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SPOTLIGHT COMMENTARY

Spotlight Commentary: Importance of dose redefining in the process of drug repurposing

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Repurposing of drugs has been around even before it was clearly defined as such. Repurposing implies identifying and using drugs for an indication different than the one originally intended, and it can be seen as both a faster and a more cost-efficient way of developing new medicines. Minoxidil can serve as one of the first examples, as it was initially approved in 1979 for arterial hypertension and later developed in a topical formulation for treating hair loss due to the observed side effects during clinical trials. There are two pharmacologically distinct types of drug repurposing. The first approach is more straightforward, and it is used if the potentially new indication is linked to the drug's known and previously demonstrated mechanism of action. In contrast, when the basis for a new indication arises from secondary, perhaps previously considered off-target drug effects, the development, approval, and ultimate drug usage will certainly require more attention from the scientific community, particularly regarding the dose that will be applied. The question that remains is: when does drug repurposing require new dose finding?

A systematic review with a case report was recently published in the *British Journal of Clinical Pharmacology* about using anticonvulsants gabapentin and pregabalin to treat aggressiveness in patients with dementia.¹ After exhausting the possible evidence-based options, Supasitthumrong et al. eventually introduced gabapentin in increasing doses for treatment of aggression and agitation in a patient with Alzheimer's disease, which led to a significant improvement in symptoms following a maximal 3,600 mg day⁻¹ dose. Reports of previous gabapentin use in similar situations indicated a wide range of doses administered (200 mg day⁻¹ to 3,600 mg day⁻¹) and even more significantly similarly wide effective dose ranges. As was acknowledged by BJCP authors, the evidence and reports were of low quality and with publication bias present. Moreover, the dose-response relationship could not be determined from the anecdotal cases mentioned, and it is known that gabapentin's pharmacological mechanism in treatment of behavioural and psychological symptoms of dementia (BPSD) may

be different from its anticonvulsant activity.² This constitutes a good example of a situation that merits a new dose finding study.

Amin et al. conducted a review of multiple, potentially new indications for the common antidiabetic metformin, which was published in BJCP.³ Metformin's mechanisms of action in these various conditions are different and simultaneously affect various cellular pathways, and thus, dose finding studies should be performed for each new specific indication of metformin in order to assess the effective dose and observe the dose-effect relationship. Ideally, data from either clinical cases or placebo-controlled interventional studies should always include a clearly explained dose rationale.

Vortioxetine is a novel atypical antidepressant with numerous mechanisms of action, and it has previously not been investigated for the treatment of insomnia in patients with major depressive disorder (MDD), but favourable results were recently reported in BJCP by Liguori et al.⁴ In this retrospective study, a dose of 10 mg was administered for the treatment of MDD. Although vortioxetine was shown to improve the subjective sleep quality, no firm conclusion on the dose-dependency of this effect could be drawn, and the independency of the uncovered effect in relation to the chief effect of vortioxetine on MDD could be questioned. It is arguable whether this study is a clear example of drug repurposing, since patients had comorbid insomnia in addition to the diagnosis of MDD, making it impossible to distinguish different drug mechanisms from overlapping disease mechanisms. Without a placebo or active comparator and by studying the previously drug-naïve patients related to a very subjective matter (without objective measures such as polysomnography), the authors correctly stated that the causality could not be confirmed. Nevertheless, this study provided valuable information for future dose-effect investigations of vortioxetine in patients with insomnia and additional MDD or insomnia only.

But there are other examples; some unlikely drugs see unexpected additions to their list of indications. Dextromethorphan is a

common over-the-counter cough suppressant developed in 1954. After a decades-long additional research during which further mechanisms of action were uncovered, it was approved in 2011 as a combination product with quinidine that here acts as a "PK enhancer" by inhibiting the cytochrome P450 2D6 activity and thereby increasing dextromethorphan systemic bioavailability and directing the pharmacology more toward that of the parent drug and away from the adverse effects of the metabolite. This combination drug was approved for the treatment of involuntary emotional expression disorder (IEED) ("pseudobulbar affect") in amyotrophic lateral sclerosis (ALS). Its effect on other symptoms that occur in ALS, including speech and swallowing difficulties, was the main topic of research published in the BJCP by Green et al.⁵ The authors found a subclinical, but objectively measurable additional benefit in patients, while the administered dose stayed the same as or remained even lower than the usual dose with antitussive properties. In this case, the intended pharmacodynamic effect is very different from the original one, and these findings therefore warrant additional studies of increased dosages and with longer drug exposures. Additional (dose finding) studies are needed whenever the risk-benefit ratio is observed in a different clinical context.

Further studies may also be conducted when the drug is administered to a new target population, such as a different age group. A remarkable example of such drug repurposing is sildenafil, a type 5 phosphodiesterase inhibitor initially developed for angina pectoris, but now mostly known for its use in treating erectile dysfunction. Sildenafil was subsequently utilised in adults with pulmonary hypertension.⁶ It is also used in infants with pulmonary hypertension following bronchopulmonary dysplasia, a common post premature birth complication. Because choosing the right dose can be particularly challenging in infants, partly due to fast rate of developmental changes that can also affect drug metabolism, Gonzalez et al. investigated sildenafil pharmacokinetics in this population.⁷ While this example does not constitute drug repurposing per se (the indication and mechanism stayed the same), it shows the importance of collecting new evidence when broadening medication usage to additional age groups.

The road to market approval of a new drug includes assessments of safety and tolerability of a compound, as well as efficacy for the specific indication investigated. While the side effect profile of a drug in certain dosage remains mostly predictable in a patient population with similar characteristics, the efficacy depends on reaching the target tissue(s) and exhibiting effects on specific cellular pathways. During clinical trials, dosing that leads to an acceptable interval of plasma drug concentrations is partly determined by the drug's safety profile. In other words, a change in a drug's indication can influence both the effective concentration and the acceptability of (side effects caused by) further dose increases. This is evident in the aforementioned example of dextromethorphan, but another excellent example is also methotrexate, which requires different dosing strategies in rheumatoid arthritis compared to leukaemia. Furthermore, without knowing the appropriate effective drug concentration, the treating physician cannot be sure that the medication has reached its

maximum potential, even if a patient might get subjectively or objectively better. Although the US Food and Drug Administration (FDA) does not require any understanding of the drug's mechanism of action, uncovering it should not be regarded as less important.⁸ Drug discovery by today's standards almost always begins by searching for a potential molecular target and the mechanistic knowledge also remains crucial for enabling therapeutic drug monitoring with specific biomarkers.

A very recent example of the importance of drug repurposing emerged during the outbreak of SARS-CoV-2 pandemic. While vaccine should bring a final solution, many approved drugs are being considered for potential repurposing in order to combat COVID-19. Hydroxychloroquine (HCQ) in particular gained a lot of attention from the scientific community for its confirmed in vitro SARS-CoV-2 antiviral activity.⁹ With its known antiviral and immunomodulatory effects, it was hoped HCQ would prove effective in vivo for SARS-CoV-2, especially since it has been shown that in severe COVID-19 patients, tissue damage may be caused largely by immunopathological mechanisms.¹⁰ However, it was unclear whether the low dosing used in treating autoimmune disorders would be ideal for the new indication. Ultimately, the FDA cautioned against the use of HCQ for COVID-19, after the new data showed significant cardiac toxicity associated with its use, together with no clinical benefit observed in hospitalized COVID-19 patients.¹¹ It is worth remembering that before concluding about the drug's efficacy or lack thereof, additional dosing schemes have to be carefully re-examined in well-designed, randomised, placebo-controlled clinical trials.

It should be noted that in this commentary, we have not examined pure commercialization purposes as one additional specific reason for investigation of new medication dosing. While the mechanism of action stays the same, a new indication can be found during the drug's lifecycle, and so to extend the compound's patent protection, additional changes to dosing and drug formulation can be made.¹²

Finally, it is obvious that the issue of dosing in drug repurposing is commonly overlooked in both drug development and trial results reporting. Data from previously conducted trials should be made available to researchers for critical analysis in their constant search for new answers to existing and emerging therapeutic problems.

COMPETING INTERESTS

There are no competing interests to declare.

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