Non Clinical To Clinical Translation Challenges in Antiepileptic Drug Development

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Introduction

Epilepsy affects millions worldwide, yet nearly one-third of patients continue to experience uncontrolled seizures despite the availability of numerous antiseizure medications (ASMs). While ASMs remain cornerstone of treatment, their limited effectiveness in drug-resistant epilepsy highlights the urgent need for better therapies.[1,2,3] However, many promising candidates fail to progress from nonclinical studies to clinical trials because findings from animal models often do not translate to real-world disease. Recognizing these translational barriers is essential for developing more effective ASMs and improving outcomes for people living with refractory epilepsy.

Challenges in Translating AED Discovery

Limitations of Preclinical Efficacy Models

Traditional seizure models have been instrumental in identifying many antiseizure medicines, but they have contributed little progress toward treatments for drug-resistant epilepsy. These models mainly rely on acutely induced, convulsive seizures and use older drugs for validation, which biases discovery toward known mechanisms. Because they do not capture the spontaneous, diverse, and chronic seizure patterns seen in humans, they often fail to represent the underlying biology of epilepsy. [2,4] This gap contributes to the frequent mismatch between preclinical efficacy and the lack of clinical success in drug-resistant epilepsy.

Pharmacokinetic and Pharmacodynamic Differences

Acute seizure models provide only basic efficacy signals and often miss compounds that could be clinically useful, particularly for spontaneous or drug-resistant seizures. *In vitro* preparations assess only parts of the epileptic network and can alter blood–brain barrier (BBB) function, reducing their predictive value. Differences in drug pharmacokinetics (PK) and pharmacodynamics (PD) across species, along with highly standardized laboratory conditions, further limit translation.[1,2,5] As a result, compounds that appear effective in controlled experiments may fail to reach therapeutic levels or show efficacy in humans.

Safety and Tolerability Prediction Issues

Preclinical safety findings often fail to translate to humans. Some risks, such as valproic acid–related teratogenicity or vigabatrin-induced retinal toxicity, are well established, while other toxicities seen in animals do not occur in humans, underscoring model limitations. Long-term use may also lead to tolerance and reduced ASM effectiveness, and overall tolerability issues can affect adherence and treatment success.[1,6]

Future Directions for Better Translation

To bridge the translational gap in AED development, more predictive models and methods are needed. Incorporating chronic and genetic epilepsy models that better mimic human seizure patterns, cross-species PK/PD assessment, human-relevant *in vitro* systems, and biomarker-guided approaches can improve the prediction of both efficacy and safety. Together, these strategies provide a practical framework for developing more effective and safer therapies for patients with epilepsy.

Conclusion

Translating novel antiseizure therapies from nonclinical studies to effective clinical treatments remains a major challenge, especially for drug-resistant epilepsy. Existing models often fail to reflect the complexity of human disease, limiting their ability to predict true clinical efficacy and safety. Advancing AED development will require more human-relevant models, integrated PK/PD strategies, and mechanistic tools that better mirror real-world biology. Strengthening these translational approaches will help accelerate the discovery of safer, more effective therapies and ultimately improve care for individuals living with epilepsy.

Literature References

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