Safety Pharmacology Society Webinar:
Seizure Liability Testing in Nonclinical Studies:
Management and Regulatory Considerations

Different Industry Needs for Seizure Liability Testing:
Different Approaches/Designs

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Different Applications for Seizure Liability/EEG Testing

- Screening for efficacy
  - Treatment of epilepsy
  - Treatment of sleep disorders (sleep onset, sleep duration, % REM)
- Qualification of normal EEG activity (absence of spiking for animals assigned to tox studies)
- Screening for compound specific safety
  - Verification of observational report of convulsion (concordance of convulsion and seizure)
  - Identification of NOAEL (identification of no-effect dose)
  - *Translational/Issue Resolution study*¹
Models For Testing

- **Efficacy Models** – Kindling, PTZ or other convulsion precipitated models (Racine scale, observation, actual EEG recording)
  
- **Screening Animals for Tox Studies, NOAEL Identification and Concordance Assessments** - Typically acute EEG recordings from animals in a sling or chair with surface or needle electrodes. No surgery required

- **Translational/Issue Resolution Studies** – Continuous EEG with observation and video/surgical implantation of electrodes for recording
Differences Between Acute and Chronic EEG Recordings

**Acute Recordings**
- No surgical implantation
- No mapping of sites
- Restrained animal
- Short duration recording
- Identification of seizure activity/spiking no pharmaco-EEG or staging qEEG
- More diagnostic rather than time expansive

**Chronic Recordings**
- Surgical implantation – surface or deep electrodes
- Can map sites
- No restraint
- 24/7 up to 3 months or more
- Identification of seizure activity/spiking, pharmaco-EEG, staging, and qEEG
- Focus on time expansive recordings
Acute One Day Designs - Questions Answered

- Does the compound block the cumulative effect of sub-threshold electrical stimulation (kindling)?
- Is the compound proconvulsive or anticonvulsant when testing in combination with a compound with known convulsant activity (PTZ, picrotoxin, kainic acid)?
- Does a compound alter EEG grossly at a specific time point?
- Relative potency of compounds
- May not be directly translatable to human situation
Rodent Capabilities

- Convulsive Liability (PTZ Infusion)
  - Infusion pumps deliver 10 mg/mL PTZ at a constant rate of 0.5 mL/minute until a clonic convulsion is noted in the animal or for a maximum of four minutes.
  - The following formula is used to convert infusion time to mg/kg dose of PTZ administered:

\[
\text{mg/kg PTZ} = \frac{(\text{Infusion time} \text{ (mL/min)}) \times (\text{mg PTZ/mL})}{(1000\text{g}) (60 \text{ seconds}) \times (\text{Animal weight in g})}
\]
Electrical Kindling – Rat

- Used to assess potential antiepileptic drugs
  - An electrode is surgically implanted in the basolateral amygdala and the rat is stimulated with a suprathreshold current until they are fully kindled.
  - A colony of fully kindled rats allows the screening of antiepileptic drugs for their ability to block seizure or alter ADT, seizure severity, and ADD.

![Graph showing percent seizures blocked by different treatments](image-url)

- Vehicle
- Diazepam 5mg/kg
- Diazepam 10mg/kg
- Diazepam 15mg/kg
- Valproic Acid 300mg/kg

Did not block

Percent Seizures Blocked

Treatment
Chronic Designs – Questions Answered

- What happens to EEG when the animal is not stressed by restraint?
- Is the compound effective at altering sleep patterns or REM (requires deep hippocampal electrode) percentage?
- Can non-seizure frequency changes in EEG (qEEG or pharmaco-EEG) be detected?
- What happens across time when EEG is monitored (day – night differences, 24/7 recording for up to 3 months)?
- What is the delayed onset seizure patterns coupled with CNS behavioral signs?
- How can EEG be effectively monitored in the clinic and are there dose escalation premonitory events that can be characterized for the clinic?
Telemetry Transmitters
Telemetric EEG and EMG Assessment

- Rat and Dog Animal Models
  Non-tethered telemetrized animals ensure high quality behavioral data

  - Continuous 24-hour data collection with concomitant video recording to corroborate EEG and EMG events indicative of seizure or convulsion across the animal’s circadian cycle

  - Qualitative and quantitative assessment, including spectral analysis if valuable

  - Preclinical EEG analysis provides a description of the progression to seizure across time with repetitive dosing of a compound that can be applied to clinical testing
Typical progression of EEG recordings:

- Series of isolated sharp waves
- EEG bursting (↑ frequency and amplitude)
- EEG bursting (↑ frequency, amplitude and duration)
- Seizure (markedly ↑ frequency, amplitude and duration)