Review Seizure/Convulsion
Review Abuse Liability

Mary Jeanne Kallman PhD, DSP
Director Global Nonclinical Neuroscience
Covance Laboratories
Facts About Seizure/Convulsion

- FDA considers convulsion an “Adverse Effect” - 10 X Margin
- Convulsion refers to the overt behavioral event while seizure refers to the electrical changes in brain (Behavioral false positives). EEG required to corroborate behavioral report
- EEG is a multi-unit recording
- EEG is the translatable clinical measure
- Usually an issue resolution endpoint
- Therapeutic compounds with seizure liability at clinical doses
- Need clinical testing plan – including subject exclusion, understanding therapeutic population, monitoring
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
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:

\[
\text{mg/kg PTZ} = \left(\frac{\text{Infusion time (mL/min)}}{60 \text{ seconds}}\right) \times \left(\frac{\text{mg PTZ/mL}}{1000g}\right)
\]

(60 seconds) (Animal weight in g)
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:

1. Series of isolated sharp waves
2. EEG bursting (↑ frequency and amplitude)
3. EEG bursting (↑ frequency, amplitude and duration)
4. Seizure (markedly ↑ frequency, amplitude and duration)
Review Abuse Liability
Controlled Substance Staff (CSS) at FDA

Dedicated group that serves as the CDER, FDA and DHHS focus for activities regarding drug scheduling, abuse and dependence

- Writes the 8-factor analyses (recommendation to DEA for new drugs)
- Serves as FDA and CDER liaison role to various components of government
- Provides consultation to other FDA centers regarding abuse liability assessment and drug scheduling matters
- Performs protocol reviews concerning pre-clinical and clinical protocols

• Dedicated group within FDA
  • Michael Klein PhD (Director)
  • Silvia Calderon PhD (Team Leader)
  • Lori Love MD PhD
  • Katherine Bonson PhD
  • James Hunter RPh, MPH
  • Morine Moody
  • Sandra Saltz
Neuroscience compounds or CNS active compounds in Phase 2

• Centrally acting
• Properties that are likely to lead to misuse
  • PK parameters (short duration of action)
  • Solubility
  • High threshold for adverse toxicity
• Continued, prolonged or excessive use leads to tolerance or dose escalation
• Capable of producing dependence

• FDA Draft Guidance for Assessment of Abuse Potential of Drugs (2010)

High Priority Indications
• Pain • Psychiatry • ADHD • Migraine • Cognitive Enhancer • Antiepileptic • Anxiolytics
• Dependence treatment • Hypnotic/Sedative • Obesity • Muscle Atrophy
Drug Classes Historically Associated with Abuse Liability and Currently Scheduled by DEA

- Opioids
- Sedative hypnotics
- Cocaine, amphetamine and other CNS stimulants
- Hallucinogens, phencyclidine and similar agents
- Cannabinoids (marijuana and related compounds)
- Nicotine-like drugs
- Chemical precursors of controlled substances
- Anabolic steroids
Drug Scheduling Process

1. Generation of preclinical and clinical data (industry)
2. Drafting of 8-Factor Analysis (industry) and finalization by FDA
3. FDA makes scientific assessment and recommends initial schedule to DEA
4. DEA schedules the new drug
Approach for Identification of CNS Activity

- **Binding Assays**
  - Neurotransmitters historically associated with abuse potential include dopamine, norepinephrine, serotonin, GABA, nicotinic acetylcholine, opioid, NMDA, and cannabinoid receptors
  - Novel mechanism -- Full binding profile would be expected

- **Routine Assays**
  - Locomotor activity, Irwin, seizure activity, microdialysis, electrophysiology, brain imaging

**Question** – Does the compound or a metabolite (10% plasma level of parent) reach the CNS?
Revised: Preclinical Flow Chart

1. Receptor Binding Panel
2. Is drug CNS active?
3. Physical Dependence
   - + signals
   - no signals
4. Drug Discrimination
5. Self-Administration
6. CPP
7. Mechanisms with established abuse potential
8. Mechanisms with no known evidence of abuse
9. Pharmacology / Safety Pharm Profile, including LMA
10. Hold
11. Discussion w/ FDA

Date: 8 November 2010
Basic biochemical and *in vitro* and *in vivo* pharmacological characterisation

Signals suggesting dependence potential present?

Insufficient information to define dependence potential?

Behavioural assessment of dependence (reinforcing properties, withdrawal syndrome)

Drug Discrimination Studies

Novel Mechanism of action?

No further non-clinical testing needed

Yes

No

No

No

Yes
Designs are tailored to the specific activity of the compound of interest. Typically these studies would be conducted in rodents as follows. PK determinations for the test compound can be verified

**Drug Dependence Study**

Repeated dosing for 2-4 weeks and evaluate signs of withdrawal from drug – including clinical signs, body weights, food intake, and other relevant assessments possible.

**Drug Discrimination Study**

Train rats to discriminate training compound from vehicle in two-lever drug discrimination FR-10 paradigm. Conduct generalization dose response for training drug and new novel compound of interest.

**Self Administration Study**

Rats are trained to self-administer a prototypical compound (i.e., cocaine or other compound) intravenously and then tested to determine if the new novel compound of interest will substitute in self-administration.
**Drug Dependence**

- Dependence phase (typically 2 weeks): test article administration daily
- Withdrawal phase (typically 1 week): no test article administration
- Optional Assessments
  - Filmed or Live Clinical Observations
  - Body Weights
  - Food Consumption
  - Body Temperature
  - Locomotor Activity

**Clinical Observations on Ethanol Withdrawal in Male F-344 Rats Given BioServ® Control or Ethanol Liquid Diet for 14 Days**

<table>
<thead>
<tr>
<th>Observation</th>
<th>Study Day/Time Point</th>
<th>Ethanol Liquid Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 14</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>Prior to withdrawal</td>
<td>control (R01174)</td>
</tr>
<tr>
<td></td>
<td>Approx. 2 hr</td>
<td>1.75% EtOH (R01174)</td>
</tr>
<tr>
<td></td>
<td>withdrawal</td>
<td>3.5% EtOH (R01174)</td>
</tr>
<tr>
<td></td>
<td>Day 14</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>Approx. 4 hr</td>
<td>7% EtOH (R01234)</td>
</tr>
<tr>
<td></td>
<td>withdrawal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Day 14</td>
<td>5.0%</td>
</tr>
<tr>
<td></td>
<td>Approx. 8 hr</td>
<td>7% EtOH (R01234)</td>
</tr>
<tr>
<td></td>
<td>withdrawal</td>
<td></td>
</tr>
</tbody>
</table>

**Rodent Ethanol Dependence Mean Body Weights**

- Dependence phase (typically 2 weeks): test article administration daily
- Withdrawal phase (typically 1 week): no test article administration
- Optional Assessments
  - Filmed or Live Clinical Observations
  - Body Weights
  - Food Consumption
  - Body Temperature
  - Locomotor Activity
Drug Discrimination

• Rats are trained to discriminate between a known reinforcing compound (CNS reference compound) and vehicle by pressing the lever associated with each condition to receive a food reward
  • Test articles are substituted for the CNS reference compound
  • Test articles that elicit a response similar the CNS reference compound may have abuse liability
Self Administration

- Rats are trained to self administer a known reinforcing compound (CNS reference compound)
- Test articles are substituted for the CNS reference compound and number of injections and rates of responding are compared to reference compounds

Figure courtesy of Tom Hudzik
Important Design Parameters for Abuse Liability Studies

- Species Selection – Rat is default
- Route of Administration – Dependence Oral, Drug Discrimination IP, Self-Administration – IV
- If IV administration not possible then consider other route or Conditioned Place Conditioning
- Dose – highest dose must produce comparable blood level to human tmax blood level at the highest therapeutic dose
- Comparator Compounds – Positive Controls, Negative Controls not required
Information in 8-Factor Analysis

1. Drug’s actual or relative potential for abuse
2. *Scientific evidence of the drug’s pharmacological effects
3. *The state of current scientific knowledge regarding the substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. *The drug’s psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

*Sections requiring details of preclinical data for final scheduling decision by Drug Enforcement Agency (DEA)