



PAC-DEE: An Extension of the Praxis Analysis of Concordance Framework for Establishing the Predictive Validity of Preclinical Seizure Models across Broad Developmental and Epileptic Encephalopathies

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BACKGROUND

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood, often characterized by severe, frequent seizures, behavioral comorbidities and increased early mortality.
- Treatment options are sub-optimal, often associated with safety and tolerability issues, with many patients refractory to current standard of care.
- Central to the development of novel treatments is testing of antiseizure activity in preclinical seizure models. While various models exist, the predictive validity of each across the spectrum of epilepsy indications, including broad DEEs, is less clear.
- The Praxis Analysis of Concordance (PAC) framework was recently developed to assess the translational concordance of common preclinical seizure models for focal onset seizures (FOS) and generalized epilepsies.

➤ Here, we sought to establish concordance between traditional preclinical seizure models, genetic epilepsy models and broad DEEs, thus extending our work to capture pediatric DEEs and neurogenetic syndromes.

CONCLUSIONS

- Extending the PAC framework to DEEs demonstrates that disease-relevant models generally outperform traditional seizure models in translational concordance across DEEs and neurogenetic syndromes.
- Together with previous findings in FOS and generalized epilepsy, the PAC-DEE analysis provides a consolidated framework for indication-aligned model selection, supporting more strategic and efficient ASM drug discovery across the full spectrum of human epilepsies.

PAC-DEE DEMONSTRATES LIMITED TRANSLATIONAL CONCORDANCE BETWEEN PRECLINICAL SEIZURE MODELS AND BROAD DEEs

Preclinical ASM Response – Traditional Seizure Models

- We previously reported the predictive performance of 32 FDA-approved ASMs across traditional seizure models.
- Sodium channel blockers (SCBs) tend to perform best in maximal electroshock seizure (MES), have mixed effects in subcutaneous pentylenetetrazole (scPTZ) and are less efficacious (or efficacious only at impairing doses) in 6-Hz.
- GABAergic and SV2A (synaptic vesicle protein 2A) modulators tend to perform best in 6-Hz, and less so in MES.
- Most ASMs show efficacy in the audiogenic seizure model, with a wide range of PI values.

Clinical ASM Response Patterns Across DEE Indications

- Use patterns tend to vary substantially across DEE indications, differing by mechanistic class and reflecting distinct pharmacological profiles across syndromes.

		Developmental Epileptic Encephalopathies									
		Dravet Syndrome	Lennox-Gastaut Syndrome	Tuberous Sclerosis Complex	EO SCN2A GOF	SCN8A GOF	West Syndrome (EES)	Ohtahara Syndrome (EIDEE)	CDKL5 Deficiency Disorder	Doose Syndrome	Angelman Syndrome
Ca, Channels	Ethosuximide										
	Methsuximide										
	Zonisamide										
	Gabapentin										
	Pregabalin										
Na, Channels	Carbamazepine										
	Cenobamate										
	Escitalopram/Acetic Acid										
	Fosphenytoin										
	Lacosamide										
Multimodal	Lamotrigine										
	Phenytoin										
	Rufinamide										
	Topiramate										
	Valproate										
GABA	Clobazam										
	Clozapepam										
	Diazepam										
	Felbamate										
	Flurazepam										
Other / Unknown	Perampanel										
	Cannabidiol										

marked efficacy perceived / common monotherapy
moderate efficacy perceived / alternative monotherapy
anticonvulsant
add-on
unknown / not typically used
mixed results
no effect (PI < 1)
proconvulsant

Clinical ASM Response in Broad DEEs. Clinical efficacy 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 Dravet Syndrome, Lennox-Gastaut Syndrome, Tuberous Sclerosis Complex, EO SCN2A GOF, SCN8A GOF, West Syndrome, Ohtahara Syndrome, CDKL5 Deficiency Disorder, Doose Syndrome, and Angelman Syndrome, resulting in a weighted scale capturing relative clinical antiseizure effect. EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain-of-function; IESS=Infantile Epileptic Spasms Syndrome

Translational Concordance – Traditional Seizure Models and Broad DEEs

- Concordance between traditional seizure models and DEE and neurogenetic syndrome indications was modest, with no preclinical acute seizure model demonstrating high concordance across the full DEE spectrum.

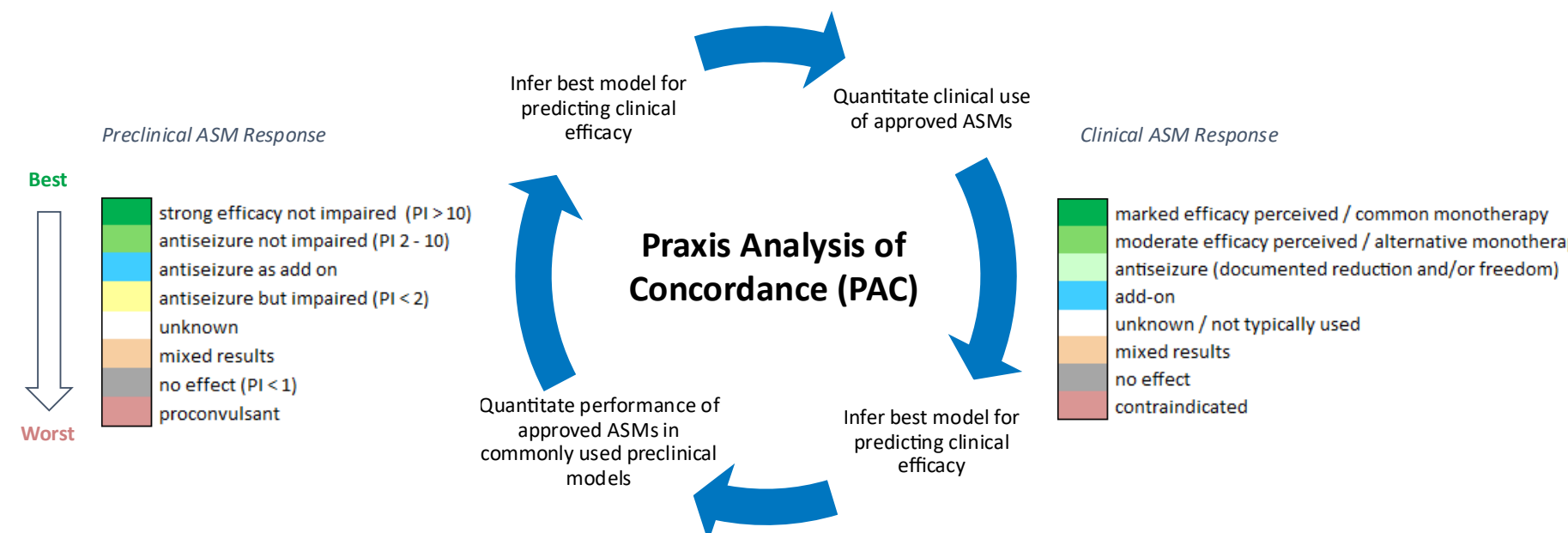
		Developmental Epileptic Encephalopathies									
		Dravet Syndrome	Lennox-Gastaut Syndrome	Tuberous Sclerosis Complex	EO SCN2A GOF	SCN8A GOF	West Syndrome (EES)	Ohtahara Syndrome (EIDEE)	CDKL5 Deficiency Disorder	Doose Syndrome	Angelman Syndrome
Generalized Seizure Models	MES m										
	scPTZ z										
	Audiogenic m										
	Bicuculline m										
	Picrotoxin m										
Focal Seizure Models	Status Epilepticus (Pilocarpine) m										
	GAERS or WADRs m										
	6-Hz (32 mA) m										
	6-Hz (44 mA) m										
	Systemic Ketate m										
Other / Unknown	Hippocampal Ketate m										
	Amygdala Ketate m										
	Conet Kindling m										
	Hippocampal Kindling m										
	LTE-restart m										

Translational Concordance between Traditional Seizure Models and Broad DEEs. Global translational concordance of each preclinical traditional seizure model across DEEs and neurogenetic syndromes. 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. EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain-of-function; IESS=Infantile Epileptic Spasms Syndrome; int=after pilocarpine-induced status epilepticus (interventive); LTG=lamotrigine; m=mouse; MES=maximal electroshock seizure; pre=before pilocarpine-induced status epilepticus (preventative); r=ratt; scPTZ=subcutaneous pentylenetetrazole; z=zebrafish

METHODS – DEFINING THE PREDICTIVE VALIDITY OF TRADITIONAL SEIZURE AND GENETIC EPILEPSY MODELS

Praxis Analysis of Concordance

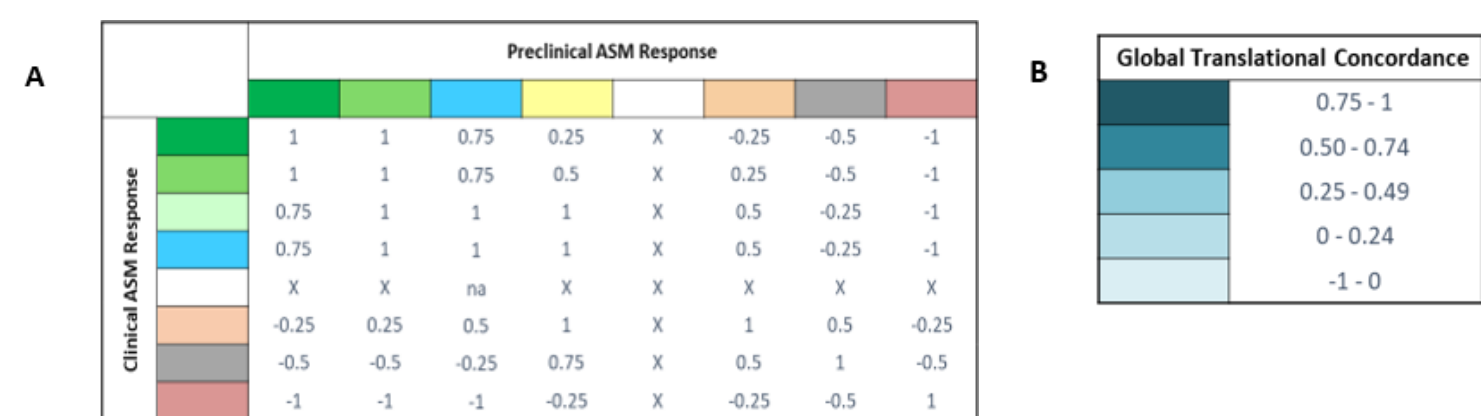
- The PAC framework was implemented to assess the translational concordance between *preclinical* and *clinical* ASM response across DEEs and neurogenetic syndromes for 32 FDA-approved ASMs available in the United States.
- Preclinical* ASM responses were collected from PubMed and the Epilepsy Therapy Screening Program (ETSP) PANACHE database for established acute seizure models, and from PubMed for disease-relevant epilepsy models while *clinical* ASM responses across DEE and neurogenetic syndrome indications were collected from PubMed, AES, Epilepsy Foundation, and NICE.



PAC Analysis Framework. An overview of the PAC analysis framework. Performance of approved ASMs in traditional seizure models as well as disease-relevant epilepsy models was evaluated based on reported TD₅₀ and ED₅₀ 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 across DEE and neurogenetic syndrome indications, with *clinical* ASM response for each indication graded according to a weighted scale.

Translational Concordance Scoring

- In order to assess and compare the predictive validity of traditional seizure and disease-relevant epilepsy 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 seizure/genetic epilepsy model and clinical indication combination. Scores were then summed and normalized to generate a *global translational concordance score*.



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-DEE HIGHLIGHTS GREATER TRANSLATIONAL CONCORDANCE BETWEEN PRECLINICAL DISEASE-RELEVANT EPILEPSY MODELS AND BROAD DEEs

Preclinical ASM Response – DEE and Neurogenetic Syndrome Models

- We further sought to evaluate the predictive performance of these 32 ASMs across models of genetic epilepsies relevant to broad DEEs and neurogenetic syndromes to examine whether these models improve translational concordance with clinical responses.
- Preclinical* ASM responses were therefore evaluated across 10 overarching disease-relevant models spanning multiple species and seizure paradigms.

		Developmental Epileptic Encephalopathy Models									
		Dravet Syndrome	Lennox-Gastaut Syndrome	Tuberous Sclerosis Complex	EO SCN2A GOF	SCN8A GOF	West Syndrome (IESS)	Ohtahara Syndrome (EIDEE)	CDKL5 Deficiency Disorder	Doose Syndrome	Angelman Syndrome
Ca, Channels	Ethosuximide										
	Methsuximide										
	Zonisamide										
	Gabapentin										
	Pregabalin										
Na, Channels	Carbamazepine										
	Cenobamate										
	Escitalopram/Acetic Acid										
	Fosphenytoin										
	Lacosamide										
Multimodal	Lamotrigine										
	Phenytoin										
	Rufinamide										
	Topiramate										
	Valproate										
GABA	Clobazam										
	Clozapepam										
	Diazepam										
	Felbamate										
	Ganaxalone										
Other / Unknown	Phenobarbital										
	Primidone										
	Stiripentol										
	Topiramate										
	Vigabatrin										
	Brivaracetam										
	Levetiracetam										
	Ethosuximide										
	Fenfluramine										
	Perampanel										
	Cannabidiol										

Preclinical ASM Response – Disease-Relevant Models. Preclinical efficacy of the 32 FDA-approved ASMs currently available in the US was examined in a total of 10 overarching models across multiple species. ASMs were grouped according to class/target, and captured calcium and SCBs, 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 TD₅₀ and ED₅₀ values for each model, resulting in a weighted scale capturing relative preclinical antiseizure effect. EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain-of-function; i=induced; IESS=Infantile Epileptic Spasms Syndrome; m=mouse; r=ratt; s=spontaneous; z=zebrafish

Translational Concordance – Disease-Relevant Epilepsy Models and Broad DEEs

- Disease-relevant preclinical epilepsy models demonstrated greater concordance than traditional seizure models for their corresponding DEE and neurogenetic syndrome indication, though data depth for most preclinical models was limited to minimal.

		Developmental Epileptic Encephalopathies									
		Dravet Syndrome	Lennox-Gastaut Syndrome	Tuberous Sclerosis Complex	EO SCN2A GOF	SCN8A GOF	West Syndrome (IESS)	Ohtahara Syndrome (EIDEE)	CDKL5 Deficiency Disorder	Doose Syndrome	Angelman Syndrome
Genetic Models	DS models spontaneous m										
	DS models induced z										
	LGS models m										
	TSC models m										
	Scn2a GOF models m										
	Scn8a GOF models m										
	Infantile spasms models (m)										
	OS models m										
	OS models z										
	CDD models m										
	Doose models m										
	AS models m										

Translational Concordance Between Disease-Relevant Epilepsy Models and Broad DEEs. Global translational concordance of each preclinical epilepsy model across DEEs and neurogenetic syndromes. 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. AS=Angelman Syndrome; CDD=CDKL5 Deficiency Disorder; DS=Dravet Syndrome; EIDEE=Early Infantile Developmental and Epileptic Encephalopathy; EO=early onset; GOF=gain-of-function; IESS=Infantile Epileptic Spasms Syndrome; LGS=Lennox-Gastaut Syndrome; LTG=lamotrigine; m=mouse; OS=Ohtahara Syndrome; r=ratt; TSC=tuberous sclerosis complex; z=zebrafish

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