Establishing the Predictive Validity of Preclinical Seizure Models in Generalized Epilepsies: An Extension of the Praxis Analysis of Concordance Framework

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Background

- Approximately 3.5 million people in the United States are diagnosed with epilepsy, almost a third of whom are refractory to conventional antiseizure medications (ASMs).
- Central to the development of novel treatments is testing of anticonvulsant activity in preclinical seizure models. While various models exist, the predictive validity of each across the spectrum of epilepsy indications is less clear.
- The Praxis Analysis of Concordance (PAC) framework was recently developed to assess the translational concordance of common preclinical seizure models, demonstrating three acute seizure models with highest predictive validity for focal onset seizures: audiogenic, maximal electroshock (MES) and 6-Hz (32mA).

➢ *Here, we sought to establish concordance between commonly used preclinical models and generalized epilepsies, thus extending our work to capture the spectrum of human epilepsies.*

Methods

Praxis Analysis of Concordance (PAC) framework

- The PAC framework was implemented to assess the translational concordance between *preclinical* and *clinical ASM response* across the clinical epilepsy spectrum for 32 FDA-approved ASMs that are available in the United States.
- *Preclinical ASM responses* in seizure models that have been used historically and that have been established by the Epilepsy Therapy Screening Program (ETSP) were collected from searches performed in PubMed and the ETSP PANAChE database.
- *Clinical ASM responses* were collected based on searches performed in PubMed, American Epilepsy Society, Epilepsy Foundation and National Institute for Health Care and Excellence websites.

Preclinical and Clinical ASM Response

- Protective indices (PI) based on reported TD_{50} and ED_{50} values were calculated for each ASM in each preclinical model. A weighted scale representing relative preclinical anticonvulsant effect was then used to grade the *preclinical ASM responses* for each seizure model, ranging from potent anticonvulsant (PI > 10) to proconvulsant.
- Published reports of ASM perceived efficacy and use in patients with focal and generalized epilepsies were similarly evaluated and a weighted scale representing relative clinical anticonvulsant potential was used to grade the *clinical ASM responses* for each indication, ranging from common monotherapy to contraindicated.

Translational Concordance Scoring

- In order to assess and compare the predictive validity of preclinical models, a unified scoring matrix was developed to assign a translational score that captured the spectrum of complete discordance (-1) to complete concordance (1) between *preclinical* and *clinical ASM responses* for each preclinical model and clinical indication combination.
- Scores were then summed and normalized to generate a *global translational concordance score.*

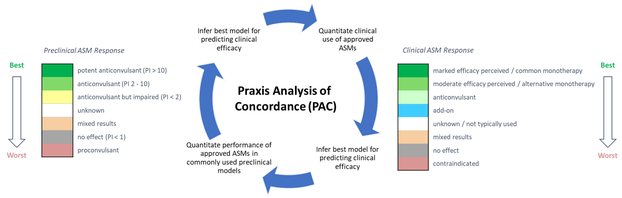
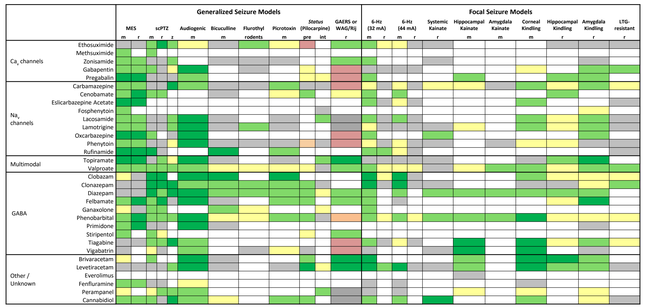


Figure 1. PAC Analysis Framework. An overview of the PAC analysis framework. Performance of approved ASMs in commonly used preclinical models was evaluated based on reported TD_{50} and ED_{50} values, with *preclinical ASM response* for each model graded according to a weighted scale. Clinical use of approved ASMs was similarly evaluated based on established reports, with *clinical ASM response* for each indication graded according to a weighted scale.

Assessing Translational Concordance Between Preclinical and Clinical Responses to Define the Predictive Validity of Common Preclinical Models

Preclinical ASM Response

- Sodium channel blockers tend to perform best in maximal electroshock seizure (MES), have mixed effects in subcutaneous pentylenetetrazole (scPTZ) and are less efficacious (or efficacious at impairing doses) in 6-Hz.
- GABAergics and modulators of SV2A (synaptic vesicle protein 2A) tend to perform best in 6-Hz, with less efficacy in MES.
- Most ASMs show efficacy in the audiogenic seizure model, with a wide range of PI values.



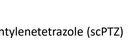


Figure 2. Preclinical ASM Response. The preclinical efficacy of 32 FDA-approved ASMs currently available in the US was examined in a total of 23 seizure models across multiple species. Preclinical seizure models were grouped according to the type of seizure induced in the model (generalized or focal). ASMs were grouped according to class/target, and captured calcium and sodium channel blockers, multimodal agents, GABAergic agents as well as agents with other mechanisms of action (including mTOR inhibitors, modulators of SV2A, selective serotonin reuptake inhibitors, and AMPA inhibitors). Colors denote grading of *preclinical ASM response* based on reported TD_{50} and ED_{50} values for each model, resulting in a weighted scale capturing relative preclinical anticonvulsant potential. rm=mouse; r=rat; pre=before pilocarpine-induced *status epilepticus* (preventative); post=after pilocarpine-induced *status epilepticus* (interventional).

Clinical ASM Response

- Use patterns tend to vary by indication across the generalized epilepsies (**Fig. 3**).

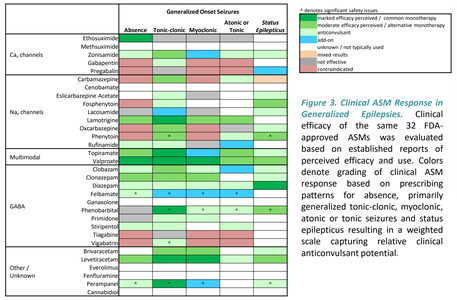


Figure 3. Clinical ASM Response in Generalized Epilepsies. Clinical efficacy of the same 32 FDA-approved ASMs was evaluated based on established reports of perceived efficacy and use. Colors denote grading of clinical ASM response based on prescribing patterns for absence, primarily generalized tonic-clonic, myoclonic, atonic or tonic seizures and status epilepticus resulting in a weighted scale capturing relative clinical anticonvulsant potential.

Calculation of Translational Concordance

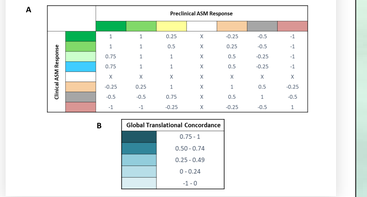


Figure 4. Translational Concordance Scoring. **A)** A unified scoring matrix was developed to assign translational concordance between *preclinical* and *clinical ASM response.* Values ranged from 1 for complete concordance to -1 for complete discordance. **B)** For each preclinical seizure model and clinical indication combination, individual ASM concordance scores were first calculated, then summed and normalized (total translational concordance score/ total number of ASMs with data available) to generate a global translational concordance score, weighted from highest (0.75 to 1) to lowest (-1 to 0) concordance.

PAC Framework Identifies Differential Translational Concordance Between Preclinical Models and Generalized Epilepsy Types

- Genetic rat models of absence seizures (GAERS and WAG/Rij) exhibited high concordance with absence and myoclonic seizure types.
- MES, audiogenic, and amygdala kindling models showed high concordance with primarily generalized tonic-clonic seizures, with findings based on robust data depth (assessed based on the number of ASMs tested in each model).
- Models with the highest concordance for atonic or tonic seizures were hippocampal kindling and amygdala kainate, but data depth is limited.
- MES, audiogenic, mouse 6 Hz (32 and 44mA) and kindling models demonstrated high concordance with *status epilepticus*.

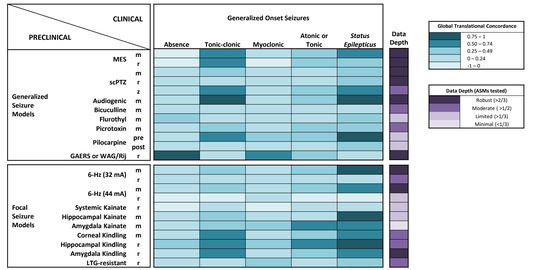


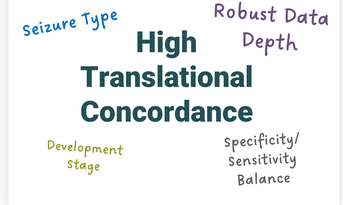
Figure 5. Translational Concordance for Generalized Epilepsies. Global translational concordance of each preclinical seizure model across generalized onset seizure types. Teal shading corresponds to weighted scale from highest (0.75 to 1) to lowest (-1 to 0) concordance scores. Data depth (purple shading) was similarly scored on a weighted scale from robust to minimal, based on the number of ASMs that have been tested in each model.

Conclusions

- **Using the newly developed PAC framework, findings from this study extend our insights into the predictive validity of commonly used seizure models across the spectrum of human epilepsies.**
- **Notably, we demonstrate differential translational concordance between preclinical seizure models and generalized epilepsy types, as well as variability in data depth across utilized models.**
- **We anticipate these findings to have important implications for supporting ongoing research efforts as well as promoting efficient resourcing for novel ASM development for generalized epilepsies.**

Drug Discovery for Generalized Epilepsies

Critical factors to consider when optimizing drug discovery workflows



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