Challenges in CNS drug development and the role of imaging

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CNS disorders represent a huge and growing unmet health need, yet drug development has stalled for some conditions and has not got off the ground at all for others. For example, there has not been a drug that does not block dopamine D2 receptors licensed to treat schizophrenia since chlorpromazine was brought to market more than sixty years ago, and there is no drug licensed to treat the core symptoms of autistic spectrum disorders (Kaar et al. 2020; Howes et al. 2018). Moreover, a number of pharmaceutical companies have markedly reduced or stopped drug development for these and other psychiatric disorders. This includes household names, such as Pfizer and Glaxo Smith Kline, as well as companies that specialized in psychiatry, such as Eli Lilly. It is clear that developing drugs for CNS disorders presents significant challenges. These challenges include difficulties in developing preclinical models of disorders, the need for drugs to cross the blood-brain-barrier, limited understanding of relevant pathophysiology, difficulties assessing target engagement, heterogeneity in clinical phenotypes, limited understanding of the heterogeneity of neurobiological phenotypes, the lack of sensitivity of clinical scales, and increasing placebo effects. Failing to address some of these challenges, such as developing a drug based on a preclinical model that does not reproduce the pathophysiology seen in patients or not assessing target engagement, leads to drugs being tested in the wrong condition or failing because they do not target the right brain system or achieve adequate action on the right system. Other challenges,

such as heterogeneity and insensitivity in clinical scales, mean that clinical trials in CNS disorders are large and costly, increasing the risk of failure, and that the drug may not be tested in the group of patients who will respond best.

Neuroimaging can help address a number of these challenges. It provides *in vivo* measures of neurobiology, advancing understanding of pathophysiology and identifying relevant brain targets, which can be drug binding targets themselves or functional targets such as brain networks. It is also translatable across species, potentially enabling the same measures to be used in preclinical and patient studies and supporting back-translation from clinical findings into preclinical models to refine these models. Imaging can also provide evidence that a drug crosses the blood-brain-barrier, a crucial pre-requisite for CNS active drugs! Establishing target engagement is a major challenge for CNS drug development, particularly once a drug is taken into human studies. This is another area where imaging can provide *in vivo* evidence and be used to establish proof-of-mechanism, for example by determining the relationship between (functional) target engagement and clinical response in the patient group. Heterogeneity in clinical presentations is common within CNS disorders and, within a disorder, is also seen across phase of disorder. Whilst how people express the functional impact of CNS pathophysiology may contribute to this, variability in underlying biological dysfunction is likely to be a major contributor to clinical heterogeneity. This highlights the value of using imaging to identify patients with homogenous underlying pathophysiology to provide a stratification methodology to evaluate a novel potential drug treatment. Clinical rating scales used for CNS conditions generally ask clinicians to score a patient's condition on an ordinal scale with a range of severity categories and are operationalized with anchor points which may not reflect the complexity of the clinical presentation. As such they are, by and large, blunt instruments. Here, imaging has the potential to provide a more sensitive marker of drug action than changes in clinical rating scales. Whilst this may be useful in early development, the best imaging markers also show a clear relationship with clinical outcomes to provide a clinically relevant endpoint.

This article belongs to a Special Issue on Imaging for CNS drug development and biomarkers

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This special issue on the use of imaging in drug evaluation brings together studies that provide examples of where imaging has been used to address the challenges outlined above. It includes a number of good examples of the use of imaging to advance understanding of pathophysiology that can be used to guide the development of new treatments, specifically for smoking and cannabis use disorders (Rangel-Pacheco et al. 2021; Blest-Hopley et al. 2021; Tamburin et al. 2021), although the principles they demonstrate apply equally to other conditions. Neurochemical imaging has proved particularly informative for understanding pathophysiology and drug action (McCutcheon et al. 2020). Okubo et al. provides a good example of the use of PET imaging to determine target engagement, in this case for a novel antipsychotic drug, albeit still acting on the dopamine D2 receptor (Sakayori et al. 2021). Alice Egerton reviews the use of another neurochemical imaging approach, magnetic resonance spectroscopy, for drug development, highlighting its potential but also a number of issues that need to be resolved (Egerton 2021). Several studies test mechanism of action of drugs to inform the development of these drugs or treatment approaches generally (Nathan & Bakker 2021; Grimm et al. 2021; Gilleen et al. 2021) and, potentially, also of a biomarker to predict recovery following treatment (Henigsberg et al. 2021). The special issue also includes reviews that draw on evidence from imaging studies to consider models of antidepressant action and how to improve personalized treatment prediction (Paulus & Thompson 2021; Godlewska & Harmer 2021).

The range of studies included in the special issue shows how imaging can be used in drug evaluation, both in guiding the development of a drug and, arguably just as important, also in determining when to stop developing a given drug and focus resources elsewhere. The special issue also identifies some areas that warrant further investment. One notable area is back translation of imaging into preclinical models, which remains a rarity, although examples are beginning to emerge (Tricklebank et al. 2021; Kokkinou et al. 2020). Another area is standardization and reliability of imaging measures across sites and approaches and over time. This will be necessary before imaging measures can be routinely deployed in early-phase validation studies, incorporated into large-scale clinical trials or, in the fullness of time, used in routine hospital practice. We encourage future submissions that address these areas. Of course, imaging is not the only tool needed to address the challenges in drug development. A recent review by Tricklebank et al. makes overarching recommendations to address these challenges, including considering where imaging contributions are likely to be beneficial (Tricklebank et al. 2021). Notwithstanding these points, the special issue illustrates the potential for imaging to catalyse stalled drug development for conditions where there has been little progress for many years and provide new fuel to supercharge efforts for disorders where there are no licensed treatments.

Declaration

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