Powering Clinical Trial Success: The Impact Of Expert PK/PD Modeling In Psychedelic Research

In recent years, there has been a remarkable resurgence of interest in psychedelic drugs as potential fast-acting treatments for a range of neuropsychiatric disorders. Compounds known for their recreational use, such as N,N-dimethyltryptamine (DMT), psilocybin and ketamine, are now at the center of rigorous medical research. These substances have demonstrated promising therapeutic effects in patients suffering from conditions like depression, anxiety, and post-traumatic stress disorder. Intriguingly, researchers suspect that the subjective experience itself may be integral to their therapeutic effects. If true, this link between perception and therapy allows scientists to study effective doses early in development, even in healthy volunteers, long before patient trials begin.

Another major advantage of studying psychedelics is that they are not entirely new territory. Ketamine has been used safely as an anesthetic since the 1960s and classic psychedelics like psilocybin and DMT were subject of intense scientific interest during the 1950s and 60s, until shifting drug laws temporarily halted most research until the early 2000s, when work was resumed with more modern tools and stricter protocols. The wealth of historical and contemporary data now available on these compounds, covering their pharmacokinetics, pharmacodynamics, and safety, provides a valuable foundation for today's clinical research.

This rich body of historical and modern data now serves as a solid foundation for advancing today's clinical research. More specifically, it allows scientists to turn to in silico (computer-based) clinical trial simulations. These advanced population pharmacokinetic-pharmacodynamic (PKPD) models use mathematical representations of drug behavior in the body to predict how different doses might perform in human participants. By simulating multiple dosing scenarios before the first volunteer ever receives a dose, researchers can narrow down the most promising approaches. The result: smaller, faster, and more efficient clinical trials.

At the Centre for Human Drug Research (CHDR), such PKPD simulations have already shaped the design of numerous psychedelic studies. For instance, optimized infusion schedules for ketamine and DMT ensured that the resulting data would best address specific research questions. In one study, CHDR scientists compared intravenous and oral ketamine to explore the role of active metabolites, by selecting doses that produced very different ketamine levels but similar metabolite exposures which allowed for a direct comparison of their effects. In another trial, ketamine infusions were designed to maintain steady and clinically relevant concentrations long enough to study exploratory physiological and biomarker responses beyond the immediate subjective experience. Similarly, simulations for DMT helped identify safe and informative dosing ranges, enabling researchers to investigate both its pharmacology and its characteristic subjective effects.

Furthermore, even before a new psychedelic compound is tested in humans, simulation-based predictions can offer crucial guidance. By combining preclinical data and existing literature on related molecules, CHDR has used literature models to forecast potential drug exposures and safety outcomes in different scenarios for psychedelic analogues, helping to fine-tune dosing strategies for first-in-human studies.

The growing use of model-informed drug development marks a new era in clinical research. Sophisticated PKPD modeling and in silico simulations allow us to anticipate outcomes, reduce uncertainty, and design smarter, leaner, and safer studies. Whether applied to psychedelics or any other class of compounds, this approach helps researchers identify effective doses and improve clinical trial efficiency.