Virginia Commonwealth University

VCU

ISGIDAR Validation Study

Robert L. Balster and Chris-Ellyn Johanson

Background: The early 1970s

- This effort began in the context of the CPDD testing programs for opioid physical dependence that were in operation at the University of Michigan (Maurice Seevers) and Virginia Commonwealth University (Louis Harris).
- Value of self-administration studies for abuse potential assessment was recognized early by regulators, pharmaceutical company pharmacologists and the scientific community
- Potential for use in regulatory decision making raised the bar for demonstrating the reliability and validity of the approach

VCU

Initial Steps

- Nathan Eddy suggested reliability/validity study at first ISGIDAR organizational meeting in February 1973
- At May 1973 CPDD meeting Bob Schuster agreed to lead this effort
  - Assigned it to Chris-Ellyn Johanson and me

VCU

Initial Steps

- Nathan Eddy suggested reliability/validity study at first ISGIDAR organizational meeting in February 1973
- At May 1973 meeting Bob Schuster agreed to lead this effort
  - Assigned it to Chris-Ellyn Johanson and me
- **Curing 1973 Chris-Ellyn developed form for collection of rhesus monkey self-administration results from all ISGIDAR laboratories**

Reporting laboratory .....
Species: *M. mulatta* ☐ ; other .....
Restraint: chair ☐ ; harness ☐ ; other .....

Investigator(s) .....
Inclusive dates of experiments .....
Environment: cubicle ☐ ; open room ☐ ; other .....

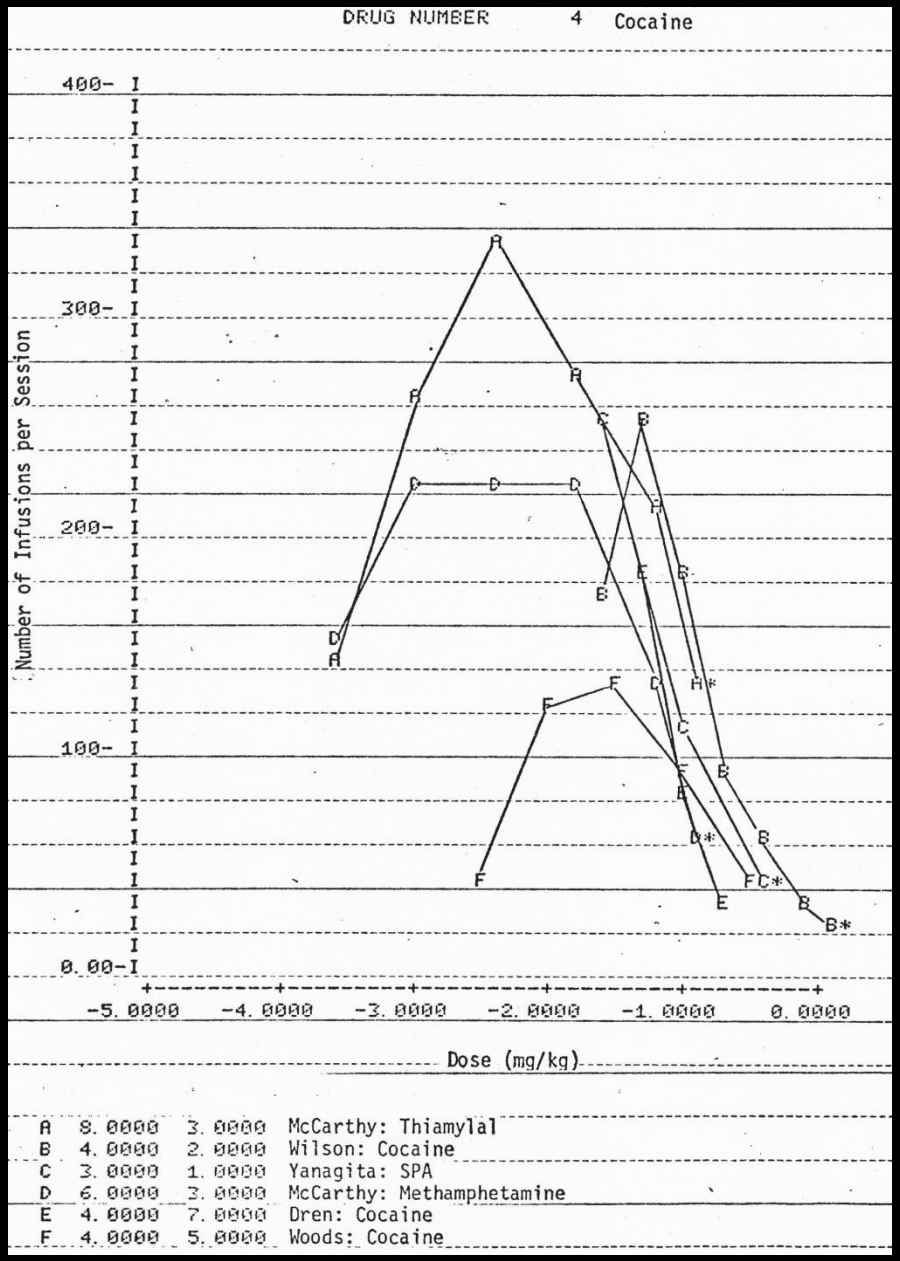
TEST DRUG a	*Drug availability*	*Reinforcement* b	*Unit dose* μ/kg c	*No. of monks*	*Ave No. respon's inj's/session* d	*Error term* e	*No. monks* c + *rate* ∧ f	*Signs and comments*
Test drug	No. of days ..... *Sessions/day* ..... Session length or other criterion(g) ..... Intersession Interval(s)	Schedule Fr ..... Fi ..... Delay(h) ..... Other						
Control Saline Other	No. of days ..... *Sessions/day* ..... Session length or other criterion ..... Intersession Interval(s)	Schedule Fr ..... Fi ..... Delay ..... Other						*Footnotes:*
BASE-LINE DRUG i								
	No. of days ..... *Sessions/day* ..... Session length or other criterion ..... Intersession Interval(s)	Schedule Fr ..... Fi ..... Delay ..... Other						

Sequence(j) of drug presentation (T = Test drug, C = Control, M = Maintenance); ....., ..., ..., ..., ..., ..., ..., ..., ..., ..., ..., ..., (days) or other time units .....
Other than constant sequence(k)-
Were drugs and control values obtained from the same monkeys? ..... Was crossover design used? .....

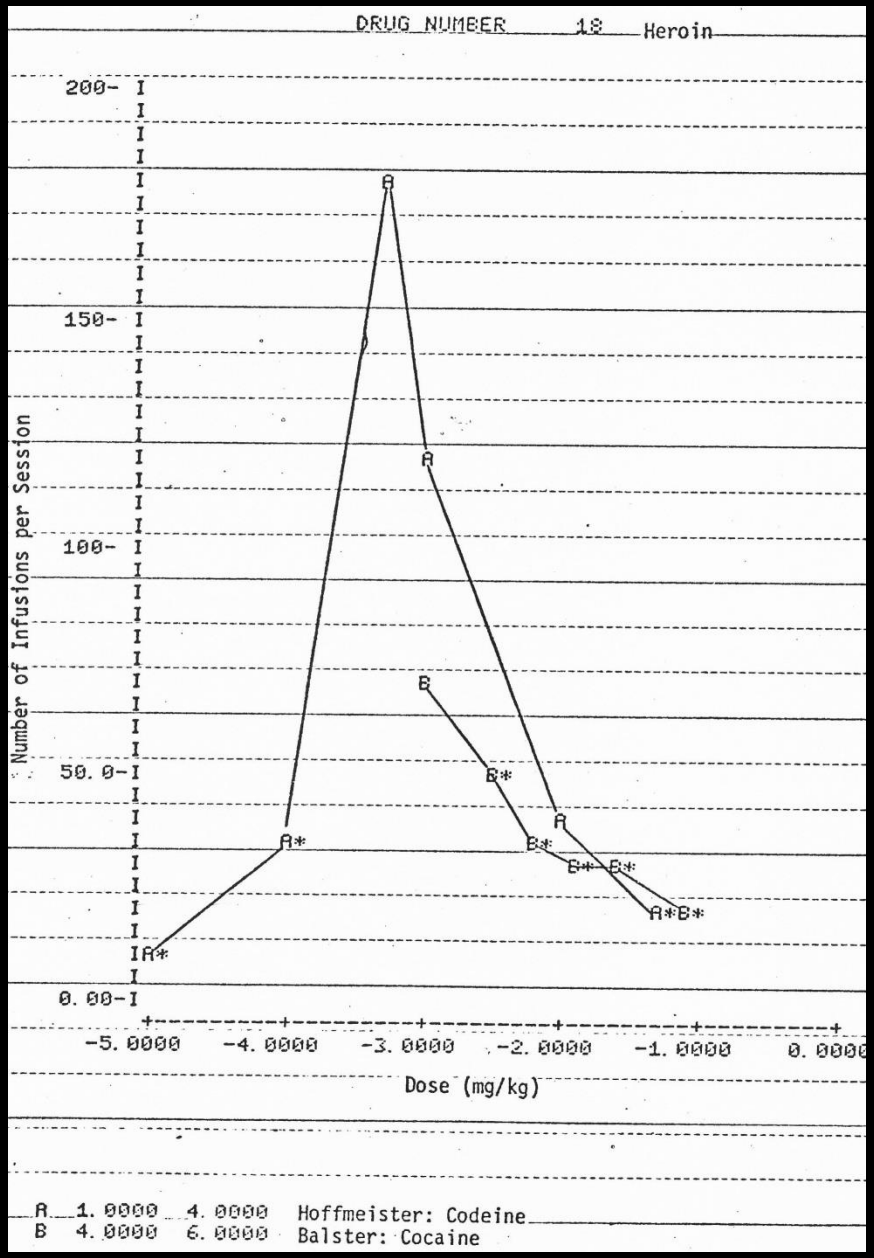
Initial Steps

- Nathan Eddy suggested reliability/validity study at first ISGIDAR organizational meeting in February 1973
- At May 1973 meeting Bob Schuster agreed to lead this effort
- During 1973 Chris-Ellyn developed form for collection of rhesus monkey self-administration results from all ISGIDAR laboratories
- **In November 1973 Chris-Ellyn presented results of substitution testing for 39 drugs for which data had been provided (Available in ISGIDAR Newsletter, Vol. 2, No. 1, February 1974) which showed excellent reliability.**

VCU

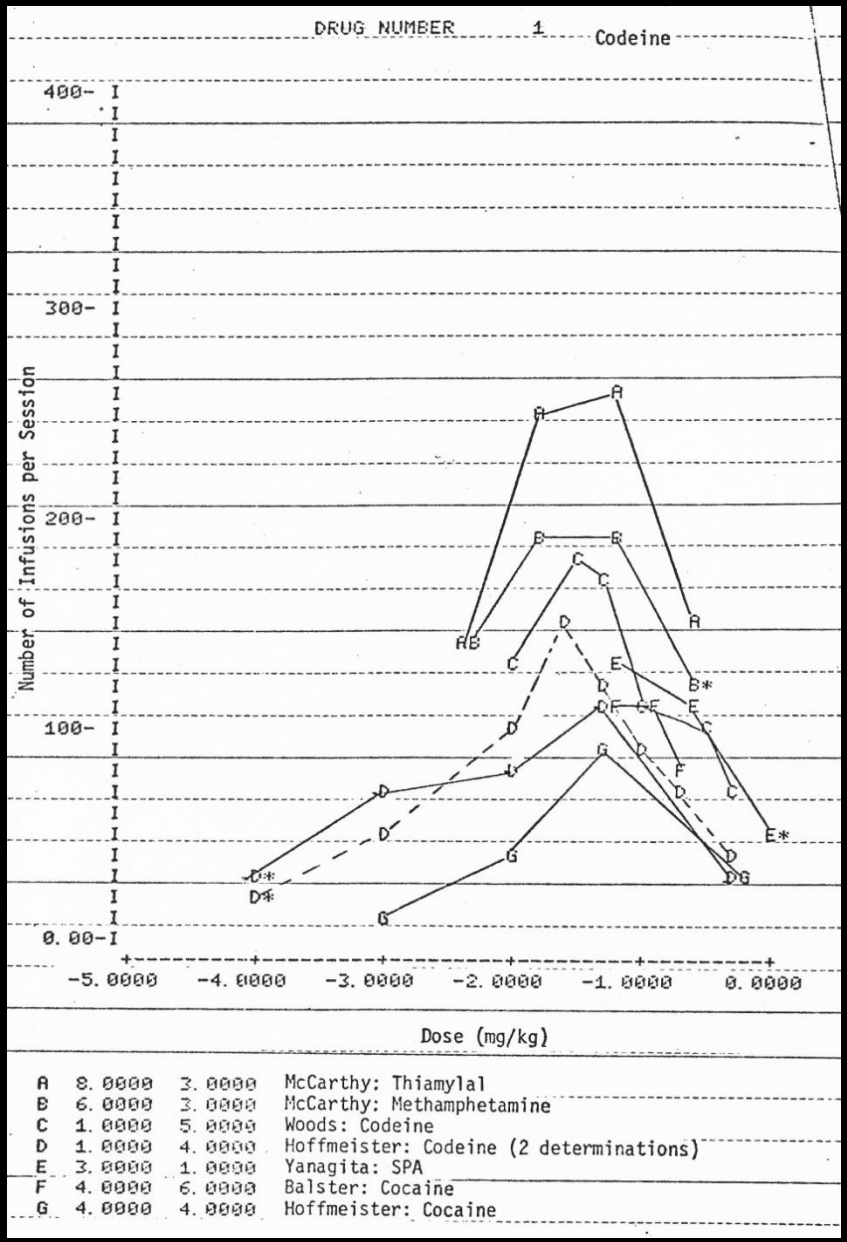


Cocaine testing in different labs with different baseline drugs



Heroin testing in two labs with codeine or cocaine baseline

VCU



Codeine testing in different labs with different baseline drugs

Next Steps

- After seeing preliminary results of ISGIDAR data sharing effort, the Study Group decided in November 1973 to obtain data on some classes of drugs that had not been tested and to send out some of the drugs to investigators blinded to the drug's identity
- In March 1974 at ISGIDAR meeting in Mexico City, negative control compounds were selected for study
  - pyrilamine, atropine and scopolamine, ephedrine, propranalol, pilocarpine, arecoline and physostigmine
- Chris-Ellyn continued to coordinate data collection and reporting and by 1977 or so we were ready to write up the results

VCU

THE FINAL PRODUCT

CE Johanson and RL Balster. A summary of the results of a drug self-administration study using substitution procedures in rhesus monkeys. *Bulletin on Narcotics* 30(3), pp. 43-54, 1978

Method

- Restricted this report to studies using substitution procedures in rhesus moneys where the data were submitted through the ISGIDAR data coordination effort
- Results came from 17 study groups representing 9 different laboratories, including 4 in pharmaceutical companies (Abbott, Smith Kline & French, Parke-Davis, Bayer) and one CRO (Yanagita)
  - Main university labs were in Michigan, Chicago and VCU
- Positive self-administration results were compared with human abuse liability
  - "If more than 50% of the animals self-administered more of the test drug than saline at least at one dose" results were considered positive
  - Criterion variable was authors' subjective assessment of whether the drug was abused or not, probably assisted by Bob Schuster

VCU

Results

- Results provided for over 90 drugs
  - Included most of the “negative controls” that had been assigned
- Tables provided for each class of drug showing drug name, result (Yes or No or Both), testing laboratory and citation (if published)
- Exceptional reliability, only chlordiazepoxide, pentazocine and tilidine showed discordant results between testing sites
- Several of the drugs which were tested were of unknown abuse liability (azidomorphine, etazocine, GPA 1657, N-propyl amphetamine)

Major Conclusion

"Most drugs which maintain responding in animals (*i.e.* are positive reinforcers) are considered drugs of abuse in humans. On the other hand, drugs which do not maintain responding are not abused"

TABLE 4

Central nervous system depressants

Drug (1)	*Result (2)*	*Laboratory (table 6) (3)*	*Reference (table 7) (4)*
Amobarbital	Yes	15	20
Barbital	Yes	15	20
Chlordiazepoxide	Yes	8	
Chlordiazepoxide	No	9	
Ethanol	Yes	8	
Flurazepam	Yes	6	
Methohexital	Yes	15	20
Pentobarbital	Yes	6, 8, 9, 10, 15, 17	20
Thiamylal	Yes	9	
Thiopental	Yes	6, 15	20

TABLE 5

Other drugs

Drug (1)	*Result* (2)	*Laboratory (table 6)* (3)	*Reference (table 7)* (4)
Antidepressants			
Amitryptiline	No	10	
Imipramine	No	10, 17	7, 27
Major tranquillizers			
Chlorpromazine	No	10, 15	7, 8
Haloperidol	No	10, 15	
Perphenazine	No	10, 11	13
Trazodone	No	9	
Hallucinogens			
LSD	No	10	
Mescaline	No	10	
STP	No	10, 17	
Δ9-THC	No	5, 17	6, 29
Miscellaneous			
Arecoline	No	9	
Chloroprocaine	Yes	11	
Dexoxadrol	No	15	
Diphenhydramine	Yes	9	
Ditran	No	10	
Ketamine	Yes	9	15
Nicotine	No	9, 17	24
Phencyclidine	Yes	3	1
Pilocarpine	No	9	
Procaine	Yes	7, 11, 14	4
Proparacaine	No	11	
Propranalol	No	9, 10	
Pyrilamine	Yes	12	
Scopolamine	No	1	

Table I. *Relationship between clinical evaluations of morphine-like signs, symptoms, and subjective effects, and animal drug self-administration results**

Animal drug self-administration	*Morphine-like signs, symptoms, and subjective effects in man*		
	No	*Equivocal*	*Yes*
Yes	Dextromethorphan	Butorphanol Nalbuphine	*l*-α-acetylmethadol (LAAM) Azidomorphine Buprenorphine Codeine α-(-)-Etazocine Etonitazine Etorphine Fentanyl (-)-2,9β-dimethyl-2′-hydroxy-5-phenyl-6,7-benzomorphan (NIH 8240) Heroin Ketobemidone Levomethorphan Levorphanol Meperidine Methadone Morphine Oxymorphone Profadol Propiram *d*-Propoxyphene HCl *d*-Propoxyphene napsylate
Equivocal		Pentazocine	Tilidine
No	Cyclazocine Dextrorphan Ethoheptazine Levallorphan Nalorphine Naloxone Naltrexone		

Griffiths, R.R. and Balster, R.L. Opioids: Similarity between evaluations of subjective effects and animal self-administration results. Clinical Pharmacology and Therapeutics **25**:611-617, 1979.

VCU

Main Conclusion

Taken together, results of ISGIDAR validity and reliability study were important in establishing i.v. self-administration procedures as useful for abuse-liability assessment.

Another Outcome