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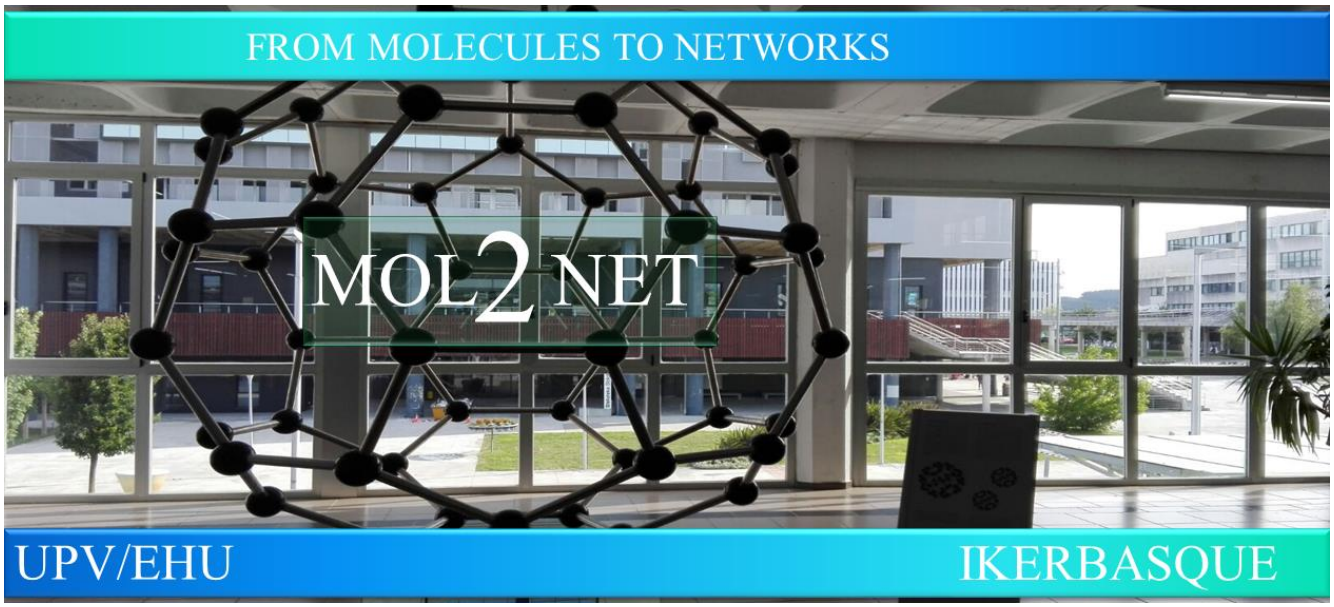

Perspectives in the field of Pharmaceutical Repositioning: advantages and challenges

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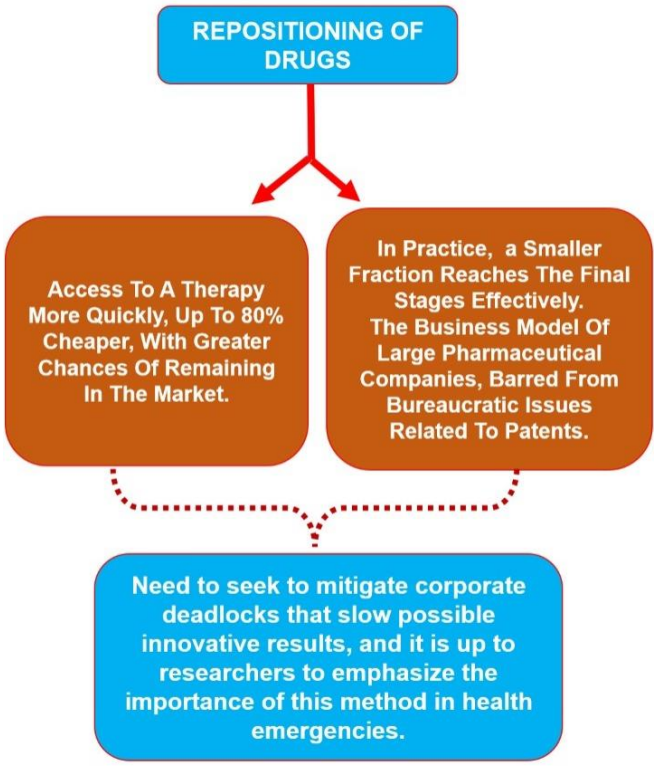
Graphical Abstract	**Abstract.**
	The process of repositioning drugs is related to the discovery of new clinical benefits of drugs known and already on the market in the treatment of other diseases, presenting an intersectoral and broad panel of advantages. However, it is necessary to verify the regulatory and economic obstacles that may permeate this process. This



study aims to present an overview of pharmacological repositioning, focusing on its advantages and disadvantages. A qualitative study was carried out, using the process of narrative and reflective review, using the PICo strategy to support the investigation. The search took place from December 2021 to February 2022, aiming at a broad bibliographic analysis with contemplation of the benefits and challenges of pharmacological reuse, not requiring the opinion of a research ethics committee for its development. The repositioning of drugs essentially presents a simplification of procedures in the face of the introduction of a drug previously approved on the market. This technique allows the final consumer, carrier of the disease, to have access to a therapy more quickly, up to 80% cheaper, with greater chances of remaining in the market. However, in practice, a smaller fraction reaches the final stages effectively. That's because a repositioned drug still needs to go through phase II and III clinical trials for its new purpose. Another theme added to the scenario of limitations is the business model of large pharmaceutical companies, barred from bureaucratic issues related to patents. Therefore, this work highlights the need to seek to mitigate corporate impasses that slow possible innovative results, and it is up to researchers to emphasize the importance of this method in health emergencies.

Introduction

The process of repositioning drugs is related to the discovery of new clinical benefits of known drugs already on the market, aiming at the treatment of other diseases (1). Historically, there are successful examples of repositioning, such as acetylsalicylic acid, thalidomide, sildenafil or dimethylfumarate, which were repositioned mainly at random (2), due to the lack of knowledge about this aspect until then (3). However, today there is already an organized and elaborate system capable of optimizing the work and offering mechanisms that make this practice even more successful (4).

The panel of cross-sector advantages is broad. The fact of prior establishment of characteristics of drugs already in use (including efficacy, pharmacokinetics, pharmacodynamics and toxicity) makes the research process faster, less expensive, safer and, therefore, very attractive (1). On the other hand,

from a more analytical perspective, it is necessary to verify the regulatory and economic obstacles that may permeate this process (2) and, even more, the related bioethical limits.

In this perspective, much has been debated during the recent pandemic, in which there have been attempts to redirect the use of antiparasitics, such as chloroquine, hydroxychloroquine and ivermectin, based on in vitro antiviral activity, animal studies and preliminary data from COVID-19 patients. 19. However, despite having previously shown promise against diseases such as malaria, SARS, HIV and multiple sclerosis, they have not been successful in the current scenario (4) (6).

In this context, this study provides an overview of the potential of drug repositioning; thus, its scope is to carry out a narrative review, identifying and analyzing the scientific literature, seeking to identify the main advantages and disadvantages of such a therapeutic development strategy. Providing a foundation for scholars, who, by better understanding these dynamics, will be able to manage drug projects more effectively, and underpinning the development of future research.

Methodology

For the preparation of this study, a qualitative, descriptive and theoretical-reflective approach was adopted. The reflective narrative review method was used to make a broad analysis of the scientific literature, with critical contemplation of a specific context of the theme. To conduct the investigation, the research question was elaborated from the PICo strategy, with P corresponding to population, I of interest and Co for context. Thus, the following question was asked “what is the general picture (Co) of drug repositioning (P) in terms of its promising results and problems faced in its employability (I)?”

From this, the scientific search was carried out, which took place during the months of December 2021 to February 2022, in electronic databases intended to index journals and scientific articles. The terms used to perform the search were, in a combined way, repositioning; drugs; clinical applicability, without delimiting a time interval. The selection of works occurred for those that explicitly portrayed in their abstract or title that the text relates to the repositioning of medications in some scenario that addressed their advantage or disadvantages. Priority was given to works published in the form of scientific articles. The search languages were Portuguese, English, Spanish and Italian.

Exclusion criteria were duplicate studies and that, after their complete reading, their content did not answer the question of this research. Data were collected after the individual study of each selected work and analyzed by correlating the findings. The review was elaborated using 10 studies, aiming to answer the guiding question.

Since the samples were obtained from public data, it was not necessary to resort to judges to carry out a qualitative treatment of the extracted data, nor was it necessary to submit the study to a research ethics committee. However, ethical scientific research protocols were followed, ensuring the authorship of all works used.

Results and Discussion

With drug repositioning techniques, many sectors are benefited, from the actors involved in the research, to the final consumer. It is a process capable of reducing costs in the pharmaceutical industry, as well as in the Research & Development sectors exponentially. In comparison, a new drug can cost an average of US$ 2 billion and US$ 3 billion, taking 13 to 15 years to develop, until it is ready for the market. Meanwhile, repositioning a drug is estimated to cost an average of US$300 million, taking only about 6.5 years to complete trials (7) (8) (9).

It is also possible to reuse drugs that have failed in initial tests or that have been in clinical practice with other therapeutic targets (7). This was the case with sildenafil, developed in 1989 for angina, which is now marketed as Viagra and widely used in the treatment of erectile dysfunction, generating annual sales peaks in this indication of over US$2 billion (2). Another example is azidothymidine, which was not successful with chemotherapeutic action, but emerged in the 1980s as a therapy for HIV (1) (7).

In view of this, the repositioning of drugs essentially presents a simplification of procedures in the face of the introduction of a drug previously approved on the market. This technique makes it possible for the final consumer, carrier of the disease, to have access to a therapy more quickly (2) (7), cheaper, up to 80% of the time and with greater chances of remaining in the market (2) (8).

In some countries, systems are used that discover molecular similarities between diseases, combined with computer models that can predict which compounds can take advantage of these similarities. There are also high-throughput screening methods capable of rapidly testing many drugs against different cell lines and mapping all connections between drugs, molecular pathways, genes, and other biologically relevant entities (7).

These computational biology platforms intelligently search a database of pharmacologically active compounds while linking them to mechanism of action, adverse events, and human target information (8). The thinking is that the more connections a drug has in common with a disease, the more likely it is to be a good candidate for repositioning. This is how Biovista Pharmaceuticals discovered that pirlindol – a generic antidepressant developed and used in Russia with potential action in the treatment of multiple sclerosis (7).

However, although the field of possibilities around drug repositioning is vast, in practice, a smaller fraction effectively reaches the final stages. That's because a repositioned drug still needs to go through phase II and III clinical trials for its new purpose. In these steps, about 68% and 40%, respectively, are discarded (2) (1) (7) (8). Furthermore, a re-examination of the safety profile of the intended drug for new conditions is required, since it will act as a new drug, presenting a change in formulation, dosage or route of administration (2).

Another theme added to the scenario of limitations is the business model of large pharmaceutical companies, barred from bureaucratic issues related to patents. The weak intellectual property protection afforded to these drugs can also reduce the return on investment and discourage companies from developing them (7) (9). Technological hurdles also exist. Currently, even with all the structure in place, there is still a lack of collaboration and updating of databases on the part of many researchers, which slows down and makes impossible the scenario of Research & Development in its entirety (5) (7).

Still, it is necessary to report that the procedures that precede the redirection of a drug on the market must be carried out in an integral and effective way, in order to avoid misinformation and harmful effects to users, as happened after the introduction of antiparasitics in the therapy of COVID-19. 19. Thus, clinical studies must be conducted only in the face of sufficient in vitro evidence, and drugs must be rigorously tested in randomized clinical trials, before being released for widespread clinical use (9) (10).

Conclusions

It is understood, therefore, that drug repositioning is fully capable of fostering the development of the pharmacological field, giving new meaning to the idea 'one drug, one target'. The effective realization of this redirection makes it possible to combat wear and tear and rising costs, therefore, one

should seek to mitigate corporate impasses that slow possible innovative results, and it is up to researchers to emphasize the importance of this method in health emergencies. It is still important to understand and act, together with the competent bodies, in encouraging scientific social education, avoiding future misunderstandings on the part of the community regarding information about new drug applications.

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