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Schizophrenia

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Statement of the issue: The purpose of this presentation is to introduce current issues around the use of imaging biomarkers in drug discovery and preclinical as well clinical drug development to treat schizophrenia. Imaging biomarkers can be used for internal decision making, e.g. to determine whether a drug hits its target in the brain, to guide dosing of clinical proof-of-concept trials, or – in a best-case scenario – as surrogate markers for clinical outcomes. Examples for each of those scenarios will be reviewed, and recent controversies and new directions in the use of neuroimaging agents in Schizophrenia research will be discussed.

Current state of the art: Schizophrenia is associated with subtle structural and functional brain abnormalities. Available data suggest that it is a heterogeneous disorder with heritable component. However, both the cause and the course of schizophrenia are poorly understood, and classical diagnostic categories of clinical symptoms have not been specifically useful in identifying its pathophysiology or predicting response to a therapeutic intervention.

Despite vast clinical experience with antipsychotics, there is still considerable scientific debate on the appropriate dose selection of these compounds. Historically, in most clinical dose-finding studies with antipsychotics, relatively arbitrarily selected doses were tested to find the "most efficient" dose range in a patient population, with no particular regard for the molecular effects of the tested drug. Brain imaging studies using nuclear medical techniques, such as positron emission tomography (PET) or single photon emission computed tomography (SPECT), can now provide a better rationale for doses, directly derived from the central effects of the drugs on neurotransmitter receptors measured in vivo. PET results indicate that occupancy of at least 65% of dopamine-2 (D_2) receptors is needed for clinical response to antipsychotics, and that occupancy rates exceeding 80% are associated with a high risk for elevation of prolactin levels and motor adverse effects. The relevance of D_2 receptor occupancy for drug administration is also borne out by studies relating the effects of antipsychotics to their D_2 receptor occupancy in relevant animal models.

Magnetic resonance imaging (MRI) studies in schizophrenia have shown both, structural and functional brain abnormalities, predominantly in the frontal and temporal cortices. Most of the abnormalities seem to be already present at illness onset. In addition there is growing evidence for treatment-related neural changes in schizophrenia, for instance enlargement of basal ganglia structures such as the caudate nucleus, possibly representing a neurotoxic effect with the use of typical neuroleptics, and increases in cortical volumes and improved functional responses, putatively through a neurotrophic effect with the use of atypical, second generation antipsychotics. More recently, brain changes during earlier, prodrome and transition-to-illness stages of schizophrenia have been described.

The possible genetic risk factors for schizophrenia are numerous. Unfortunately, the connection between a given genotype and time-course, or outcome of the disease has yet to be established. Brain imaging methods that study the structure or function of the cortical and subcortical regions have identified distinct patterns that distinguish schizophrenics from controls, and that may identify meaningful subtypes of schizophrenia. The predictive relationship between these imaging phenotypes and disease characteristics such as treatment response is only emerging. The emergence of the field of imaging genetics, combining genetic, and neuroimaging data, holds much promise for the deeper understanding and improved treatment of schizophrenia.

Conclusion: Neuroimaging can contribute to understanding the underlying biology of CNS diseases like schizophrenia. In addition, it can be used to elucidate the pharmacodynamic mechanisms of a therapeutic intervention. Currently, imaging biomarkers are used in developing novel drugs to treat schizophrenia to establish whether a specific drug hits it putative target and for PK/PD modeling purposes to help with clinical dose selection. Unfortunately, at this time there exists no validated imaging biomarker that seems promising as a surrogate for clinical efficacy.

References

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