Cocaine vaccination: 'magic bullet' or 'shot in the dark'?

Dr Anne Lingford-Hughes
Reader in Biological Psychiatry
& Addiction.
University of Bristol.

Why?

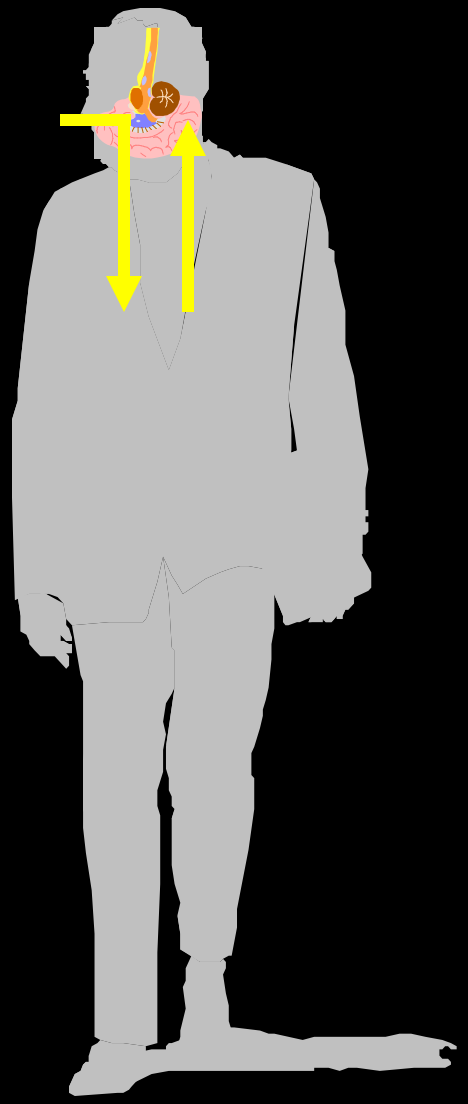
Cocaine misuse is a huge problem

Lack of an efficacious pharmacological approach

Potential pharmacotherapy for cocaine abuse

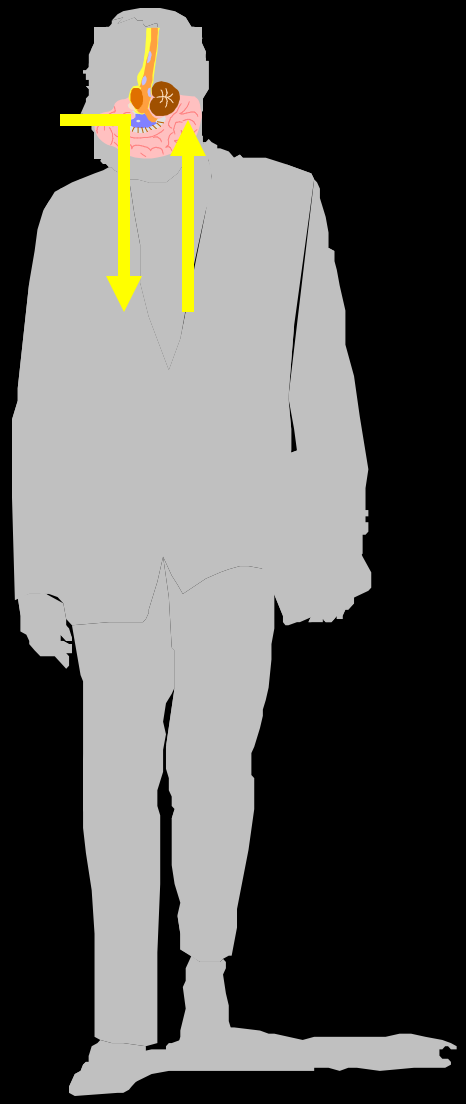
CCKB - Food Effects	Amantadine	Disulfiram
CCKB - Interaction	Amlodipine	Selegiline TS
Cocaine Vaccine	Baclofen	
GBR 12909	Bupropion	**Planned**
disulfiram	Cabergoline	Baclofen
Metyrapone	Disulfiram	
Modafinil	Fluoxetine	
NS 2359	Gabapentin	
Quetiapine	Isradipine	
	L-dopa+carbidopa	
	Memantine	
Planned	Methylphenidate	
BP 4897	Naltrexone	
DAS 431	Ondansetron	
GVG	Oxazepam	
Biostream	Progesterone	
Cabergoline	Propranolol	
	Reserpine	
	Taurine	
	Tiagabine	
	Triazolam	
	Venlafaxine	

Vaccination:
Targeting the drug rather than the brain



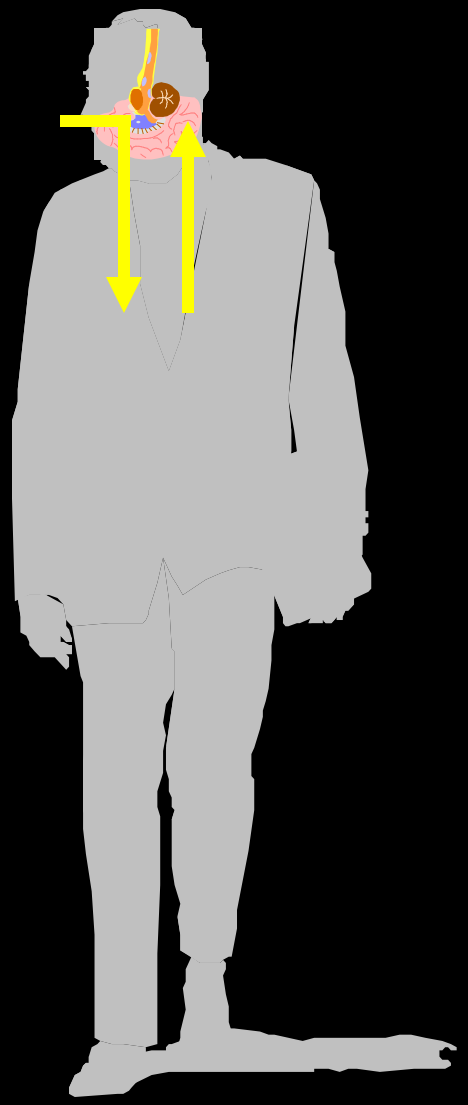
Vaccination:
Targeting the drug rather than the brain

- Not reinforcing.



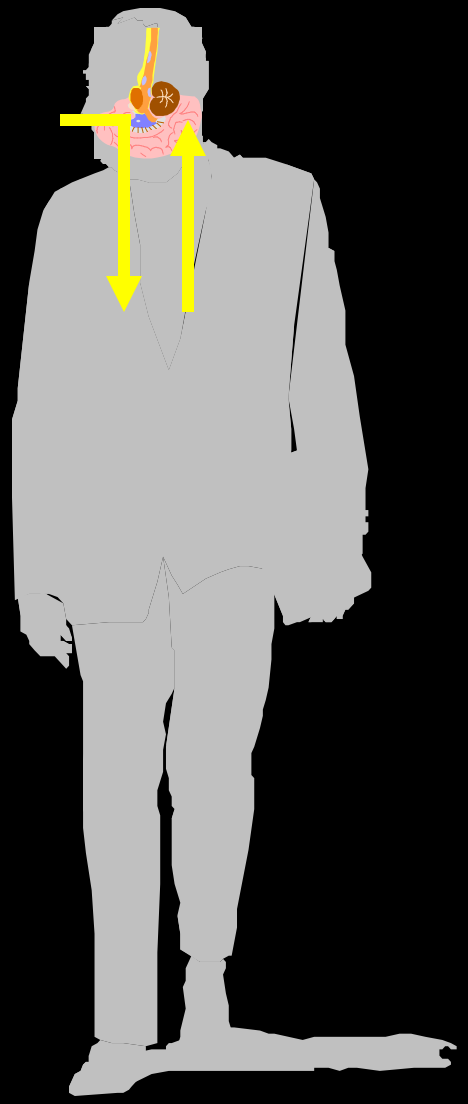
Vaccination:
Targeting the drug rather than the brain

- Not reinforcing.
- Reduced side-effects.



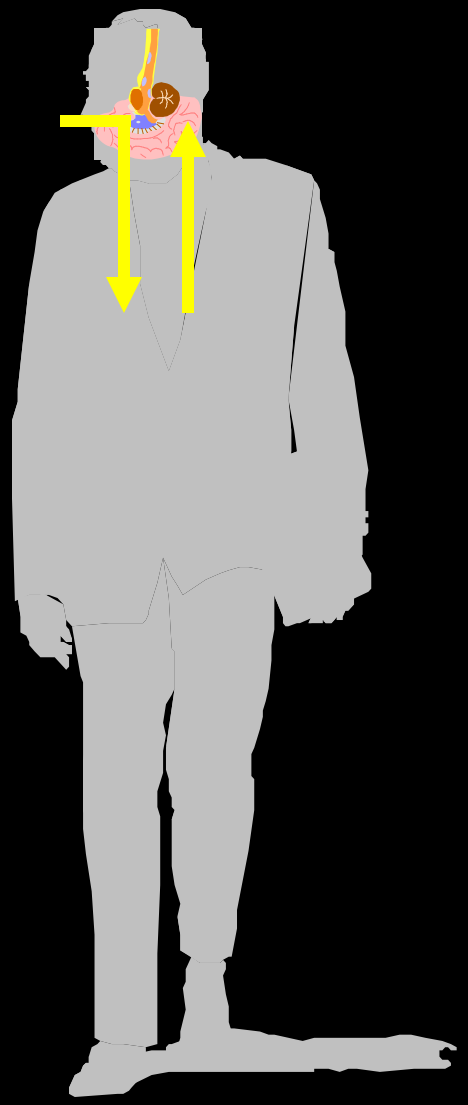
Vaccination:
Targeting the drug rather than the brain

- Not reinforcing.
- Reduced side-effects.
- Minimizes potential interactions with pharmacotherapy & allows both approaches to be used simultaneously.



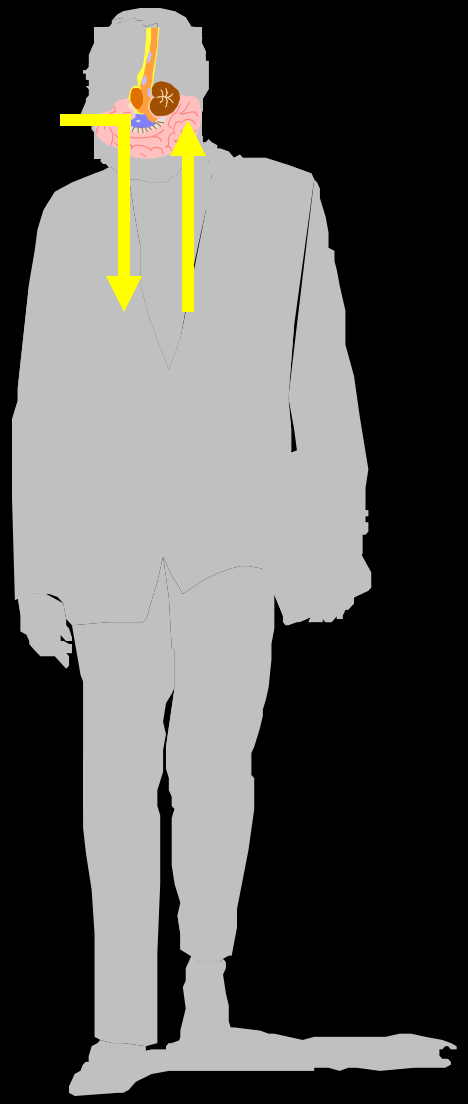
Vaccination:
Targeting the drug rather than the brain

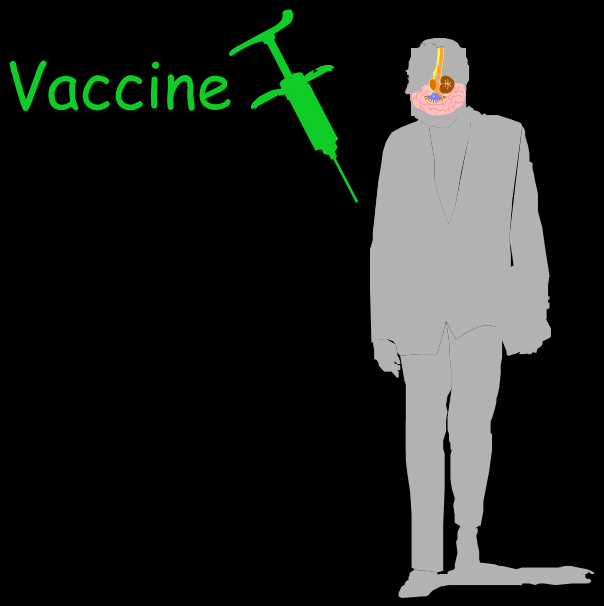
- Not reinforcing.
- Reduced side-effects.
- Minimizes potential interactions with pharmacotherapy & allows both approaches to be used simultaneously.
- Complements behavioural strategies.



Vaccination:
Targeting the drug rather than the brain

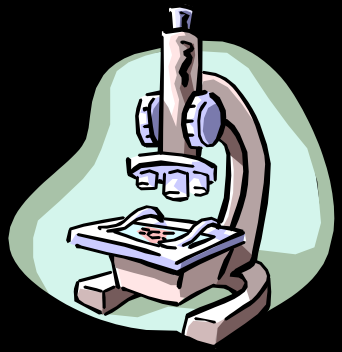
- Not reinforcing.
- Reduced side-effects.
- Minimizes potential interactions with pharmacotherapy & allows both approaches to be used simultaneously.
- Complements behavioural strategies.
- Used to treat or prevent cocaine addiction.

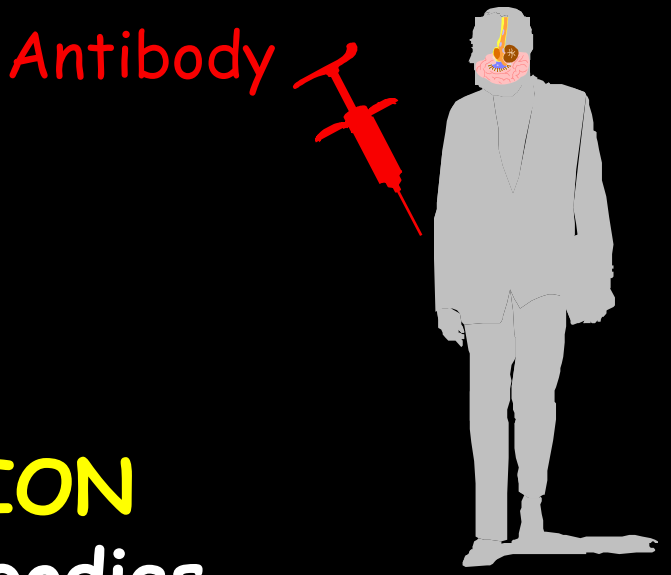




ACTIVE IMMUNIZATION

Vaccination

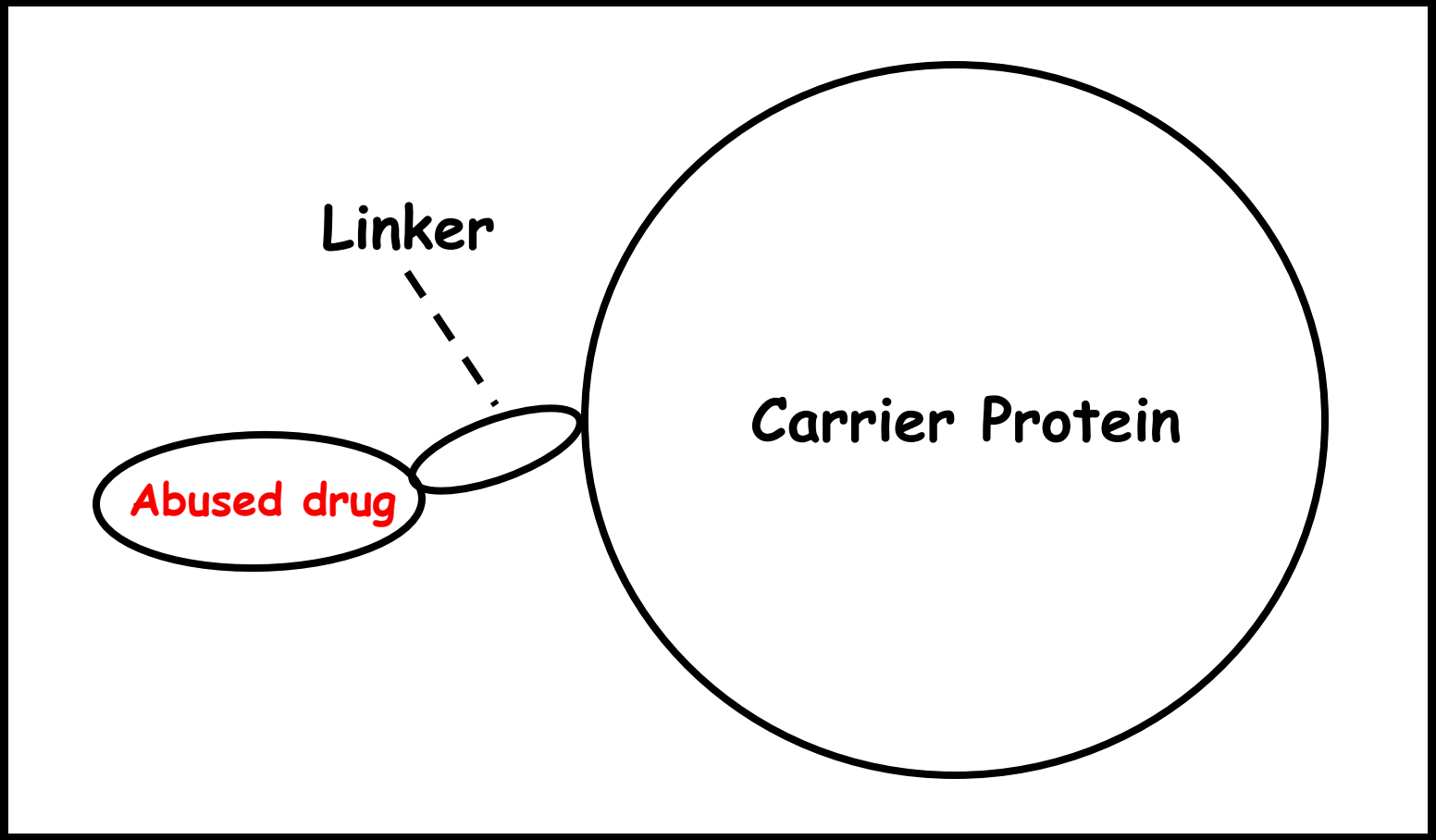




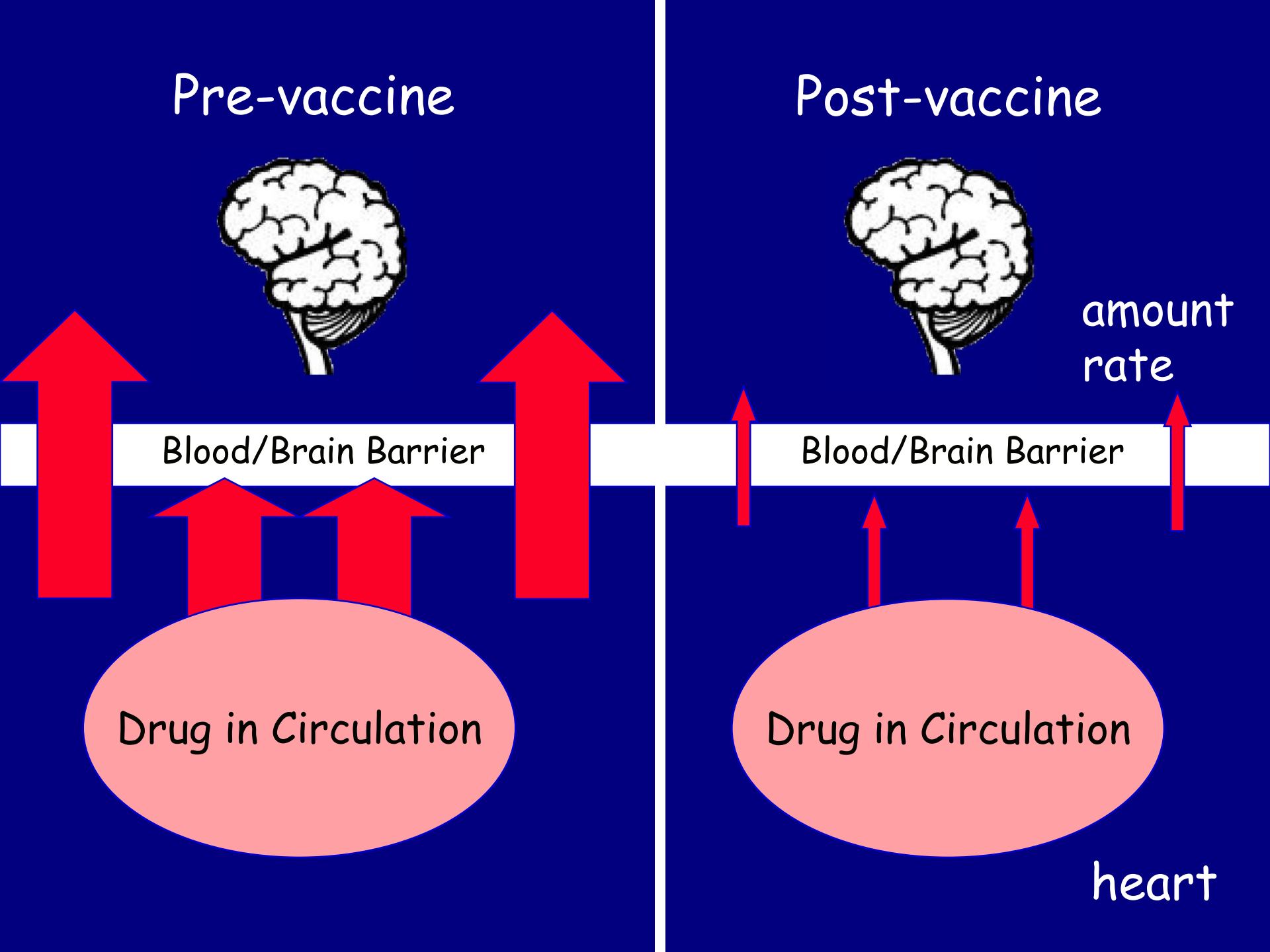
PASSIVE IMMUNIZATION

Monoclonal Antibodies

Immunogen for Active Vaccination

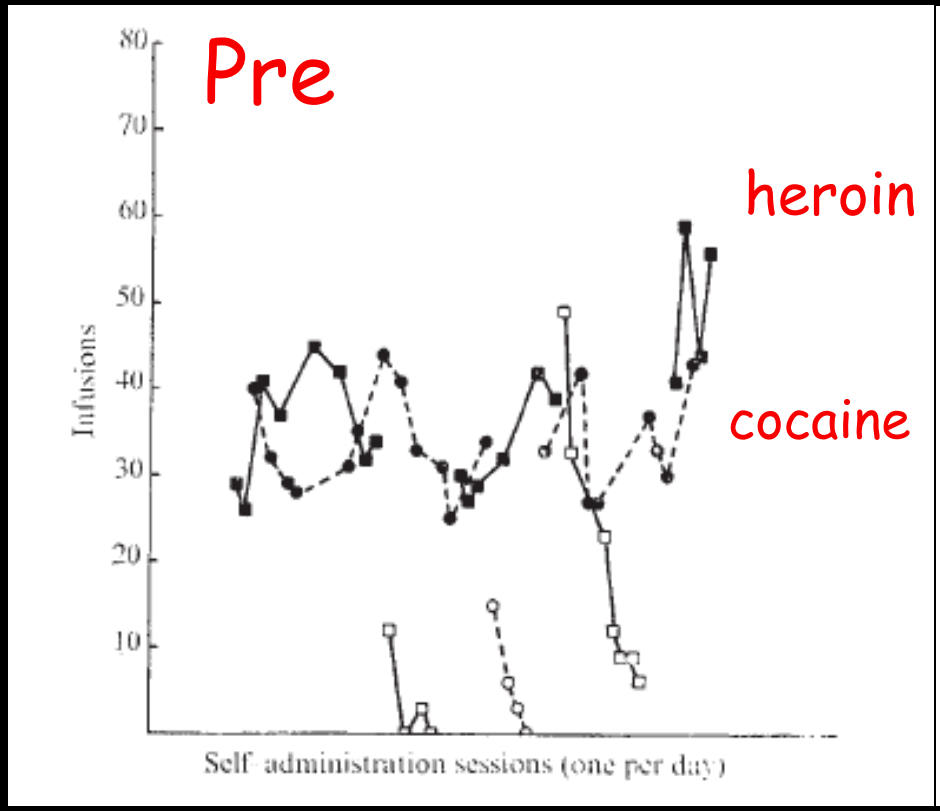


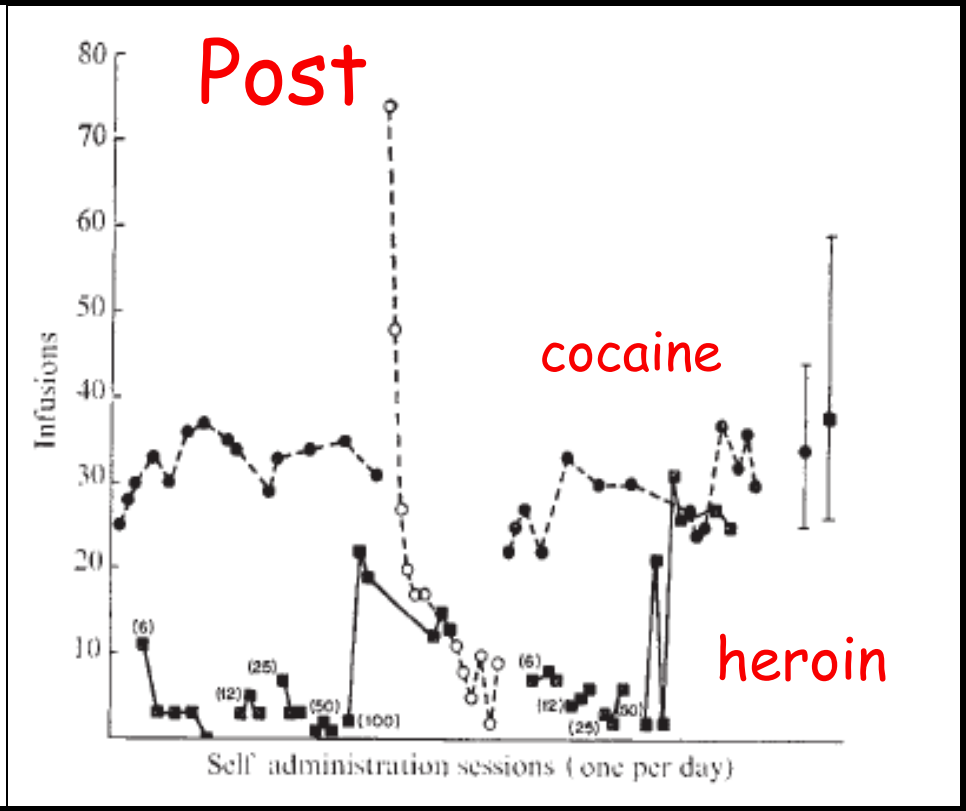
- Abuse of drug will not boost or maintain antibody titers
- Boosting requires administration of immunogen


Pre-vaccine
Post-vaccine
amount
rate
Blood/Brain Barrier
Blood/Brain Barrier
Drug in Circulation
Drug in Circulation
heart

Possibility of vaccination for drug misuse – for opiates in 1974; Bonese et al

Changes in heroin self-administration in rhesus monkey after morphine immunization.

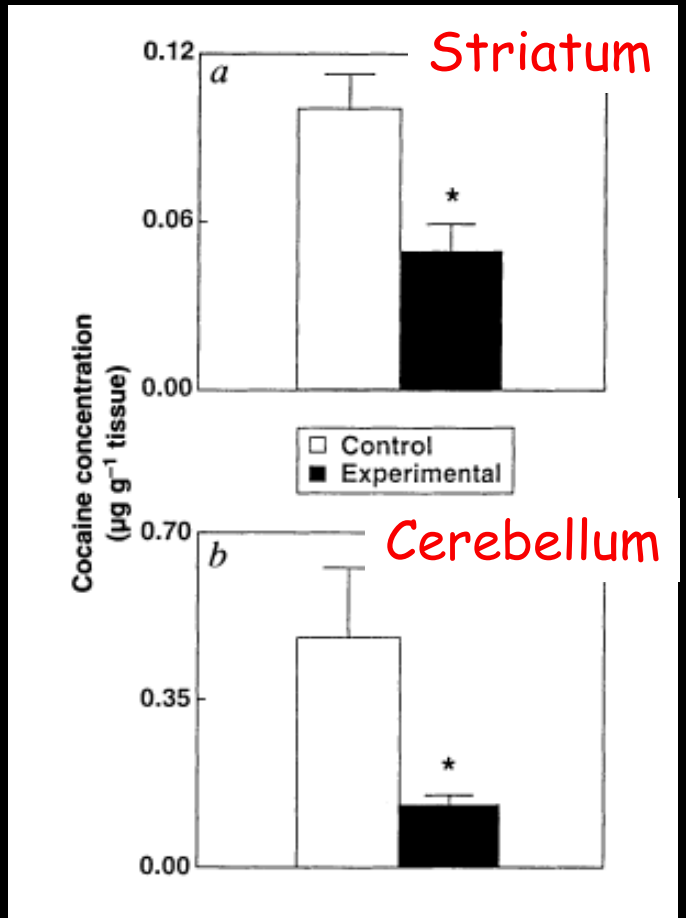


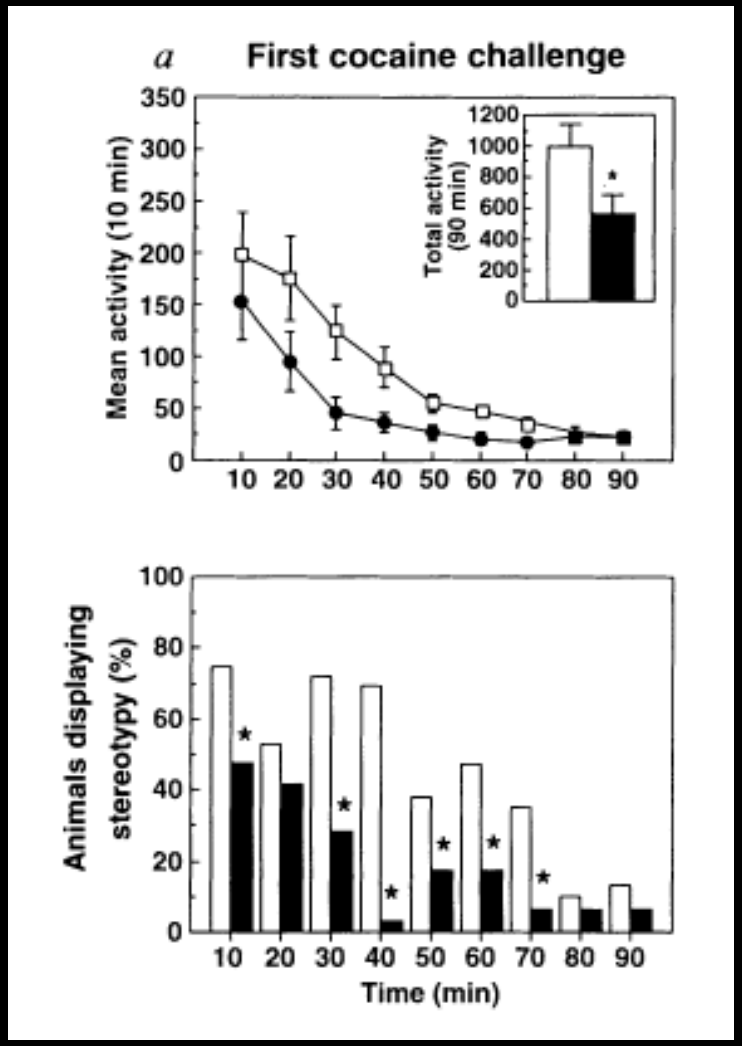


Suppression of psychoactive effects of cocaine by active immunization

M. Rocío A. Carrera, Jon A. Ashley*, Loren H. Parsons, Peter Wirsching*‡, George F. Koob‡ & Kim D. Janda*†‡

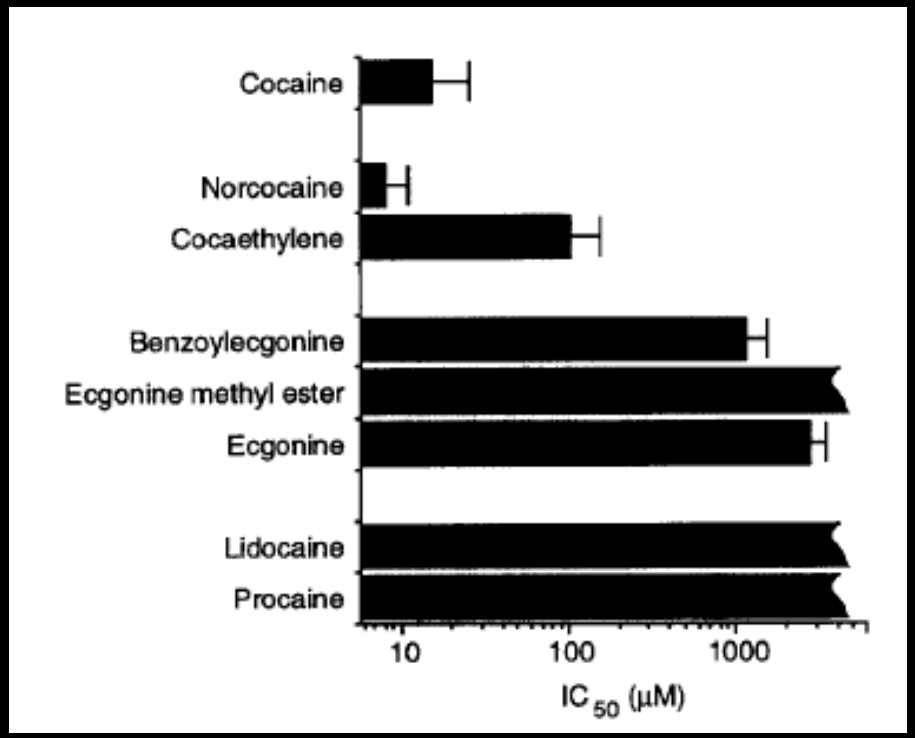
Nature 1995

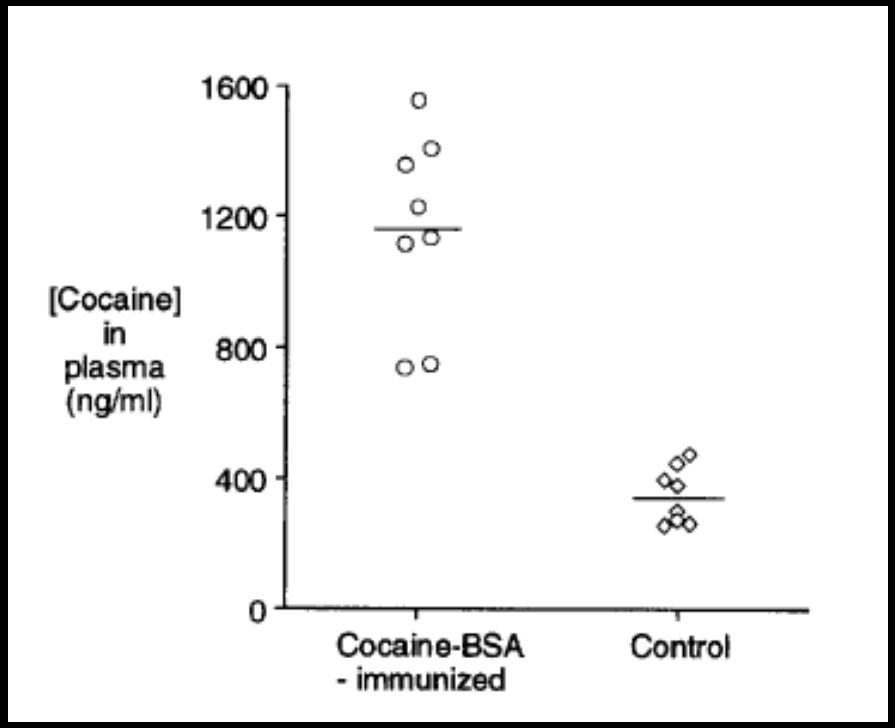




Reduction of cocaine in brain and effects on locomotion

Efficacy of a therapeutic cocaine vaccine in rodent models. *Fox et al 1996*



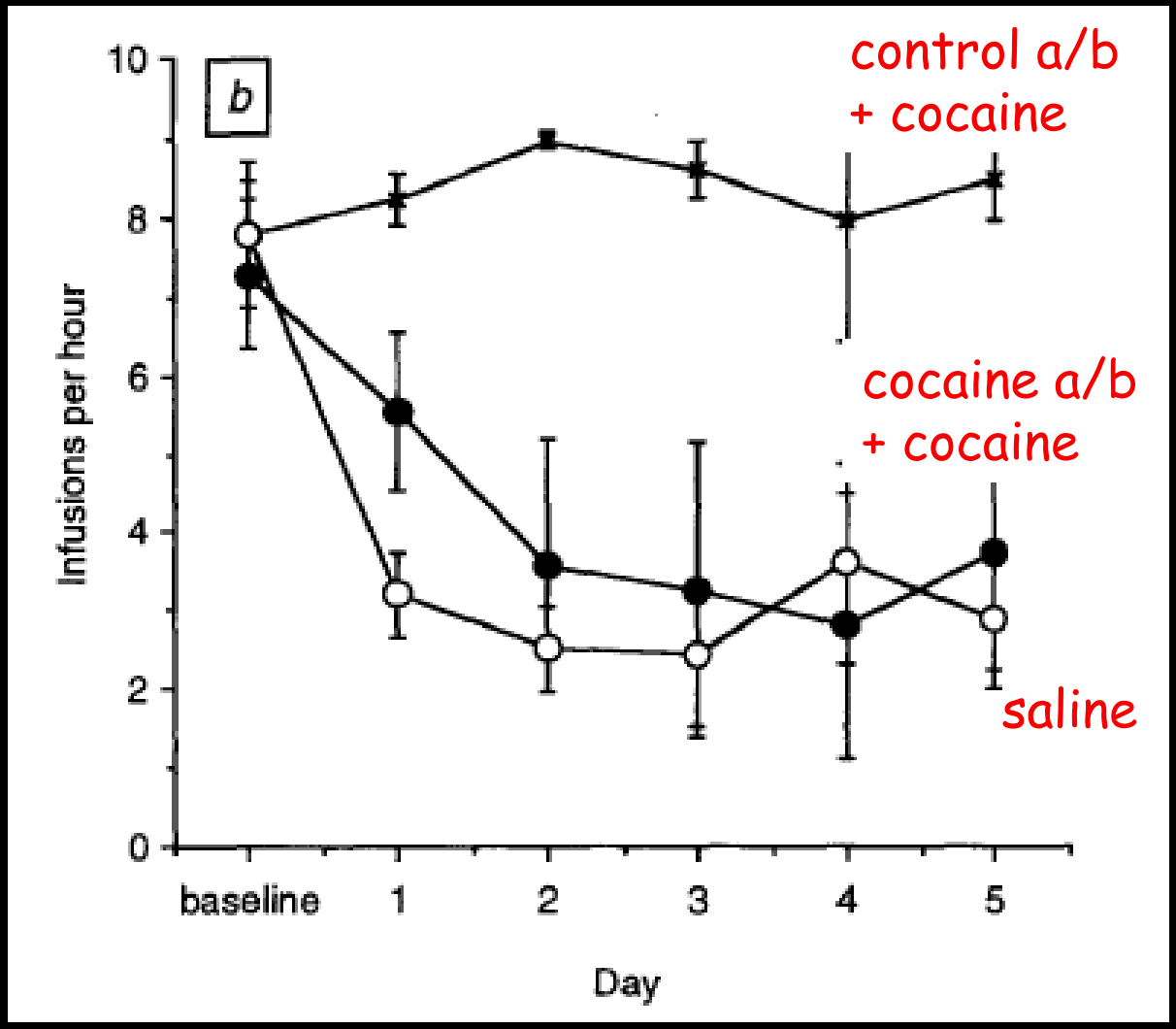


Antibody did not recognise inactive cocaine metabolites

Antibody able to retain cocaine in plasma within 30 seconds

Anti-cocaine antibody extinguishes cocaine self-administration.

Fox et al 1996

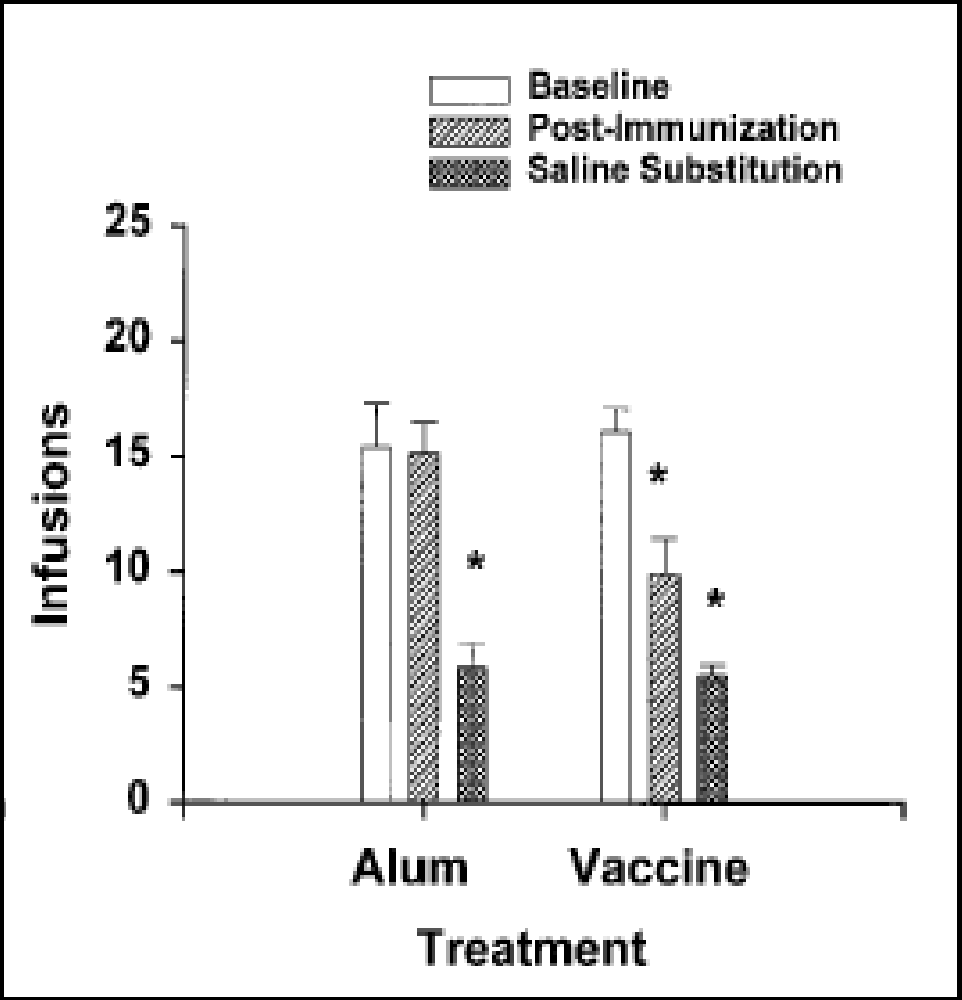


Kathleen M. Kantak · Stephanie L. Collins
Elizabeth G. Lipman · Julian Bond · Kate Giovanoni
Barbara S. Fox

Evaluation of anti-cocaine antibodies and a cocaine vaccine in a rat self-administration model

2000

- Relapse
  - Low doses of cocaine trigger a return to cocaine-seeking which was not seen in vaccinated rats.



Treating cocaine addiction with viruses

M. Rocio A. Carrera*†, Gunnar F. Kaufmann*†, Jenny M. Mee*, Michael M. Meijler*, George F. Koob‡, and Kim D. Janda*§

2004

Whereas previous protein-based treatments have relied on peripheral drug-protein interactions, this approach delivers the therapeutic protein agent directly into the CNS, the site of drug action.

- Bacteriophage: penetrates the CNS when taken intranasally.
- can display cocaine-binding proteins on its surface that sequester cocaine in the brain.
- can block the psychoactive effects of cocaine.

Human Studies of Cocaine Vaccine TA-CD

The TA-CD cocaine vaccine is comprised of succinylnorcocaine (SNC) molecules covalently linked to a carrier protein derived from the cholera B toxin (rCTB; widely used)

Cocaine specific antibodies can sequester cocaine molecules in the bloodstream & naturally occurring cholinesterases convert cocaine to inactive metabolites, which are excreted.

Xenova Research Ltd /Celtic Pharma

ELSEVIER

Vaccine 20 (2002) 1196–1204

Vaccine

www.elsevier.com/locate/vaccine

Human therapeutic cocaine vaccine: safety and immunogenicity

Thomas R. Kosten [a,*], Marc Rosen [a,1], Julian Bond [b], Michael Settles [b], John St. Clair Roberts [c], John Shields [c], Lindsay Jack [c], Barbara Fox [d]

[a] *Department of Psychiatry, School of Medicine, Yale University, 950 Campbell Avenue, West Haven, CT 06516, USA*
[b] *TGA Sciences, Inc., 200 Boston Avenue, Suite 1850, Medford, MA 02155, USA*
[c] *CANTAB Pharmaceuticals Research Ltd., 310 Cambridge Science Park, Milton Road, Cambridge CB4 OWG, UK*
[d] *Addiction Therapies, Inc., 25 Main Street, Suite3, Wayland, MA 01778, USA*

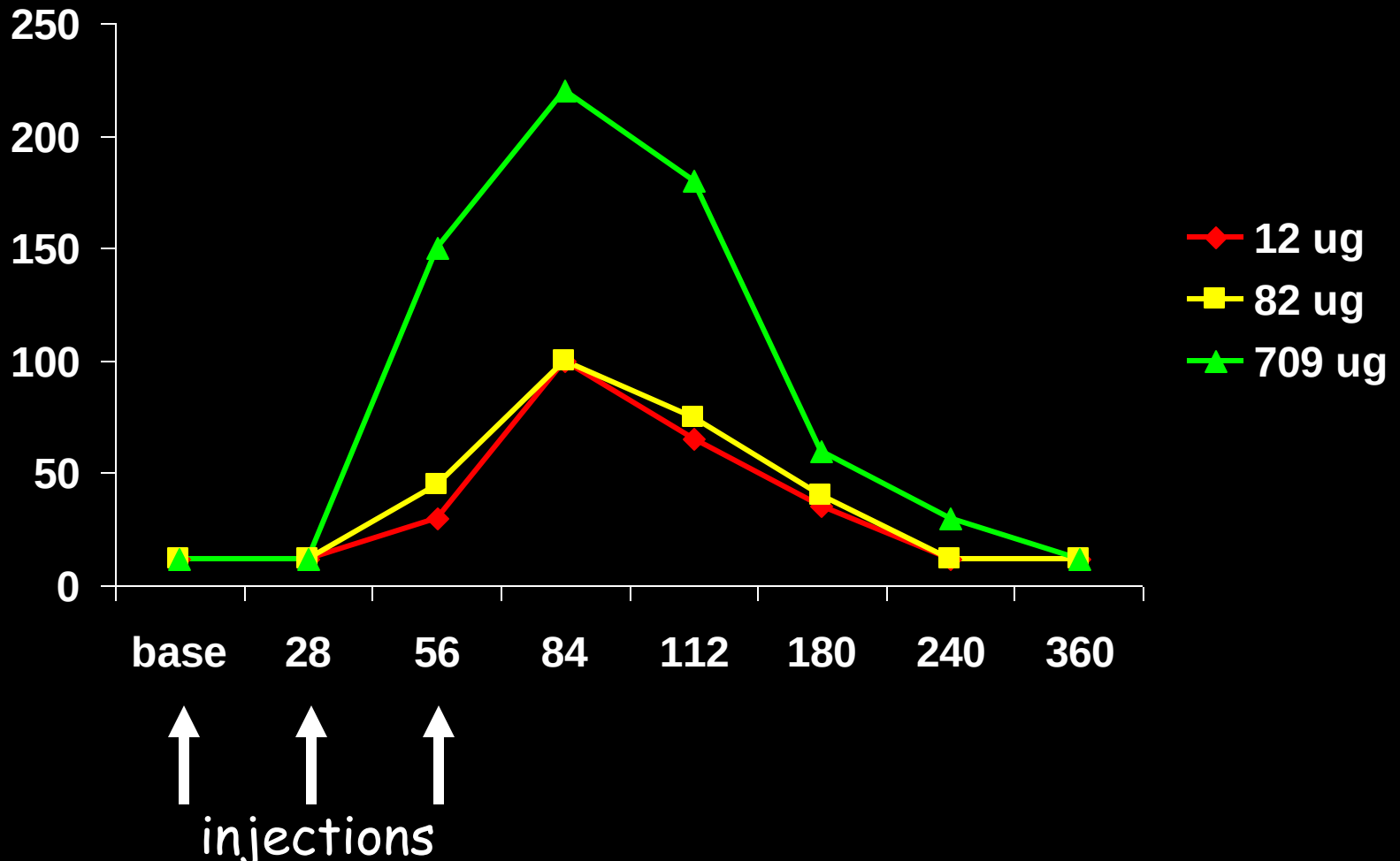
Received 29 July 2000; received in revised form 17 September 2001; accepted 25 September 2001

Phase 1 Vaccine Safety Trial Design

- Three cohorts of ex-cocaine dependent individuals
- Active vaccine nor-cocaine coupled to carrier protein formulated with alum adjuvant:
  - 12, 82, 709 ug : 10 patients each
  - 8 got active vaccine, 2 got alum only
- Each patient received a course of three intramuscular injections at 0, 4 and 8 weeks
- Follow-up points at 4, 6, 9, and 12 months
- Assessed antibody levels & adverse effects

Antibody Levels during 1 year

Phase I Subjects – 3 injections detectable by day 42



Conclusions for Phase 1
Cocaine Antibodies in Humans

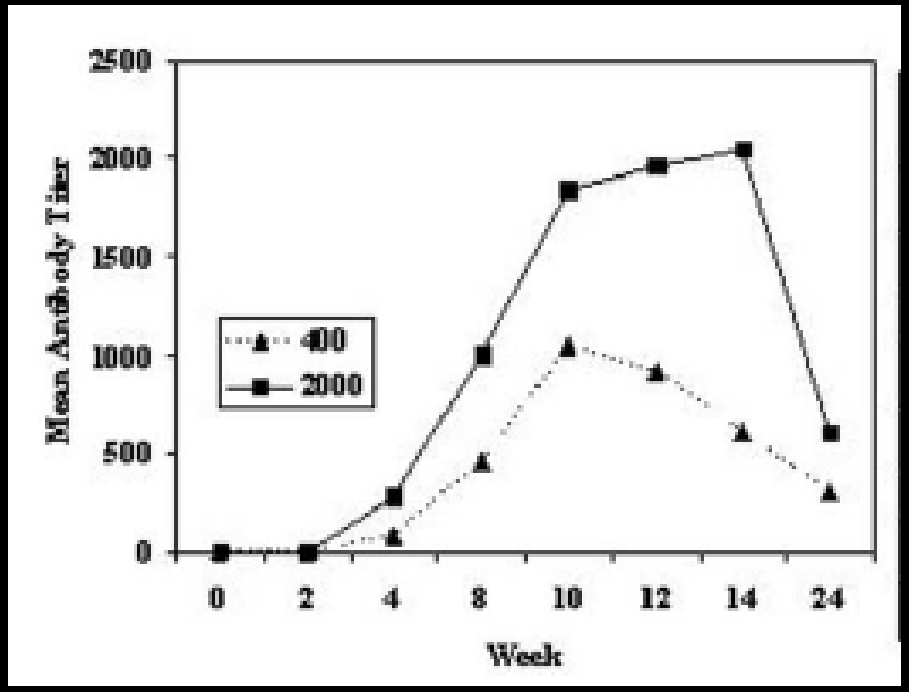
- Safety: no major adverse events during year follow-up
- Injection events: temperature elevations (minimal), mild pain & swelling at injection site
- Rise in antibody detectable after second dose and increasing after third dose.
- Decline in antibody levels from peak at 3 months evident by four months after initial vaccination

Vaccine Pharmacotherapy for the Treatment of Cocaine Dependence

Bridget A. Martell, Ellen Mitchell, James Poling, Kishor Gonsai, and Thomas R. Kosten 2005

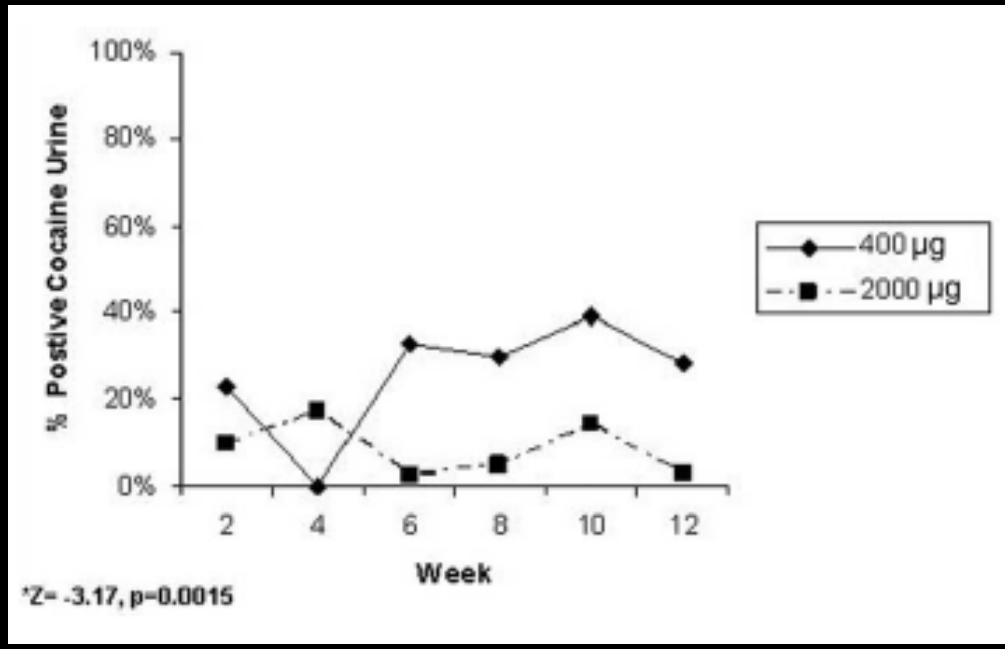
- cocaine dependent persons in early recovery

- 14 week, open label, dose escalation clinical trial designed to test the safety and immunogenicity of two doses of a phase IIa human cocaine vaccine (TA-CD)
  - 400 g (4x100g over 8 weeks)
  - 2000 g (5x400g over 12 weeks)



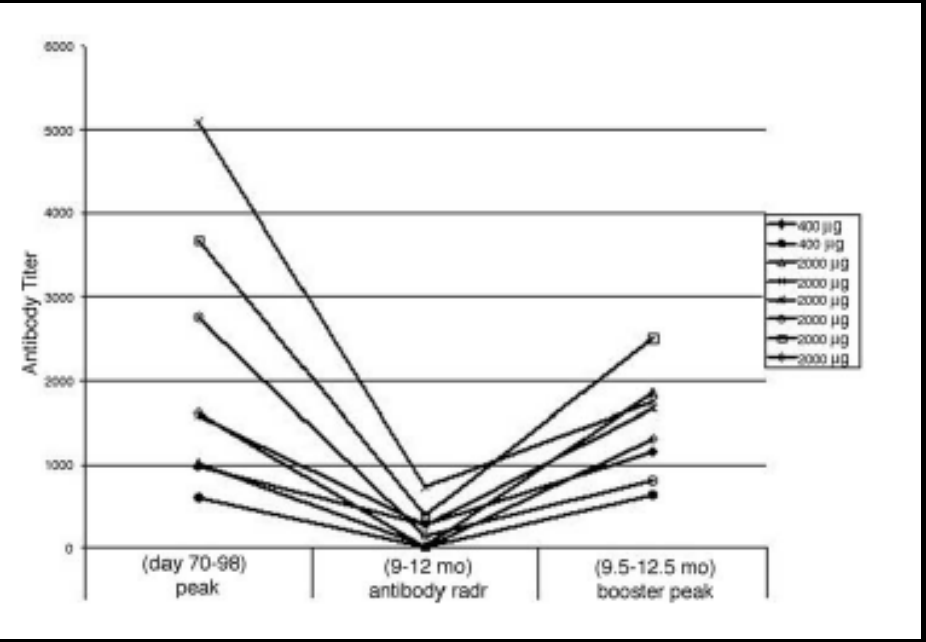
Mean antibody levels in all vaccination groups.

Percent cocaine positive urines in 400g and 2000g vaccination groups.



How long does the antibody response last?

- antibody titers waned at 6 months with nondetectable titer values by 12 months
- Booster vaccination 9-12 months (at nadir), increased antibody titer levels.
- 2-4 weeks after booster - 6-x higher antibody



Conclusions
Cocaine Antibodies in Humans

- Safety of vaccine itself: no major adverse events; vaccine well-tolerated
- Safe in combination with cocaine
- Cocaine use less with higher dose vaccine

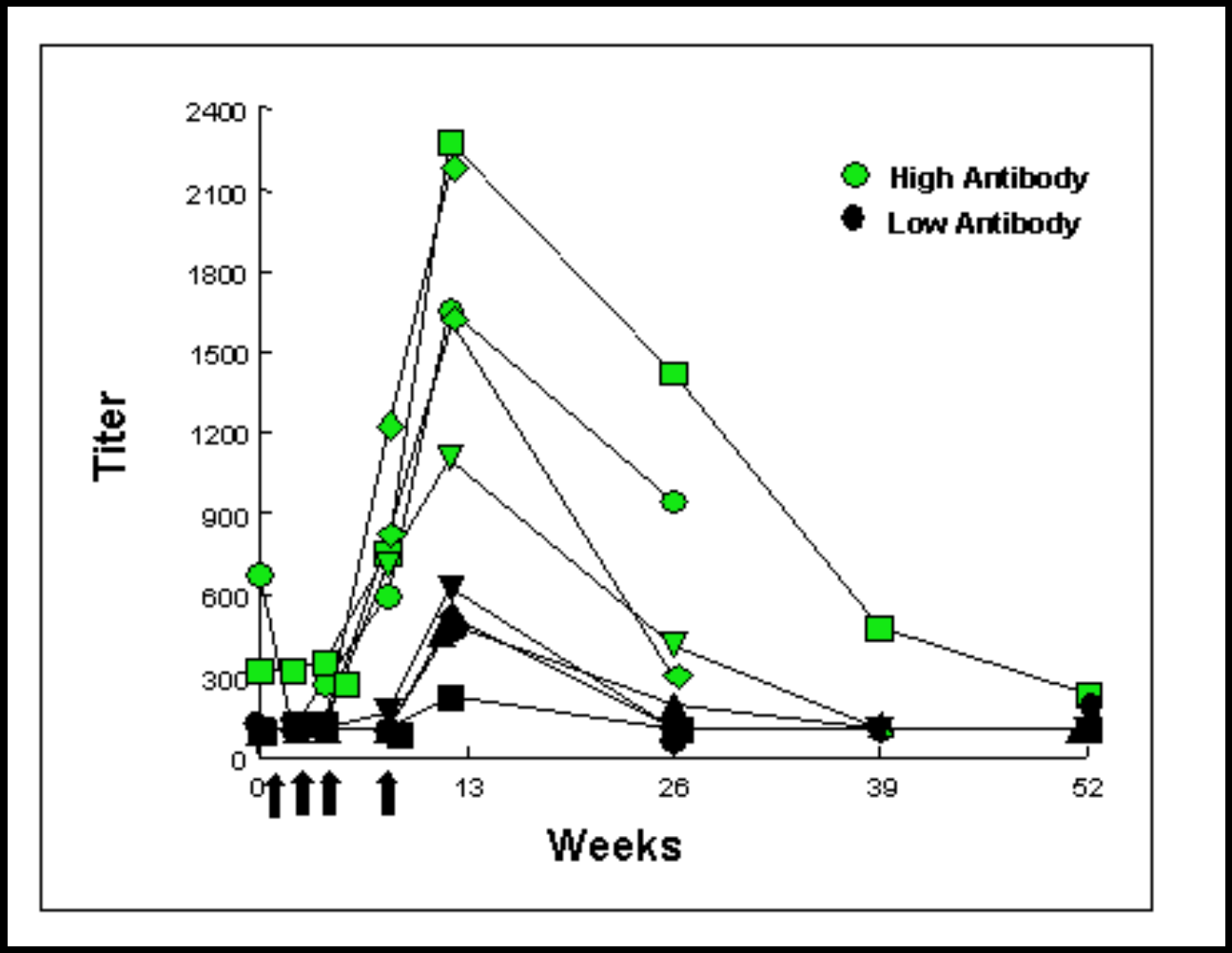
- Thus vaccine warrants further clinical studies

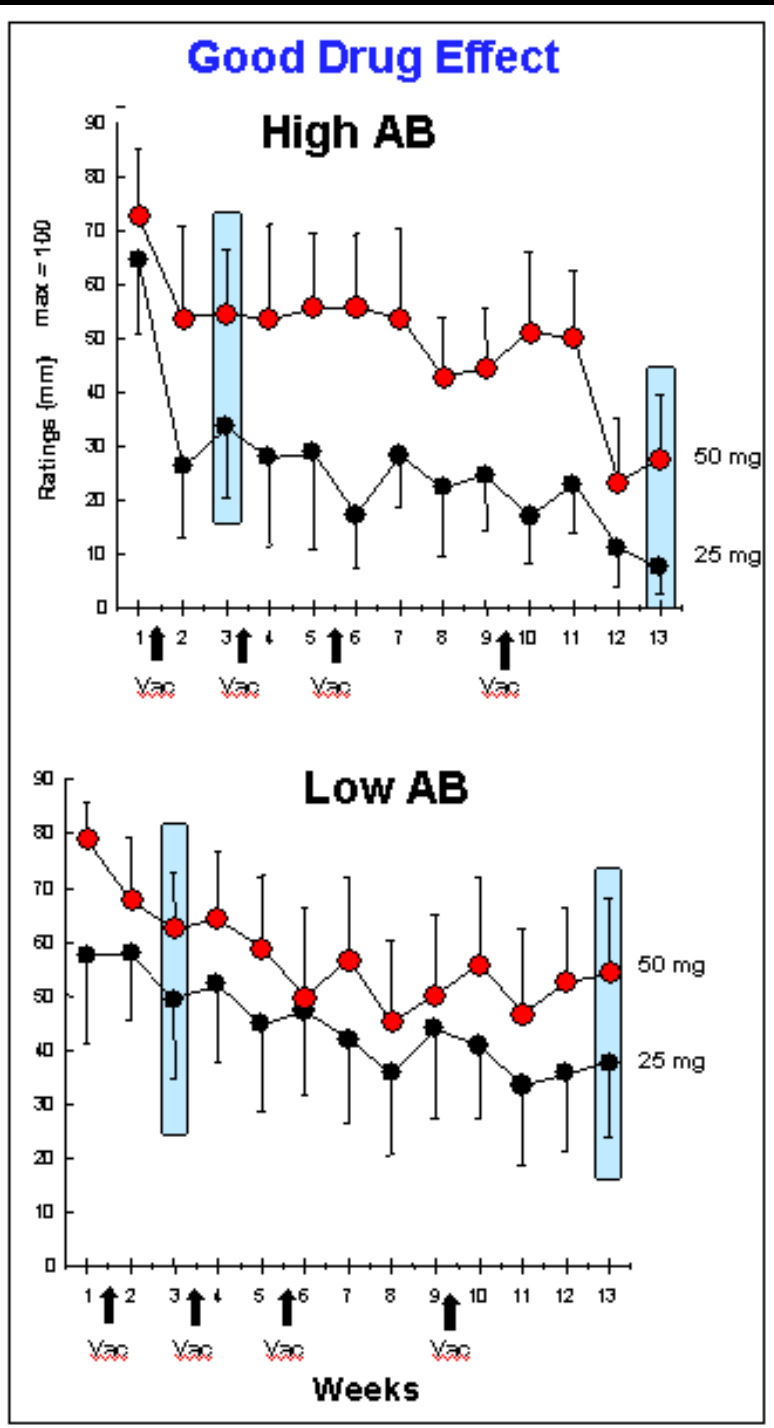
Phase IIa study of TA-CD Preliminary results: Haney et al 2006

- Impact of vaccinating chronic cocaine dependent volunteers who were *not* actively seeking to reduce or stop their cocaine use

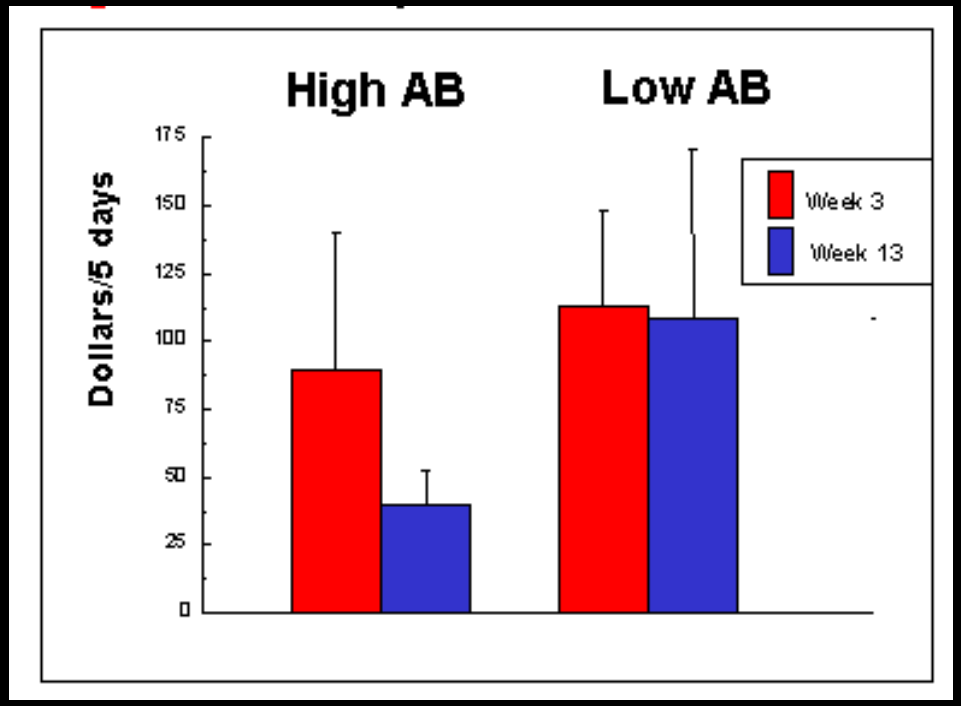
- Vaccinations were given at weeks 1, 3, 5 and 9

Antibody response: variable





Reduction in 'good drug' effect in those with high titre & reduction in amount of cocaine used.



Phase IIb; Kosten
Cocaine users also in methadone maintenance programme

- Primary endpoint was improvement in abstinence from cocaine for 3 consecutive weeks
  - Challenging (!) in those who have abused cocaine for 13 yr.
  - & not achieved – higher than expected placebo response
  - But in treatment group – twice as many patients achieved 50% or greater increase in cocaine free days (urinalysis)

Overview.

- Vaccination appears to be associated with limited side-effects and is well tolerated.
  - In non-treatment seeking cocaine addicts
  - In methadone maintenance population

- Reduction in 'high' reported under lab. conditions
- Reduction in use of cocaine in clinical population

Clinical Utility of Immunotherapy

- Uses
  - Decreases relapse, **NOT** craving or withdrawal

Clinical Utility of Immunotherapy

- Uses
  - Decreases relapse, **NOT** craving or withdrawal
- Attractive features
  - Infrequent dosing, long duration → compliance
  - Novel mechanism: combine with other medications
  - Safety/side effects – no effect on neurotransmitter systems eg dopamine - mood

Clinical Utility of Immunotherapy

- Uses
  - Decreases relapse, **NOT** craving or withdrawal
- Attractive features
  - Infrequent dosing, long duration → compliance
  - Novel mechanism: combine with other medications
  - Safety/side effects – no effect on neurotransmitter systems eg dopamine - mood
- Limitations
  - Need high titers of antibody, repeated injections
  - Individual variability
  - Slow onset
  - Surmountable – could antibody titer be readily overcome?
  - Specific for a particular drug of abuse

Abused Drug Targets and Immunotherapy Approaches

- Nicotine – vaccines and monoclonals
- Phencyclidine – monoclonals
- Methamphetamine – monoclonal
- Cocaine - vaccine

Ethical and legal issues raised.

Debate is needed now to address potential ethical and legal questions.

Cocaine addiction is akin to an infectious disease that is a major public health issue

Protection to the individual or wider population (herd effect)

Cohen, 1997 Drug Alc Dep

Ethical and legal issues raised.

- Could be used to prevent and treat cocaine misuse – or only 'dependence'?
  - Studies so far only as a treatment
- At the moment is assumed that regulatory bodies will approve a vaccine
- Is it different for nicotine vaccine?
  - Or methamphetamine?

Ethical principles.

- Autonomy
  - ..right to determine what should be done with their own body … unless harmful to others
- Beneficence
  - To promote patient's well-being
- Non-maleficence
  - Physician to do no harm; treatment to help sick ..but.. never to injure or wrong them
- Justice
  - To provide fair, equitable and appropriate distribution in society

Potential for stigmatisation.

- Privacy and confidentiality
- Possible to detect the antibody
- Information in medical records about immunisation

- Suggest that those vaccinated were
  - Cocaine addicts – or still are
  - Vulnerable to becoming an addict

Potential for coercion:
Who will or should be vaccinated?

- Consenting adults and children
  - Assume is safe and effective
  - Few problems for competent adult and those children deemed competent
  - Will parents have the *right* to vaccinate their children?
    - In USA, if vaccine proves safe, the pressure to vaccinate children is expected to increase
    - Would they switch to another drug of abuse?
    - Long-term effects unknown

Consent.

- Can an addict ever give informed consent?
  - 'Brain damage'
  - Assume more of a paternalistic role?

Potential for coercion:
Who will or should be vaccinated?

- Convicted criminals.
  - Condition of parole or probation or non-custodial sentence
  - Could you coerce someone to be vaccinated?
    - Has finite duration of action
  - Only to be used in those convicted of drug related offences?
    - Or more widely used since drug addiction is 'endemic' in those convicted of a number of crimes

Treatment under legal coercion

- WHO: Compulsory treatment was legally and ethically justified if and only if:
  - (1) the rights of the individuals were protected by "due process", and
  - (2) effective and humane treatment was provided

  - Offered choice of treatment or detention
  - Then offered a range of different treatments

- Until vaccine is proven safe, coercion would be problematic

Potential for coercion:
Who will or should be vaccinated?

- Addicts who have not committed a crime
  - Use of law?
  - Forced on a pregnant woman to protect developing fetus?

Ashcroft & Franey, 2004

- The principal risk, as we see it, of a vaccine is that it encourages a quick fix for society, while reducing social attention to the other needs of the drug user.

Prevention:
Much more speculative

- Non-addicted population
  - When an individual is susceptible to addiction – or everyone?
    - how to / who determines this?
    - More likely to involve children
    - Parents wanting child vaccinated
    - Use more cocaine or other drugs
    - Cost
    - Would eliminate/reduce stigmatisation!
  - Mandatory?

Cocaine vaccination: 'magic bullet' or 'shot in the dark'?