New Approaches for Rare CNS Drug Development

The central nervous system is hit by a number of disorders and diseases, treatments for which are benefiting patients in more ways than one

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Breakthrough treatments and new disease classifications have emerged as researchers gain insight into the pathophysiology and genetic underpinnings of central nervous system (CNS) conditions. In rare disease, that means one disease can be classified into multiple ultra-rare diseases – all of them potential targets for new drugs. Researchers have also identified overlaps between diseases previously considered distinct conditions.

For example, we now understand the highly conserved C9orf72 gene implicated in the neuronal accumulation of TDP-43 protein in some patients with frontotemporal dementia (FTD) may also explain some dementia-like symptoms observed in people with amyotrophic lateral sclerosis (ALS) (1). Researchers now place ALS and FTD on the spectrum of TDP-43 diseases. Researchers also discovered that the C9orf72 triplet repeat can cause either ALS, FTD, or combinations of both.

The replacement of larger classifications of common disorders with more precisely defined spectrums of individual rare and ultra-rare diseases has significantly changed the drug development landscape. A new landscape requires a new approach to clinical trial design.

The Clinical Development Landscape

Deepened understanding of the cellular and molecular mechanisms involved in rare CNS diseases such as Huntington's disease, Wilson's disease, and Angelman's syndrome has led to more effective and targeted treatments. For Huntington's disease, therapies that target the cytosine, adenine, and guanine segment of the Huntingtin (HTT) gene are currently in development (2). Roche recently stopped trials on a therapy that targets the HTT protein while it collects data and determines next steps (3).

Researchers at the University of North Carolina, US, have made progress in Angelman's syndrome by looking at its genetic underpinnings. In mouse models, researchers found that turning on the ubiquitin-protein ligase E3A gene effectively prevented seizures (4). In another experiment, researchers used CRISPR/Cas9 gene editing technology to activate gene function.

Clinical trials that target rare disease subsets based on genetic mutations naturally involve smaller sample sizes, benefiting from nontraditional trial models. For example, a clinical trial sponsor could run a basket trial to evaluate a genetically targeted therapy in subsets of two different diseases with the same genetic driver.

They also require strategic approaches to recruitment, measuring safety and efficacy, and monitoring outcomes. Studies beginning evaluation prior to intervention allow for subjects to act as their own controls, which, therefore, reduces the sample size needed.

Operational Strategies for Rare CNS Studies

Gene-based therapies for rare diseases and rare disease subsets require highly specialised research sites and investigators. Identifying sites with experience in the disease being studied, with access to the targeted patients, and with the expertise and support functions to administer treatment and manage any associated adverse effects is critical.

It's also crucial to help patients and caregivers understand all that's required to participate. When it comes to enhancing the patient experience, one can never do too much. Here are a few strategies to keep in mind:

- ***Patient centricity is paramount:*** When studying rare CNS diseases, it's important to consider patient needs. Many of the diagnostic tools used to determine whether patients fall within the inclusion/exclusion criteria and to determine a baseline are typically

time-consuming and involve input from the patient, the caregiver, and a clinician

- ***Develop and deliver an appropriate risk-benefit profile from the moment of protocol design and throughout clinical trials:*** To make sure patients understand that profile, provide clear, well-written informed consent, as well as consent aids, such as videos or illustrations, that explain procedures to patients, caregivers, and/or parents. If the subject is suffering from a disease that impacts cognition to the point where they are not able to consent, a legally authorised representative is needed. Globally, there are different required processes to be followed to ensure the patient is properly consented.

  During patient recruitment, explain the duration and frequency of these procedures as well as how to keep diaries and report observations. Better understanding helps remove the fear factor of participating in studies, especially in the younger or cognitively impaired population. Sometimes providing videos of the environment or the procedure can help the patient prepare for the visit

As you design your protocol, make sure endpoints don't place undue burden on the patient. A few options include:

- Reduce the frequency of site visits and procedures as much as possible. Replace site visits with telemedicine visits or home healthcare where feasible
- Engage the family and caregivers early and often
- Pair televisits with home healthcare nurses and direct-to-patient delivery of medicines to make participation easier. Use direct-from-patient services to collect reusable, disposable, and recyclable materials, specimens, and other items
- Offer transportation and accommodation for patients, caregivers, and family. Think concierge-level service
- To lessen feelings of isolation, connect patients with advocacy groups and communities
- Connect the referring physician and new treating physician to make sure the new doctor understands the patient's social environment, travel situation, and disposition
- ***Build physician referral networks well in advance of any rare CNS study:*** Leverage registry data, advocacy group relationships, your existing study investigators' connections, and any of your existing relationships to expand the patient pool. To make the most of this network, engage regularly to keep your study top of mind. Train local associates to use sponsor-approved messaging to reach out to investigators via phone, email, newsletters, and in-person visits (when possible)
- ***Shore up your supply chain:*** Precision medicine involves transporting highly valuable, fragile substances between the manufacturer, site, and patient under highly controlled conditions and tight timelines. Work with a supply chain partner with experience in your type of study with a network that facilitates global distribution and logistics. Your interactive response technology can also be programmed to distribute investigational product in a just-in-time approach when possible, therefore reducing the overall amount of supply 'stranded' at sites that don't have an eligible patient at that time

New Approaches to Rare CNS Development

Developing a rare CNS therapy requires delicate decisions around patient identification, treatment delivery, and measuring safety and efficacy. Obtaining accurate measurements often involves invasive procedures of the spine and brain, such as measuring cerebrospinal fluid (CSF). Less invasive approaches using newer techniques and technology hold promise for both patients and researchers.

Clearly defined rare diseases or subsets of rare diseases require a patient selection strategy based on the appropriate biology or genetic mutations. Researchers usually identify these criteria through analysis of biomarkers, molecular PET scans, and/or germline DNA.

CSF collection is one way to measure disease markers; but it involves an invasive procedure, and precautions must be taken. When introducing CSF collection in a clinical trial, work closely with the site to pre-empt any patient, family, or investigator fear or resistance. Investigators must use appropriate needles to prevent spinal fluid leakage and the resulting headache. They must also attend to factors that may impact the analyses, such as circadian fluctuation in various markers.

Delivering treatment, and confirming that delivery, for rare CNS diseases often involves invasive intracerebral, intrathecal, or systemic methods when measuring large molecules, cell therapy, or gene therapy. Delivery shouldn't be taken for granted, but it's often challenging to measure.

For treatments intended to slow disease progression, clinical confirmation of efficacy may take several months or years. Confirming delivery of treatment and its impact on biological pathways becomes particularly important in this case.

Crossing the Blood-Brain Barrier

One of the primary impediments to developing rare CNS therapies is the lack of effective strategies for delivery through the blood-brain barrier. Researchers have experimented with surgical approaches that deliver therapies directly into the brain, as well as intravenous administration of therapies into CSF. Both approaches have had mixed results.

Lipid-soluble drugs may diffuse across the blood-brain barrier. Receptor-mediated and absorptive endocytosis can also help macromolecules reach the brain. These processes may allow otherwise non-penetrant therapies to cross the blood-brain barrier, but effective delivery remains a challenge.

Viral vectors may allow certain CNS therapies to reach the target on a genetic level. When used in gene therapy, they hold the potential to modify the genome of the target cells, often resulting in a one-time treatment.

Measuring Safety and Efficacy

Once we deliver the therapy, the question becomes: did it reach the CNS? And if so, how did it affect the biology?

To determine whether treatment reached the CNS, it's possible to place microdialysis catheters within the brain to sample parenchymal extracellular fluid concentrations. This is a highly invasive procedure, however, and rarely performed in patients.

For selective therapies, PET labelling may confirm entry and analysis of receptor binding and confirm brain injury and target engagement. This approach is commonly used for psychiatric therapies.

It's also common to measure CSF concentration; however, while CSF is formed in part from brain extracellular fluid, a significant portion is produced by the choroid plexus. Drug concentrations within the CSF do not necessarily reflect concentrations within the brain.

While it's difficult to confirm brain entry, researchers are more concerned with the therapy's impact on CNS biology. While concentrations may not match those in the brain, CSF biomarkers are very often useful indicators of changes within the brain.

As an alternative to invasive lumbar punctures, many physicians are moving toward plasma biomarkers, including neurofilament light (NfL) chain protein, p-Tau, and brain-derived exosomes. This approach is revolutionising our ability to diagnose and track treatment effects. Changes in plasma NfL have been observed in response to putative ALS therapeutics, and by measuring neuronal and glial-derived exosomes, collected from plasma, researchers can examine gene expression and intracellular protein changes.

Evaluating Patient Outcomes

The ultimate goal is to improve patient outcomes, whether by reducing or relieving symptoms, improving quality of life, or providing a cure. With this in mind, when studying treatments in small sample sizes, pay careful attention to rater training and retraining.

CNS studies require a number of complex scales and outcome measures. To add to the complexity, the protocol may require separate safety and efficacy raters. Raters must receive thorough training and evaluation at the outset of the study, with periodic retraining through the duration of the trial.

Rigorous training and retraining ensure consistency and accuracy across sites, which leads to the most accurate reproducible data. It is important to implement central monitoring or oversight of the key assessments. Visualising a lot of these data also helps detect patterns and potential issues. Is one site generating abnormally high or low values or exhibiting signs of scoring drift? Investigate to determine if that site needs more training.

Home monitoring, either using patient-worn sensors or by capturing movements and activities on video, allows study teams to obtain objective confirmation of the clinical impact. Clinicians can also educate patients and caregivers on subtle symptoms to watch for, which can help them provide more accurate electronic patient reported outcomes and/or electronic clinical outcomes assessments.

Conclusion

As drug and biologics developers direct more attention on rare CNS diseases, they're discovering genetic markers that have led to multiple subsets of disease. With collections of diseases, researchers can develop more precise treatments; however, those small subsets make designing and running clinical trials more challenging. By prioritising patient comfort, confidence, and convenience, and by careful attention to study design, developers can improve the odds of bringing life-changing therapies to patients who need them.

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