

TRENDS AND PERSPECTIVES

Strategies to Address Challenges in Neuroscience Drug Discovery and Development

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Abstract

The paucity of novel drugs for neuropsychiatric indications contrasts with the remarkable recent advances in neuroscience research. We have identified 5 challenges the field needs to address and recommend potential solutions. First, we need to drive discovery efforts based on human data. Second, we need to think more carefully about animal models, embracing them as tools to test pathophysiological alterations. Third, we need to develop strategies to select more homogenous groups of patients in our clinical trials. Fourth, we need to develop and validate translational biomarkers, which can be used for pharmacodynamic assessments as well as for patient selection. Fifth, we need to adopt more reliable and objective measures to capture clinical efficacy. The tools that will allow these solutions to be implemented may already be in place but not routinely adopted or are still being developed. Overall, a change in mindset to adopt science- and data-driven paths is needed.

Keywords: clinical trials, target discovery, neuropsychiatry, biomarkers, patient selection

The Challenges of Neuroscience Drug Development

Despite strong recent advances in basic neuroscience research, the successful development of novel therapeutic approaches for neuropsychiatric indications has been limited. We are now capable of identifying the genetic, molecular, cellular, and neurocircuitry aspects governing behavior. We can probe brain activity in humans and experimental animals with a degree of sophistication that could not be envisioned a decade ago. Yet these developments have not resulted in the delivery of new medications for the most devastating neuropsychiatric disorders. Current treatments and recent approvals are still largely variations on previously identified mechanisms and pathophysiological hypotheses, which for the most part were identified serendipitously. Here, we briefly address 5 key challenges in neuroscience drug discovery and development and highlight opportunities to move the field forward (Table 1).

Putting failures due to poor compound quality aside, many issues may have contributed to the repeated failures to get novel neurotherapeutics approved. We may have selected the wrong targets or misinterpreting or overinterpreting the emerging biology related to the disorders of interest. We may not have been brave enough to choose different pathways to explore, as we often fit new biological findings to preexisting hypotheses. We may have been misguided in the use of preclinical assays and models, neglecting to focus on translatability and human relevance of animal studies. We may have also been careless in pivotal late-stage trials, sacrificing adequate patient selection for speed and milestone achievements as well as using low-precision endpoints to detect efficacy. All these elements and a few others have likely played a role in the current dearth of novel drugs for neuropsychiatric indications.

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Table 1. Key Challenges in Neuroscience Drug Discovery and Opportunities to Address Them

Challenges	Description	Opportunities to Address
Patient populations	Heterogeneous patient populations, often grouped by clinical symptomatology rather than measurable pathophysiology	Increased use of patient selection and stratification biomarkers, along the RDoC approach
Target selection	Novel mechanisms tested so far have not provided positive data	Increased focus on human genetics-defined targets (“Reverse Translation”) Adopt human neurobiology-informed approaches for novel target identification, based on pathophysiology hypotheses and clinical observations
Preclinical models	Limited understanding of disease pathophysiology Animal models lack complexity of human brain	Increase use of translatable biomarkers linked to behavioral assessments and clinical endpoints Adopt animal models that capture specific domains of pathophysiology, instead of pretending to fully reproduce complex disorders in preclinical species (“Reverse Translation”)
Clinical endpoints	Often limited to highly variable, subjective, questionnaire-based endpoints leading to need for a large N in trials	Increased use of objective biomarker-based endpoints Digitally captured endpoints that allow for repeated testing, increasing statistical power
Translatable biomarkers	Lack of translatable molecular biomarkers and access to human tissue	Increased use of imaging and electrophysiological biomarkers to show target engagement and central pharmacodynamic activity

Abbreviation: RDoC, NIH Research Domain Criteria.

Target Selection

Has the selection of novel targets been misguided? To answer this question properly, we need to know whether the hypotheses have been properly tested in the clinic. Several new mechanisms have been proposed over the past couple of decades, and pharmaceutical companies embarked on developing novel compounds that addressed pathophysiology based on emerging neuroscience data, such as the role of N-methyl-D-aspartate (NMDA) receptor hypofunction or inhibitory interneuron deficits in schizophrenia. To date, all recent clinical trials focused on these hypotheses, whether attempting to restore NMDA receptor function in schizophrenia by blockade of the glycine transporter, elevating D-serine (through direct administration or enzymatic inhibition), or reducing excess glutamate with a metabotropic glutamate receptor 2,3 agonist, have failed to provide clear evidence of efficacy. We do not know yet if these were improper targets or whether patient heterogeneity and unreliable endpoints negatively impacted the clinical data. Addressing efficacy of compounds targeting novel mechanisms has a high bar: we need to identify a specific pathophysiological hypothesis to be tested, define disease-relevant biomarkers, and establish an association of changes in these biomarkers with clinical outcomes with high precision. More work needs to be done to validate those approaches.

For new discovery efforts, there is a clear path forward. We must seek targets with strong association with disease biology and that are based on high-quality, robust human data. In schizophrenia, for example, genome-wide association studies have revealed several loci with genetic variants associated with risk for the disease ([Schizophrenia Working Group of the Psychiatric Genomics, 2014](#)). While it is clear the genes associated with these loci provide a very small amount of risk for the disorder, they do highlight biological pathways that may have relevance to pathophysiology and, hopefully, treatment ([Schubert et al., 2014](#)). Indeed, to identify novel targets, the genetic variant or anomaly needs to be placed in the context of a wealth of biological processes upstream or downstream of the specific gene, the developmental trajectory of its expression, and many adaptations that may also take place. Drug development should move away from “treatments for all” to “treatments for defined subpopulations.” Other sources of human data can help

with discovery efforts, including analyses of gene expression in diseased vs control brains, the use of neurons derived from patient inducible pluripotent stem cells (iPSCs), or the exploration of organoids driven by patient-derived cells. These data will need to be carefully aligned with clinical profiles of the patients from whom the cells were obtained. It will also be critical to use these tools to assess single cell-type data and ideally the impact of potential target modulation on circuitry function. Emerging technologies such as single-cell RNASeq, DropSeq, and neural organoids have the potential to allow such precise phenotyping. Furthermore, patient phenotypic information, including clinical data, imaging, and human neurophysiology, also provide the bases to think about novel approaches to address pathophysiology. All these efforts are in their infancy but are changing the way novel targets are being thought about.

Preclinical Models

Neuropsychiatric disorders are complex conditions that include several unique human aspects. Preclinical studies relevant to drug development in neuroscience may not have been adequate. First, many studies employed normal animals. The impact of a novel molecule is likely to be different in a normal vs diseased brain. It is therefore important that preclinical studies are run in deficit models representative of the pathophysiological process to be corrected. The term “model” has been frequently and improperly used to define behavioral assays, which for the most part were run in normal animals. A model is a manipulation by which we introduce changes in brain structure and function, often with the aim of reproducing aspects of the disorder of interest. A behavioral assay is a tool to assess whether a model exhibits disease-relevant outcomes. Although the belief that we can reproduce conditions such as schizophrenia or depression in a rodent is certainly naïve, this does not invalidate *in vivo* preclinical work. While it is true that the validity concepts for these models are flawed, the models may nonetheless be useful ([O'Donnell, 2013](#)). The usefulness of animal models relevant to psychiatric indications resides in capturing a hypothesized pathophysiology that novel targets are intended to fix. Thus, a genetic or environmental manipulation that yields rodents with altered parvalbumin interneurons, for example, is a model of cortical circuitry dysfunction(s) that may be relevant

to at least a subset of patients with schizophrenia (O'Donnell, 2011). Preclinical work will continue to be essential, and we need to conduct it with an eye on exploring “biological disease phenomena” (not disorders) and in a manner that helps us identify human-relevant biomarkers for novel assets addressing dysfunction of the circuitry being modeled.

Patient Selection

Were subjects with demonstrable glutamate alterations chosen for the clinical studies assessing NMDA-related targets in schizophrenia? Neuropsychiatric disorders are heterogeneous, and studies evaluating all-comers are almost certainly bound to fail. There are many stories of promising Phase 2 results that are not replicated in later stage studies. It is conceivable that the efficacy in earlier, smaller studies was the result of studying more homogeneous patient populations. We need to improve patient homogeneity in clinical trials.

The most obvious way to improve patient homogeneity is to adopt biomarkers that capture the relevant pathophysiology. For most neuropsychiatric disorders, fluid biomarkers to assess pathophysiological profiles are not available. If we want to test a molecule that targets glutamate or GABA neurotransmission, for example, it will be critical to identify patients in which these neurotransmitters are altered. Some tools allow a direct measure of these amino acids, such as magnetic resonance spectroscopy, but they are not specific to measuring neurotransmitter pools or scalable for use in clinical trials. As an alternative, we can assess circuitry modulation that depends on these neurotransmitters with neurophysiological markers. This is a rapidly evolving field, and new devices and analytical approaches that will help improve the sophistication of patient selection are emerging. Specifically, higher resolution electrophysiological approaches and their associated analytical tools now permit assessing circuitry state in patients in a reliable and inexpensive way. Emerging tools allow circuit-based assessments with wearable devices, enabling a wide deployment of these readouts in clinical trials. These tools will improve our ability to match subjects with functional brain alterations that are relevant to the mechanism of action of the test target and therefore more likely to respond positively.

Another complicating factor related to disease heterogeneity is the complex, sometimes overlapping presentation of symptoms in multiple disorders. Different disease domains are driven by specific circuitry alterations. Therefore, it is important that efforts aimed at developing biomarkers for patient selection focus on markers related to specific disease domains. There has been a growing effort in identifying biological mechanisms associated with specific domains, and the NIH Research Domain Criteria (RDoC) initiative is driving the field to assess molecular, cellular, and circuitry aspects relevant to specific domains. This ongoing effort can be leveraged to define domain-related biomarkers, not only to capture pharmacodynamic aspects of novel compounds but also to help with selecting the appropriate patient population to be studied.

Lastly, treatment history with established compounds and stage of the disease may affect the response to novel treatments. Most novel approaches for schizophrenia involve glutamate or GABA-based pharmacology and are aimed at reversing cognitive impairment and/or negative symptoms. These agents have been generally tested in chronic patients and as an add-on to antipsychotics. As D2 antagonists may have a deleterious effect on cognitive performance and mood, it is possible the impact of the novel treatments is blunted by antipsychotic history.

Indeed, prior haloperidol exposure reduced responses to a novel GABA-alpha 5 compound in a rodent model of hippocampal hyperactivity and loss of interneuron function (Gill et al, 2014). Furthermore, post hoc analyses of the (failed) studies with the novel antipsychotic, pomeglumetad, revealed antipsychotic efficacy in patients early in the disease (Kinson et al., 2015).

Clinical Endpoints

Most trials have relied on clinical endpoints that are rather imprecise and/or have poor psychometric properties. Detecting a change with highly variable endpoints becomes a herculean task that requires enrolling large numbers of subjects—which, due to operational considerations, can lead to compromises in achieving patient cohort homogeneity. Furthermore, as multiple sites are incorporated into clinical trials, the cross-site variability makes the problem worse. Additional issues to consider for late-stage trials include differences in health care services across countries in multinational studies, rater training and monitoring, dealing with duplicate and professional patients, nonadherence, and, most importantly, minimizing placebo response. So, how can we optimize the reliability of the data generated in clinical trials? A key consideration is to incorporate more objective measures that can be confidently repeated within and between subjects.

One way to reduce the imprecision of clinical endpoints is to adopt quantitative measures that can supplement self-reports or clinician rater-based assessments. Traditionally, neuropsychiatric trials have used interview-type clinician assessments or subject self-assessments to capture data relevant to mood and cognition. There are now many interesting tools that can capture similar data in a more objective and reproducible manner. With these technological developments and the widespread use of wearable devices, it is high time to incorporate these tools in clinical studies. There are algorithms available to capture emotional responses to faces using hand-held devices, and assessment of voice cadence can provide similar information. Of course, these novel approaches need to be validated, but being able to adopt them will make clinical trials more reliable and informative.

Since the low precision of clinical endpoints is related to the complexity of the disease, we also need to deconstruct these complex diseases by focusing on smaller clusters of symptoms (which are more likely to be affected by the mechanism of action of the test target) to improve the precision of detecting a signal of clinical efficacy. Adopting endpoints that are domain-relevant (e.g., as in RDoC) will be essential.

The Need for Translatable Biomarkers

Molecular biomarkers have not been readily available in neuropsychiatry due to the lack of available tissue for sampling. CSF collection is somewhat invasive, and brain tissue biopsies are impossible. This is in stark contrast to oncology, where the use of biomarkers from tumor tissue has ushered in a golden era of precision medicine. It is therefore critical to use alternative modality biomarkers in neuroscience drug development, taking advantage of the nervous system's unique feature of electrical activity. Imaging and electrophysiology biomarkers that can capture neurocircuitry modulation relevant to specific disease domains in humans are being identified, and we need to make sure these biomarkers have a measurable preclinical counterpart to properly aid preclinical development efforts. The RDoC initiative provides a framework for translatable domain-relevant

assessments. We need to move beyond the current focus on molecular biomarkers and PET ligands to embrace markers that capture circuitry function and dysfunction. Fortunately, there has been some significant work back-translating human electrophysiology endpoints (adapting mismatch negativity, e.g., to rodents [Amann et al., 2010; Cabungcal et al., 2014]) and cognitive assessments (back-translating the probabilistic reward task to rodents [Der-Avakian et al., 2013], among many others). Reverse translation of validated circuitry-relevant human endpoints will be required to help properly assess novel compounds in a way that can inform clinical studies. Conversely, there is an impressive development of preclinical tools to study neural circuits that we may need to translate and adopt for human studies. Combining these efforts will enable us to start testing complex biological hypotheses in a clinical setting.

Conclusion

Clinical trials in this age of deep understanding of the brain need to be smarter and more informed than historical designs that have consistently fallen short of expectations. In addition, a greater focus on project quality and deeper biological understanding is needed (Cook et al., 2014). We need to develop novel medications based on disease domains that are robustly linked to validated biological mechanisms. It is essential that we focus on more homogeneous patient populations for novel targets. We need to incorporate biomarkers that capture circuitry dysfunction, ensure that there is a translatable version for preclinical studies to choose the right molecules, and optimize these biomarkers for clinical trials. We also need to adopt less subjective endpoints for clinical studies, exploiting the current growth of devices and analytical tools that can capture information in real-world settings (and therefore expanding the possibilities of running studies in many sites or even at home) in a more reliable manner. We are at an interesting point in time. Technology and neuroscience have evolved, and there are now tools available to implement and pressure test these ideas. It will not be a single pharmaceutical company that delivers the change. This will require a concerted effort from government agencies, academic institutions, foundations, and the private sector that has already begun but needs to continue to advance swiftly and bravely to deliver breakthrough precision medicines. Let's continue the momentum; patients are waiting.

Statement of Interest

All authors are employees and shareholders of Takeda Pharmaceuticals.

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