Translating preclinical insights into early psychopharmacology trials: application of the IB-Derisk analyser tool

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CHAPTER I

INTRODUCTION

1. CURRENT STATUS OF PSYCHIATRIC DRUG DEVELOPMENT

Central nervous system (CNS) drug development in general and psychiatric drug development in particular have suffered a number of important setbacks over the past two decades.[1-4] Despite heightened expectations for innovative pharmacological treatments driven by advancements in neuroscience, which have deepened our understanding of the functional processes behind CNS disruptions in psychiatric illnesses, drug development has largely failed to convert new insights into approved novel treatments in psychiatry.[5] Psychiatric drug development is characterised by higher failure rates in late stage drug development due to lack of safety and efficacy compared to other fields of drug development (Figure 1).[6-9] To illustrate, between 2011 and 2021, 12 new drugs in psychiatry were approved by the US Food and Drug Administration (FDA), while 50 new drugs in neurology and 135 new drugs in oncology were approved over the same period, respectively (Figure 2).[5,10] Moreover, of the novel pharmacological treatments for psychiatric disorders that have reached the market, only a handful include compounds featuring truly novel mechanisms of action.[11,12] As a consequence, several major pharmaceutical companies announced either reduction or discontinuation of their CNS research and development programs over the past two decades.[1-4,6,13-15] Although there have been recent successes in psychiatric drug development, such as the FDA approval of esketamine and brexanolone – two rapid-acting antidepressants with novel mechanisms of action – and while initial results from the renewed interest in psychedelic-assisted psychotherapy appear promising, further advancements are necessary to reduce the relatively high failure rates in late-stage drug development in this field.[16,17]

Figure 1 High rate of late-stage failure in psychiatry

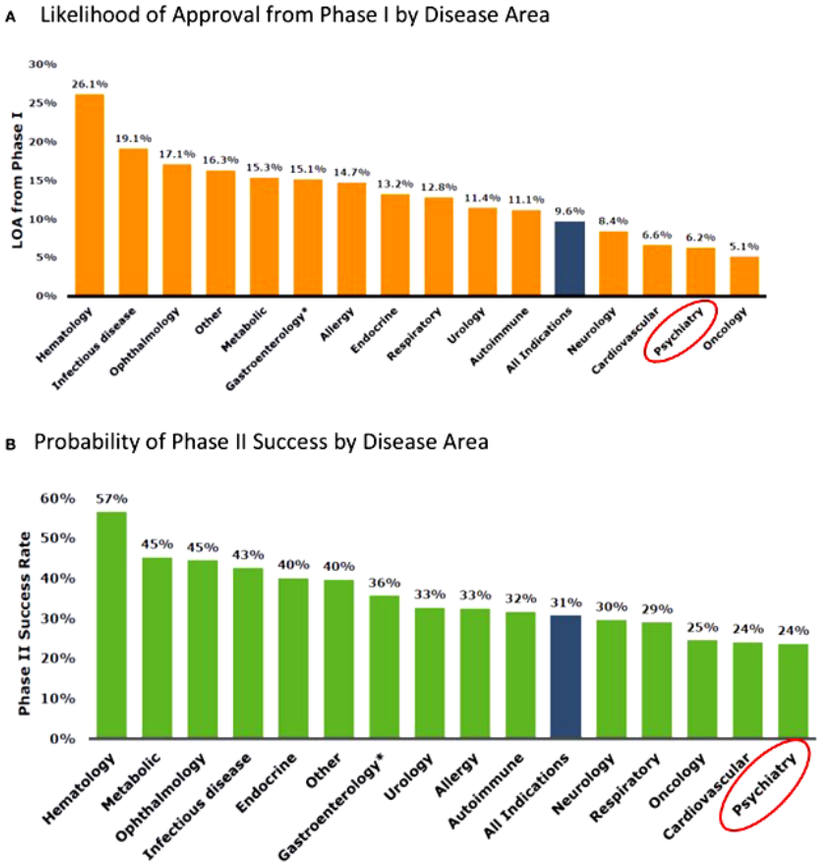

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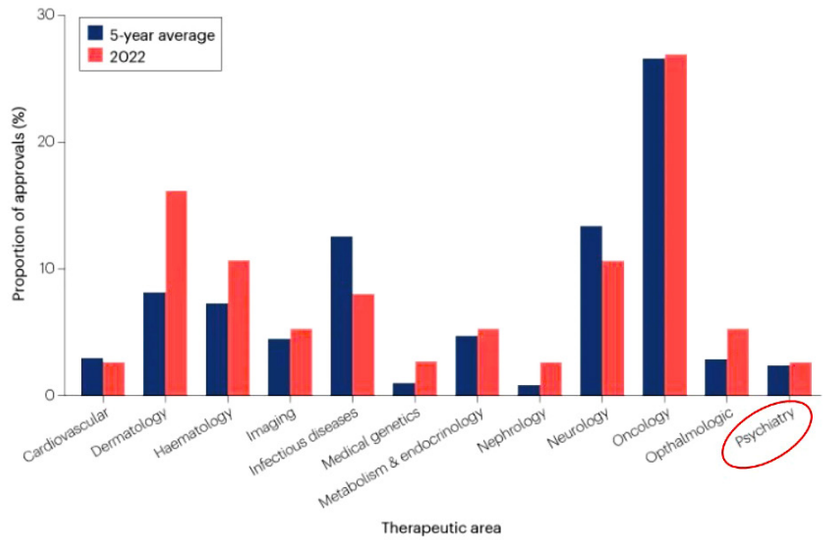
Figure 2 Approval rate per drug development field



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2. LACK OF PRECLINICAL MODELS THAT RELIABLY TRANSLATE TO PSYCHIATRIC DISORDERS IN HUMANS

The lack of predictive preclinical models to test potential novel therapeutic compounds is often cited as a major cause for the high failure rates in the field of psychiatric drug development.[1,3,18-20] To illustrate, the forced swim test (FST) and tail suspension test (TST) continue to be widely used for nonclinical efficacy testing in drug development for Major Depressive Disorder (MDD).[18,21,22] Both tests were developed many decades ago, when antidepressants exclusively targeted monoaminergic activity, and both seem to reflect acute stress-related behaviour, rather than chronic mood disturbance.[18] In the FST, developed in 1977, a rodent (usually a mouse or rat) is placed in a container filled with water from which it cannot escape.[23] The test measures the animal's behaviour in response to the stressful situation, typically over a short period (e.g., 6 minutes).[18] A shorter duration of immobility and/or a longer latency to become immobile, compared to control groups, is interpreted as an indicator of potential antidepressant efficacy in humans.[18,23] The TST, developed in 1985, is based on the same assumption as the TST: substances with antidepressant properties will cause animals to struggle longer in physically stressful situations.[24] The TST involves administering a compound and then attaching a mouse by its tail to a suspension bar or shelf ledge using tape.[24] The experimenter records the time the mouse spends making escape-oriented movements, such as trying to reach the surrounding walls.[24] Some antidepressants have been found to increase these escape-oriented behaviours in certain strains of mice.[25] The interpretation of these tests by regarding reduced immobility, increased latency to immobility, and increased escape-related behaviours as indicators of antidepressant activity has faced criticism.[18,21,22] It is argued that this concept lacks construct, face and predictive validity.[18,22]

Construct validity refers to the extent to which the model accurately represents pathophysiological mechanisms and theoretical constructs of the human disease it aims to simulate.[22] However, especially in the field of psychiatric drug development this is challenging given the poorly understood pathophysiology of psychiatric disorders, as these result from a complex interplay of biological, psychological and social factors that are still being unravelled.[3,4,22,26,27] The construct validity of the FST and TST as a model of MDD can be assessed as poor, amongst others because depressive disorders in humans do not develop within the course of 15 minutes or even a few days.[18] Face validity implies that a model replicates essential anatomical, biochemical, neuropathological, or behavioural features of a human disease.[22] However, there are limited, if any, neurobiological abnormalities conclusively recognised as hallmarks or biomarkers for common mental illnesses.[22] Additionally, certain mainly internal and emotional dysregulations, leading to psychiatric symptoms such as hallucinations, delusions, sadness and guilt, are arguably unique to humans and cannot be definitively modelled or objectified in animals.[22] Even when there are apparent behavioural readouts in animals, like abnormal social behaviour, motivation, working memory, emotion, and executive function, the correspondence may only be approximate, and if there are plausible anthropomorphic interpretations, these have rarely been convincingly linked to pathophysiology.[21,22] Face validity of the FST and TST as models of MDD can also be assessed as poor because 'escape behaviour' is not a diagnostic feature of MDD in humans.[18] Predictive validity indicates that a model responds to treatments in a way that predicts the effects of those treatments in humans.[22] However, most models in neuropsychiatry, such as the FST and TST, developed to measure the effect of novel compounds are not mechanistic models of therapeutic activity.[18,22] Generally, these models have not been demonstrated to reflect either the pathophysiological processes of human disease, nor the therapeutic mechanism of action of existing compounds and for most new targets.[18,22] Consequently, it remains uncertain whether these models will be sensitive to the pharmacological effects of novel investigational compounds with new mechanisms of action.[18,22] Taken together, modelling human neuropsychiatric disorders in animals is highly challenging due to the

complexity and limited understanding of the pathophysiology, the heterogeneity and subjective nature of many symptoms, and the absence of biomarkers and objective diagnostic tests of psychiatric disorders.[22]

3. *How to improve translational value of psychiatric research*

Many scientists argue that to improve the translatability of preclinical experiments to therapeutic efficacy in humans, the quality of these experiments must be improved by addressing species differences, experimental environment, complications from genetically altered animals, methodology, and different forms of bias.[21] While these improvements are important, efforts to enhance translatability will remain superficial unless the scientific rationale behind the experiments is solid.[21] It is therefore argued that it would be more effective to develop preclinical models that simulate a single measurable pathological aspect of the disorder instead of attempting to model the entire disease.[21,26,28] It is recommended that preclinical models are developed to explore aspects of the disorder, in such a way that it helps to identify human-relevant biomarkers for novel compounds targeting the dysfunction of the modelled circuitry.[3,26] For example, imaging and electrophysiology biomarkers that capture neurocircuitry modulation relevant to specific disease domains in humans are being identified.[3] These biomarkers can be used in both preclinical models and clinical studies to measure target modulation by the investigational compound.[3] Furthermore, clinical research should carefully consider the results from preclinical studies to ensure that novel compounds are tested at appropriate doses and account for patient heterogeneity in psychiatric disorders by focusing on relevant subpopulations, characterised by specific disease characteristics and biomarkers that match the underlying pathophysiological and pharmacological mechanisms.[21,26,28]

While psychiatric drug development will likely benefit from advancements in preclinical research, the existing preclinical animal models for psychiatric disorders continue to play a valuable role in the drug development process. First, data from these studies can be used to assess the 'translatability' of a novel compound.[29] Within this context, translatability is defined as the property of a compound to elicit similar responses across preclinical species at equivalent ranges of exposure.[29] If a compound exhibits desired pharmacological effects at low concentrations in animal models, with undesirable effects consistently manifesting at higher levels in the same or even in other species, it raises the likelihood that this dose-responsiveness reflects a pharmacologically active range that will also be translated to humans.[29] On the contrary, the presence of significant interspecies differences in preclinical observations raises uncertainty concerning translatability to humans.[29] This can warrant further research to understand the difference between animal models, before proceeding to a human study; or influence the design of the clinical study, such as by including additional pharmacological biomarkers or safety measures.[29] Second, preclinical efficacy experiments provide insight into the dose range and/or exposure value at which the investigational compound elicits its effects or is pharmacologically active.[29] From this perspective, preclinical models should thus not be viewed as tools that directly predict therapeutic efficacy in humans but rather as resources that offer insights into the translatability of a novel compound and the dose range at which pharmacological effects can be anticipated.

4. *How to improve the design of early phase clinical drug development studies in psychopharmacology*

In order to reduce the relatively high attrition rates in CNS drug development, early-phase clinical study designs must be improved, alongside optimising the methodology and interpretation of preclinical models.[3,28,30,31] Analyses by AstraZeneca and Pfizer into their failed small-molecule drug projects categorised as efficacy failures in phase II demonstrated that in respectively 21% and 43% of studies, fundamental characteristics such as compound exposure at the site of action and/or confirmation of modulation of the pharmacological target, were not properly investigated. Consequently, it remained uncertain whether a compound had validated the mechanistic hypothesis.[30,32] For the drugs that could be advanced into phase III trials, action site penetration and target engagement had been demonstrated significantly more often than for compounds that failed earlier.[30] To improve attrition rates, it is therefore recommended that fundamental PK and pharmacodynamic (PD) properties, consisting of exposure at site of action and target modulation, must be investigated during early phases of clinical drug development.[30,32-35] This approach ensures that, in the event of a negative trial, researchers can differentiate whether this was due to inadequate drug exposure at the site of action or inadequate target modulation; or because the targeted mechanism turned out not to be relevant for the disease.[30,36] This means that, even in the case of a negative trial, there is still an advancement in knowledge about the pharmacological mechanism of the novel compound or understanding of the disease.[30,36]

According to this experience, early phase clinical drug development studies must be designed in such a manner that the essential characteristics of novel compounds, including their ability to reach the site of action and perform target modulation are thoroughly investigated.[35] This entails that biomarkers measuring pharmacological effects of investigational compounds, should be included in First-in-Human (FIH) studies.[30,33-35,37] The NeuroCart, which consists of a battery of drug-sensitive CNS tests, measuring effects on different CNS domains, such as neurophysiologic functioning, visuomotor coordination, balance and subjective feelings, provides a set of biomarkers that can easily be applied in FIH studies.[38] In recent years, the NeuroCart has

been employed to study numerous compounds with a wide variance of action mechanisms.[38] Consequently, there is a comprehensive understanding of how the NeuroCart tests are influenced by different compounds.[38] These established 'NeuroCart profiles' enable comparisons of results from investigational compounds, aiding in the assessment of whether observed effects align with the expected mechanism of action for these compounds.[38] Additionally, recent advancements in the field of neuroscience are of considerable benefit to measure fundamental pharmacological characteristics of investigational compounds.[3] Neuro-imaging techniques, such as PET-imaging with CNS-penetrating radioligands or functional Magnetic Resonance Imaging (fMRI) have enormously improved over the past years, and can also be employed to furnish evidence of a drug effectively crossing the blood brain barrier (BBB).[39] Next to that, advancements in electrophysiological techniques, such as Polysomnography (PSG) and Electroencephalography (EEG), whether used independently or in conjunction with Transcranial Magnetic Stimulation (TMS), enable non-invasive exploration of neuronal network activity in humans.[37] This facilitates the evaluation of various cortical properties, including excitability and connectivity, as well as the impact of novel drugs on these properties.[37] Taken together, an increasing variety of neurofunctional biomarkers has been shown to be able to demonstrate pharmacological effects in early-phase clinical trials in psychopharmacology, which can demonstrate target modulation either indirectly through for example NeuroCart or electrophysiological techniques, or directly through for example imaging techniques.

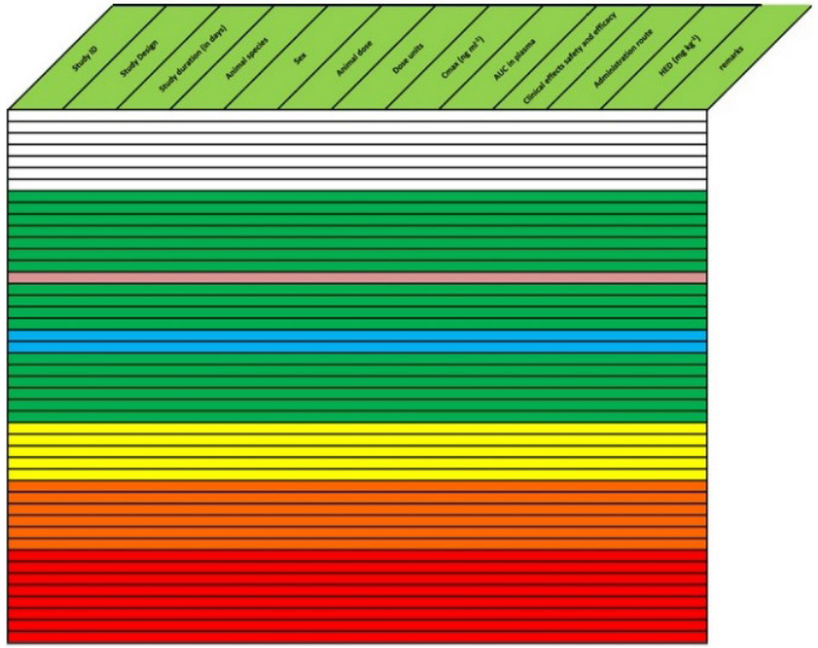
5. *THE IB-DERISK ANALYSER*

Overall, it can be stated that the relatively high failure rates in late stages of CNS drug development could be mitigated by properly interpreting preclinical data and investigating the fundamental PK and PD characteristics of novel compounds during early clinical phases.[3,30-32,35] In practice, however, predictions of clinically active dosages can be highly challenging, because of the diversity and the lack of standardisation within the preclinical development program.[29] This includes not only the absence of validated disease models discussed earlier, but also the vast amount of available preclinical data, varying reporting styles across different preclinical experiments, and incomplete data reporting of preclinical experiments, such as missing PK information from preclinical efficacy studies.[29] Furthermore, there is a communication gap between preclinical and clinical researchers.[20,28] To provide an integrated assessment of the varied and incomplete preclinical data, the IB-Derisk analyser tool was developed.[29] The IB-Derisk analyser tool can be used to summarise the often lengthy and complex preclinical data as described in the Investigator's Brochure (IB) in an organised one-page overview.[29] Additionally, the overview can be updated with emerging findings from ongoing early-phase clinical studies to contextualise and verify whether the actual outcomes align with predictions.[29] By inputting the results from all performed nonclinical and clinical experiments into the overview, a comprehensive representation of the investigated compound is generated.[29] This aids in identifying missing critical data, detecting safety issues, contextualising findings, and promoting communication among researchers.[29]

For in-depth details on the IB-Derisk analyser tool, the original publication can be consulted.[29] Essentially, the IB-Derisk analyser overview is obtained in four steps of data entry and manipulation.[29] The first step consists of selecting all single-dose PK studies and enter for all of these studies per species and per administration route, the maximum concentration after administration (C_{max}) and total exposure (area under the curve (AUC)) in the tool.[29] If different doses are given, each dose is considered a separate experiment that is individually entered in the tool.[29] In the second step single dose non-PK studies, for example disease model or safety pharmacology studies, in the same species for which separate PK experiments were entered in the first step, are entered.[29] For these kind of studies, PK values are often not reported, but the missing C_{max} and AUC values can be reasonably derived from the PK-studies in the same species.[29] The third step involves entering the multiple dose experiments, some of the acute toxicology studies, and sometimes models of special interest in a specific laboratory animal.[29] For these experiments missing PK data can often be estimated based on extrapolation of the PK studies.[29] The final step consists of colour coding the different studies based on the observed effects.[29] When the colour coding is added, the experiments can be arranged on C_{max} or another pharmacokinetic parameter, to obtain a visual impression of the dose-response curves (Figure 3).[29]

The obtained overview must then be correctly 'read'. To evaluate the translatability of a compound, it is necessary to examine the IB-Derisk overview on whether comparable effects occur at similar exposures in different species. A homogeneous distribution over different species increases the chance that humans will also fit into this pattern.[29] This is readily identifiable through the colour-coded system (Figure 3).[29] Furthermore, when selecting a starting dose and make decisions on dose escalating steps for a clinical study, the overview can be used to make an estimation of the pharmacologically active dose range.[29] When observations of pharmacological activity in early phase clinical studies deviate significantly from predictions based on preclinical data, it suggests a limited understanding of the pharmacology of the novel compound or the pathophysiology of the targeted disease.[29] Investigating this discrepancy can deliver important information on the drug target or on the pathophysiology.[29] On the other hand, when predictions of pharmacological activity based on preclinical data are met in FIH studies, our understanding of a compound and pathophysiology of a disease are strengthened.[29] Integration of all this information then provides a solid base for decisions on further development of an investigational compound.[32]

Figure 3 Schematic example of an IB-Derisk overview



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6. OUTLINE OF THIS THESIS

In short, over the past two decades the numbers of drug development for CNS disorders in general and psychiatric disorders in particular have been disappointing.[1-4] It is being argued that this is caused by a lack of preclinical models predicting therapeutic efficacy.[1,3,18-20] Improving this deficiency would require a thorough reconsideration of psychopathological cascades and psychiatric disease constructs, which considering the complexities is not easily accomplished.[20] However, no direct CNS-active compound can be expected to be therapeutic, if it does not exerts its intended pharmacological activity within the brain.[38] This is illustrated by empirical analyses of drug development programs, which have demonstrated that in up to almost half of studies failing due to a lack of efficacy in phase II, fundamental PK and PD characteristics, such as exposure at the site of action and target modulation, were not investigated or demonstrated in the early phases of clinical development.[30,32] It is therefore suggested that late-stage failures in CNS drug development can be reduced by designing preclinical and clinical studies and integrating their results in a manner that provides a thorough understanding of a compound's pharmacological profile during the early phases of clinical development.[30-32,35] To facilitate this the IB-Derisk analyser tool was developed.[29]

This thesis serves as an investigation of how the IB-Derisk analyser tool can be applied in early phase clinical development of neuropsychiatric drugs. First, the results of a semi-quantitative analysis are described, evaluating how accurately preclinical data, as summarised using the IB-Derisk analyser tool, can predict safe and pharmacologically active dose ranges in humans for CNS-active compounds. In the subsequent chapters, the individual results of three early phase clinical drug development studies in healthy volunteers are described. These studies involve investigational compounds with highly innovative mechanisms of action, in development for the potential treatment of psychiatric disorders. For each novel compound an IB-Derisk analyser overview was generated prior to study start and supplemented with emerging data from the clinical studies while these were ongoing. In all studies included in this thesis, the NeuroCart was performed to investigate the pharmacological characteristics of the novel compound. Each chapter contains an appendix evaluating the IB-Derisk analyser overview concerning the investigational compound. The appendices present the results obtained with the IB-Derisk analyser prior to initiation of the clinical studies, supplemented with the actual outcomes of the clinical studies. Lastly, in the final chapter the added value of using the IB-Derisk analyser tool in early phase drug development studies is discussed. This chapter includes recommendations for the future of drug development in psychiatry.

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