Regulatory perspective on select topics in preclinical methodologies for abuse potential assessment

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September 28th, 2023

Disclaimer

Opinions expressed in this presentation are my own and do not necessarily reflect the views and policies of the FDA

Overview

This presentation will provide a regulatory perspective on select topics from preclinical methods in abuse liability testing, such as:

- Self-administration
  - Considerations for progressive ratio procedures
- Drug discrimination
  - Positive controls selection
  - Study design parameters for training and challenge sessions
  - Interpreting outcome measures

Animal Abuse-Related Behavioral Pharmacology Studies

- When a drug is CNS-active, abuse-related animal behavioral studies should be conducted
- Specific abuse-related studies typically evaluate:
  - Whether a drug has reinforcing properties (self-administration)
  - Whether a drug has effects similar to known drugs of abuse (drug discrimination)
- The results of these studies are useful to inform the necessity and design parameters of a human abuse potential (HAP) study

Animal Abuse-Related Behavioral Pharmacology Studies

- Generally conducted at EOP2, when final therapeutic doses are established
  - Doses for animal studies should be based on plasma levels produced in humans and utilize final therapeutic and supratherapeutic levels
- Studies should use classic, well-established designs and utilize rodents unless a different species is justified
- Sponsors should justify design parameters (e.g., positive control comparators) and dose selection(s)

Self-Administration

- Considered the “gold standard” of preclinical abuse potential evaluation
  - Directly examines the reinforcing properties of a drug and results in a binary evaluation of reinforcing effects (e.g., “yes/no” rather than magnitude or relative reinforcing efficacy)
  - If a drug produces self-administration in animals, it is likely to be reinforcing in humans and exhibit an abuse potential
- Not all drugs of abuse are self-administered
  - Hallucinogens and psychedelics typically aren’t self-administered
  - THC is self-administered under (relatively) limited conditions

Self-Administration – Design Considerations

- Intravenous route is preferred
- Animals should be trained from an FR1 to FR10
- Doses of the test drug should be fractions of the doses that produce therapeutic plasma levels
- Training drug should be a known drug of abuse, scheduled under the CSA
  - Preferably from the same pharmacological class or indication
  - Saline is an adequate (negative) control, the training agent may serve as a positive control

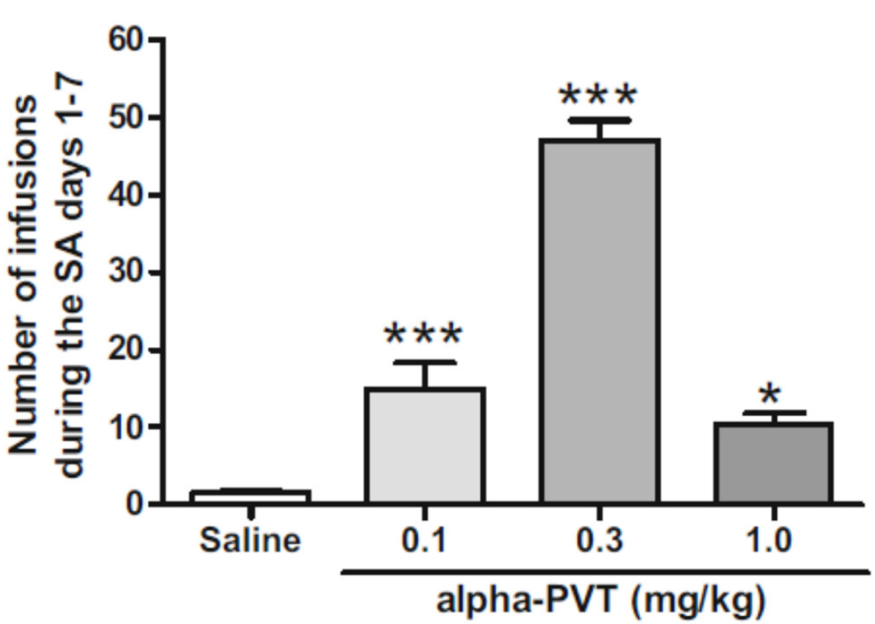
Self-Administration – Design Considerations

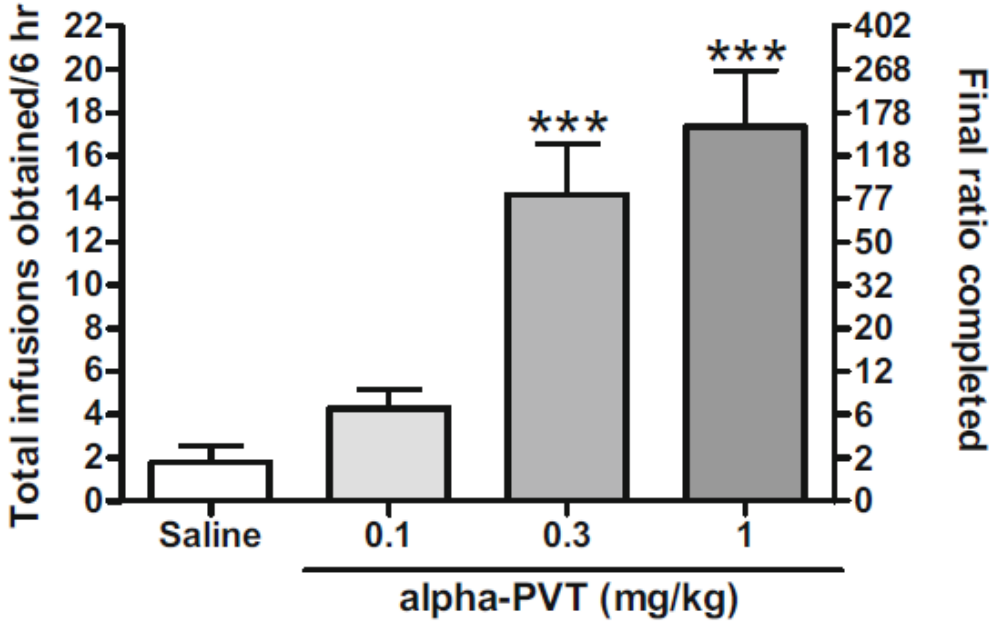
- Once self-administration with a known drug of abuse is established, the new drug is introduced to the animals in a substitution procedure
  - Animals must be exposed to the new drug in order to evaluate its reinforcing efficacy

Self-Administration – Design Considerations

- Session length should be justified
  - Longer sessions may maximize the likelihood of observing self-administration and are appropriate for examining drugs with a long half-life
- What is the utility of progressive ratio (PR) and behavioral economic analyses in-self administration?

Traditional Self-Administration VS. PR





SOURCE: Cheong JH, Choi MJ, Jang CG, Lee YS, Lee S, Kim HJ, Seo JW, Yoon SS. Psychopharmacology (Berl). 2017

Self-Administration – Design Considerations

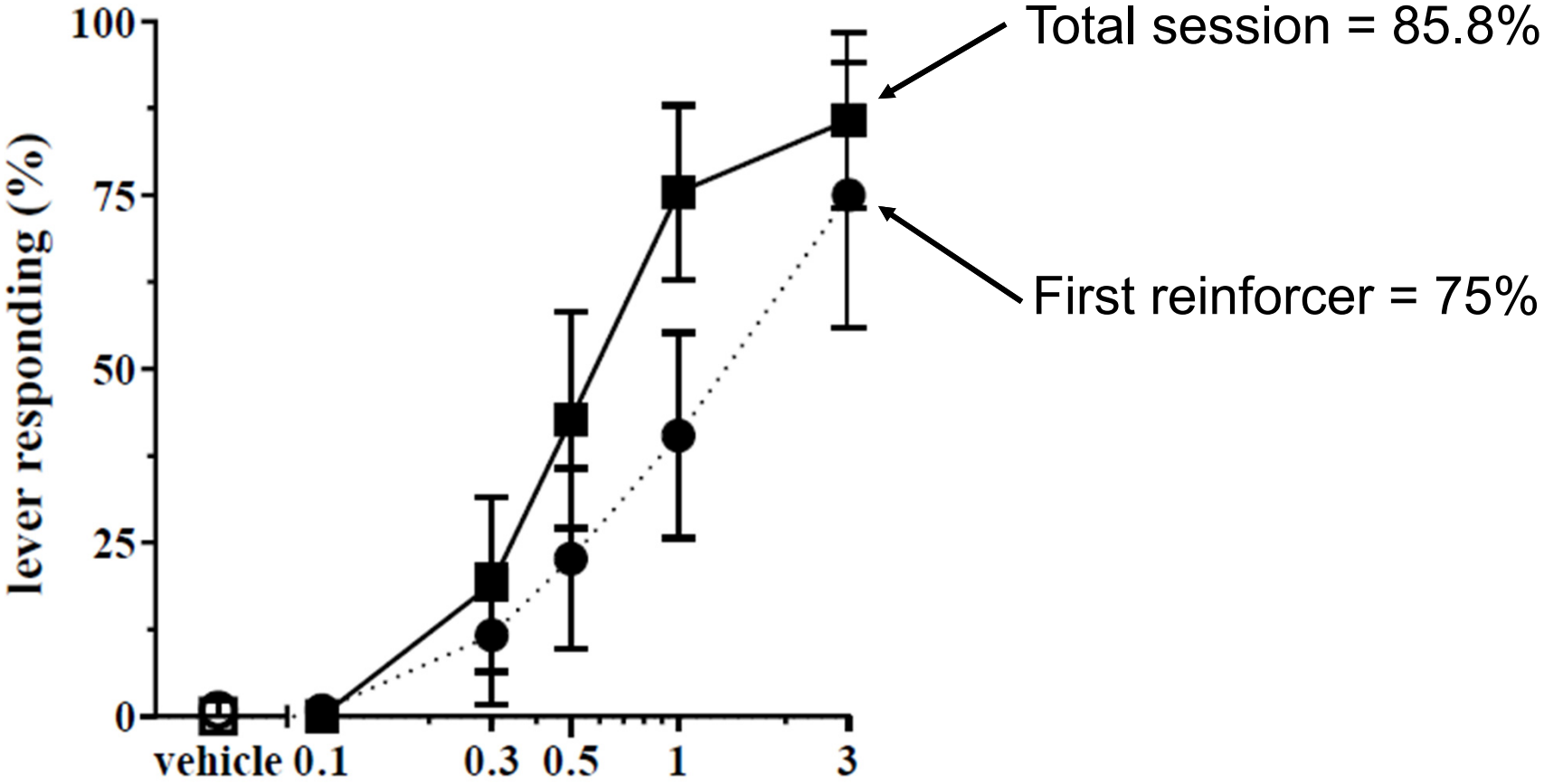
- PR procedures may be acceptable under *limited* circumstances
  - PR procedures would be *in addition* to standard (e.g., FR=10) self-administration studies

Drug Discrimination

- Drug discrimination evaluates whether a test drug produces "interoceptive cues" (e.g., sensations) that are similar to those produced by a known drug
  - Often used as a model of subjective effects
- In this paradigm, animals are trained to bar press a lever after administration of drug, and trained to press an opposite lever after saline or no drug
  - A food reinforcer incentivizes the animal to press each bar
  - Animals are trained on an FR10

Drug Discrimination – Design Considerations

- Once animals reliably associate each interoceptive cue (e.g., drug and saline) with ≥80% responding, test sessions begin
- How should NMEs with a novel mechanism(s) of action be evaluated in drug discrimination studies?
- CSS has typically recommended two approaches:
  1. Train animals to discriminate the novel NME from saline, followed by substitution tests with prototypical drugs of abuse (e.g., a cannabinoid, stimulant, sedative, opioid, and hallucinogen)
  2. Train separate groups of animals to discriminate prototypical drugs of abuse from saline and perform cross tests with the NME
- Are there situations where we should forgo discrimination testing based on the *in vitro* receptor binding profile of the NME?


100
75
50
25
0
lever responding (%)
vehicle
0.1
0.3
0.5
1
3
Total session = 85.8%
First reinforcer = 75%

Drug Discrimination – Design Considerations

- Drug discrimination results are typically categorized as full substitution (≥80% drug-appropriate responding), no substitution (≤20% drug-appropriate responding) or partial generalization (≥20% and ≤80% drug-appropriate responding)
  - How should partial generalization be interpreted?
- During challenge sessions, once animals complete an FR10, the session ends
  - Should we consider completion of the *first* reinforcer, as well as percentage of lever presses across the *entire session*?

Drug Discrimination – design considerations

- Should challenge sessions be reinforced (or not)?
- Should sessions reset FR values for incorrect lever presses (e.g., mistakes?)

Conclusions

- Self-administration provides robust, preclinical information about the reinforcing effects of a drug
  - There may be situations where adaptations of traditional self-administration procedures provide additional data
- Drug discrimination provides information about the interoceptive effects of a drug
  - NMEs with novel mechanism(s) of action present unique challenges in drug discrimination methodology and study designs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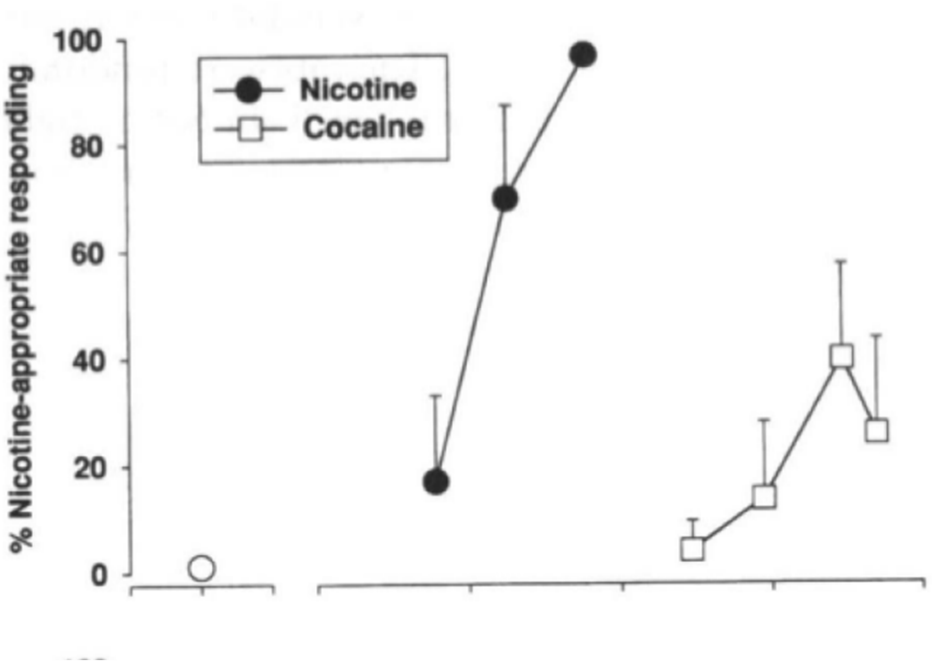
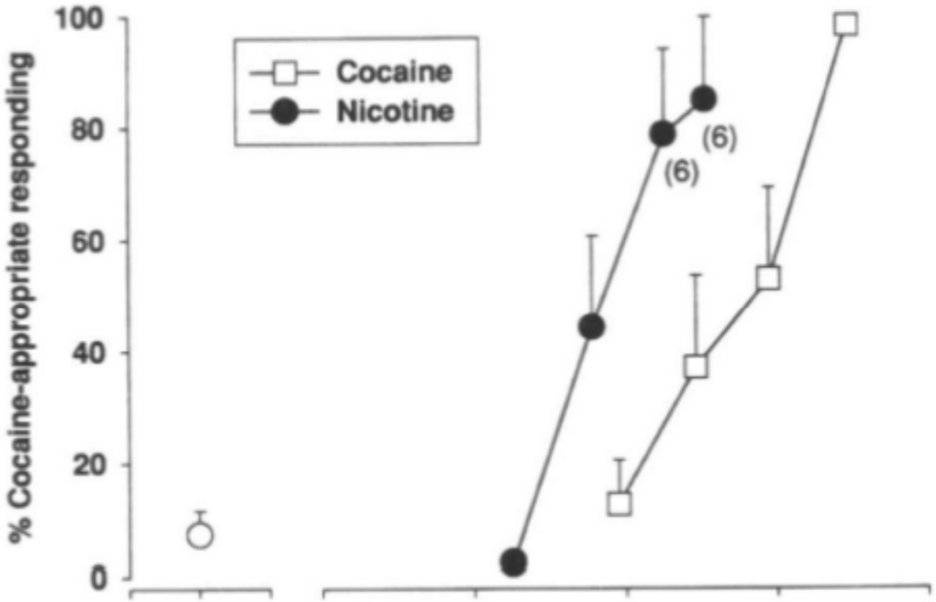
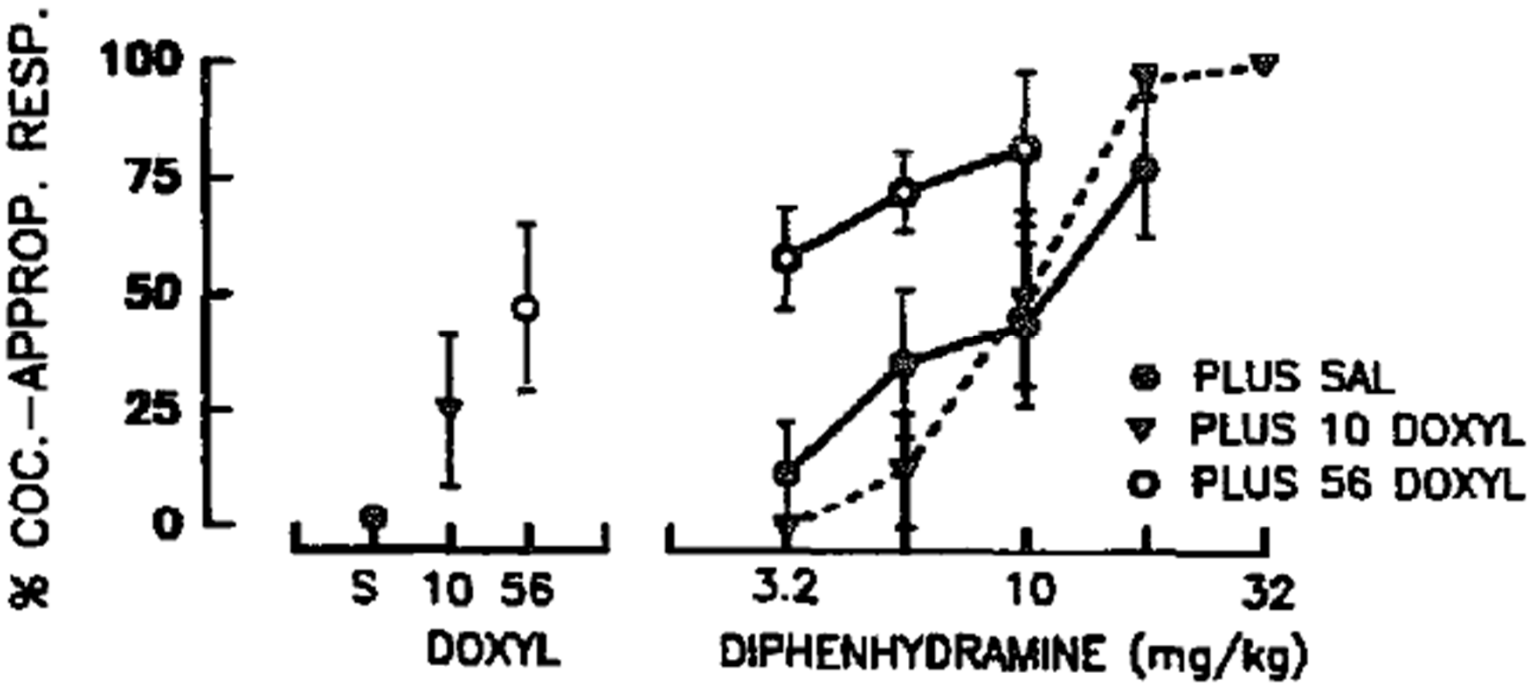
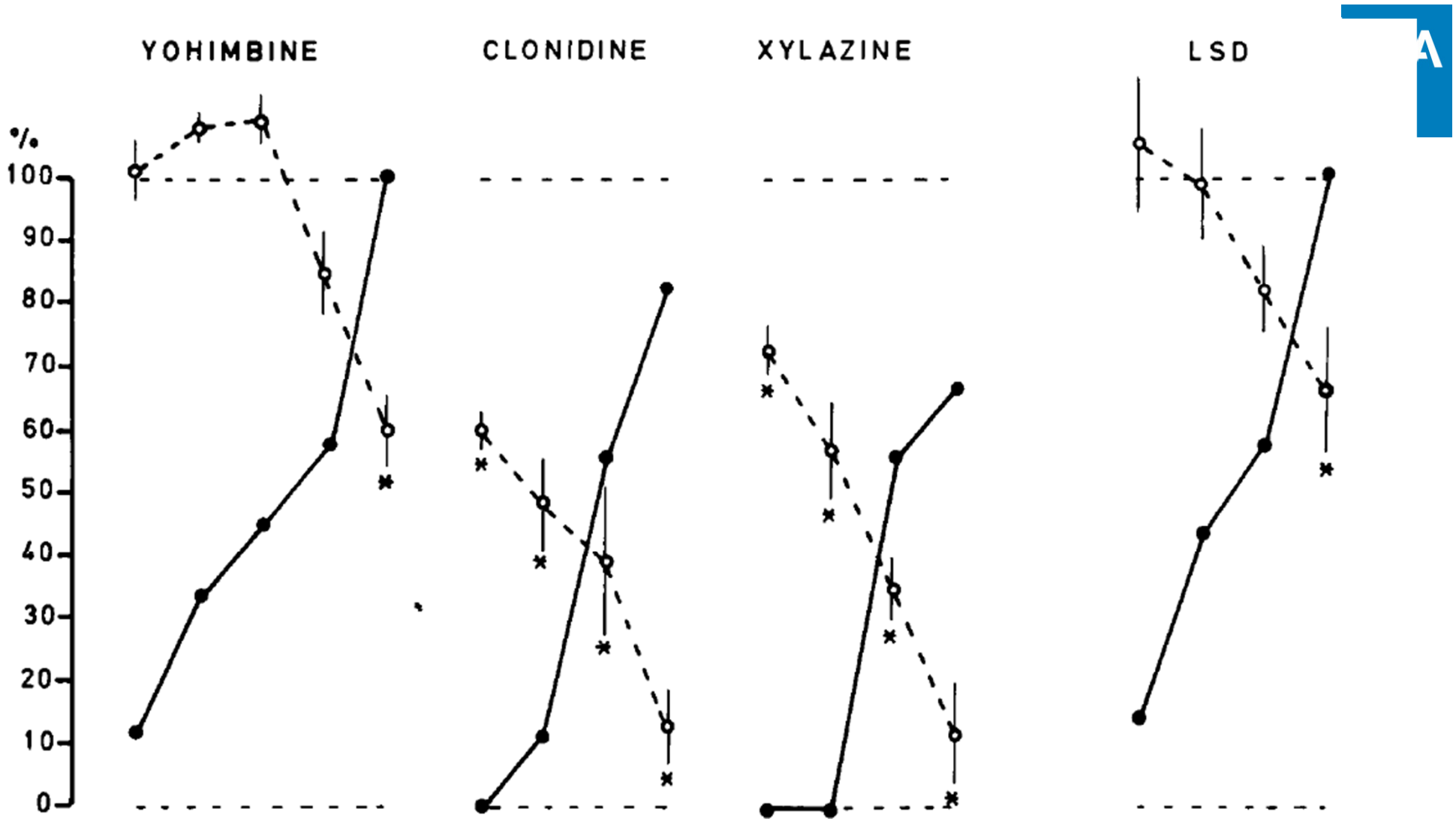
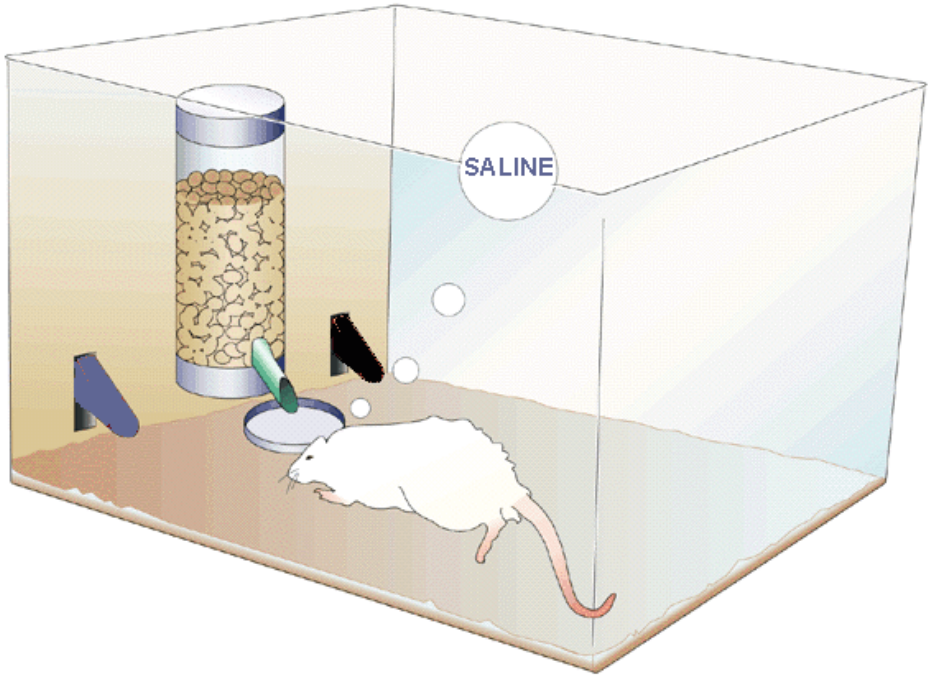

% Nicotine-appropriate responding
100
80
60
40
20
0
Nicotine
Cocaine


% Cocaine-appropriate responding
100
80
60
40
20
0
Cocaine
Nicotine
(6)
(6)


% COC.–APPROP. RESP.
100
75
50
25
0
S
10
56
DOXYL
3.2
10
32
DIPHENHYDRAMINE (mg/kg)
PLUS SAL
PLUS 10 DOXYL
PLUS 56 DOXYL

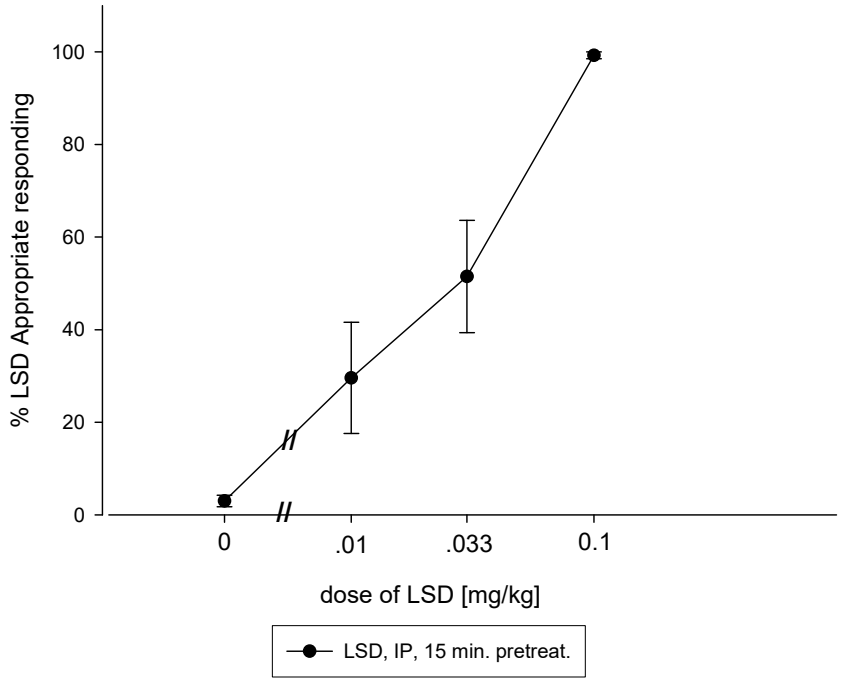

YOHIMBINE
CLONIDINE
XYLAZINE
LSD
%
100
90
80
70
60
50
40
30
20
10
0

DRUG Discrimination



Drug Discrimination

- Example: Rodents can reliably discriminate LSD from saline



Reissig et al. The 5-HT1A receptor and the stimulus effects of LSD in the rat. Psychopharmacology (Berl). 2005 Oct;182(2):197-204

Self-Administration – Design Considerations

- Can other models of self-administration be informative to abuse potential assessment?

Table 1
Measures of SA.

Swain et al, 2021

Stage of Addiction	SA Model	Operational Measure	Example Study
Initiation of drug use	Acquisition	Average number of infusions earned during first days of drug SA	Belin et al., 2008; Nishida et al., 2016; Smith et al., 2015; Suto et al., 2001
Reinforcing efficacy of drug	Progressive ratio schedule of reinforcement; Behavioral economics	Breakpoint, or the highest fixed ratio at which the animal maintains responding for drug; Elasticity of demand or essential value	Hodos, 1961; Katz, 1990; Richardson and Roberts, 1996; Grebenstein et al., 2013; Swain et al., 2018; Stafford et al., 2019
Loss of control over drug use	Escalation	Increase in number of infusions earned after duration of daily access to drug is extended	Kitamura et al., 2006; Edwards and Koob, 2013; Ahmed and Koob, 1999
Drug use despite negative consequences	Resistance to punishment	Reduction in drug SA when infusions are accompanied by aversive consequence (e.g., foot shock)	Deroche-Gamonet et al., 2004; Belin et al., 2008
Relapse to drug use following exposure to drug-associated environmental cues, stress, or the drug itself	Cue-/stress-/drug-induced reinstatement	Increase in drug-seeking (active lever pressing) following extinction of SA and exposure to drug-associated cue stimuli, stress (e.g., foot shock), or non-contingent injection of previously self-administered drug	Childress et al., 1993; Epstein et al., 2006; McNamara et al., 2010; de Wit, 1996; Banna et al., 2010; Sinha, 2001