# The future of pharmacological treatment.

Anne Lingford-Hughes
Professor of Addiction Biology, Imperial College.

Hon Consultant CNWL NHS Foundation Trust.

Imperial College London

Central and North West London NHS
NHS Foundation Trust

# What substances and when?

What

- Nicotine
- Alcohol
- Cannabis
- Opiates
- Stimulants
  - Cocaine
  - Methamphetamine
  - Amphetamine
- Ecstasy
- Benzodiazepines

When

- Prevention
  - starting
- Substitution
- Detoxification
- Relapse prevention
- Complications
  - Preventing
  - Treating

# What substances and when?

What

- Nicotine
- Alcohol
- Cannabis
- Opiates
- Stimulants
  - Cocaine
  - Methamphetamine
  - Amphetamine
- Ecstasy
- Benzodiazepines

When

- Prevention
  - starting
- Substitution
- Detoxification
- Relapse prevention
- Complications
  - Preventing
  - Treating

# What substances and when?

What

- Nicotine
- Alcohol
- Cannabis
- Opiates
- Stimulants
  - Cocaine
  - Methamphetamine
  - Amphetamine
- Ecstasy
- Benzodiazepines

When

- Prevention
  - starting
- Substitution
- Detoxification
- Relapse prevention
- Complications
  - Preventing
  - Treating

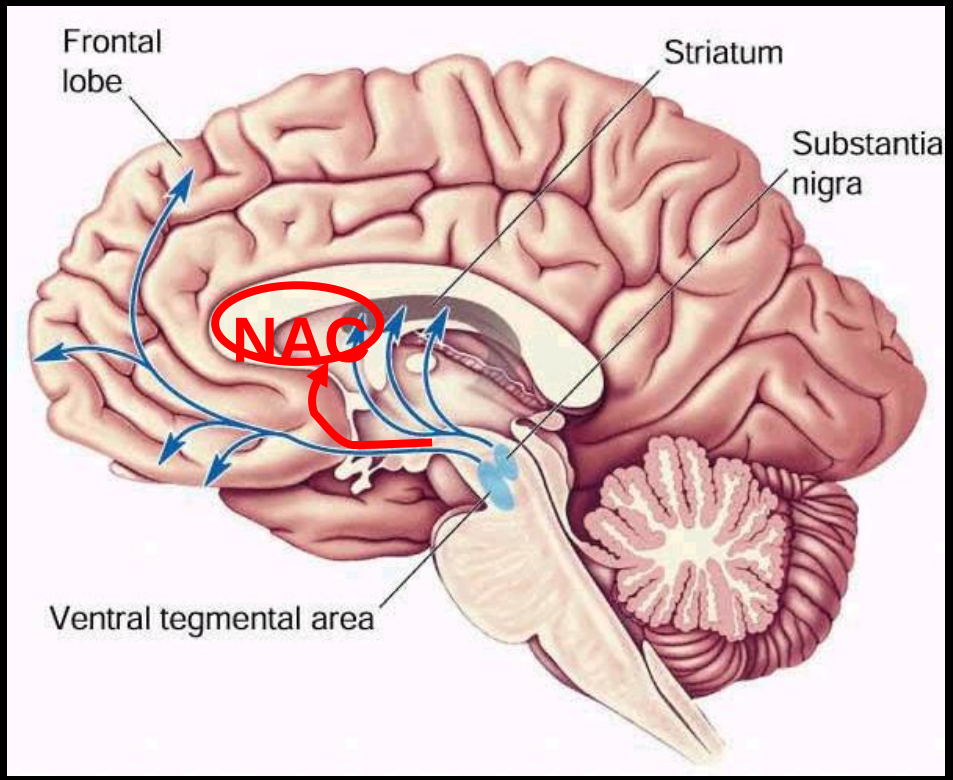
# How is pharmacotherapy developing?

- Understanding more about neurobiology
- Using medications with other licensed indications but have 'appropriate' pharmacology.
- Different ways of delivery
  - Implants eg naltrexone (Hulse et al 2009)
- Less about serendipity

Dopamine.

- Acutely, increase in dopamine
- Low dopamine D2 receptors associated with drug-'liking', impulsivity
- Chronically, dopaminergic hypofunction

cocaine,
amphetamine
alcohol,
opiates,
nicotine,
cannabinoids,
MDMA



# Dopamine & pharmacotherapy for addiction

Block DA-ergic function to prevent 'high'

- D2 antagonists
  - Antipsychotics
    - First generation
    - Second generation
- D3 antagonists

Boost DA-ergic function to reduce dysphoria, irritability

- DA-ergic 'agonists'
  - bromocriptine
  - disulfiram
  - methylphenidate

# The dopamine D3 receptor plays an essential role in alcohol-seeking and relapse

Valentina Vengeliene,*[,1,2] Fernando Leonardi-Essmann,*[,1] Stephanie Perreau-Lenz,* Peter Gebicke-Haerter,* Karla Drescher,† Gerhard Gross,† and Rainer Spanagel*

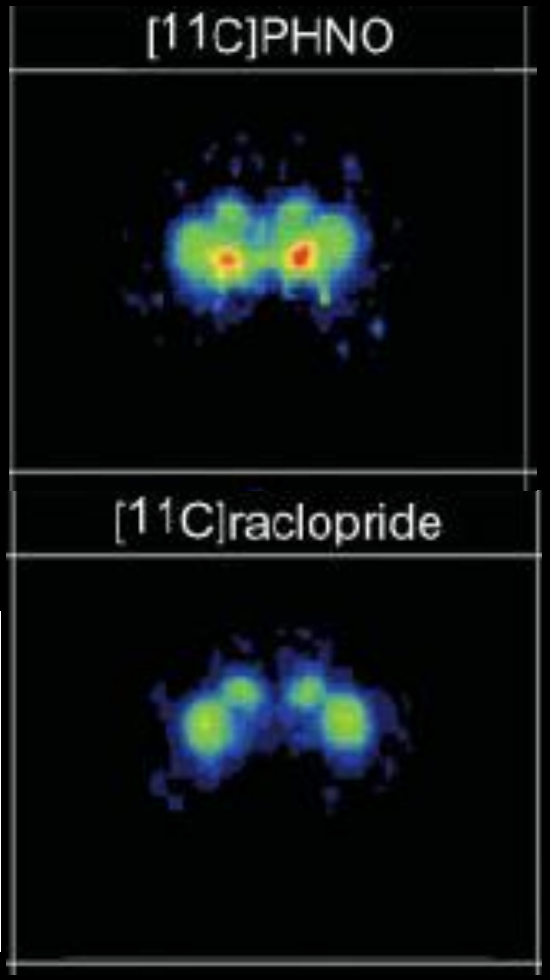
# Selective inhibition of cocaine-seeking behaviour by a partial dopamine $D_3$ receptor agonist

Maria Pilla, Sylvie Perachon, François Sautel, Fabrice Garrido, André Mann, Camille G. Wermuth, Jean-Charles Schwartz, Barry J. Everitt & Pierre Sokoloff

*Nature* 400, 371–375 (1999)

# Dopamine ($D_{2/3}$) Receptor Agonist Positron Emission Tomography Radiotracer [$^{11}$C]-(+)-PHNO is a $D_3$ Receptor Preferring Agonist In Vivo

RAJESH NARENDRAN,[1,2]* MARK SLIFSTEIN,[1,2] OLIVIER GUILLIN,[1,2] YUYING HWANG,[1,2] DAH-REN HWANG,[1,2,3] ERICA SCHER,[1,2] STEPHANIE REEDER,[1,2] EUGENII RABINER,[3] AND MARC LARUELLE[1,2,3]



# Dopamine & pharmacotherapy for addiction

Block DA-ergic function to prevent 'high' or drug seeking

- D2 antagonists
  - Antipsychotics
- D3 antagonists

Boost DA-ergic function to reduce dysphoria, irritability

- DA-ergic 'agonists'
  - bromocriptine
  - disulfiram

What about partial agonists?
Can act as agonist or antagonist depending on state of dopaminergic system.
Some but not all early studies show promise

*Journal of Clinical Psychopharmacology* • Volume 28, Number 1, February 2008

# A Randomized, Multicenter, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Aripiprazole for the Treatment of Alcohol Dependence

*Raymond F. Anton, MD,* Henry Kranzler, MD,† Christopher Breder, MD, PhD,‡ Ronald N. Marcus, MD,‡ William H. Carson, MD,§ and Jian Han, PhD‡*

- 12 weeks, 295 pts
- 2mg titrated to 30mg by 28days
- Primary endpoint: % days abstinent
  - No difference between groups
  - But higher rate of discontinuation & side effects in aripiprazole group (>15mg)
- Secondary endpoints:
  - However aripiprazole group had lower CDT (an LFT), less severe dependency, fewer drinks/drinking day

# A Comparison of Aripiprazole, Methylphenidate, and Placebo for Amphetamine Dependence

Jari Tiihonen, M.D., Ph.D.
Kimmo Kuoppasalmi, M.D., Ph.D.
Jaana Föhr, M.D.
Pekka Tuomola, M.D.
Outi Kuikanmäki, M.D.
Helena Vorma, M.D., Ph.D.
Petteri Sokero, M.D., Ph.D.
Jari Haukka, Ph.D.
Esa Meririnne, M.D.

**Objective:** Problems related to illegal amphetamine use have become a major public health issue in many developed countries. To date, evidence on the effectiveness of psychosocial treatments has remained modest, and no pharmacotherapy has proven effective for amphetamine dependence.

**Method:** Individuals meeting DSM-IV criteria for intravenous amphetamine dependence (N=53) were randomly assigned to receive aripiprazole (15 mg/day), slow-release methylphenidate (54 mg/day), or placebo for 20 weeks. The study was terminated prematurely due to unexpected results of interim analysis. An intention-to-treat analysis was used. The primary outcome measure was the proportion of amphetamine-positive urine samples.

**Results:** Patients allocated to aripiprazole had significantly more amphetamine-positive urine samples than patients in the placebo group (odds ratio=3.77, 95% CI=1.55–9.18), whereas patients who received methylphenidate had significantly fewer amphetamine-positive urine samples than patients who had received placebo (odds ratio=0.46, 95% CI=0.26–0.81).

**Conclusions:** Methylphenidate is an effective treatment for reducing intravenous drug use in patients with severe amphetamine dependence.

*(Am J Psychiatry 2007; 164:160–162)*

Increase in amphetamine +ve urines with aripiprazole.
Reduction with methylphenidate

# Other partial agonists – provide a mix of boosting and blocking

- Buprenorphine
  - Partial mu opiate agonist, kappa antagonist
- Nalmefene
  - Mu opiate antagonist but is also some evidence that it is a partial agonist at kappa receptor
    - Kappa agonists are psychomimetic
    - Stimulating kappa receptor can reduce cocaine consumption in preclinical models.
- Varenicline
  - Nicotine, smoking cessation

# Cocaine and stimulants

- Over 60 medications tried
- Some still actively being investigated
  - Modafinil
    - Glutamate enhancer
  - Atomoxetine
    - Noradrenaline reuptake inhibitor - substitution
    - ADHD
  - Topiramate
    - Anticonvulsant

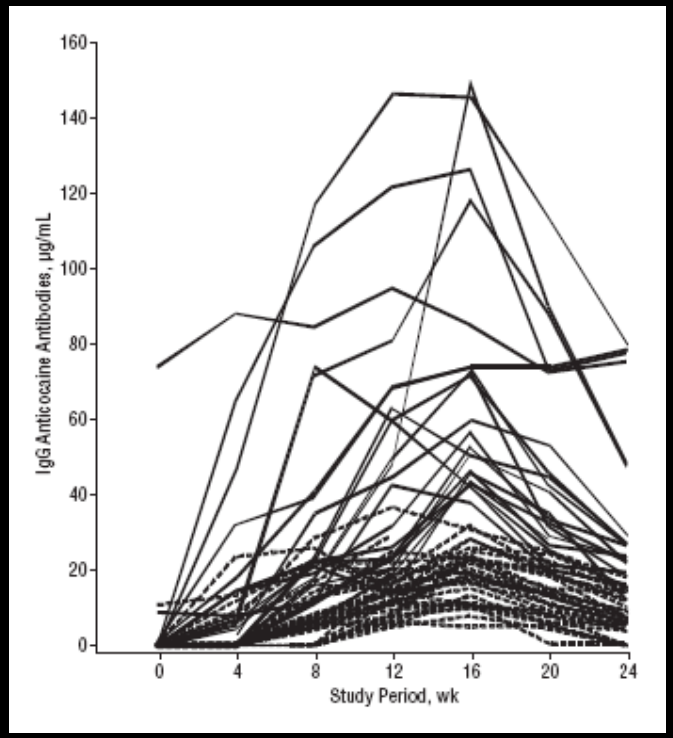
ORIGINAL ARTICLE

# Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients

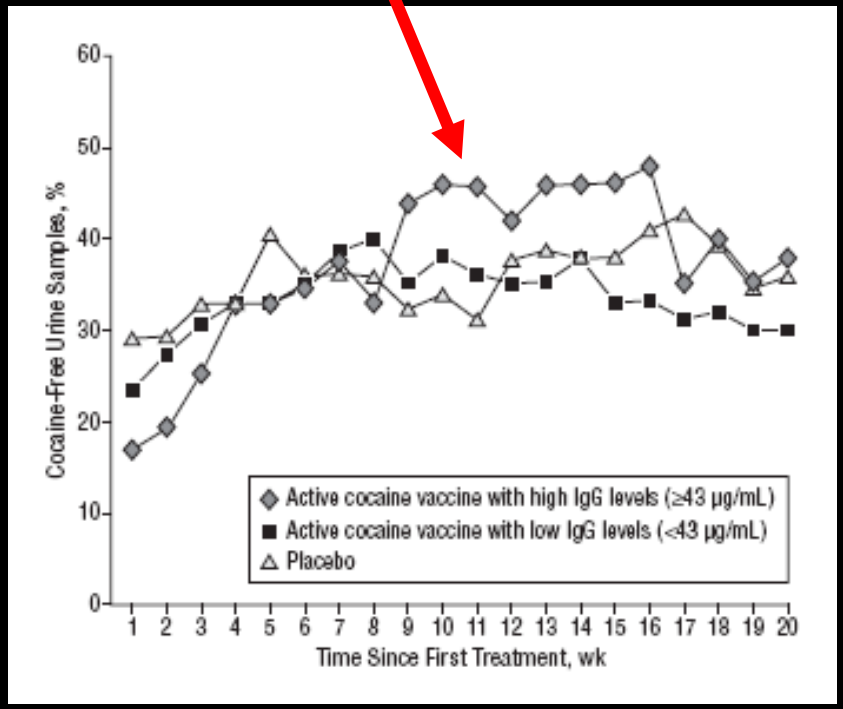
*A Randomized, Double-blind, Placebo-Controlled Efficacy Trial*

*Bridget A. Martell, MD, MA; Frank M. Orson, MD; James Poling, PhD; Ellen Mitchell, RN; Roger D. Rossen, MD; Tracie Gardner, PhD; Thomas R. Kosten, MD*

Variable antibody response
Need boosters




If >43mcg/ml, more cocaine free urine

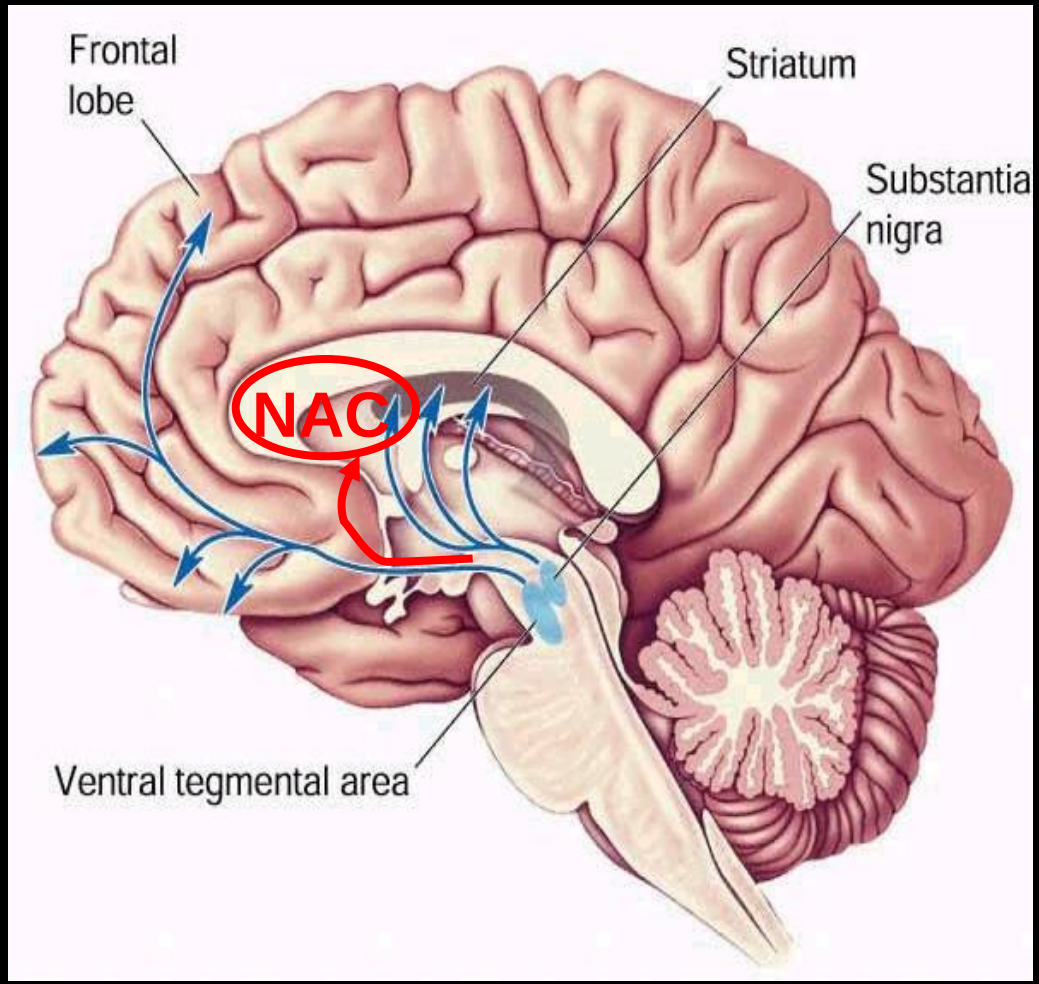


# Drugs of abuse increase dopamine concentration in the nucleus accumbens of the mesolimbic system

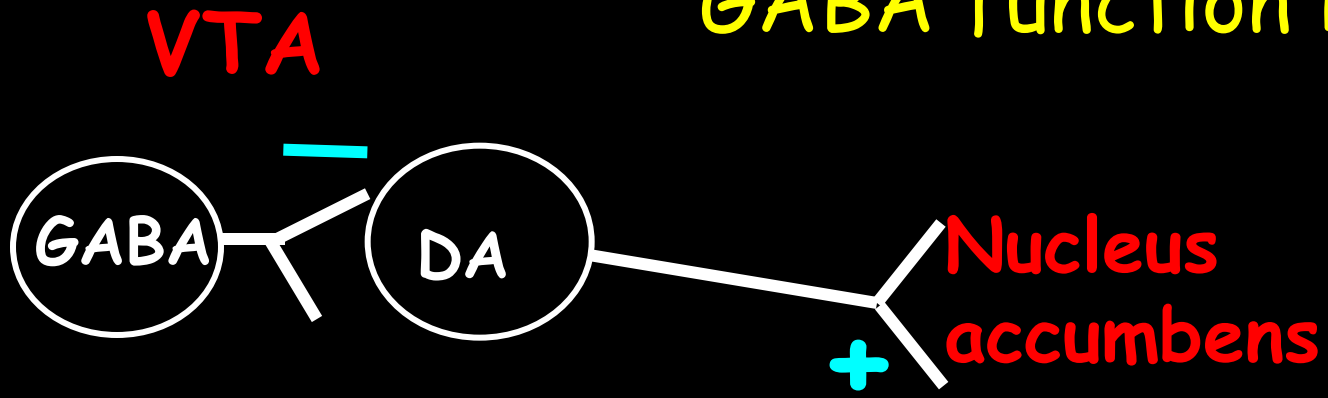
Dopamine system is modulated by other neurotransmitters:

GABA – inhibitory on dopamine neuron

Opioids – inhibitory on GABA-ergic neuron

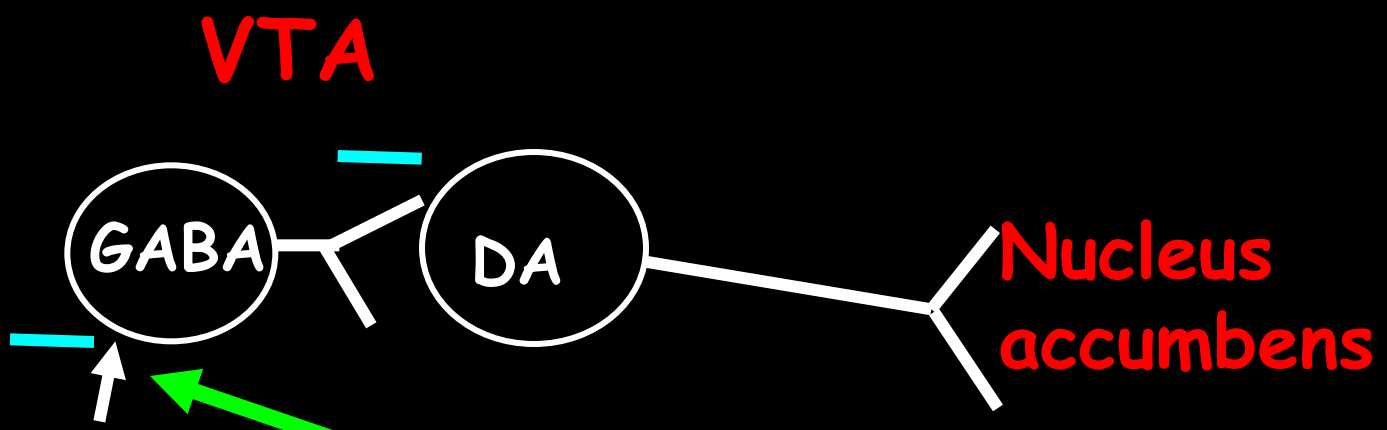


# GABA function in the VTA




- Increasing GABA inhibitory activity
  - GABA-B receptor - baclofen is agonist
    - pre-clinical reduces consumption and response to cues – heroin, cocaine, alcohol
    - clinical – alcohol, cocaine
  - other drugs that increase GABA levels have similar effect – alcohol, cocaine
    - tiagabine, vigabatrin, gabapentin, topiramate

# The dopamine reinforcement pathway: where substances of misuse interact.




- opiates (mu)
- alcohol (via opiate mu)
- nicotine
- cannabis (CB1)

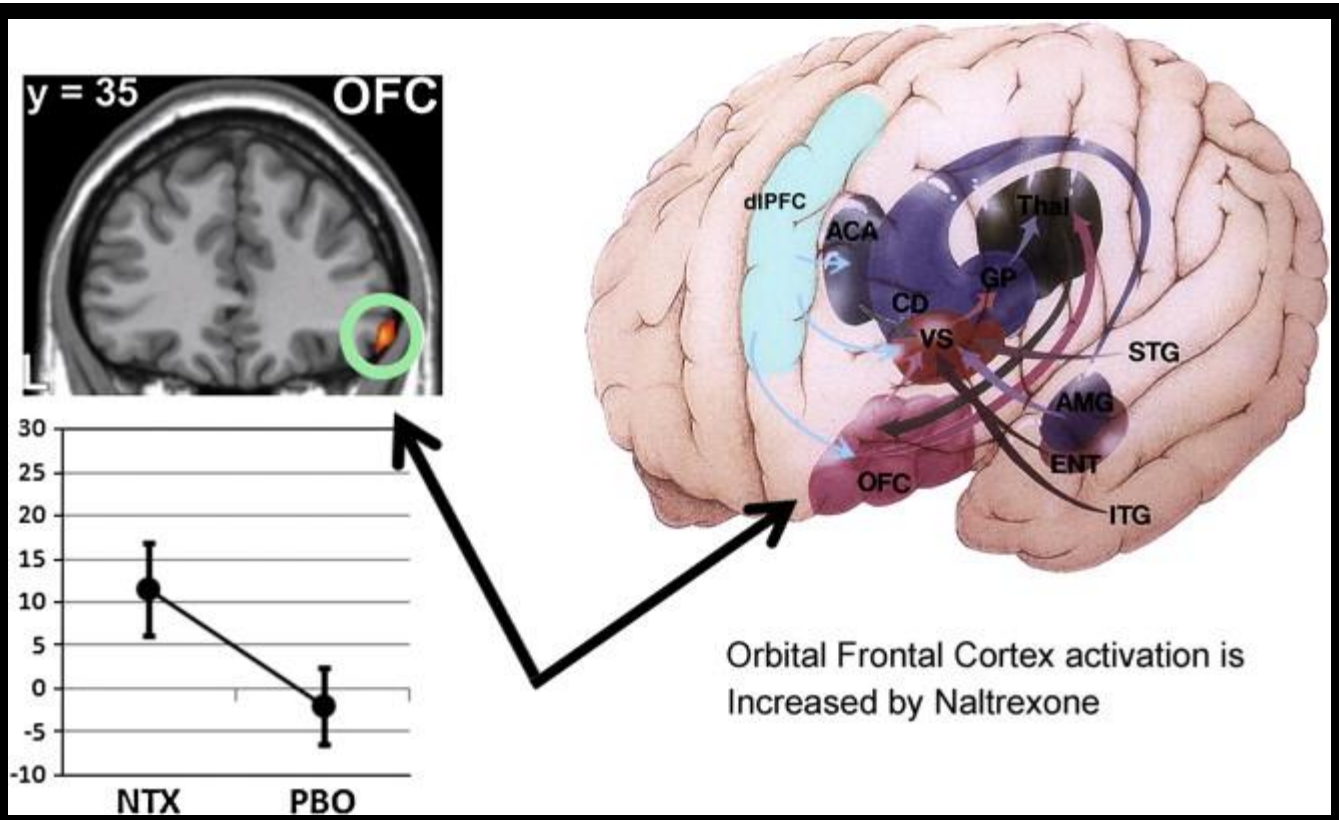
*All inhibit GABA neuron leading to increased DA-ergic neuronal firing.*

Naltrexone blocks the mu opiate receptor leading to reduced DA-ergic activity.

Alcohol misuse – yes
Other substances - ???

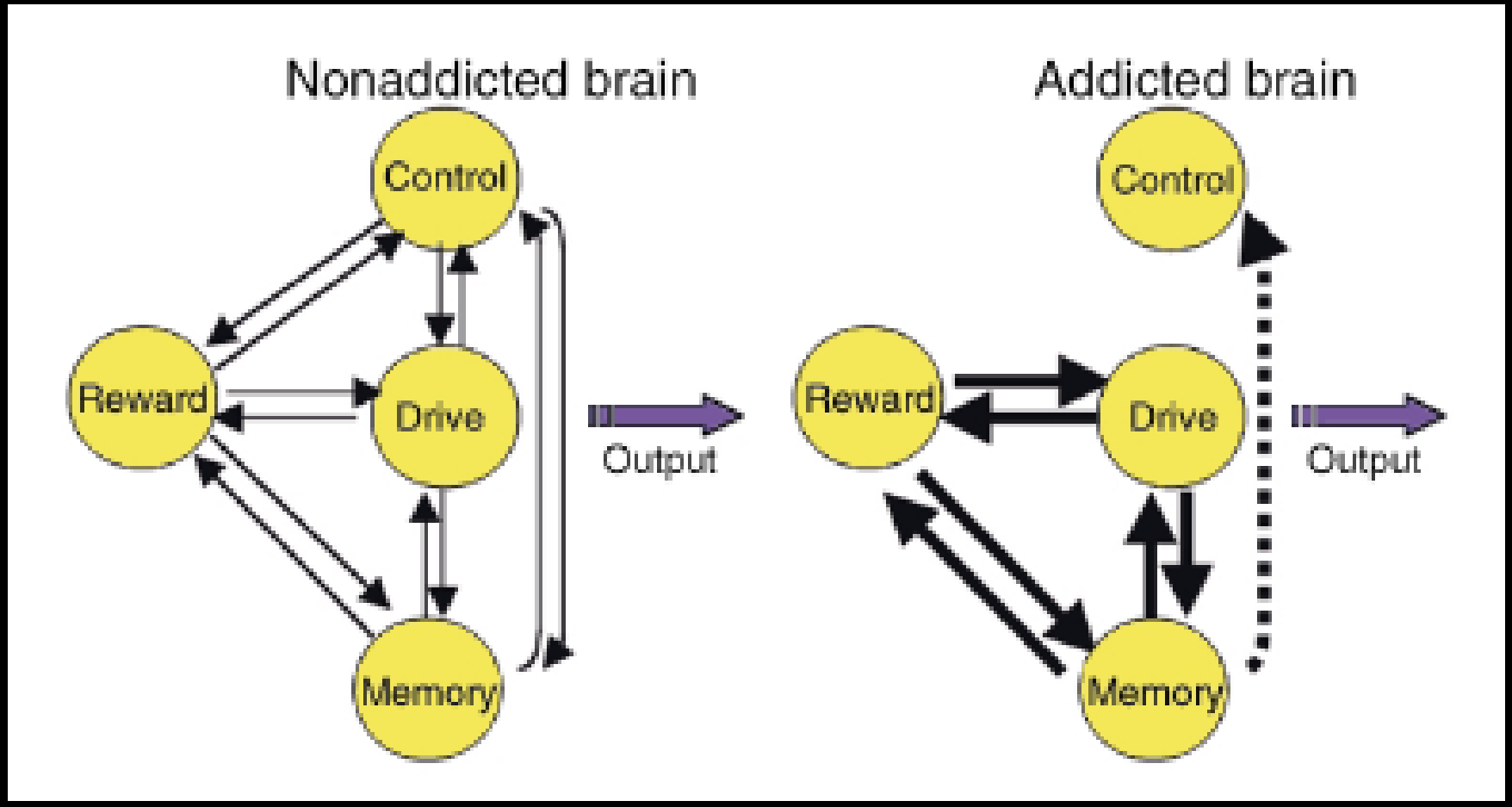
*Now* or *Later*? An fMRI study of the effects of endogenous opioid blockade on a decision-making network

Charlotte A. Boettiger [a,e,*], Elizabeth A. Kelley [b], Jennifer M. Mitchell [b,c], Mark D'Esposito [d,f], Howard L. Fields [b,c]




Naltrexone significantly elevates activity during decision-making (immediate reward vs later reward) in the OFC: Same area previously shown to predict 'later' decision-making

# Model proposing a network of four circuits involved with addiction: reward, motivation/drive, memory, control



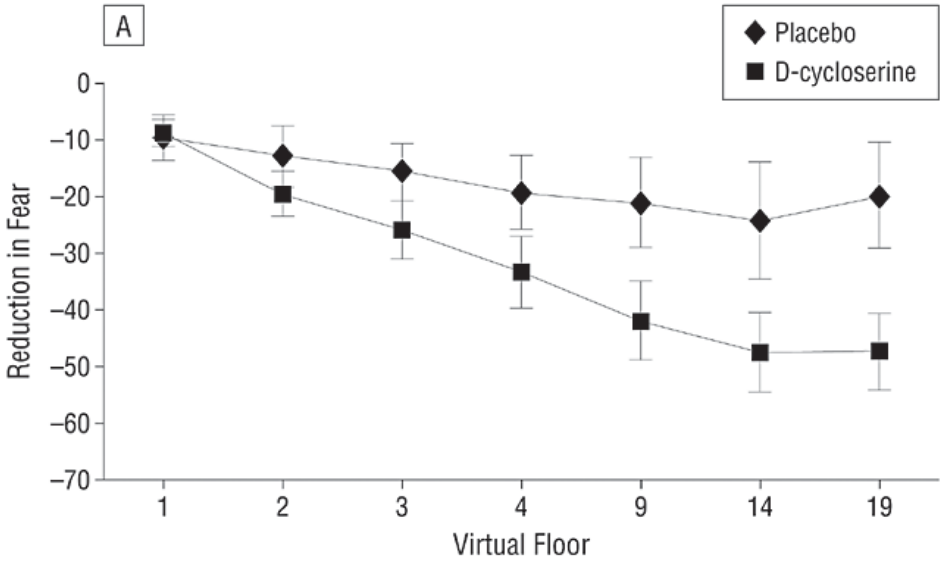

Volkow

# Can we use drugs to unlearn maladaptive behaviours?

## New learning & anti-learning drugs

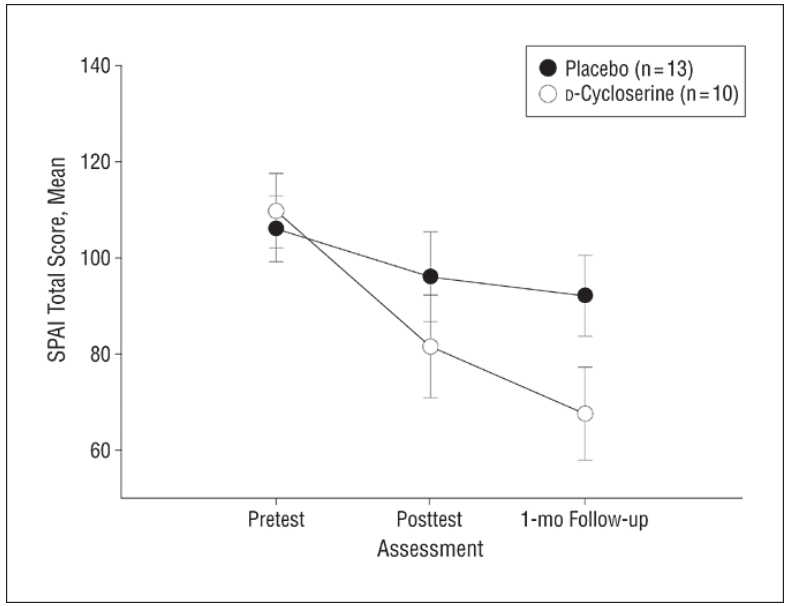
- e.g. D-cycloserine & other glutamatergic agents

### Cognitive Enhancers as Adjuncts to Psychotherapy: Use of D-Cycloserine in Phobic Individuals to Facilitate Extinction of Fear




*Ressler et al 2004*

### Augmentation of Exposure Therapy With D-Cycloserine for Social Anxiety Disorder




*Hofmann et al 2006*

# Can we use drugs to unlearn maladaptive behaviours?

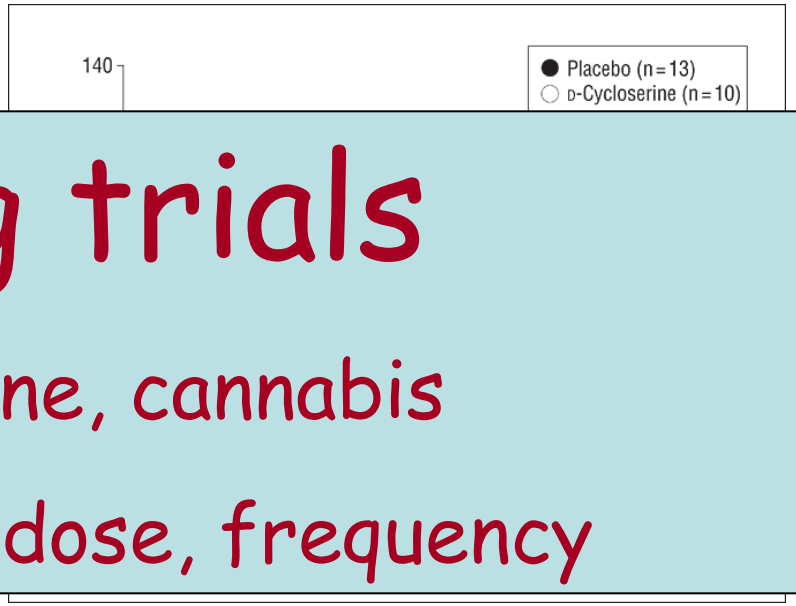
## New learning & anti-learning drugs

- e.g. D-cycloserine & other glutamatergic agents

Cognitive Enhancers as Adjuncts to Psychotherapy: Use of D-Cycloserine in Phobic Individuals to Facilitate Extinction of Fear


Ressler et al 2004

Augmentation of Exposure Therapy With D-Cycloserine for Social Anxiety Disorder



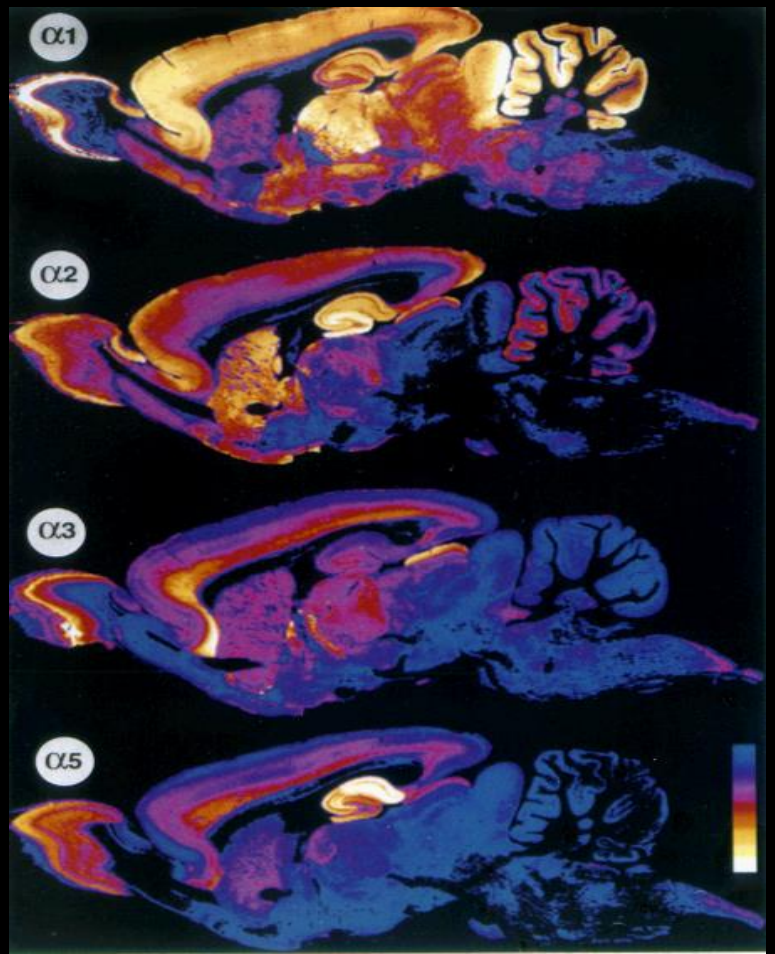

Hofmann et al 2006

## Ongoing trials

Alcohol, nicotine, cannabis

Issues: exposure, dose, frequency

# GABA-benzodiazepine receptors are involved in learning and memory. Different GABA-benzodiazepine receptors in different parts of the brain



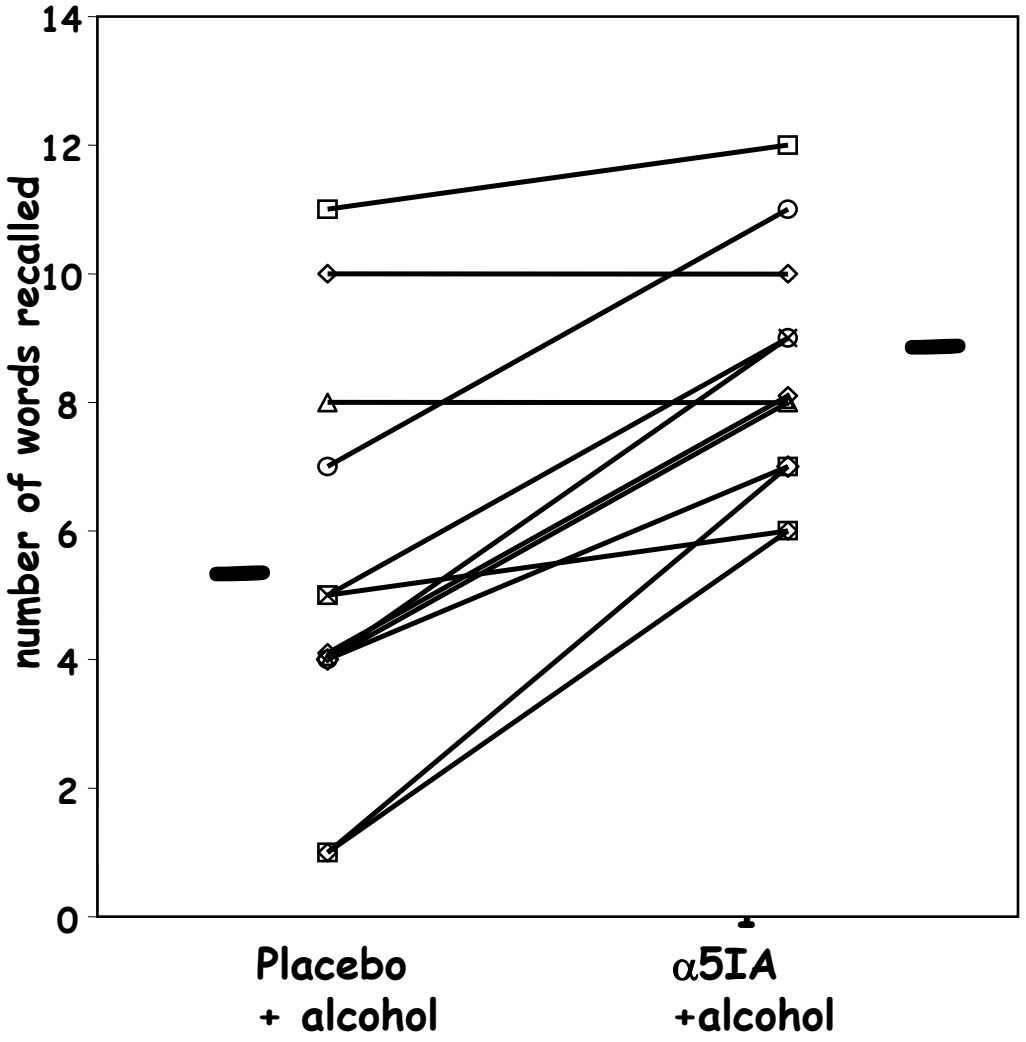

Sedation, amnesia, seizures

Anxiety

Anxiety

Learning, memory

# A drug that works through alpha5 subtype, α5IA, reverses alcohol's amnestic effect in humans




Max score = 20

Normal control
~ 8-10 words

Blood alcohol

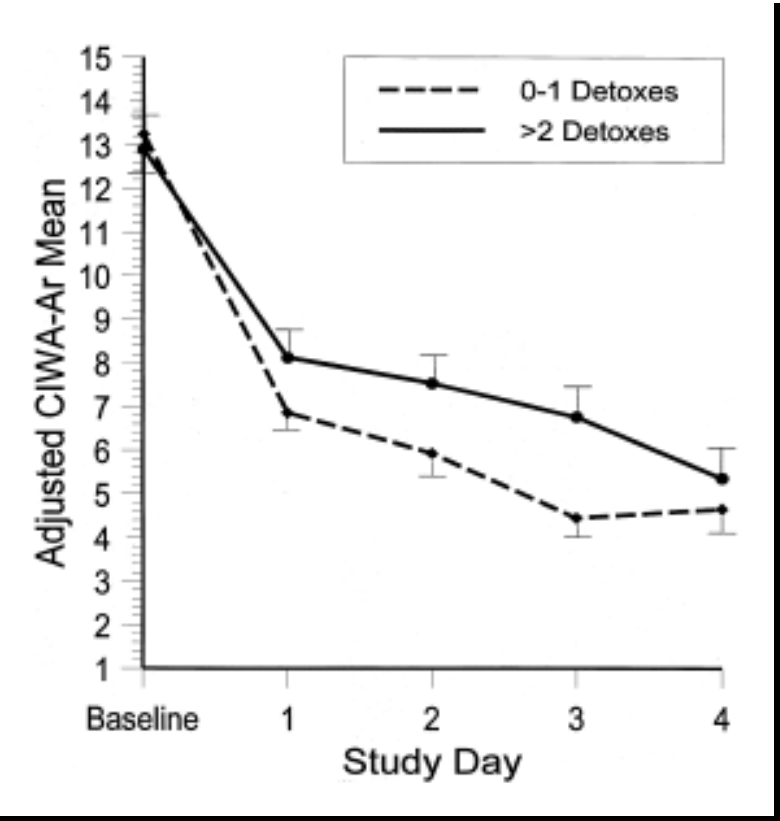
= ~ 130 mg%

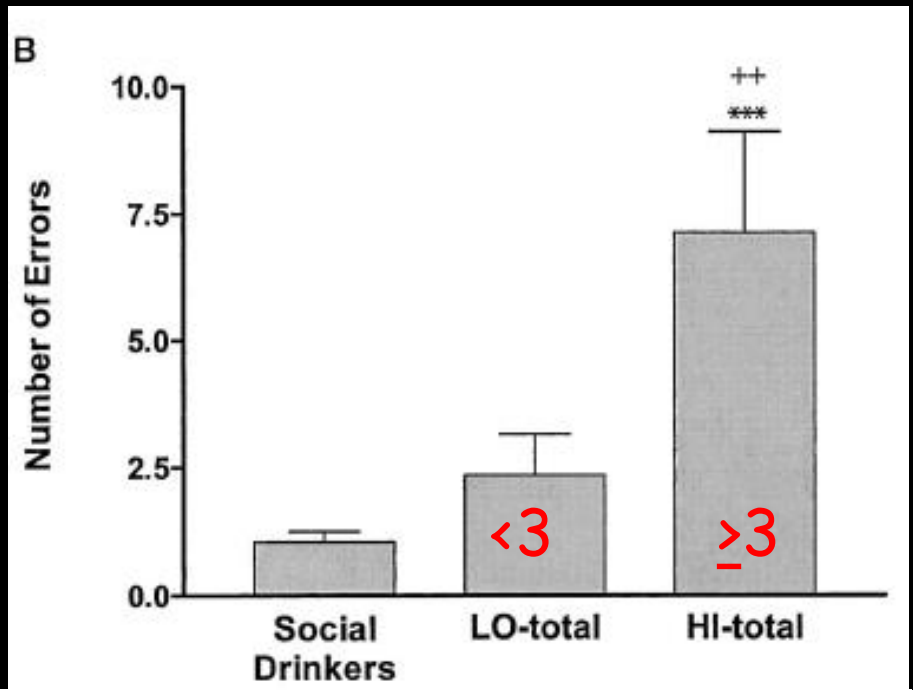
*Nutt et al 2007 Neuropharmacology*

# Alcohol detoxification.

# Multiple previous detoxifications are associated with less responsive treatment and heavier drinking during an index outpatient detoxification☆

R. Malcolm*, J.S. Roberts, W. Wang, H. Myrick, R.F. Anton



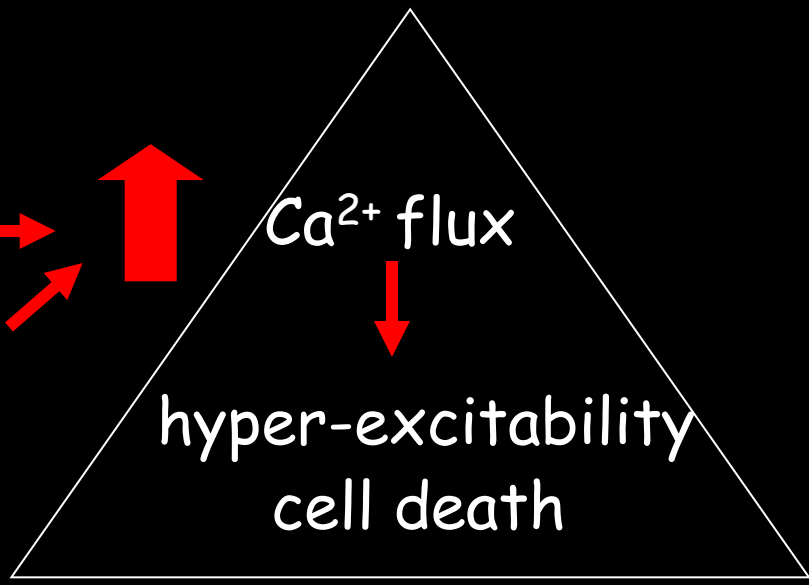

0145-6008/03/2710-1563$03.00/0
ALCOHOLISM: CLINICAL AND EXPERIMENTAL RESEARCH
Vol. 27, No. 10
October 2003

# Impairment in Cognitive Functions After Multiple Detoxifications in Alcoholic Inpatients

Theodora Duka, Julia M. Townshend, Kirsty Collier, and David N. Stephens

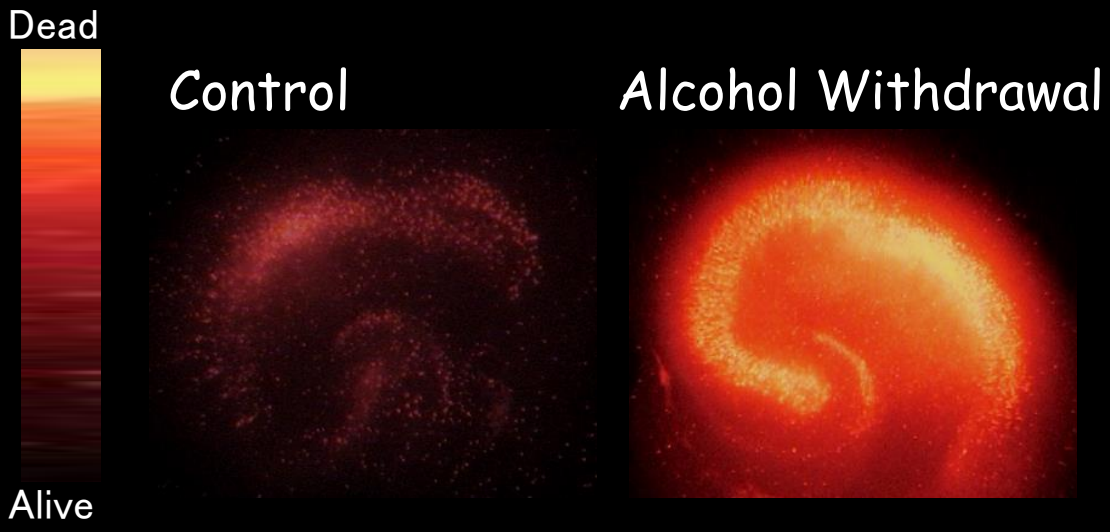
# Alcohol withdrawal – toxic time for brain – dysregulation in excitatory and inhibitory activity

- increased excitation
  - NMDA receptor
  - L-subtype of $Ca^{2+}$ channel




- decreased inhibition
  - GABA-ergic activity
  - $Mg^{2+}$ inhibitory system (NMDA receptor)

# Hippocampal damage during alcohol withdrawal – *CA1*




courtesy of Prendergast & Littleton

# Acamprosate and other 'anti-glutamatergic' reduces this damage during alcohol withdrawal.


cell death also :
reduced with other
'antiglutmatergic' drugs

courtesy of Prendergast & Littleton

# ADEPT.
# Alcohol detoxification in primary care treatment

A feasibility study of conducting a randomised trial in primary care comparing two pharmacological regimens.

**Study Design:** The study involves a randomised double-blind placebo controlled trial comparing:

- Usual medication (chlordiazepoxide) + thiamine + daily monitoring/contact + acamprosate with
- Usual medication (chlordiazepoxide) + thiamine + daily monitoring/contact + an identical placebo

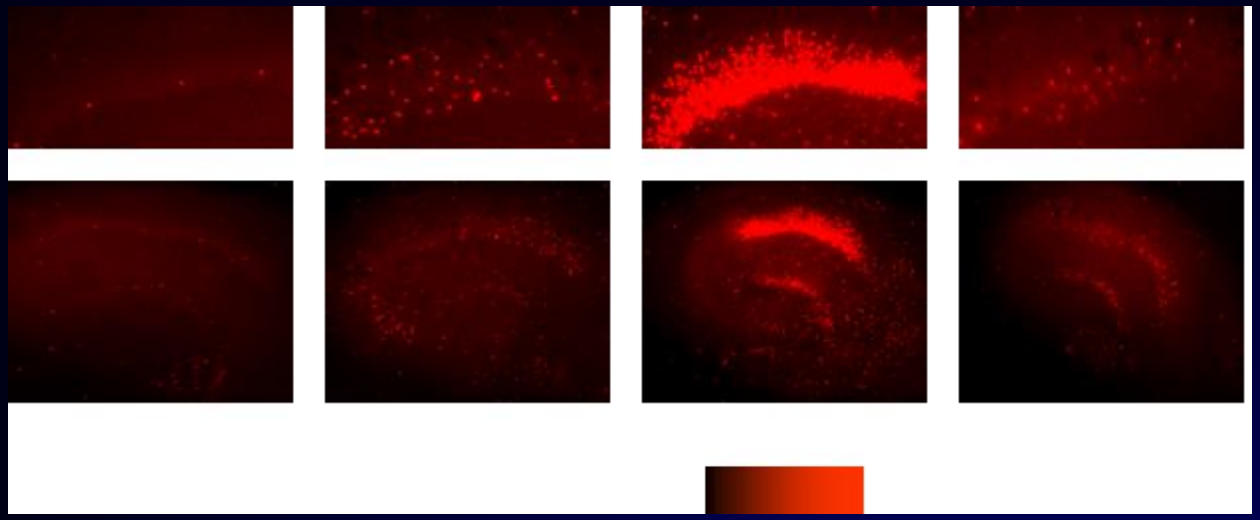
Funded by 'Research for patient benefit', NIHR.

# Another strategy for alcohol detox

- Stress - HPA, cortisol/corticosterone
  - Preclinical studies show increase in brain concentrations of the glucocorticoid, corticosterone after alcohol withdrawal
- Involved in alcohol-induced brain damage?
- Effects of glucocorticoid receptor (type II) antagonist.
  - mifepristone – reduces excitability, prevents memory deficit

Courtesy of Hilary Little

# Effects of Mifepristone on Neuronal Damage in Organotypic Hippocampal Cultures




Corticosterone greatly increased the neuronal damage caused by withdrawal of alcohol

Mifepristone (but not a Type I glucocorticoid receptor antagonist) prevented this effect of corticosterone

Collaboration with P. Mulholland and M. Prendergast, University of Kentucky

Courtesy of Hilary Little

# Clinical trial of mifepristone in alcoholics

MRC funded clinical trial in progress at the Institute of Psychiatry, with Colin Drummond and Abigail Rose

Participants - alcoholics entering the Alcohol Unit for detoxification

Treatment - mifepristone or placebo for two weeks from cessation of drinking

Testing - BDI-II and CANTAB, plus other questionnaires

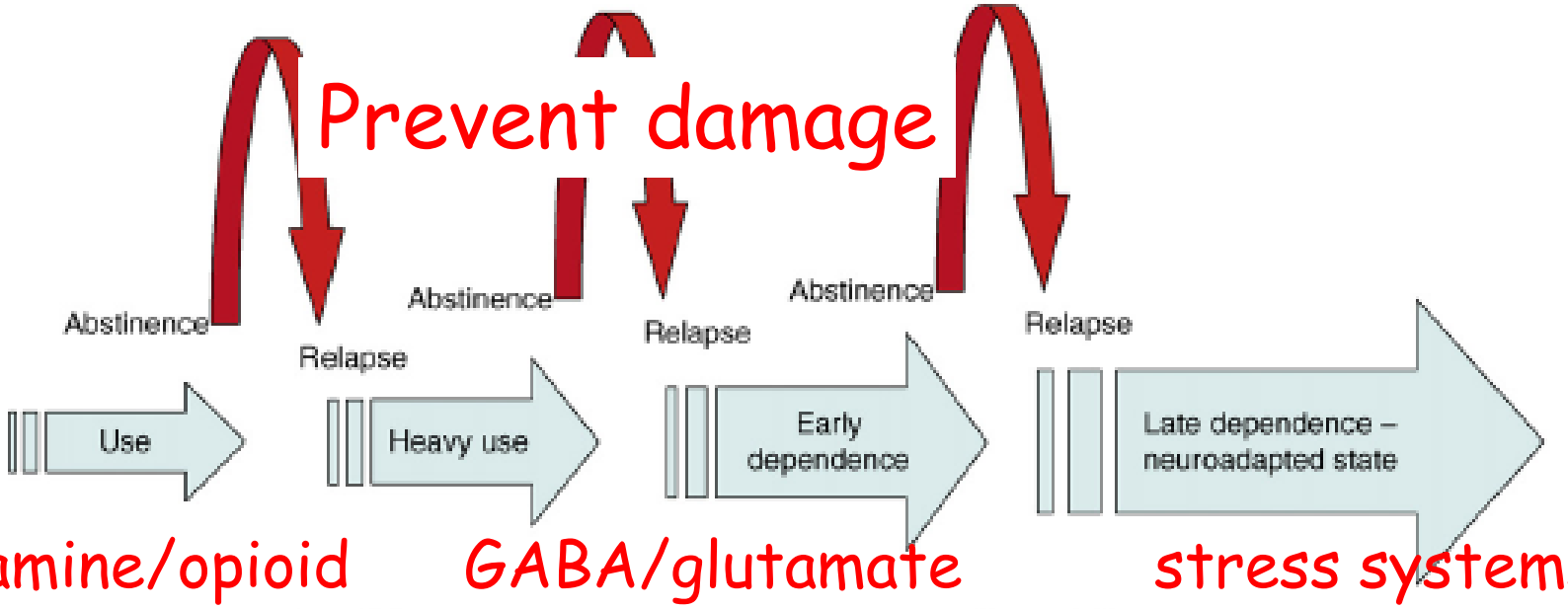
Courtesy of Hilary Little

# Stress system: more targets. Relapse prevention

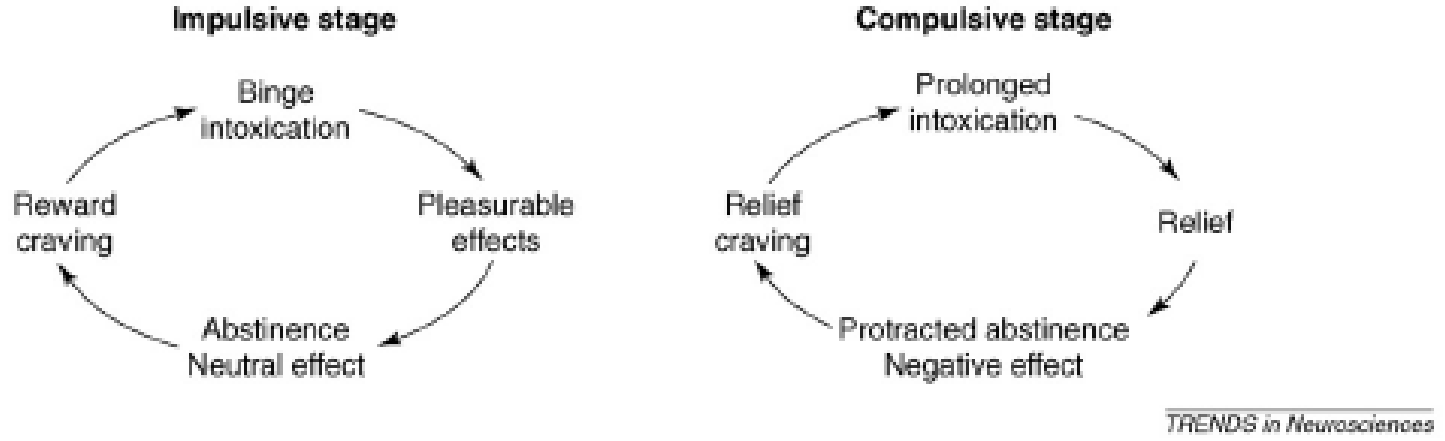
| System | Principle |
| --- | --- |
| Corticotrophin releasing hormone | CRH 1 antagonist |
| NK 1 *(Substance P )* | NK 1 antagonist |
| Nociceptin | NOP agonist |
| Neuropeptide Y | Y2 antagonist |
| Orexin | OX1 antagonist |

# Summary

## Lots of targets eg in time, neurotransmitter.




Dopamine/opioid GABA/glutamate stress systems




Adapted from Heilig & Koob, 2007

# Future directions?

- Impact on reward pathway to learning, memory, decision making
- Predictors for treatment efficacy
  - For many medications hard to find any in terms of patient profile
  - Pharmacogenetics
    - Naltrexone in alcohol misuse
    - Polymorphism of mu opioid receptor
- Optimising interactions with psychosocial approaches
- Polydrug misuse
- Role for antagonists?