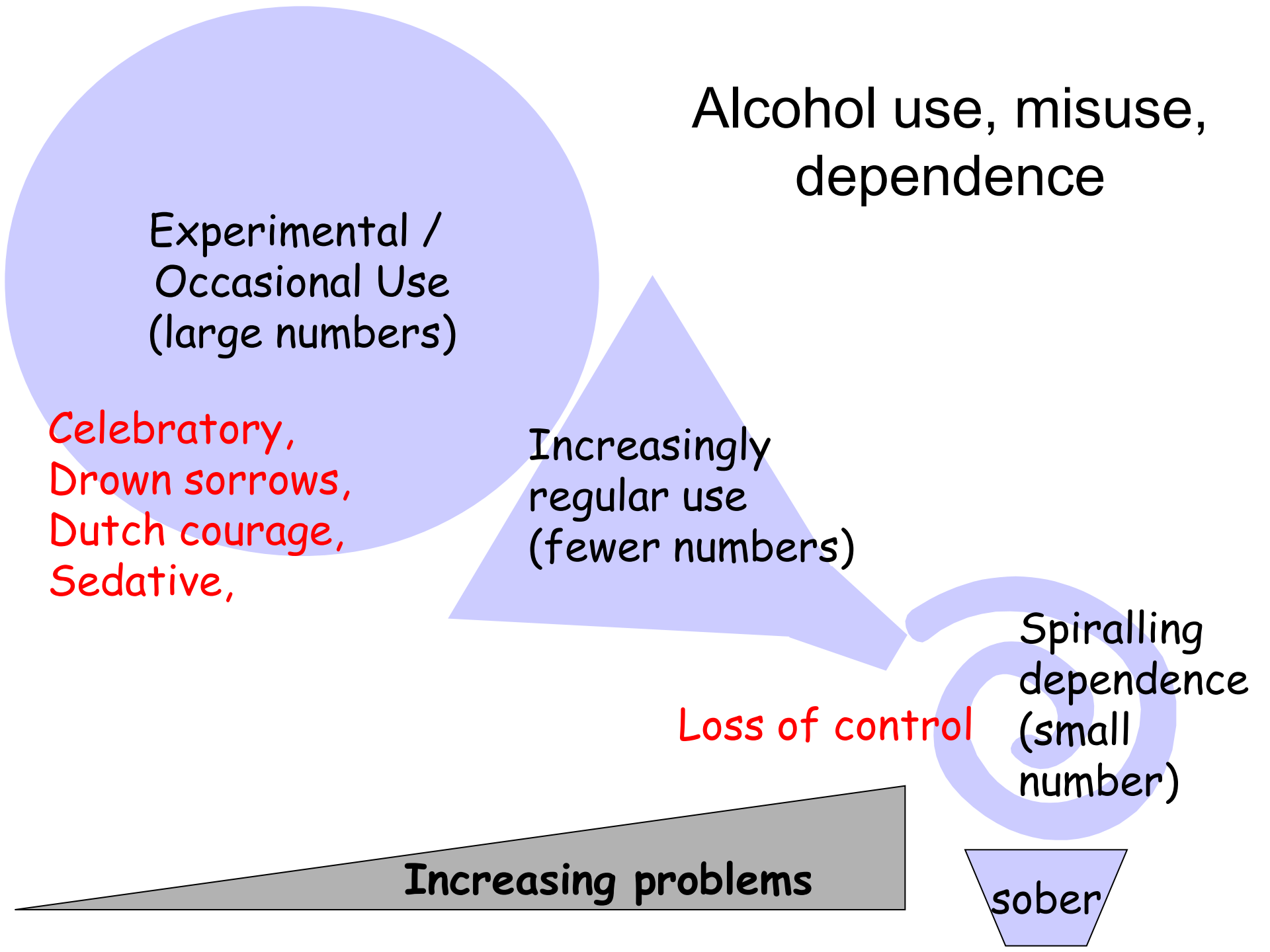
Brain mechanisms of intoxication, dependence and damage.

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

MRC Clinical Sciences Centre

Imperial College London

Alcohol use, misuse, dependence

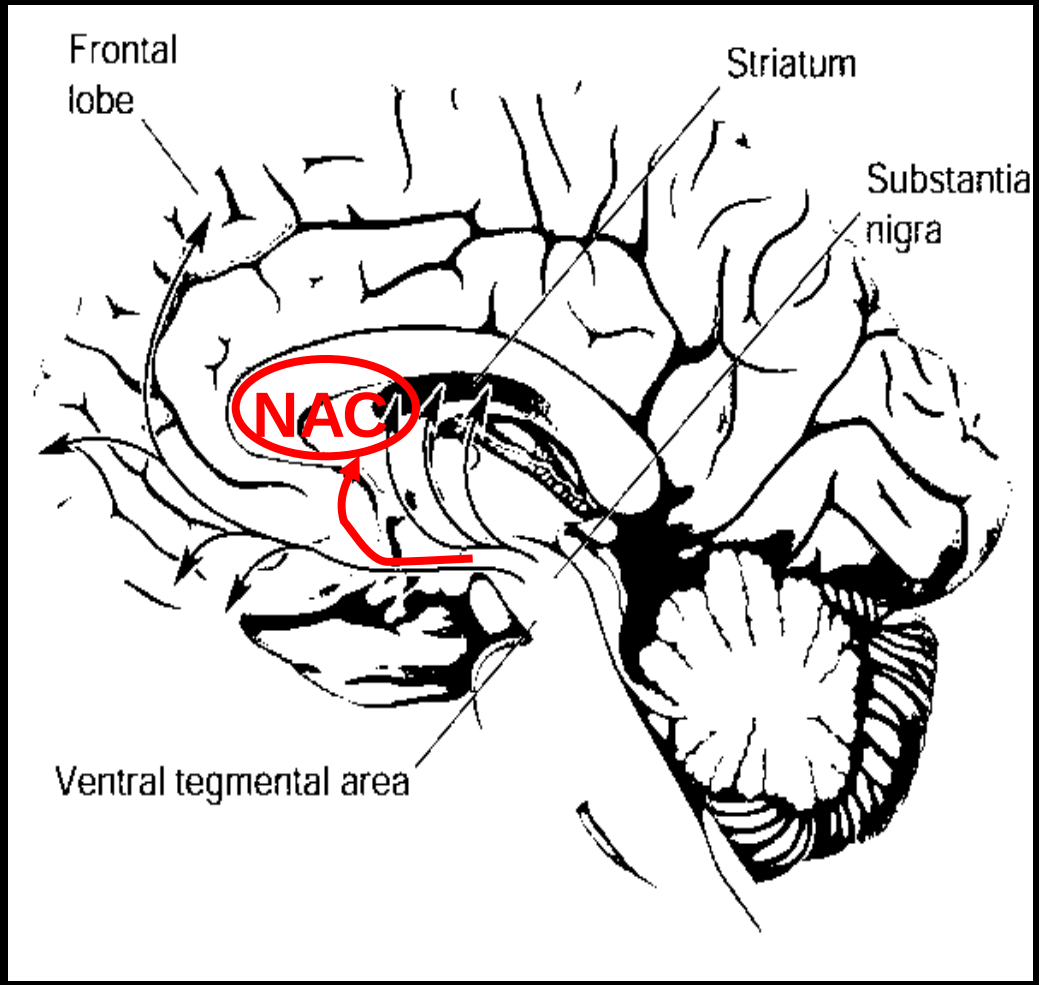


Pleasure
Reward
Drug seeking

Dopamine

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

↑ DA :
cocaine,
amphetamine
alcohol,
opiates,
nicotine,
cannabinoids,
MDMA



Alcohol Promotes Dopamine Release in the Human Nucleus Accumbens

ISABELLE BOILEAU,[1] JEAN-MARC ASSAAD,[2,4] ROBERT O. PIHL,[2] CHAWKI BENKELFAT,[3] MARCO LEYTON,[3] MIRKO DIKSIC,[1] RICHARD E. TREMBLAY,[4] AND ALAIN DAGHER[1]*

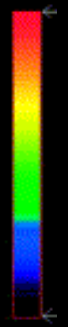
Increase in dopamine release in nucleus accumbens / ventral striatum

- related to impulsiveness from novelty-seeking dimension of TPQ but not high / intoxication

Synapse, 2003

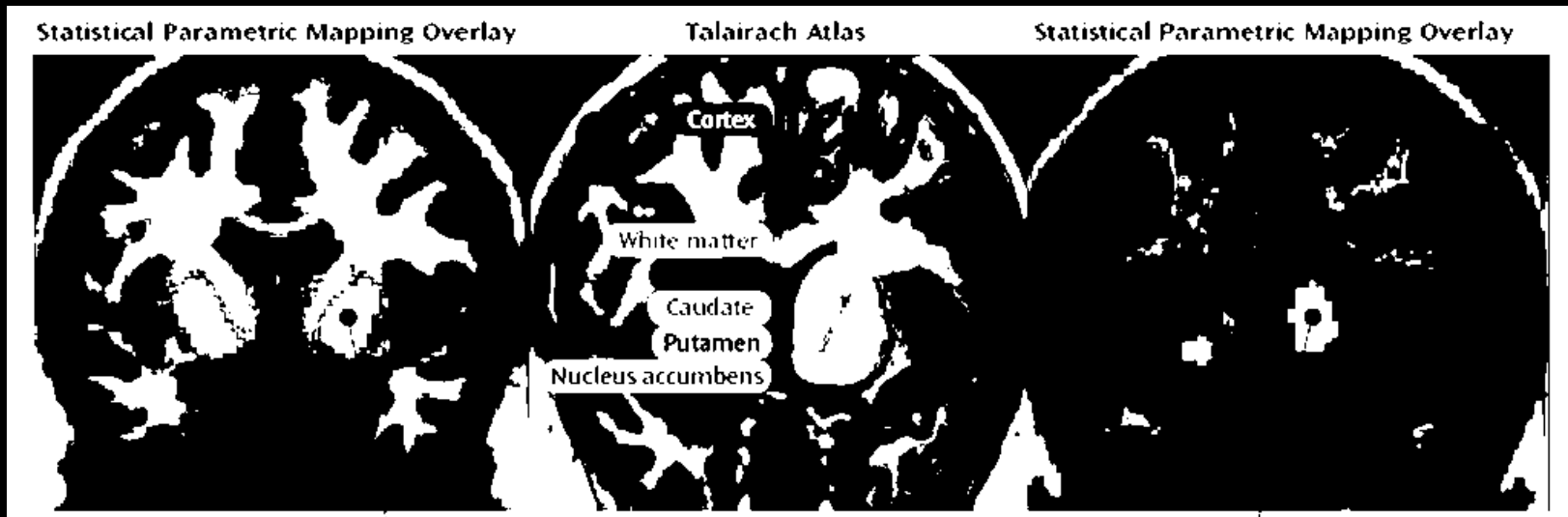
But in dependence, have reduced dopamine function and receptors.
Little recovery with abstinence.

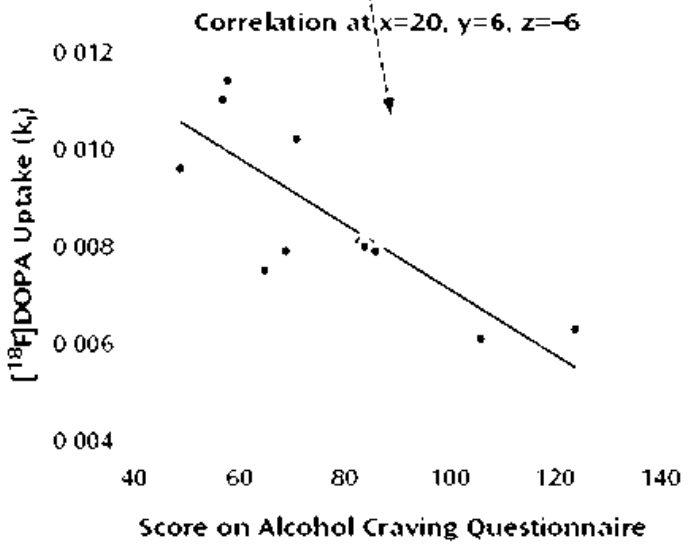
cocaine

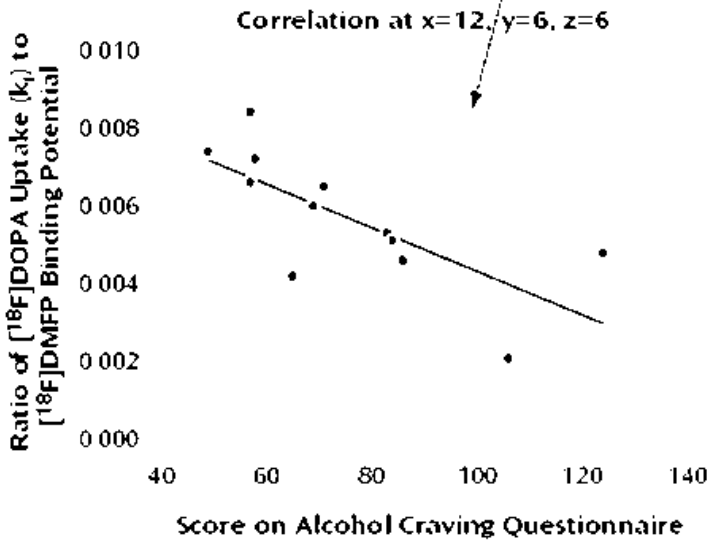


alcohol

Correlation of Alcohol Craving With Striatal Dopamine Synthesis Capacity and $D_{2/3}$ Receptor Availability: A Combined [^{18}F]DOPA and [^{18}F]DMFP PET Study in Detoxified Alcoholic Patients

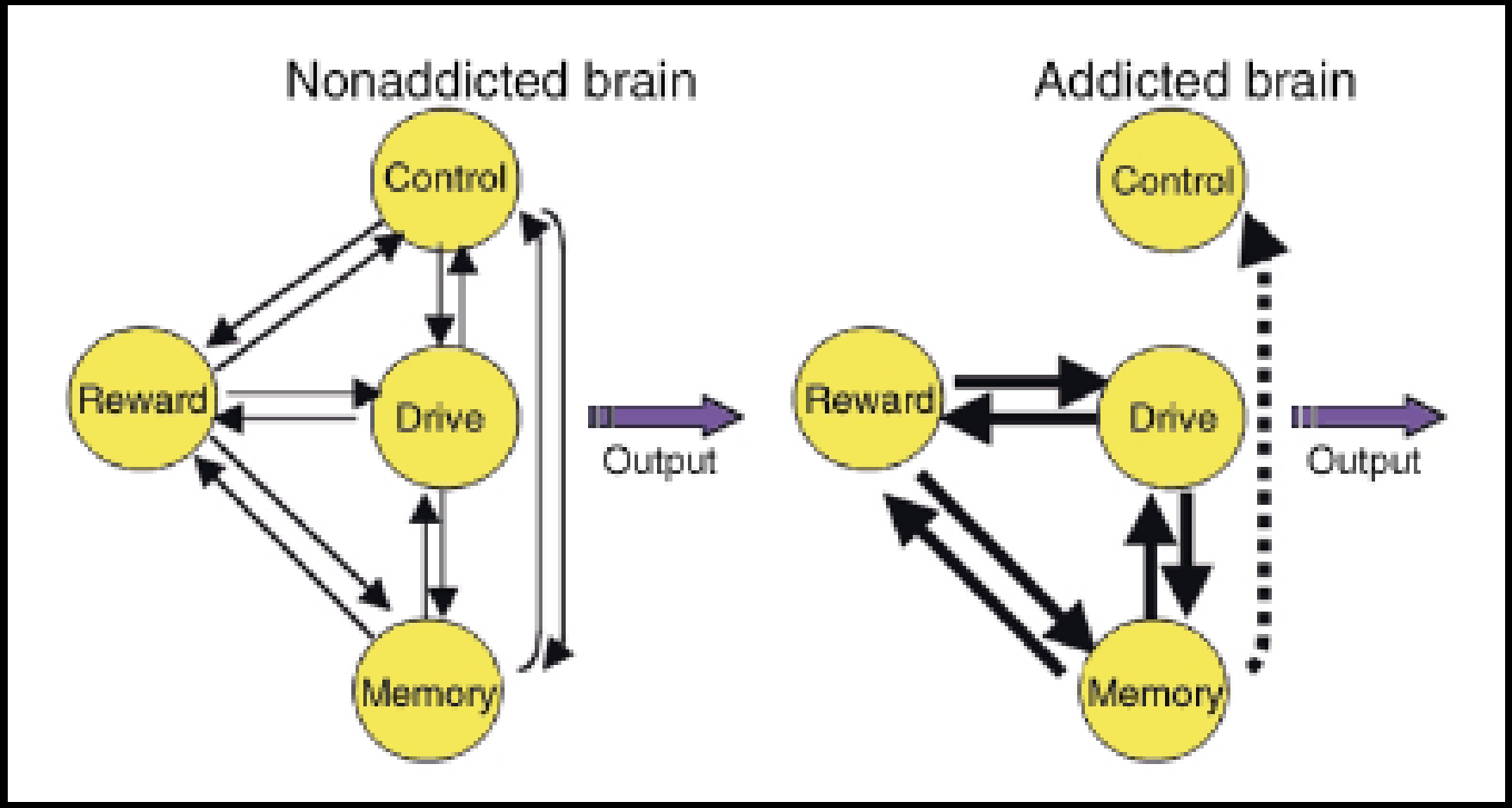






Heinz et al 2005

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

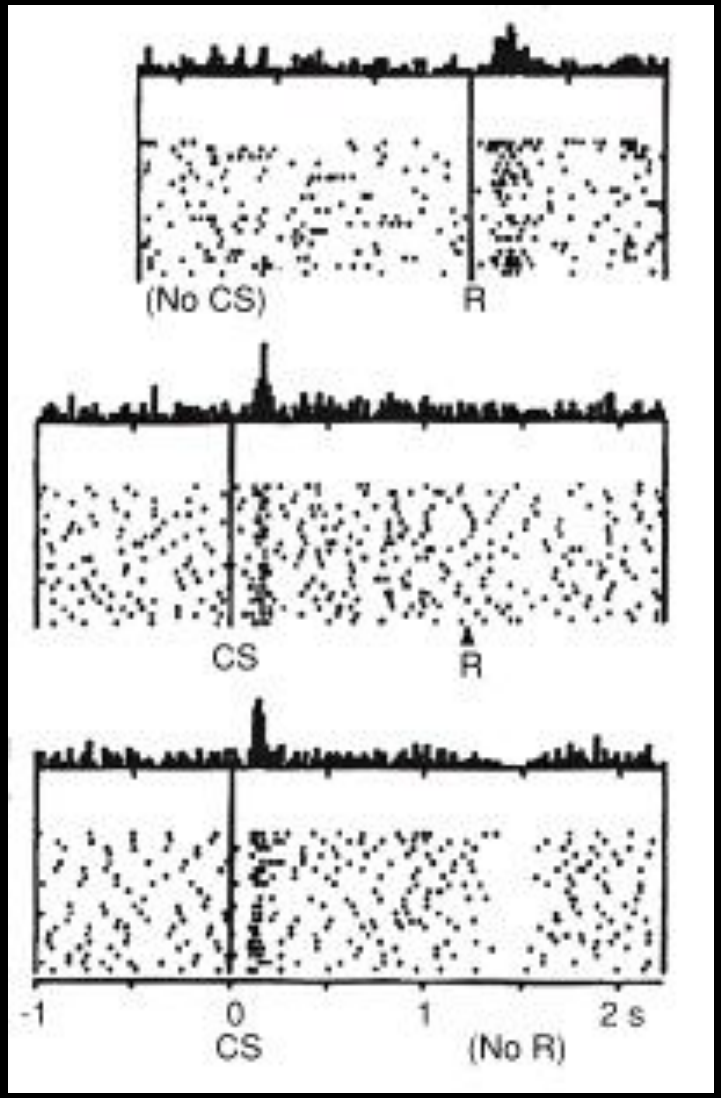


Volkow

Dopamine

Role after 'pleasure'

Expected vs unexpected rewards – the role of anticipation *[Schulz]*



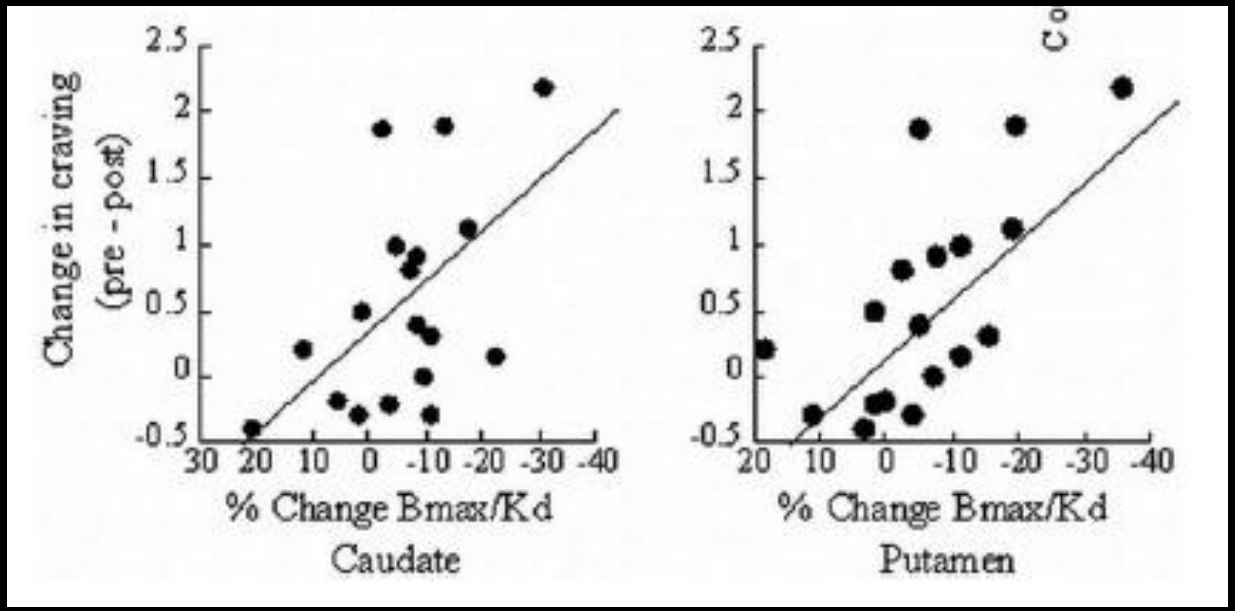
No prediction
Reward occurs
⇧ *in DA neuronal firing*

Reward prediction
Reward occurs
⇧ *in DA neuronal firing to cue*

Reward predicted
No reward occurs
⇩ *in DA neuronal firing at time of reward*

Cocaine Cues and Dopamine in Dorsal Striatum: Mechanism of Craving in Cocaine Addiction

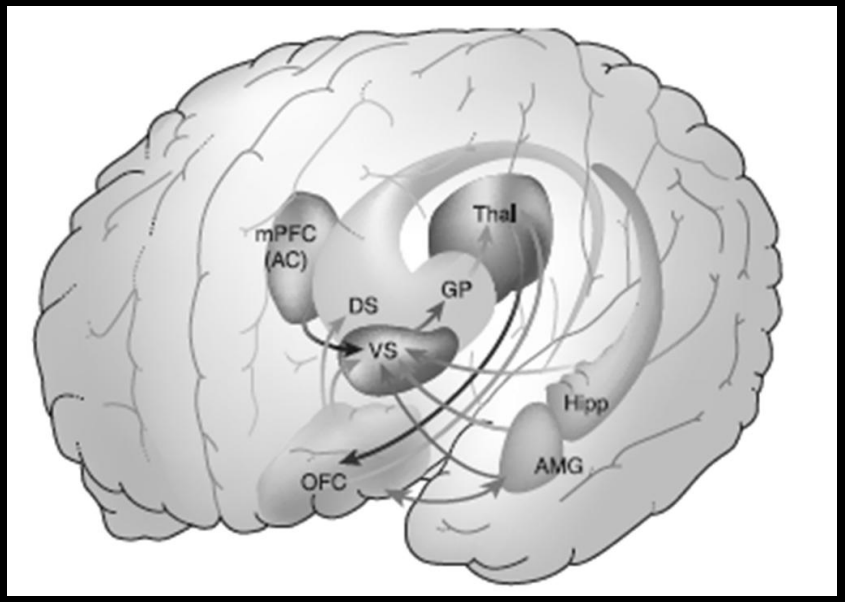
Nora D. Volkow,[1] Gene-Jack Wang,[2] Frank Telang,[1] Joanna S. Fowler,[3] Jean Logan,[3] Anna-Rose Childress,[4] Millard Jayne,[1] Yeming Ma,[1] and Christopher Wong[3]

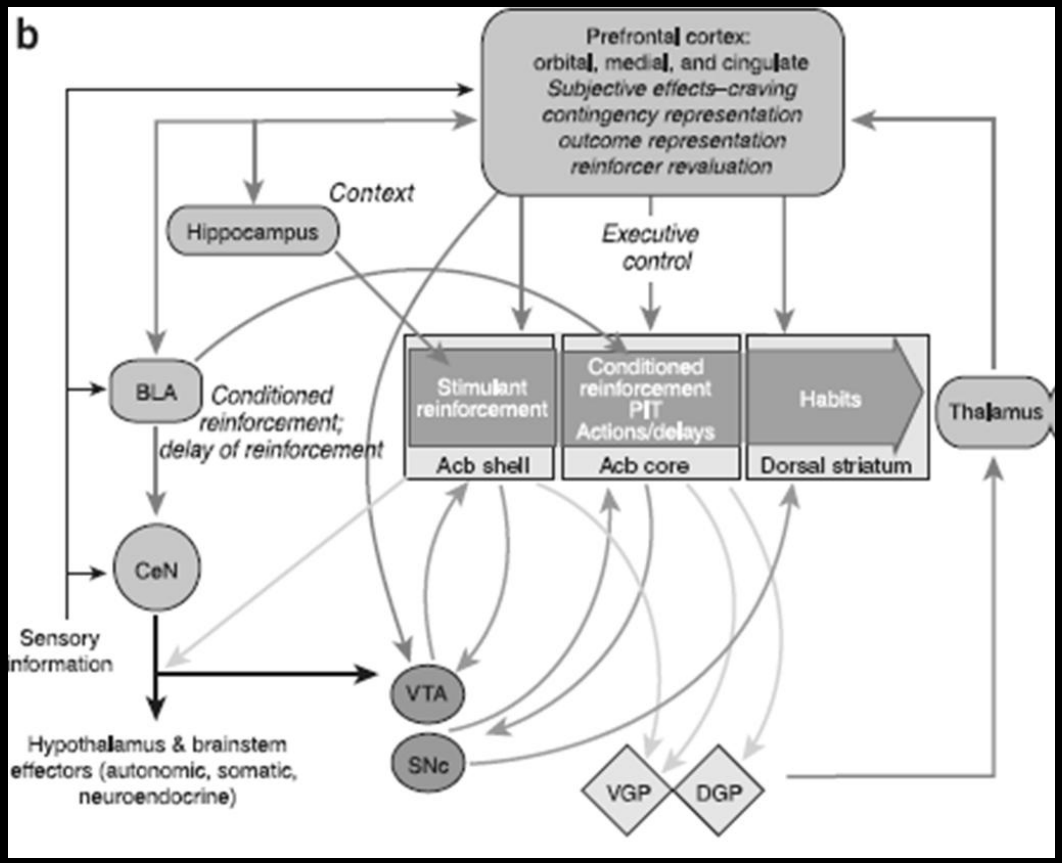


Cocaine cues increase dopamine levels in the dorsal but not ventral striatum

Neural systems of reinforcement for drug addiction: from actions to habits to compulsion

Barry J Everitt & Trevor W Robbins





Dopamine & pharmacotherapy for addiction

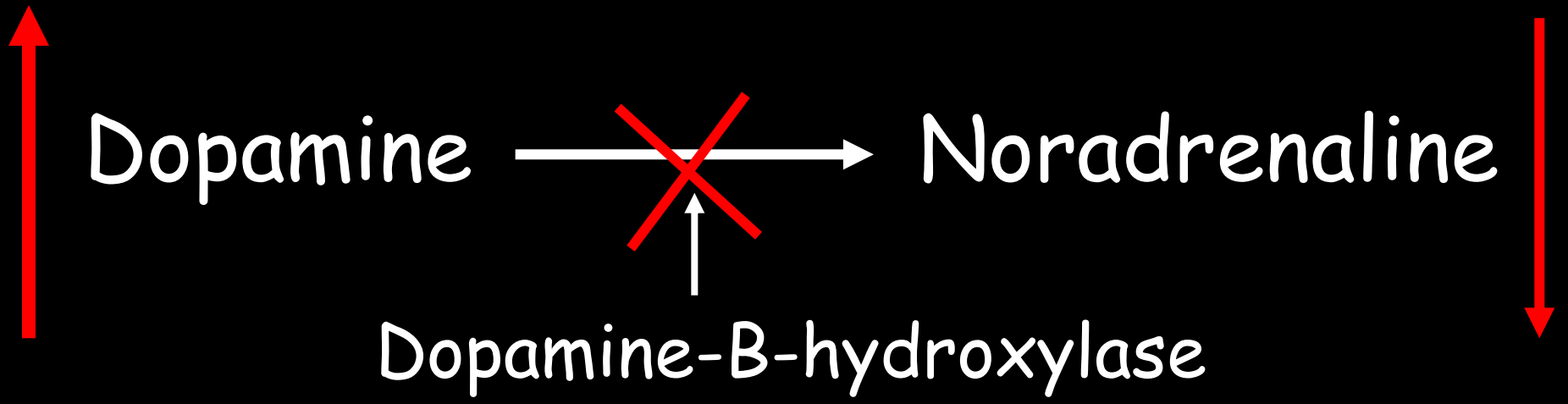
Block DA-ergic function to prevent 'high' or drug seeking

- D2 antagonists
  - Antipsychotics
- D3 antagonists

Boost DA-ergic function to reduce dysphoria, irritability

- DA-ergic 'agonists'
  - bromocriptine
  - disulfiram

How does disulfiram increase dopamine?



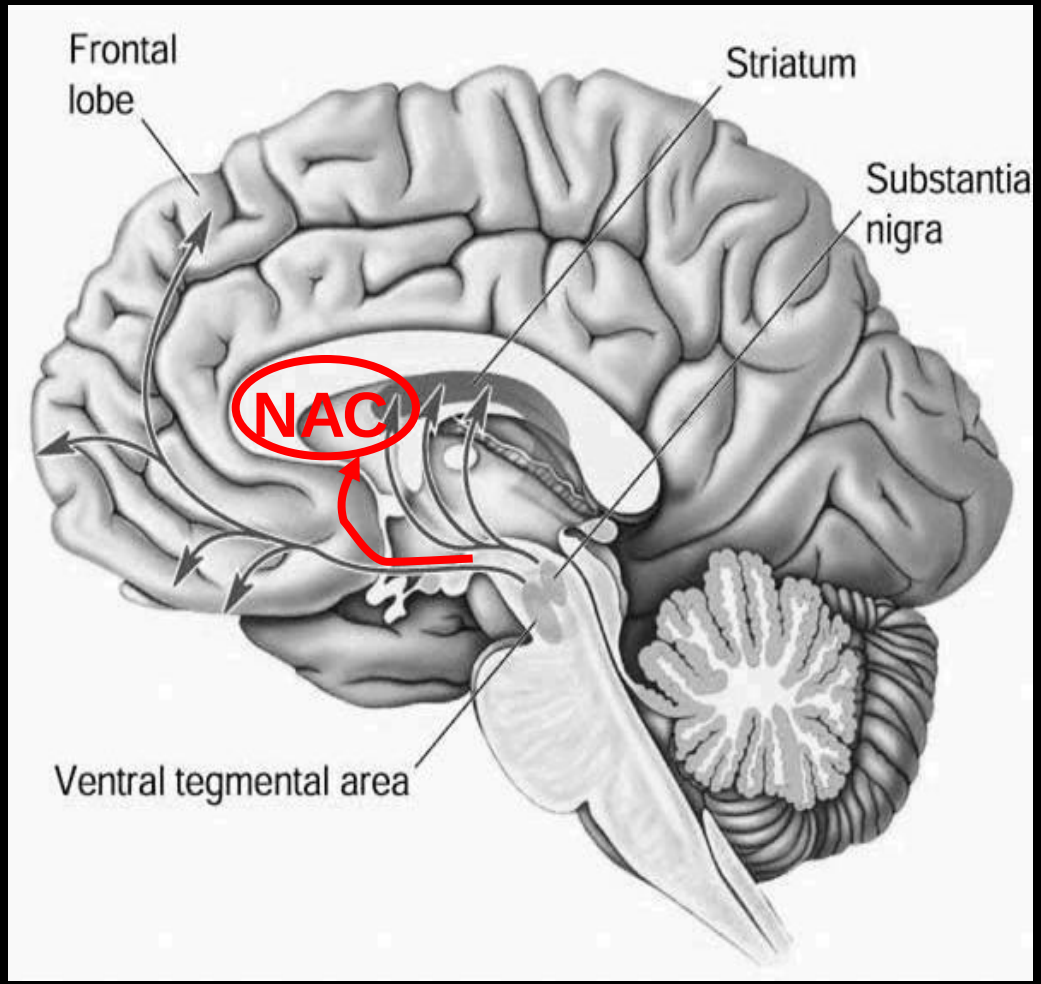
Can precipitate anxiety, mania, psychosis, depression

- However when higher doses were used (1-2g vs 200mg).
- In presence of cocaine, get these 'adverse' effects and reduced use.
- Not just mediated by change in drinking behaviour

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

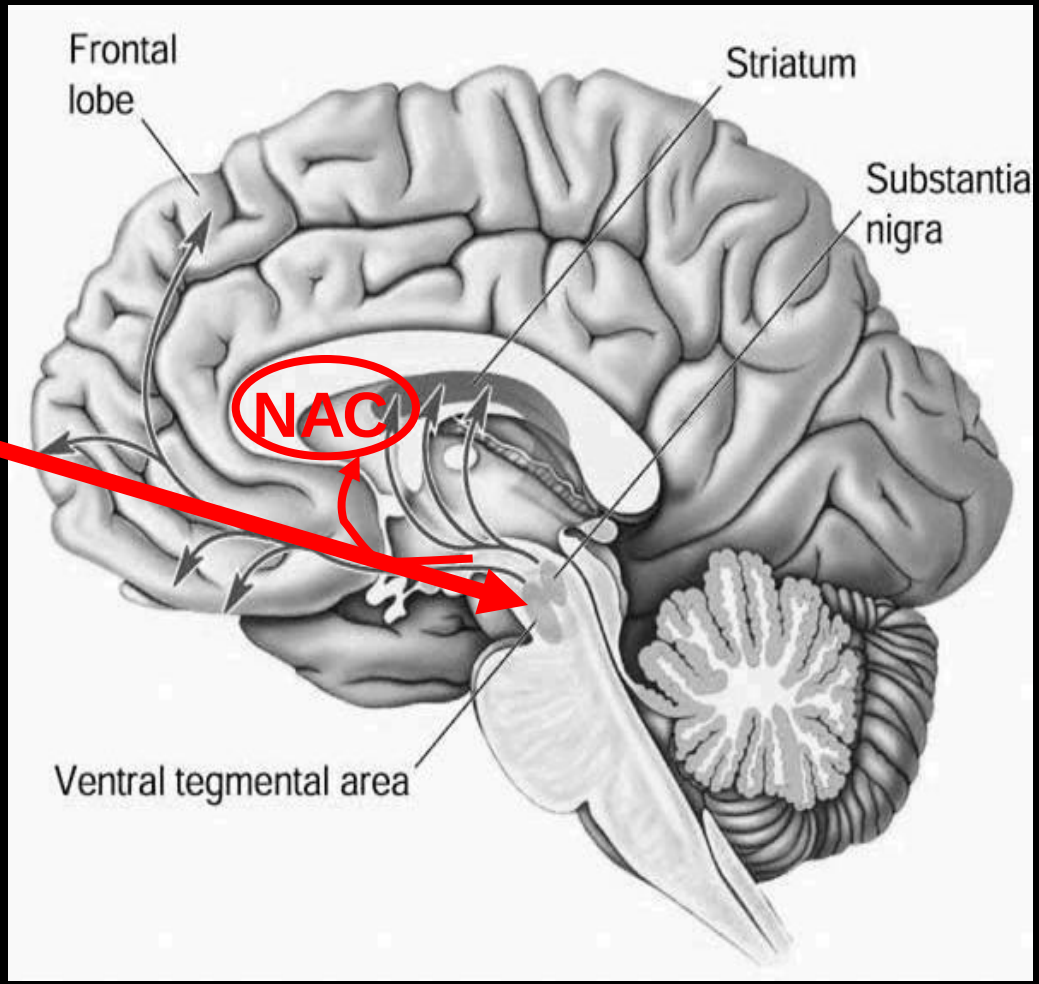
Dopamine system is modulated by other neurotransmitters:

Glutamate
GABA
Opioids
5HT
cannabinoid

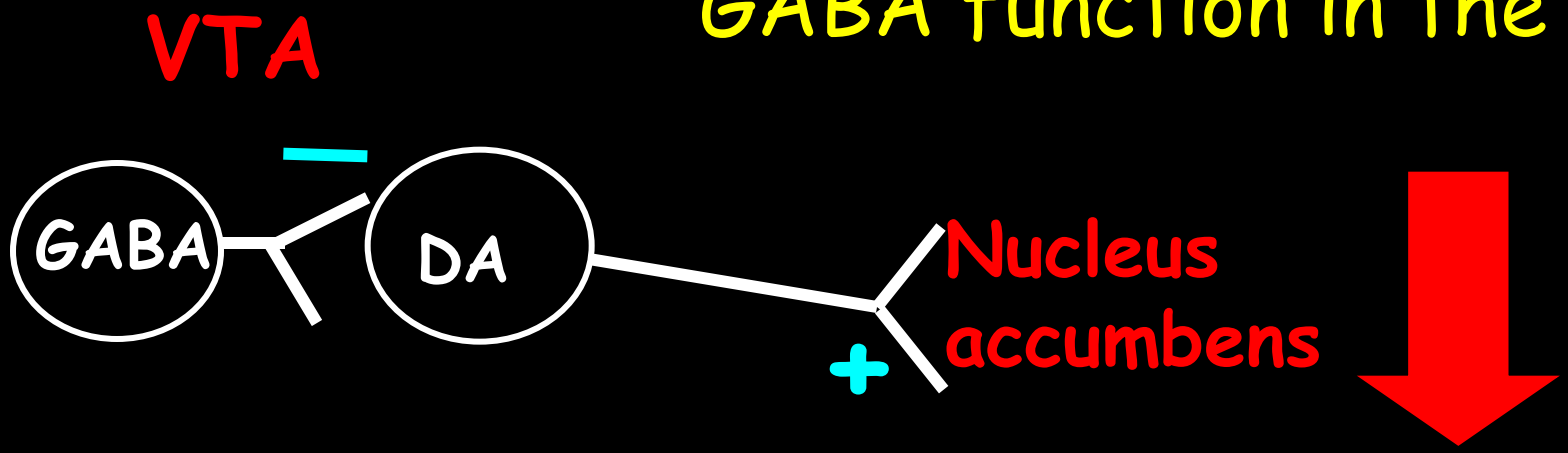


Drugs of abuse increase dopamine concentration in the nucleus accumbens of the mesolimbic system

Principle 'brake' on dopaminergic cell firing is the GABA system – the brain's inhibitory system

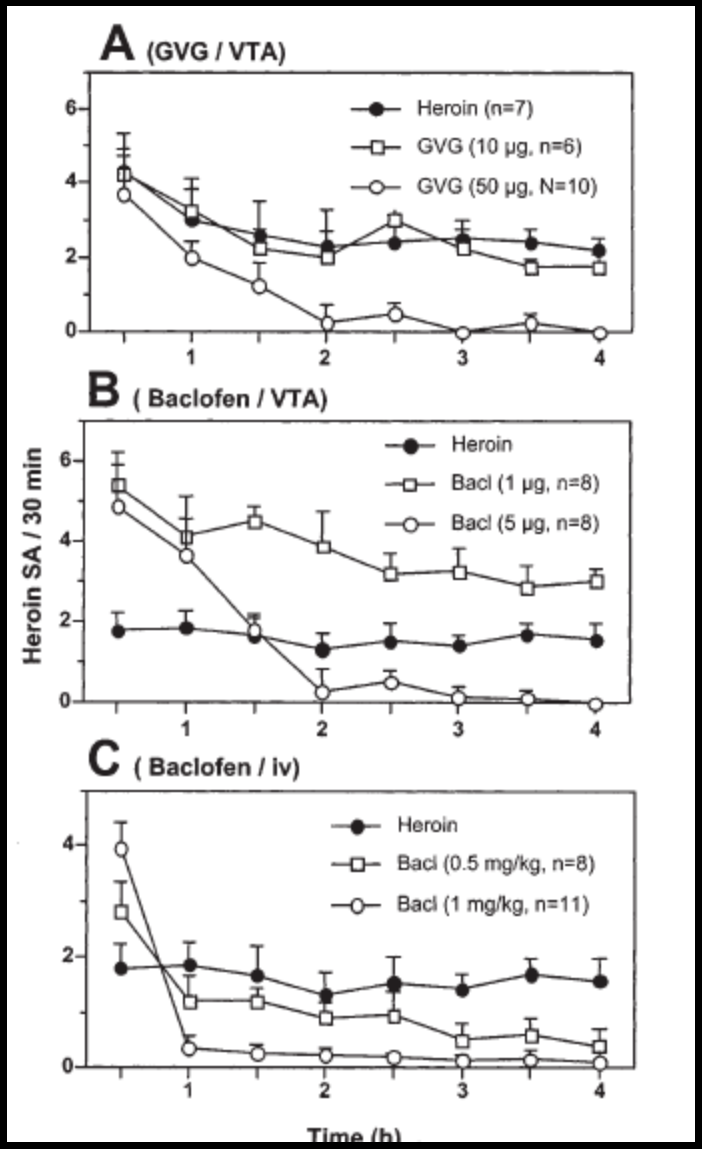


GABA function in the VTA



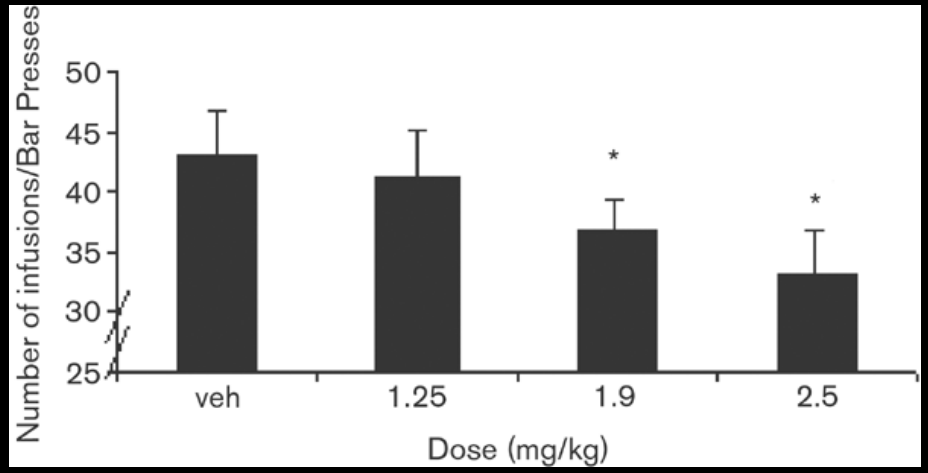
- GABA neurotransmission in VTA is via GABA – B receptors
  - baclofen is typical agonist
  - other drugs that increase GABA levels have similar effect
    - tiagabine, vigabatrin, gabapentin, topiramate

Baclofen:
Pre-clinical

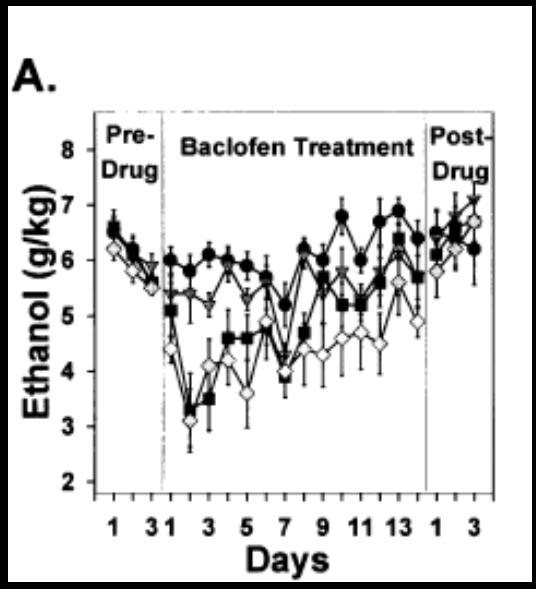


Xi & Stein

Reduces cocaine self-administration and response to salient cues



Reduces alcohol self-administration



Reduces heroin self-administration

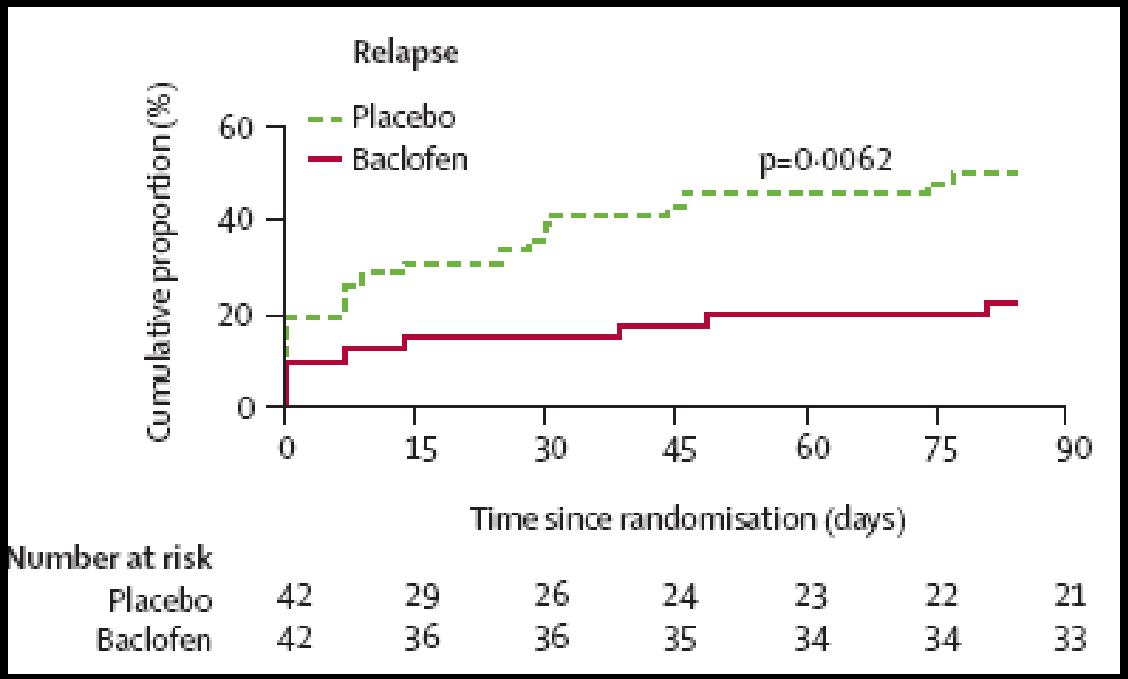
Effectiveness and safety of baclofen for maintenance of alcohol abstinence in alcohol-dependent patients with liver cirrhosis: randomised, double-blind controlled study

Giovanni Addolorato, Lorenzo Leggio, Anna Ferrulli, Silvia Cardone, Luisa Vonghia, Antonio Mirijello, Ludovico Abenavoli, Cristina D'Angelo, Fabio Caputo, Antonella Zambon, Paul S Haber, Giovanni Gasbarrini

Summary

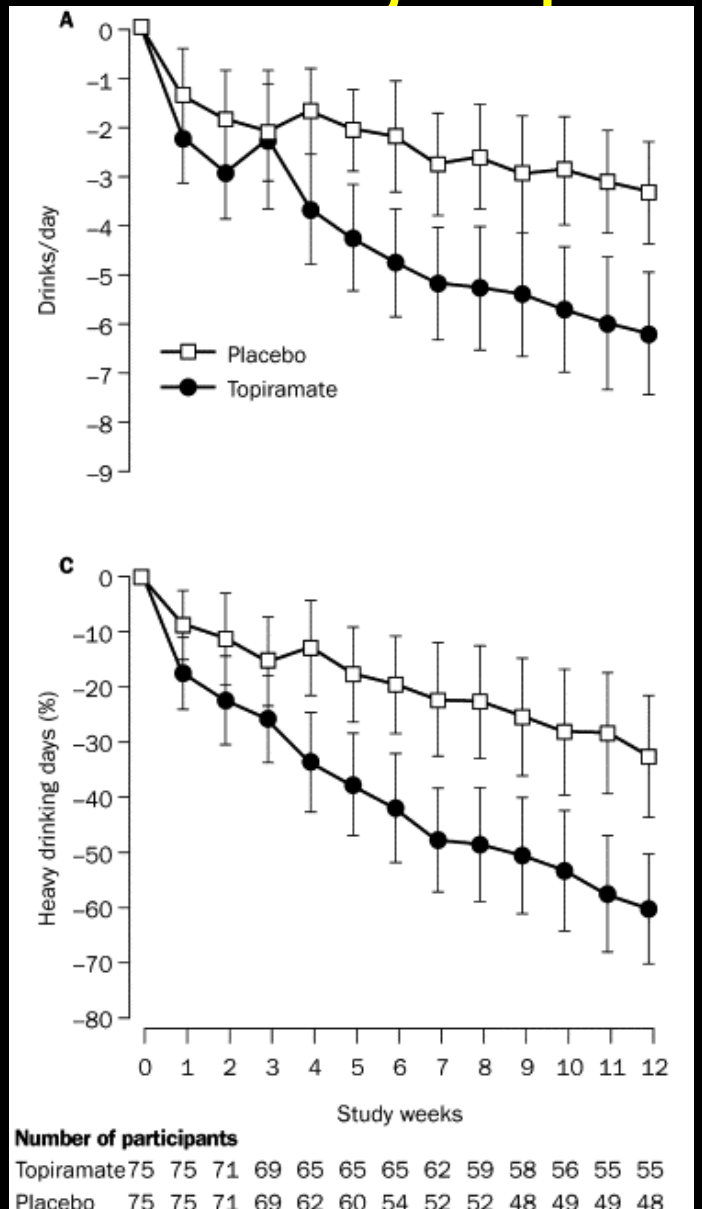
Background Intervention to achieve alcohol abstinence represents the most effective treatment for alcohol-dependent

Lancet 2007; 370: 1915–22



- 84 patients
- 12 weeks of baclofen
  - 5mg tds for 3 days; then 10mg tds
- Well tolerated, no difference in drop-out rates
  - Main side effect was sedation (reduce dose)
- Less likely to lapse and relapse

Other drugs that increase GABA function e.g. topiramate *(Johnson et al 2003; 2007)*



- Also antagonises glutamate (AMPA) & reduces dopaminergic activity

- reduces drinking days and drinks/day

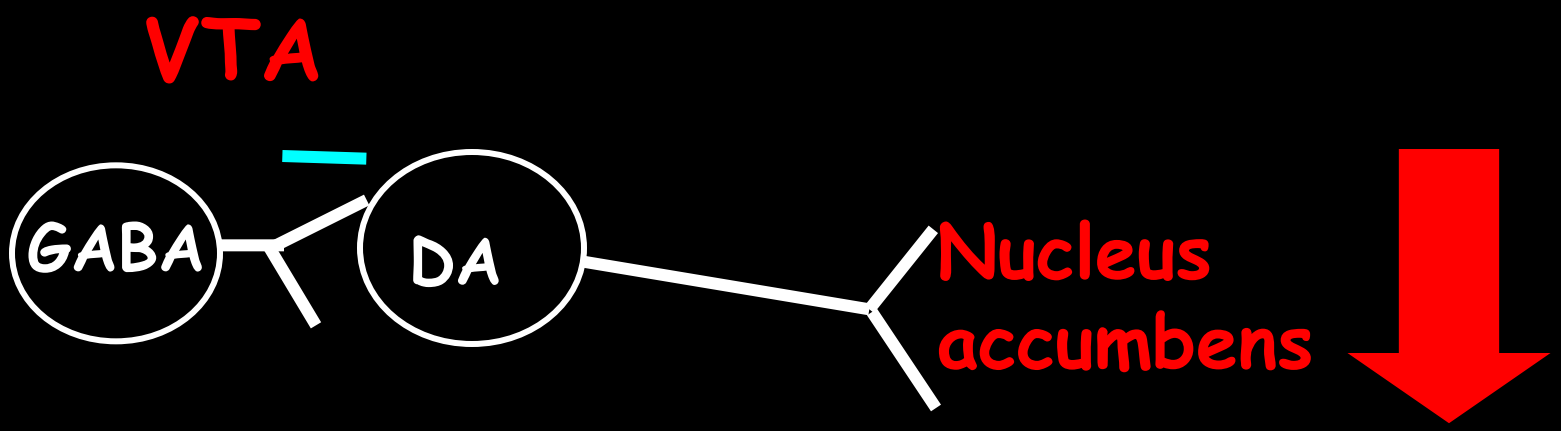
- dropouts: eg due to paresthesia, sedation
  topiramate vs placebo
  19% vs 3%.
  appears more at dose >150mg

However USA study of baclofen is 'negative' - why?

- Other component
  - In USA study had more intensive psychosocial support (BRENDA; effective alone) than Italian study (support)
- Recruitment and type of patients
  - In USA is via advert; Italian, cirrhotic pts
  - USA pts did not have meds for detox, Italian did, had higher withdrawal symptoms and were more anxious.
- Treatment goal
  - USA only 24% wanted abstinence, 45% wanted occasional use, 38% drink regularly but reduce; in Italian study, 100% abstinence

➢ Baclofen may be better for more severely dependent alcoholics, those aiming for abstinence

The dopamine reinforcement pathway: where substances of misuse interact.



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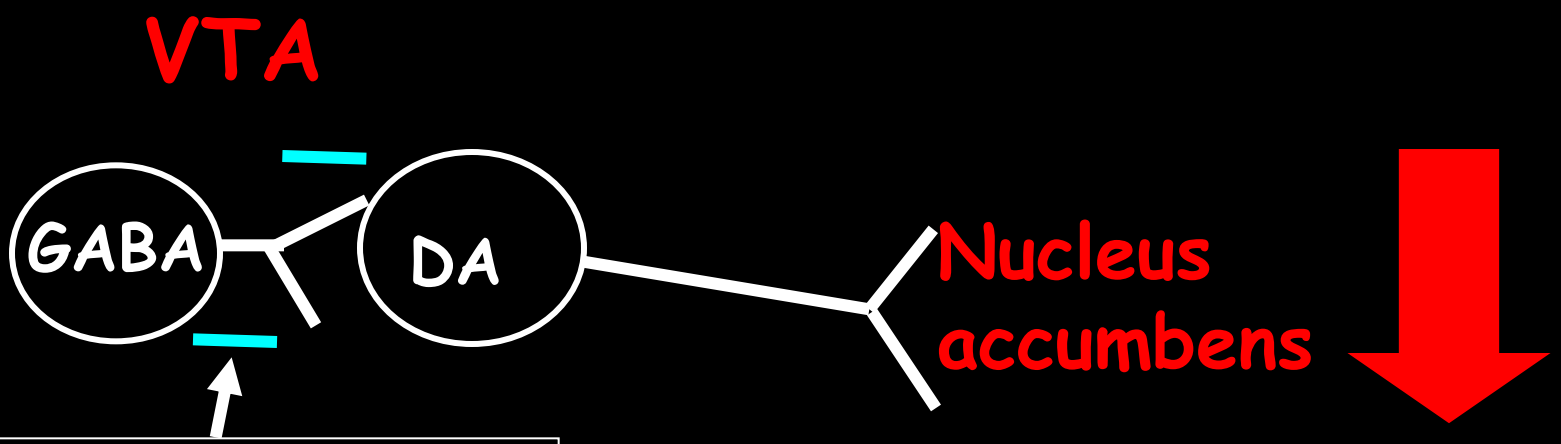
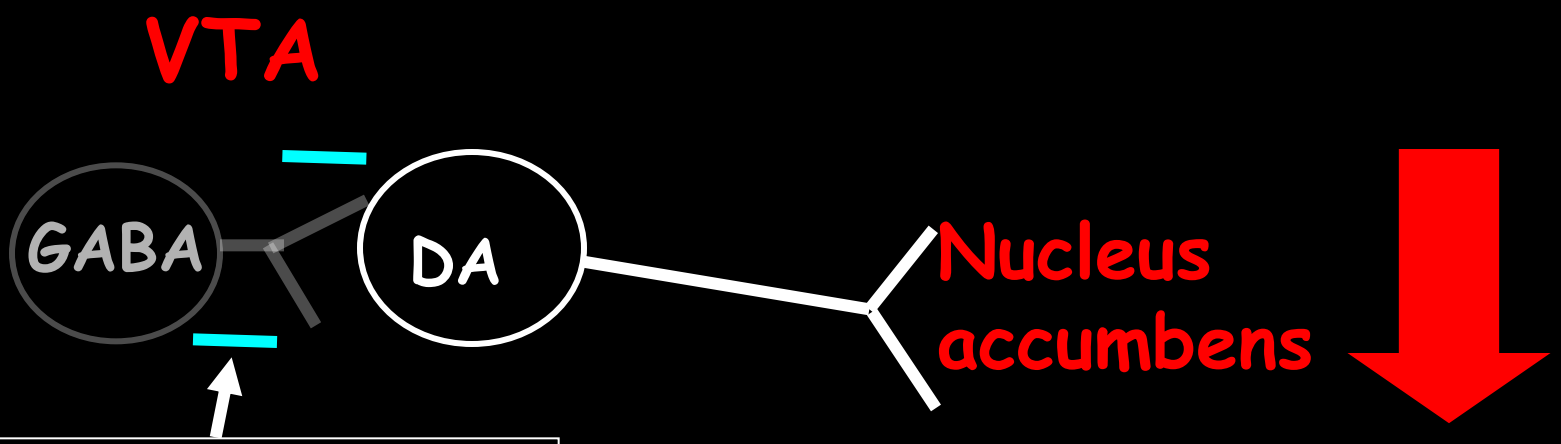


Opioid – endorphin

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

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

The dopamine reinforcement pathway: where substances of misuse interact.



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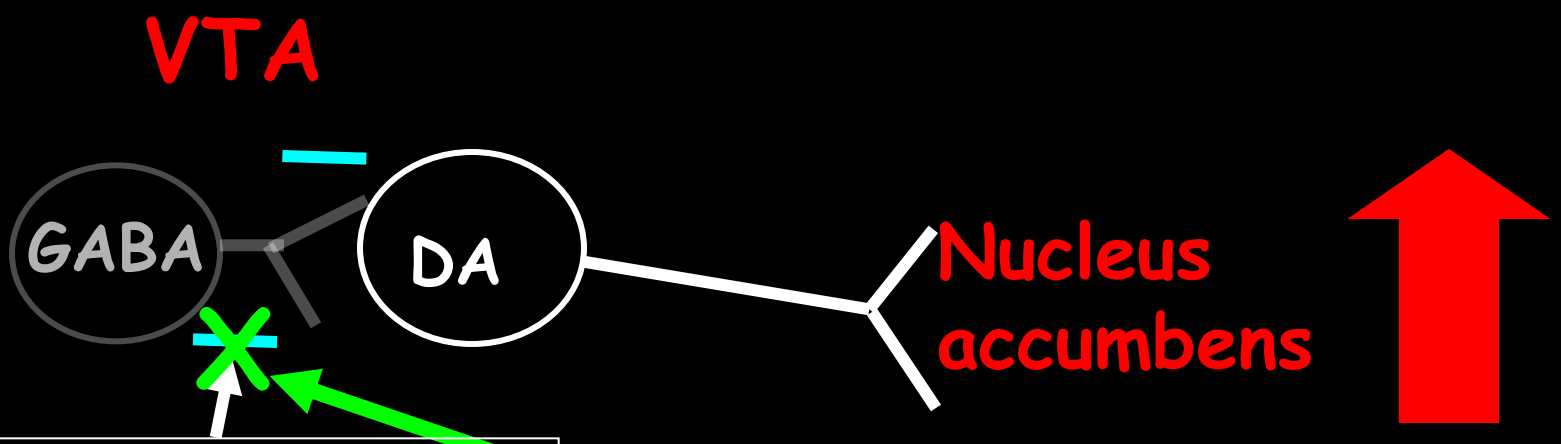


Opioid – endorphin

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

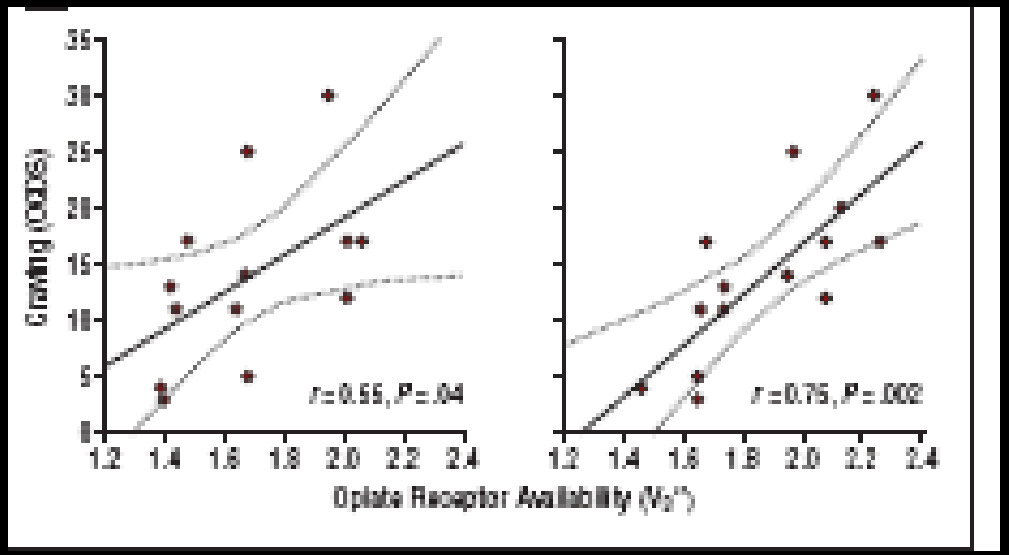
All inhibit GABA neuron leading to increased DA-ergic neuronal firing.

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

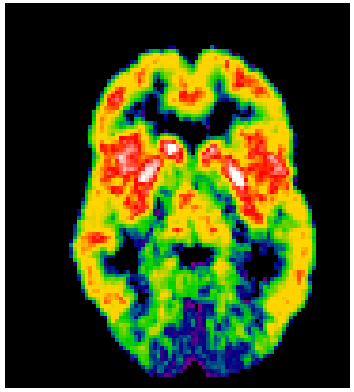
Correlation of elevations in striatal μ-opioid receptor availability in detoxified alcoholic patients with alcohol craving.

Alcohol dependent	***Control***

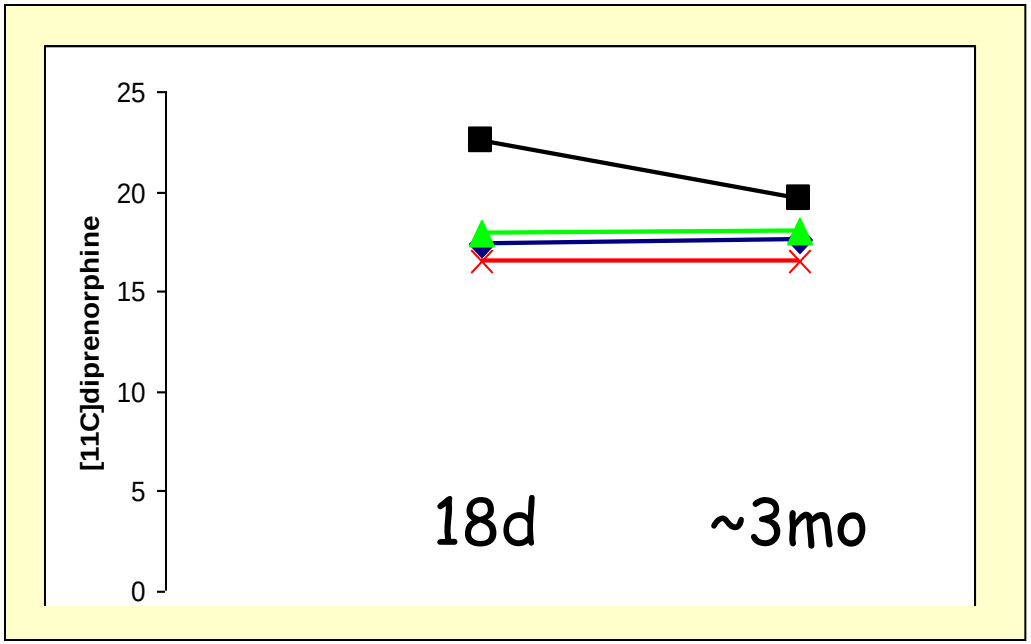
L ventral striatum *R ventral striatum*



Heinz et al 2005



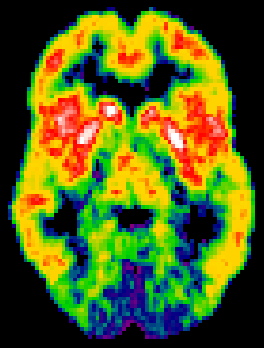
Opioid receptor levels during abstinence: [11C]diprenorphine PET



- Four alcohol dependent patients remained sober for ~3 months and were rescanned (80, 89, 89, 132 days).

No significant change in [11C]diprenorphine VD in whole brain or any specific region

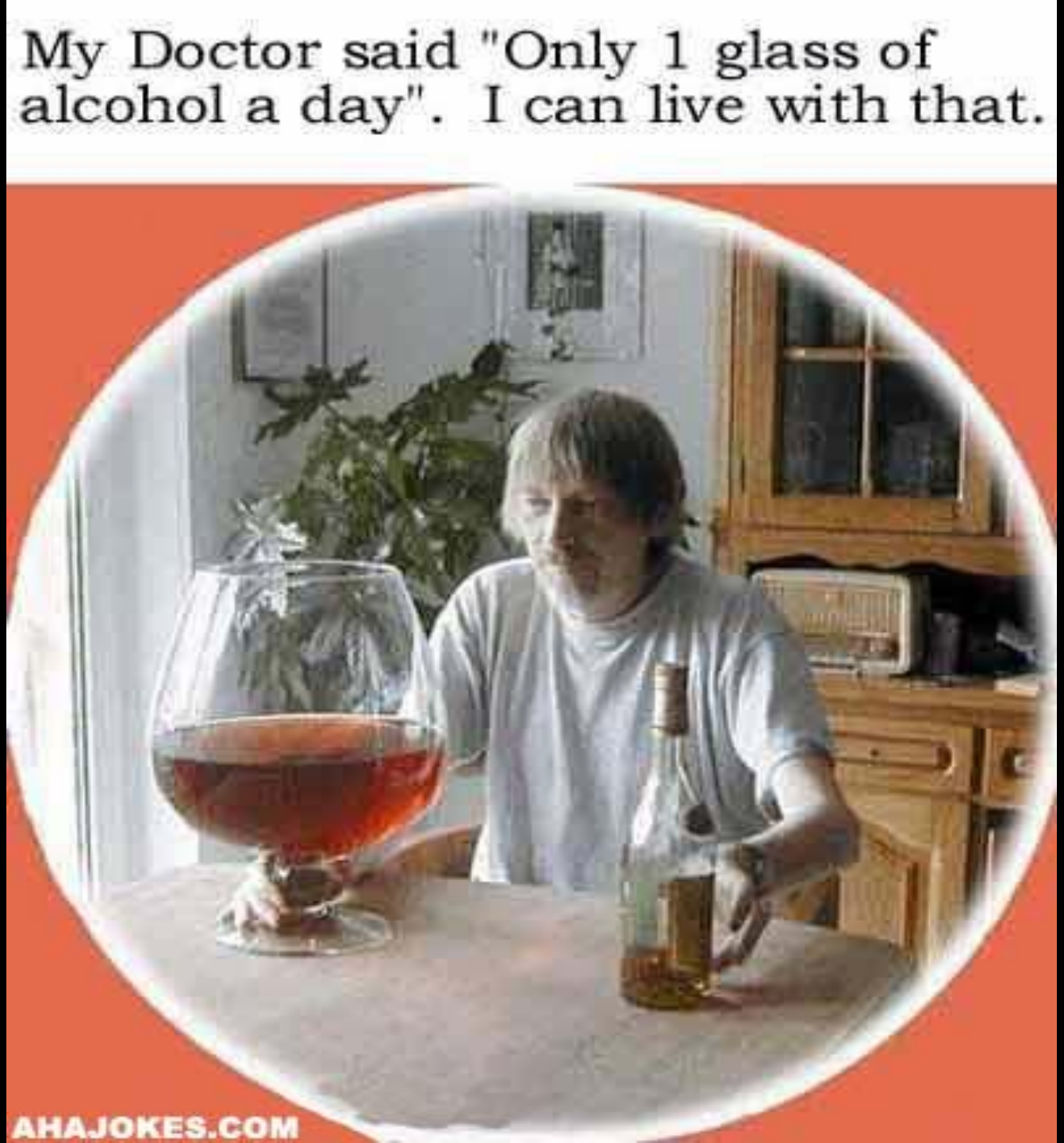
The opioid receptor in addiction.



- Increase in opioid receptor availability in subjects recently detoxified from
  - Opioids
  - Alcohol
  - Cocaine

  ? → related to craving

Suggesting that changes in the opioid system play a fundamental role in addiction and possibly craving



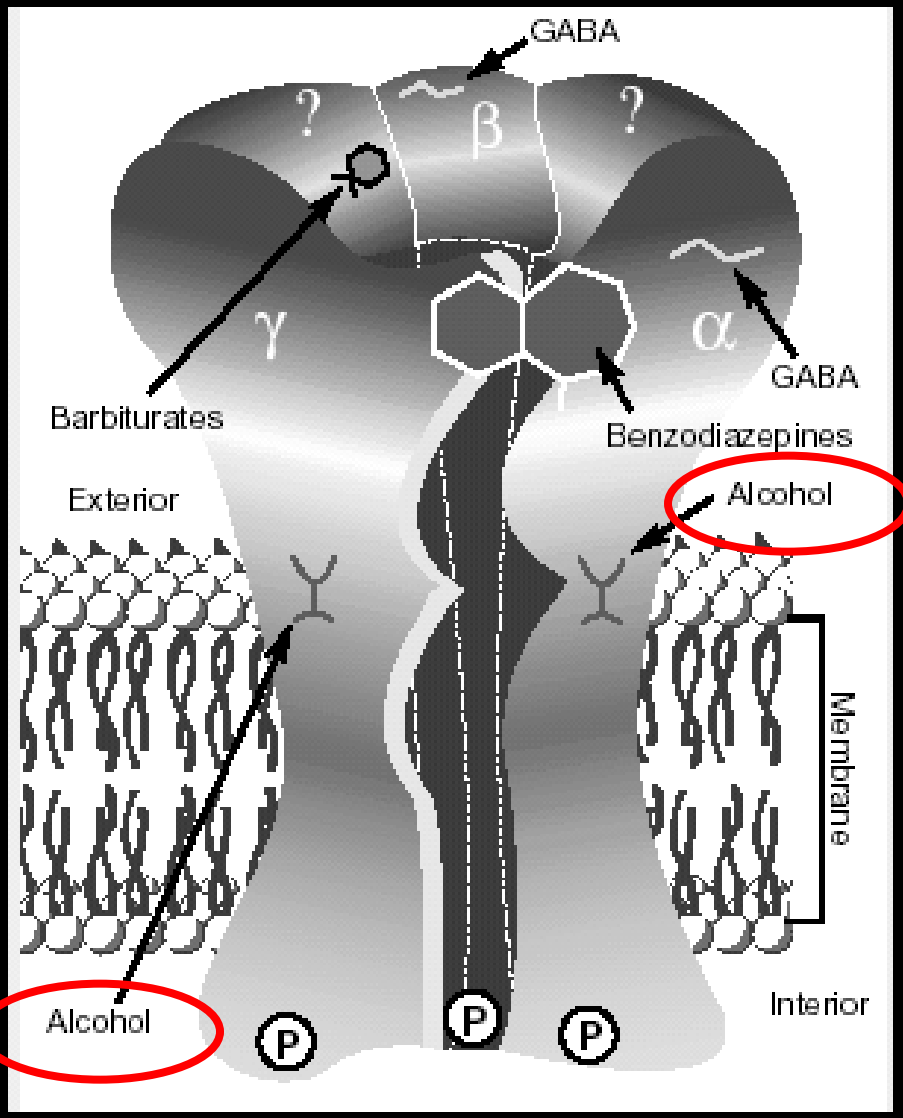
Alcohol

tolerance, damage

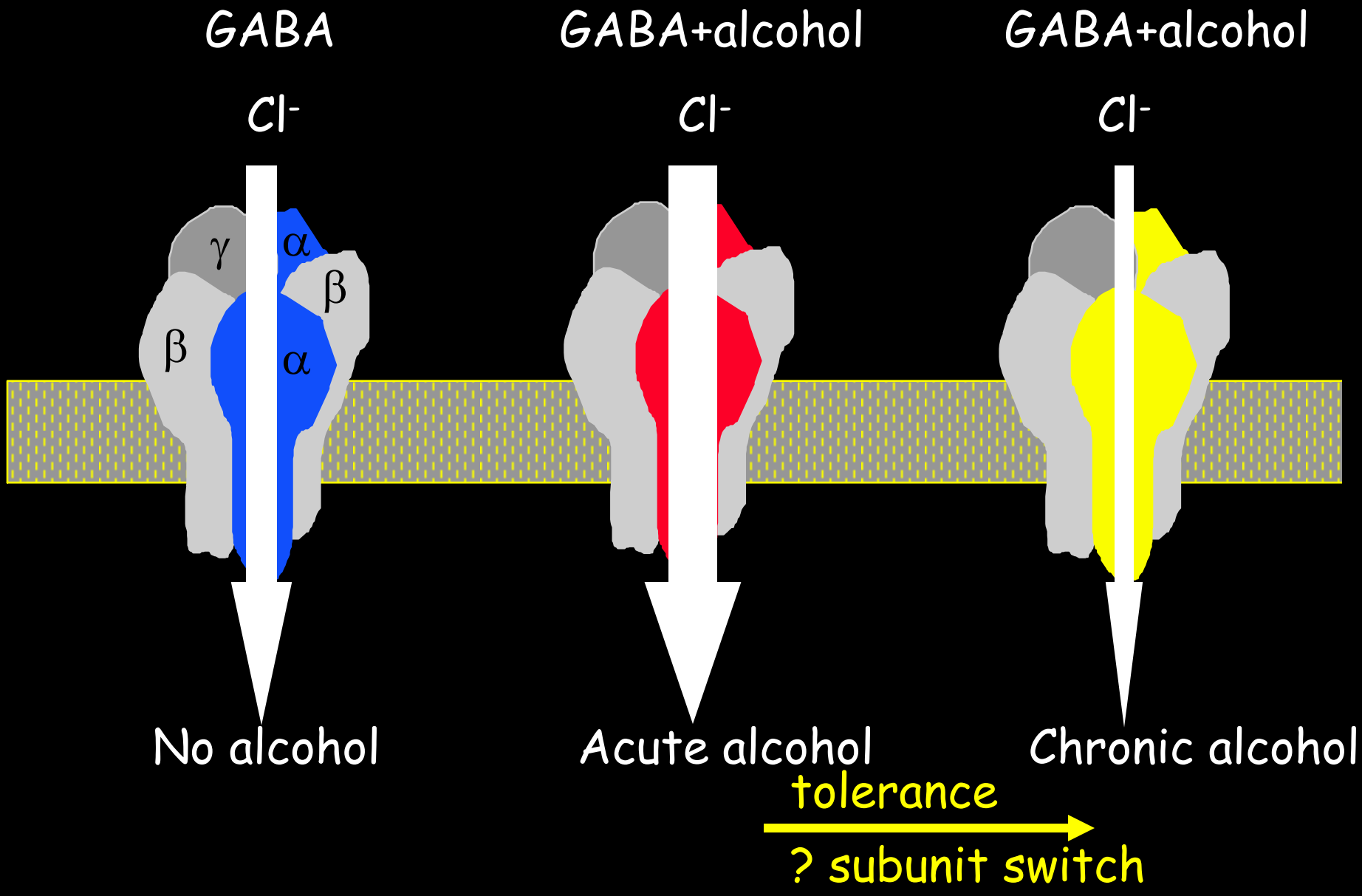
Alcohol : modulates the brain's inhibitory system - the GABA-benzodiazepine receptor.

Acutely : alcohol increases GABA-ergic function leading to

- reduced anxiety, ataxia, slurred speech, sedation, amnesia, disinhibition, reduced levels of consciousness.



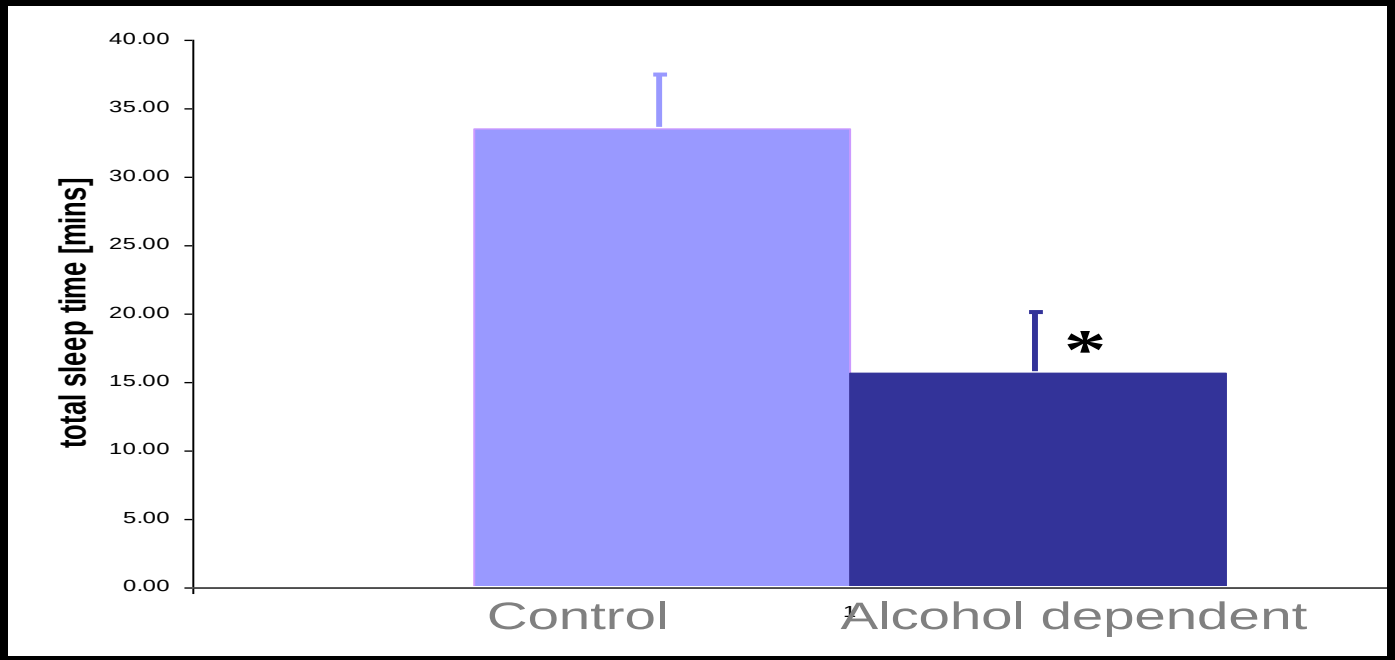
The $GABA_A$ receptor & alcohol



Tolerance: reduced sensitivity to the sleep inducing effects of benzodiazepine in alcoholism

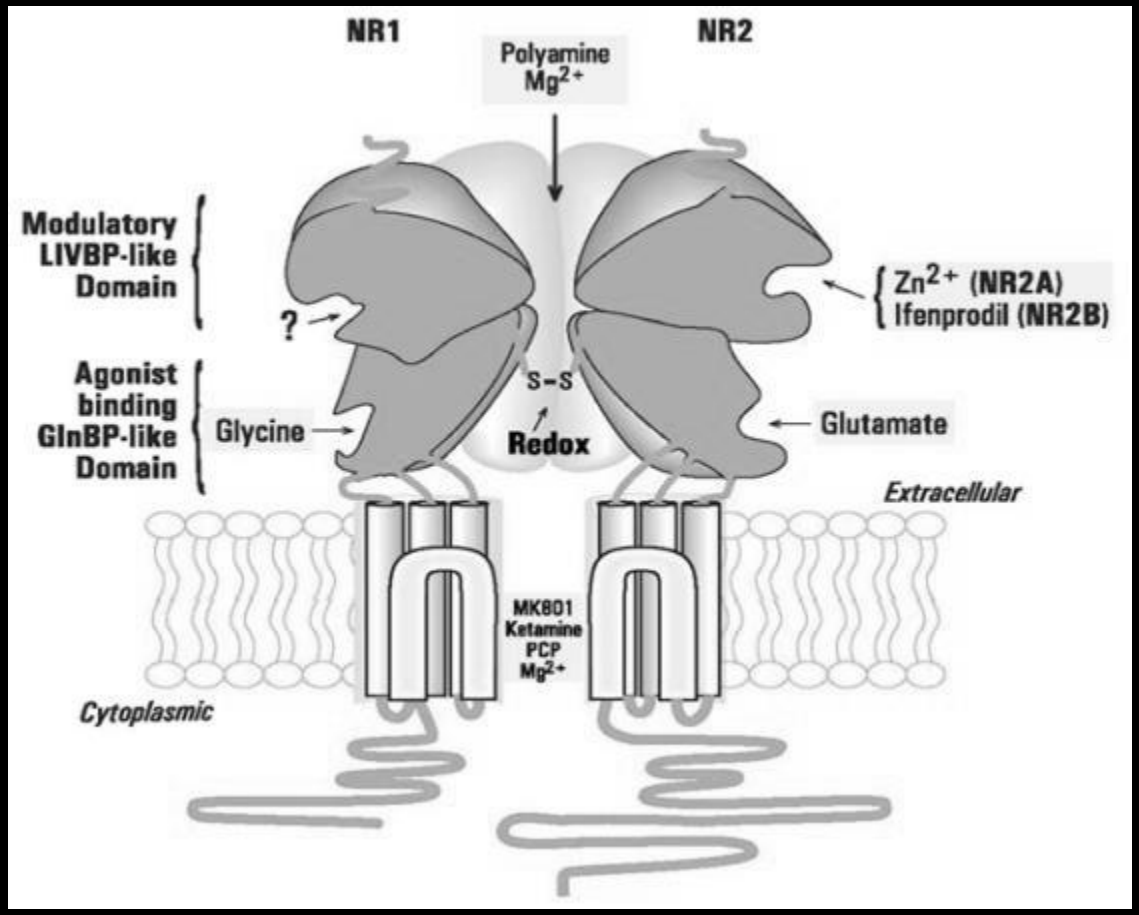
Reduced BDZR levels in alcohol dependence

Give midazolam:
No difference in BDZR occupancy but reduced total sleep time



Lingford-Hughes et al 2005

Alcohol : modulates the brain's excitatory system, glutamate.

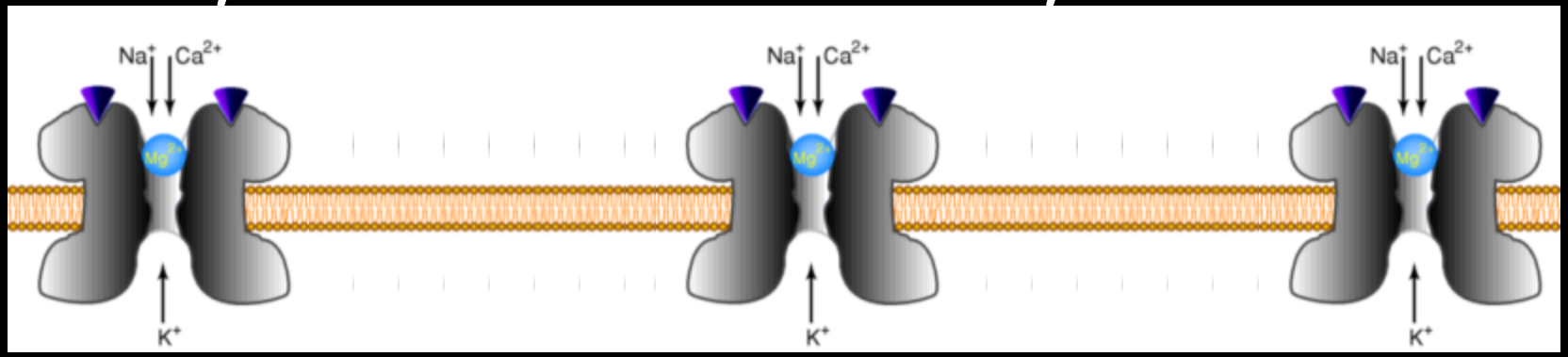


Alcohol is an NMDA receptor antagonist

→ ↓Ca^{2+} flux → ↓excitation

Glutamate : 'excitatory system'

- Acutely, alcohol inhibits this system : NMDA



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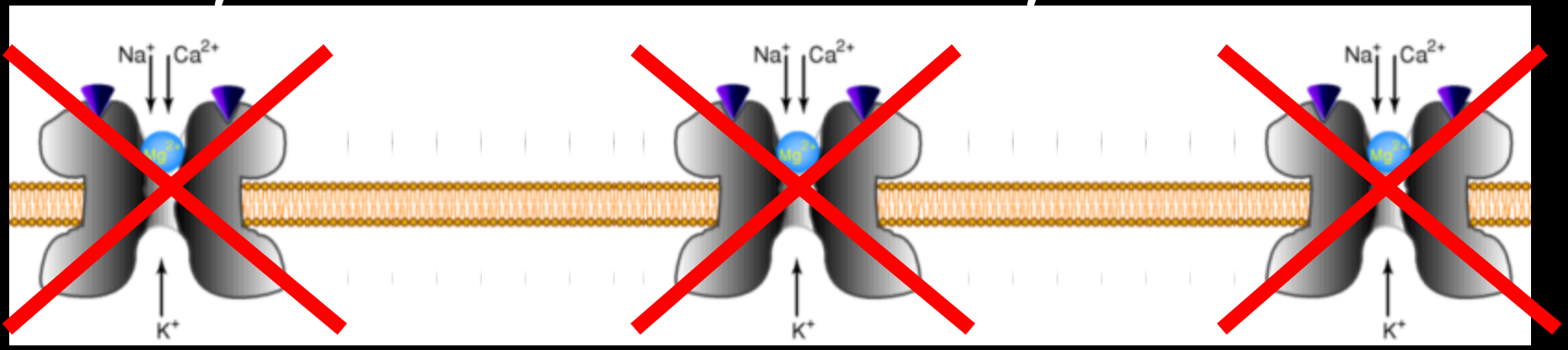

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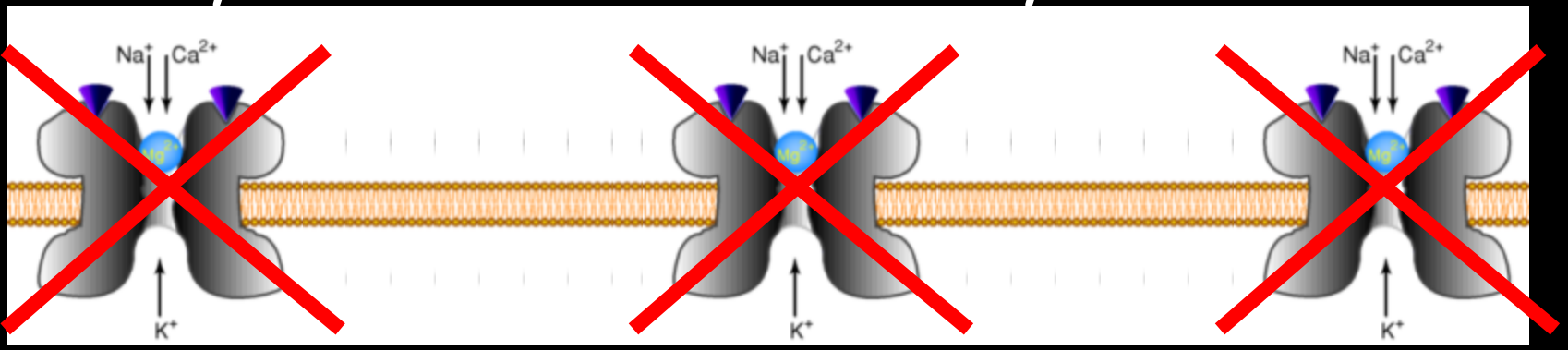
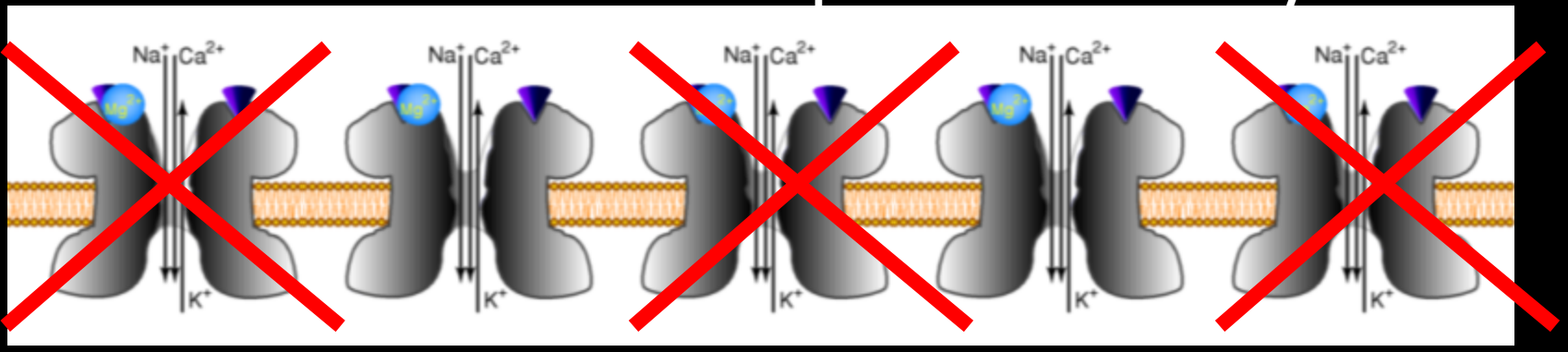
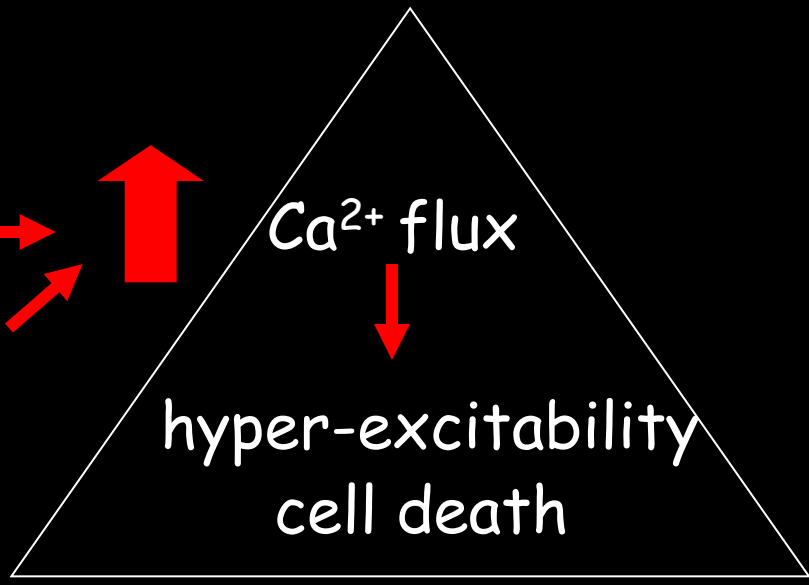


- Chronic alcohol leads to receptor up-regulation - associated with impaired memory



Alcohol withdrawal

- increased activity in
  - NMDA receptor
  - L-subtype of Ca^{2+} channel



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

Acamprosate and neuroprotection

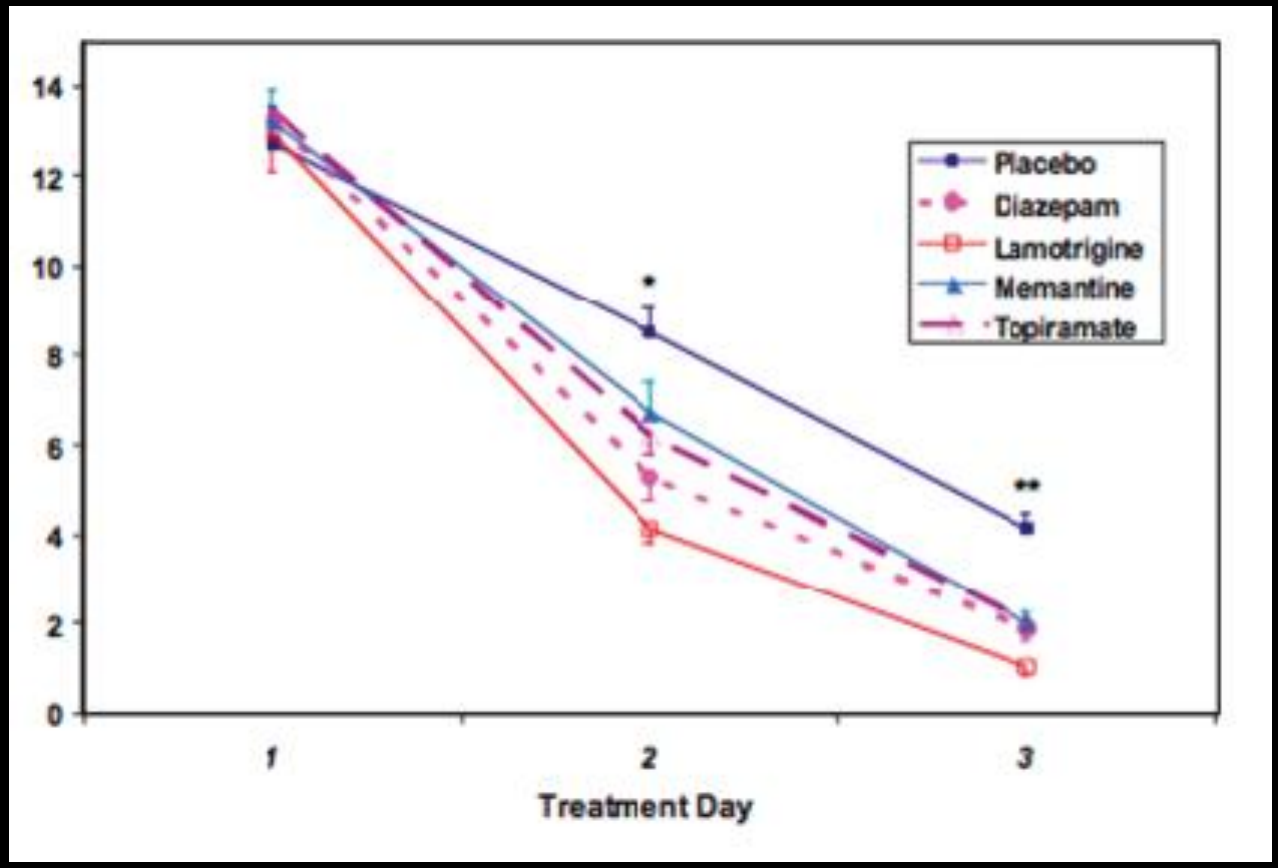
- Pre-clinical *Dahchour & De Witte; Mhatre, Boeijinga*
  - Ethanol withdrawal is associated with increases in glutamate in the brain
    - Acamprosate blocks this
  - Repeated ethanol withdrawal leads to greater levels of glutamate & increased mortality
    - Acamprosate blocks this
  - Diazepam suppressed withdrawal symptoms but did not alter seizure susceptibility in animals undergoing multiple cycles of ethanol withdrawal
- Clinical
  - Acamprosate [8d prior to detox to d15 after] decreased the arousal level as reflected by α slow-wave index and improved sleep ie reduced hyper-excitability in alcohol dependence.

Antiglutamatergic Strategies for Ethanol Detoxification: Comparison With Placebo and Diazepam

Evgeny M. Krupitsky, Anatoly A. Rudenko, Andrey M. Burakov, Tatyana Y. Slavina, Alexander A. Grinenko, Brian Pittman, Ralitza Gueorguieva, Ismene L. Petrakis, Edwin E. Zvartau, and John H. Krystal

- 3 antiglutamatergic strategies
  - memantine : N-methyl-D-aspartate glutamate receptor antagonist: 30mg/d
  - topiramate : AMPA/kainate receptor inhibitor: 100mg/d
  - lamotrigine : glutamate release inhibitor: 100mg/d
- ALD, CIWA >10, average 12U/d
- 7 days of medication – diazepam 30mg/d

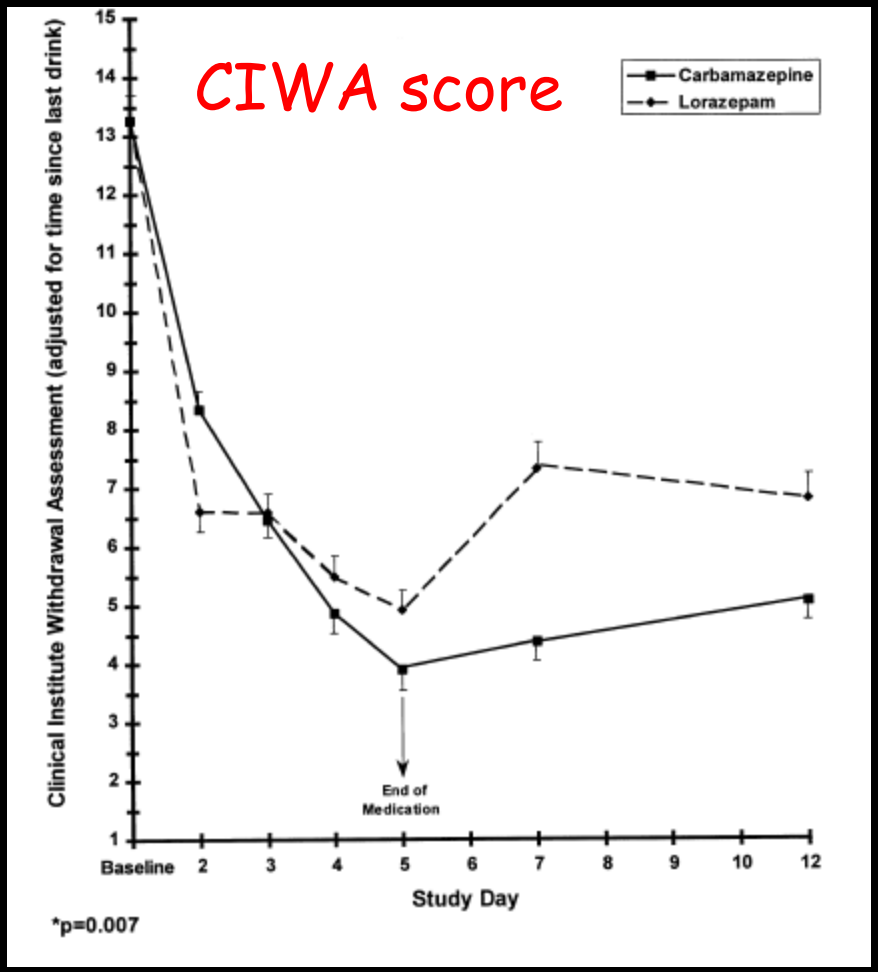
Clinical Institute Withdrawal Assessment—Alcohol, revised (CIWA-Ar) scores.

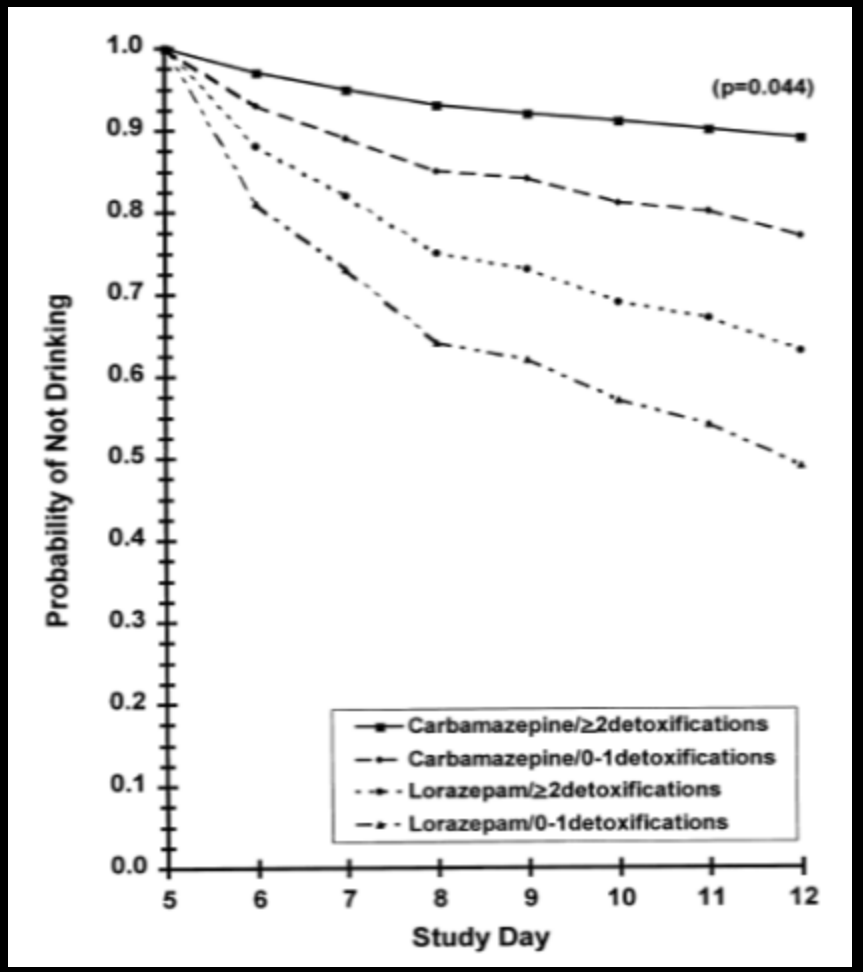


- When averaged over time – only diazepam and lamotrigine were significantly better than placebo.
- Other 2 drugs were at time 2 and 3
- No difference between active drugs

The Effects of Carbamazepine and Lorazepam on Single versus Multiple Previous Alcohol Withdrawals in an Outpatient Randomized Trial

R. Malcolm, MD, H. Myrick, MD, J. Roberts, PhD, W. Wang, MS, R. F. Anton, MD, J. C. Ballenger, MD





Number of previous detoxes moderates outcome
- >2 : do better on carbamazepine

Stress system: targets.

System	Principle	Compound	Status
CRH	CRH 1 antagonist	antalarmin	Under tox
NK 1 *(Substance P)*	NK 1 antagonist	Eli Lilly	Phase IIa
Nociceptin	NOP agonist	Confidential	Under tox
Neuropeptide Y	Y2 antagonist	Confidential	Evaluation

Neurokinin 1 Receptor Antagonism as a Possible Therapy for Alcoholism

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- Proof of concept study.
- NK1 knockout mice
  - Reduced voluntary alcohol consumption, increased sedative effects.
- Recruited anxious alcoholics, treated with 50mg LY686917 for 3 weeks
  - Reduced spontaneous craving & to social stress test, attenuated cortisol response
  - fMRI: reinstated response to positive images that is generally blunted in alcoholism.

Alcohol use, misuse, dependence