Therapeutic innovations in neuroscience: what's new on the horizon?

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Therapeutic Innovations in Neuroscience: What's New on the Horizon?

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The theme of this issue of *Clinical Pharmacology & Therapeutics* (CPT) encompasses neuroscience in the broad sense to include neurology and psychiatry, nonclinical and clinical aspects, novel clinical trial methodologies, and modeling and simulation approaches applicable to central nervous system (CNS) drug development and therapy. While naturally the last two years have been dominated by coronavirus disease 2019 (COVID-19), it is important not to forget that drug development for other indications has not been stopped, albeit many trials were affected in terms of delays in recruitment and collection of clinical data.

There are numerous rare to ultrarare neurological diseases in which the very limited number of patients, combined with the lack of reliable biomarkers and targeted therapies, pose a real challenge for traditional drug development, including appropriate dose-finding studies. Abuasal *et al.*[1] discuss the role of regulatory flexibility in the approval of new drugs and give examples from US Food and Drug Administration (FDA) scientific assessment and conclusions based on a relatively limited data set, using modeling and simulation to select the optimal dose, extrapolation among populations, or pharmacodynamic biomarkers. The authors also provide an optimistic outlook into the future regarding the expected role of quantitative systems pharmacology, artificial intelligence, and machine learning, as well as disease progression models using real-world data (Figure 1).

Stephenson *et al.*[2] discuss whether and how innovative trial designs and technologies, including multiarm adaptive platform designs and digital health tools to monitor progression in rare diseases like Duchenne muscular dystrophy and amyotrophic lateral sclerosis (ALS), can drive the advancement of treatments for common neurological diseases like Parkinson's disease. At the same time, the authors provide an excellent insight into the importance of collaborative efforts: Novel platforms containing data from completed clinical trials, registries, natural history studies, and preclinical data do not only foster data sharing but also provide a means of connectivity to sophisticated tools like disease progression models and clinical trial simulation applications.

Clinical trials in neuroscience are frequently challenged by the extensive heterogeneity between patients and their survival and a non-negligible number of patients dying during the course of a clinical trial, particularly in rapidly progressive diseases like ALS. Van Eijk *et al.*[3] present an overview of commonly used strategies to address death in efficacy end points for clinical trials, which may have implications for the interpretation of the study results. Exemplified by clinical trials in ALS, their review provides guidance to define the exact research question of a trial, to align its objectives with the study design, including

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Figure 1 *Clinical Pharmacology & Therapeutics* April 2022 cover image: Innovations in Neuroscience.

the analytical strategy for handling death, and to ultimately aid study planning and analysis.

Particularly for rare diseases, drug development initiatives forged by patients and their advocates play an emerging and vital role. Romer *et al.*[4] present a moving perspective on family-driven development of treatments for rare pediatric neurological diseases. The authors' journey started with months in search of reasons for the fact that their children stopped developing at the same pace as other children, followed by the devastating diagnoses of the rare and fatal pediatric neurological diseases Tay-Sachs and GM1 gangliosidosis. The authors describe how—after converting their initial anger into urgency and purpose—they managed to mobilize a substantial network of resources, leading to consortia of scientists and clinicians, trials of gene therapy for Tay-Sachs in animal models, and finally translation of the nonclinical research into clinical development for both Tay-Sachs and GM1 gangliosidosis.

Since the first FDA approval in 2017 of voretigene neparvovec-rzyl (Luxturna), a gene therapy to treat a specific form of retinal dystrophy leading to progressive blindness, gene therapy has been raising hopes for treating rare genetic diseases despite many clinical setbacks in the past. In their State-of-the-Art article, Flotte and Gessler[5] cover basic principles, obstacles, and future directions of gene therapy for rare neurological disorders. The diversity of rare CNS disorders calls for diverse therapeutic strategies and technological platforms in CNS gene therapy presented in the article, including viral vector platforms like recombinant adeno-associated virus, nonviral platforms, oligonucleotide-based therapeutics, gene editing, and cell therapies. Preclinical gene therapy development, translational efforts up to clinical trials, and regulatory considerations are illustrated for different groups of CNS disorders like ALS, spinal muscular atrophy (SMA), lysosomal storage diseases, Canavan disease, or RPE65 mutation–associated retinal dystrophy. Particular focus is placed on the multiple challenges associated with gene therapy development, ranging from the number of patients eligible for enrolment, safety concerns (particularly in the context of immune responses),

definition of the therapeutic window, and costs. Promising developments in the field comprise delivery routes beyond intravenous administration. For example, cerebrospinal fluid delivery is being evaluated in the clinical setting for onasemnogene abeparvovec (Zolgensma), an intravenous gene therapy product for SMA.

Efforts to improve drug delivery to the brain have been intensified in recent years also for other increasingly available biologic modalities like antibodies or nucleic acid-based therapeutics (e.g., antisense oligonucleotides). Sadekar *et al*.[6] discuss the delivery of biologic modalities to the brain via the cerebrospinal fluid and multiple CNS access routes, e.g., intracerebroventricular, intrathecal-cisterna magna, intrathecal-lumbar, intraparenchymal, and intranasal. There have already been successful developments of antisense oligonucleotides (ASOs) delivered via the intrathecal route, like nusinersen (Spinraza), an ASO targeting the survival of motor-neuron 2 (SMN2) in SMA patients, whereas others like tominersen (anti-HTT ASO) for Huntington's disease and tofersen (anti-SOD1 ASO) for ALS have failed so far to deliver in the pivotal trials despite promising exploratory results and are still under clinical investigation.

De Lange *et al*.[7] complement the topic of drug delivery to the CNS by outlining quantitative approaches to describe blood-brain barrier transport and intra-CNS distribution to different CNS target sites, together with innovative methods to influence CNS drug delivery.

Zhu *et al*.[8] explain the rationale behind the FDA's accelerated approval on the use of aducanumab, an antibody against beta-amyloid (Aβ) in patients with early Alzheimer's disease based on reduction in Aβ plaque in the brain. By summarizing literature from seven anti-Aβ antibodies investigated in late-phase trials, the authors discuss a potential threshold of Aβ plaque reduction for clinical effect. Kesselheim,[9] one of the experts advising the FDA in the procedure, presents the counterpart argument. He argues that while amyloid plaque is a marker for Alzheimer's disease, its clinical usefulness as a surrogate measure in clinical trials has never been demonstrated, despite many trials with products which reduce production, inhibit aggregation, promote disaggregation, and increase brain clearance of beta-amyloid.

In summary, various challenges, including the variety of neurological and psychiatric disorders and the diversity of the affected patients, demand sophisticated clinical pharmacology strategies to successfully translate discoveries into effective treatments. This special-themed issue of CPT brings into focus an extract of the wealth of experimental, translational, diagnostic (e.g., imaging), and computational tools that have been innovating the field of neuroscience in an effort to develop new effective treatment strategies for common and rare diseases.

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