British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2019) **85** 680–689 680

REVIEW

Using human experience to identify drug repurposing opportunities: theory and practice

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Received 8 October 2018; **Revised** 7 December 2018; **Accepted** 18 December 2018

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Keywords drug reprofiling, drug repurposing, drug rescue, retrospective data, therapeutic switching

Retrospective evidence drawn from real-world experience of a medicine's use outside its labelled indication is one of a number of techniques used in drug repurposing (DRP). Relying as it does on large numbers of real incidences of human experience, rather than individual case reports with limited statistical support, preclinical experiments with poor translatability or *in silico* associations, which are early-stage hypotheses, it represents the best validated form of DRP. Cancer is the most frequent of such DRP examples (e.g. aspirin in pancreatic cancer, hazard ratio = 0.25). This approach can be combined with pathway analysis to provide first-in-class treatments for complex diseases. Alternatively, it can be combined with prospective preclinical studies to uncover a validated mechanism for a new indication, after which a repurposed molecule is chemically optimized.

Introduction

Drug repurposing, also called drug repositioning, reprofiling or therapeutic switching is an innovative way of finding new indications for existing drugs and is now considered to be one of the major strategies to improve productivity in pharmaceutical research and development [1, 2]. The strategy offers shorter times for new medicine innovation, as well as reduced costs (most obviously the costs of the discovery phase) and lower rates of developmental attrition – which is unacceptably high [3, 4]. In a recent analysis of the economics of pharmaceutical innovation, Grabowski and DiMasi calculated that out-of-pocket costs for a new chemical entity were $1.395bn, compared to the costs for a *postapproval* product of $466 m [5]. Accordingly, it may be possible to obtain three repurposed medicines for the investment in one new chemical entity. This is important because high innovation costs are driving increasingly unaffordable drug costs for the healthcare systems of developed countries, not just in the publicly funded European systems, but also now in the USA. In addition, the public interest in new medicines to address unmet medical needs (particularly for the 95% of rare diseases for which there are no approved treatments) requires urgent solutions; such urgency is incompatible with innovation timescales than run slower than disease progression, as so vividly displayed by the debate about providing unapproved medicines for serious life-threatening conditions [6].

Approaches

Typically, a drug purposing strategy consists of three steps before taking the candidate drug further through the late stages of product development and approval: (i) identification of a candidate molecule for a given indication or candidate indication for given molecule (hypothesis generation); (ii) mechanistic assessment of the drug effect in preclinical models (validation); and (iii) evaluation of efficacy in phase II clinical trials (assuming there is sufficient safety data from phase I studies undertaken as part of the original indication). Of these, the identification of the right drug for an indication of interest with a high level of confidence is critical, and this is where the modern approaches for hypothesis generation could be most useful.

DOI:10.1111/bcp.13851

The identification of a new use for an existing drug is not a new idea – it is a common feature of the pharmacopeia. Historically, however, discoveries of this kind have not generally involved a systematic approach: for example, the use of thalidomide for erythema leprosum nodosum was based on serendipity whereas the discovery of the use of sildenafil (Viagra) citrate for erectile dysfunction resulted from astute clinical observation in a trial where the effect was not preplanned. Recently, various systematic approaches have been increasingly employed for the association of new indications for candidate molecules, including computational and experimental methodologies.

The purpose of this review is not to re-evaluate the world of drug repurposing as a whole, but to draw attention to the use of data from patients treated with Drug A for Indication A in order to discover, or underpin, the new use of Drug A for Indication B. This may be done to validate serendipitous clinical findings, as well as outputs from more systematic approaches to drug repurposing; but it can also be instantiated in a more purposeful way, to search for new uses from existing data absent such hypothetical foundations. Retrospective analysis is not a necessary component of the development of a new use for an existing drug. It was not, for example a component of the development of thalidomide for erythema leprosum nodosum: this arose from the case report of one doctor's prescription of thalidomide to a severely ill patient, and subsequent expansion by the same doctor of the evidence base to a case series, followed by clinical trials. Indeed, given the withdrawal of thalidomide from most markets in the 1960s, and the rarity of leprosy as a disease, retrospective analysis would be unlikely to be a fruitful approach.

Individual case reports, which often involve unexpected findings can often be the initiation point for drug repurposing developments, but are not statistically robust and, for the purposes of this review, are not included in the definition of retrospective human evidence. For example, the repurposed use of amantadine for Parkinson disease arose from a case report of one individual who reported an improvement in rigidity, tremor and akinesia while taking amantadine for flu. This observation was taken forward in a series of clinical trials of increasing size and power, resulting eventually in a regulatory approval of the use of amantadine for the treatment of Parkinson disease [7]. Again, retrospective data were not a component in either the validation or the development of this repurposed medicine.

Although neither necessary nor sufficient for drug repurposing development, as shown in Figure 1, the use of data from human experience can nevertheless be of significant value in either discovering or validating new indications for a particular drug at various stages in the translation into a new medicine.

Scientific complexities in translating repurposing hypotheses into marketed drugs

Despite the lower attrition rates, drug repurposing developments are not always successful. It is important to realise that

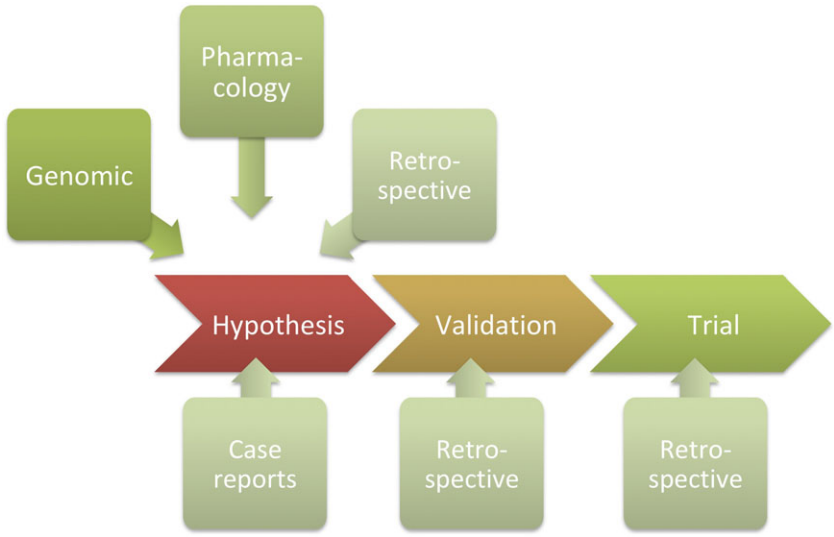

Figure 1

Purposeful involvement of retrospective analysis of human data at various stages in a drug repurposing development. Such analysis can be used for hypothesis generation, to validate hypotheses generated from genomic or pharmacological analysis, or can be used to refine indications and subgroups of patients in which medication is particularly beneficial from trial results. For example, the potential use of metformin in dementia can be evaluated: (i) as a hypothesis, from looking at cognitive performance of diabetic patients treated with metformin; (ii) to validate a hypothesis generated from genomic analysis associating genes most regulated in dementia with genes regulated by metformin; or (iii) from a trial in patients with cognitive dysfunction treated with metformin, to determine the relative benefit in situations involving vascular dementia relative to Alzheimer disease. Although case reports are often the bases for repurposing hypotheses, they lack statistical rigour and, for the purposes of this review, are not included in the definition of retrospective human evidence

the technology used for hypothesis generation is closely related to the confidence of its accuracy [8]. As in pharmaceutical research and development as a whole, there is a hierarchy of reliability, with *in silico* methods generally delivering less predictive power than preclinical pharmacological experiments, and these in turn providing less confidence than observations in humans. Pharmacological results from *in vitro* experiments are less reliable than from *in vivo* experiments, and repurposing hypotheses based on clinical data are more persuasive than any other form. This order of reliability is inverse to the costs of each technology, and one of the advantages of repurposing hypotheses based on *in silico* technology is the scale over which they can be conducted. This breadth can give rise to more novel hypotheses, from which may derive more robust patents. However, in almost all cases, *in silico* predictions are of little value until they are validated. Some examples of drug repurposing failures are shown in Box 1.

Box 1

Problems in translating drug repurposing hypotheses

Gene predictions: Several drug repurposing studies have been developed around an inverse signature methodology, including that of Sirota *et al*. [7], which tested for 'oppositeness' of gene expression signatures of disease to drug-induced signatures. Dudley *et al*. [8] compared the gene expression signature of inflammatory bowel diseases (IBD) to the gene expression profile of 164 drugs. Gene expression signature of the anti-epileptic drug topiramate anti-correlated with the gene expression signature of IBD. The potential efficacy of topiramate in IBD was validated using a rodent model of IBD in which topiramate significantly reduced diarrhoea, visual manifestations of colitis on endoscopy, and microscopic manifestations of disease on colonic biopsy. However, a recent retrospective cohort study has failed to show a beneficial effect of topiramate [9], leading to much uncertainty about the eventual utility of this drug in IBD: an appropriately designed and powered randomized-controlled trial would be required to definitively answer the question of whether topiramate can be used therapeutically in IBD.

In vivo pharmacology: latrepirdine (later trademarked as Dimebon) was an old nonselective antihistamine sold in Russia for the treatment of allergies. However, mechanistic studies also showed it had glutamatergic (NMDA) antagonistic and acetylcholinesterase inhibitory properties, both of which posited potential in neurodegenerative diseases such as Alzheimer and Huntington. Investigations in various animal models confirmed this potential utility and also indicated that the drug could affect the mitochondrial permeability transition and had neuroprotective effects against β-amyloid toxicity [10]. In a large Phase II clinical trial in mild–moderate Alzheimer's disease, 12 months of treatment showed a significant improvement in cognition relative to placebo [11]. Unfortunately, Phase III clinical trials produced negative results, without any significant gains on any of the five efficacy endpoints *vs*. placebo after 6 months of treatment, including *mini-mental state examination*, a standard measure of cognition. A further three Phase III trials also failed to show benefit in both Alzheimer and Huntington disease.

Clinical data: a variety of observational studies have been performed with respect to glioblastoma multiforme, the most lethal form of brain cancer, and the use of sodium valproate, an antiepileptic drug. Patients treated with sodium valproate for epilepsy have showed a improved outcome with respect to survival time and recurrence compared to patients treated with other antiepileptic drugs [12]. However, a more recent meta-analysis suggests this benefit is mainly found in older studies and in younger patients, indicating the need to exercise caution in assuming generalizability of the pooled effect. Overall, there is a considerable risk of bias in the current interpretation of the literature, and larger, prospective studies are required for validating these findings [13].

Despite much literature attention being paid to algorithmic approaches to drug repurposing, comparatively little attention has been paid to examples of new pharmaceutical uses deriving from retrospective clinical analysis. This is surprising because such analyses are validated in humans rather than *in vivo*, *in vitro* or *in silico*, generally using the same route of administration and dose as the marketed use, and they are therefore well positioned for rapid development to a new medicine with little or no experimental preamble and at low risk of technical failure. This comprehensive review attempts to correct this deficit.

Strategies for use of retrospective clinical evidence in repurposing development

Conventional medicinal innovation requires efficacy evidence to result from predeclared endpoints: these are prospective studies. This is the basis for randomized controlled trials upon which regulatory approval of pharmaceuticals is predicated. The prospective nature of the studies reduces the possibility of a chance finding. However, there are instances in which other things are found at the same time, which might be unexpected or unanticipated, and these observations can be taken further in subsequent prospective studies. In the much-quoted example of the discovery of sildenafil for erectile dysfunction, the role of cyclic GMP phosphodiesterase in the control of smooth muscle relaxation within the corpus cavernosum was suggested from academic research in the early 1990s [9]. In 1993, a pharmacokinetic study, which was conducted as part of a research programme designed to develop sildenafil for stable angina pectoris, reported sustained penile erections in volunteers treated with the drug. This led to the realization of the potential use of sildenafil for erectile dysfunction, and the initiation of a small efficacy trial in males with impotence. The significant success

of this trial then led to further large scale Phase IIb and Phase III investigations, and the approval of sildenafil in 1998. The success of this innovation stemmed from the observation in the original pharmacokinetic trial, which was not designed for this purpose. There has been a significant debate about whether this result was expected or unexpected, given the status of understanding of the biochemistry of smooth muscle relaxation in the early 1990s [9], leading to an invalidity judgement for the method of use patent by the European Patent Office, but it was unanticipated in the sense that the trial was not designed to discover this effect. Moreover, there is no doubt of the important role of the clinical study staff in the pharmacokinetic trial in making the observation which led to the repurposing of the drug. Generally, the retrospective analysis of clinical trial data as a means of uncovering new indications has been dealt with before [10] and is analogous to the use of patient data, which is the main focus for this review.

Another more obvious example of a chance observation, this time after the product had been marketed, is that of latanoprost. This is a prostaglandin-based drug, trade-named Xalatan, an ophthalmic solution used to reduce pressure inside the eye for the treatment of ocular hypertension and open angle glaucoma. Soon after the product was marketed, a patient comment about the eyelashes of her latanoprost-treated eye prompted unmasked examination of subsequent patients taking unilateral latanoprost. An observational study of patients reported increased thickness and length of eyelashes as a result of glaucoma treatment [11]. This led to the understanding that prostaglandin F agonists could cause hypertrichosis of the eyelash, and ultimately to the development of a related prostaglandin, bimatoprost, as a cosmetic for incorporation in mascara and eyeliner products under the tradename Latisse. There are two points to make here: first, unlike the sildenafil example, latanaprost was a marketed drug, and so observational data could be used to validate the initial finding; and secondly, this is not a new pharmaceutical use, but a cosmetic one, and required separate regulatory approval. The serendipitous nature of the finding is suggested by the fact that, while the side effect of increased iris pigmentation was uncovered during the clinical trials that led to the approval of latanoprost, the effect of the drug on eyelash thickening was not revealed until the report from a patient who had applied it in one eye.

A third example is that of raloxifene, a selective oestrogen receptor modulator (SORM), which was launched in the UK under the trade name Evista for the prevention of osteoporosis in postmenopausal women in 1998.

SORMs mimic oestrogen in some tissues and have antioestrogenic activity in others; the first SORM was tamoxifen, which was discovered in the 1950s and used from 1973 for the treatment of breast cancer. The original purpose of the research programme that led to raloxifene was not to discover drugs for osteoporosis, but for the treatment of breast cancer patients who were either resistant to tamoxifen or became so after starting treatment. Raloxifene was tested in a small 14-patient study, where it showed a poor response in the treatment of tamoxifen-resistant breast cancer patients, and this indication was abandoned for further development [12]. The developing company Lilly then made a deliberate decision to switch indications, bearing in mind the known involvement of oestrogen in osteoporosis, based on the high prevalence of osteoporosis in postmenopausal women, when oestrogen levels decline. In a randomized, double-blind, placebo-controlled trial, nearly 8000 women were treated for up to 2 years and effects on bone mineral density and reductions in vertebral fracture risk were assessed. The analysis showed that women taking raloxifene were 52% less likely to have a first spinal fracture. They used interim results from this study for the regulatory filing, which was granted a priority review by the Food and Drug Administration and subsequently approved for this indication in the USA in 1999. Slightly later, Lilly also evaluated it for the *prevention* (as opposed to treatment) of breast cancer. Looking at a continuation of the osteoporosis trial, they retrospectively analysed the risk of breast cancer in postmenopausal women receiving raloxifene for the treatment of osteoporosis. It appeared that there was a reduction of about 60% in the incidence of newly diagnosed breast cancer in this group of patients, and this led ultimately to the approval of raloxifene for reducing the risk of invasive breast cancer in postmenopausal women. In summary, while initially a failure in the *treatment* of tamoxifen-resistant breast cancer, raloxifene had proven to be effective in both treating osteoporosis and secondarily in the *prevention* of breast cancer; in the latter, it had proven to be a superior treatment to tamoxifen, in terms of risk of uterine and ophthalmic side effects [13]. This example of drug repurposing involves firstly the deliberate decision, based on scientific knowledge, to pursue osteoporosis when the initial development in tamoxifen-resistant breast cancer was unsuccessful, and then the observationally-based switch into prevention of breast cancer, as a result of *posthoc* analysis of patient data.

From the above examples, it is clear that observational analysis, whether during development or from measurements carried out later, represents a powerful way of finding associations in real patients. One promising way of finding new uses (as well as validating hypotheses derived from other repurposing methods) for drugs is to analyse outcomes from patients. Importantly, unlike *in silico* studies or pharmacological experiments, examinations of what happens to patients reveal effects that are relevant to the specific dose and by the specific route of administration relevant to the product for the primary indication. A particularly valuable UK resource in this regard is the Clinical Practice Research Datalink, based on the experiences of the National Health Service in the 70 years since it was established. The Clinical Practice Research Datalink is a rich source for retrospective analysis of this kind [13]. Cancer protection is an area that is particularly likely to be identified as an unintended benefit of a treatment because the observation of malignancy is a possible indication of carcinogenicity of a drug and should therefore always be recorded as a potential *adverse* side effect. However, if the incidence of cancer for patients on a particular drug is less than would be anticipated by chance, the drug may be exerting a protective anticancer effect. A number of interesting anti-cancer associations have been found, and drugs as diverse as metformin (an antidiabetic), propranolol (an antihypertensive) and clomipramine (an antidepressant) may have useful anticancer properties (see Table 1 below). Metformin in particular has raised hopes not just for preventing, but also for treating cancer, and a number of trials have begun for the use of this drug, including a large-scale

Table 1

Retrospective associations suggesting novel uses for existing pharmaceuticals

Mechanism (where known) or drug	Indication	Reference
5-HT uptake inhibitor	Myocardial infarction	[26]
ACE inhibitor	Alzheimer disease	[27]
ACE inhibitor	Cachexia	[22]
ACE inhibitor	Immune downregulation	[28]
ACE inhibitor; Angiotensin II (AT1) antagonist	Nonalcoholic steatohepatitis	[29]
Acetylcholinesterase inhibitor	Autism	[30]
Angiotensin II (AT1) antagonists	Alzheimer disease	[31]
Beta-2-adrenergic antagonist	Parkinson disease	[32]
Beta-adrenergic antagonist	Alzheimer disease	[27]
Beta-adrenergic antagonist	Cancer	[33]
Beta-adrenergic antagonist	Cancer metastasis; cancer, breast	[34]
Beta-adrenergic antagonist	Cancer, liver	[35]
Beta-adrenergic antagonist	Cancer, lung	[36]
Beta-adrenergic antagonist	Cancer, ovarian	[37]
Beta-adrenergic antagonist	Cancer, prostate	[38]
Beta-adrenergic antagonist	Melanoma	[39]
Beta-adrenergic antagonist	Osteoporosis	[40]
Bisphosphonate	Sepsis, ARDS	[41]
Calcium channel blockers	Alzheimer disease	[42]
Calcium channel blockers	Cancer, lung	[43]
Dipeptidyl peptidase (DPP-IV) inhibitor	Inflammatory bowel disease	[44]
Gefitinib	Asthma	[45]
Glibenclamide	Sepsis	[46]
Glycogen synthase kinase 3 (GSK-3) inhibitor	Cancer	[47]
Histamine H2 antagonist	Lung fibrosis	[48]

(continues)

Table 1

(Continued)

Mechanism (where known) or drug	Indication	Reference
HMG-CoA reductase inhibitor	Age-related macular degeneration	[49]
HMG-CoA reductase inhibitor	Alzheimer disease	[50]
HMG-CoA reductase inhibitor	Asthma	[51]
HMG-CoA reductase inhibitor	Bacterial diseases	[52]
HMG-CoA reductase inhibitor	Burn injury	[53]
HMG-CoA reductase inhibitor	Cancer	Oesophageal [54]; liver [55]; prostate [56]
HMG-CoA reductase inhibitor	Cataracts	[57]
ACE inhibitor; HMG-CoA reductase inhibitor	chronic obstructive pulmonary disease	[58]
HMG-CoA reductase inhibitor	Depression	[59]
HMG-CoA reductase inhibitor	Epilepsy	[60]
HMG-CoA reductase inhibitor	Glaucoma	[61]
HMG-CoA reductase inhibitor	Influenza, chronic obstructive pulmonary disease	[62]
HMG-CoA reductase inhibitor	Osteoporosis	[63]
HMG-CoA reductase inhibitor	Periodontitis	[64]
HMG-CoA reductase inhibitor	Pneumonia	[65]
HMG-CoA reductase inhibitor	Rheumatoid arthritis	[66]
HMG-CoA reductase inhibitor	Sepsis	[67]
HMG-CoA reductase inhibitor	Transplant rejection	[68]
Hydroxychloriquine	Diabetes (type II)	[69]
Ibuprofen	Parkinson disease	[70]
Ketamine	Fatigue	[71]
Metformin	Alzheimer disease	[72, 73],
Metformin	Cancer	Bladder [74, 75]; colorectal [76]; endometrial [77]; liver [78]; lung [79]; pancreatic [80]; prostate [81];

(continues)

Table 1

(Continued)

Mechanism (where known) or drug	Indication	Reference
Metformin	Psoriasis	[82]
Modafinil	Depression	[83]
NSAIDs	Cancer	Breast [84]; colorectal [85]
NSAIDs	Depression	[86]
NSAIDs	Sepsis, ARDS	[87]
Na+/K+ ATPase inhibitor (digoxin)	Cancer	Lung [88]; prostate [89]
NMDA antagonist	Bipolar disorder	[90]
PPAR γ-agonists	Cancer, colorectal; cancer, liver	[91]
PPAR γ-agonists	Parkinson disease	[92]
PPAR γ-agonists	Psoriasis	[82]
Quinolone antibiotic	Cancer	[93]
SORM (selective oestrogen receptor modulator)	Kidney disease, chronic (renal failure)	[94]
Sulfonylureas	Stroke	[19]
TNF antagonist	Cancer	[96]
TNF antagonist	Diabetes (type II)	[97]
TNF antagonist	Kawasaki disease	[98]
TNF antagonist	Stroke	[95]
TNF antagonist	Systemic vasculitis	[98]
Tricyclic antidepressants	Cancer	[99]
Valproic acid	Cancer, prostate	[100]
VEGF monoclonal antibody	Brain and spinal cord injury	[101]

Abbreviations. ACE, angiotensin converting enzyme; HMG-CoA, 3-hydroxy-3-methyl-glutaryl-coenzyme A; NMDA, N-Methyl-D-aspartate; NSAID, non-steroidal anti-inflammatory drug; PPAR, peroxisome proliferator-activated receptor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor

adjuvant study in breast cancer [14]. It is important to differentiate the effect from this analysis as a cancer-preventative agent with its utility as a cancer-curative agent: prevention may relate to an effect against mutation or metastasis, whereas treatment of advanced cancer may not benefit from a drug confined in its effect to these early aspects of malignancy (similar to the situation described earlier with raloxifene); and secondly, the retrospective identification of an association is not proof positive from a prospective viewpoint. These two issues aside, this type of study is of significant power in drug repurposing.

A survey of retrospective evidence in a variety of possible secondary indications is shown in Table 1 below. One of the most important, and best-evidenced examples of retrospective data underpinning an additional use is that of aspirin in cancer. Aspirin's effects in oncology actually represent the third utility for this most widespread of medicines, since its use beyond inflammatory analgesia, as an antithrombotic, were revealed by mechanism-based studies of cyclooxygenase inhibition by Sir John Vane in the 1960s. Its pharmacological effects in preventing platelet aggregation were translated, in a purposeful way, into a clinically substantiated use to prevent heart attacks and stroke in the 1980s, and specific low-dose aspirin formulations are now sold for this effect. But the attribution of an anticancer effect relies mainly on a retrospective analysis of the incidence of various cancers in patients taking aspirin for long-term cardiovascular purposes. In a very large meta-analysis of 25 000 such patients and controls [15], daily treatment with aspirin was associated with a significant reduction in various gastrointestinal cancers. In the case of pancreatic cancer, the hazard ratio for death from the disease in patients having used aspirin for 5 years or more was 0.25 (P = 0.04), whereas that for colorectal cancer was 0.41 (P = 0.05). Despite this evidence, the translation of the associative relationship into an approved anticancer aspirin-based product has not yet transpired; the differences between preventative and curative effects are salient in this regard, but so are the problems for a company seeking to commercialize such a development against a backdrop of widespread generic availability of aspirin for other uses. The other caveat for this third use of aspirin is its safety, since gastropathy is a risk in all patients who take such medication long-term.

It is clear from Table 1, that retrospective effects have been identified in many areas in addition to cancer. A further example of the difference between prevention and treatment, is revealed by the example of the use of β-hydroxy β-methylglutaryl-CoA reductase inhibitors (statins) in sepsis. In this case, rosuvastatin was not associated with an improvement in 60-day mortality in sepsis-associated acute respiratory distress syndrome (ARDS) [16], despite the various epidemiological associations of reduced mortality in statin users with sepsis. The difference between the two results can be attributed to the need for long-term dosing with statins for the production of their benefits against vascular leak, through inhibition of RhoA prenylation, an off-target effect of these drugs. A clinical benefit of statins in an emergency situation involving sepsis would require a much more immediate effect than can be produced by this mechanism. Similarly, the effect of aspirin in ARDS revealed from retrospective analysis [17] was not repeated in a prospective trial where no significant difference was found in newly developed ARDS [18].

Strategically, an effect revealed by retrospective analysis does not necessarily lead to development of that agent in a new indication. In some cases, it can provide excellent target validation for another discovery programme. For example, the antidiabetic sulfonylureas, which inhibit ATP-sensitive K^+ (K_{ATP}) channels in pancreatic β-cells and stimulate insulin release in diabetes mellitus, mediate their effect on K_{ATP} channels via a high-affinity sulfonylurea receptor (SUR). When looked at retrospectively in diabetic patients with ischaemic stroke, sulfonylurea drugs such as glibenclamide conferred

protection against swelling and symptomatic haemorrhagic transformation. Analysis of the brain tissue obtained intraoperatively from such patients showed upregulation of the SUR1 subtype of the sulfonylurea receptor [19]. Further cellular analysis of the SUR1 receptor in astrocytes showed that its effect on cytotoxic oedema is mediated via a nonselective cation channel, the NC (Ca-ATP) channel [20, 21]. This represents a potential new therapeutic approach to stroke.

An interesting example of retrospective analysis leading to a clinically effective agent is in the area of cachexia. Cachexia is formally defined as the loss of >5% of body weight over a period of <12 months, normally in association with a chronic disease. It occurs commonly with not only cancer, but also chronic heart failure, kidney disease and chronic obstructive pulmonary disease. A re-examination of various clinical trials of therapeutic agents for chronic heart failure, specifically those of ACE inhibitors [22] and β-blockers [23], looked at weight as a marker for cachexia. Both these classes of drug have been formally investigated for the treatment of chronic heart failure. Weight is, of course, routinely measured in any clinical trial protocol, so the re-analysis could be done without the need for additional measurements. In the case of the β-blockers, a stratification exercise to delineate the mechanistic basis indicated the involvement of β-1 and β-2 adrenergic as well as 5-HT1A receptors for optimal activity, and identification of S-pindolol (which possesses all three of these activities) as a preferred agent with greater efficacy than other similar agents, including its racemate [24]. Interestingly, in the subsequent ACT-ONE clinical trial, at therapeutic doses that do not decrease blood pressure, the product is not only highly effective for alleviation of catabolism, but also promotes anabolism and improves functional ability in cancer cachectic patients [25].

Conclusion

In conclusion, retrospective or observational analysis of human experience may prove of substantial benefit in identifying novel uses for existing drugs. The examples described herein involve such analysis in various stages in a drug's life, from early in development where a pharmacokinetic trial gave rise to the discovery of sildenafil for erectile dysfunction, through to an unexpected observation of increased eyelash growth in an antiglaucoma drug. In some cases, the secondary use might have been (almost) identified at the start of the project, as in the case of raloxifene, which was initially tested (unsuccessfully) for the treatment of breast cancer, and later became used for the prevention of breast cancer. The advantages of retrospective analysis include the fact that the dose and route of administration have been specified, in the biological species of interest, but nuances and uncertainties still persist. Most particularly, an association observed *post facto* does not necessarily imply a causal relationship, and prevention of a condition is not the same as treating it, since the latter implies a more stringent requirement to reverse the pathology.

Conflicts of Interest

The author is principal and director of Numedicus Limited, a drug repurposing consultancy.

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