new indication.

Key Words: Drug Repurposing, Dose, Pharmaco-Dynamic, Pharmaco-Kinetic

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INTRODUCTION

"Drug-repurposing" or "Drug-repositioning" is frequently promoted as a cost-effective and time-effective mechanism to generate new drugs [1-4]. Intuitively this seems a rational approach which is supported by the occasional and often striking examples of success. However, when considering drug-repurposing, there often appears to be inadequate consideration of the many drugs proposed for repurposing that fail to achieve the ultimate goal: the generation of sufficient data to achieve regulatory approval or sufficient data to justify the "off-label" use of the drug in the new indication. Without achieving these goals, the drug-repurposing effort is futile.

As a result of the inherent challenges involved in drug-repurposing there are many more failures than successes, which has led to the conclusion that drug-repurposing efforts are no more likely to achieve a successful outcome than "traditional" (or *de-novo*) drug discovery/development [5,6].

LITERATURE REVIEW

The key elements for successful drug development are common to both *de-novo* drug discovery/development and to drug-repurposing. Some important aspects however are unique to drug repurposing and are frequently overlooked. This is particularly so for drug-repurposing efforts undertaken by well-intentioned academic groups but with insufficient resources and expertise in driving drug-repurposing programs to their successful conclusion [5].

The challenges that are typically overlooked include:

A clear understanding of the clinical and commercial environment that determines whether the proposed clinical program will generate a drug that will ultimately satisfy an unmet medical need.

The dose and schedule of the drug in the first indication is very likely to be quite unrelated to the dose and schedule required to achieve target-coverage and the desired Pharmaco-Kinetic (PK e.g drug half-life) and Pharmaco-Dynamic (PD e.g. evidence of pathway inhibition) effects necessary in the repurposed indication. It may, in fact, be necessary to repeat preclinical efficacy and safety/toxicity studies with doses and schedules relevant in the new indication to demonstrate both safety and efficacy. Similarly additional phase 1 clinical studies may be required to confirm the relevant PK/PD relationship in the new indication.

The importance of obtaining clinical-grade material for administration to patient should not be overlooked. Drug supply and generation of clinical-grade material is an expensive and highly-regulated process.

Clinical equipoise provides the ethical underpinning for human clinical trials and is frequently overlooked during considerations of drug-repurposing. This critical consideration has multiple dimensions [5,7]. Clinical equipoise is clearly important at the level of each individual subject or patient, but is also important in terms of the design and execution of each clinical study. Many individuals/patients participate in clinical studies believing that, even if there is little or no personal benefit, their contribution will benefit others. Clinical equipoise therefore requires that the clinical studies provide an important, clear conclusion which has the potential to change the practice of medicine. It is unethical to submit individuals/patients to a clinical study if the question under study has already been compellingly answered. If the clinical study itself cannot provide a compelling answer, the study should at least provide the foundation for the next clinical study that can provide a definite conclusion to an important question.

Additional elements related to clinical equipoise involve, for example, the ethical considerations related to with-holding (or perhaps not even offering) a patient an effective standard of care therapy while proposing instead a repurposed drug for which there may be little data supporting its use in the new indication, or little or no data demonstrating that it is equivalent to the accepted standard of care therapeutic.

Clinical equipoise is not met if the proposed clinical study cannot answer the question that is being posed-this might be because of insufficient power, poor clinical trial design, or poor execution.

Equally the ethics of a clinical program are suspect if upon completion of the study, there is no path forward. That would be the case if there was no way to attract sufficient funding to complete a registration-quality clinical study to provide a definitive answer. In that situation, the prior studies were futile and the involvement of well-intentioned individuals/patients was wasted.

Equally, the clinical study would be unethical if, upon completion, the answer obtained was trivial, and of insufficient interest or importance to impact clinical behaviour. In such a case, that should have been known from the outset and the clinical study should never have been undertaken.

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Intellectual Property (IP) considerations are critical in drug repurposing efforts. It can be wrong to assume that the entity owning the molecule being assessed for repurposing will be supportive of drug repurposing efforts. The owner may have ultimate control of the process. It is therefore important to understand the issues related to IP at the outset of the program and to engage with the owner of the drug at the earliest opportunity.

The requirement for sufficient evidence to attract the necessary funds for completion of clinical programs to achieve the ultimate goal. This typically involves the generation of new Intellectual Property (IP). However, while the generation of new IP is certainly attractive and important to potential investors, often what might superficially appear to be new IP has often already been captured by the innovator company that first developed the drug? The lack of sufficient funds to complete a clinical program often results in the publication of preliminary clinical reports that are underpowered and insufficient to alter clinical behaviour. As such, these reports only serve to expand the CV of the researchers.

A consideration of the clinical and regulatory development path to generate clinical data supporting the drug in the repurposed indication. This might involve large phase 3 clinical studies that directly compare the repurposed drug with the existing standard of care, with a requirement to show equivalence or superiority over the existing agents.

For deadly diseases, drug repositioning is a "universal strategy" because: 1) a reduced number of required clinical trial steps could reduce the time and costs for the medicine to reach market; 2) existing pharmaceutical supply chains could facilitate "formulation and distribution" of the drug; 3) the known possibility of combining with other drugs could allow for more effective treatment; and 4) The repositioning may make it easier to find "novel mechanisms of action" for ancient people.".

Breakthroughs in human genomes, network biology, and chemoproteomics have all aided drug repurposing. It's sometimes referred to as a serendipitous process, in which repurposable drugs are discovered by chance. It's now possible to find promising repurposing candidates by looking for genes implicated in a certain disease and determining if they interact with other genes in the cell that are known drug targets. According to studies, medications that target human genetic targets are twice as likely to succeed as all other drugs in development. Because it can be a time and cost effective strategy for treating dreadful diseases like cancer, drug repurposing is being employed as a solution-finding technique to combat the COVID-19 pandemic.

There have been a number of successes, the most notable of which being sildenafil (Viagra) for erectile dysfunction and pulmonary hypertension, as well as thalidomide for leprosy and multiple myelomas. Posaconazole and ravuconazole have been tested in clinical studies for Chagas disease. Clotrimazole and ketoconazole, two more antifungal drugs, have been studied for anti-trypanosome therapy. Antimicrobial repositioning has resulted in the development of broad-spectrum medicines that are effective against a variety of infections. Repurposed medications are emerging as viable choices for treating severe mental illnesses in psychiatry.

As a result of these under-appreciated challenges, drug-repurposing typically fails to fulfil its promise. There are multiple examples of drugs proposed for repurposing that have failed to demonstrate any success and prominent among them is the diabetes therapy, metformin. Metformin has >25,000 publications suggesting therapeutic potential in cancer, >240 clinical trials but with little evidence of any benefit to cancer patients [5]. Another prominent example is the anti-parasitic drug, ivermectin, that was initially proposed for repurposing as a potential treatment for COVID-19 but that was ultimately demonstrated in randomised clinical trials not to have sufficient activity to provide patient benefit [8,9].

There are however, rare examples of successful drug repurposing. The most deserving examples include thalidomide, moxidectin, dimethylfumurate and most recently fluvoxamine as a treatment for COVID-19 [10-12].

There are also common misconceptions, so some often cited examples of drug repurposing are actually more appropriately considered examples of industry's data-driven approach to drug development (e.g. sildenafil and minoxidil) or "label expansion" or "line extensions" that were conceived from the outset of the program.

There are, however, genuine examples of industry's success at drug repurposing. Selected examples include bevacizumab (from cancer indications to age-related macular degeneration), rituximab (from non-Hodgkin's lymphoma to rheumatoid arthritis, immune thrombocytopenia), adalimumab (from rheumatoid arthritis to autoimmune diseases more broadly) [5].

DISCUSSION AND CONCLUSION

In conclusion, while there are genuine opportunities for drug repurposing, and important examples of success. Although intuitively this might appear to be a simple and straight forward process, that is seldom the case. It is critical therefore to understand and address the challenges that could derail well-intentioned drug repurposing efforts.

REFERENCES

1. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004;3(8):673-83.
2. Pushpakom S, Iorio F, Eyers PA, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov.2019;18(1):41-58.
3. Verbaanderd C, Rooman I, Meheus L,et al. On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. Front Pharmacol.2020;10(1):1664.
4. A Breckenridge, R Jacob. Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov.2019; 18(2):1–2.
5. Begley CG, Ashton M, Baell J, et al. Drug Repurposing: Misconceptions, Challenges & Opportunities Facing Academic Researchers. Sci Transl Med. 2021;13(1): 612-25.
6. Cha Y, Erez T, Reynolds IJ, et al. Drug repurposing from the perspective of pharmaceutical companies. Br J Pharmacol. 2018;175(2):168-80.
7. Freedman B.Equipoise and the ethics of clinical research. N Engl J Med. 1987;317(1):141-145.
8. Caly L, Druce JD, Catton MG, et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 *in vitro.* Anti-Viral Res.2020;178(1);104787-91.
9. Reis G, Silva EA, Silva DC,et al. Effect of Early Treatment with Ivermectin among Patients with Covid-19. N Engl J Med. 2022;10(1);1-2.
10. Rehman W, Arfons LM, Lazarus HM, The rise, fall and subsequent triumph of thalidomide: Lessons learned in drug development. Ther Adv Hematol.2011;2(1):291–308.
11. Maheu-Giroux M, Joseph SA. Moxidectin for deworming: From trials to implementation. Lancet Infect Dis.2018;18(1) 817-819.
12. Boulware DR, Abassi M. Fluvoxamine for the treatment of COVID-19. Lancet Glob Health.2022;10(3):e329.