Is locomotor activity a sufficient assessment for determining abuse liability?

Safety Pharmacology Society, Phoenix AZ
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National Institute on Drug Abuse

No conflicts to declare
Is locomotor activity a sufficient assessment for determining abuse liability?
Is locomotor activity a sufficient assessment for determining abuse liability?

No!
Is any one test/procedure sufficient for determining abuse liability?
Is any one **test/procedure** sufficient for determining *abuse liability*?

No!
Is any one species sufficient for determining abuse liability?
Is any **one species** sufficient for determining abuse liability?

No!
Is any one species sufficient for determining abuse liability?

No!

With the possible exception of humans
Public Health Question

Does the compound have the potential to be abused?
Public Health Question

Does the compound have the potential to be abused?

Preclinical Laboratory Questions

Equivalent to reference compound (drug of abuse)?

Positive reinforcing effects?

Physical dependence (tolerance)?
Primary Data on Abuse Potential

a. Chemistry
b. Preclinical pharmacology
c. *Animal behavioral and dependence pharmacology*
d. Pharmacokinetics/pharmacodynamics
e. Human abuse potential laboratory studies
f. Clinical trial data relative to abuse and dependence potential
g. Integrated summaries of safety and efficacy
h. Foreign experience with the drug

(FDA Guidance for Industry, Assessment of Abuse Potential of Drugs, January 2010)
Types of Preclinical Studies

1. Self administration ("...if animals...work to receive drug...likely the drug is rewarding in humans.")

2. Conditioned place preference ("...not as rigorous a test...as self administration...")

3. Drug discrimination ("...produces...perceptions similar to...a drug of abuse.")

4. Psychomotor tests ("...comparison with drugs of abuse")

5. Dependence potential ("...give rise to need for repeated doses...often characterized by withdrawal")

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Equivalence to reference compound(s)?

- Antinociception
- Anticonvulsant
- Learning and memory
- Food intake
- **Locomotion**

Similarities/differences **do not provide insight on mechanism or abuse liability**
Relevance of Locomotion

Dopamine systems mediate locomotor activation

Some drugs of abuse $\uparrow$ dopamine neurotransmission

Some drugs of abuse $\uparrow$ locomotion

Other drugs of abuse $\downarrow$ locomotion
Drug that \( \uparrow \) locomotion *might* be a stimulant (e.g. cocaine)

Drug that \( \downarrow \) locomotion *might* be a sedative (e.g. benzodiazepine)
Limitations of Locomotion

All drugs ↓ locomotion

Non-abused drugs ↑ locomotion

Insensitive to important factors (pharmacokinetics)

Challenging to study in some species (primates)
Variations on Locomotion

Sensitization to locomotor effects
Variations on Locomotion

Sensitization to locomotor effects
- increased response over repeated testing
- cross sensitization among some drugs of abuse
- "neuroplasticity" is hallmark of abuse?
Variations on Locomotion

Sensitization to locomotor effects
  Lack of covariance
  Occurs with non-abused drugs
  Evident only under selected conditions

Relationship to reinforcing effects?

Relevance to substance abuse?
Is locomotor activity a sufficient assessment for determining abuse liability?

No, but it is useful!
Types of Animal Studies (FDA)

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(FDA Guidance for Industry, Assessment of Abuse Potential of Drugs, January 2010)
Drug Discrimination: Methodology

Subjective effects in humans

Drug discrimination in non-humans
Drug Discrimination: Methodology

Heroin versus saline discrimination

HEROIN

FOOD
Drug Discrimination: Methodology

Heroin versus saline discrimination

HEROIN

FOOD
Drug Discrimination: Methodology

Heroin versus saline discrimination
Drug Discrimination: Methodology

Heroin versus saline discrimination

HEROIN

FOOD

SALINE

FOOD
Drug Discrimination: Methodology

Heroin versus saline discrimination

HEROIN

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FOOD
Drug Discrimination: Methodology

Heroin versus saline discrimination

TEST

HEROIN?

FOOD

SALINE?

FOOD
Drug Discrimination: Methodology

• Heroin versus saline discrimination in rats
Drug Discrimination: Methodology

• Heroin versus saline discrimination in rats
• Morphine substitution
Drug Discrimination: Methodology

- Heroin versus saline discrimination in rats
- Morphine substitution
- Pharmacological specificity - cocaine
Drug Discrimination

- **Strengths**
  - Pharmacologic specificity

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## Drug Discrimination

### Strengths
- Pharmacologic specificity

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**TEST SUBSTANCE**  

| TEST SUBSTANCE | ? | ? | ? | ? |
Drug Discrimination

• **Strengths**
  – Pharmacologic specificity

Cocaine-like stimulant (dopamine)
Drug Discrimination

- **Strengths**
  - Pharmacologic specificity

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Drug Discrimination

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Midazolam-like sedative/hypnotic (GABA_A)

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Question Determines the Answer

• Which comparison(s)?
  – Cocaine/amphetamine (dopamine, DAT)
  – Heroin (opioid)
  – Benzodiazepine (GABA)
  – Phencyclidine (NMDA)
  – LSD (5-HT)
  – THC (CB₁)
Drug Discrimination

• Strengths
  – Pharmacologic specificity (pharmacodynamics)
  – Consistent across species
  – Stable baseline
  – Relatively insensitive to pharmacokinetics
Drug Discrimination

• Limitations
  – Not necessarily related to abuse liability
    • Discrimination on non-abused drugs
Drug Discrimination

• Limitations
  – Discrimination of non-abused drugs

![Graph showing % U50488 lever responding in Rhesus monkey. The graph compares saline, U50488, and morphine.](image)
Drug Discrimination

• Limitations
  – Not necessarily related to abuse liability
    • Discrimination on non-abused drugs
    • PK factors relatively unimportant for discrimination
Drug Discrimination

- Limitations
  - Not necessarily related to abuse liability
    - Discrimination on non-abused drugs
    - PK factors relatively unimportant for discrimination
  - Constraints of high pharmacological specificity
    - Multiple mechanisms can mask relevant signal
Drug Discrimination: Masking Stimuli

- Mechanism A
- Mechanism B
- Mechanism C
- DAT

TRAINING SUBSTANCE

TEST SUBSTANCE
% Morphine-lever responding

Dose (mg/kg) morphine

Control
Morphine-lever responding

Control

+ 1 mg/kg Δ⁹THC

Dose (mg/kg) morphine

% Morphine-lever responding
Drug Discrimination

• Limitations
  – Not necessarily related to abuse liability
    • PK factors relatively unimportant for discrimination
  – Constraints of high pharmacological specificity
    • Multiple mechanisms can mask relevant signal
    • Novel mechanisms and false negatives
midazolam trained

cocaine trained

heroin trained

nicotine trained

alcohol trained

phencyclidine trained
midazolam trained

nicotine trained

phencyclidine trained

cocaine trained

heroin trained

alcohol trained

TEST SUBSTANCE
Question Determines the Answer

• Train discrimination with novel compound
  – Stimulus control confirms activity (likely in brain)
  – Lack of stimulus control does not prove lack of activity/abuse
Question Determines the Answer

• Train discrimination with novel compound
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• Test known drugs of abuse
  – Cocaine
  – Heroin
  – Midazolam
  – Phencyclidine
  – Nicotine
  – Δ⁹THC
NOVEL SUBSTANCE TRAINED
NOVEL SUBSTANCE TRAINED
A diagram showing a NOVEL SUBSTANCE TRAINED category connected to both a cocaine test and a heroin test.
- NOVEL SUBSTANCE TRAINED
- cocaine test
- heroin test
- alcohol test
NOVEL SUBSTANCE TRAINED

cocaine test

heroin test

phencyclidine test

alcohol test
NOVEL SUBSTANCE TRAINED

- cocaine test
- heroin test
- nicotine test
- alcohol test
- phencyclidine test
NOVEL SUBSTANCE TRAINED

- midazolam test
- nicotine test
- cocaine test
- heroin test
- phencyclidine test
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• Relationship to abuse?
Question Determines the Answer

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• Relationship to abuse?
  – Positive result = implicates specific mechanism of action
  – Negative result = can exclude specific mechanism(s) of action but does not exclude abuse potential
Lack of discrimination does not exclude abuse

Discrimination does not predict abuse

Value is identification/confirmation of mechanism
Objectives are to test for equivalence, positive reinforcing effects, and dependence

Locomotor behavior and drug discrimination test for equivalence in a very general and a very specific manner, respectively

A compliment of procedures in multiple species increases the likelihood of accurate assessment
Species: Which One?

Rats

– Studies in drug-naïve subjects
  • Control drug/behavioral history
  • Drug discrimination with test substance
  • Initiation of self administration with test substance

– Cost
– Less compound needed
– Between-subjects design (>n)
– Same as other preclinical work (biochemical)
Species: Which One?

Mice

- Studies in drug-naïve subjects
- Cost
- Still less compound needed
- Genetically-modified animals available but very challenging
- Procedures not well developed or validated
Species: Which One?

• Non-human primates
  – Preferred by some
  – Phylogenic closeness to humans
  – PK most likely to match human
  – Long-term preparation
    • Within-subjects design
      – PK and behavior in same individual
      – Dose-response in same individual
      – Within-subjects = small group number
      – Drug history might be better model of human abusers
    • Long training
      – Complex tasks
      – Chronic dosing in developmentally stable subject
  – Need more compound
  – Extensive comparative literature
What Dose(s) & Dosing?

• Range of doses increases predictive value
  – Abusers do not attend to recommended dose
  – Multiples of therapeutic dose

• Dose selection
  – Behaviorally active dose (operant responding)
  – Based on other data/measures
    • Behavior (therapeutic target)
    • Biochemical/physiological target
      – Blood concentration
      – Relationship to binding *in vitro*
      – Imaging and receptor/transporter occupancy

• Route of administration
  – Multiple routes recommended
  – Clinical and another (i.v.)

• Confirm exposure in behavioral study with PK study
• Directly study metabolites?
• Formulations for risk reduction
Disclosure

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Consultant: Porsolt Inc., USA