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Drug repurposing: new tricks for old drugs

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Introduction

Drugs that have been used for indications other than their originally intended purpose date back to at least the 1950s,[1] with some authors proposing that the earliest examples date as far back as over a century ago.[2] Despite this, the first formal definition of drug repurposing only appeared in the literature in 2004.[3] Many definitions now exist, which explain drug repurposing as a "novel way of finding new uses outside the scope of the original indication for existing drugs".[1] Also known in the literature as "drug repositioning, drug reprofiling, drug retasking"[2,4,5] or "therapeutic switching",[4] this process has been popularised because of the many advantages it has over de novo drug production, in an age where time is money.

The early days of drug repurposing have been described as "serendipitous".[1,2,6,7] Drugs that were initially developed with a specific indication in mind were instead eventually used for other indications because of side effects that clinical trial participants experienced, which were in some cases unanticipated. Fortunately, these side effects were postulated and proven to be efficacious for other disease processes. Some of the most famous examples of this 'drug serendipity' include sildenafil, aspirin, thalidomide and minoxidil.

Sildenafil

Sildenafil is a phosphodiesterase inhibitor which was initially developed for the purpose of treating angina and heart failure. Sound pharmacological knowledge regarding phosphodiesterase inhibition resulting in vasodilation, as well as the need to develop an agent with similar effects as the nitrates, but without their side effects, led to the development of compound "UK-92,480".[1] During the premarket phase in the early 1990s, participants in clinical trials using this compound reported expected side effects, such as headaches and hot flushes secondary to the vasodilatory effects of the drug, with few participants reporting penile erections.[1] However, despite seemingly mild side effects in premarket trials, the use of sildenafil for cardiovascular indications became an unattractive option because of its very short half-life and disastrous interaction with nitrates. In 1993, the first clinical trial using sildenafil for the indication of erectile dysfunction was undertaken in healthy participants without cardiovascular disease.[1] Five years later, sildenafil was approved for the treatment of patients with erectile dysfunction in America and Europe. Furthermore, sildenafil has proved useful in the treatment of pulmonary arterial hypertension and was approved to treat this disease process in 2005.[1]

Acetylsalicylic acid

Acetylsalicylic acid, also known as aspirin, is a non-specific inhibitor of the enzyme cyclo-oxygenase (COX). This compound was developed in 1899 and sold on the market as an analgesic agent.[4] Subsequently, aspirin was also found to be an effective inhibitor of platelet aggregation and so it was reprofiled in the 1980s into a cardiovascular drug.[4] It is currently used at low doses for the prevention of atherosclerotic disease in those at risk and for the treatment of myocardial infarctions and strokes.[2,8] Newer indications for aspirin include a place in the management of prostate cancer[2] and colorectal cancer,[7,9] because of its anti-inflammatory effects.

Thalidomide

The once popular anti-emetic thalidomide was widely used by women during pregnancy to treat nausea and vomiting during the 1950s.[1] That is, until a link was made between congenital limb malformations and the use of the drug during pregnancy, which ultimately led to its complete withdrawal from the market in 1962.[4] However, thalidomide found its therapeutic place in 1998 for the treatment of erythema nodosum leprosum due to its inhibition of tumour necrosis factor-alpha (TNF α), a proinflammatory cytokine.[4] In 2006, thalidomide was once again repositioned as a first-line agent in the treatment of multiple myeloma.[4] The initial hypothesis leading to this repositioned indication was that the limb growth abnormalities caused by thalidomide were due to the anti-angiogenic properties of the drug. This was subsequently shown to be beneficial in the treatment of cancers such as multiple myeloma because of an inhibited blood supply to the malignancy.[4]

Minoxidil

The antihypertensive agent minoxidil has been, since its introduction into the market, repurposed for use in patients

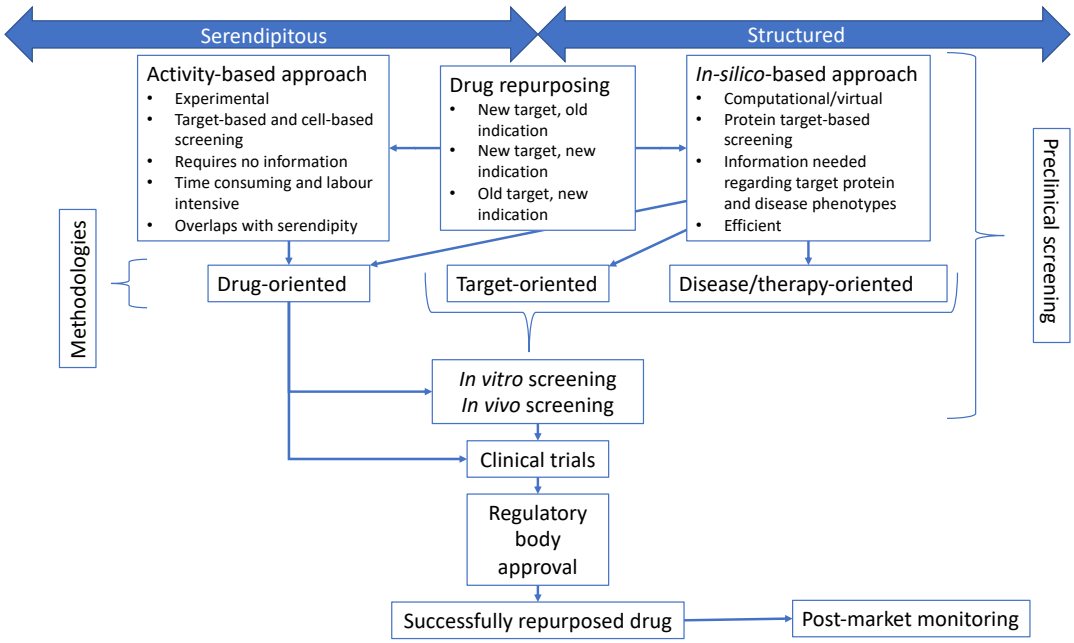

Figure 1: A representation of the process of drug repurposing[2]

suffering from androgenic alopecia.[2] The well-understood mechanism of action of the drug, which opens potassium channels and causes vasodilation, has been shown to improve blood flow to hair follicles and improve hair growth.[2,10]

Advantages of drug repurposing

With many efficacious examples of drug repurposing on the market, there has been a need to transform this once serendipitous process into one which is formal and structured. This would result in drastic and almost immediate improvements in the management of difficult clinical conditions. It is agreed that the time and money invested into new molecular entity (NME) development can possibly be cut in half or more, using structured drug repurposing approaches.[2] By understanding the pharmacology of available compounds that have already undergone safety testing and preclinical trials to elucidate unwanted side effects, time is saved.[5]

The process of drug repurposing

What is imperative to the process of repurposing drugs is two-fold. Firstly, it is important to appreciate the specific molecular in vivo targets of drugs and, secondly, to have an in-depth understanding of the pathophysiological molecular pathways of disease development.[1] Attempts are then made to find conditions where these knowledge paths regarding drugs and diseases may overlap. These matches can be generated with the help of technology. There currently exist in-depth databases categorising drugs in terms of their molecular structure, intended uses, side effects and in vivo targets.[2] This then, using artificial intelligence in combination with clinical acumen, can be matched to disease processes.[1] Seeing as premarket safety testing is already complete for these known compounds, all that remains is for the drug to undergo testing toward the proposed new indication prior to release on the market and following regulatory body approval.[2]

There are various strategies and approaches to repurposing drugs. The strategies used can be divided into two categories: on-target and off-target.[2] On-target drug repurposing matches a drug with its known molecular target to different diseases with the same molecular target.[2] For example, minoxidil produces its two different therapeutic effects (vasodilation and hair growth stimulation) through the same molecular target. Off-target strategies match drugs and diseases through newly discovered molecular targets.[2] For example, aspirin was intended as an analgesic but was also found to inhibit platelet aggregation, which is useful in atherosclerosis. As described by Pushpakom,[1] systematic repurposing harnesses big data and artificial intelligence with high throughput screening to find new indications for known compounds. The use of databases and computational approaches is common in the process of drug reprofiling[1] and forms part of the in-silico-based approach.[2,4,5,11] This is compared with an activity-based approach which is somewhat serendipitous, experimental and may rely on assays to determine new molecular targets within disease models which can be in vivo or in vitro.[2,5] Currently, laboratories may use a mixed approach which incorporates artificial intelligence and drug databases with biological experiments to determine whether the treatment of 'new' diseases with old drugs will be successful.[2]

There are three broad methods that can be used to repurpose drugs using the described approaches: drug-oriented, target-oriented and disease- or therapy-oriented.[2,5,12] The first method uses an evaluation of a drug in terms of its pharmacology and adverse effects. For example, sildenafil was found to produce penile erections, which was later proved to be an efficacious treatment for erectile dysfunction. The target-oriented method uses technology to screen drug databases that would provide information crosslinking drugs with known molecular targets to different biological targets of interest. This method has a high

success rate as compared with the drug-orientated method.[2] When more information regarding the disease is available, the disease- or therapy-oriented method is used, where the disease is used to guide drug repurposing.[2] Figure 1 summarises the approaches and methodologies of drug repurposing.

Rudrapal et al.[2] divide the process of NME production into five steps: discovery and preclinical, safety, review, clinical research, regulatory body review and post-market safety monitoring. NMEs may take up to 16 years from drug conception to market release.[2] As seen from the examples above, there is still no guarantee that the new drug will be successful despite more than a decade in production, safety trials, as well as regulatory body approval. In contrast, it is reported that the structured drug repurposing process may take only up to three years in some cases.[2] As a function of the reduced time taken to repurpose drugs, the costs involved are also reduced with an increased success rate.[1,2] The estimated cost of NME development is estimated to be $300 million, compared with drug repurposing, which is estimated to cost only about $3 million.[1,5]

Disadvantages of drug repurposing

While the process of drug repurposing seems to have many tangible advantages over new drug development, it does not come without challenges. One of the biggest challenges is an issue with intellectual property rights of already produced compounds.[4,13] Many pharmaceutical companies are not able to reintroduce a known compound for a new indication into the market until the patent for that compound and its original indication has lapsed.[4] Alternatively, companies could apply for a new patent, preferably based on a different preparation process for the compound and its new indication.[4] This issue has prevented repurposed drugs from entering the market even after confirmation by researchers that these drugs would be successful treatment options for other diseases than what was originally intended.[2]

However, the need for repurposed drugs to enter the market after regulatory body approval also depends on demand. The once serendipitous process of repurposing can now target specific drugs for new specific indications, often aimed at diseases which are rare or have been difficult to treat.[2] As explained by Jourdan et al., intellectual property issues may be offset if pharmaceutical companies are incentivised to repurpose drugs for rare diseases – a niche gap in the medical and pharmaceutical industry.[4] Such incentives might include drug production fee discounts, as well as a time on the market that is exclusive.[4] For example, pharmaceutical companies that successfully repurpose a drug for the treatment of a rare disease, would have sole production rights for the drug and its new indication, for a period of time. Additionally, Pushpakom[1] and Ahmed et al.[11] highlight issues with artificial intelligence and its use in medicine, which is dependent on sound network links and robust data on drugs and which is made widely available to researchers and clinicians.

Anaesthetic agents

There has been much research into the impact of anaesthetic agents on cancer and their role as chemotherapeutic agents. Many patients with cancer may require anaesthesia at some point in their therapeutic journey, either to facilitate resection of the cancer or to receive treatment, such as radiation therapy.[14] One of the abovementioned drug databases which was published in 2018 and is titled 'ReDO_DB', lists anaesthetic agents that may possess anticancer properties, such as ketamine, propofol, midazolam and lignocaine.[15] The most recent illustrations of drug repurposing, however, may have been born out of desperation during the COVID-19 pandemic. An editorial by Kholi et al.[16] emphasises the important role that anaesthetists and critical care physicians played during the pandemic. This role included crisis management and care of the critically ill patient, both of which are skills inherent to the profession. Furthermore, the knowledge anaesthetists have regarding pharmacology and the relative ease with which drugs can be accessed, have proved beneficial in the management of patients with COVID-19. This is despite the use of these drugs, in this instance, being a deviation from their original indication in the operating room.[16]

Dexamethasone

Dexamethasone is a glucocorticoid with many uses in the setting of anaesthesia and analgesia. It is known to be an effective adjunct to antiemesis following anaesthesia, it may help regulate pain responses when injected perineurally or intravenously and is effective at reducing airway swelling.[17] During the COVID-19 pandemic, it has also proved to be effective in modulating a patient's immune response to the virus which was dysregulated and devastating. Patients with COVID-19 who received dexamethasone showed improved survival compared with those who had not.[18]

Ketamine

The phencyclidine derivative ketamine is an antagonist at the N-methyl-D-aspartate (NMDA) receptor and is widely used as a sedative, anaesthetic and analgesic agent.[14] There has been much interest in its therapeutic use for a wide range of psychiatric disorders including depression, with or without suicidal ideation, as well as for anxiety disorders.[19] As highlighted by Kholi et al.,[16] ketamine has proved ideal for the treatment of resistant depression and related disorders, which have shown an increase in prevalence in patients who have suffered from COVID-19. This is because of its repurposed role in psychiatry, together with its ability to downregulate inflammatory cytokines,[16] which creates a suitable therapeutic environment for patients suffering physically and mentally from coronavirus. Ketamine has also shown an ability to cause neuroapoptosis in the developing brain of rats and rhesus monkeys.[20,21] While this has led to a reluctance of its use in human neonates,[21] researchers surmise that it may have a beneficial role to play in the treatment of cancer via an inhibition of malignant cell growth[14] in many organs including the pancreas, liver, lung and gastrointestinal tract.[22]

Propofol

Propofol, a gamma-aminobutyric acid (GABA) agonist, is another induction agent routinely used in anaesthesia. Its activity produces central nervous system depression and results in sedation or general anaesthesia depending on the dose used and its titration into the patient. There are some reports indicating that propofol may have anti-inflammatory properties and an ability to enhance the cytotoxic action of natural killer cells, which may be advantageous in cancer therapy.[14] Propofol has been shown to inhibit gastric cancer proliferation through molecular mechanisms which involve regulation of ribonucleic acid (RNA) and downstream oncogenes.[14] It may also slow progression of oral squamous cell carcinoma.[14] More in vivo clinical research is needed however, to confirm these hypotheses and translate them into clinical practice, which would involve repurposing the drug. Over and above this, Wei et al.[23] suggest that propofol may facilitate pulmonary recovery in patients who have had COVID-19 due to potential antiviral effects which include the upregulation of angiotensin-converting enzyme-2 (ACE 2). This has been shown to be protective of vascular structures such as the pulmonary artery, while also contributing to the inhibition of vascular endothelial cell death.[23] Additionally, in vitro studies showed that propofol may inhibit entry of the virus into the cell.[23] Lastly, there is also research into the usefulness of propofol in the setting of persistent vegetative states. Duclos et al.[24] studied the use of propofol in combination with electroencephalogram (EEG) monitoring in 12 critically ill patients with persistently low conscious states, as a potential prognostic indicator of the likelihood of patients regaining consciousness. Those patients with a normal EEG response to propofol were more likely to regain consciousness than those patients with abnormal, or no response.[24]

Benzodiazepines

Another class of drugs acting on central GABA receptors is the benzodiazepines. The indications for midazolam include anxiolysis, treatment of seizures as well as induction and maintenance of anaesthesia, in the appropriate setting. Wu et al.[14] describe a wealth of literature supporting the use of midazolam as an anticancer agent through its peripheral receptor effects which has been observed in both in vitro and in vivo animal models targeting lung cancer, leukaemia, colon cancer and neuroblastoma. This effect is produced by the peripheral benzodiazepine receptor, which, when bound by midazolam, induces cancer cell apoptosis.[14]

Volatile anaesthetic agents

There has been attention drawn to the use of volatile anaesthetic agents for purposes other than induction and maintenance of anaesthesia. During the COVID-19 pandemic there was interest in the use of sevoflurane to sedate intubated patients in the setting of the intensive care unit (ICU).[16] It was also, apart from being used as a sedative agent, postulated to have immune-modulating effects with decreased levels of TNF α and other inflammatory cytokines.[25] In addition to these newer indications, Wang et al.[26] describe in detail the mechanisms by which many volatile anaesthetic agents may produce anticancer effects. Sevoflurane is described to inhibit cell proliferation and migration as well as induce apoptosis of some cancer cells such as glioblastoma multiforme.[14] The mechanism of this is postulated to be an inhibition of insulin-like-growth factor-1[14] and regulation of RNA expression.[26] There are similar findings for desflurane, isoflurane and xenon for a variety of cancers including lung and liver cancer.[26] More research is needed to fully elucidate the role volatile anaesthetic agents can play in the treatment of cancer to improve outcomes.

Local anaesthetics

The local anaesthetics are potent sodium channel blockers that block the propagation of neuronal action potentials. Along with the use of these drugs for local and regional anaesthesia, lignocaine is also indicated for the treatment of ventricular arrhythmias both in the setting of cardiac arrest and also for the treatment of stable monomorphic ventricular tachycardias. It is postulated that lignocaine and bupivacaine (including the enantiomer, levobupivacaine) may additionally have a potential off-target cytotoxic effect,[14] which inhibits cell proliferation, migration and invasion.[27] This could be useful in the treatment of cancers such as prostate, ovarian, gastric and lung cancer,[14] as well as breast, liver, colorectal, skin, brain and tongue cancer.[27,28] Lignocaine has also been reported to improve the sensitivity of resistant cancer cells to chemotherapeutic agents, such as cisplatin.[27] Furthermore, in the fight against antimicrobial resistance, which is an enormous problem in critically ill patients, it has been hypothesised that both lignocaine and bupivacaine may be useful.[29] The supposed mode of action, which has been tested on a number of gram-positive and gram-negative organisms, includes a disruption of the bacterial cell wall, inhibition of the cell wall and DNA synthesis, as well as inhibiting membrane-bound enzymes.[29]

Dexmedetomidine

Dexmedetomidine is an alpha two (α2) receptor agonist which is indicated for ICU and procedural sedation for procedures such as awake fibreoptic intubation. During the COVID-19 pandemic, dexmedetomidine was used to augment sedation in intubated patients with coronavirus. It was also suggested to have protective effects on immunity by enhancing T cell function and suppressing sympathetic tone, while increasing parasympathetic tone.[30] There is also more recent research into the use of dexmedetomidine in the management of patients suffering from a stroke, due to its positive actions on the endoplasmic reticulum.[31]

Off-label drug use

In an attempt to perhaps circumvent patenting issues, off-label drug use has become a common practice amongst some clinicians. Off-label drug use refers to the use of drugs outside their regulatory body-approved indications[32] and, in that way,

differs from repurposed drugs. Drugs might be used anecdotally without approved indication and, in some cases, with very little literature to support the drug's efficacy in these clinical circumstances.[32] Caution must be exercised in all instances where drugs are used for indications outside their regulatory body approval and especially where there is little evidence of benefit. Indeed, a study by Eguale et al.[33] showed that there was a higher incidence of adverse drug reactions in adult patients when drugs were used in this manner, without strong scientific support.

Conclusion

There are many different medical specialities that will benefit from already available compounds being repurposed for the treatment of a wide variety of diseases. What is clear is that there needs to be a move away from both serendipitous drug repurposing, which is time-consuming and off-label drug use, which is potentially dangerous, to a more structured drug repurposing approach supported by science. The cost and time benefits of drug repurposing make it an attractive approach in identifying 'novel' treatment options for new and existing diseases, in an efficient, safe and efficacious manner. Anaesthetists are uniquely positioned in medicine in terms of having an all-inclusive foundation in pharmacology and physiology with access to a myriad of drugs which are beneficial not only perioperatively, but potentially across many spheres of medicine.

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