A Novel Translational Concordance Framework Identifies Preclinical Seizure Models with Highest Predictive Validity in Focal Onset Seizures

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Background

- Epilepsy is a prevalent, complex disease characterized by unprovoked spontaneous seizures.
- In the United States, an estimated 3.5 million have an epilepsy diagnosis, approximately 60% of whom have focal onset seizures (FOS).
- Despite the availability of several antiseizure medications (ASMs), approximately 30-40% of patients are refractory to current treatments, thus highlighting an urgent need for novel treatment options.
- Central to the development of novel treatments is screening for anticonvulsant activity in preclinical seizure models.
- While various well-established acute and chronic seizure models exist, the applicability and predictive validity of each model for clinical efficacy in FOS is less clear.
- Optimized allocation of resources to streamline drug discovery in a high-throughput manner for early identification of useful and impactful therapies for focal epilepsy is a critical translational goal.

➢ **Here, we sought to establish the translational concordance between ASM response in commonly used preclinical seizure models and patients with FOS to define model(s) with the highest predictive validity, and thus broadest utility, for novel FOS early drug development efforts.**

Methods

Praxis Analysis of Concordance (PAC) framework

- The Praxis Analysis of Concordance (PAC) framework was implemented to assess the translational concordance between *preclinical ASM response* in commonly used seizure models and *clinical ASM response* in patients with FOS for 32 FDA-approved ASMs that are currently available in the United States.
- *Preclinical ASM responses* for 23 seizure models across multiple species were collected from searches performed in PubMed and the PANAChE database, an NIH National Institute of Neurological Diseases and Stroke (NINDS) resource established by the Epilepsy Therapy Screening Program (ETSP).
- *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 index (PI) values based on reported TD_{50} and ED_{50} values were calculated for each ASM in each preclinical model. A weighted scale representing relative 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 use in patients with FOS were similarly evaluated and a weighted scale representing prescribing patterns and perceived efficacy was used to grade the *clinical ASM responses* ranging from marked efficacy perceived / 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.
- Scores were then summed and normalized to generate a global translational concordance score.

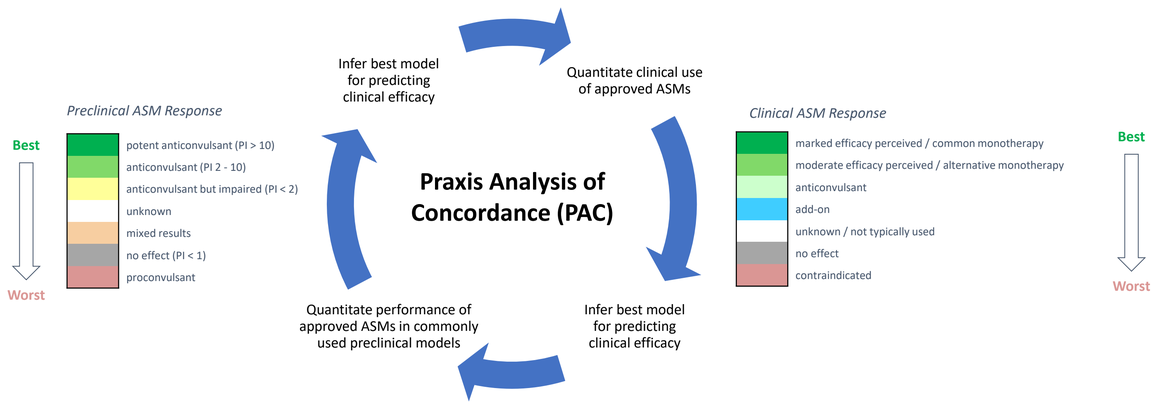


Figure 1. PAC Analysis Framework. An overview of the PAC analysis framework. Performance of approved ASMs in commonly used preclinical models was evaluated based on reported TD_{50} and ED_{50} values, with *preclinical ASM response* for each model graded according to a weighted scale. Clinical use of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

Clinical ASM Response

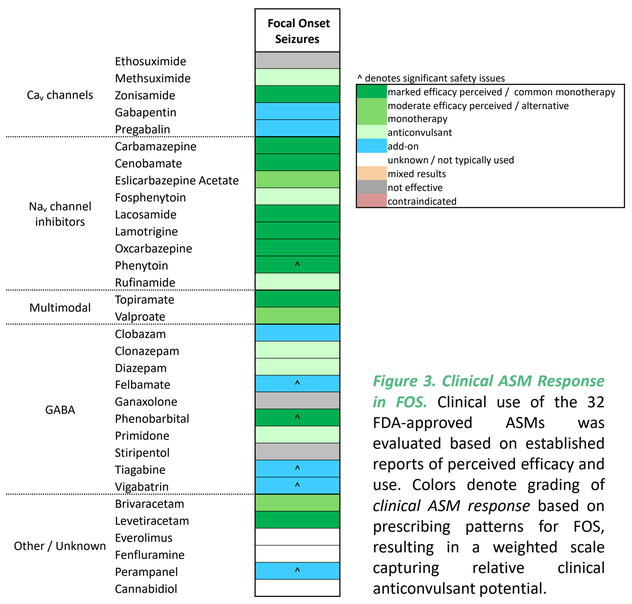


Figure 3. Clinical ASM Response in FOS. Clinical use of the 32 FDA-approved ASMs was evaluated based on established reports of perceived efficacy and use. Colors denote grading of *clinical ASM response* based on prescribing patterns for FOS, resulting in a weighted scale capturing relative clinical anticonvulsant potential.

PAC scoring matrix

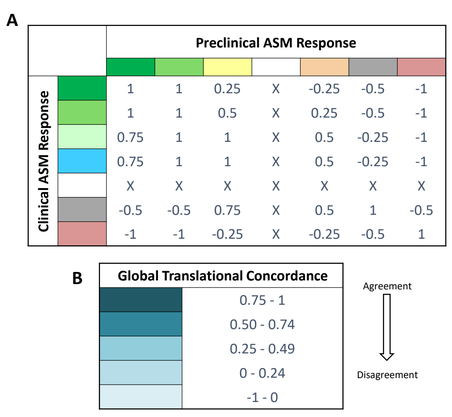


Figure 4. Translational Concordance Scoring.
A) A unified scoring matrix was developed to assign translational concordance between *preclinical* and *clinical ASM response*. Values ranged from 1 for complete concordance to -1 for complete discordance. **B)** For each preclinical seizure model, individual 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.

Preclinical ASM Response

- Most ASMs show efficacy in the audiogenic seizure model, with a wide range of PI values.
- Sodium channel blockers tend to perform best in maximal electroshock seizure (MES) 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.

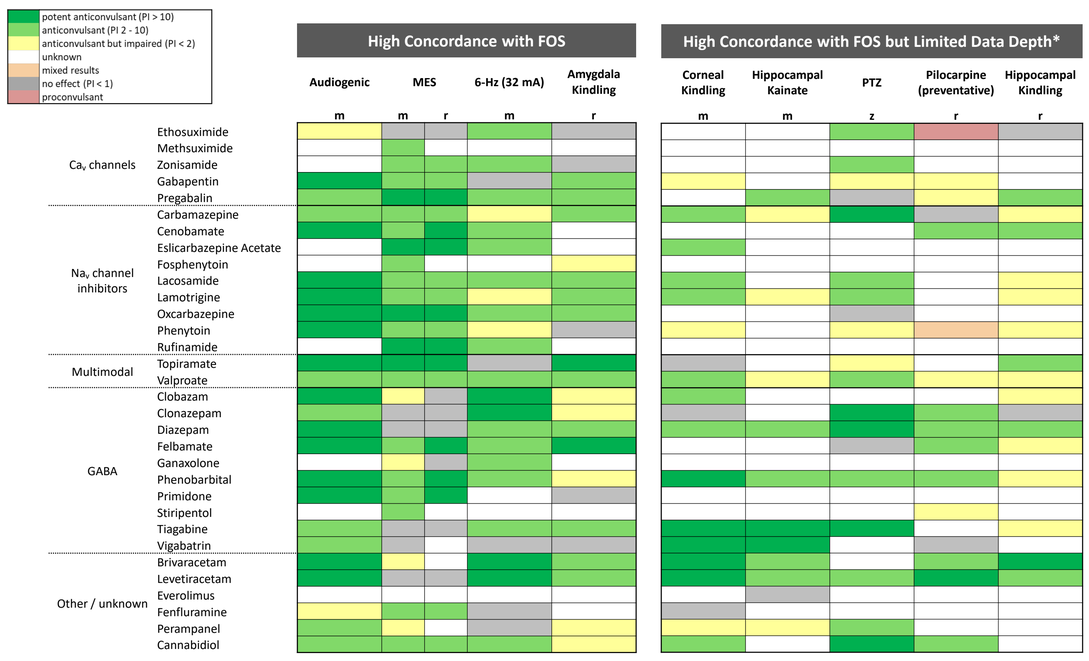


Figure 2. Preclinical ASM Response. Colors denote grading of *preclinical ASM response* based on reported TD_{50} and ED_{50} values for each model to calculate a PI value, resulting in a weighted scale capturing relative preclinical anticonvulsant potential. Preclinical seizure models were grouped according to class/mechanism of action: 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) and those exhibiting high concordance with FOS, or high concordance with FOS but with limited data depth. m, mouse; r, rat; z, zebrafish; MES, maximal electroshock seizure, PTZ, pentylenetetrazole.
*Limited data depth defined as models where less than 2/3 of ASMs have been tested. Models with low concordance not presented.

Mouse MES, Audiogenic and 6-Hz 32 mA Models Offer Greatest Versatility for FOS Drug Discovery

- Preclinical models that had the highest concordance were audiogenic, MES (mouse and rat), zebrafish PTZ, preventative pilocarpine, mouse 6 Hz (32 mA), hippocampal kainate, 60 Hz corneal kindling and hippocampal and amygdala kindling.
- Excluding models where <2/3 of ASMs have been tested (ie with limited data-depth), the list condenses to four main models: audiogenic, MES, mouse 6 Hz (32 mA) and amygdala kindling.

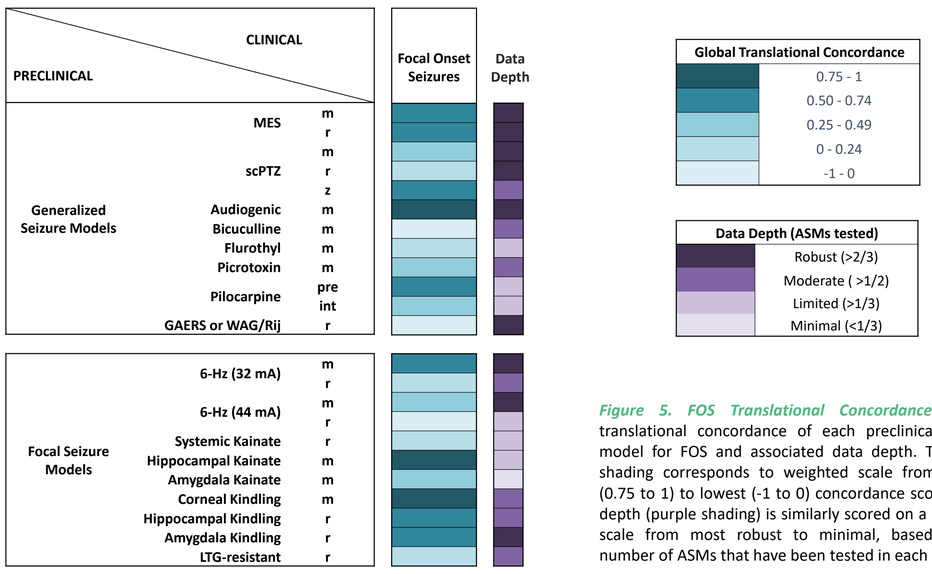
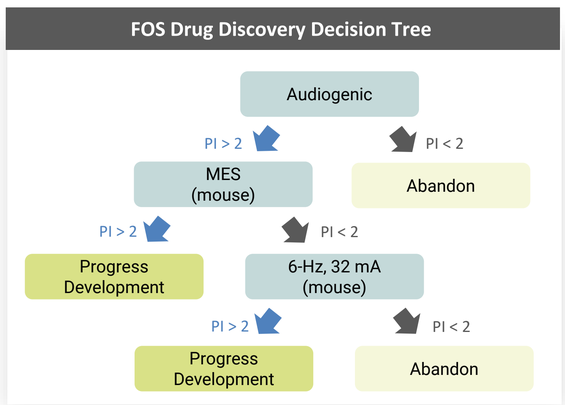


Figure 5. FOS Translational Concordance. Global translational concordance of each preclinical seizure model for FOS and associated data depth. Teal color shading corresponds to weighted scale from highest (0.75 to 1) to lowest (-1 to 0) concordance scores. Data depth (purple shading) is similarly scored on a weighted scale from most robust to minimal, based on the number of ASMs that have been tested in each model.

The PAC Framework identifies mouse MES, audiogenic and 6-Hz 32 mA as models with greatest predictive validity and versatility for FOS drug discovery

Conclusions

- **Using a newly developed scoring matrix to assess translational concordance and predictability, this study provides novel insights into the clinical validity of commonly used preclinical seizure models for FOS.**
- **Notably, we highlight mouse MES, mouse audiogenic and mouse 6-Hz (32mA) as three acute seizure models demonstrating high predictive validity for FOS.**
- **Based on these findings, we provide a pragmatic approach with decision tree (*right*) to support efficient use of resources and in consideration of the 3Rs of animal ethics for novel ASM development for FOS.**



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