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RESEARCH ARTICLE

The 'Orange Card' Initiative: The Search for 'Tertiary Effects' of Drugs

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ABSTRACT

Marketed drugs are known to possess both therapeutic (primary) effects and side (secondary) effects. Occasionally, during the course of treating a specific disease, unexpected beneficial outcomes, referred to as "tertiary effects," may emerge. These tertiary effects have shown great potential for drug repurposing, particularly in the context of rare diseases. Unfortunately, the observation of such effects often falls to physicians, nurses, and pharmacists who lack a proper system for effectively communicating these findings to the healthcare community. In this proposal, I suggest the development of an innovative solution called the "Orange Card," which aims to facilitate the reporting of suspected unexpected beneficial effects associated with a particular treatment. This system would leverage the existing well-established framework employed by most countries for reporting side effects, enabling seamless integration and enhancing communication within the healthcare system.

Introduction

I am writing to draw attention to the untapped potential of drug repurposing and propose an innovative solution to uncover the hidden therapeutic possibilities offered by existing medications. The identification of new therapeutic targets for drug development has long been a focal point in research grant proposals, yet the translation of these discoveries into clinical practice remains disappointingly slow[1]. It is evident that we need a fresh approach to expedite the arrival of effective treatments into the hands of patients.

Currently, many drugs are being used off-label for therapeutic purposes that differ from their initial intended use[2]. Serendipitous discoveries have played a pivotal role in the field of drug repurposing, yielding remarkable successes such as sildenafil for sexual impotence[3,4] or methotrexate for arthritis[5]. The recently reported beneficial effects of GLP-1 receptor agonists combined to SGLT-2 inhibitors is resulting as a real explosion of off-label use for obesity treatment[6]. Indeed, several drugs currently used to treat CNS diseases were diverted to other uses after clinical improvements unrelated to the disease originally targeted were observed, including promethazine[7] or imipramine[8], tetrabenazine and their derivatives for chorea associated to Huntington disease[9]. Also antidepressants are widely used as analgesics[10,11], antiepileptics like topiramate for migraine prevention[12], antihistaminic as over the counter sleep drugs. Indeed, aspirin is no longer used as an anti-inflammatory drug but as antiplatelet agent[13]. However, these occurrences rely on chance observations made by individual physicians who rarely communicate their findings to the wider scientific community.

A special case of drug repurposing has been thalidomide. A drug that was retired in the sixties after its catastrophic congenic side effects. Thalidomide was however reintroduced in 1998 for the treatment of leprosy and it is currently has a relevant use in the therapy of multiple myeloma[14].

Repositioning means that most of these drugs did not have to repeat the travel through the long, torturous, and expensive road started from initial development. Drug repurposing is therefore gaining popularity. Most of the current efforts are carried out by companies, big hospitals and health foundations and this research is usually focused on specific novel indications. However, identifying new uses for old drugs –*tertiary effects*- is often a serendipitous process, and most of these potential 'small' discoveries are the fruit of observations conducted by individual physicians, out of the hospital systems, who rarely communicate them to the scientific community (see for instance the FDA page *The Rare Disease Repurposing Database*[*]). Indeed, how such findings can be communicated are exceedingly limited.

In contrast, adverse drug reaction reporting systems, commonly known as the '*Yellow Card*' initiative, have been instrumental in efficiently detecting and communicating the side effects of medications. These systems have established a robust global network involving healthcare professionals, patients, and their families to collect data on potentially harmful effects[15]. The occurrence of side effect notification systems has been also used to identify beneficial effects of drugs[16]. It is high time we extended this successful model to encompass the reporting of unexpected positive effects, creating what I propose to call the *'Orange Card'* initiative.

The *'Orange Card'* initiative aims to collect and consolidate information on the tertiary effects of drugs, encompassing both unexpected improvements in patients undergoing treatment for other conditions and unreported potential uses of medications. This invaluable resource would be particularly beneficial for rare diseases, where patient populations are small, and comprehensive data collection necessitates a wide-reaching reporting system. It is crucial to note that research on rare diseases is often hindered by the limited resources available to pharmaceutical companies, as the high costs of research and development are compounded by the small commercial markets.

By centralizing and concentrating communications regarding the tertiary effects of drugs, the *'Orange Card'* initiative would enable us to unlock tremendous clinical benefits. It would encourage those with access to such information to share it with others, fostering collaboration and accelerating the discovery of novel therapeutic applications. While certain legal considerations, such as intellectual property rights, would need to be addressed during the implementation of such a system, the *'Orange Card'* initiative offers a cost-effective alternative to the traditional, time-consuming drug development process.

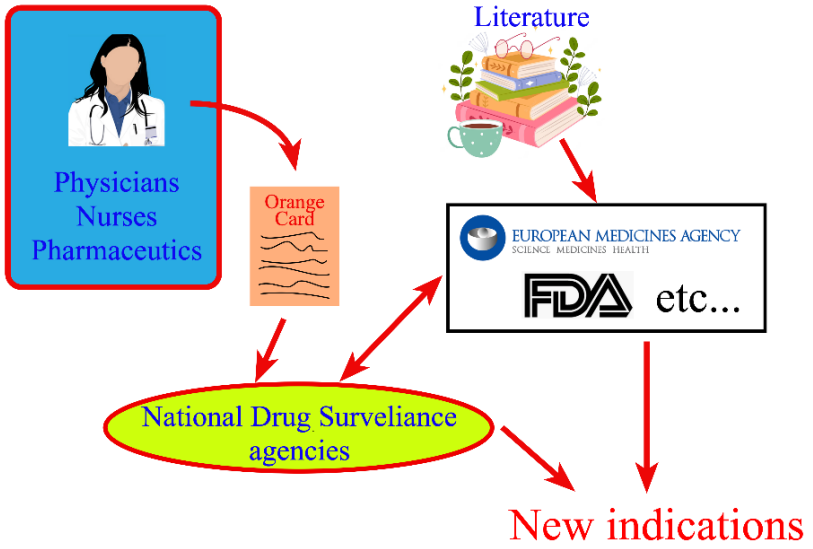

Figure 1. The Orange Card Initiative aims to facilitate the communication of unexpected beneficial effects. The process begins with an observation made by a physician or reported by a patient. These reports can also come from other healthcare professionals. Once the Orange Card is filled with relevant data, it is forwarded to a local or national agency for initial evaluation. Subsequently, the reports are shared with supranational entities. When a sufficient accumulation of data points toward positive tertiary effects, the agencies can propose new indications for a given drug.

In Figure 1, I have depicted a simple representation of how the communication of unexpected positive effects mirrors the structure of the existing yellow card notification system. By adapting and expanding this proven model, we can harness the power of collective knowledge to identify lead compounds that can be further refined in future drug development programs[17].

Notably, the European Union is currently developing the STAMP (Safe and Timely Access to Medicines for Patients) expert group[18], a non-profit program focused on drug repurposing. However, the approach taken by STAMP does not rely on individual observations from healthcare professionals as proposed in the '*Orange Card*' system.

In essence, the '*Orange Card*' system for drug repositioning, akin to the *Yellow Card* system for adverse effects, would consolidate crucial data to identify beneficial tertiary effects of existing drugs. By preventing the dispersion of significant observations and avoiding their dissipation into background noise, such a system would provide a much-needed boost to the pharmaceutical industry's drug discovery programs. Moreover, it would enhance patient care by rapidly expanding the clinical drug armory with new therapeutic options.

Conclusion

The *'Orange Card'* initiative represents an innovative proposal to drug repurposing that has the potential to revolutionize the field of medicine. By capitalizing on the successes of existing adverse drug reaction reporting systems, we can establish a robust network to uncover the hidden therapeutic possibilities of established drugs. I urge the scientific community, healthcare professionals, and policymakers to support and champion this initiative, which has the potential to bring about meaningful and cost-effective advancements in patient care.

*http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm216147.htm

I declare that I have no conflicts of interest.

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