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CURRENT OPINION

Drug Repurposing of Generic Drugs: Challenges and the Potential Role for Government

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Abstract

Drug repurposing is the process of identifying a new use for an existing drug or active substance in an indication outside the scope of the original indication. Drug repurposing has important advantages including reduced development time and costs, and potentially large societal healthcare cost savings. However, current generic drug repurposing research faces a number of challenges in obtaining research funds. Furthermore, regardless of the success of a repurposing trial, commercial parties often lack interest in pursuing marketing authorisation for financial reasons, and academic researchers lack the knowledge, time and funding. Therefore, the new indication of a repurposed drug often does not make it 'on label'. We propose a large increase in public funding for generic drug repurposing research, including funds for the marketing authorisation process when a trial is successful, and a reduction in the regulatory burden of the marketing authorisation process for repurposed generic drugs.

Key Points for Decision Makers

Advances in generic drug repurposing are hampered by lack of finances and legislative barriers.

Public funding and public–private partnerships for generic drug repurposing should be increased.

Regulatory requirements for label extension of generic drugs should be reduced.

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1 Introduction

The field of drug repurposing has been receiving increasing attention over the past 5 years, especially since the coronavirus disease 2019 (COVID-19) pandemic. A search on the term 'drug repurposing' on PubMed yields over 8000 results in the past 5 years, of which 6000 have been published since 2020 [1]. The goal of drug repurposing is to use an existing active substance, or medicine, for a new indication for which it does not have marketing authorisation. The European Medicine Agency (EMA) and the Safe and Timely Access to Medicines for Patients (STAMP) working group define

drug repurposing as: "The process of identifying a new use for an existing drug/active substance in an indication outside the scope of the original indication".

Drug repurposing can be subdivided into three main categories: (i) repurposing of an active substance which has never previously received marketing authorisation; (ii) repurposing of a medicine with marketing authorisation, and with remaining marketing protection in the form of a patent and/or data exclusivity; and (iii) repurposing of a medicine with marketing authorisation for which all marketing protection has expired (i.e. generic drug). New drug targets, or targets shown to be critical in rare diseases, are routinely screened with a chemical library of generic drugs, whether the experiments are performed in academia or industry. An example is the ReFrame collection at Calibr at Scripps [2]. Another approach is based on deep learning, and using artificial intelligence to perform in silico screening. While generic drugs may be used to merely validate further screening for new chemical entities, they themselves may also be proposed for new therapeutic uses based on the screening. Examples of the therapeutic breadth of some of these proposals is shown in Table 1 [3–30]. However, nearly all of the proposals remain untested in the clinic, many for the reasons outlined in this article.

There are several advantages to drug repurposing of generics compared with the development of new drugs. The preclinical toxicology, pharmacokinetics, pharmacodynamics and safety profile of the drug are usually well known provided that dose, treatment duration and target population are comparable. Therefore, preclinical, phase I and phase II studies are not required for (phase III) clinical trials, thus reducing the chances of late attrition. However, phase II studies are required when the dose–response curve might be different in the new targeted indication/population (e.g. paediatric population). Despite these advantages, as we discuss below, the existing drug dossier may not satisfy registration criteria.

The importance of generic drugs has increased as the body of prescription drugs has aged, and patents have expired. The US Food and Drug Administration (FDA) has set up an office of generic drugs, as 9 out of 10 drug prescriptions are for generic drugs, saving an approximate 2.2 trillion USD between 2009 and 2019 [31]. The FDA has issued 93 first-time generic drug approvals in 2021, as opposed to 50 new drug (i.e. new molecular entity), or use approvals [32, 33]. Generally, while pharmaceutical companies are willing to invest in the aforementioned first two drug repurposing categories, they lack interest in the repurposing of generic drugs [34]. Research into the repurposing of generic drugs is, therefore, often performed by academic researchers and non-profit organisations. Naturally, a repurposed generic drug has lower developmental times and costs that translate into a more inexpensive product for patients, thus reducing societal healthcare costs. These lower costs are of increasing importance in the light of ever-increasing prices for new drugs, an issue discussed at length elsewhere [35, 36]. Despite clear advantages, there are several barriers faced by researchers, especially when the repurposed drug is a generic. These barriers need to be addressed to allow this growing field to fulfil its full potential. In this article we will be focusing on the challenges faced when repurposing generic drugs, and their potential solutions, from the perspective of clinical pharmacologists and drug discovery scientists working in academia.

2 Financial Barriers to Drug Repurposing and Possible Solutions

One of the major challenges is the funding of repurposing trials, and the subsequent marketing authorisation process if a trial is successful. This is, on the one hand, due to lack of interest from commercial parties and, on the other, lack of public funding.

2.1 The Role of Commercial Parties, Marketing Protection and Pricing of Repurposed Generic Drugs

Generic drugs lack marketing protection, which leads to higher market competition. Thus, commercial parties are often hesitant to invest in repurposing of generic drugs, as the chances of recuperating their investment are deemed low [37]. Marketing protection comes in the form of patents (for generics usually 'second medical use' patents) issued by a patent office and data/marketing exclusivity granted by regulatory authorities. While the EU offers 1 year, and the US 3 years, of market exclusivity for a repurposed generic drug, provided certain conditions are met, these periods are too short to recuperate investments costs [38, 39]. Additionally, obtaining 'second medical use' patents for generic drugs can be difficult, as the repurposed indication may not be novel due to already published literature [38, 40]. Furthermore, enforcing a patent and/or marketing exclusivity of a repurposed generic may be difficult [38]. Another issue for commercial parties is that in many countries drug prices are fixed at the national level, and they may not be allowed to increase the price of a drug when they add a new indication, especially when the drug is old and sold at a low price [37]. This makes it harder to recoup their investment. For example, the repositioning and price negotiation of hydroxyurea for the treatment of chronic myeloid leukaemia was challenging, and even involved the highest national legal court in France. All these factors make it difficult for academic researchers to attract commercial partners. An example of a successfully repurposed generic drug is viloxazine, a

Table 1 Indications where generic drugs have been screened on potential targets and proposed for therapeutic use, without or with insufficient clinical advancement

Potential use	Drug name or class	Original indication or use	References
Acute coronary syndrome	Calcium channel blocker	Hypertension	Shimada et al. [25]
Amyotrophic lateral sclerosis	Ambroxol	Mucolytic agent	Bouscary et al. [5]
Alcohol use disorders	Topiramate	Epilepsy	Burnette et al. [6]
	Gabapentin	Epilepsy	
	Varenicline	Smoking cessation	
	Aripiprazole	Schizophrenia	
	Ondansetron	Nausea	
	Mifepristone	Medical abortion	
	Ibudilast	Asthma	
	Prazosin	Hypertension	
	N-acetylcysteine	Mucolytic agent	
	Suvorexant	Insomnia	
Alzheimer's disease	Bupivacaine	Local anaesthetic	Lee et al. [15]
	Topiramate	Epilepsy	
	Selegiline	Depression	
	Iproniazid	Depression	
Skin infections	Bumetanide	Edema	Palaniappan et al. [17]
Breast cancer	Ferumoxytol	Iron-deficiency anemia	Sillerud et al. [26]
Chagas disease	Levothyroxine	Hypothyroidism	Bellera et al. [4]
Clozapine-induced constipation	Lubiprostone	Constipation	Torrico et al. [29]
Cocaine use disorders	Zolmitriptan	Migraine	Garcia et al. [9]
Dermatological therapy	Levothyroxine	Hypothyroidism	Paus et al. [18]
Epilepsy	Losartan	Hypertension	Klein et al. [12]
	Isoflurane	Anaesthetic	
	Anakinra	Immunosuppressive agent	
	N-acetylcysteine	Mucolytic agent	
	Atorvastatin	Hypercholesterolemia	
	Ceftriaxon	Antibiotic	
	Sirolimus	Immunosuppressive agent	
	Fingolimod	Multiple sclerosis	
Familial amyloid polyneuropathy	Benzbromarone	Gout	Cotrina et al. [8]
Gaucher's disease	Ambroxol	Mucolytic agent	Kumar et al. [28]
Hematopoietic progenitor cell Transplantation	Treprostinil	Pulmonary hypertension	Kazemi et al. [11]
Invasive mycosis	Erythromycin	Antibiotic	Rossi et al. [21]
	Chenodiol	Gallstones	
	Riluzole	Amyotrophic lateral sclerosis	
	Nortriptyline	Depression	
	Promazine	Psychosis	
	Nisoldipine	Hypertension	
	Suloctidil	Arterial vasospasm	
	Ciclopirox	Dermatomycosis	
	Auranofin	Rheumatoid arthritis	
	Tamoxifen	Infertility	
	Triclabendazole	Fascioliasis	
Leprosy	Thalidomide	Morning sickness	Thangaraju et al. [27]
	Minocycline	Antibiotic	
	Apremilast	Psoriasis	
	Tenidap	Rheumatoid arthritis	

Table 1 (continued)

Potential use	Drug name or class	Original indication or use	References
Lichen planopilaris	Pioglitazone	Type 2 diabetes mellitus	Sanz et al. [24]
	Tofacitinib	Rheumatoid arthritis	
	Barcitinib	Rheumatoid arthritis	
	Apremilast	Psoriasis	
Myasthenia gravis	Ambroxol	Mucolytic agent	Cao et al. [7]
Myeloma	Tofacitinib	Rheumatoid arthritis	Lam et al. [13]
Neurodegenerative disease	Omarigliptin	Type 2 diabetes mellitus	Ayoub et al. [3]
Neuorinflammation	Thalidomide	Morning sickness	Jung et al. [10]
Non-alcoholic fatty liverdisease	Rosuvastatin	Hypercholesterolemia	Rotman et al., 2016 [22]
	Pentoxifylline	Peripheral arterial disease	
	Solithromycin	Antibiotic	
Primary biliary cholangitis	Rituximab	Lymphoma	Ronca et al. [20]
	Abatacept	Rheumatoid arthritis	
	Ustekinumab	Psoriasis	
	Fenofibrate	Hypertriglyceridemia	
	Simtuzumab	Fibrosis	
Rattlesnake bites	Batimastat	Metastatic cancer	Layfield et al. [14]
	Marimastat	Metastatic cancer	
Refractory chronic cough	Amitriptyline	Depression	Ryan et al. [23]
	Gabapentin	Epilepsy	
	Pregabalin	Epilepsy	
	Morphine	Analgesic	
	Tramadol	Analgesic	
Renal cell carcinoma	Penfluridol	Psychosis	Tung et al. [30]
	Metformin	Type 2 diabetes mellitus	Rausch et al. [19]
Zika virus	Sunitinib	Renal cell carcinoma	Lin et al. [16]

selective noradrenaline uptake inhibitor, which was originally approved and marketed for the treatment of depression in Europe but was never approved or marketed in the USA [41]. When viloxazine was subsequently repurposed for the treatment of attention-deficit hyperactivity disorder, it could therefore be classified as a new molecular entity in the USA (i.e. in the USA it was deemed a new drug instead of an existing drug with a new indication). This allowed for pricing that may cover development costs.

2.2 Orphan Drug Status

Many drugs are repurposed for rare, or orphan, diseases, where the patient population and potential market may be small. The Innovative Medicines Initiative recently reviewed this aspect [42]. Obtaining 'orphan drug status' from the EMA or FDA or in Japan can lead to 10 years of market protection, free regulatory advice for academic investigators and small companies, and potentially faster development. Thus, this can be a way of protecting future sales to reimburse development costs. However, as mentioned earlier, enforcing marketing protection may be difficult if the generic drug is already on the market, especially if the drug is available at the same dose as would be used in the rare, or orphan, disease and in a cheap dose form, as it may still be bought at the cheaper price. On the other hand, older drugs are not necessarily marketed around the world, so in some cases this problem can be avoided, as was the case with viloxazine.

2.3 The Role of Public Research Funding

There also is a lack of research funding agency and/or governmental research funding for larger drug repurposing trials and especially the subsequent marketing authorisation process, which represent an integral part of the drug repurposing process. While there are successful publicly funded projects, for example in cancer or COVID-19 research [43–45], most funding initiatives are aimed at earlier stage development and/or have insufficient funds for larger-scale clinical trials [46, 47]. Another issue, especially in disease areas where pharmaceutical companies are performing well-funded trials testing patented new molecular entities, is that

these well-funded trials compete with marginally funded drug repurposing trials for participating sites. Therefore, hospitals may be more reluctant to participate in drug repurposing trials due to budgetary constraints.

2.4 Examples of Repurposed Drugs: Successes and Failures

A famous success for repurposing was the use of sildenafil for erectile dysfunction, when the drug was being developed for cardiovascular disease [48]. Propranolol is used for shrinking infantile haemangiomas, based on serendipitous clinical observation, and is now a first-line therapy [49]. Similarly, sirolimus showed high efficacy in congenital therapy-resistant low-flow vascular malformations [50]. More recently, Hutchinson–Gilford progeria syndrome has been a target for repurposing. This rare disease, causing accelerated ageing, was modelled by analysing the steps involved in the production or degradation of mutant progerin, key to the disease [51]. Multiple agents were identified for repurposing, and some have progressed to clinical trials, with beneficial effects being reported for pravastatin, zoledronate and lonafarnib [51]. While this approach in a clearly defined rare disease may be hopeful, the small number of patients limits the number of clinical trials which can be performed. Progressing such an approach to ageing itself is fraught with difficulties. Agents such as metformin, rapamycin, aspirin, resveratrol, statins, melatonin and antioxidants have as of yet not revealed remarkable efficacy, as trials would require vast numbers of patients to counter the variables involved in testing the aged population [52]. However, the very precise decline in human performance in healthy individuals indicates that ageing may be related to entropy and may be difficult to treat [53].

Ambroxol is a safe mucolytic drug sold in 77 countries. Ambroxol has been found to modify glucosylceramidase activity by inhibiting the non-lysosomal enzyme, GBA2, while acting as a chaperone for the lysosomal enzyme GBA1 [5, 54–56]. Consequently, the drug is proposed for testing in phase II for amyotrophic lateral sclerosis (ALS), and in phase III for Parkinson's disease and Lewy body disease; however, funding has limited the extent of clinical trials [5, 57, 58]. Fortunately, it was recently announced that Cure Parkinson's will co-fund a phase III trial of ambroxol in Parkinson's disease [59].

Another example is the implementation of colchicine in the treatment of cardiovascular disease. Two large and one smaller randomised controlled trials showed the potency of colchicine in the prevention of cardiovascular events [60–62]. In addition, colchicine reduced healthcare costs in cost-effectiveness analyses [63]. This has led to the inclusion of colchicine in the most recent European Society of Cardiology guideline on cardiovascular disease prevention [64]. Two of these trials were completely publicly funded [61, 62]. The other trial was funded by a large contribution from a consortium of pharmaceutical companies and contributions from several public sources [60]. These are examples of successful academia-driven repurposing trials as well as a model for the potential of collaborative funding for such projects. However, as of yet colchicine does not have marketing authorisation for the treatment of cardiovascular disease despite one of the trials being co-sponsored by a consortium of pharmaceutical companies [60]. This is partly due to an earlier lack of interest from these companies to pursue marketing authorisation, as they were not allowed to increase drug prices. Consequently, colchicine can only be prescribed off-label for this indication at this time, which hampers its implementation in clinical practice. The legal responsibility of prescribers will not automatically be covered, for example. This ultimately results in an unnecessary public health loss, which, at its core, is a governmental concern.

2.5 Potential Solutions to Increase Funding for Generic Drug Repurposing

In our opinion, the largest stakeholder (i.e. the government) should bear the greatest financial burden, as it stands to gain the most from the public health benefit. Therefore, governmental organisations should increase their funding for drug repurposing research and the implementation process of repurposed drugs, which have shown benefit in clinical trials and are proven to be cost-effective. In the European Union, for example, a large dedicated drug repurposing funding programme similar to 'Horizon Europe' and the 'Computer-aided Drug Repurposing for Cancer Therapy Project' could be created [46, 65]. Second, insurance providers, whether public in the form of a governmental institution [e.g. the National Health Service (NHS) in the UK], or privatized in the form of insurance companies (e.g. as in the USA), are an important stakeholder in the healthcare system. These providers may benefit directly, in the form of cost-savings, if an inexpensive and cost-effective drug can be used for the treatment of a disease that places a significant financial burden on healthcare expenditure. Therefore, insurance providers should be incentivized to fund, or increase funding for, research on promising repurposed drugs in diseases that are costly to the healthcare system. Third, pharmaceutical companies should be encouraged to put more effort in the assessment of potential business models for repurposed drugs on a case-by-case basis. For instance, some repurposed drugs may have a large target population, and therefore a potentially large yearly production volume providing a good business model for generic pharmaceutical companies. Indeed, this was the case for colchicine, and a consortium of pharmaceutical companies are now pursuing label extension. Academic researchers performing drug repurposing could

play a role in convincing potential commercial parties. Others suggested extension of market exclusivity for repurposed (generic) drugs, which will attract commercial parties or other funding strategies such as 'social finance' as a possible solution for the lack of funding issue [38, 66].

3 Regulatory Barriers to Drug Repurposing and Possible Solutions

Despite confirmation of clinical effectiveness in clinical trials, a repurposed drug must obtain marketing authorisation from the regulatory authorities before the new indication can be added to the label and fully implemented in clinical practice.

3.1 Barriers to Obtaining Marketing Authorisation

Obtaining marketing authorisation is an important hurdle for academic researchers, as the regulatory process is complex. While academic researchers have knowledge on how to perform high-quality clinical trials, they often lack detailed knowledge of the authorisation process, time and other resources to obtain regulatory approval. Furthermore, academic researchers are usually not marketing authorisation holders, and often have no interest in becoming marketing authorisation holders themselves. Commercial parties (i.e. pharmaceutical companies), which are marketing authorisation holders, often lack interest in pursuing authorisation. Currently, regulatory requirements to extend a label are not risk proportionate for generic drugs which have been on the market for a long time. A critical factor is dose definition for safety and efficacy in the new indication, taking into account the publicly available data for a generic drug. The available toxicology data may be very old, and balancing safety based on clinical experience means being very careful about dosage increments. An unfortunate issue has arisen with the EMA in 2022, as they can now demand the original toxicology reports for registration. This means that the original pharmaceutical developer can negotiate a go/no-go situation after academic institutions, or small to medium enterprises, have taken on board all the risks and financed the clinical trials, even for very rare diseases where additional regulatory studies are prohibitively expensive to justify for the patient population. The original marketing authorisation holder might also be reluctant to disclose a dossier that was regulatory compliant 40 years ago but that will encounter numerous gaps if assessed using the current regulations. Furthermore, pharmacovigilance data in other populations will possibly raise new questions for their own marketing authorisation. In addition, it might be tempting to keep the dossier just in case new opportunities occur. Finally, after the marketing authorisation has been obtained, and the project leader moves to other activities/companies, retrieving all relevant documentation requires significant efforts. Discussions with regulatory bodies, and ethical committees, are critical, particularly if the pharmaceutical company which originally developed the compound is not cooperative in releasing data.

3.2 Current Initiatives to Ease the Marketing Authorisation Process

This issue has not gone unnoticed, and the EMA has recently launched a pilot project aimed at supporting academia and non-profit organisations to generate sufficient evidence on the use of a repurposed generic drug with the aim of having the new indication formally authorised by a regulatory authority [67, 68]. This is a good initiative, but it does not, however, address the lack of funding issue. While the EMA (or national competent authority) encourages the generation of a data package, academics still have to secure their own funding to perform the necessary research. Furthermore, they still have to fulfil the same strict regulatory requirements. Meanwhile, in the UK the NHS is developing a multifaceted strategy to support generic drug repurposing [69].

3.3 Potential Solutions for the Marketing Authorisation Process of Repurposed Generic Drugs

We propose that the regulatory authorities simplify the marketing authorisation process for repurposed generic drugs. A potential solution is to provide the regulatory authorities with tools to adapt rules, originally developed for the first marketing authorisation of a drug, when they have to assess a new indication for a generic drug, provided that the safety profile of the generic drug has been proven in clinical practice (by exposure of many thousands of patients) in the same dose as proposed for the new indication, and with no (or trivial) manufacturing change. This would reduce the burden of the marketing authorisation process both financially and in time investment. Consequently, more lucrative opportunities for commercial parties (or other parties) to pursue the marketing authorisation process will be created. Interestingly in the UK, a NHS-owned pharmaceutical contract manufacturer is a marketing authorization holder for some drugs [69]. This, at least in some countries, could be an interesting model to get repurposed drugs on label if researchers are unable, or unwilling, to become marketing authorization holders themselves.

Table 2 Lipophilic drugs liable to cause phospholipidosis which have been reported to be active in reducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in vitro (adapted from Tummino et al. [71])

Amiodarone	Chlorprothixene	Fluoxetine	Opipramol	Tamoxifen
Amodiaquine	Clemastine	Flupenthixol	Promethazine	Thioridazine
Astemizole	Clomipramine	Fluphenazine	Propafenone	Tilorone
Bix01294	Clomiphene	Haloperidol	Quinidine	Trifluoperazine
Cepharanthine	Desloratadine	Loperamide	Raloxifene	Trimipramine
Chloroquine	Ebastine	Maprotiline	Sertraline	Triparanol
Chlorpromazine	Fendiline	Nortriptyline	Spiperone	

4 Other Topics in Generic Drug Repurposing

4.1 Drug Repurposing During the COVID-19 Pandemic

The COVID-19 pandemic highlighted both the potential, as well as pitfalls, of generic drug repurposing. During the COVID-19 pandemic many generic drugs were claimed to be useful for the therapy of COVID-19, but were in many cases proven to be inefficacious. There are 3050 PubMed entries associated with the terms 'repurpose' and 'COVID-19'. Hydroxychloroquine, azithromycin, lopinavir/ritonavir and umifenovir were the most prescribed drugs worldwide up until the end of 2020, but with very little, or no, therapeutic benefit [70]. Nearly all the drugs that were proposed were lipophilic amphiphiles (Table 2) which can accumulate massively in cell membranes, and this can give positive results in vitro which do not translate in the clinic [71]. While ultimately not providing clinical success, the WHO-funded Solidarity trial is a good example of the value of large, well-designed, drug repurposing trials [45]. This trial was a collaboration between many countries and researchers, and set out to provide high-quality randomized clinical evidence on several drugs at a time when such evidence was lacking [72]. Dexamethasone was proven to have clinical benefit in the largely publicly funded RECOVERY trial [44]. These trials clearly demonstrate the value of drug repurposing and should encourage similar large-scale collaborations and funding for drug repurposing trials in the future. Following the RECOVERY trial, the EMA initiated a review by the Committee for Medicinal Products for Human Use (CHMP) which defined its safe and effective use in COVID-19. This allowed generic companies to quickly add this indication to their label using the recommendation issued by the CHMP. Unfortunately, if such a mechanism were to be generalised, there would be little incentive for private companies to perform clinical trials without full patent protection.

4.2 Tropical Diseases and Resource-Limited Countries

One of the great therapeutic needs is for the development of generic drugs in resource-limited countries (RLCs) where cheaper drugs may have a big health impact, especially for complex tropical diseases which may not be actively researched in high-income countries. The drug development process is very complex, frequently requiring resources that only pharmaceutical companies can provide, and it is therefore difficult for RLCs to meet requirements when they are the main beneficiaries of such trials. This is a highly relevant societal debate, and it is the same situation for rare diseases where financial returns do not relate to potential therapeutic value.

4.3 Post-Marketing-Authorisation Issues

A final issue is that academic scientists usually do not have any experience in sourcing, manufacturing, quality control (CMC) and supply chain, as well as regulatory affairs. Furthermore, maintaining a pharmacovigilance department in compliance with regulations and assuring drug supply to patients is a full-time job. This further limits the ability of academic scientists to successfully bring a repurposed drug to market.

5 Conclusion

In summary, the current generic drug repurposing research faces a number of challenges in obtaining research funds. Furthermore, regardless of the success of a repurposing trial, commercial parties often lack interest in pursuing marketing authorisation for financial reasons, and academic researchers lack the knowledge, time and funding. Therefore, the new indication of a repurposed drug often does not make it 'on label'. We propose a large increase in public funding for generic drug repurposing research, including funds for the marketing authorisation process when a trial is successful, and a reduction in the regulatory burden of the marketing authorisation process for repurposed generic drugs.

Declarations

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