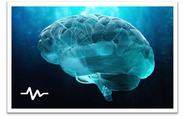
A Novel Method to Define an EEG Composite for the Detection of Drug Effects of Next Generation Small Molecules for Epilepsy

Amulya Garimella, Aadila Jasmin, Karl Hansen, Marcio Souza

Praxis Precision Medicines, Boston, MA 02110 USA

Background

- Almost a third of epilepsy patients are refractory to conventional anti-seizure medications, implicating an urgent need for novel agents.
- Alongside this is a need for sensitive and reliable biomarkers to facilitate and accelerate drug development.
- To date, detection of target engagement and therapeutic response to CNS drugs has been complicated by a lack of defined biomarkers, with quantitative EEG (qEEG) often attempted as a surrogate measure of target modulation and treatment-related brain activity.
- This approach is limited in sensitivity due to high inter-subject variability and a lack of power inherent to single parameter methods, with changes typically only detected at drug concentrations at, or very close to, toxic levels.
- Combining complementary information from complex EEG signals has the potential to better characterize target engagement and, potentially, treatment effects.
- ➢ *Here, we used machine learning methods to develop a composite qEEG biomarker to predict CNS presence and target engagement for novel agents.*



Methods

Quantitative EEG

- Standard resting-state EEG data were collected as part of Phase 1 studies of three next generation small molecules in development.
- Absolute band powers from the eyes-closed state (frequencies from 1-100 Hz) and utilizing two EEG electrode locations (frontal and central midline) were used for analysis.
- In addition to the five standard powers (delta, theta, beta, alpha, gamma), standard frequency band subsets were used for more granular information.
- Absolute power data were transformed according to a common average reference for denoising purposes.

Machine Learning: qEEG Composite Derivation

- Machine learning algorithms were trained to compute the optimal combination of EEG features for predicting treatment effect.
- A qEEG composite was constructed for each dataset using optimized coefficients generated from a logistic regression model trained to classify treated or placebo arms.
- Classification accuracy, precision, recall and F1 scores (balancing precision and recall) were calculated to evaluate performance of the qEEG composite within each dataset, along with areas under the receiver-operator characteristic (auROC) and precision-recall curves (auPRC).
- Data preprocessing and statistical analyses were conducted using Python (v3.10.6), the Scikit-Learn library (v1.1.1) and SAS (v9.4).

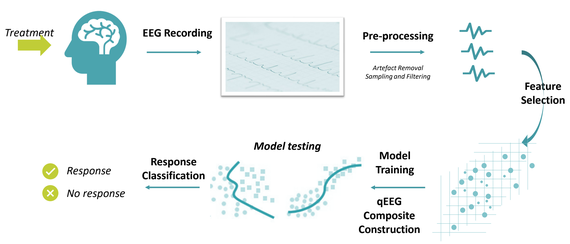


Figure 1. qEEG Composite Construction for Prediction of Treatment Response.

qEEG Composite Accurately and Sensitively Detects Early Pharmacodynamic Effects

- qEEG machine learning was able to predict and quantify the relative effect of drug in the brain for all tested small molecules.
- Across all datasets, qEEG analysis revealed pharmacodynamic (PD) effects that were significantly different from placebo at all treatment dose levels.
- Notably, constructed qEEG composites consistently discriminated treated vs placebo subjects with high accuracy and sensitivity (>84% accuracy; f1 score >0.9; auROC >0.93; auPRC >0.98), with distinction from placebo evident as early as treatment day 1.
- Observed PD effects were consistent with known PK profiles of tested molecules.

Composite accurately discriminates arms in PRAX-628 SAD study

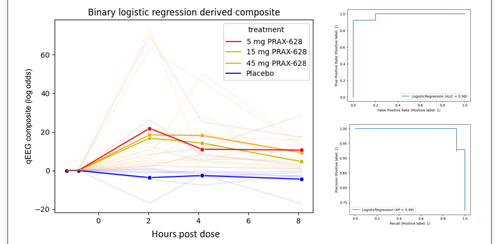


Figure 2. qEEG Composite Application to the PRAX-628 SAD Study. PRAX-628-101 was a randomized, double-blinded, placebo-controlled Phase 1 trial (n=40) investigating the effects of single (SAD, Part A) and multiple (MAD, Part B) ascending doses of PRAX-628 in healthy adults aged 18-55 years. In SAD cohorts, where participants received single oral doses (5–45 mg), qEEG analysis revealed PD effects that were significantly different from placebo at all tested dose levels, with the composite accurately and sensitively discriminating treated vs placebo subjects.

Composite accurately discriminates arms in PRAX-628 MAD study

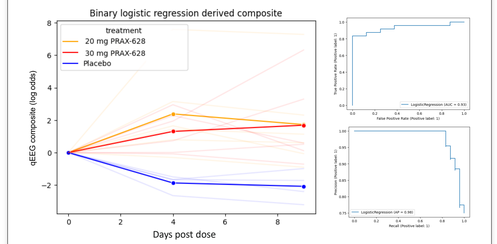


Figure 3. qEEG Composite Application to the PRAX-628 MAD Study. PRAX-628-101 was a randomized, double-blinded, placebo-controlled Phase 1 trial (n=40) investigating the effects of single (SAD, Part A) and multiple (MAD, Part B) ascending doses of PRAX-628 in healthy adults aged 18-55 years. In MAD cohorts, where participants received multiple doses (20 and 30 mg, for 10 days), qEEG analysis revealed PD effects that were significantly different from placebo at both tested doses, with the composite accurately and sensitively discriminating treated vs placebo subjects.

Composite accurately discriminates arms in PRAX-562-102 study (Part A)

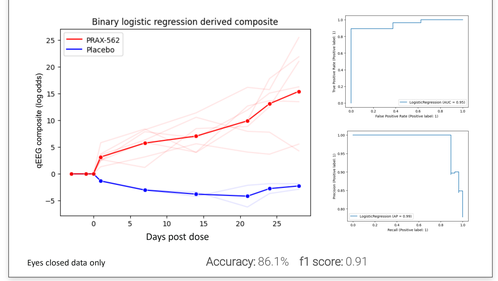


Figure 4. qEEG Composite Application to the PRAX-562-102 Study (Part A). PRAX-562-102 was a 2-part randomized, placebo-controlled Phase 1 trial in healthy participants aged 18-55 years. Part A (n=30) evaluated the effects of PRAX-562 (90 mg, 28 days QD) vs placebo. qEEG analysis revealed PD effects that were significantly different from placebo, with the composite accurately and sensitively discriminating treated vs placebo subjects.

Composite accurately discriminates arms in PRAX-562-102 study (Part B)

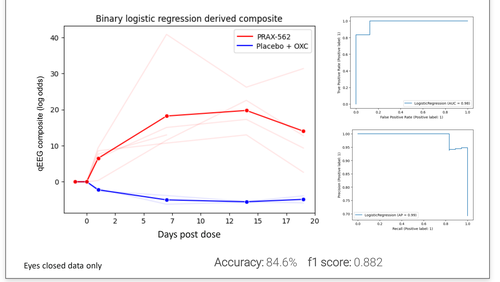


Figure 5. qEEG Composite Application to the PRAX-562-102 Study (Part B). PRAX-562-102 was a 2-part randomized, placebo-controlled Phase 1 trial in healthy participants aged 18-55 years. Part B (n=18) evaluated the effects of oxcarbazepine (OXC) in combination with PRAX-562 (120 mg, 28 days QD) vs. OXC alone. qEEG analysis revealed PD effects that were significantly different from placebo, with the composite accurately and sensitively discriminating treated vs placebo+OXC subjects.

qEEG Composite Consistently Separates Drug vs Placebo, Irrespective of Drug Class, at First Point Measured

Composite accurately discriminates arms in PRAX-944-105 study (Part B)

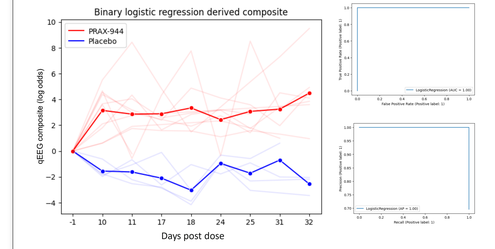


Figure 6. qEEG Composite Application to the PRAX-944-105 Study (Part B). PRAX-944-105 was a two-part, Phase 1 clinical trial of a fixed dose titration of ulixacaltamide conducted in healthy adults aged 18–55 years. Part B (n=14) assessed effects of a fixed oral dose titration regimen (from 60 to 120 mg, QAM, 31 days) Previous work demonstrated comparable PD effects across all PRAX-944 doses, thus dose levels were combined for qEEG composite analysis. PD effects were observed that were significantly different from placebo, with the composite accurately and sensitively discriminating treated vs placebo subjects.

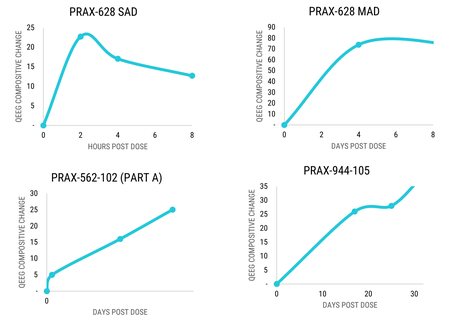


Figure 7. Placebo-adjusted qEEG Composite Summary of Findings. Applicability of qEEG composite to three distinct small molecules reveals clear PD effects irrespective of dose or drug class, and within hours/days of administration.

Conclusions

- **Application of machine learning methods to EEG data has the potential to accelerate drug development in epilepsy by definitively revealing PD effects of novel agents that are clearly distinguishable from placebo.**
- **We demonstrate applicability of a qEEG composite to three distinct next generation small molecules, with expected generalizability to any small molecule irrespective of class/target.**

References

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@PraxisMedicines
Praxismedicines.com
clinicaltrials@praxismedicines.com

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