Partial Generalization in Drug Discrimination: Considerations for Interpretation

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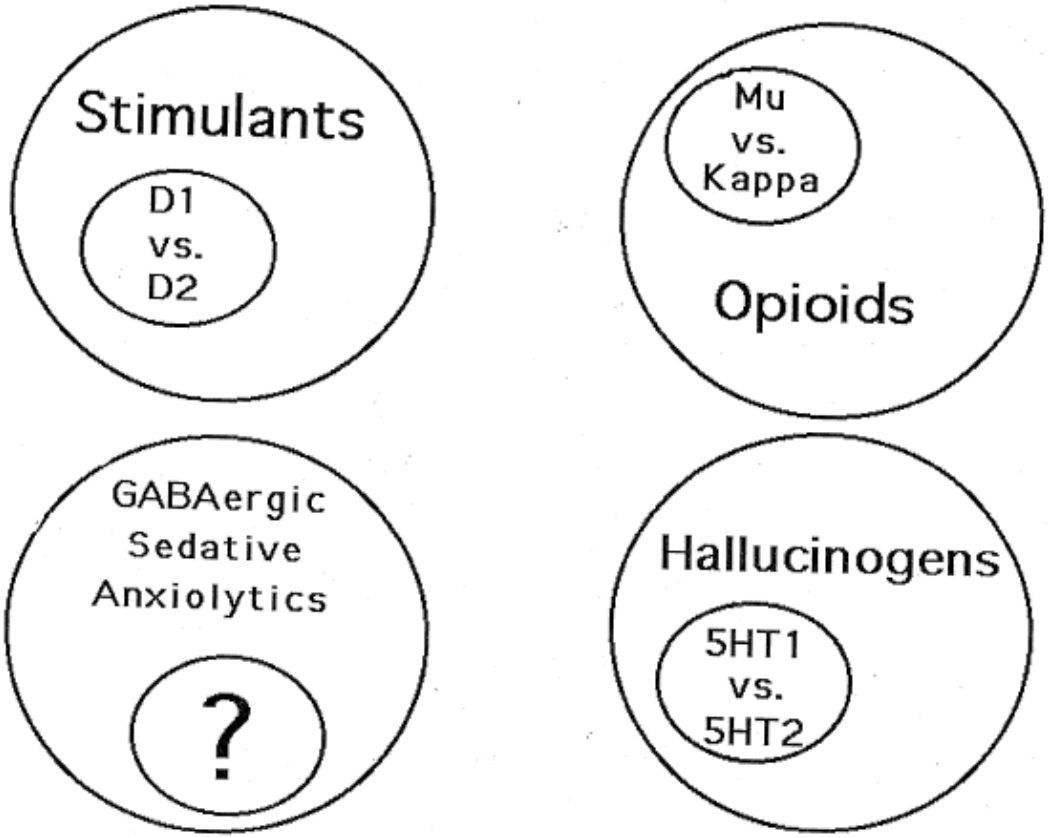
Drug Discrimination: Animal model of "subjective" effects

- An "Expert" compares test drugs to his "Standard," reporting whether the test drug is like/unlike the standard. (Similar to drug users reporting whether a novel drug is like or unlike a familiar drug.)
- Great pharmacological and neuropharmacological specificity, depending on the selectivity of the drug used to train the discrimination. Animals do not learn a global "sedative effect" or "stimulant effect."
- Discriminative effects are not isomorphic with reinforcing effects.

Selectivity in Drug Discrimination Test Profiles



Drug Discrimination: Methodological considerations

- Fixed-ratio schedule of reinforcement: A "consecutive-response" requirement assures avoidance of a "superstitiously" learned win-stay/lose-shift performance, and can define "choice."
- Training criterion for accuracy in performance prior to testing: 80%? 90% 95%? coupled with lack of "win/stay/lose shift" on first pellet? Bottom line is reliably meeting criterion with vehicle and training dose in test sessions.
- Response rate in the test session is very important for interpretation of whether a "choice" has been made.

Usual Conventions for interpreting results of DD testing

- Full generalization: >/= 80% on lever paired with training drug
- No generalization: </= 20% on lever paired with “no drug” (V)
- Partial generalization:
  - Default definition: >20% and <80% on lever paired with training drug
  - CDER definition: 60-80% on lever paired with the training drug
- Goals of this presentation are to:
  - Show that “intermediate” percentages of responding regularly occur in individual animals as a function of test dose and time since dosing.
  - Show drug discrimination data in relation to self-administration data: each procedure measures something different.

Drug Discrimination: Methods for data presented today.

•FR: 15-40 consecutive responses for baboons; 10 consecutive responses for rats; generally, 20-minute sessions.

•Training criteria:

95% with no "win-stay/lose-shift" evident on first pellet.

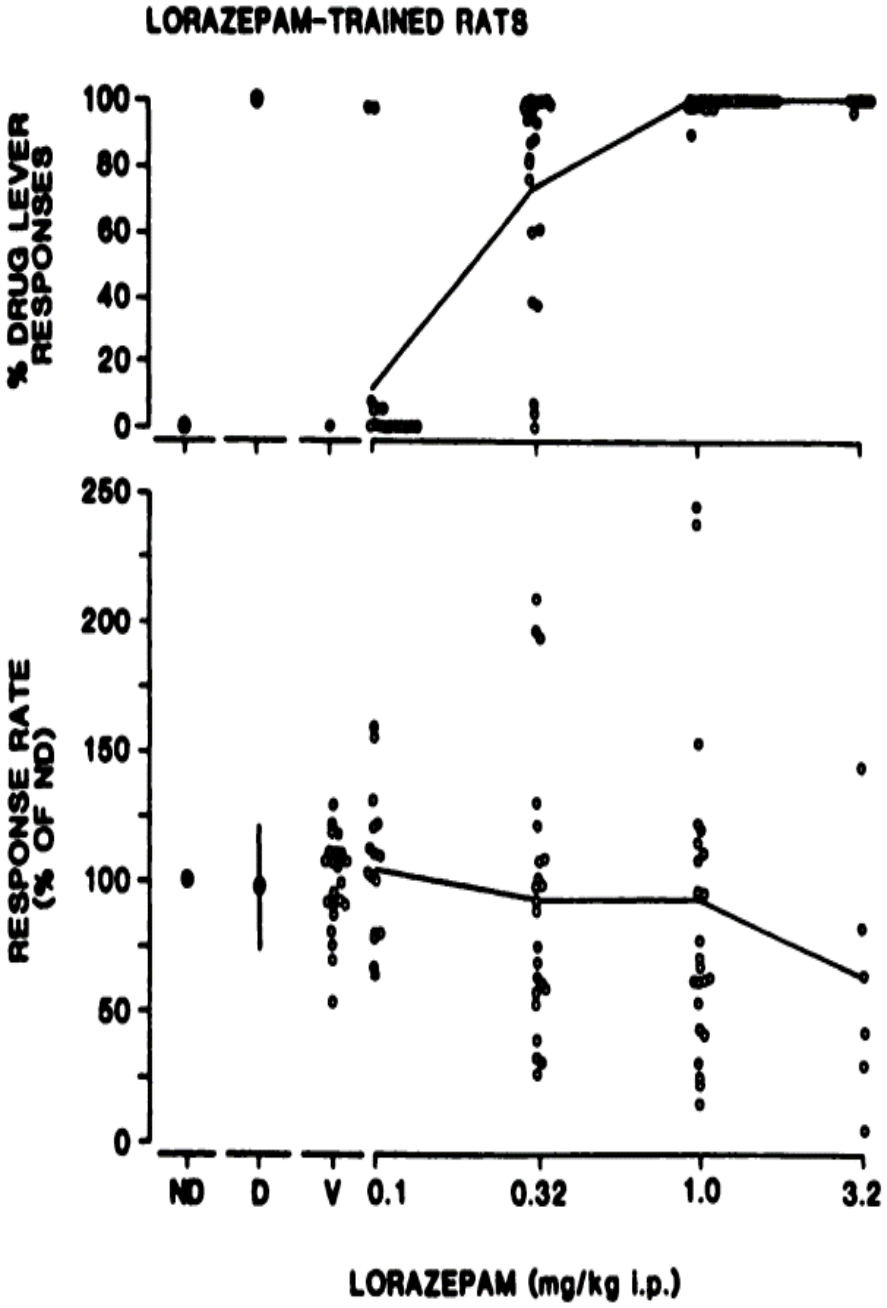
• Stimulus control above 80% level in training tests.

•Testing in reinforcement: "The well-trained subject is always right." Advantages:

- **Avoids subject learning that "novel" drug on board = zero reinforcement.**
- **Permits concomitant assessment of response rate dose-effects.**

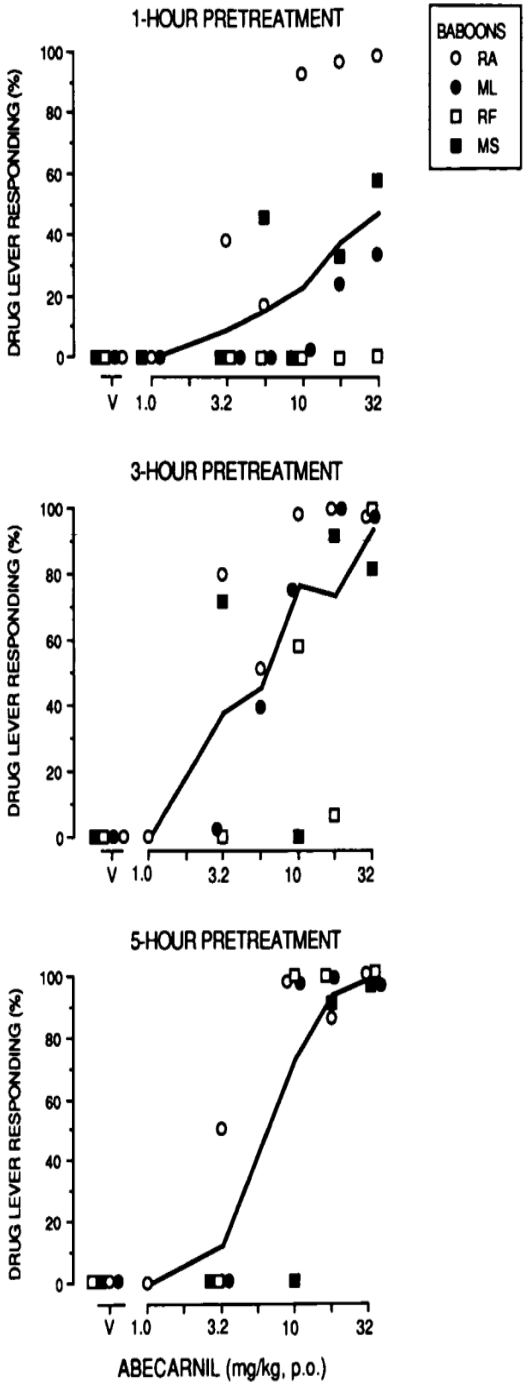
Ator & Griffiths 1986, JPET.

Data for individual rats trained to discriminate 1.0 mg/kg, i.p., FR 10 consecutive responses



Partial generalization in individual rats.

Testing the beta-carboline, abecarnil, in lorazepam-trained baboons.



Partial generalization as a function of slow onset of effects.

Sannerud, Ator, & Griffiths, Behav. Pharmacol., 1992, Fig. 4.

Partial generalization in time course study.

Ator & Griffiths, 1983, JPET.

•Time course of the blockade of discriminative effects of lorazepam by flumazenil across 24 hours

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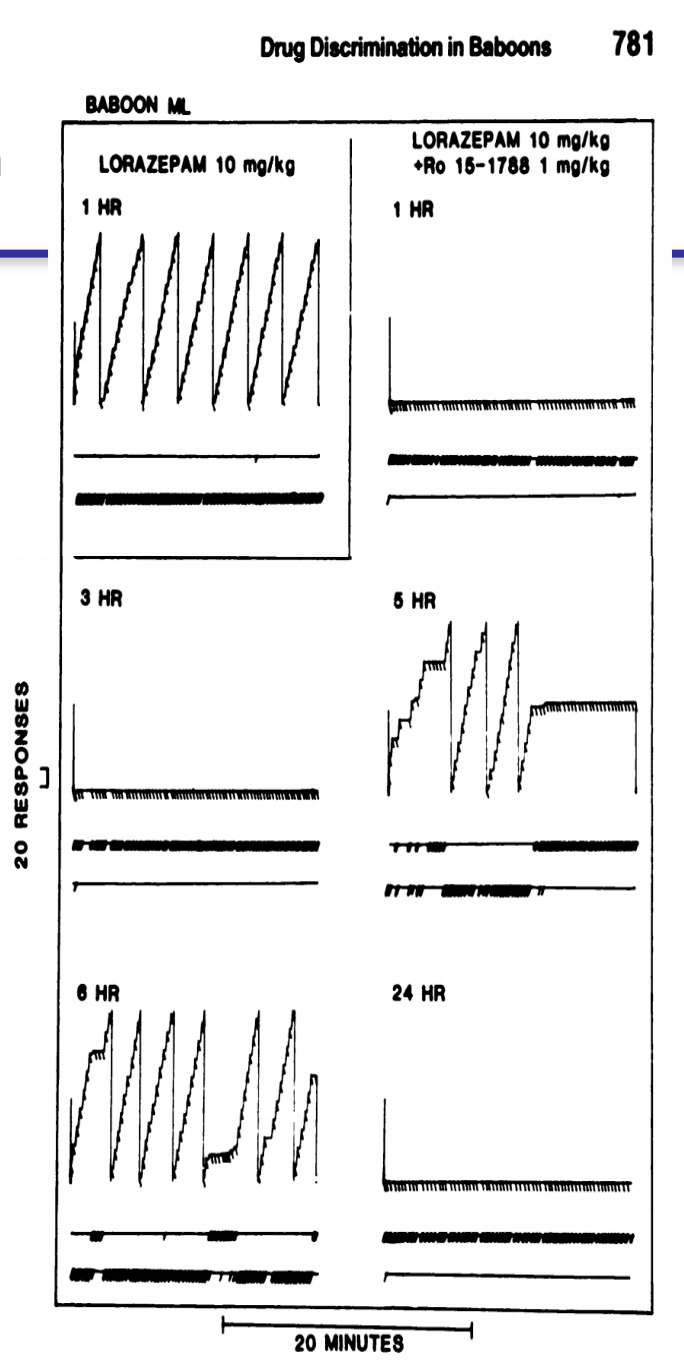
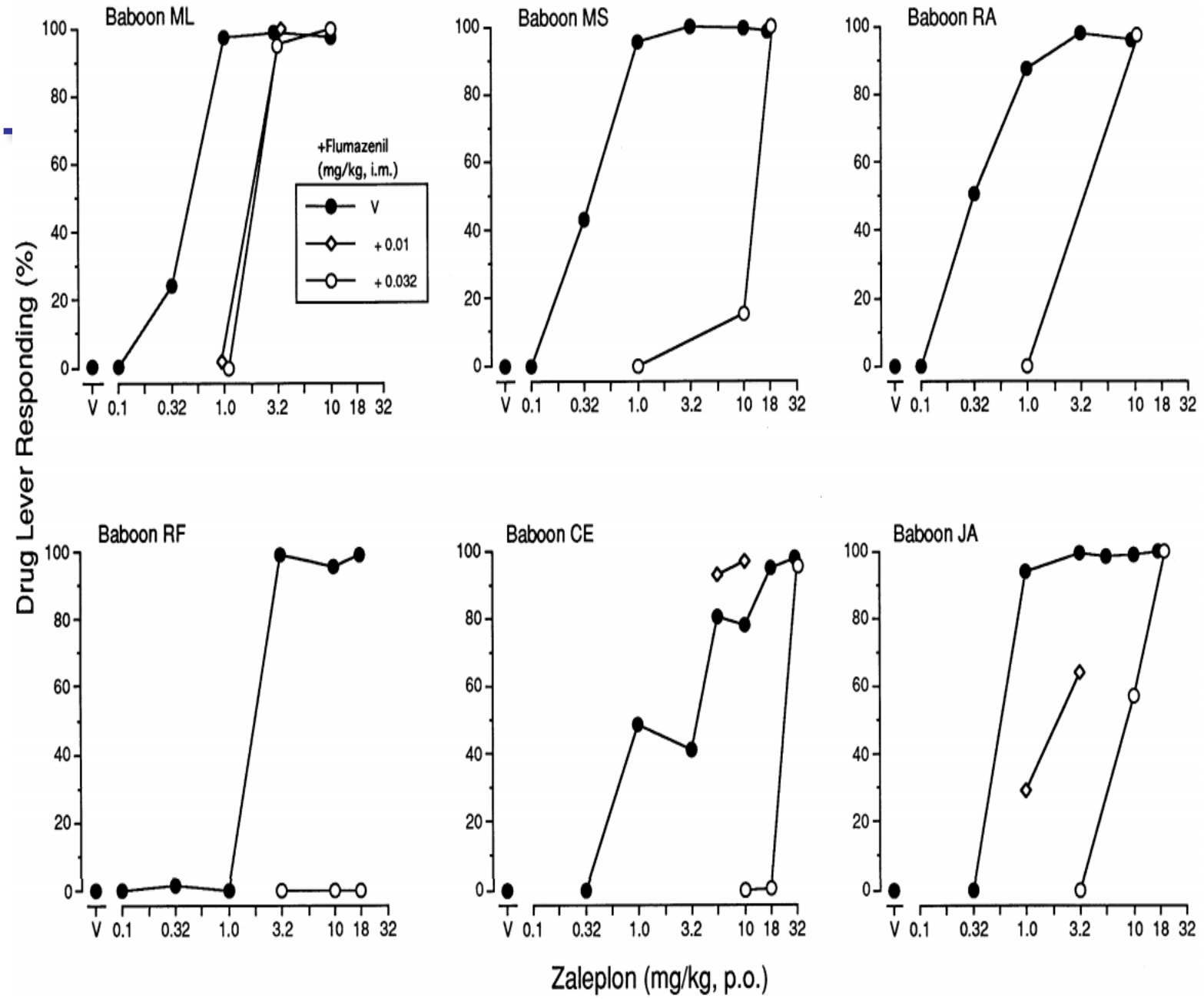
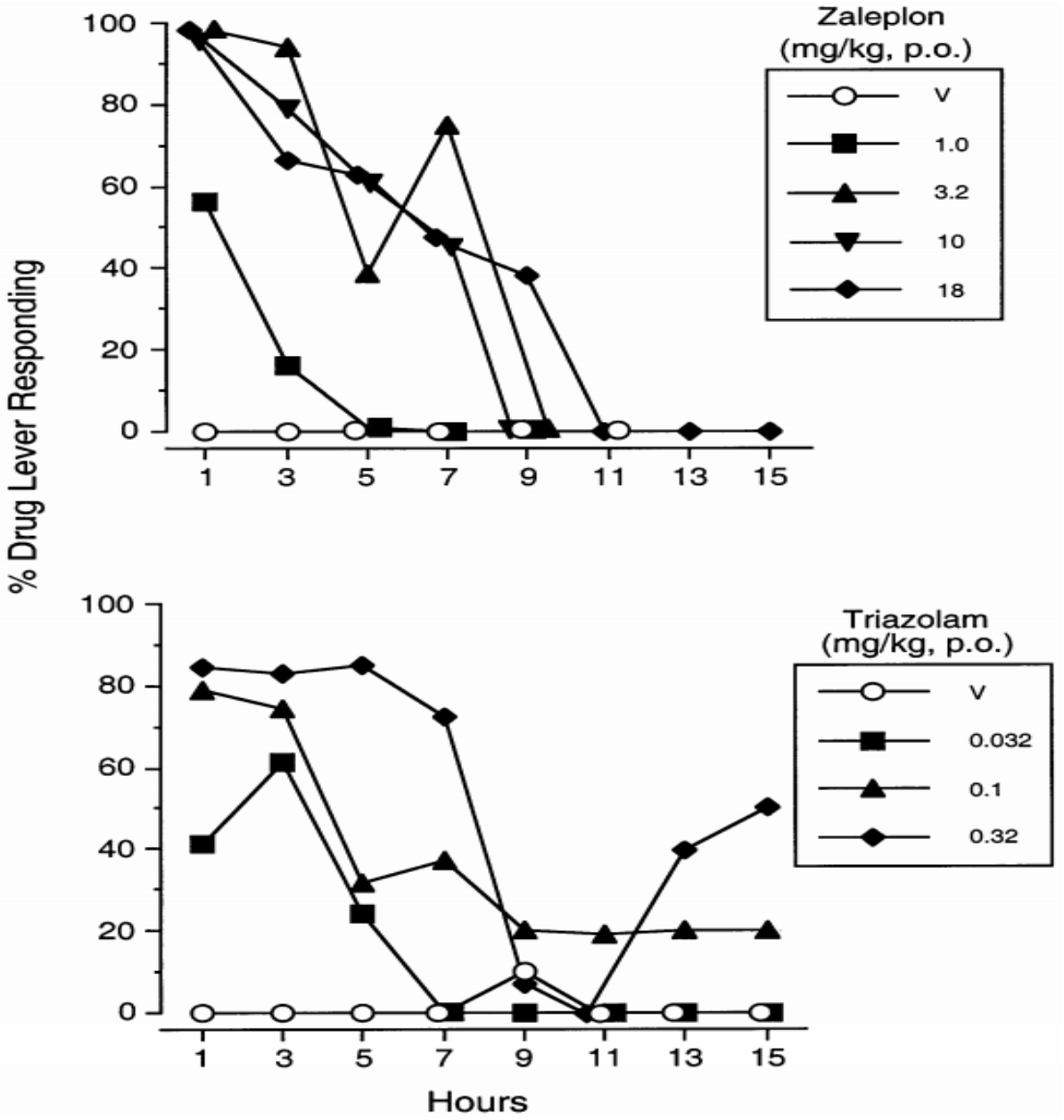


Note emergence of distribution of responses across both levers as flumazenil wore off yet return to virtually 100% lorazepam lever by 6 hr and 100% no-drug responding in the final session the next morning.


Baboon ML
Baboon MS
Baboon RA
Baboon RF
Baboon CE
Baboon JA
+Flumazenil
(mg/kg, i.m.)
V
+ 0.01
+ 0.032
Drug Lever Responding (%)
Zaleplon (mg/kg, p.o.)
V 0.1 0.32 1.0 3.2 10 18 32
0 20 40 60 80 100

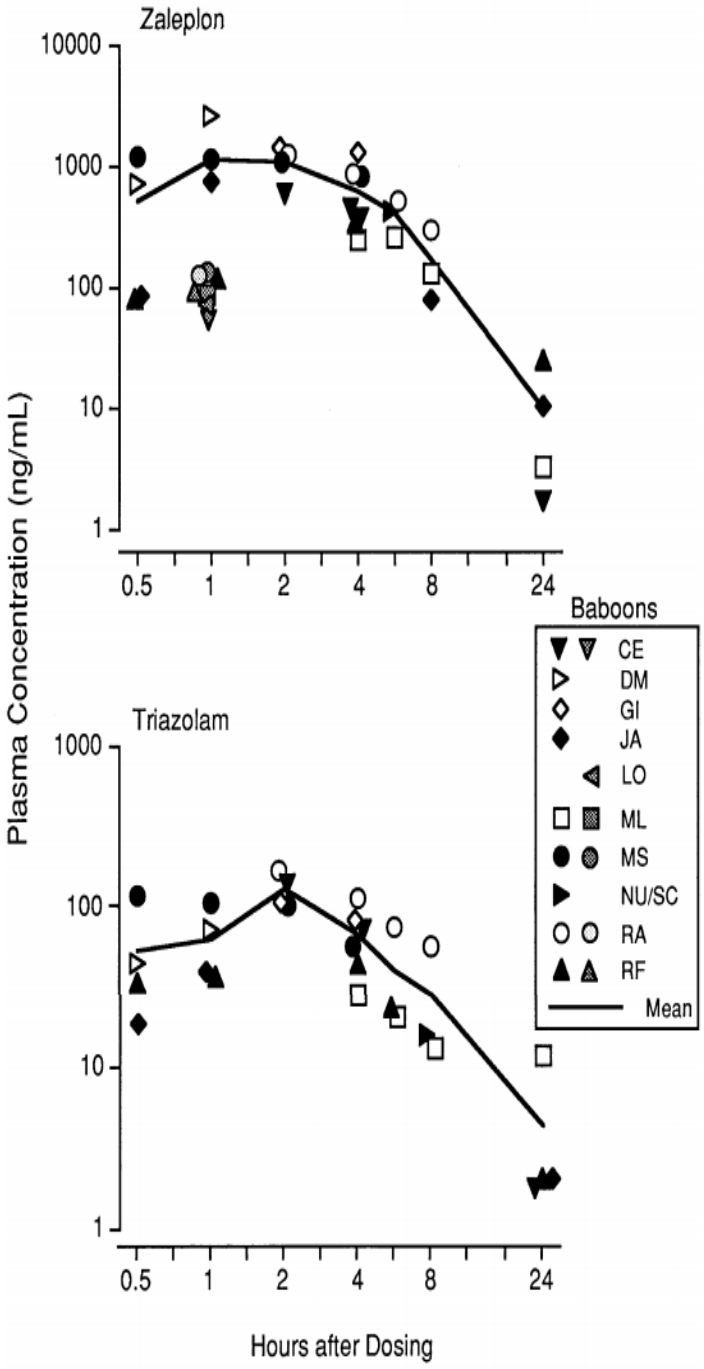
Ator, DAD, 2000

Partial generalization: Time course of effects in lorazepam-trained baboons.

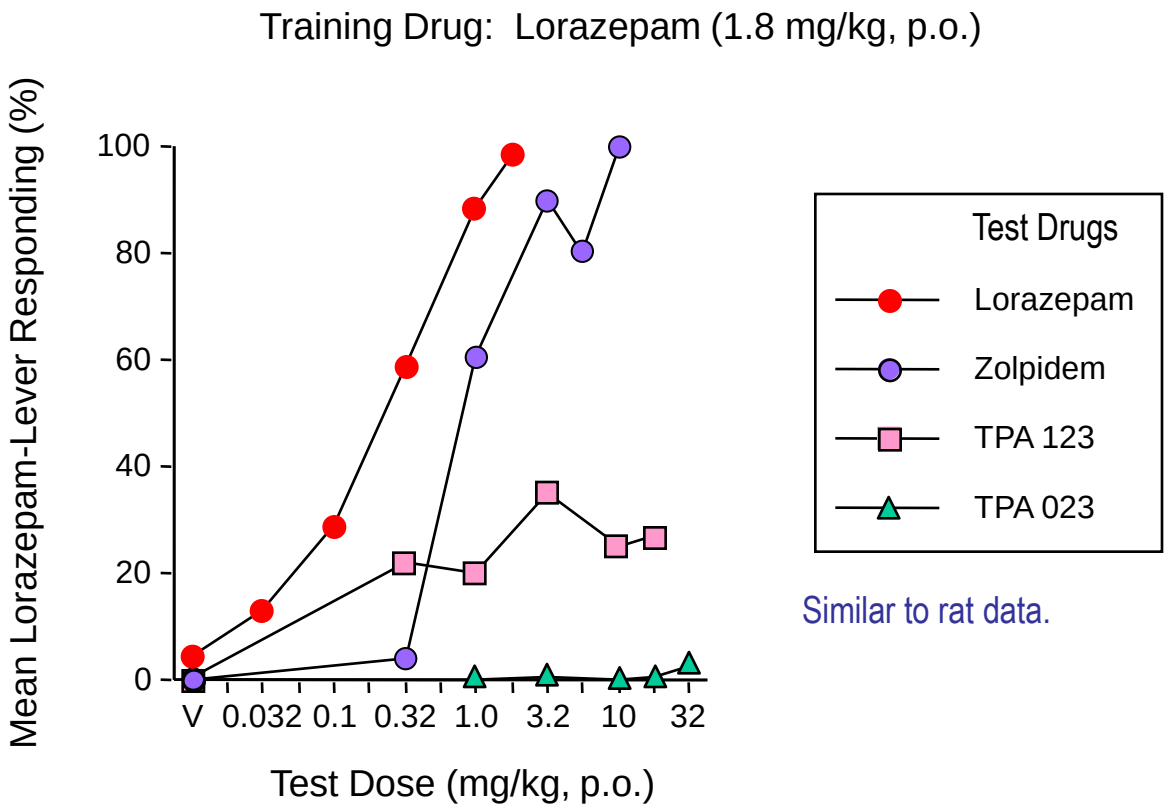


Ator, DAD, 2000

Plasma levels of the drugs in the same baboons as in the previous slide. Discriminative effects seemed to parallel blood levels well.

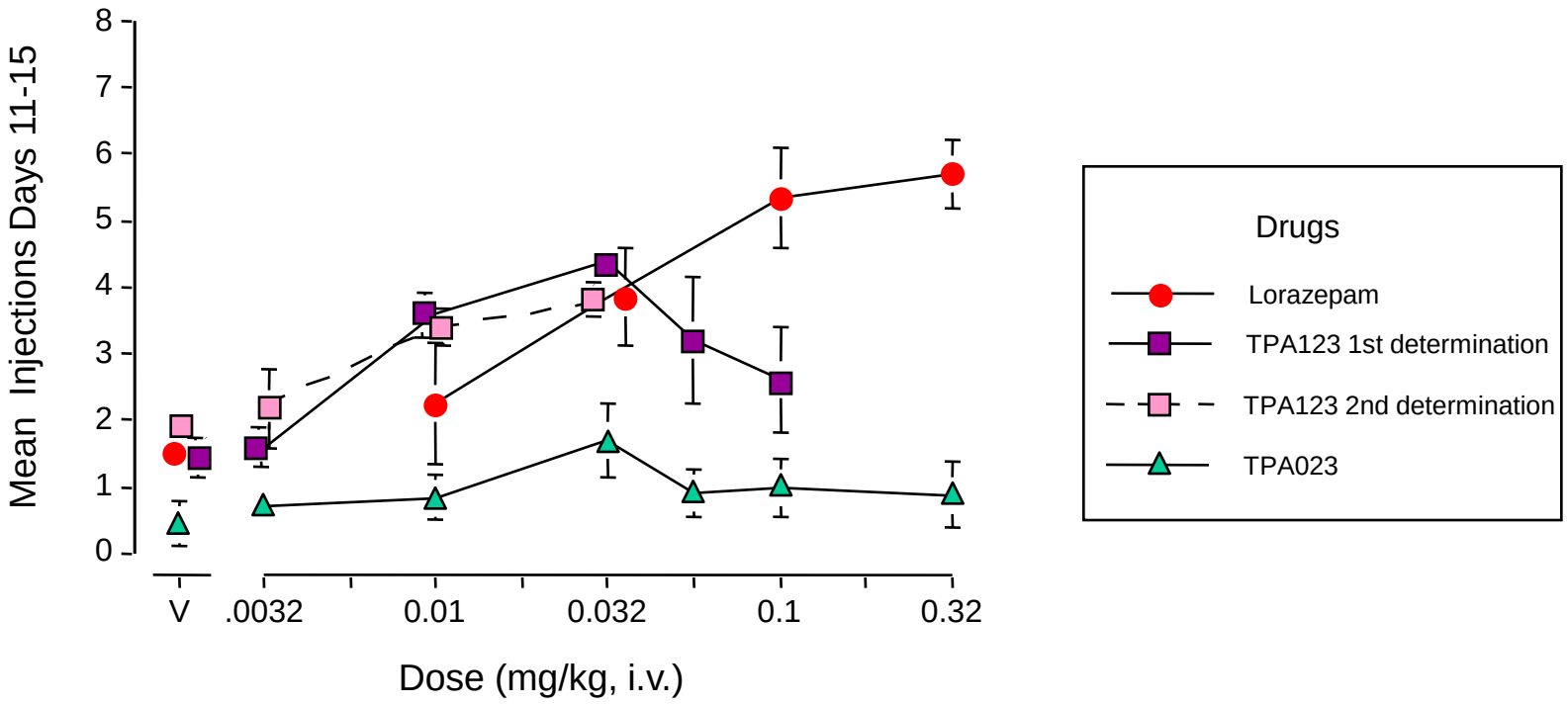


Baboons: Generalization from Lorazepam Training Dose to Other Lorazepam Doses, Zolpidem, TPA 123 and TPA 023

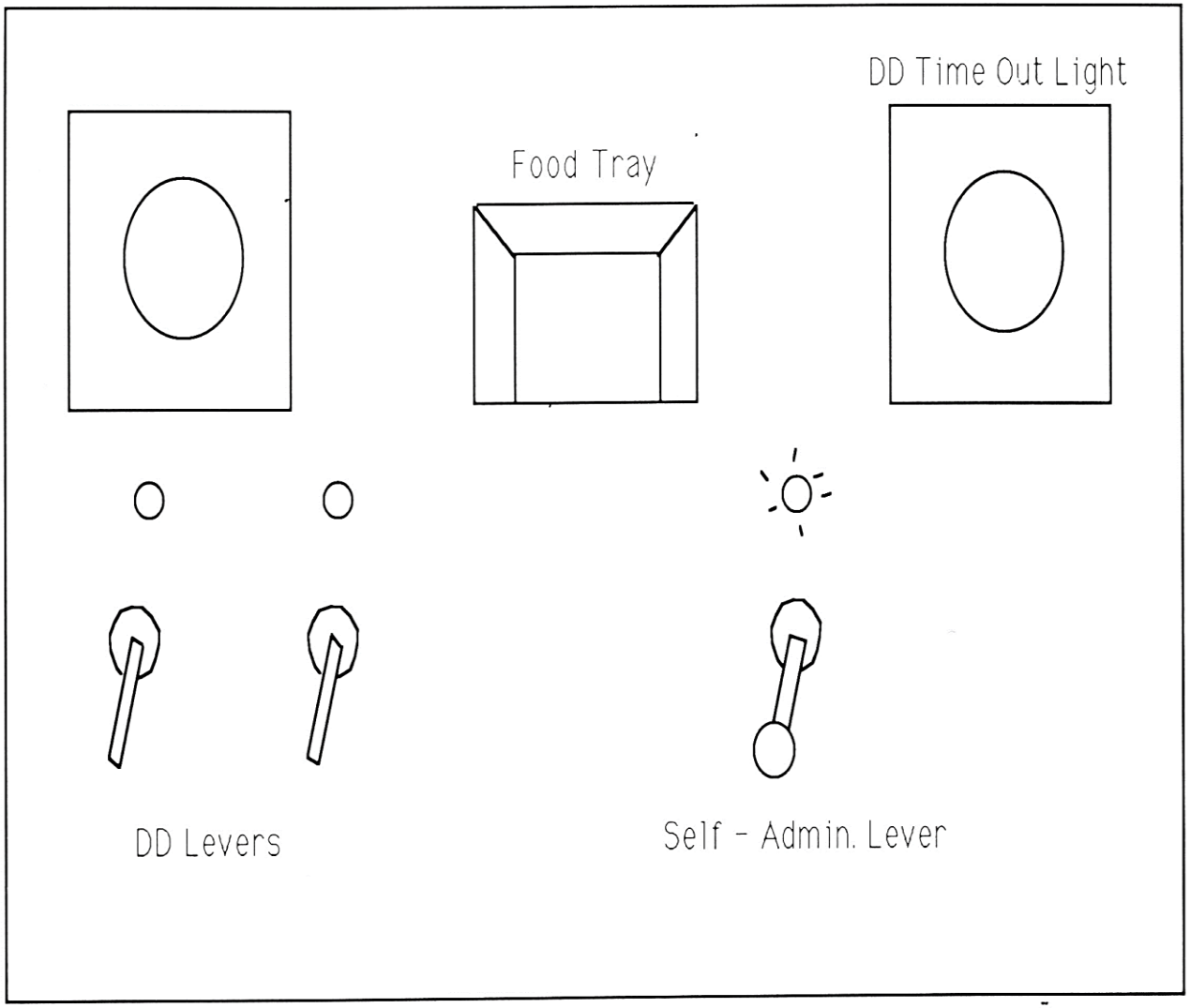


Similar to rat data.

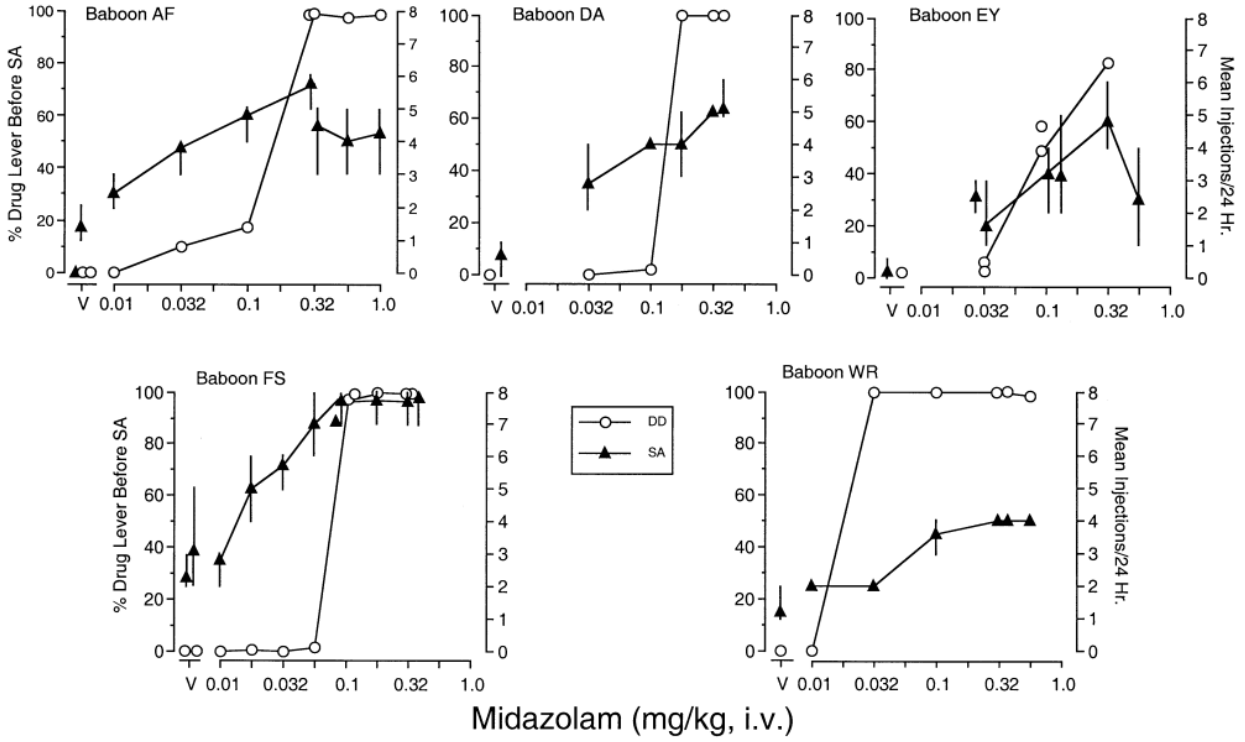
Self-administration of Lorazepam, TPA123, and TPA023 in Baboons



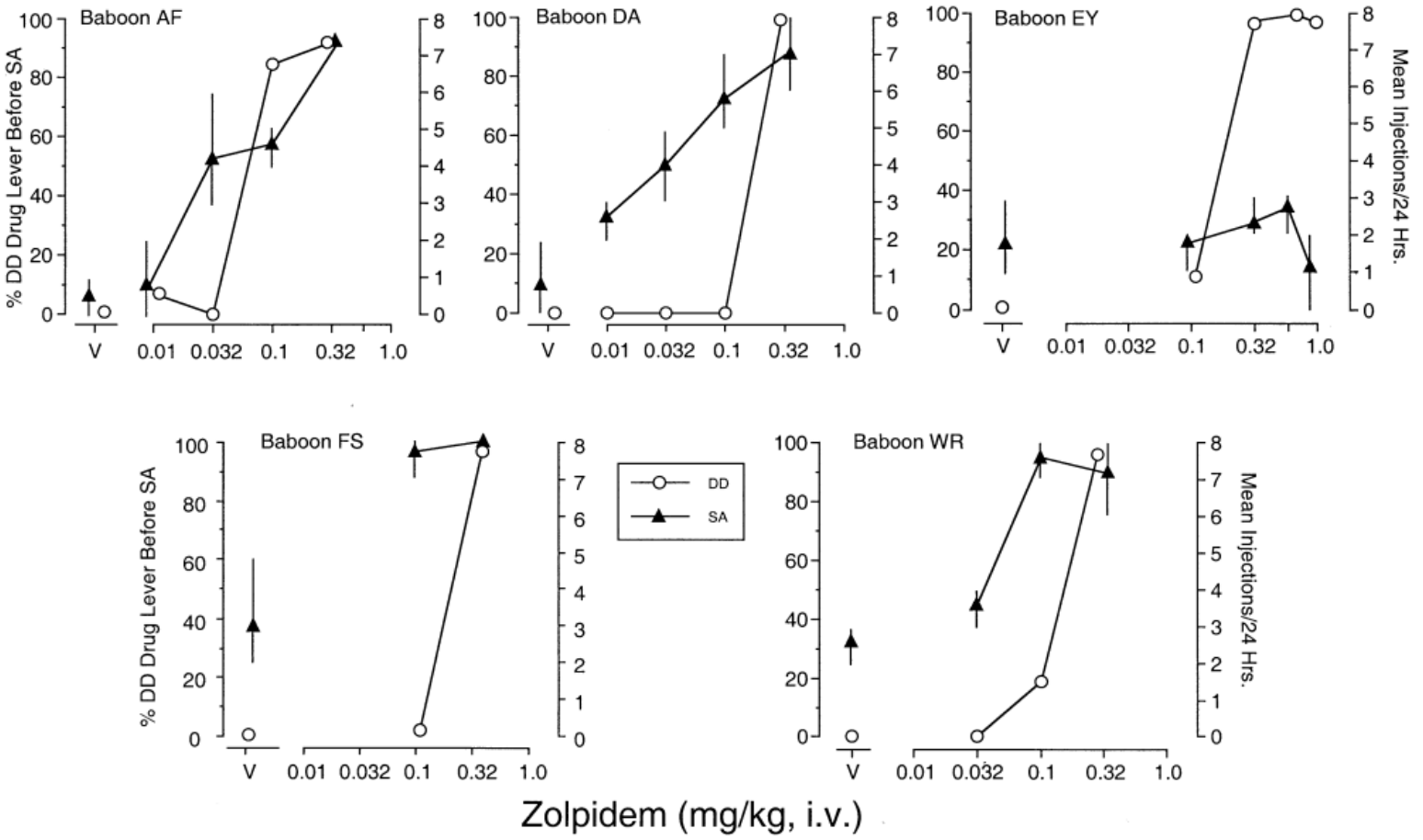
Intelligence panel: Drug Discrimination/Self-administration Study



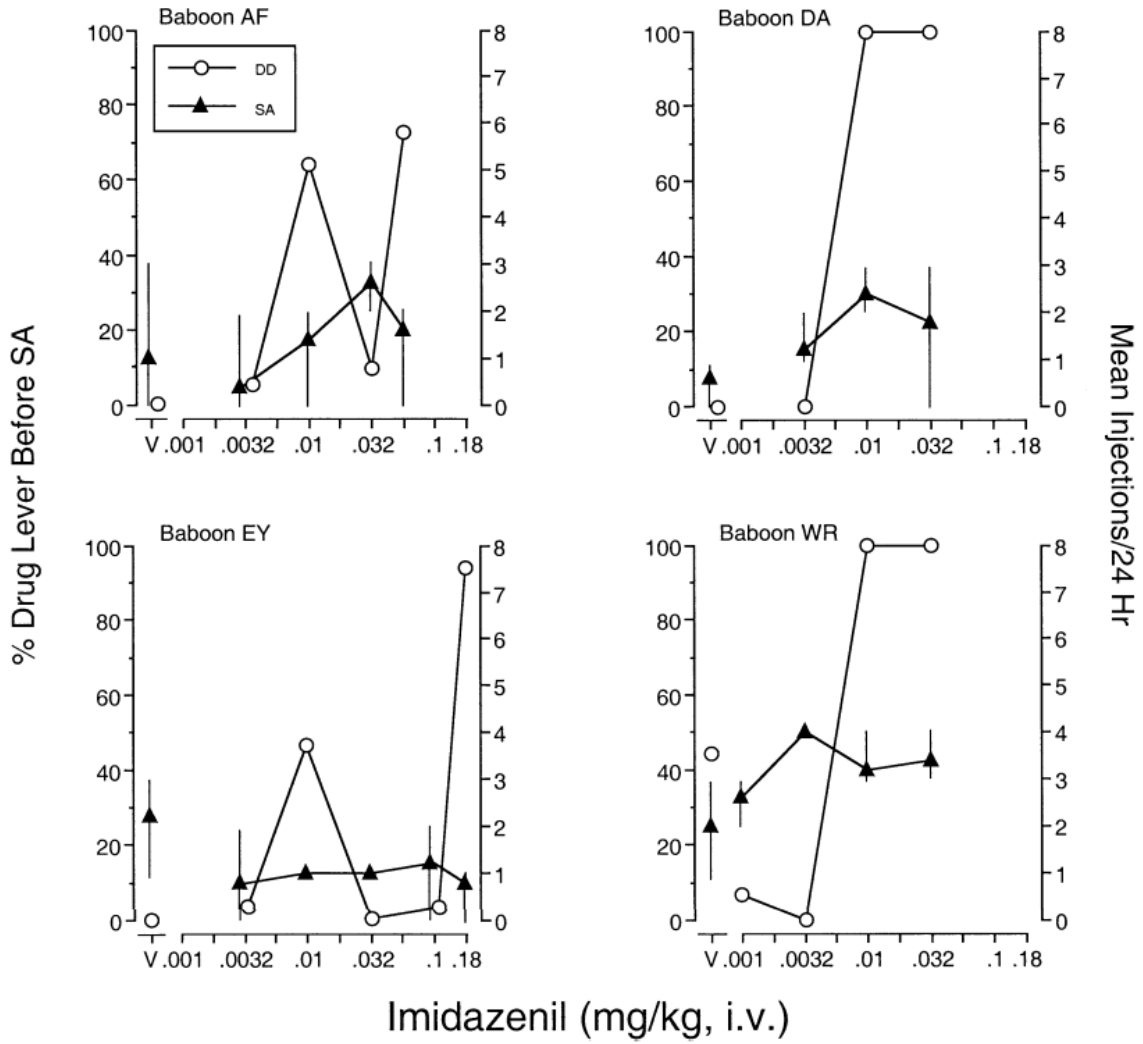
Midazolam DD training: Discriminative and reinforcing effects of midazolam



Midazolam DD training: Discriminative and reinforcing effects of zolpidem



Midazolam DD training: Discriminative and reinforcing effects of imidazenil



Overall Take-away Points

- "Partial generalization" occurs in individual animals at "intermediate" drug doses. (This has parallels to thresholds determinations for auditory and visual stimuli.)
- Well-trained drug discrimination performances can be robust, making the animals valuable "reporters" of whether interoceptive stimulus effects are like those of the training drug or not and for time-course studies in relation to pharmacokinetics.
- Generalization in DD does not "predict" drug reinforcing efficacy.