

## Rare & Orphan Disease Endpoints: Challenges & Examples from Neurodevelopment

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### Personalized Medicine Requires Personalized Measurement

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On January 31, 2018, Noven Pharmaceuticals, the US subsidiary of the Japanese Hisamitsu Pharmaceuticals, announced positive results from their Phase III trial of the transdermal (skin patch) formulation of asenapine, first approved for the treatment of bipolar I and acute schizophrenia in April 2009. This news comes on the heels of another approval of a marketed compound based on a novel mechanism of action, Otsuka's digital aripiprazole, Abilify MyCite, in November of last year. There are some similarities in these two approvals: both are by Japanese pharmaceuticals smaller than some biotech companies, the innovation is not in the underlying compound but in the delivery method, and the target is one of the most severe and persistent mental illnesses, which has eluded successful treatment despite its heavy human and financial cost.

Clinical trials of drug treatments for Central Nervous System (CNS) diseases like schizophrenia, bipolar, depression, Alzheimer's Parkinson's, and many others, follow oncology as the second largest area of pharmaceutical research in terms of R&D spending, but the success rate has been low and approvals rare. In CNS drug development, it is common for investigational therapies to show promising effects in earlier trials, only to fail in the final stages of testing. Some of the

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reasons can be attributed to the technical difficulty of getting drug molecules to their targets across the blood-brain barrier, which in protecting the brain also protects the disease. However, the number of failed Phase III trials following exceptional Phase II results point to another underlying problem in CNS: having a drug that works is necessary — but not sufficient — to demonstrate efficacy at the magnitude that merits approval.

The Noven and Otsuka news point to what many practicing clinicians have long known and an increasing number of investigators and researchers are finding out: the efficacy of drug treatment is partially delivered by the context of the patient's life, experience, and support system. The most efficacious drug, taken infrequently because of behavioral, social, or economic reasons, will have a next-to-no chance of working. The transdermal patch, similarly to the digital pill, helps to convert efficacy to effectiveness by targeting the problem of compliance.

The data on non-adherence are staggering: between 25% and 50% of patients simply do not take their medication. Add to that the high rates of placebo response in psychiatric disorders, and it is no wonder that mental illness contributes the highest proportion of overall healthcare costs, higher than other chronic diseases or end of life care. Pharmaceutical companies now recognize the transformative potential of taking approved (therefore safe and efficacious) compounds and delivering them in innovative ways that help patients stay compliant. It is an applied approach to a patient-centered model of drug development.

The medical, social, and financial value of unlocking treatment adherence is one important takeaway here; another important takeaway is methodological. The outcomes in CNS clinical trials are subjective compared to other areas of medicine, with primary outcome measures based not on blood tests or imaging, but improvements measured on clinician-observed or patient-reported questionnaires. The science of behavioral measurement has advanced significantly and continues to evolve with the new digital health tools. But our trials are still haunted by the specter of high placebo response, patient misclassification, and unreliable outcomes.

A thriving niche has been established in the last 10-15 years in looking for solutions to these measurement problems. Our colleagues in this area have tried many approaches: making patient selection independent or consensus-based, improving the outcome measures themselves, using technology solutions to enhance detection of change, training of investigators to achieve standardization, training of patients and caregivers to improve reliability of reporting, patenting adaptive protocol designs, "enriching" patient sampling with increasingly complex screening approaches, seeking out "drug-naïve" patients, etc. And just like in clinical practice, we have found that none of these solutions work if applied in isolation. Noven's success —in one of the hardest indications in the hardest therapeutic area— was won through an empirically-driven application of

some components of all of these approaches. Looking at the Phase II data, we can analyze underlying trends and quantify risks to outcome data. The important next step is to remain uncompromising in the focus of applying those insights to the selection of a carefully calibrated set of measurement tools to be used in the trial.

The Otsuka and Noven successes portend a new era of drug development, one in which treatment efficacy is established in the context of the patient's overall life and behavior. It is time for measurement science to follow and embrace the fact that how we measure outcomes will evolve from applying one solution to finding an empirical basis for a highly customized application of all of them, enabled by technology. Personalized medicine needs a more personalized approach to measurement.

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