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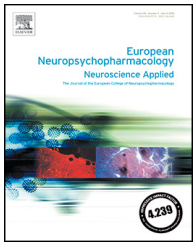

REVIEW

New approaches in psychiatric drug development

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Abstract
Numerous novel neuroscience-based drug targets have been identified in recent years. However, it remains unclear how these targets relate to the expression of symptoms in central nervous system (CNS) disorders in general and psychiatric disorders in particular. To discuss this issue, a New Frontiers Meetings of European College of Neuropsychopharmacology (ECNP) was organized to address the challenges in translational neuroscience research that are impeding the effective development of new treatments.
The main aim of this meeting was to discuss scientific insights, concepts and methodologies in order to improve drug development for psychiatric disorders. The meeting was designed to bring together stakeholders from academia, pharmaceutical industry, and regulatory agencies.

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Here we provide a synopsis of the proceedings from the meeting entitled 'New approaches to psychiatric drug development'. New views on psychiatric drug development were presented to address the challenges and pitfalls as identified by the different stakeholders. The general conclusion of the meeting was that drug discovery could be stimulated by designing new classification and sensitive assessment tools for psychiatric disorders, which bear closer relationships to neuropharmacological and neuroscientific developments. This is in line with the vision of precision psychiatry in which patients are clustered, not merely on symptoms, but primarily on biological phenotypes that represent pathophysiological relevant and 'drugable' processes. To achieve these goals, a closer collaboration between all stakeholders in early stages of development is essential to define the research criteria together and to reach consensus on new quantitative biological methodologies and etiology-directed treatments.

1. Introduction

The neuroscience field is currently advancing insight into the functional processes that underlie central nervous system (CNS) derangement in psychiatric illness. Such progress is the result of the development of more advanced technologies in the field, that include but are not limited to neuroimaging, and various 'omics'-technologies like (epi)genomics, transcriptomics, proteomics and metabolomics. Advances in other medical disciplines, such as clinical genetics and immunology, also contribute to a better understanding of brain disorders. In addition, innovative ways to quantify human and animal behaviour, such as by means of clinical phenotyping, provide new translational research options. By applying sophisticated biological mechanism based methodologies, an increasing number of potential 'drugable' CNS targets have been identified which may potentially benefit both clinical management of psychiatric conditions and psychiatric drug development in the future. However, a major concern is that psychiatry has been unable to effectively exploit the advances that neuroscience has yielded up to now. For many novel neuroscience-based targets, it still remains unclear how they relate to symptoms or to clinical expression of the disorders that make up psychiatric diagnostic entities. Therefore, stakeholders have yet to reach agreement on how to move forward (Hyman, 2016).

The number of US Food and Drug administration (FDA) approved new drugs in the last decades shows that psychiatric drug development is lagging behind compared to other medical disciplines (Bjornsson, 2016). To illustrate, in 2015 the total number of new registered drugs since 1975 was 33 in psychiatry versus 54 in neurology (Bjornsson, 2016). One aspect of the backlog of drug approvals in psychiatry is a limited number of new mechanisms of action. In many areas, such as neurology and oncology, drugs regularly appear on the market that have novel or significantly modified mechanisms of action. In psychiatry, however, only very few mechanisms of action have been introduced since the development of monoamine reuptake inhibitors in the eighties and nineties (Bjornsson, 2016). This can be illustrated by the time course of an 'innovation index', which can be defined as the numbers of mechanism of action divided by the number of registered drugs. Highly innovative disciplines like immunology and oncology have innovation indices of 40%-60%. It is interesting to compare the course of drug development in psychiatry and neurology, which both deal with the same human organ, the brain. Fifteen years ago, neurology and psychiatry both had innovation indices of about 30%, meaning that in each disciplines three registered drugs shared a single mechanism of action. In neurology, the index has since increased slightly to a stable level of 35%, which reflects developments in multiple sclerosis, epilepsy, Parkinson's disease, stroke and other indications. Psychiatry, however, has seen a steady decline of the index to about 20% (4-5 drugs per mechanism). Psychiatry and cardiology are the only medical fields where the innovation index has decreased since the beginning of this millennium (Bjornsson, 2016). In cardiology, significant advances were made in preventive and innovative surgical and radiological interventions. In psychiatry, however, improvements in cognitive behavioural strategies and changes in the quality of psychiatric care have offered no compensation for the slow development of new psychiatric medications.

The complexity of psychiatric drug development is related to several factors. First, there are pharmacological restrictions due to the inviolability of the human brain. It is difficult to achieve blood-brain barrier (BBB) penetration and to assess target engagement, and complex methods are required to determine this (in)directly, such as in vivo positron emission tomography (PET) imaging, functional CNS tests, post-mortem studies and CSF sampling. Neurology is helped in this respect by its focus on structural abnormalities. Second, there is a disconnection between the definition of the biological processes that underlie animal models and human research, which has limited the identification of cross-species clinically relevant mechanisms. As a consequence, insights from animal studies cannot be translated directly into human drug targets. Innovative disease models in neurology have profited more from scientific advances, particularly in genetics and immunology. Third, there is a clinical heterogeneity in psychiatric disorders since their classification is based on the predominantly phenomenology based Diagnostic and Statistical Manual of Mental Disorders (DSM) and the neurobiological mechanisms for most disruptions of CNS functions (behavioural, emotional, cognitive) have only partly been unraveled.

The treatment of a psychiatric patient may require a multifaceted and interactive approach. This is not an easy situation for drug development, and many large pharmaceutical industries have shied away from this area. Nonetheless, because of the large social, economic, and personal burden of

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