NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Discovering And Developing Drugs To Treat Addictions: From Models To Medicines

Phil Skolnick, Ph.D., D.Sc. (hon.)

Director, Division of Pharmacotherapies and Medical Consequences of Drug Abuse

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

The Gains In Medications To Treat SUDs Are Incremental

Bloomberg

Titan's Implanted Addiction-Drug Device Works Better Than Placebo in Study

By Nicole Ostrow - Oct 12, 2010

Titan Pharmaceuticals Inc.'s implanted drug-delivery device helped people fight addiction to heroin and prescription painkillers better than a placebo, a company-funded study found.

The Titan product, shaped like an inch-long match-stick, is implanted under the skin and delivers continuously the drug buprenorphine. Patients implanted with the device showed they were free of illegal opiates in about 40 percent of urine tests in the first 16 weeks, compared with 28 percent of those getting the placebo implant. People on the drug had fewer withdrawal symptoms, according to research published today.

The experimental device, Probuphine, is designed to help addicts who either skip or forget to take doses of buprenorphine, a medicine that reduces craving for opioids and symptoms of withdrawal. The study represents the third of three phases of tests generally required for U.S. Food and Drug Administration approval. Titan plans to seek clearance of Probuphine in the U.S. and Europe.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Why Haven't We Been More Successful At Developing Medications To Treat Addictions ?

- Historically, big pharma has not embraced developing medications to treat addictions*

(*with the exception of nicotine)

Some of the factors often cited for this indifference:

-Cost of developing an NCE (current estimates: a bit south of $2BB including cost of capital)

-Perceived small market size (translates to return on investment)
Suboxone sales (2009) of >$750,000,000 belie this perception

-Difficulties in executing a clinical trial campaign using patients with SUDs (often many comorbid conditions + lifestyle issues)

-Stigma associated with addiction to illegal substances

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

SUDs: Not rare, but "neglected"

- There are no approved medications to treat addictions to :

-Cocaine

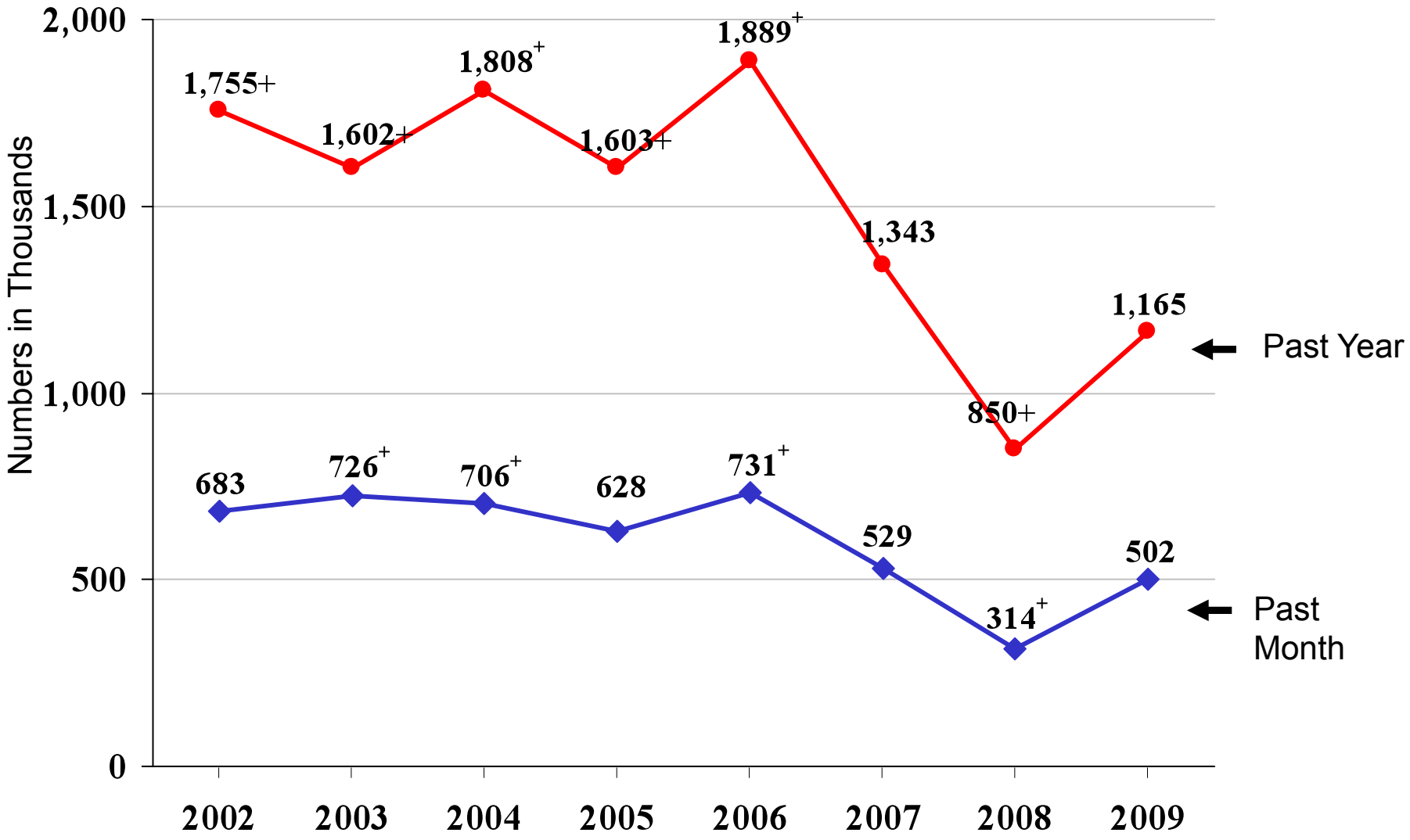
-Methamphetamine

-Cannabis

Addiction to these substances is a serious public health issue

NIDA
NATIONAL INSTITUTE ON DRUG ABUSE

Past Year and Past Month Users of Methamphetamine among Persons Aged 12 or Older: 2002-2009



+ ***Difference between this estimate and the 2009 estimate is statistically significant at the .05 level.***

SAMHSA (2010). Results from the 2009National Survey on Drug Use and Health: Volume I. Summary of National Findings (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4586Findings). Rockville, MD.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Developing Pharmacotherapies to Treat Methamphetamine : Economic Perspectives

Cost Contributors	Cost of Meth Use in the United States in 2005 (millions of dollars)			
	Lower Bound	Best Estimate		Upper Bound
	n	n	%	n
Intangibles/premature death	12,514	16,625	71	28,549
Crime and criminal justice	2,578	4,210	18	15,741
Child endangerment	312	905	4	1,166
Lost productivity	379	687	3	1,055
Drug treatment	299	546	2	1,071
Health care	116	351	2	611
Meth production/hazards	39	61	< 1	89
Total	16,237	23,384	100	48,281

NOTE: Because of rounding, numbers may not sum precisely.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Why Haven't We Been More Successful At Developing Medications To Treat Addictions ?

-**Recent mergers (e.g. Pfizer/Wyeth, Schering-Plough/Merck) have resulted in a consolidation (read: net loss) of programs, including CNS.**

-Several big pharmas (GSK, A/Z) have dropped discovery medicine programs in psychiatry .

-Both a reduction in the number of potential partners AND lack of enthusiasm for drugs to treat psychiatric disorders dampens enthusiasm for investment in CNS based startups/biotechs, often the drivers of innovation.

The Current Probability of Success in Developing Drugs to Treat CNS Disorders Is Dismal

Lead	C.C.	Ph. I	Ph . II	Ph. III	NDA
3% →	8% →	17% →	25% →	59% →	85%

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Pharma Retrenchment Will Affect The SUD Pipeline

-Most molecules that we explore are “repurposed” – with the cutback in psychiatry R&D, many promising early –mid stage molecules will not be developed.

-The upside: there may be a bumper crop of mid-stage molecules in the near-intermediate term.

-The trend away psychiatry research in big pharma will have a **negative, trickle-down** effect on CNS focused biotech/small pharma, since there are fewer “end game” (licensing) partners.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

THERAPEUTIC STRATEGIES TO TREAT SUDs

- Replacement/Substitution (e.g. methadone, buprenorphine, nicotine)
- Magic Bullets and Arrows (e.g. cocaine vaccine; nicotine vaccine; mAbs to methamphetamine; engineered cocaine esterases)
- New Age [targets developed because of a better understanding of the neuroscience of addiction] (e.g. mGluR5 antagonists, 5HT2C agonists, D3 antagonists)

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Many Putative Targets To Treat SUDs Have Been Identified

-Kappa opioid receptor antagonists

-Dopamine (D_3) receptor antagonists

-$5HT_{2A}$ receptor antagonists

-$5HT_{2C}$ receptor agonists

-$mGluR_5$ receptor antagonists

-CRH_1 antagonists

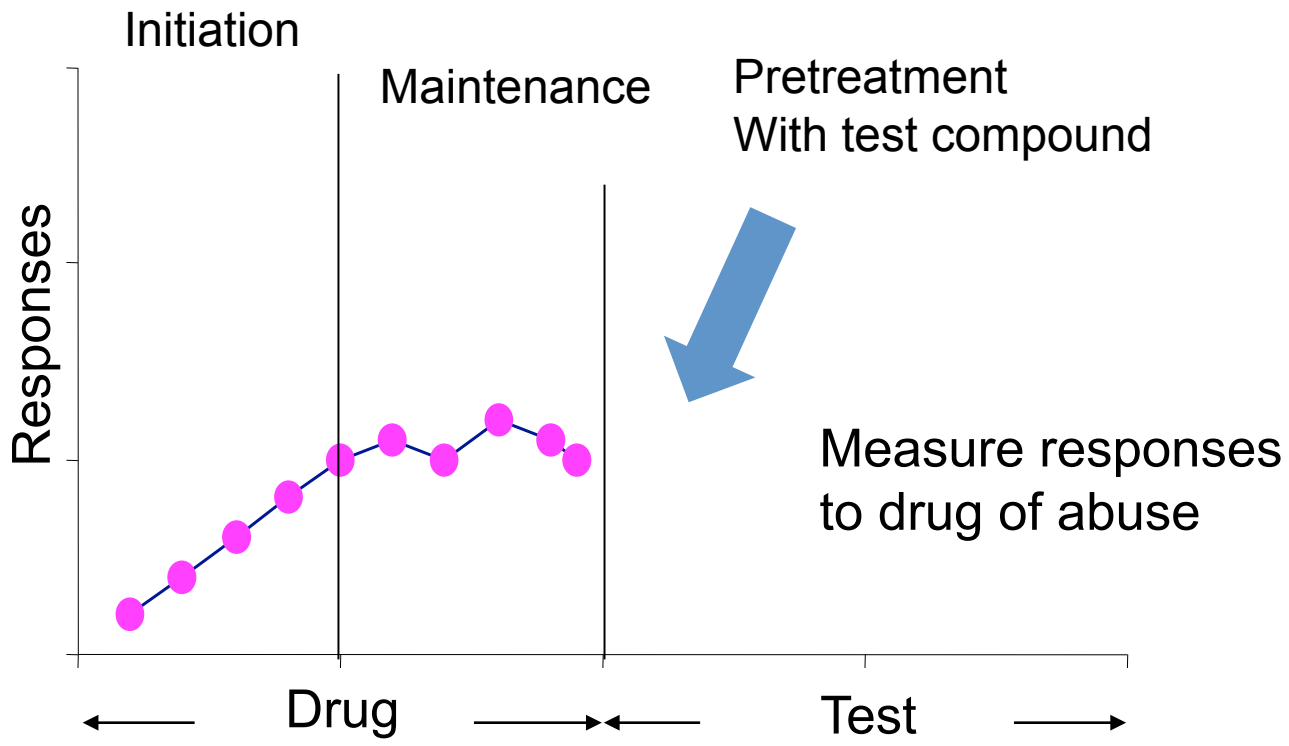
-FAAH inhibitors

-Orexin antagonists

Compounds acting at several of these targets may be effective against multiple drugs of abuse

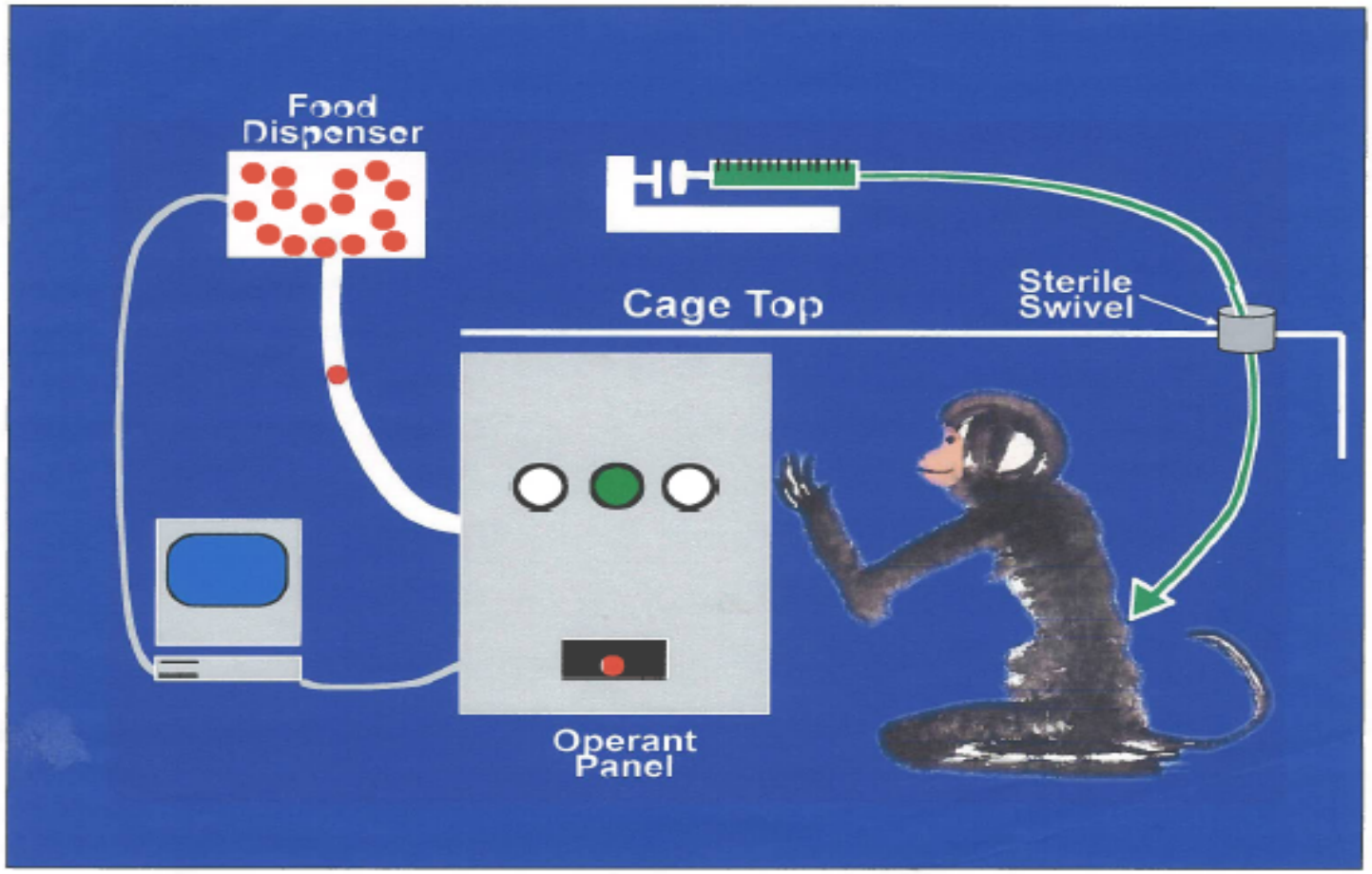
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Drug Self-Administration models



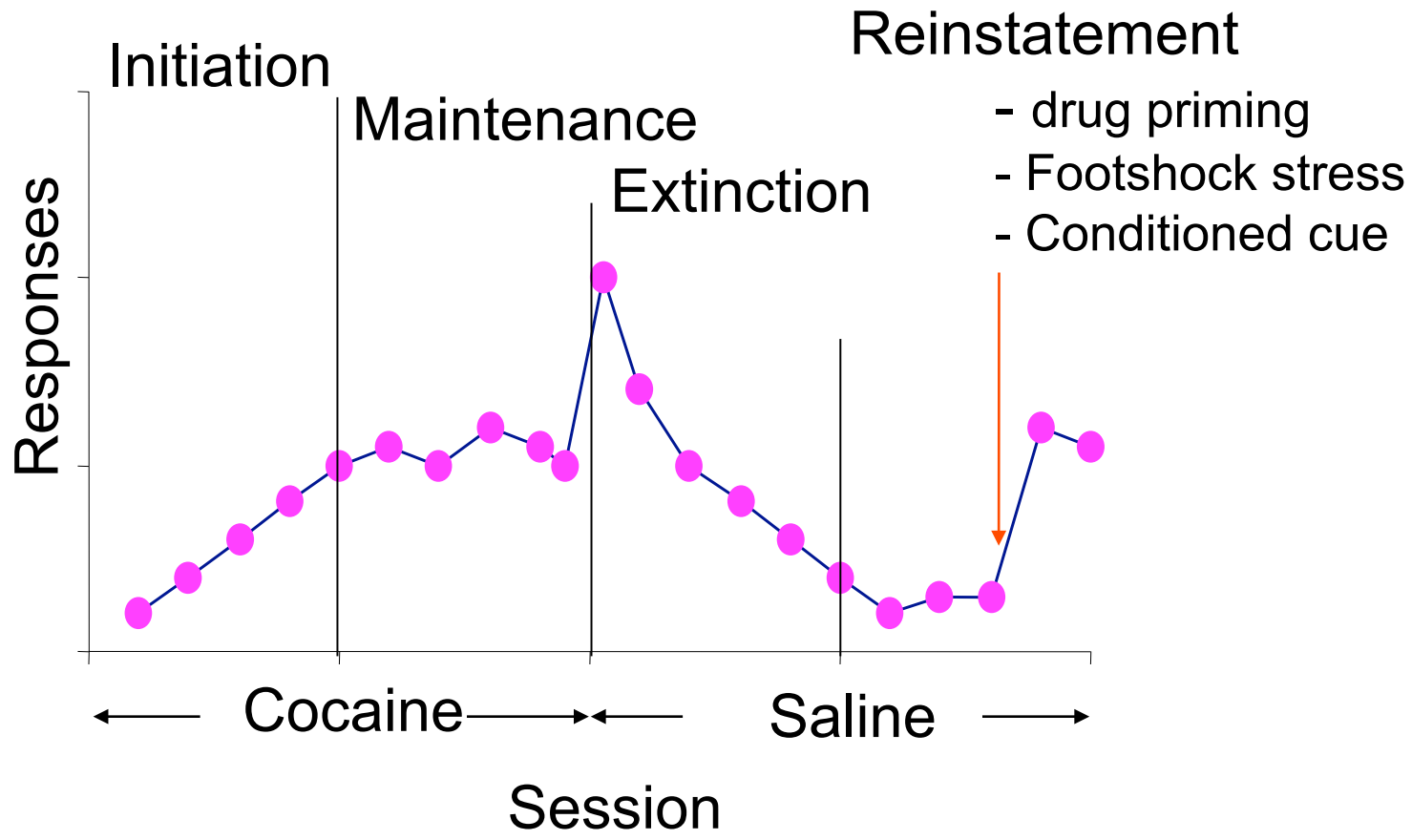
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Putative Anti-addictive Medications Can Be Examined in Primates (or Rodents)



NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Reinstatement models



Adapted from Erb, Shaham and Stewart, 1996

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Many Putative Targets Have Been Identified Based On Preclinical Studies

-Kappa opioid receptor antagonists

-**Dopamine (D_3) receptor antagonists**

-$5HT_{2A}$ receptor antagonists

-$5HT_{2C}$ receptor agonists

-$mGluR_5$ receptor antagonists

-CRH_1 antagonists

-FAAH inhibitors

-Orexin antagonists

Compounds acting at several of these targets may be effective against multiple drugs of abuse

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Current perspectives on selective dopamine D_3 receptor antagonists as pharmacotherapeutics for addictions and related disorders

Christian A. Heidbreder[1] and Amy H. Newman[2]

[1]Reckitt Benckiser Pharmaceuticals, Global Research & Development, Richmond, Virginia, USA. [2]National Institute on Drug Abuse, Medicinal Chemistry Section, Intramural Research Program, Baltimore, Maryland, USA

Address for correspondence: Christian A. Heidbreder, Reckitt Benckiser Pharmaceuticals, Global Research & Development, 10710 Midlothian Turnpike, Ste. 430, Richmond, VA 23235. Voice: 804-594-4456; fax: 804-379-1215. christian.heidbreder@reckittbenckiser.com

(2009)

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Buspirone - (D3 antagonist +)

- First marketed as Buspar by Bristol Myers-Squibb (1980s)

- Approved for the management of anxiety disorders (proposed mechanism: $5HT_{1A}$ receptor partial agonist)

- Despite low efficacy and delayed onset compared to benzodiazepines, gained market share because it did not produce bz-like side effects (muscle relaxation = hip fractures in elderly) and is not DEA scheduled (no abuse liability).

- Now available as generic

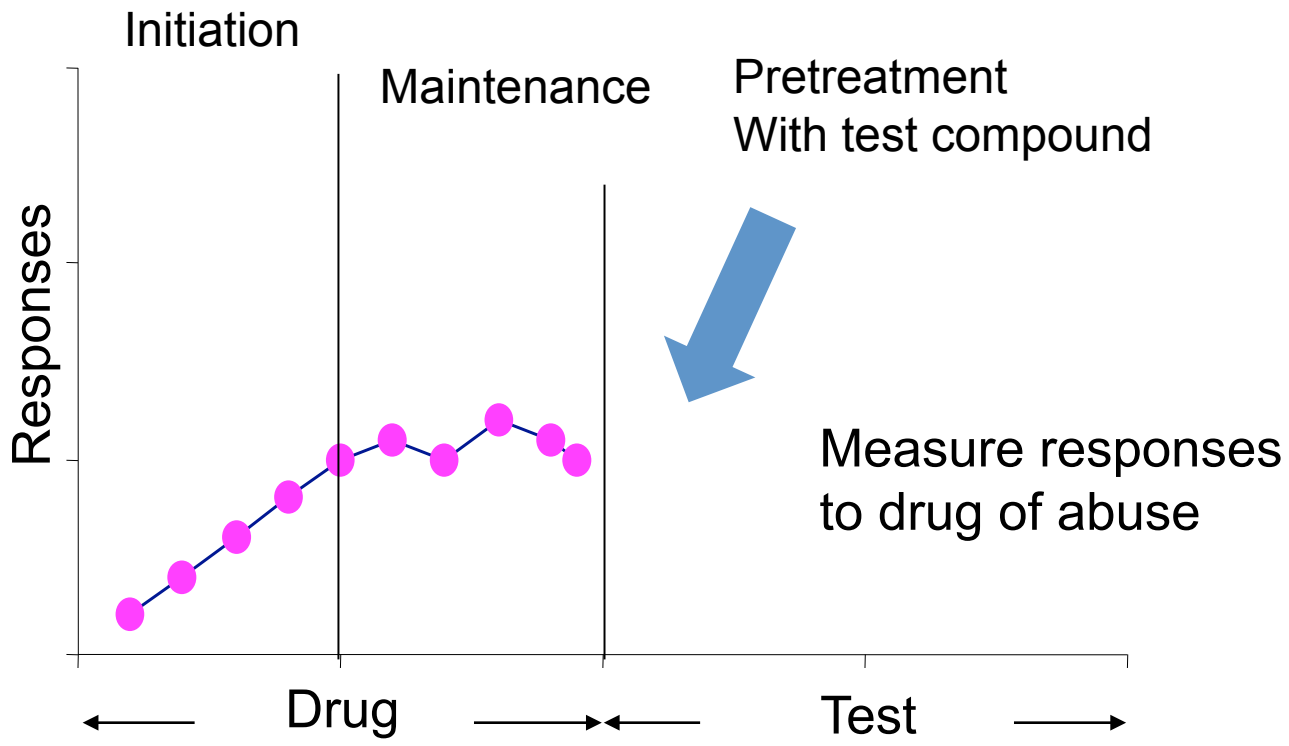
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Buspirone Is A D3 Receptor Antagonist

	Binding (Ki)	Functional Potency (IC50 or EC50)	Efficacy	Kula et al, 1994
5HT1A	15	98←	Partial Agonist	
D1	>10,000			
D2		49	Partial agonist	Ki=260 nM
D3	**35**	**8.6←**	**Antagonist**	**Ki=3.5 nM**
D4	Not determined			

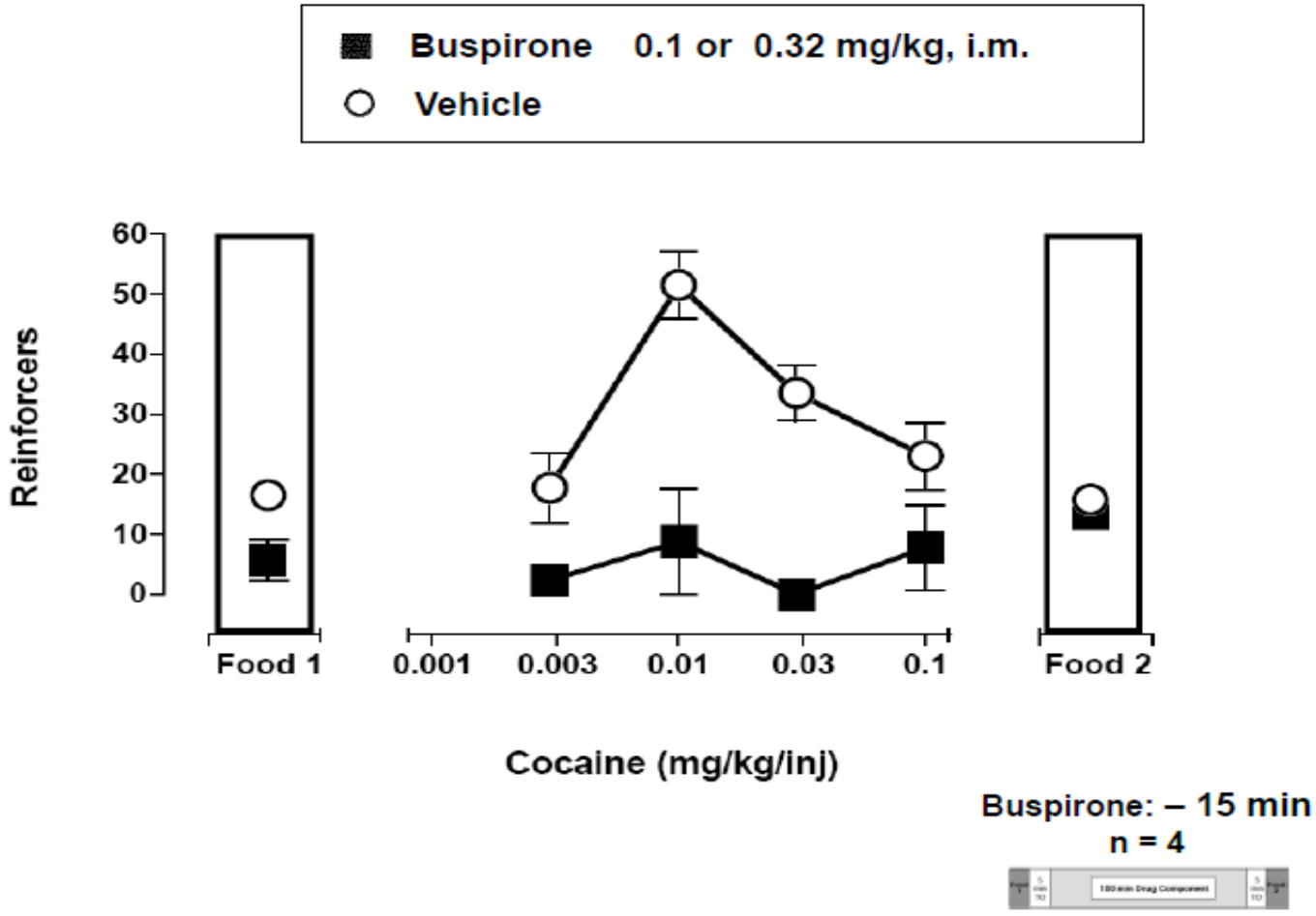
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Drug Self-Administration models



NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Buspirone Reduces Cocaine SA In Rhesus Monkeys

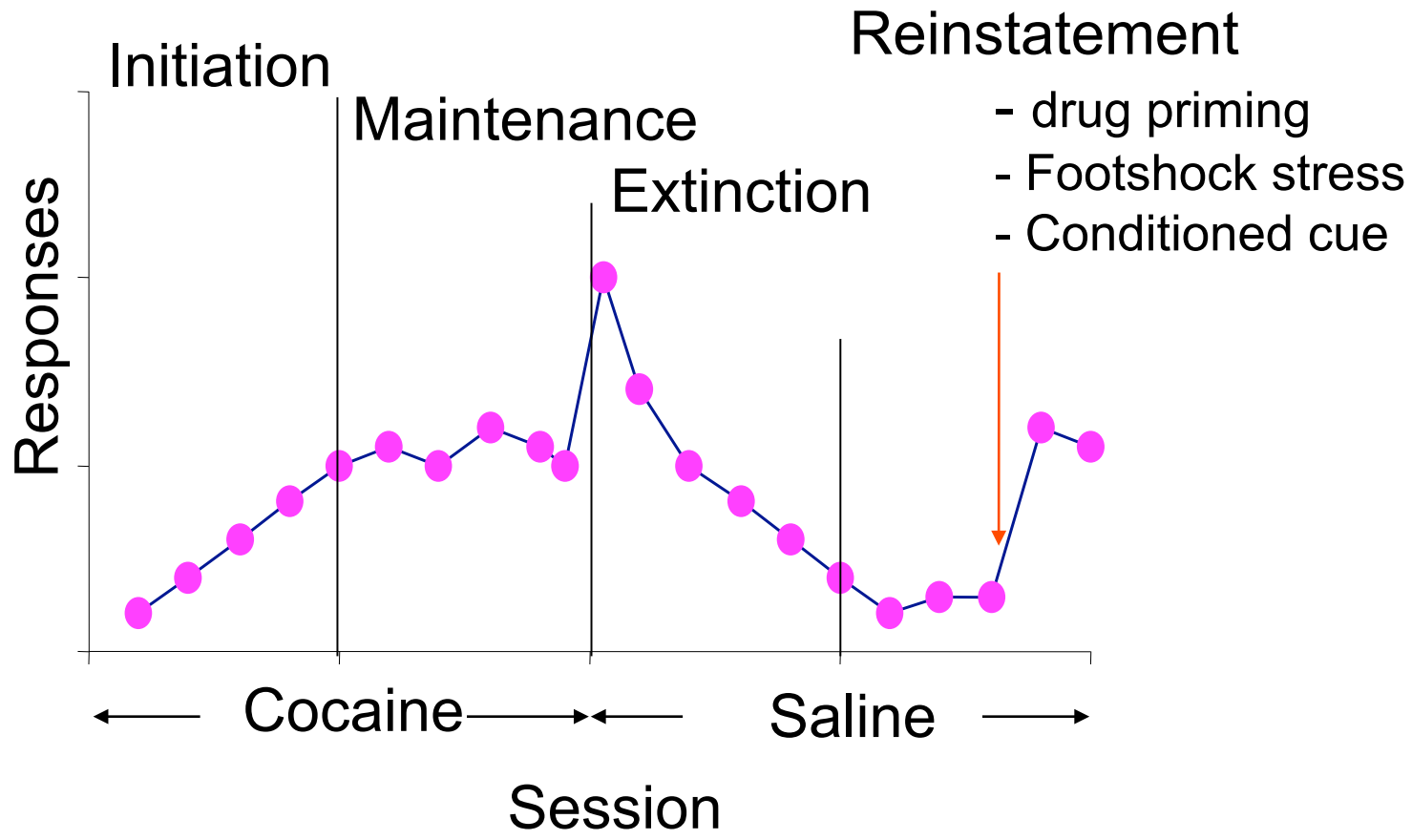


Buspirone: – 15 min
n = 4

N. Mello, et al.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

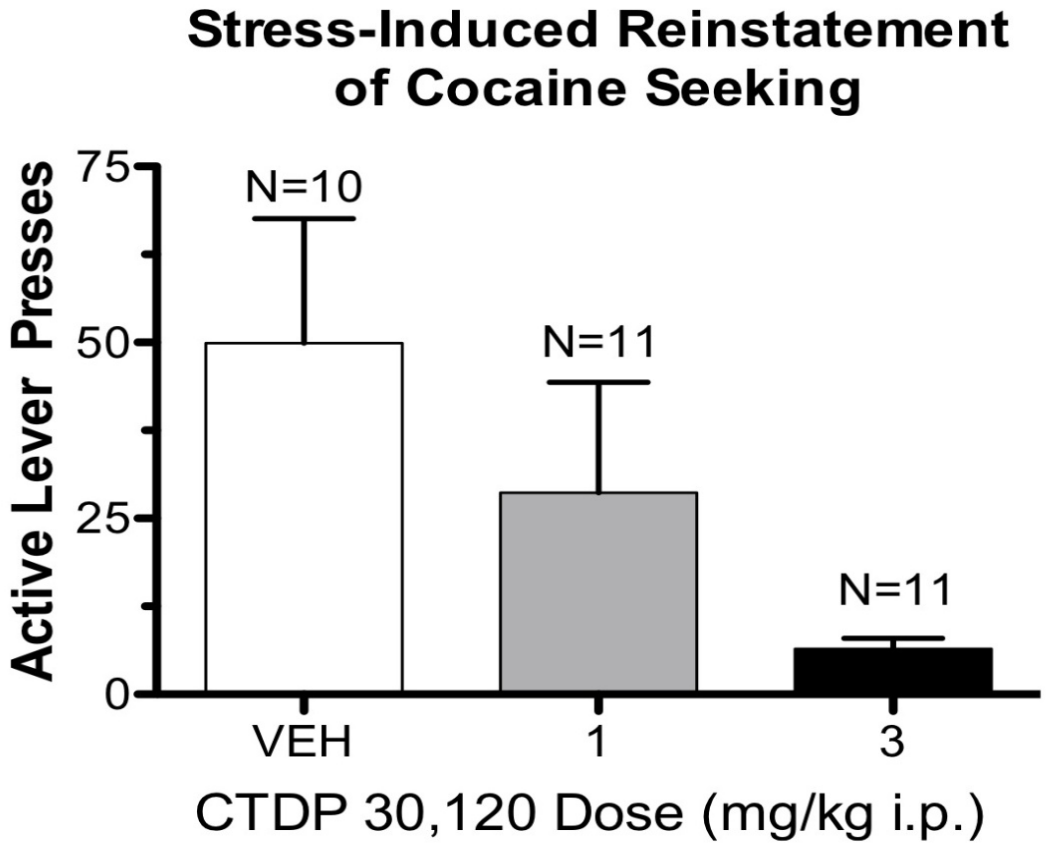
Reinstatement models



Adapted from Erb, Shaham and Stewart, 1996

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Buspirone Blockade of Stress-Induced Reinstatement To Cocaine



Beardsley, et al., 2010

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Buspirone: Next Steps

- Do pharmacologically relevant doses of buspirone engage D3 receptors?

- Does buspirone alter subjective effects produced by cocaine administration? (human lab study)

- Double blind, placebo controlled trial of buspirone (patients actively seeking treatment and/or abstinent individuals who want to remain abstinent)

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Why Haven't We Been More Successful At Developing Medications To Treat Addictions ?

Our Targets Are Only As Good As Our Models

- Animal models of the addiction process appear to possess good construct and face validity <this is the exception in animal models of neuropsychiatric disorders>. However, the predictive validity of these models (i.e., how accurately can the model predict that a drug will be effective), particularly for stimulants (cocaine, methamphetamine) is unknown.

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Why Haven't We Been More Successful At Developing Medications To Treat SUDs?

Clinical Trial Conduct/Execution

- There are multiple reasons why clinical trials fail; while most often blamed, the failure of a mechanism/ validity of our models is only one potential source of failure.
- For SUD trials, the three most important aspects of trial conduct are: COMPLIANCE, COMPLIANCE, AND COMPLIANCE

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Vigabatrin vs. Cocaine (Mexico)

	Abstinence During Last 3 Weeks	
	Failures	Successes
Placebo	49 (92.5%)	4 (7.5%)
Vigabatrin	36 (72%)	14 (28%)

3.7 x

Brodie *et al.*, 2009

P = 0.009

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

Noncompliance May Have Spoiled Cocaine Dependence Drug Trial

- SAN FRANCISCO (EGMN) - A trial of the anticonvulsant ***vigabatrin*** to treat cocaine dependence may have failed because the patients weren't taking it and not because the drug didn't work, an analysis of the study results suggests.
- A subsequent analysis of urine samples retained from the study showed that fewer than 40 percent of 53 patients in the vigabatrin arm who completed the 12-week study had urine drug levels that would indicate adherence to the medication regimen. The subsequent urinalyses suggested that at five of the 11 study sites, fewer than half of the patients had taken the medication as prescribed.
- Treatment adherence was rated at 85% using pill counts and patient self-reports to measure treatment adherence.

(headline from HEALTH DAILY NEWS)

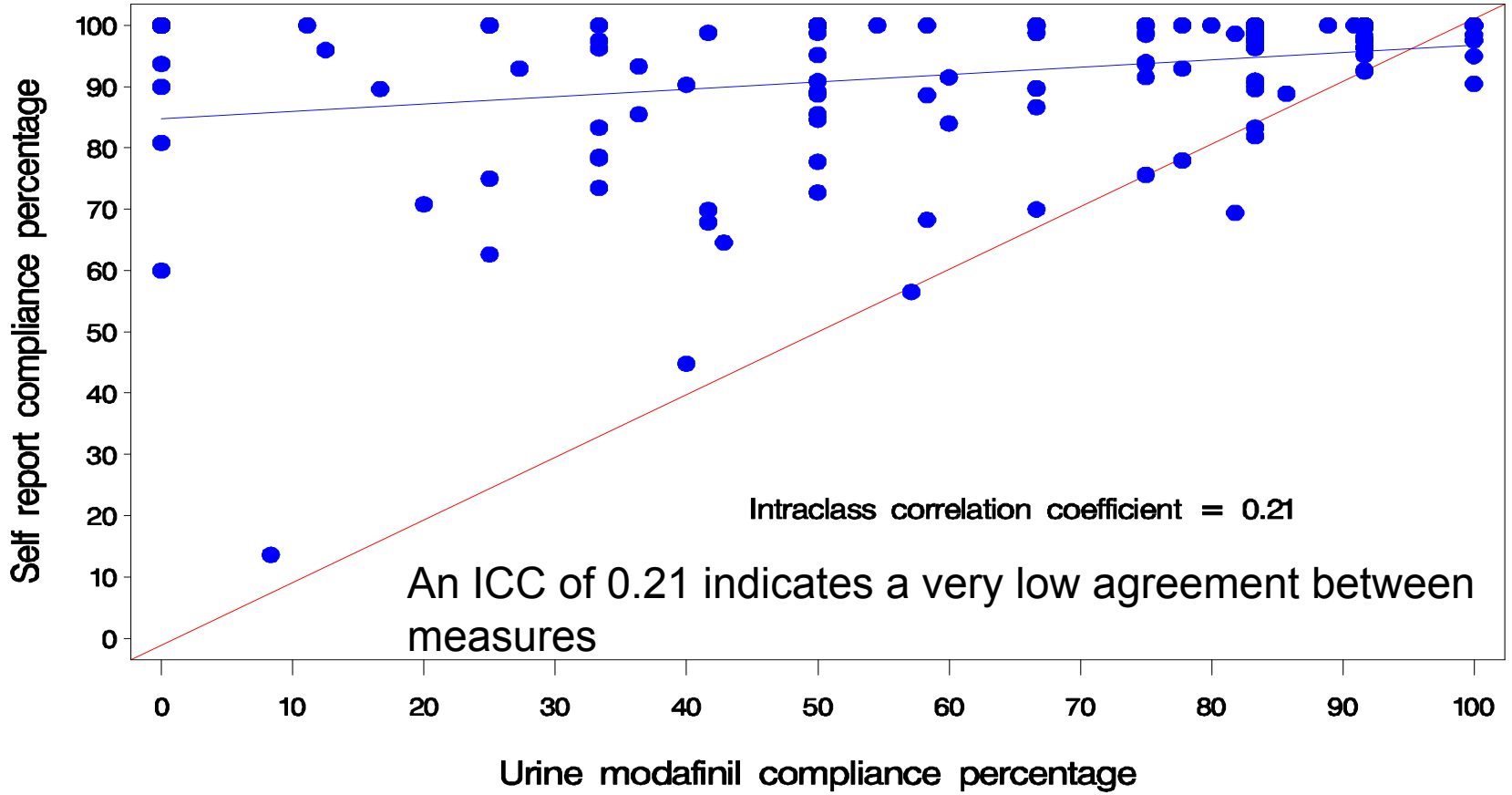
NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

VACSP/NIDA Study # 1026
Phase 2, Double-Blind, Placebo-Controlled Trial of Modafinil for Methamphetamine Dependence

Placebo	68
Modafinil 200 mg	72
Modafinil 400 mg	70

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

VA/NIDA Study #1026: Modafinil for Methamphetamine Dependence



Analysis 2: Agreement Analysis of self report compliance with urine modafinil compliance

NIDA
NATIONAL INSTITUTE
ON DRUG ABUSE

The Conduct Of Clinical Trials Is Unlikely To Change in The Short/Mid Term: How do we tackle the compliance problem?

- Electronic monitoring (e.g. MEMS) [easily gamed]
- Measurement of drug/metabolite in a biological fluid should be incorporated into every SUD trial protocol. Use of "compliant" subjects in statistical evaluation.
- Recognition by regulatory authorities that a "snapshot of compliance" may be the only practical surrogate in a real world setting.
- Incorporation of riboflavin into formulations has been used as a means of detecting compliance in both placebo and drug groups. Alternatively, the use of "homeopathic" amounts of drug in the placebo, sufficient for detection in blood/urine, prevents subjects from "gaming" the trial.