Application of Abuse Liability Endpoints to Toxicology Studies: Considerations

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*AbbVie provided no support outside of Thomas Hudzik being an employee of AbbVie. The presentation contains no proprietary AbbVie data.*
Overview

Abuse Liability Assessment Overview

Physical Dependence

Practical Considerations for Behavioral Studies

Application to GLP Toxicology Studies
  • Use of FOB for Physical Dependence
  • Use of Locomotor Activity
Criteria for Preclinical ALA assessment (Tier 1)

CNS Penetration (whether CNS drug or not)

- Direct measurement of CNS concentration
- Observation of behavioral effects (stim, depression, performance changes)
- Effects on CNS circuitry
  - EEG
  - Cerebral Microdialysis

Novel Modes of Action

- FDA are more conservative in approaching
  - Need to prove that unlike standard drugs of abuse

Active Metabolite > 10% of parent: all considerations apply

Biologics are not excluded from consideration at this time
Measurable Aspects of Abuse Liability – Tier 2

- Self-administration
- Reinforcing effects
- Drug discrimination
- Discriminative effects
- Physical dependence
- Discontinuation syndrome
Mechanisms of Tolerance & Withdrawal

Repeated CNS-active drug administration can produce neuroadaptive changes in the brain

These changes are often opposite to the intoxicating effects

- Example: drug produces hyperthermia; adaptive effect = hypothermia

- Can off-set the “high” to maintain homeostasis

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## Pharmacology vs Withdrawal

<table>
<thead>
<tr>
<th>Opioid Pharmacology</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased GI Mobility</td>
<td>Cramping, GI distress, diarrhea</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Hyperalgesia</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Dysphoria</td>
</tr>
<tr>
<td>Sedative Pharmacology</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Sleep Induction</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Anticonvulsant effects</td>
<td>Convulsion</td>
</tr>
<tr>
<td>Anxiolysis</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Stimulant Pharmacology</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Euphoria</td>
<td>Depression, dysphoria</td>
</tr>
<tr>
<td>Appetite suppression</td>
<td>Hyperphagia</td>
</tr>
<tr>
<td>Motor stimulation</td>
<td>Motor suppression</td>
</tr>
</tbody>
</table>
## Acute Withdrawal Timeframes

<table>
<thead>
<tr>
<th>Substance</th>
<th>Withdrawal Time Human</th>
<th>Withdrawal Time Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>5-7 days</td>
<td>1-2 days</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1-4 weeks</td>
<td>&gt; 3 days</td>
</tr>
<tr>
<td>Cannabis</td>
<td>5 days</td>
<td>≥ 96 h</td>
</tr>
<tr>
<td>Nicotine</td>
<td>2-4 weeks</td>
<td>4-14 days</td>
</tr>
<tr>
<td>Opiates</td>
<td>4-10 days</td>
<td>72 h</td>
</tr>
<tr>
<td>Stimulants</td>
<td>1-2 weeks</td>
<td>10 days (cocaine)</td>
</tr>
</tbody>
</table>

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### Typical Physical Dependence Study Design

**Pre-dose baseline**

- **Bwt**: 1-2 days prior
- **Clin Obs**: X
- **FOB**: X
- **LMA**: X

**Dosing Phase**

- **Bwt**: Daily
- **Clin Obs**: Daily
- **FOB**: X
- **LMA**: X

- **(day 1, 2...final)**

**Withdrawal**

- **Bwt**: Daily
- **Clin Obs**: Daily
- **FOB**: X
- **LMA**: X

- **(day 1, 2...final)**

**Endpoints**

- FOB (Continuous Endpoints)
- Thermal Response
- Measured Forearm Grip Strength
- Measured Hindlimb Grip Strength
- Body Weight
- Body Temperature
- Respiration
- Urination
- Measured Hindlimb Splay
- FOB (Incident Endpoints)
- Presence
- Rate of Removal
-食品 Intake
- Locomotion
- Polyphasic Cycles
- Piloerection
- Emptiness
- Salivary
- Clinical Movements
- Ventilatory
- Gait
- Mobility
- Acidosis
- Vocalization
- Respiratory
- Sneeze
- Bladder Behavior
- Approach Response
- Touch Response
- Click Response
- Tail Pinch Response
- Paw Response
- Fighting Reflex
General Considerations for Behavioral Studies

Circadian Influence

Experimenter / Handler Experience / Consistency

Physical Conditions

(noise, temp, lighting)

Feed used

Locomotor Activity as an Adjunct Endpoint

All of the above applies, and changes in activity can be a product of many different factors or combinations of factors.
Fundamental issue with the standard studies: Drug Classes associated with dependence vs Endpoints*

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>FOB</th>
<th>Startle</th>
<th>LMA</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu Agonist Opioids</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>Decr. Operant</td>
</tr>
<tr>
<td></td>
<td>GI, LM,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor Stimulants</td>
<td>(-)</td>
<td>+/-</td>
<td>+/-</td>
<td>ICSS, operant</td>
</tr>
<tr>
<td>CNS Depressants</td>
<td>(+)</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>(-)</td>
<td>+</td>
<td>(-)</td>
<td>Anxiogenic</td>
</tr>
<tr>
<td>Caffeine</td>
<td>(-)</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>(-)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nicotine</td>
<td>GI</td>
<td>+</td>
<td>+/-</td>
<td></td>
</tr>
</tbody>
</table>

+ An effect in withdrawal noted (+), not noted (-), +/- mixed
Variables to Consider

Species (rat generally sufficient)
• But should account for affinity differences from human

Precipitated vs spontaneous withdrawal

Duration of drug treatment
• Justify based on available literature. Min 21 days

Dose Frequency
• Justify based on half-life.

Route of Administration
• Match the clinical in most cases

Appropriate dose of drug (1, 3 and higher (e.g., 10) X max therapeutic/tolerated in human)

Reference drugs
• Eg., Opioids for other analgesics, stimulants for other ADHD drugs, etc.

Duration of post-WD Observations: 7 d typical, but if very long t1/2 drug, may consider longer
• Multiple assessments on each of first few days
• Telemetry may be best for physiological measures

PK of drug: capture when fully eliminated (≈ 5 t_{1/2s})

Both within and between group comparisons
Sample Design

Veh Tox → Clin Obs, etc → Histopath

Tox 10X
Tox 30X
Tox 100 X
## Sample Design

### Veh Tox

<table>
<thead>
<tr>
<th>Event</th>
<th>Veh Tox</th>
<th>Tox 10X</th>
<th>Tox 30X</th>
<th>Tox 100X</th>
</tr>
</thead>
</table>

### Pre-dose baseline

<table>
<thead>
<tr>
<th>Event</th>
<th>Bwt</th>
<th>Clin Obs</th>
<th>FOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 days prior</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Bwt</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Clin Obs</td>
<td></td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>FOB</td>
<td></td>
<td></td>
<td>{Early, Mid}</td>
</tr>
</tbody>
</table>

### Dosing Phase

<table>
<thead>
<tr>
<th>Event</th>
<th>Recovery Veh Tox</th>
<th>Recovery Tox 3X</th>
<th>Recovery Tox 10X</th>
</tr>
</thead>
</table>

### Histogram

<table>
<thead>
<tr>
<th>Event</th>
<th>Recovery Veh Tox</th>
<th>Recovery Tox 3X</th>
<th>Recovery Tox 10X</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Daily</th>
<th>Daily</th>
<th>Daily</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>X</th>
<th>X</th>
<th>X</th>
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<table>
<thead>
<tr>
<th>Event</th>
<th>(day 1, 2...final)</th>
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<tr>
<td>Event</td>
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<td>Event</td>
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Summary

Of the 3 types of abuse liability related studies, only physical dependence appears to be measurable in the context of a withdrawal study.

- Extended operant training / repeated administration of other drugs, surgery for iv catheter make the other 2 types of studies untenable.
  - Conditioned place preference possible, but requires larger N than used in a tox study, and often looked at as inferior to self-administration

When could one consider applying physical dependence endpoints to tox studies?

- Low risk compounds (cns penetration, but little in the way of behavioral activity).
- High risk compounds (engages 5-HT, GABA, ion channels, DA, glutamate, lots of behavioral effects, etc) should have a dedicated study.

Doses often are different than tox doses (additional groups)

Well-trained individuals are required