PERSPECTIVE

Neurodevelopmental framework for drug discovery neurodevelopmental disorders

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ABSTRACT

There has been a revolution in genetic findings in Neurodevelopmental Disorders (NDDs) during the last decade, with several discoveries crucial to understanding their aetiology and pathophysiology. Clinical studies with single-gene disorders like fragile X syndrome show how difficult it is to find new treatment targets in NDDs. Incorporating a developmental viewpoint into the drug development process for NDDs should aid in overcoming some of the present challenges in identifying and evaluating new treatments. This publication summarises the proceedings of the European College of Neuropsychopharmacology's 'New Frontiers Meeting' on neurodevelopmental diseases, which was held in collaboration with the AIMS-2-TRIALS project, which is funded by the Innovative Medicines Initiative. It brought together academic and industrial professionals in developmental genetics, autism, neurodevelopmental disorders, and therapeutic trials, as well as regulators, patient and family organisations, and other stakeholders. From a neurodevelopmental standpoint, the meeting aimed to provide a platform for concentrated exchange on scientific insights, difficulties, and techniques that might be applied to the development of CNS treatments. Multidisciplinary translational consortia that produce basic and clinical research at the same time could be crucial in furthering knowledge in the sector. Although it is commonly agreed that clinical trials for NDDs in children are necessary, safety concerns should influence every aspect of their design. With regulatory backing, industry and academics should collaborate to enhance knowledge of the biology of brain development, determine the ideal timing of interventions, and translate these results into novel pharmaceuticals that meet the requirements of users and families.

Key Word: *Autism; Clinical trials; Drug discovery; Genetics; Neurodevelopmental disorders*

INTRODUCTION

Neurodevelopmental Disorders (NDDs), which include Autism Spectrum Disorder (ASD) and Intellectual Impairment (ID), are a group of illnesses in which brain development is disrupted. NDDs have a wide range of clinical symptoms and severity, and they're linked to varied levels of cognitive and adaptive functioning as well as impairment. The prevalence of restricted, repetitive interests and/or behaviours, as well as persistent difficulties in social communication and social interaction across numerous situations, characterises ASD (American Psychiatric Association, 2013). Although prevalence estimates vary widely between nations and studies, it is estimated that about 1% of children worldwide have autism, with rates rising in recent decades. ID is defined by the existence of childhood-onset deficits in general intellectual capacities that impede adaptive functioning in the conceptual, social, or practical aspects of life, and has an estimated prevalence of 1%. NDDs have a complex aetiology, with rare and frequent genetic variations as well as environmental variables playing a role in their pathophysiology (Kiser et al., 2015) [1].

NDDs impact approximately 120 million individuals globally and are linked to a considerable loss in life expectancy as well as high rates of impairment, particularly among young people (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). As a result, novel treatment options for NDDs are urgently needed to satisfy unmet requirements and reduce related disability. For example, there are few effective pharmacological therapies for ASD core symptoms, which can be extremely debilitating for many autistic people. Despite significant breakthroughs in our understanding of the physiology of brain illnesses and efforts to find new disorder-modifying chemicals, the science of NDDs has hit a wall in the last two decades. In comparison to most other fields of drug

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development, the failure rate for novel medications addressing CNS illnesses is significant, especially for so-called disease-modifying drugs (drugs that try to change the course of a disease or condition [2]. Given our growing recognition of the clinical, biological, and aetiological heterogeneity inherent in NDDs and other psychiatric disorders and the substantial overlap among disorders, one of the reasons for this repeated failure could well be the use of clinical categories with insufficient biological validity. Another important problem is that in clinical trial development, the developmental trajectories of mental diseases are likely to be overlooked [3].

Understanding the dynamic nature of the pathophysiological mechanisms behind NDDs and other brain illnesses is critical for developing effective treatments and prevention methods. Developmental therapeutic windows have not been appropriately considered in the design and selection of possible participants for psychotropic medication studies in mental disorders to date. Despite encouraging preclinical and early phase trial data and a compelling rationale based on sound mechanisms of action, recent mechanistically driven trials in NDDs such as Fragile X Syndrome (FXS) have produced poor phase IIb or III findings. These experiments were done on adults and teenagers, and one can wonder if they should have been done on much younger people, as it may be difficult to reverse decades of atypicalities and their cascade consequences with just a few months of treatment. Beyond the CNS, there are other examples of therapies that are helpful for disease modification only within a certain therapeutic window (e.g., congenital hypothyroidism and myocardial infarction). As a result, it's likely that patients were denied access to effective treatments since trials were conducted outside of the therapeutic window. However, the benefits of a medicine that affects early neurodevelopmental trajectories must be weighed against the unknowns about its long-term consequences and the risks of such interventions on brain development [4,5].

FMRP levels appear to be low in a variety of brain disorders, including ASD, schizophrenia, mood disorders, and epilepsy, and its targets include many genes and proteins linked to NDDs, such as ASD and other neuropsychiatric disorders (Bernard et al., 2013; Fatem. FMRP levels have also been linked to cognitive functioning in schizophrenia and healthy controls, as well as the age of onset in schizophrenia patients. The importance of downstream glutamatergic signalling as a biological link between some syndromic and non-syndromic types of autism has been supported by functional variations in genes involved in post-synaptic FMRP control, such as CYFIP1 and CAMK4, which have the potential to become therapy targets [6].

Studying molecular mechanisms in FXS can help us understand some of the phenotypic commonalities among illnesses and enhance our knowledge of pathways that can be targeted to guide drug discovery for NDDs, since FMRP signalling appears to be troublesome in other NDDs besides FXS. Preclinical research in FXS has shown those alterations in synaptic function, as well as some aspects of the cognitive and behavioural phenotype can be rescued using both genetic approaches aimed at reactivating the affected gene and pharmacological strategies aimed at compensating for the lack of FMRP. This resulted in more than 20 clinical trials in persons with FXS being completed between 2002 and 2017 [7]. Clinical experiments targeting FMRP utilising mGluR5 antagonists and GABAB receptor agonists did not provide indisputably good findings in FXS (Berry-Kravis et al., 2017b), underlining some of the obstacles of assessing potentially disease-modifying treatments for NDDs.

Failed clinical trials evaluating mGluR5 inhibitors and GABAB agonists for FXS (Berry-Kravis et al., 2017b) can lead to the following conclusions:

- Trials using mGluR5 antagonists for FXS were sufficiently well powered for their primary outcome measure and lengthy enough to reach a negative conclusion. In all age groups, clinically active medications for ASD and other psychiatric illnesses demonstrate benefit in treatments lasting less than three months.
- Participants in trials evaluating mGluR5 antagonists ranged in age from 12 to 40 years, allowing for the discovery of age-related therapeutic advantages within this age range. When examined in very young subjects with longer treatment durations, mGluR5 antagonists could lead to benefits in developmental trajectory and cognition. A signal was detected in the 5–11 year subgroup (but not in adolescents or adults) for medications having a distinct mechanism of action, such as arbaclofen, suggesting that earlier therapies may be required for disease change.
- Although trials investigating mGluR5 antagonists for FXS were appropriately powered for their major outcome measures, well-powered RCTs for NDDs with a low prevalence, especially for rare illnesses, are generally challenging to execute. To attain the final sample size in one of the largest trials using a mGluR5 antagonist in children, adolescents, and adults with FXS, researchers had to examine over 650 people at 24 sites. In such cases, a trade-off between potentially relevant data and the low power given by short trials, which frequently uncover signals in many post-hoc analyses that cannot be duplicated, may be appropriate.
- Even with relatively large sample numbers, studies may lack the capacity to stratify or conduct secondary analyses evaluating additional outcome measures due to differences in dosage and/or treatment groups. It may be necessary to use different methods or designs to examine dosage strategies or stratification.
- Due to relatively successful results in animal models, these studies' results were also influenced by high expectations and placebo effects; however the placebo impact was comparable to that reported in previous pharmacological trials (Berry-Kravis et al., 2016) [8,9].

A neurodevelopmental framework for drug discovery could help to enhance the treatment of NDDs and other brain disorders, as well as contribute to the implementation of a mental health prevention strategy. There have been significant advances in terms of genetic findings and translational research on NDDs in the last decade, with many critical discoveries in their aetiology and pathophysiology that could guide the development of new drugs. It is necessary to investigate the temporospatial dynamics of molecular-level brain dysfunction during the early stages of development. This could help guide different degrees and phases of targeted therapies, such as psychopharmacological techniques, to reverse early dysfunction or its homeostatic repercussions and prevent their functional and morbid

effects, especially during key neurodevelopmental times.

Research on single-gene illnesses like fragile X syndrome provides the ground for more research in the field and supports the idea that intervention timing is important. The inclusion of younger people in clinical studies for NDDs appears to be justified, although caution and safety must always take precedence [9]. Thus, medications should be tried first in paediatric populations only when there is compelling logic for doing so, and only after meticulous preclinical and phase I investigations to assure maximal participant safety.

CONCLUSION

To make this procedure go more smoothly, close collaboration with regulatory agencies is recommended. To guarantee that the clinical trial design serves their requirements and that clinically meaningful outcome measures are employed, user and advocacy groups, as well as other key stakeholders, must be involved in the medication development process from the beginning. The identification and practical implementation of reliable, valid, and sensitive outcome measures, including stratification biomarkers, is still required in clinical trials for NDDs. Observational studies may provide crucial information about the temporal course of these conditions' pathophysiology and aid in the discovery of potential biomarkers. In order to stimulate the discovery of innovative treatments for NDDs and other brain disorders, as well as enhance the care and outcomes of persons living with these disabling conditions, a "4P's" strategy to intervention is required.

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