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Medicine for Managers

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Drug Repositioning

The term 'drug repositioning' may not be familiar to many but is essentially used to describe a drug which has been discovered and marketed for one purpose and which has subsequently been identified as having particular effects which provide a new indication for its use. Successes in the repositioning of some drugs have confirmed, not only its medical and public health benefits, but also its commercial value for the pharmaceutical industry.

Perhaps the most globally known repositioned drug, which had disastrous effects, was ***thalidomide***. The drug was developed in the 1950s by a West German pharmaceutical company and was originally introduced as a ***sedative*** or ***tranquilliser***.

However, it quickly became used for a variety of other conditions including colds and influenza and, most significantly, ***morning sickness in pregnant women***.

The drug company's testing resulted in the claim that the drug was 'harmless to humans' and in Germany it was sold over the counter without prescription.

So popular was it as a treatment that, by the late 1950s, it was being marketed by fourteen pharmaceutical companies in 46 countries under 37 different trade names.

In the UK, it was sold by the ***Distillers Company*** and the best known brand name was ***Distaval***.

The company advertisement claimed that:

> *Distaval can be given with complete safety to pregnant women and nursing mothers without adverse effects on mother or child.*

The foetal effects of thalidomide were unknown.

No testing was done and because it was used in so many countries under so many different names, it took five years for the thalidomide tragedy to be recognised and the effects of ***phocomelia*** (arrested limb development), sight or hearing loss, paralysis and organ damage to be understood when the drug was used between three and five weeks after conception.

As a result of repositioning, the disaster which unfolded during the 1960s damaging thousands of children worldwide.

However, it was not the end for the drug.

In 1964, a physician in Israel identified the drug's dramatic effect against a complication of ***leprosy*** and it is now commonly used in treatment, subject to stringent contraceptive measures.

Furthermore, the drug's effect on pregnancy was recognised as a potential mechanism which led to its use to block or destroy blood vessels supplying malignant tumours.

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*In 2006 it was introduced as a first line treatment for **multiple myeloma**, a type of bone marrow cancer.*

Drug repositioning does have considerable advantages in repurposing an active pharmaceutical agent already on the market.

It does reduce both the costs and concerns about a drug which often occur with the proposed introduction of a completely new drug.

Medicine has been influenced and changed by the introduction of a number of examples of repositioned drugs, including some that are very old. In most of the cases of identifying new uses for a drug, it is the result of good fortune that a serendipitous benefit is recognised.

The process of recognising new indications has now matured and conferences, research programmes and even a Journal have emerged to identify new uses for old drugs.

Originally, additional uses were identified in drugs that were either generic or branded.

A ***generic drug*** is a pharmaceutical agent which contains the same chemical substance as a drug originally protected by chemical patents.

Generic drugs can be sold after the patents for original drugs expire. A ***branded drug*** is a new medicine, patented and sold under a brand name. When a patent ***expires*** generic versions of the drug may be sold by other companies.

They differ in minor ways from the branded version but must have similar efficacy.

Both branded and generic drugs have already been investigated in depth and approved by drug authorities and so less testing (and costs) are associated with repositioning an existing drug than introducing a completely new one.

It results in much simpler regulatory processes because there has already been compliance with such processes for its previous release for another indication. The cost of repurposing a drug could save up to 80% of the costs of introducing a completely new drug.

Sometimes a drug is recognised as having a new purpose in circumstances where the original active drug substance failed the clinical phase of its development because it lacked adequate efficacy or displayed unacceptable side effects.

About ***one hundred drugs*** have been successfully repositioned and entered the market, and some have been very successful indeed. It has been estimated that the top five repurposed drugs each generate over ***one billion dollars a year*** in their new indication.

Some of the drugs which have been repurposed are very old or have a new use which exceeds their use for the original purpose. Examples include:

Aspirin.

The drug was originally marketed by the Bayer company in 1899 for pain relief, and is still well used for that purpose. However, nearly one hundred years later, in the 1980s it was found to reduce the 'stickiness' of ***blood platelets*** which reduces cardiovascular events such as heart attack and stroke.

The original discovery was made following research by a California GP who noticed that the use of aspirin to control pain postoperatively in tonsillectomy patients resulted in increased postoperative bleeding. It led to the discovery that inhibition of an enzyme in the synthesis of prostaglandins inhibited ***platelet agglutination***.

Currently research on aspirin has shown that daily administration of aspirin for at least five years may prevent the development of cancers, in particular colo-rectal cancer, by affecting mechanisms of cell death.

Apoptosis is a mechanism where a series of molecular steps in a cell lead to its death. In this way, the body eliminates unneeded and abnormal cells. Apoptosis may be blocked by cancer cells, resulting in their exuberant growth. Aspirin may block this feature of cancer cells, leading to the death of malignant cells.

Sildenafil.

This drug is universally known as ***Viagra*** throughout the world. It was originally investigated by Pfizer in the 1980s as an anti-hypertensive drug. It produced vasodilation, lowering blood pressure. It was also trialled as a treatment for angina.

However, unexpectedly during clinical trials, in the presence of sexual stimulation, it was found to cause an erection in men. Ultimately, this led in 1998 to the release of Viagra which, at its peak, generated sales of over $2 billion dollars a year globally.

It has subsequently been repurposed to treat ***pulmonary arterial hypertension*** (raised blood pressure in the lung arteries), at one fifth of the dose of Viagra, since 2005 and marketed as ***Revatio***.

Dimethyl fumerate

First synthesised in 1819 and was used to protect against the development of mould in leather. It caused allergies and was banned in 2009.

However, it has been found to be effective against severe psoriasis and has been marketed as ***Skilarence*** as a second-line treatment.

More recently it has also been marketed for the use in ***active relapsing multiple sclerosis*** under the trade name ***Tecfidera***.

Other drugs have also been repurposed and include ***tamoxifen***, originally used for treating metastatic breast cancer but more recently found to assist patients with bipolar disorder.

The antibiotic ***rapamycin*** was approved in 1999 to prevent rejection in organ transplantation. It has also been found to be effective in treating a ***lymphoproliferative syndrome*** where the body produces too many lymphocytes. Interestingly,

current research has shown that it prolongs life in female (but not male) fruit flies. Women already live longer than men, but the research team have as objectives "to make men live as long as women and women as healthy as men in later life".

A large number of existing drugs are now undergoing investigation and trials for use in other diseases and disorders. It was estimated in 2017 that over 100 drugs were undergoing trials for the treatment of Alzheimer's disease.

In the UK the ***Medicines Repurposing Programme*** reviews existing medication with a view to finding new ways in which to use them.

The programme, hosted by NHS England, is supported by the DHSC, NICE, and the MHRA.

It was established in 2021 to assist with working with existing medicines to provide assistance in the collection of evidence, support with the necessary elements of patient access etc., and also assisting with successful product licence variations.

In November 2023 the first licence variation was achieved when the drug ***anastrozole***, previously licensed for breast cancer treatment, successfully achieved a license for use in the prevention of breast cancer in some post-menopausal women.

In the recent 'Annual Highlights' report from the programme, they report a number of examples where repurposing is in process.

Spironolactone originally used for raised blood pressure control, is now being used by dermatologists for acne and the Programme is looking to support wider prescription by GPs.

Similarly, ***candesartan***, which is an ARB (angiotensin receptor blocker) used in blood pressure control and heart failure, is being assessed for the treatment of migraine in general practice.

The Programme reports that it is awaiting the results of 99 clinical trials which will inform and provide evidence for repurposing and varying licences.

The Medicines Repurposing Programme, in its conclusion, states that it is maturing, expanding and starting to deliver treatment options for NHS patients. A range of plans is laid out for its future development.

Certainly the use of repurposing is important in using already tried and tested drugs for new applications, reduces risk and saves a high proportion of the cost of new drug discoveries.

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