Editorial

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Re-Engineering Cns Drug Discovery and Development Using Computer Aided Modelling

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Short Commentary

Many experimental drugs can successfully "treat" preclinical transgene animal models of "CNS disorders", only to find out later that they fail in clinical trials. Translating biological knowledge into useful therapeutic interventions for patients is a steep challenge. Of all the indications, Neurology and Psychiatry rank among the lowest in success rate for clinical development likely because the brain is an extremely complex organ with many non-linear feedback circuits. In addition, the brain is not accessible to the same extent as other organs and biomarkers are limited.

Another exciting development is related to the concept of "synthetic virtual placebo patients" where the clinical trajectory of individual patients that are enrolled in the active treatment arm would be simulated as if they were allocated to the placebo arm. This would allow reducing the number of patients in a clinical trial by limiting the intrinsic variability which in turn would accelerate enrolment and the availability of successful therapeutics.

Central Nervous System (CNS) disorders represent an area of major unmet medical need. Personalized Medicine (PM) is a new paradigm that capitalizes on known variability in patients, which results in differences in disease susceptibility and responses to medicines. The European regulatory network is facilitating the development of PM approaches for CNS disorders, including pharmacogenomics, Biomarkers (BMs), companion diagnostics, and rare diseases; novel methodologies and innovative clinical trial designs; and advanced therapies. A greater focus on patient centricity and involvement of patient groups has led to enhanced regulatory support, including dedicated scientific advice resources, new guidance documents, and multistakeholder platforms to address challenges in PM development. These initiatives have resulted in some successes (e.g., BM qualification), and it is hoped that these will facilitate future approval of personalized CNS medicines

Discussion topics include analysis of the biological mechanisms underlying each disease, currently approved products, and available animal models for development of new therapeutic agents. Analysis of currently approved therapies shows that all products depend on the molecular properties of the drug or pro-drug to penetrate the BBB. Novel technologies, capable of enhancing BBB permeation, are also discussed relative to improving CNS therapies for these disease states.

CNS drug design balance physicochemical properties for optimal brain exposure. The human brain is a uniquely complex organ, which has evolved a sophisticated protection system to prevent injury from external insults and toxins. Designing molecules that can overcome this protection system and achieve optimal concentration at the desired therapeutic target in the brain is a specific and major challenge for medicinal chemists working in CNS drug discovery. Analogous to the now widely accepted rule of 5 in the design of oral drugs, the physicochemical properties required for optimal brain exposure have been extensively studied in an attempt to similarly define the attributes of successful CNS drugs and drug candidates. This body of work is systematically reviewed here, with a particular emphasis on the interplay between the most critical physicochemical and pharmacokinetic parameters of CNS drugs as well as their impact on medicinal chemistry strategies toward molecules with optimal brain exposure.