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Curriculum Development of Human Clinical Trials for the Next Generation of PhD Students and Early Career Researchers in the Medical, Science, Pharmacy and Health Professions

CHAPTER 13

DRUG REPURPOSING

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Content

1 Introduction to the drug repurposing

2 Advantages of drug repurposing

3 Challenges

4 Examples of repurposed drugs
- 4.1 Aspirin
- 4.2 Thalidomide
- 4.3 Sildenafil
- 4.4 Dimethyl fumarate

5 Conclusion

Time required to complete this chapter

Core content:	10m
Additional/advanced content (yellow boxes):	50m
Activities/practical exercises (blue framed boxes):	05m
Total time:	**1h 05m**

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1 Introduction to the drug repurposing

Drug repurposing is also called drug repositioning, reprofiling, redirecting, switching. It is a relatively recent concept that appears to have emerged in 2004 with an article by Ashburn and Thor,[1] who provided an initial definition. They defined drug repositioning as the process of finding new uses for existing drugs, sometimes but not necessarily when they fall into the public domain and become generic drugs.

To help us understand why this has potential to be both effective for patients, be a faster avenue to new treatments and economically beneficial, let's look at the case of EB (Epidermolysis bullosa). Epidermolysis bullosa is a group of rare diseases that cause the skin to be fragile and to blister easily. Tears, sores, and blisters in the skin happen when something rubs or bumps the skin. They can appear anywhere on the body. In severe cases, blisters and sores may also develop inside the body, such as in the mouth, oesophagus, stomach, intestines, upper airway, bladder, and genitals.

To learn more about drug repurposing and its importance for EB, go to this link and watch this short 2-minute video "What is drug repurposing?".[2]

This original definition of drug repurposing has been extended to include active substances that failed the clinical phase of their development due to their toxicity or insufficient efficacy, as well as drugs withdrawn from the market because of safety concerns. It does not, however, include substances that have never been subjected to clinical investigation. The concept of drug repurposing thus excludes any structural modification of the drug. Instead, repurposing makes use in a new indication of either the biological properties for which the drug has already been approved (possibly according to a different formulation, at a new dose or via a new route of administration), or the side properties of a drug that are responsible for its adverse effects.

Listening
Watch this 5-minute interview with a dermatologist in the UK "Drug repurposing for EB – an expert's view",[3] where he discusses drug repurposing for EB and how and why this should be part of the conversation for patient treatments.

2 Advantages of drug repurposing

Drug repurposing has a number of interrelated advantages.

1. They essentially consist of the simplification in the regulatory procedures for introducing a previously approved drug on the market for a new indication, especially in certain countries such as the United States. This procedure takes into account data previously acquired, in

[1] Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Discov 2004; 3: 673–683.
[2] https://youtu.be/tYP3Kr0vaao
[3] https://youtu.be/4MYeWeSDUDI

particular on the drug's safety and toxicity, which can make the initial phases of development for a repurposed drug considerably faster.

2. They may be cheaper, to bring to market.
3. Being repurposed increases the chances of introducing the drug on the market for a new indication.

3 Challenges

One important consideration is that, due to the level of safety required for a drug is highly dependent on its indication, the adverse effects of a drug will be proportionately less acceptable when repurposed for a disease that is less serious or severe than its original indication. Any change in formulation, dosage, or route of administration will require re-examination of the drug's safety profile under these new conditions, in what will be a new medicinal product.

Another challenge faced by those working on repurposing a drug lies in the relatively weak intellectual property protection given to such medicinal products, which can reduce their return on investment and discourage companies from developing them.

Further, making the new indication "on-label" via the process of marketing authorisation means overcoming many regulatory, administrative and financial hurdles. Most of the repurposing research is conducted by independent or academic researchers. However, they often lack the regulatory knowledge and resources to pursue the drug to be authorised. Therefore, prescribing a drug off-label is still common. Off-label use can be defined as any intentional use of an authorised product not covered by the terms of its marketing authorisation, for example, for another indication, a different patient group, another dose, dose interval, or by another route of administration than indicated in the summary of product characteristics. Nevertheless, in the long term, off-label use entails important safety, liability and financial risks for patients, physicians, and society. [4]

If you are interested more in the regulatory pathways of on-label and off-label use, granting marketing authorisation of repurposed drugs and pricing and reimbursement decisions, read the article by Verbaanderd et al., 2020.

4 Examples of repurposed drugs

4.1 Aspirin

Initially marketed by Bayer in 1899 as an analgesic, aspirin was first repurposed in the 1980s, at low doses only, as an antiplatelet aggregation drug. It is still widely used today in this second indication to prevent cardiovascular events. In essence, it is a blood thinner. Aspirin may soon be repurposed again, this time in oncology. It has been shown that daily administration of aspirin for at least 5 years can prevent the development of many cancers, and in particular

[4] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020 Jan 31;10:1664. doi: 10.3389/fphar.2019.01664. PMID: 32076405; PMCID: PMC7006723.

colorectal cancer. Although this second potential repurpose of aspirin offers great promise from a public health point of view, there is little encouragement for it from the pharmaceutical industry, probably due to the intellectual property issues outlined above.

4.2 Thalidomide

Taken as an antiemetic (anti-sickness) for pregnant women, it is well known that the World Health Organization (WHO) banned thalidomide in 1962 due to the birth defects it caused.

Listen here to a 12 minute video on its history and effects "The Shadow of the Thalidomide Tragedy | Retro Report | The New York Times".[5]

Despite this, it was repurposed for the treatment of leprosy. In Brazil in 1965 it was licensed as a treatment for skin lesions, one of the complications of leprosy. Its use must obviously be accompanied by drastic measures to prevent exposure to the drug during pregnancy, including stringent contraceptive measures. This example illustrates how even drugs with an exceptionally dangerous toxicity profile in pregnancies can be repurposed if the new indication in a rare disease (the estimated incidence of leprosy is 250 000 cases per year).

However, despite alerts to the danger to pregnancies and strict controls for its use, Brazil has experienced a new generation of "thalidomide babies" with severe birth defects. This illustrates the difficulties of necessary drugs for a deliberating disease and its dangerous side effects, if the rules for taking it are not followed.

You can read the BBC report on Brazil's new generation of Thalidomide babies here.[6]

4.3 Sildenafil

Sildenafil is an example of a pharmaceutical substance that was repurposed before it reached the market. Sildenafil was initially investigated by Pfizer in 1985 as a potential antihypertensive drug. It was shown to produce vasodilation and to inhibit platelet aggregation. An unexpected side effect emerged during clinical trials conducted in the United Kingdom, in the form of penile erections. This physiological effect led Pfizer to market sildenafil in 1998 for erectile dysfunction, under the brand name Viagra®, generating peak annual sales in this indication in excess of $2 billion.

Sildenafil was subsequently repurposed for a second time. Pfizer continued to study its potentially therapeutic effects, exploiting the vasodilation it produces, to treat pulmonary arterial hypertension, at one-fifth of the dose used in erectile dysfunction. The idiopathic form of pulmonary hypertension is considered a rare disease (2–3 million cases per year) and is potentially fatal, which explains why it was relatively easy for Pfizer to obtain approval for a second sildenafil product, Revatio®, in 2005 in this new indication.

[5] https://youtu.be/41n3mDoVbvk
[6] https://www.bbc.com/news/magazine-23418102

4.4 Dimethyl fumarate

Dimethyl fumarate was first synthesised in 1819. For 150 years, it was only known as a mould inhibitor to protect leather and a cause of allergies, which led to a ban on its use in Europe in 2009. Nevertheless, dimethyl fumarate has also been marketed as a drug since 1994. It is commonly used to treat psoriasis, under the brand name Fumaderm®.

Having discovered dimethyl fumarate's anti-inflammatory activity, Biogen proposed its use in another autoimmune disease, multiple sclerosis (MS), at higher doses. It was marketed for this indication in 2013, under the brand name Tecfidera®. It constituted a major advance in the treatment of MS, because it could be taken orally and is less cardiotoxic (toxic to the heart) and hepatotoxic (toxic to the liver) than the other drugs used in this condition, although it does expose patients to the risk of developing progressive multifocal leukoencephalopathy (PML), a serious virus that attacks the brain and can cause death.

5 Conclusion

The repurposing of drugs for a therapeutic indication other than the one for which they were initially marketed is a growing trend. Repurposing is also one of the key opportunities in medicine development for rare diseases. The main aim of drug repurposing is to combat rising costs of drug development, which are having a dramatic effect on the number of new drugs entering the pharmaceuticals market. However, this approach must be considered as an add-on rather than an alternative to the search for novel drugs.