Further Musing on Best Practice for Nonclinical Assessment of Physical Dependence and Withdrawal

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Background

- The physiological underpinnings of development of dependence and discontinuation syndrome has been well-understood for decades
  - Opponent Process (F1 = -F2)
    - Some challenges in CNS space
- Detection window is clear (PK-based)
- Yet, as an industry, we can do a better job of detecting PD preclinically, despite access to numerous tools to do so

Example CNS drug classes initially not predicted to cause a discontinuation syndrome

Drug Class	Clinical Signs in Discontinuation
Stimulant medications	Mood changes, cognitive disruption
CNS Depressants	Anxiety, sleep disturbance
Antidepressants	Sensory disturbances, anxiety, sleep disturbance, rebound depression
Antipsychotics	Super-sensitivity psychosis
Beta Blockers	Tremor, tachycardia, mood changes

Why has this been so difficult?

- Overly *conservative* toxicologists, safety pharmacologists and clinical development scientists
  - "We've always done it this way and FDA have been happy with it. Why rock the boat!?
  - "What if we see something we don't like or understand?
  - "What if FDA hate what they see?

If your development team looks like these guys….

- Consider that doing the work can help guide what to monitor clinically
- Consider that NOT doing the work can result in surprises, problems and delays down the line

Considerations for increasing sensitivity

1) Narrow Focus

- Specifically look within the physiology of the target
  - Look for evidence of physiology moving in direction opposite to the pharmacology upon withdrawal

2) Broad Focus

- Consider endpoints that reflect commonly reported AEs

3) Continuous Focus

- Apply telemetry to support the monitoring of physiology and behavior
- Addresses the 'snapshot' problem

4) Don't worry. It is extremely rare that such 'extra' will result in clinical hold.

1) Narrow Focus

Translating Observations to Endpoints

Noted in the preclinical safety evaluations….	When planning the AP evaluation…..	Examples	Comparator example
Increased LMA	Tune assessment to capture increases	Low-rate operant behavior (DRL); Habituated LMA	(d)-amphetamine
Decreased LMA	Tune assessment to capture decreases	High-rate operant behavior (FR); Non-habituated LMA	Phenobarbital
Increased agitation/reactivity	Dedicated study to measure cognitive-emotive variables	Acoustic startle response threshold/maximum	Drug class comparator

HAP Study

2) Broad Focus

Common Clinical Signs in Discontinuation	
Cognitive disruption	Somnolence
Hypersomnia	Sleep disturbance
Anxiety	Sensory disturbances
Depression	Rebound psychosis, rebound anxiety, rebound depression
Increased nociception	Irritability
Lethargy	Headache

Some Additional Behavioral Endpoints for Consideration

CCALC
Cross Company Abuse Liability Council

Cognitive/Emotive	Motor/Reflex	Sleep/circadian activity
Startle Reflex	Spontaneous LMA	ctivity
Y-maze (alternation learning)	Wh	EEG
Peer interaction i housing (video)	timing	Feeding behavior
Spontaneous Ultrasonic Vocalization	Operant Learning (overnight acquisition)	Hormonal measurement
Anhedonia (ICSS)	Repeated LMA (habituation)	Nest building
Elevated +/0 Maze0	Nociception (analgesia, hyperalgesia)	Automated video analysis

Obviously will require discussion and agreement on which categories, endpoints and assays should be used

3) Continuous Monitoring

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The Promise of Automated Home-Cage Monitoring in Improving Translational Utility of Psychiatric Research in Rodents

Alfred Mingrone,[1] Ayal Kaffman,[2] and Arie Kaffman[2,*]

System/company/institution	Key features	Pros	Cons	References
Chora feeder – AM Microsystems and the Instituto Italiano di Tecnologia	• Simple automated wall feeder	• More affordable (about $5,000 per unit) • Up to 250 Chora feeders can be connected and processed simultaneously to a single computer • Can assess working memory, feeding, flexibility, time-keeping over an extended period of time • Compatible with other Chora-brand modules • Measurements are refreshed every 10 ms providing high temporal resolution of behaviors	• Likelihood of device malfunction increases over time, may result in data loss or removal of animals from study • Dispensers need to be cleaned, requiring down-time (data loss) and unintentionally subjecting rodents to extinction • Requires single housing	• Tucci et al., 2014 • Balzani et al., 2016 • Lassi et al., 2016 • Balzani et al., 2018
IntelliCage – TSE Systems	• RFID transponders and computerized regulated access to operant conditioning corners for a group of up to 16 rodents	• Social grouping for extended period of time • Individual mice can be identified using RFID • High flexibility in controlling access to liquid including timing, place, cue-mediated consumption, and punishment with an air puff. • Automated data acquisition	• No visual tracking info • High upfront cost ($65 k for one cage), but cost needs to be also considered in the context of the large number of rodents that can be tested at the same time. • Work with males is possible but more challenging due to aggression • No information on social interaction between specific individuals	• Safi et al., 2006 • Branchi et al., 2010 • Radwanska and Kaczmarek, 2012 • Nowak et al., 2013 • Benner et al., 2014 • Masuda et al., 2016 • Alboni et al., 2017 • Dere et al., 2018
PhenoTyper – Noldus Information Technology	• Top-down infra-red video recording linked to trainable visual system	• Highly accurate information about locomotor activity • Relatively low cost when purchasing multiple boxes (38,000 for four boxes) • Has been successfully used to assess anxiety (spot-light test) • Can be easily accessorized to add running wheel, lickometer, and operant learning wall • Compatible with optogenetics and calcium imaging • Reliable data across labs	• Single housing and thus relatively low behavioral throughput • Relatively bulky cage that requires large room to house multiple units • Camera provides top-down view that limits finer behavioral assessment	• Aarts et al., 2015 • Robinson et al., 2018 • Logan et al., 2019 • Prevot et al., 2019
Actual-HCA (Home Cage Analyzer) – Actual Analytics	• Visual monitoring with an infra-red camera that sits alongside the home cage and a RFID transponder system for monitoring position of multiple rodents in a standard housing cage	• Detailed visual information integrated with positional information for group housed animals • Can be used to assess social proximity • RFID system can also provide information on body core temperature • Compatible with standard IVC racks	• Not cheap (about $17,000 per cage) • Requires two IVC rack spaces per cage	• Bains et al., 2016 • Tse et al., 2018 Mitchell et al., 2020a • Mitchell et al., 2020b

Summary

In addition to the standard FOB,

- Look for physiological or behavioral endpoints which reflect opposing or otherwise relevant pharmacology
  - If already within the FOB, amplify resolution of measurements
  - Apply or add in additional measures as necessary
- Consider utilizing types of measurements that may reflect the more pervasive signs (fatigue, anhedonia, sleep/circadian disruption)
- Use longer sampling times, continuous measurements ideal when possible
  - Numerous companies support rigorous measurement of endpoints (e.g., application of AI/ML)