Drug repurposing in neurological diseases: an integrated approach to reduce trial and error

Alexander E. Clout,[1] Oscar Della Pasqua,[1,2] Michael G. Hanna,[3] Mine Orlu,[1,*] Robert D.S. Pitceathly[3,*]

Affiliations:

1. UCL School of Pharmacy, London, United Kingdom
2. GlaxoSmithKline, Clinical Pharmacology Modelling & Simulation, UK
3. MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology and National Hospital of Neurology and Neurosurgery, London, United Kingdom

*Joint last authorship.

Correspondence may be addressed to:

Robert D.S. Pitceathly

MRC Centre for Neuromuscular Diseases, UCL Queen Square Institute of Neurology and National Hospital of Neurology and Neurosurgery, Queen Square, London WC1N 3BG, United Kingdom.

Phone: 02031087527

Email: r.pitceathly@ucl.ac.uk

Correspondence may also be addressed to:

Mine Orlu

UCL School of Pharmacy, 29-39 Brunswick Square, London, WC1N 1AX, United Kingdom.

Phone: 02077535968

Email: m.orlu@ucl.ac.uk

References: 47

Word count: 4571

Abstract

Identifying effective disease modifying therapies for neurological diseases remains an important challenge in drug discovery and development. Drug repurposing attempts to determine new indications for pre-existing compounds and represents a major opportunity to address this clinically unmet need. It is potentially more cost effective and time efficient than *de novo* drug development and has yielded notable successes in neurological disorders. However, across all medical disciplines only 30% of repurposed drugs, and 10% of novel candidate molecules, gain market approval. One potentially significant contributor towards this limited success rate is an incomplete knowledge of the exposure-response relationships for the compounds of interest, and how these relate to the new indication, prior to commencing a new trial. We will provide an overview of the current approach to early stage drug repurposing and consider the issues contributing to inconclusive, or possibly falsely negative, Phase II and III trial outcomes in neurological diseases by including examples that illustrate the limitations of empirical evidence generation without a strong scientific basis for the dose rationale. We conclude with a framework suggesting a translational, iterative approach that integrates pharmacological, pharmaceutical and clinical expertise towards preclinical and early clinical drug development. This ensures appropriate dosing regimen, route of administration, and/or formulation are selected for the new indication before their evaluation in prospective clinical trials.

Keywords: repurposing; repositioning; neurological diseases; dose rationale; formulation; clinical trials; PKPD

Abbreviations: ALS = amyotrophic lateral sclerosis; EMA = European Medicines Agency; FDA = US Food and Drug Administration; FIH = first-in-human; GCP = good clinical practice; GLP = good laboratory practice; GMP = good manufacturing practice; IMP = investigational medicinal product; MAD = multiple ascending dose; MDS = Myelodysplastic Syndrome; NCATS = National Center for Advancing Translational Sciences; NIH = National Institute of Health; PK = pharmacokinetic; PKPD = pharmacokinetic-pharmacodynamic; POC = proof-of-concept; PPAR-γ = peroxisome proliferator-activated receptor-γ; RRMS = Relapsing-Remitting Multiple Sclerosis; SAD = single ascending dose; SPMS = Secondary Progressive Multiple Sclerosis.

Introduction

'Drug repurposing' encompasses a variety of different strategies employed to existing compounds, that have been partly or fully developed for one or more diseases, with the ultimate aim of successfully registering the drug for a new, and potentially patentable, indication. The two main approaches to drug repurposing comprise: 1) repositioning – the pathway by which the formulation of a drug used for one indication is trialled for treatment of a new indication; and 2) reformulation – altering an existing formulation for administration of a new dose, via a new route, or both. These two strategies can also be combined – repositioning aided by reformulation – to develop a new formulation from a known drug for a new indication [1]. As with *de novo* development, both routes to a successfully repurposed drug necessitate a thorough understanding of the dosing requirements for the intended indication.

Frequently, the decision to repurpose a drug centres on insights gained from the mechanism of action underpinning the pharmacological effect for the treatment of a particular condition, or signals arising from experimental evidence or clinical use. These insights arise as a consequence of experience and are accompanied by the benefit of the potential time and money saving they confer over *de novo* development on route to market approval [2], given that relevant preclinical (including both non-clinical and Phase 0, Figure 1) and clinical safety data for the original indication are often available. However, the subsequent steps to drug development from Phase II onwards often harnesses existing preclinical data focused on the original indication, with little consideration afforded to the pharmacology, dose rationale and formulation requirements of the compound in relation to the new disease being targeted (Figure 1). Consequently, researchers are simply repositioning when they should be reassessing the dose rationale, repositioning and reformulating. From 1980 to 2012 only 24% of repurposed drug candidates were successfully marketed and only 2% achieved success in an unrelated therapeutic arena to that of the original indication [3]. Although some of these failures were a direct consequence of poor efficacy, it is highly probable that many trial outcomes were falsely negative because of the incorrect assumption that the dose and route of administration for one indication should automatically apply towards another. Two such examples of a dose dependent drug effects include: 1) amitriptyline, which should be used at relatively low doses (up to 75 mg) for migraine prevention and neuropathic pain, while higher doses (up to 150 mg) are required for effective treatment of major depressive disorder [4]; and 2) zonisamide, dosed at 300 mg/day when treating focal seizures in adults with newly diagnosed epilepsy, but with proven efficacy in the case of Parkinson's disease at doses of 25-50 mg/day [5].

From 2006 to 2015 the proportion of new drugs targeting neurological diseases entering Phase I trials successfully achieving market approval was 8.4%, versus 9.6% of drugs in all therapeutic arenas (including neurology). However, the real difference between these figures is considerable, given that neurology had the second highest number of drug candidates entering Phase I trials in the period examined and, together with oncology, significantly lowered the overall success levels across all medical domains [6]. Moreover, historically neurological disease characterisation has relied upon the clinical phenotype, rather than an in-depth understanding of the underlying pathophysiology. Thus, the mechanism of action by which a drug achieved its therapeutic effect was not necessarily fully understood [7]. CNS active drugs would therefore often produce off-target effects [8], commonly due to known secondary pharmacological activity resulting from poor selectivity of the compounds for a single target. There is therefore a major opportunity for drug repurposing in neurological disorders, particularly given that the highest success rates are gained from compounds within the same therapeutic area [3]. In 2012 the US National Institute of Health (NIH) launched a drug repurposing scheme, as part of the National Center for Advancing Translational Sciences (NCATS), for 58 previously abandoned therapeutics, 30% of which had originally been considered for CNS indications [9]. This library has since grown to 2,500 approved small molecules and 1,000 unapproved investigational compounds [10]. Although NCATS, and other similar initiatives, have the potential to deliver life-changing therapies for neurological diseases more efficiently than *de novo* methods, it is crucial the drug development process adopts a translational iterative approach, harnessing the combined expertise from the scientific, clinical, preclinical, and regulatory sectors. Sheiner's learning and confirming paradigm [11], by which initial experimental data is generated in an effort to learn as much as possible about the particular element of the investigation, should also be applied at each iteration. Optimised studies are then undertaken to confirm what has been learned.

Drug repurposing can bypass some of the costs linked to the early phases of *de novo* drug development. However, these savings are not always reinvested back towards establishing in-depth understanding of the pharmacology of both the drug and the disease prior to exploratory or even confirmatory efficacy trials. Irrespective of the gaps in knowledge about the mechanism of action of a candidate compound, evaluation of the exposure–response relationship remains an essential requirement of the repurposing developmental path. Evidence that the drug reaches the target tissue, binds to its target(s) or receptor(s) and produces the required activity/inhibition, yielding the expected pharmacological downstream effects, is necessary prior to repositioning and/or reformulation. The existing data for the compound should also be scrutinised to determine the optimal route of administration and

whether this is likely to be therapeutically feasible or effective. If not, further human pharmacology studies are required. Once these data are available, it is possible to define the requirements not only for the most effective formulation but also identify suitable dosing regimens. This cyclic process should not be perceived as inefficient, but rather the foundation on which to build conclusive evidence of the therapeutic dose necessary for the repurposed condition. For example, results of therapeutic confirmatory studies (conventionally referred to as Phase III) [12] may necessitate further therapeutic exploratory (Phase II) or human pharmacology (Phase I) studies, eventually resulting in another cycle of therapeutic confirmatory (Phase III) studies.

We utilise case studies to illustrate current strategies and potential flaws to drug repurposing, the relevance of pharmacokinetic-pharmacodynamic (PKPD) relationships for establishing the dose rationale for the newly proposed indication and the challenges associated with the translation, in a strictly quantitative manner, of drug effects in preclinical experimental models of disease. The implication of such limitations for drug repurposing, and how these contribute towards the high attrition during late clinical development and licensing stages, is discussed. Finally, we propose an approach to drug product design that ensures integration of pharmacology, formulation and clinical expertise during the preclinical and early clinical phase, with an emphasis on the utility of PKPD relationships as a predictor or marker of efficacy for the repurposing of compounds for neurological diseases. We also discuss the requirements for a combined analysis of existing toxicology, clinical safety and safety pharmacology data before the implementation of a clinical trial protocol. This knowledge has been underutilised, preventing the optimisation of experimental protocols, and consequently the potential for regulatory approval. Re-examining failed repurposing attempts suggests numerous factors contribute towards the high attrition rate, ranging from a lack of representative disease animal models to an emphasis towards drug efficacy, without adequate investigation of the mechanism of action in the proposed new indication. However, in this review, we will focus primarily on the need for a robust dose rationale to avoid falsely negative trial outcomes, highlighting the importance of integrating PK data at an early stage of the clinical program to ensure data generation yields evidence of a dose-exposure-response curve.

Case studies

Numerous examples exist of failed and successful drug repurposing attempts in neurological diseases (Table 1). A recent report [7] lists 118 repurposed drug products for 203 new CNS indications prior to January 2016; 102 approved and 101 in development. One common feature to the many failed attempts at drug repurposing relates to the poor dose rationale and inadequate preclinical PKPD studies, as reflected by empirical dose selection and absence of data suitable for the characterisation of dose-exposure-response relationships. In the next paragraphs, different, informative case studies are described, including both failed and successful attempts at drug repurposing, and explore the factors that influenced the outcomes.

First, riluzole, a drug successfully licensed for the treatment of amyotrophic lateral sclerosis (ALS), has been repurposed to treat Huntington's disease. Selecting riluzole to treat Huntington's disease was based on the previously documented neuroprotective properties on quinolate-induced neuronal damage in rats [13]. Riluzole exhibited promising results in preclinical animal disease models, in which a twice daily intravenous dose of 8 mg/kg produced significant reduction in the dyskinesia index of baboons with chemically induced progressive striatal degeneration. In one follow up study by the same group, when delivered intravenously at a dose of 8 mg/kg/day, riluzole reduced the volume of chemically induced striatal lesions in rats. The same animals showed reduced loss of motor function as compared to those in the group treated with the vehicle alone. Three pilot human studies [14–16] demonstrated similar results, in addition to a reduction in chorea intensity. However, riluzole failed to meet efficacy outcome measures during Phase III clinical trials due to inadequate dose selection (50 mg twice daily), which was based on that shown to be efficacious and exhibiting the "best safety profile" with regard to liver toxicity when trialled for use in ALS [17]. This choice did not consider a putative target exposure levels in pre-clinical models or in patients, i.e. doses were selected without assessing the implications of interindividual pharmacokinetic differences. In addition, analysis of the original dose-ranging study in patients with ALS [18] demonstrates little difference in the safety profile of 100 mg/day and 200 mg/day doses, suggesting a two-fold increase in dose size would not have been untenable. Reformulating riluzole might therefore have been feasible during its repurposing for Huntington's disease. Whilst incomplete understanding of the mechanism by which riluzole achieves its therapeutic effect in ALS and Huntington's disease highlights the challenges one faces for the evaluation of efficacy, clinical development of both *de novo* and repurposed drugs is clearly compounded by the absence of relevant pharmacokinetic data.

Second, pioglitazone, a PPAR-γ (peroxisome proliferator-activated receptor-γ) transcription factor activator used to treat diabetes, was chosen as a repurposing candidate to target ALS, given its neuroprotective and anti-inflammatory properties. It was also shown to increase the survival of a transgenic mouse model of ALS [19–21]. It was utilised as an add-on therapy in conjunction with riluzole. However, the Phase II trial was terminated as interim analysis suggested no tendency in favour of the treated group [22]. The explanations for the negative outcome included inadequate design of the preclinical animal studies, which did not comprise the assessment of PKPD relationships, poor correlation between the animal model and the disease in humans, and the masking of the therapeutic effect of pioglitazone by concurrent treatment with riluzole. However, the negative outcome was not attributed to the pharmacokinetic properties of the compound, which has a volume of distribution of 0.25 L/kg (i.e.,17.5 L for a 70 kg adult patient) [23]. This figure indicates that pioglitazone does not distribute much beyond the extravascular space, making it unsuitable for an indication that requires CNS penetration. Riluzole, in contrast, has a volume of distribution of 3.4 L/kg [24]. In addition, the authors state in their justification that the experimental regimen was based on the doses used for diabetes, an indication for which a small volume of distribution is desirable. Disregard for pharmacokinetics along with the lack of insight into target tissue distribution also explains the failure of five clinical trials with pioglitazone and rosiglitazone in Alzheimer's disease [25].

Third, mexiletine, an antiarrhythmic drug, has been repurposed to treat myotonia congenita [26] following the success of procaine, a lidocaine derivative [27,28]. Despite the success of mexiletine, it appears that the protocol did not adopt a comprehensive evaluation of the dose rationale or feasibility of different routes of administration. On the basis of the efficacy detected after 200 mg three times a day, the first controlled clinical trial of mexiletine [29] was designed to include a "moderate" dose of 400 mg/day in either two or three daily doses, with the possibility to increase it up to 600 mg/day. Clearly, the proposed doses and dosing regimens were limited to those known to be effective and safe for the prior indication (i.e. arrhythmia). Similarly, there was no attempt to characterise the underlying exposure-response relationship.

Finally, doxycycline, a second-generation tetracycline, has shown promising neuroprotective effects in animal models of Parkinson's disease by reducing neuroinflammation [30]. Given that anti-inflammatory treatments alone have proven an inadequate preventative against neurodegeneration, González-Lizárraga *et al* recently investigated the capacity of doxycycline to disrupt the formation of fibrils from the accumulation of α-synuclein amyloid aggregates in neural or glial cells, a common occurrence in neurodegenerative disorders

such as Parkinson's disease, dementia with Lewy bodies and multiple system atrophy [31]. These data confirmed that doxycycline acts to interfere with α-synuclein early aggregation intermediates and generates off-pathway species that do not form fibrils, while blocking the seeding capacity of preformed aggregates. The investigation included dose ranging with different treatment arms. Assessment of the dose-response curve indicated that the dose of doxycycline required to achieve neuroprotective effects was 20-40 mg per day, significantly lower than the 200 mg twice daily antimicrobial dose. Equally important, this sub-antibiotic dose is low enough that it does not induce bacterial resistance to the drug [30].

At first glance, these examples seem to follow an entirely appropriate rationale for drug repositioning; they all had mechanisms of action proven to show potential therapeutic benefit in the proposed indication. In the cases of riluzole and pioglitazone, medicines formulated for one indication were applied to another without considering reformulation, optimal dose range, pharmacokinetic, or pharmacodynamic properties. Consequently, two of the four compounds failed in their respective trials due to the "apparent" lack of efficacy. Despite the discontinuation of the clinical trials, it is possible that a positive outcome might have been achieved with riluzole, if the dose, route of administration, or both had been further examined to establish optimal dosing regimen for the target patient population.

Failure to demonstrate efficacy is not confined to repurposed drugs; similar limitations are also common at the early clinical phase of *de novo* drugs as well. Nevertheless, negative clinical studies can contribute significantly towards understanding the potential of drug repurposing, if results are conclusive. i.e., the absence of clinical benefit is supported by insight into target tissue exposure along with the underlying dose-exposure-response relationship. Irrespective of the level of understanding of the mechanism(s) of action, the availability of such data within early phase studies may prevent progression of non-efficacious compounds and reduce attrition during later stages of development.

In the case of mexiletine, empirical evidence of efficacy was associated with both repositioning and reformulation. However, the implications of uncertainty about the dose rationale should not be overlooked. The lower therapeutic dose for the new indication clearly highlights the need for accurate characterisation of the exposure-response relationship for the new indication. By contrast, for doxycycline, the investigators consideration of the dose-response relationship during the initial clinical trials, possibly driven by the fear of antibiotic resistance, echoes the approach proposed in this article, and has shown the two-fold benefit, namely the selection of the appropriate dose for the new indication, while avoiding the instigation of antibiotic resistance.

The first two case studies also demonstrate that clinical trials are often undertaken without the necessary understanding of the role of pharmacokinetics and target tissue distribution, thereby ignoring the relevance of characterising PKPD relationships. Furthermore, they highlight the fact that efficacy and safety data from small clinical trials alone cannot be taken at face validity. i.e. they do not necessarily provide irrefutable evidence of causality. Frequently, choices concerning the dose and dosing regimen, route of administration, and formulation are based on time and cost minimisation, including opportunities to avoid additional data generation or regulatory scrutiny. As a result, even statistically powered studies suffer from a poor scientific rationale. In the absence of clear understanding of the mechanism of action (and target or receptor system associated with the disease or condition), basic quantitative clinical pharmacology concepts become critical for the identification of potentially efficacious and safe exposure range [32]. These concepts can then be applied to formulation development to ensure the appropriate pharmacokinetic profile is identified prior to the clinical evaluation in patients.

Outstanding challenges and potential solutions

Drug candidates repurposed for new indications frequently fail at Phase II and III trials because of perceived failures in efficacy [38], despite initial evidence from preclinical and clinical protocols suggesting a therapeutic benefit in the new indication. In most cases, these failures are compounded by insufficient attention afforded to a more comprehensive, quantitative characterisation of the PKPD relationships and dose rationale prior to the undertaking of human clinical trials. Moreover, in any repurposing effort, there must not only be clarity about the primary question (is the drug efficacious?) but also the requirements for progression to regulatory approval. Rather than focusing on finding the quickest route to demonstrate efficacy in the proposed indication, via hasty proof-of-concept studies, time should be devoted to defining a well-thought development plan that takes into account information obtained during previous development cycles and uses this knowledge to streamline the work necessary at each phase. It is essential that researchers no longer view the stages of drug repurposing as a hierarchy, with preclinical processes, such as the assessment of pharmacology and reformulation, at the bottom and clinical questions the top. Instead, preclinical investigations as well as historical clinical data needs to be fully integrated into the development plan and the value of its associated data given the same weight as prospective clinical trials.

We propose that prior to embarking on preclinical and clinical compound evaluation the following characteristics should be considered: 1) *drug pharmacology*, including pharmacokinetics (systemic and target tissue exposure), pharmacodynamics, and exposure-

response relationships relevant to the new indication; 2) *drug formulation design*, for example dose strength, route of administration, and qualitative/quantitative composition of the investigational medicinal product (IMP); and 3) *safety and quality requirements*. A simultaneous approach, incorporating pharmaceutics and quantitative clinical pharmacology at an early stage of development offers the potential to translate existing knowledge into experimental protocols with the strongest possible chance of clinical success. It is also important that researchers are mindful of regulatory requirements for good laboratory practice (GLP), good clinical practice (GCP), and good manufacturing practice (GMP), and the appropriate stages of development at which to implement these to achieve subsequent regulatory approval.

At the outset, knowledge of the pharmacokinetics and pharmacodynamics (including predicted receptor occupancy if putative target is known) of the compound is essential. A scientifically sound dose rationale cannot be established without understanding the relationship between tissue levels and pharmacological effects and equilibration kinetics between plasma and brain; drug levels necessary for a therapeutic effect in one disease may be different to that of another, even if the drug target is the same. Thus, it is imperative that repurposing attempts do not bypass scientific scrutiny at the very early stage of development. Such a scrutiny implies the use of quantitative approaches, rather than "best guess" for the integration of existing clinical data and subsequent determination of the desired exposure, along with the corresponding dose and dosing regimen. Numerous examples highlighting the utility of *in silico* modelling to improve drug bioavailability exist [39–42], and demonstrate that changes to a formulation, including dose strength, result in improved drug delivery. Additionally, the identification of the effective route of administration and safe dose of the candidate compound via that route, through PKPD modelling provides confidence for early abandonment of candidate molecules predicted to require a unsafe or likely toxic doses, thus saving significant time and resources [38].

Even when data are available, many investigators have a tendency to neglect the relevance of such a preliminary evaluation. Instead, dose and formulation selection for a new indication is based on that shown to be effective previously, irrespective of differences in bioavailability due to changes in route of administration, or changes in drug disposition due to differences in the patient population. This is an approach destined for failure, as demonstrated by a compelling 2012 perspective from Pfizer [38], which presents the necessary "three Pillars of survival" that should be demonstrated for a drug progressing into Phase II: 1) exposure at the target site or organ; 2) binding to the target; and 3) evidence of pharmacological activity at the target. Candidate molecules that demonstrate these three pharmacological principles

have a high chance of success, and evidence for these three pillars should be obtained before moving onto formulation. At this stage safety data from prior investigations must be thoroughly scrutinised and, if reformulating, utilised to optimise the design of further safety studies necessary for the new formulation. It is also essential that the work carried out at this early stage applies GMP standards to ensure the highest levels of quality and to avoid the unnecessary costs of repeat investigation.

Given the clinical and regulatory implications of evaluating dose levels and/or route of administration which are not approved, or off-label for the existing indications, it becomes crucial to adopt an integrated, translational framework, with clinicians, formulation scientists and clinical pharmacologists working closely, during the preclinical and early clinical phases of repurposing. Such a collaboration can minimise the risk of false negative results in clinical trials, whilst dismissing compounds which are unlikely to produce clinically meaningful, therapeutic drug effects.

Pharmacological prerequisites which can lead to effective therapies

Prior to undertaking clinical trials that provide evidence of efficacy of an investigational medicinal product (IMP) for a new indication, efforts should be made to establish a sound understanding of the pharmacology of the drug. Initial *in silico* prediction of drug-target interactions [43] can help to guide subsequent work in which three questions should be addressed – is there evidence that the drug: 1) distributes to the relevant tissue(s) and reaches the pharmacological target; 2) produces the predicted activity/inhibition at the target site; and 3) induces the desired pharmacological downstream effects?

Answers to these questions may take months, or years, to establish, particularly when considering clinical end-points for chronic neurological diseases. Such a hurdle may be partly overcome by the identification and assessment of biomarkers of the pharmacological activity (.e.g, PET imaging). Availability of such measures at this early stage has the potential to significantly reduce these timelines [44]. Whilst the identification and validation of predictive markers of treatment response remains challenging for CNS drugs, knowledge gained from compound selectivity, as well as use of the drug in previous indications may provide valuable insight into potential biomarkers [45,46]. Biomarkers can be used to establish whether evidence of drug-target interaction leads to downstream effects, potentially saving time and guiding the design of clinical trials. Biomarkers can also provide the basis for dose selection if sufficient validation has been performed, including long term studies in patients and/or healthy subjects. Once these issues have been considered and estimates of the dose range are available, reformulation work can be effectively implemented for the new indication. Unfortunately, a biomarker approach may not be applicable to every clinical

condition, as biological understanding of the pathophysiology of the disease as well as knowledge about the targets and pathways associated with therapeutic response for many neurological conditions is limited. Consequently, it may not be feasible to assess or monitor the impact of the pharmacological intervention on a pre-defined pathway or physiological process.

Obtaining such data requires adoption of a translational approach at the preclinical stage of drug repurposing. First, it should be clear that intravenous pharmacokinetic data offers essential information about drug disposition. Whenever possible, such experiments should be combined with other techniques to establish CNS tissue concentrations. In fact, data from intravenous route should be obtained even if the treatment is to be delivered by oral route. Together, intravenous and oral data may inform pharmaceutical scientists about oral bioavailability and consequently provide insight into formulation requirements. These data can be then integrated with knowledge obtained from the development of the drug for previous indications using PKPD modelling and simulation to optimise the dose and exposure profile to be achieved in patients during the course of treatment. During this time, formulation scientists must work in parallel with both pharmacologists and clinicians to develop the most appropriate dosage form for the new indication taking into account the PK and PKPD estimates derived from the integrated analysis of all available data for the compound [47].

In summary, to increase the successful outcomes for clinical studies of repurposed drugs, the minimum starting point should be an optimal understanding of the preclinical data prior to commencing a trial in humans. Complementary expertise, including pharmacokinetics, pharmacodynamics, safety, formulation and quality requirements, is critical for the development of a robust pipeline that adequately evaluates and integrates existing data of the compound. If available, biomarkers that provide evidence of drug-target engagement may increase one's confidence that a repurposed drug will be effective in the newly proposed indication.

Even though the implementation of such a highly iterative framework may not always be feasible, it does represent an opportunity to improve decision-making, enabling the design of informative, efficient protocols. These interactions also ensure optimisation of the formulation at an early stage of drug product development by the selection of smart excipients (e.g. polymers to control the drug release, and absorption enhancers to improve bioavailability) as well as advanced manufacturing methods (such as 3D printing to personalise the dose and encapsulation of the drug into particle associated carriers to

control drug release), thus optimising the delivery and desired PKPD profile and, ultimately, increasing the likelihood of a successful study.

Concluding remarks

We are not the first to highlight the importance of a more integrated approach to drug development. Guidelines on clinical trials issued both by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have previously described the shortcomings of a linear process for drug development, categorised by phases [12]. Instead, a question-based approach should be considered, in which evidence is generated to address relevant clinical and scientific questions that ultimately support the optimal use of a medicinal product by the intended patient population. From the perspective of repurposing in neurology, it is crucial that research proposals evolve and divert from the current paradigm. To this purpose, one should make sure data generation addresses pre-defined questions and, in cases where this does not occur, such results should influence the design of subsequent studies, even if it entails modification of the development plan.

In order to benefit from the approach outlined here, academic research laboratories will require a different attitude towards training and collaboration. Moreover, funding organisations will have to adopt a different paradigm that supports preclinical work aimed at dose finding and reformulation, enabling efforts to bridge the gap that often exists between promising *in vitro* data and the successful application of repurposed drugs in clinical trial. Thus, rather than rushing into Phase II or III trials, one should aim to start repurposing projects by defining a set of critical questions whereby data on pharmacology, pharmacokinetics and safety are generated and integrated to support the dose rationale. This step should include a comprehensive analysis of existing data from unsuccessful studies, coupled with computational approaches to identify potential clinical value of repurposing candidate molecules, while enabling early rejection of those with a low probability of progressing towards market approval.

Funding

A.E.C. is funded by the Lily-Stoneygate Research Awards Programme “Treatments for Mitochondrial Disease” 2016/2017. R.D.S.P. is supported by a Medical Research Council Clinician Scientist Fellowship (MR/S002065/1).

Competing interests

The authors report no competing interests.

References

1 Murteira S, Ghezaiel Z, Karray S, *et al.* Drug reformulations and repositioning in pharmaceutical industry and its impact on market access: reassessment of nomenclature. *J Mark Access Heal Policy* 2013; **1**:21131.

2 Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. *Nat Rev Drug Discov* 2004; **3**:673–83.

3 Neuberger A, Oraiopoulos N, Drakeman DL. Renovation as innovation: is repurposing the future of drug discovery research? *Drug Discov Today* 2018; **24**:1–3.

4 mhra.gov.uk. Amitriptyline Tablets BP 10mg - Summary of Product Characteristics (SPC) - (HMRC). 2018. http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1538108004747.pdf (accessed 15 Jan 2019).

5 Murata M, Murahashi Y, Shimazu R, *et al.* Zonisamide's effects in Parkinson's disease patients with tremor; a meta-analysis of three placebo-controlled studies. *Mov Disord* 2014; **29**:S253.

6 BIO industry analysis. Clinical development success rates 2006-2015. 2016.

7 Caban A, Pisarczyk K, Kopacz K, *et al.* Filling the gap in CNS drug development: evaluation of the role of drug repurposing. *J Mark Access Heal Policy* 2017; **5**:1299833.

8 Molinoff PB. Neurotransmission and the Central Nervous System. In: Brunton LL, ed. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. New York: : McGraw-Hill 2011. 363.

9 Mullard A. Drug repurposing programmes get lift off. *Nat Rev Drug Discov* 2012; **11**:505–6.

10 NCATS. NCATS 2016 REPORT Improving Health Through Smarter Science. 2016.

11 Sheiner LB. Learning versus confirming in clinical drug development. *Clin Pharmacol Ther* 1997;**61**:275–91.

12 European Medicines Agency (EMA). General Considerations for Clinical Trials. ICH Top. E 8 Gen. Considerations Clin. Trials. 1998;:1–17.

13 Mary V, Wahl F, Stutzmann JM. Effect of riluzole on quinolinate-induced neuronal damage in rats: comparison with blockers of glutamatergic neurotransmission. *Neurosci Lett* 1995;**201**:92–6.

14 Huntington Study Group. Dosage effects of riluzole in Huntington's disease A multicenter placebo-controlled study. *Neurology* 2003;**61**:1551–6.

15 Rosas HD, Koroshetz WJ, Jenkins BG, *et al.* Riluzole therapy in Huntington's disease (HD). *Mov Disord* 1999;**14**:326–30.

16 Seppi K, Mueller J, Bodner T, *et al.* Riluzole in Huntington's disease (HD): An open label study with one year follow up. *J Neurol* 2001;**248**:866–9.

17 Landwehrmeyer GB, Dubois B, de Yébenes JG, *et al.* Riluzole in Huntington's disease: a 3-year, randomized controlled study. *Ann Neurol* 2007; **62**:262–72.

18 Lacomblez L, Bensimon G, Meininger V, *et al.* Dose-ranging study of riluzole in amyotrophic lateral sclerosis. *Lancet* 1996; **347**:1425–31.

19 Kiaei M, Kipiani K, Chen J, *et al.* Peroxisome proliferator-activated receptor-gamma agonist extends survival in transgenic mouse model of amyotrophic lateral sclerosis. *Exp Neurol* 2005; **191**:331–6.

20 Schutz B. The Oral Antidiabetic Pioglitazone Protects from Neurodegeneration and Amyotrophic Lateral Sclerosis-Like Symptoms in Superoxide Dismutase-G93A Transgenic Mice. *J Neurosci* 2005; **25**:7805–12.

21 Shibata N, Kawaguchi-Niida M, Yamamoto T, *et al.* Effects of the PPARγ activator pioglitazone on p38 MAP kinase and IκBα in the spinal cord of a transgenic mouse model of amyotrophic lateral sclerosis. *Neuropathology* 2008; **28**:387–98.

22 Dupuis L, Dengler R, Heneka MT, *et al.* A Randomized, Double Blind, Placebo-Controlled Trial of Pioglitazone in Combination with Riluzole in Amyotrophic Lateral Sclerosis. *PLoS One* 2012; **7**:e37885.

23 MHRA. UKPAR Pioglitazone 15 Mg , 30 Mg and 45 Mg Tablets Pl 24837 / 0032-34 Ukpar. 2011. http://www.mhra.gov.uk/home/groups/par/documents/websiteresources/con131987.pdf

24 Rilutek – Summary of Product Characteristics. 2001.

25 Miller BW, Willett KC, Desilets AR. Rosiglitazona y pioglitazona para el tratamiento de la enfermedad de Alzheimer. *Ann Pharmacother* 2011; **45**:1416–24.

26 Statland JM, Bundy BN, Wang Y, *et al.* Mexiletine for symptoms and signs of myotonia in nondystrophic myotonia: a randomized controlled trial. *JAMA* 2012; **308**:1357–65.

27 Geschwind N, Simpson JA. Procaine amide in the treatment of myotonia. *Brain* 1955; **78**:81–91.

28 Leyburn P, Walton JN. The treatment of myotonia: A controlled clinical trial. *Brain* 1959; **82**:81–91.

29 Kwieciński H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. *Acta Neurol Scand* 1992; **86**:371–5.

30 González-Lizárraga F, Socías SB, Ávila CL, *et al.* Repurposing doxycycline for synucleinopathies: remodelling of α-synuclein oligomers towards non-toxic parallel beta-sheet structured species. *Sci Rep* 2017; **7**:41755.

31 Wong YC, Krainc D. α-synuclein toxicity in neurodegeneration: mechanism and therapeutic strategies. Nat Med. 2017; **23**:1-13.

32. U.S. Department of Health and Human Services FDA. Providing Clinical Evidence of

Effectiveness for Human Drug and Biological Products. 1998. https://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4227B1-02-02-FDA-Appendix1.pdf

33 Bristol-Myers Squibb. SYNOPSIS Clinical study report IM101200. 2004. http://ctr.bms.com/pdf/IM101200.pdf (accessed 20 Apr 2018).

34 Khoury SJ, Rochon J, Ding L, *et al.* ACCLAIM: A randomized trial of abatacept (CTLA4-Ig) for relapsing-remitting multiple sclerosis. *Mult Scler J* 2017; **23**:686–95.

35 Berry JD, Shefner JM, Conwit R, *et al.* Design and Initial Results of a Multi-Phase Randomized Trial of Ceftriaxone in Amyotrophic Lateral Sclerosis. *PLoS One* 2013; **8**.

36 Cudkowicz ME, Titus S, Kearney M, *et al.* Safety and efficacy of ceftriaxone for amyotrophic lateral sclerosis: a multi-stage, randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014; **13**:1083–91.

37 Manning DC, Alexander G, Arezzo JC, *et al.* Lenalidomide for Complex Regional Pain Syndrome Type 1: Lack of Efficacy in a Phase II Randomized Study. *J Pain* 2014; **15**:1366–76.

38 Morgan P, Van Der Graaf PH, Arrowsmith J, *et al.* Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving Phase II survival. *Drug Discov Today* 2012; **17**:419–24.

39 Danhof M, Van der Geest R, Van Laar T, *et al.* An integrated pharmacokinetic–pharmacodynamic approach to optimization of R-apomorphine delivery in Parkinson's disease. *Adv Drug Deliv Rev* 1998; **33**:253–63.

40 Amidi M, Krudys KM, Snel CJ, *et al.* Efficacy of pulmonary insulin delivery in diabetic rats: Use of a model-based approach in the evaluation of insulin powder formulations. *J Control Release* 2008; **127**:257–66.

41 Sahota T, Della Pasqua O. Feasibility of a Fixed-Dose Regimen of Pyrazinamide and Its Impact on Systemic Drug Exposure and Liver Safety in Patients with Tuberculosis. *Antimicrob Agents Chemother* 2012; **56**:5442–9.

42 Mathias NR, Crison J. The Use of Modeling Tools to Drive Efficient Oral Product Design. *AAPS J* 2012; **14**:591–600.

43 Gonen M. Predicting drug-target interactions from chemical and genomic kernels using Bayesian matrix factorization. *Bioinformatics* 2012; **28**:2304–10.

44 Cohen AF, Burggraaf J, van Gerven JMA, *et al.* The Use of Biomarkers in Human Pharmacology (Phase I) Studies. *Annu Rev Pharmacol Toxicol* 2015; **55**:55–74.

45. van den Brink WJ, van den Berg DJ, Bonsel FEM, *et al*. Fingerprints of CNS drug effects: a plasma neuroendocrine reflection of D2 receptor activation using multi-biomarker pharmacokinetic/pharmacodynamic modelling. *Br J Pharmacol.* 2018; **175**:3832-3843.

46. Cole PE, Schwarz AJ, Schmidt ME. Applications of imaging biomarkers in the early clinical development of central nervous system therapeutic agents. *Clin Pharmacol Ther.* 2012; **91**:315-20.

47 Xue H, Li J, Xie H, *et al.* Review of Drug Repositioning Approaches and Resources. *Int J Biol Sci* 2018; **14**:1232–44.

LEGEND/CAPTION

Figure 1: The diagram depicts the typical linear pathway used for repurposing of a compound relative to the steps required for the development of a novel chemical or biological entity. The arrows emphasise the need for a translational, iterative approach that integrates pharmacological, pharmaceutical and clinical expertise towards preclinical and early clinical drug development. This approach ensures the characterisation of pharmacokinetic-pharmacodynamic (PKPD) relationships, and consequently the selection of an appropriate dosing regimen, route of administration, and/or formulation for the new indication before the evaluation of efficacy and safety in prospective clinical trials. Insight from PKPD relationships may also enable early termination of compounds with a low probability therapeutic benefit.

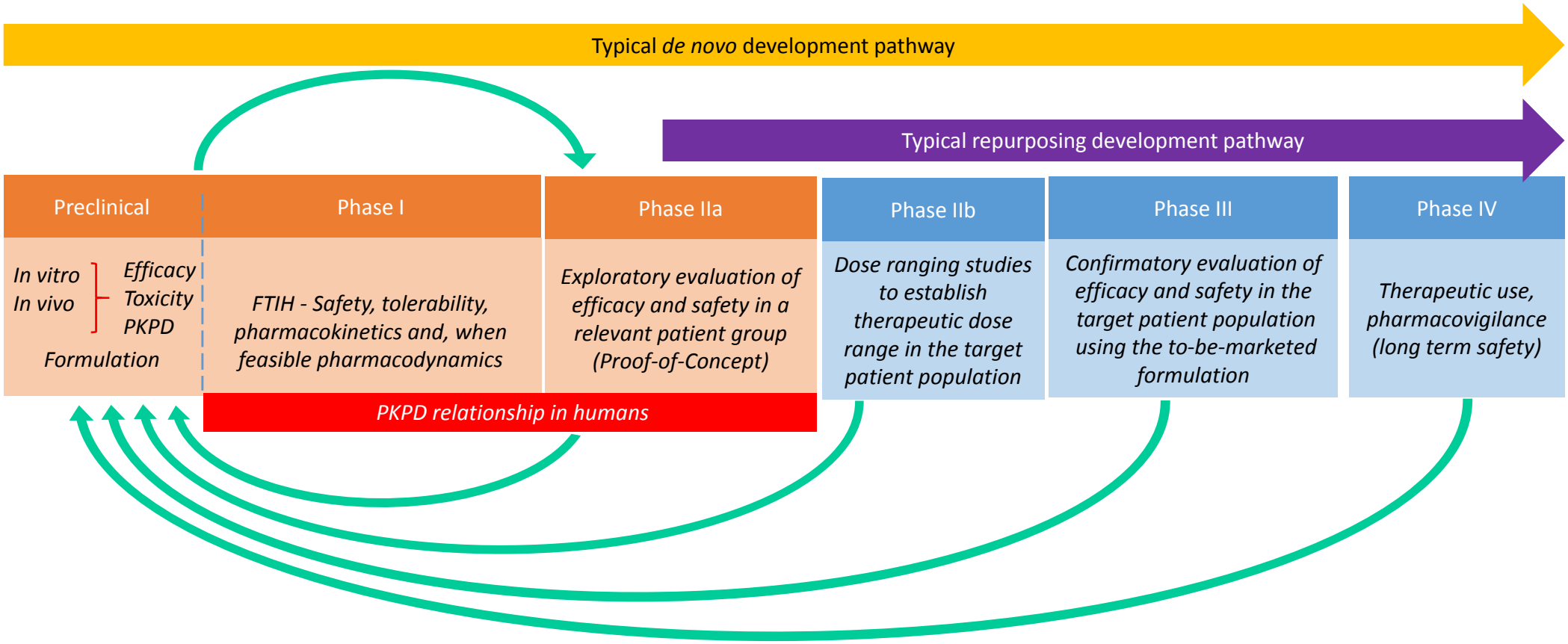
Typical *de novo* development pathway
Typical repurposing development pathway
Preclinical
Phase I
Phase IIa
Phase IIb
Phase III
Phase IV
In vitro
In vivo
Efficacy
Toxicity
PKPD
Formulation
FTIH - Safety, tolerability, pharmacokinetics and, when feasible pharmacodynamics
Exploratory evaluation of efficacy and safety in a relevant patient group (Proof-of-Concept)
Dose ranging studies to establish therapeutic dose range in the target patient population
Confirmatory evaluation of efficacy and safety in the target patient population using the to-be-marketed formulation
Therapeutic use, pharmacovigilance (long term safety)
PKPD relationship in humans

Table 1: Examples of drugs repurposed for neurological diseases that failed to progress beyond Phase II/III clinical trials.

DRUG	ORIGINAL INDICATION	NEW INDICATION	OUTCOME
Abatacept	Rheumatoid arthritis	RRMS	Phase II terminated. Exacerbation of MS in one subject and increased lesions in others (NCT00035529) [33]. Phase II failed. Lack of efficacy in reducing new lesions or disease activity. Dosing based on adult RA (NCT01116427) [34].
Ceftriaxone	Antibiotic	ALS	Phase III terminated. Failed to show clinical efficacy in increasing survival and reducing rate of functional decline (NCT00349622) [35,36].
Lenalidomide	Multiple myeloma, MDS	Complex regional pain syndrome, Type 1	Phase IIb terminated. Treatment and placebo showed equal effect. Dosing based on MM but significantly lower (NCT00109772) [37].
Pioglitazone	Type II diabetes	ALS	Phase II terminated. No tendency in favour of the treated group (NCT00690118) [22].
Piracetam	Cortical myoclonus	Post-traumatic epilepsy	Phase II terminated. Low enrolment (NCT00566046).
Riluzole	ALS	Huntington's disease	Phase III failed. Lack of efficacy. Dose chosen that showed efficacy within safety profile for ALS (NCT00277602) [17].

Abbreviations: ALS, Amyotrophic Lateral Sclerosis; MDS, Myelodysplastic Syndrome; MM, Multiple Myeloma; RA, Rheumatoid Arthritis; RRMS, Relapsing-Remitting Multiple Sclerosis; SPMS, Secondary Progressive Multiple Sclerosis.