Study Design Considerations and Thoughts on Best Practice for Nonclinical Physical Dependence/Withdrawal

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Salient Points for Regulatory Studies

- FDA expressed desire to elevate physical dependence to be applied to all CNS drugs, regardless of whether abuse liability is likely
  - Safety signal, nevertheless
- Our preclinical measures miss drugs that produce discontinuation syndrome in clinic (e.g., SSRIs)
- The standard physiology measures in an FOB capture a lot of what FDA are interested in, but
- Recent direct CSS feedback: FOB only looks at a narrow slice in time (want >= 15 min observation period per rat), and may not capture all of the signs

Example Drug Classes with poorly predicted discontinuation syndrome

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Drug Class	Clinical Signs in Discontinuation
Psychomotor Stimulants	Somnolence, drug craving, anxiety, cognitive disruption
CNS Depressants	Anxiety, sleep disturbance
SSRI/SNRIs/TCAs	Sensory disturbances, Anxiety, Sleep disturbance
Antipsychotics	Super-sensitivity psychosis
Cannabinoids, Cannabidiol?	Sleep disturbance, anxiety, irritability
Caffeine	Headache, lethargy
Nicotine	Sleep disturbance, anxiety, irritability, cognitive disruption

How to Best Address?

- At least several means possible
  - Specifically look within the physiology of the target
    - Evidence of physiology moving in direction opposite to the pharmacology upon withdrawal?
  - Look for more generic, widely applicable endpoints
  - Use telemetry and do continuous monitoring of physiology, behavior

Opposing Pharmacology and Physiology

Drug	Direct pharmacologic effect	Observation in withdrawal
Diazepam	Hypoactivity, anxiolysis	Hyperactivity, anxiety
Amphetamine	Elevated body temperature	Lowered body temperature
Morphine	Analgesia, Euphoria	Hyperalgesia, dysphoria
Clonidine	Hypotension	Hypertension
Aspirin	Reduced platelet aggregation	Increased fibrinogen binding to platelets Increased platelet aggregation. Thrombosis risk.
Stimulants	Appetite Suppression, Euphoria	Hyperphagia, dysphoria

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Any Patterns Emerging?

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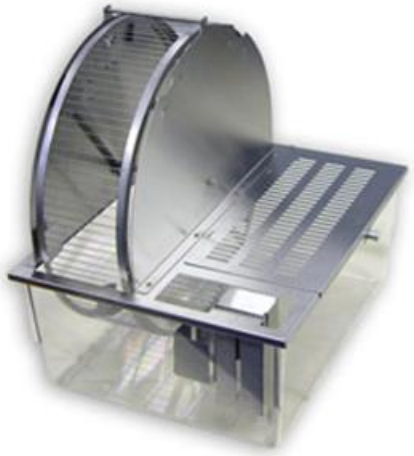
Additional Behavioral Endpoints for Consideration

Spontaneous Behavior	Elicited Behavior	Learned Behavior
Spontaneous LMA	Startle Reflex	Operant Behavior (eg. fixed ratio)
Wheel-running	Nociceptive response	Operant Behavior (fine motor / timing)
Feeding (preferred foods)	Forced Swim	Conditioned place aversion
Nest building	Elevated + Maze	Repeated LMA (habituation)
Ultrasonic Vocalizations	Ultrasonic Vocalization under stress	Operant Behavior : motivation (Progressive ratio)
Continuous, Circadian activity	Aggression	ICSS

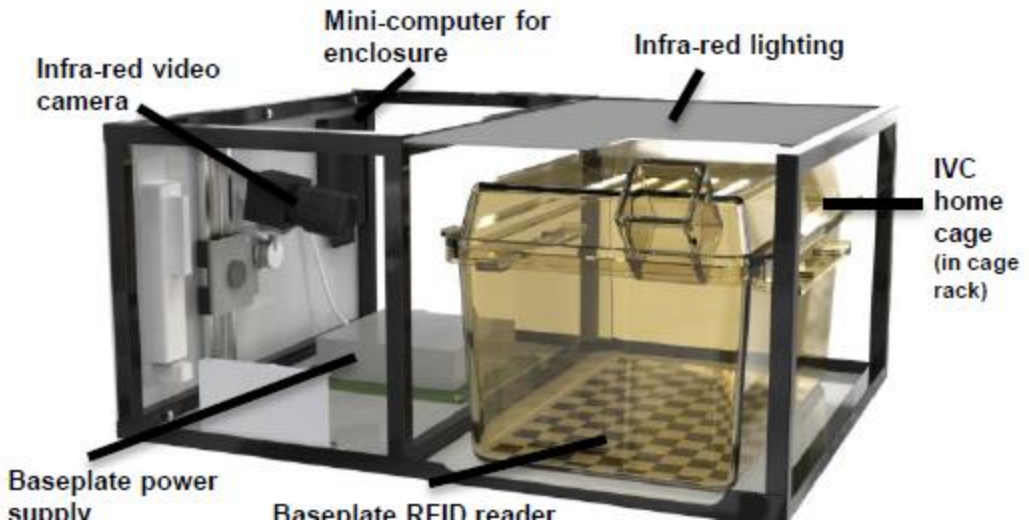
Wheel Running Behavior

- Different from spontaneous LMA
  - Does not habituate
  - Behaves as a reinforcer
    (so can reflect motivational state)
  - Easy to quantify continuously over a study duration or can do limited access periods
  - There is a circadian pattern
  - Applicable to rats and mice
- Validation Needed



Continuous Video Capture and Analysis

- A number of commercial systems available
- Differ in terms of resolution, whether group or individual housing, accuracy of behavioural assessment
  - Amount of manual video analysis needed
- Circadian pattern
- Validation needed



Summary

- Conduct standard FOB, but
- 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
- Use longer sampling times, continuous measurements preferred
- Consider utilizing types of measurements may reflect the more pervasive signs (fatigue, anhedonia, sleep/circadian disruption

Question For FDA

- Do you see these suggested, additional endpoints as potentially adding value?
- Should we work toward standardization of ancillary methods?
- Additional Suggestions?
- Risks?

Backups

FOB/CNS Obs Editorial Comment

- Numerous Endpoints – Physiologic and behavioral
- Each animal handled / observed for a brief period of time (3mins).
  - Like a brief neurological / mental status exam
  - FDA specifically requested minimum of 15 min obs per animal.
    - Unlikely to yield more info, but good to know if only method being used

Physical Dependence Studies Endpoints

Possible Endpoints:

- locomotor activity; increase activity (diazepam)

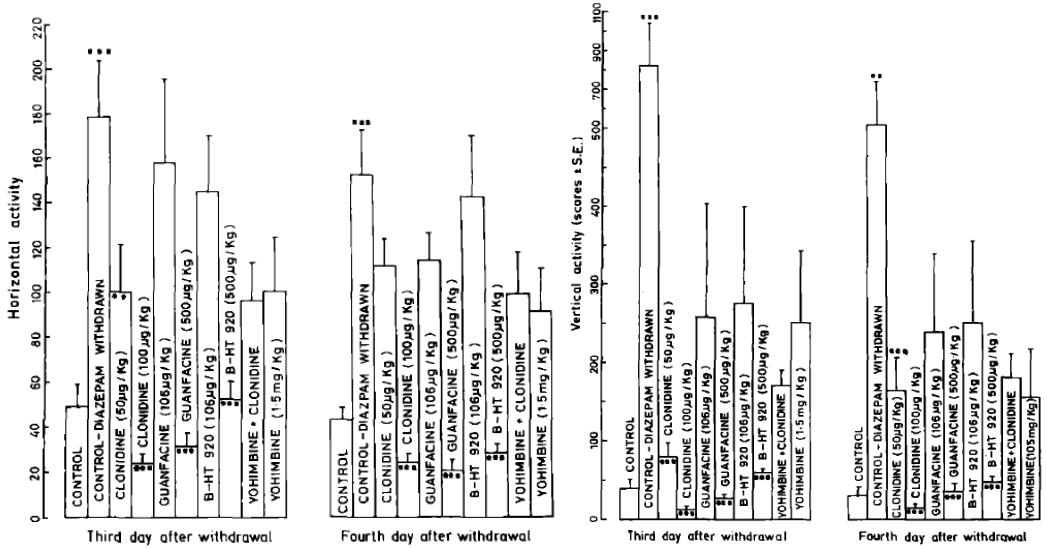


Fig. 2. Effect of clonidine, guanfacine, B-HT 920 and modification of clonidine (100 µg/kg) effect by yohimbine (1.5 mg/kg) on horizontal activity of rats on the 3rd and 4th day of diazepam withdrawal measured in a photoactometer for a period of 10 min (** $P<0.025$; *** $P<0.005$). Each *bar* represents mean ± SE of aminimum of five observations

Psychopharmacology (1986) 90:198–202

Drug treatment schedule. On completion of chronic treatment with diazepam for 3 weeks, the rats were divided into different groups for drug treatment and each group consisted of a minimum of five animals.

Physical Dependence Studies Endpoints

Possible Endpoints:

- locomotor activity; decreased activity (morphine)

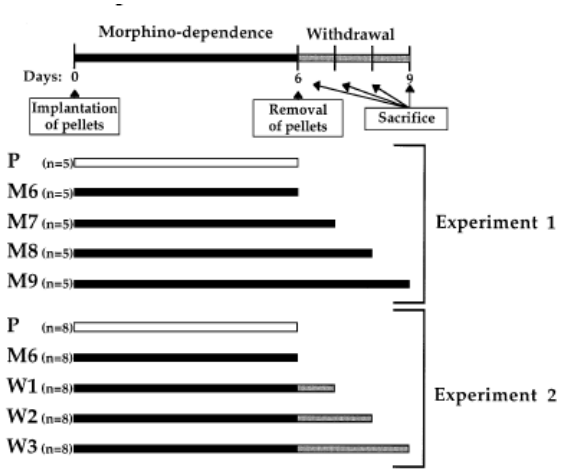


FIG. 1. Experimental schedule for Experiments 1 and 2. P indicates the placebo treatment. M6, M7, M8 and M9 are the 6-, 7-, 8- and 9-day treatments with morphine, respectively, W1, W2 and W3 indicate morphine withdrawal states following 1, 2 or 3 days of abstinence, respectively. The results for the M6 group were duplicated as they were needed in both sets of experiments.

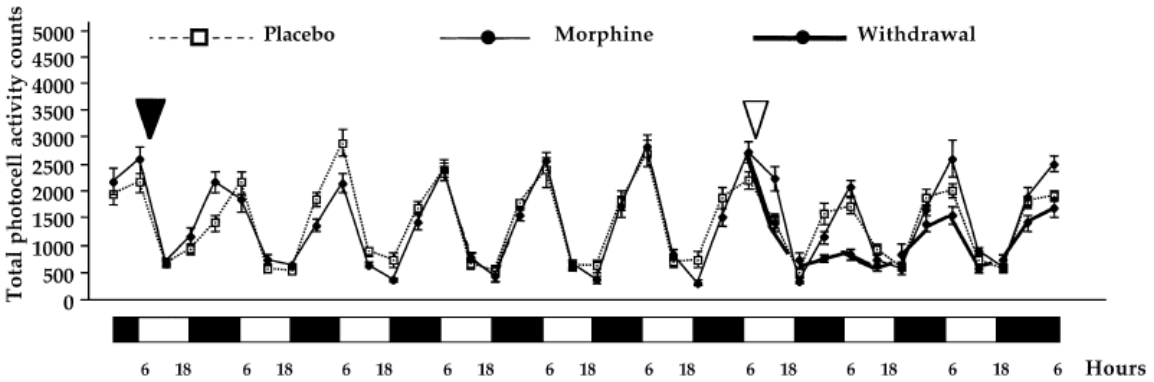
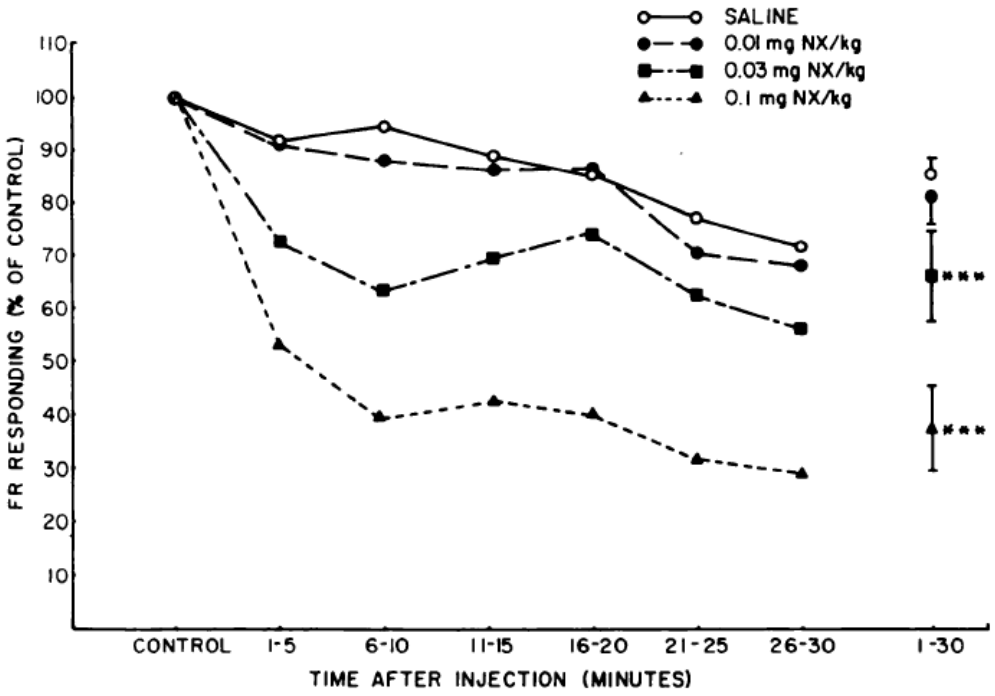


FIG. 2. Time course of total motor activity (total photocell activity counts per 6-h period) recorded in rectangular activity cages during the 9 days following implantation of the pellets (black arrowhead). Placebo-treated rats (n = 8): white squares and dotted lines. Chronic morphine-treated rats (n = 8): black circles and thin solid lines. Abstinent rats (n = 8) white arrowhead indicate removal of the pellets (black circle and thick solid lines). The spontaneous locomotor activity of morphine-dependent rats was similar to that of placebo-treated rats, but it was disrupted during the first and second days of withdrawal.

Physical Dependence Studies Endpoints

Possible Endpoints:

- instrumental behaviour: operant lever pressing for food



Naloxone-induced morphine withdrawal

Behavioral Sensitivity > Somatic for Opioids

Relative Sensitivity to Naloxone of Multiple Indices of Opiate Withdrawal: A Quantitative Dose-Response Analysis[1,2]

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But every mechanism can be different

Pharmacology vs Withdrawal : When Opponent-Process Applies

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Opioid Pharmacology	Withdrawal
Decreased GI Mobility	Cramping, GI distress, diarrhea
Analgesia	Hyperalgesia
Euphoria	Dysphoria
Sedative Pharmacology	**Withdrawal**
Sleep Induction	Insomnia
Anticonvulsant effects	Convulsion
Anxiolysis	Anxiety
Stimulant Pharmacology	**Withdrawal**
Euphoria	Depression, dysphoria
Appetite suppression	Hyperphagia
Motor stimulation	Motor suppression

There are behavioral signs which appear to be more pervasive across classes such as fatigue, stress, sleep disturbance, malaise; but are more difficult to quantify.

Typical Study Design

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Bwt	1-2 days prior	Daily	Daily
Clin Obs	X	Daily	Daily
10 sec cage-side FOB	X	X X (Early, Mid)	X X X
3-min observation LMA	X	X X	(day 1, 2…final)

Typical Study Outcome

Table 1: CNS Observations During the Dosing Phase

Table 1: CNS Observations in Male Sprague Dawley Rats to Assess the Physical Dependence and Withdrawal from A-913958.46, Study 8263237

↑A = increased activity
AGH = aggressive to handler
↑ER = escape response
↑IR = Irritability
N = normal
RE = increased response to stimuli
V = increased vocalization

	Time Point / Observation*		
	Day 1	Day 1	Day 1
	1 hour post dose	3 hours post dose	6 hours post dose
0.0 mg/kg vehicle	N = 10 ↑ER = 1 ↑RE = 1 ↑V = 1	N = 11 ↑V = 1	N = 12
3 mg/kg A-913958.46	N = 11 ↑IR = 1 ↑V = 1	N = 11 ↑V = 1	N = 11 ↑RE = 1
10 mg/kg A-913958.46	N = 8 ↑RE = 3 AGH = 1	N = 11 ↑V = 1	N = 11 ↑A = 1 ↑RE = 1
15 mg/kg d-Amphetamine	N = 7 ↑RE = 3 ↑A = 2 ↑V = 1	↑RE =5 ↑A = 4 N = 3 ↑V = 2 ↑ER = 1	N = 5 ↑RE = 5 ↑A = 2

* Values represent the number of rats (n=12) showing the observation on respective study day, unless otherwise noted in table.

Table 1: (continued) CNS Observations in Male Sprague Dawley Rats to Assess the Physical Dependence and Withdrawal from A-913958.46, Study 8263237

↑A = increased activity
AGH = aggressive to handler
AL = alert
AP = apprehensive
EB = eye blinking
ELRB = eye lacrimation reddish-brown material
↑ER =escape response
IR = irritability
Reddish left ear = Left ear pinna vascular (reddish)
N = normal
NRB = reddish-brown material found around the nose
↑RE = increased response to stimuli
ST head movement = stereotypy head movement
↑V/V = vocalization

	Time Point / Observation*		
	Day 4	Day 4	Day 4
	1 hour post dose	3 hours post dose	6 hours post dose
0.0 mg/kg vehicle	N = 11 ↑V = 1	N = 12	N = 12
3 mg/kg A-913958.46	N = 7 ↑RE = 2 ↑V = 2 AL = 1 ELRB = 1 NRB = 1	N = 9 ↑V = 2 AGH = 1 ELRB = 1 NRB = 1 ↑RE = 1	N = 7 ↑A = 4 NRB = 3 ↑V = 2 AL = 1 EB = 1 IR = 1 Reddish left ear = 1
10 mg/kg A-913958.46	N = 8 ↑RE = 3 ELRB = 1 NRB = 1	N = 5 ↑ER =2 ST head = 2 ↑V = 2 AP = 1 NRB = 1	N = 9 ↑ER =2 ST head = 2

* Values represent the number of rats (n=12) showing the observation on respective study day, unless otherwise noted in table.