



**17^e Congrès International
d'Addictologie de l'ALBATROS**
17th International Congress of Addictology

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Targeting the opioid system to treat alcohol use disorder: Is the NOP receptor system an option?

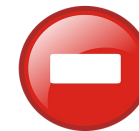
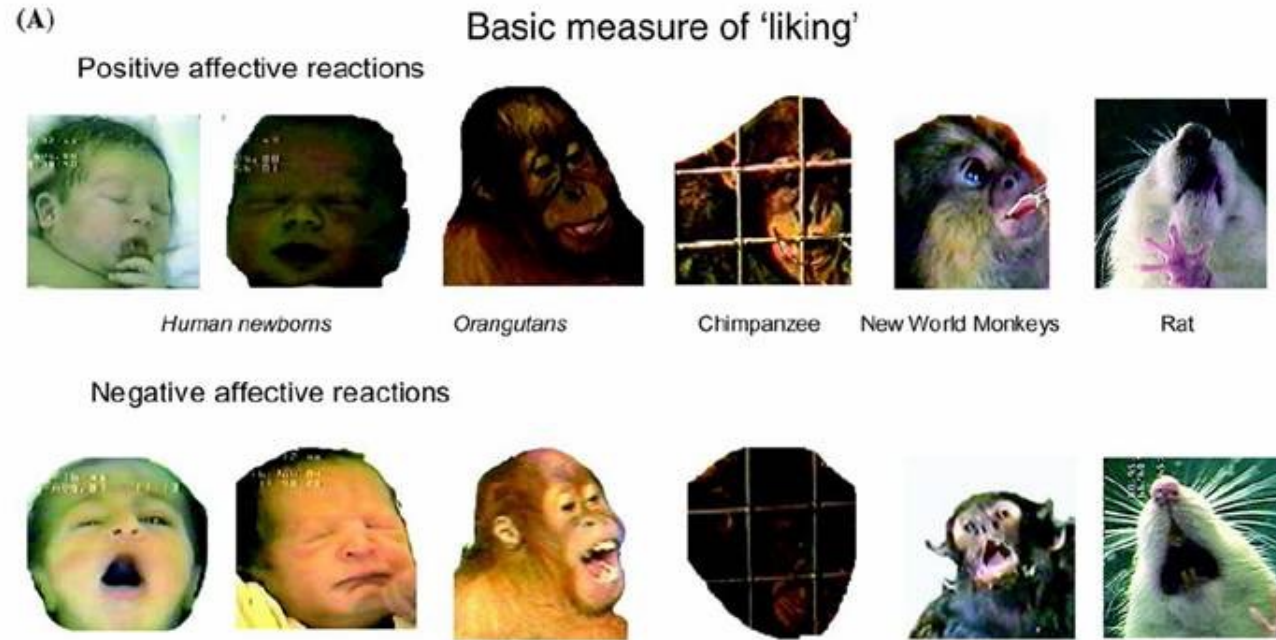
Roberto Ciccocioppo
University of Camerino

Reward is a fundamental survival mechanism

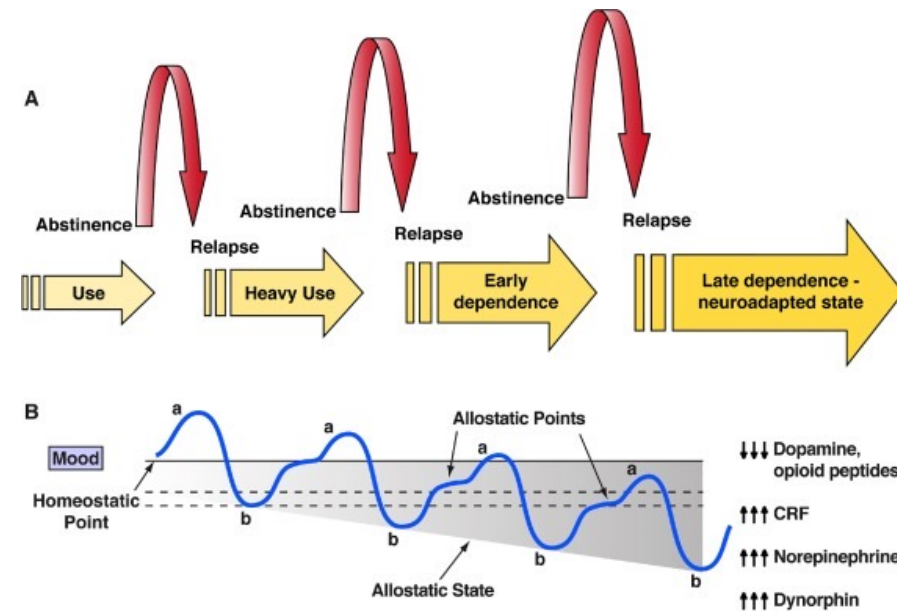
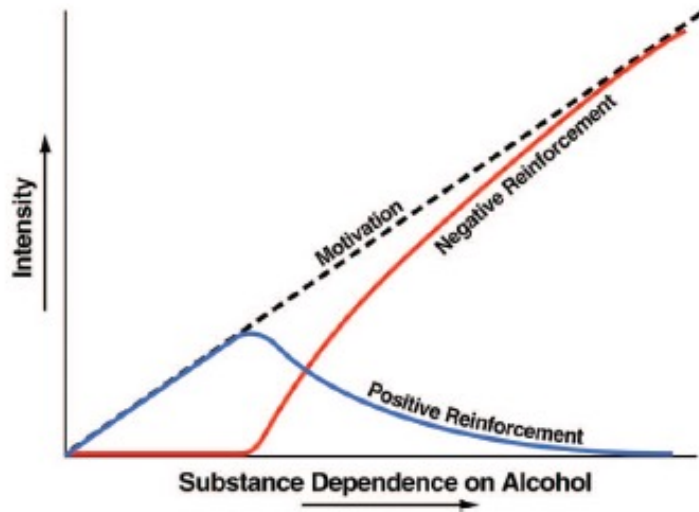
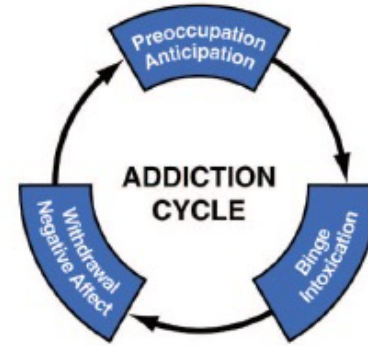
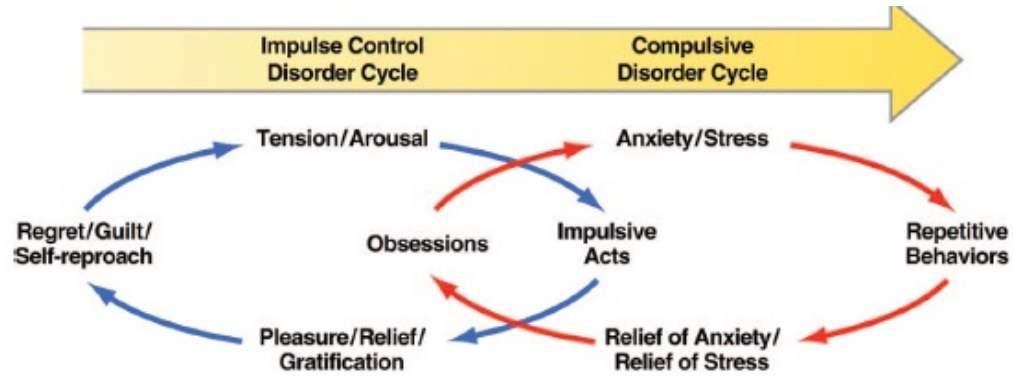


Behaviors that play a role in promoting the survival of the individual or species generally produce a feeling of pleasure

K.C. Berridge / Brain and Cognition 52 (2003) 106-128

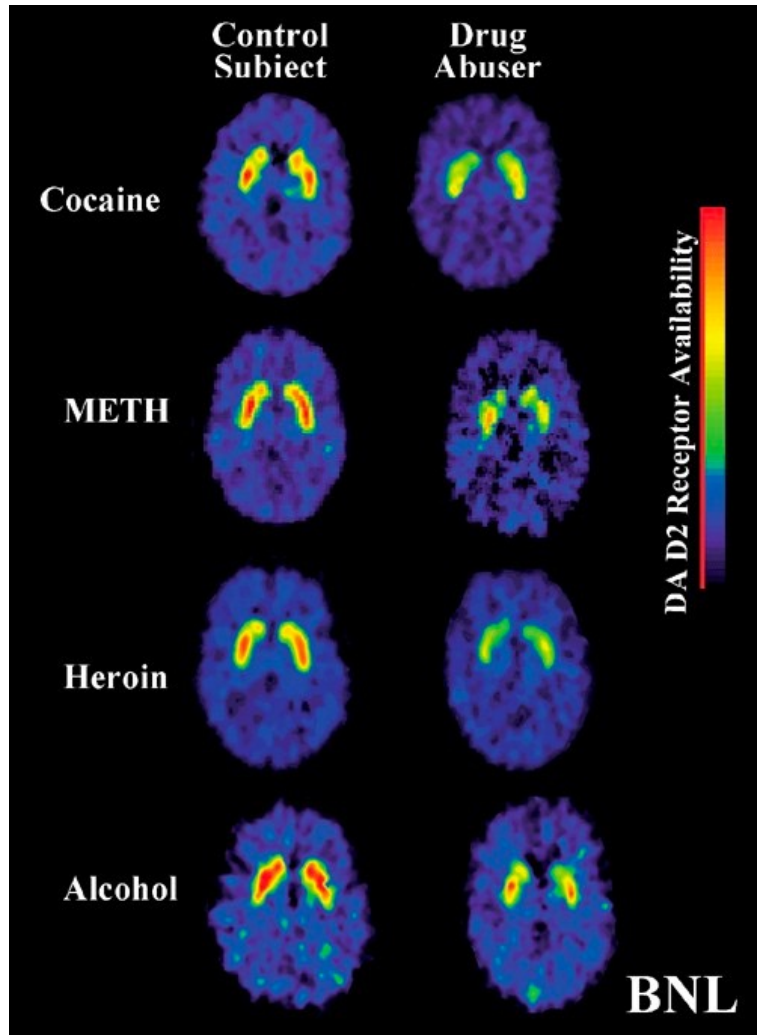


Neurobiology of Addiction

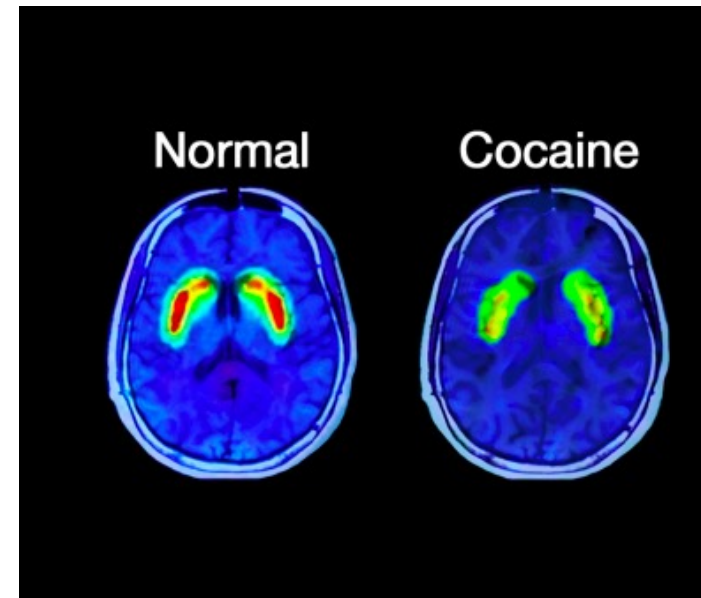


Dopamine in drug abuse and addiction: results from imaging studies and treatment implications

ND Volkow^{1,2,3,5}, JS Fowler⁴, G-J Wang³ and JM Swanson⁶



In substance-dependent subjects, the activity of the mesolimbic dopaminergic (D2) system is decreased

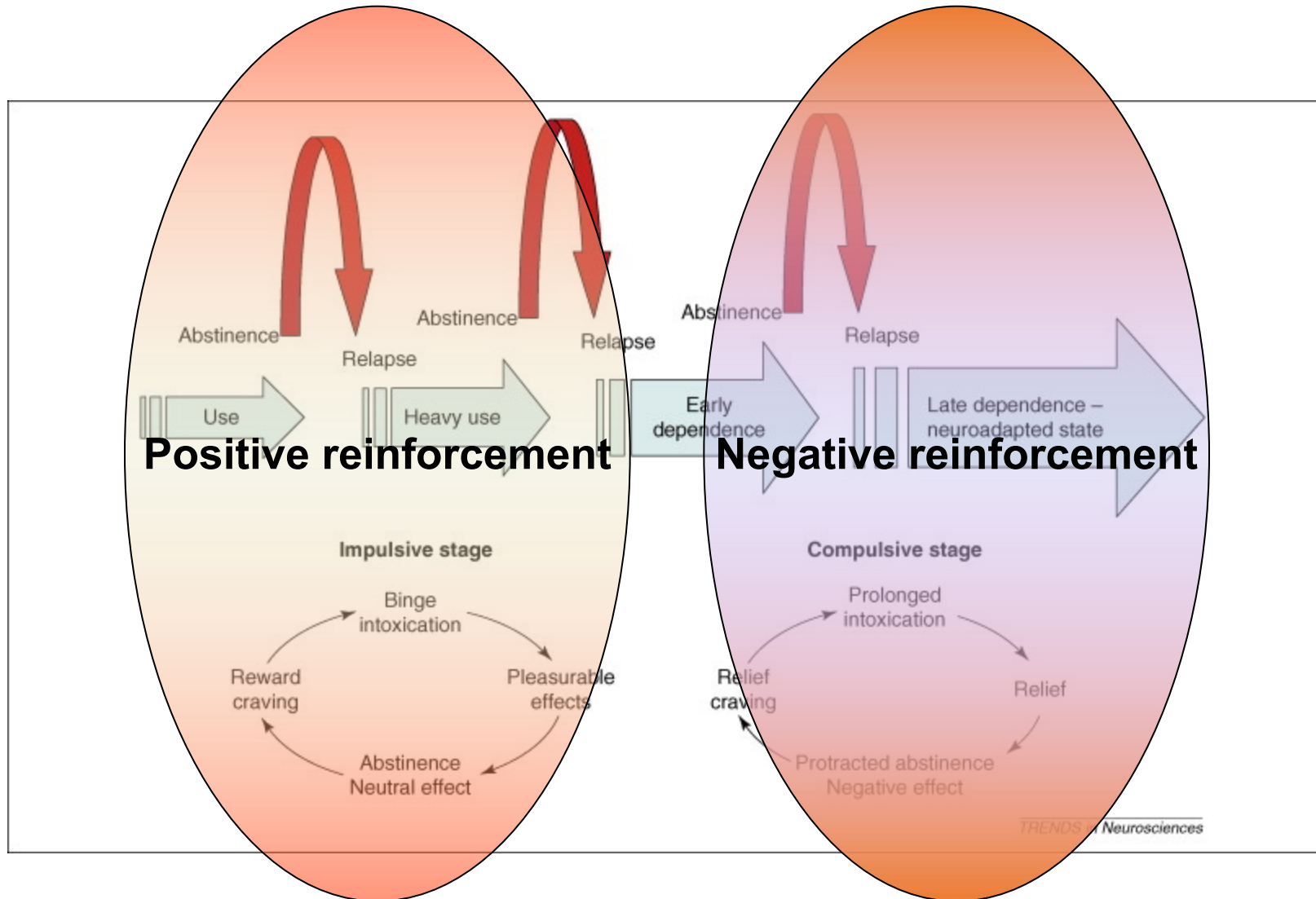


Molecular Psychiatry (2004) 9, 557–569

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www.nature.com/mp

The progression of drug dependence over time.



Adapted from Koob & Heilig

Approved Pharmacotreatments for SUD

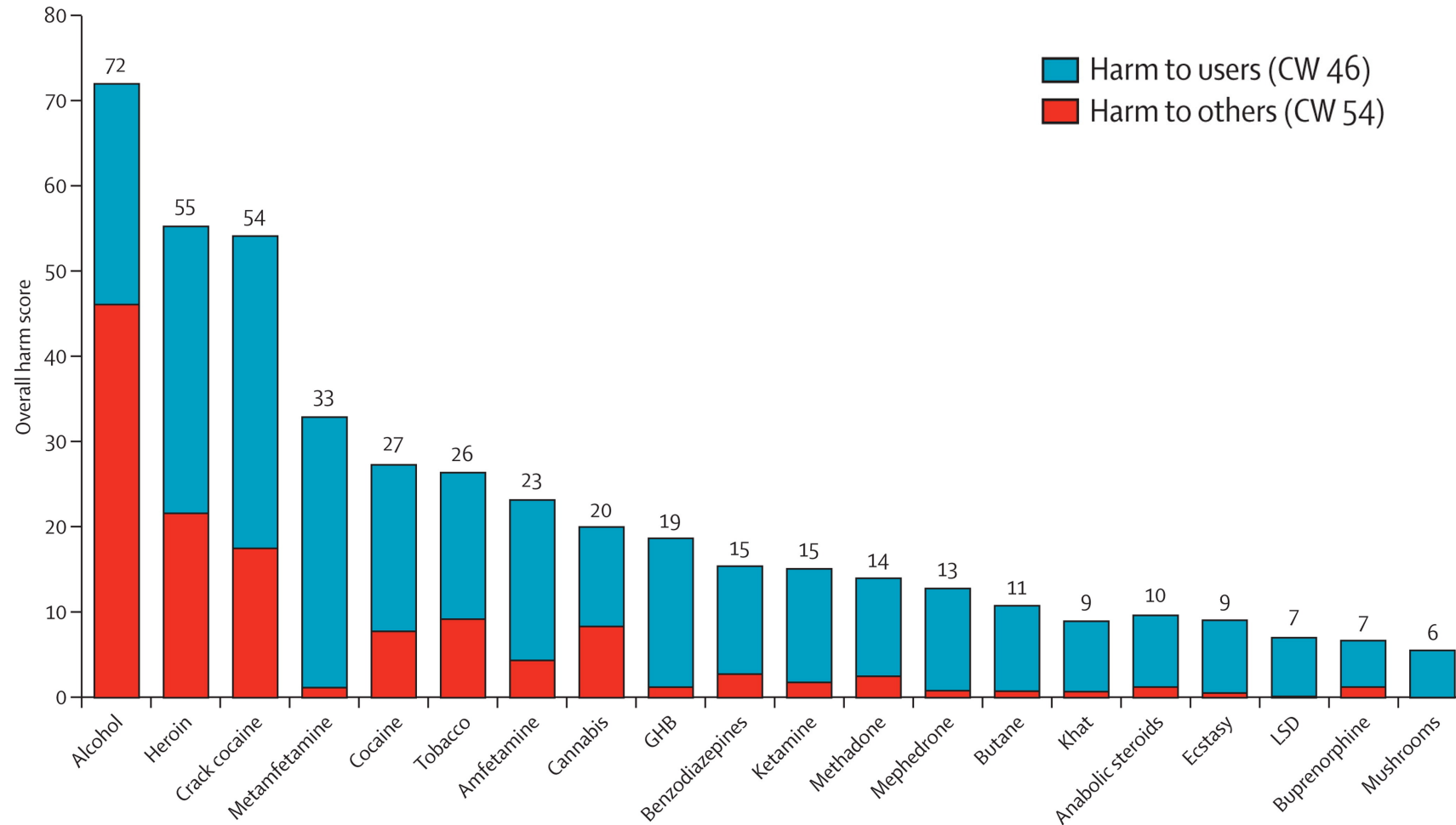
Table 1. Pharmacotherapies Used for the Treatment of Addictive Disorders

	Medication	Delivery System	Mechanism of action	Type of Addiction	Efficacy
Supportive Therapies	Methadone	Oral solution or tablet	μ opioid agonist	Opioid	Effective in retaining patients in treatment and reducing heroin use (Mattick et al., 2003)
	Buprenorphine	Sublingual tablet alone or with naltrexone	Partial μ opioid agonist and κ opioid antagonist	Opioid	Effective in retaining patients and reducing heroin use (Mattick et al., 2004)
Reward Blocking Approach	Naltrexone	Oral tablet, Extended-release injectable suspension	Opioid antagonist	Opioid	Better opioid use outcomes in high retention groups (Johansson et al., 2006)
				Alcohol	Significantly reduces relapses but not to drinking (Srisurapanont and Jarusuraisin, 2005)
	Disulfiram	Oral tablet	Increases acetaldehyde by inhibition of aldehyde dehydrogenase	Alcohol	May reduce drinking in compliant patients. Overall efficacy is questionable (Mann, 2004)
	Acamprosate	Oral tablet	NMDA receptor modulator	Alcohol	Two-fold increase in abstinence rates at 1 year (Mason and Heyser, 2010)
Supportive Therapies	Nicotine Replacement Treatments	Transdermal patch, gum, lozenge, nasal spray, and oral inhaler	nAChR agonist	Nicotine	Two-fold increase in the odds of quitting smoking (Fiore et al., 2008)
	Bupropion	Oral tablet	DA and NE reuptake blocker, and nAChR antagonist	Nicotine	Two-fold increase in the odds of quitting smoking (Eisenberg et al., 2008)
	Varenicline	Oral tablet	Partial agonist for the $\alpha 4\beta 2$ and full agonist for the $\alpha 7$ nAChR	Nicotine	2- to 3-fold increase in the odds of quitting smoking at 6 months (Cahill et al., 2010)

Abbreviations: DA, dopamine; nAChR, nicotinic cholinergic receptor; NE, norepinephrine; NMDA, n-methyl-d-aspartate.

- **Is opioid agonism a viable treatment option for AUD treatment ?**
- **Which molecule should be used ?**
- **Which subgroup of patients should be treated ?**

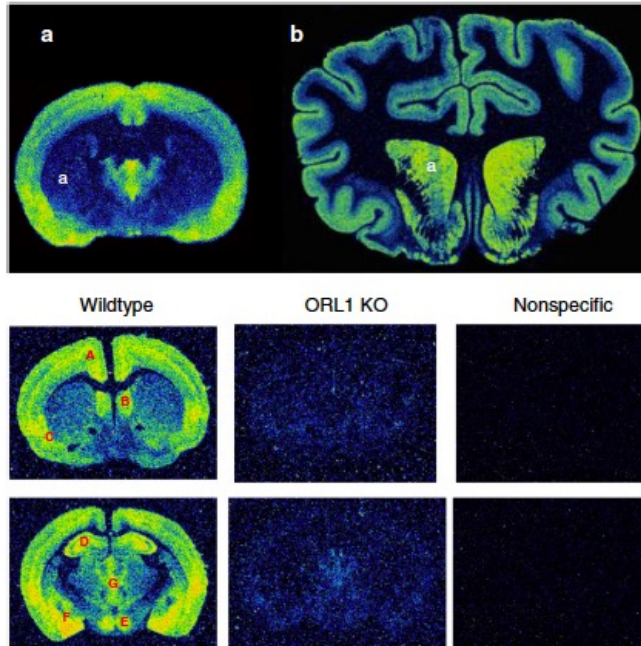
Alcohol is more harmful than opioids



- **Is opioid agonism a viable treatment option for AUD treatment ?**
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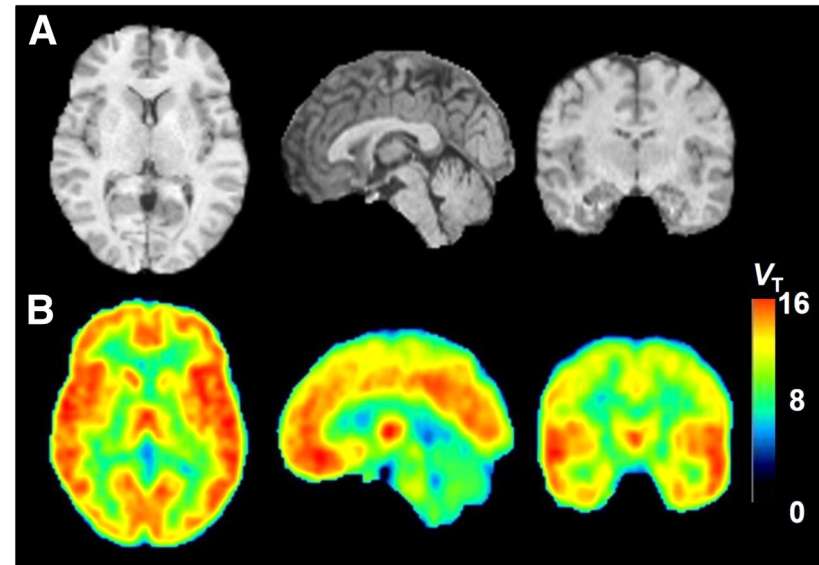
Autoradiographic localization of NOP receptor binding sites in the rat, dog and human brain.

J.M. Witkin et al. / Pharmacology & Therapeutics 141 (2014) 283-299

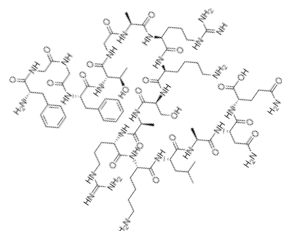


The biology of Nociceptin/Orphanin FQ (N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence[☆]

Jeffrey M. Witkin^{a,*}, Michael A. Statnick^a, Linda M. Rorick-Kehn^a, John E. Pintar^b, Michael Ansonoff^b, Yanyun Chen^a, R. Craig Tucker^a, Roberto Ciccocioppo^c



MRI and MA1 parametric PET images of 44-y-old healthy man injected with 738 MBq of ¹¹C-NOP-1A: MRI. Talakad G. Lohith et al. J Nucl Med 2012;53:385-392



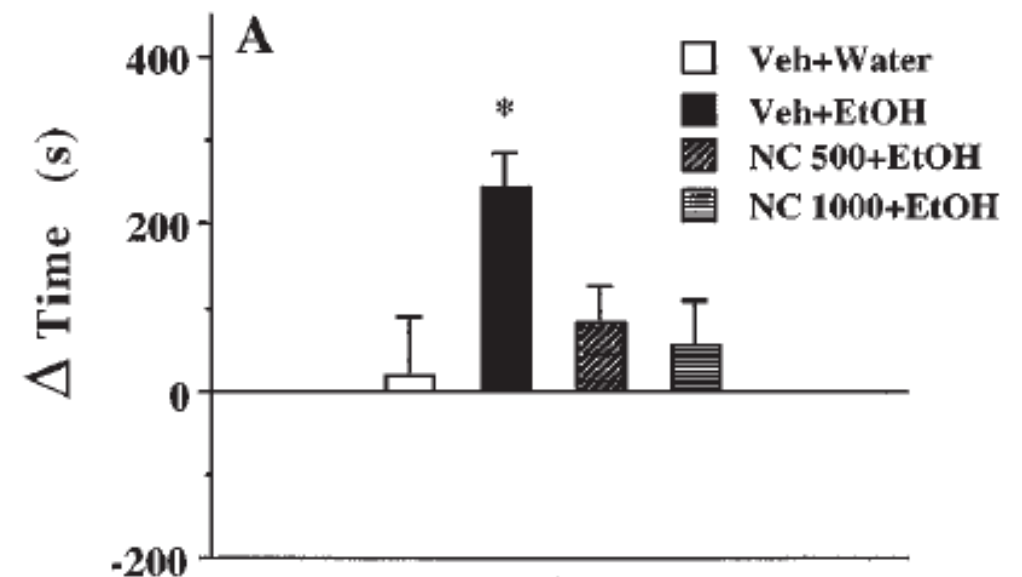
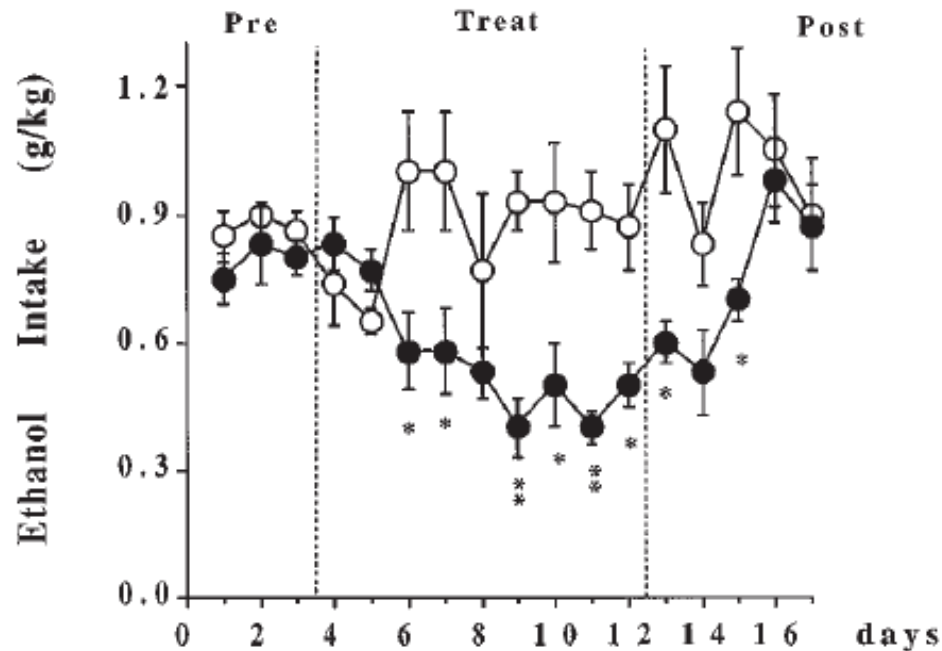
Nature Vol 377 12 October 1995

Science Vol 270 3 November 1995

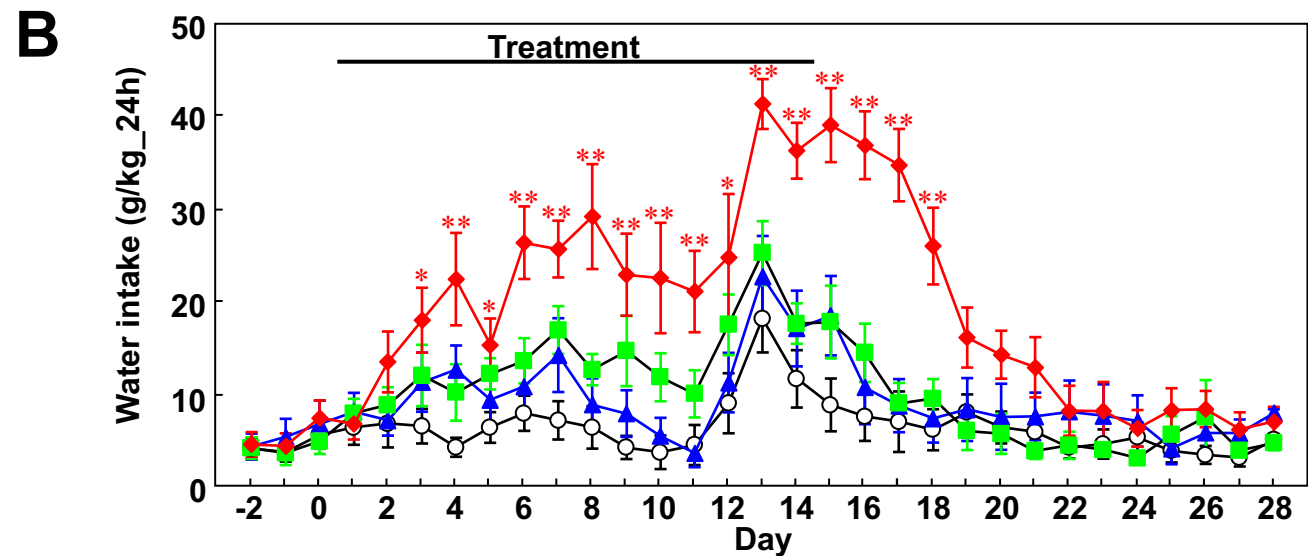
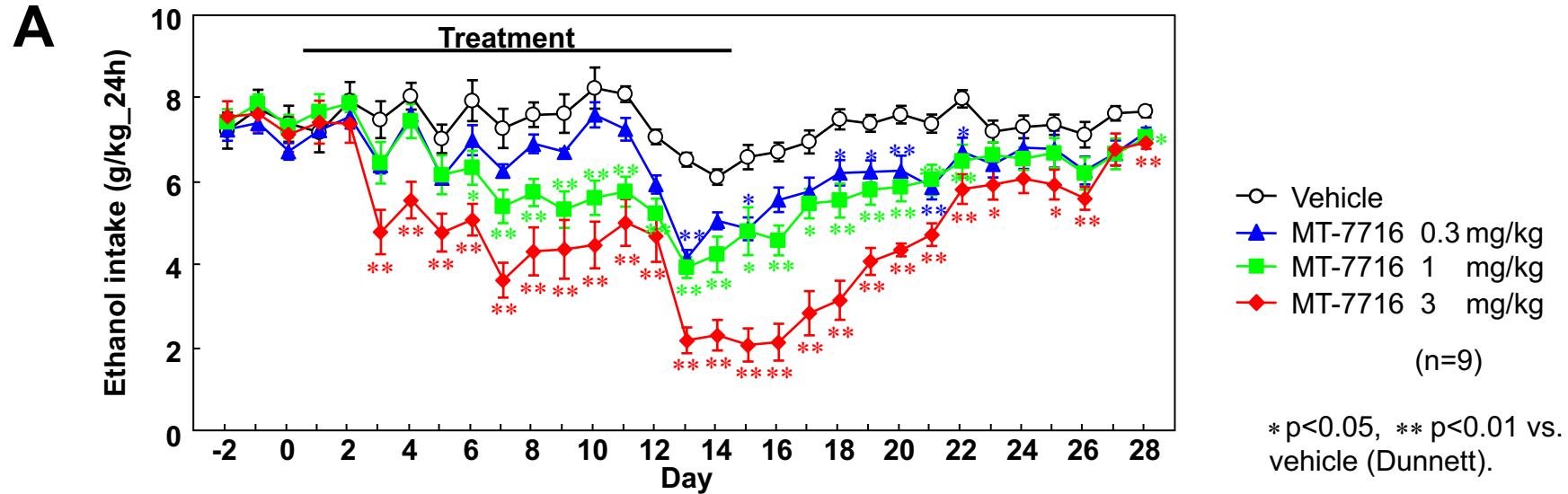
RAPID COMMUNICATION

Roberto Ciccocioppo · Izabela Panocka
Carlo Polidori · Domenico Regoli · Maurizio Massi

Effect of nociceptin on alcohol intake in alcohol-preferring rats

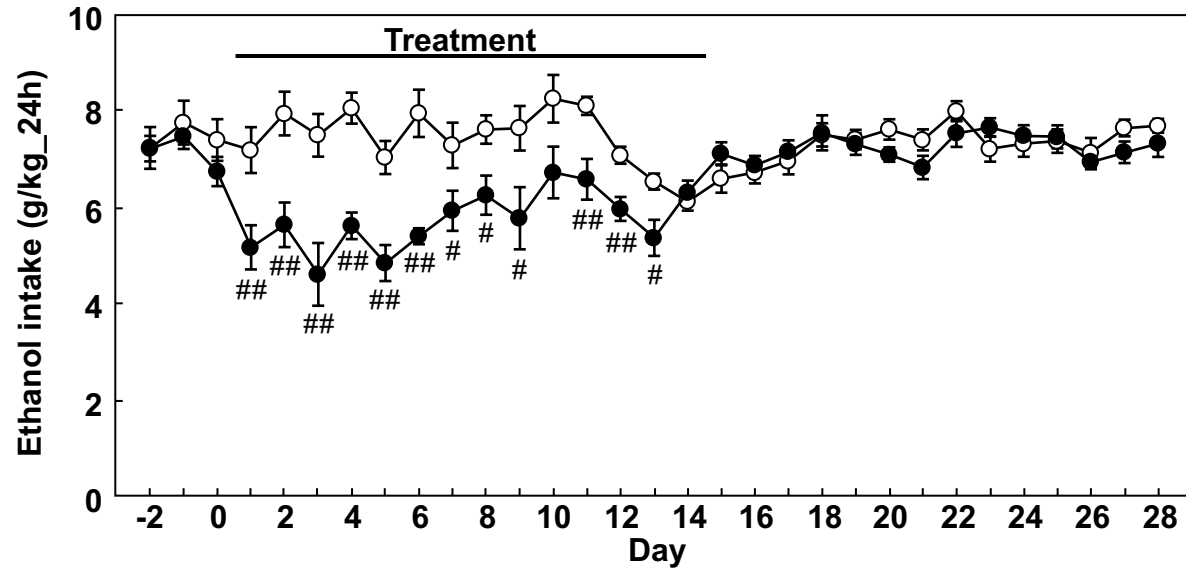


Stimulation of NOP receptor by MT-7716 reduces the motivation for alcohol in the rat

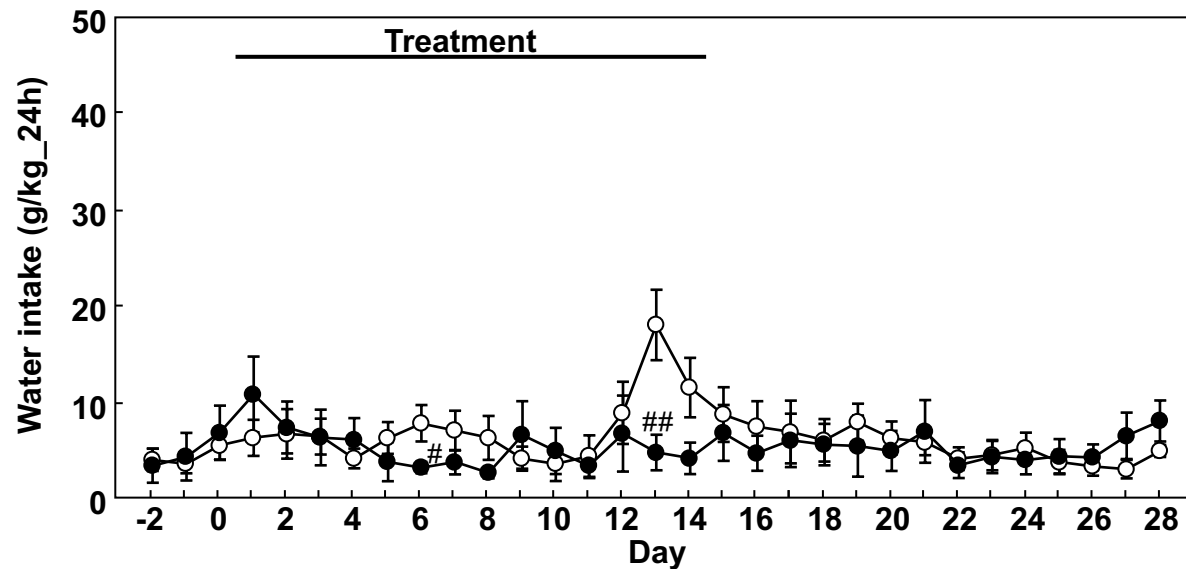


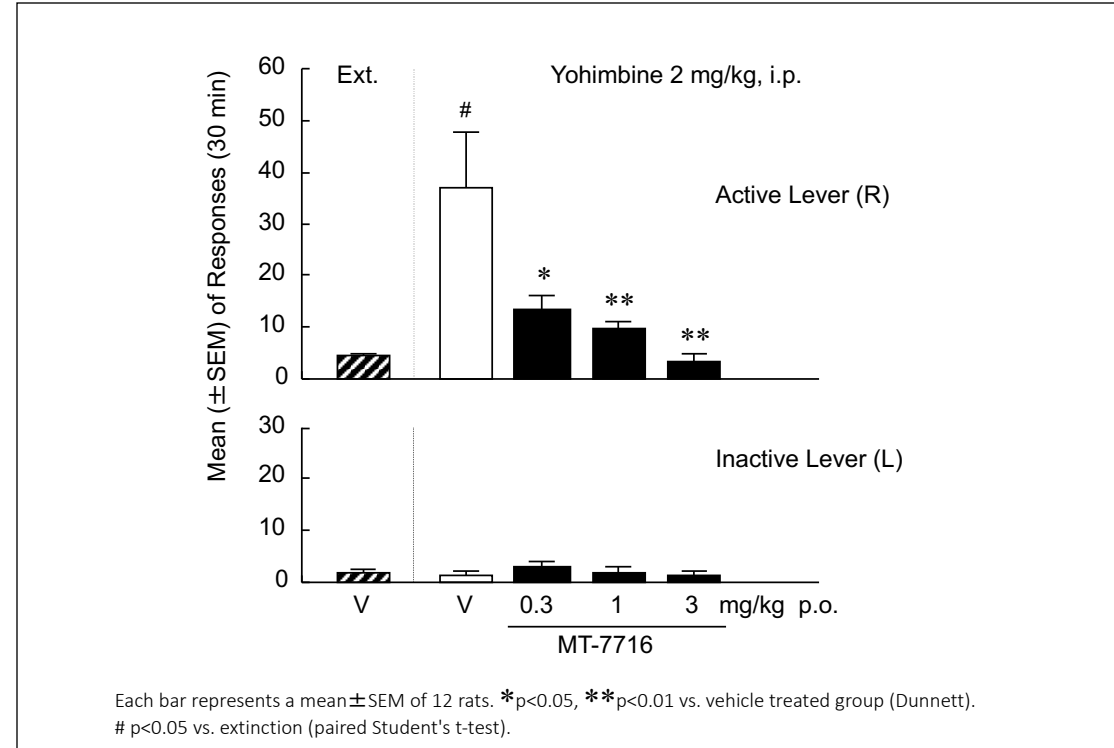
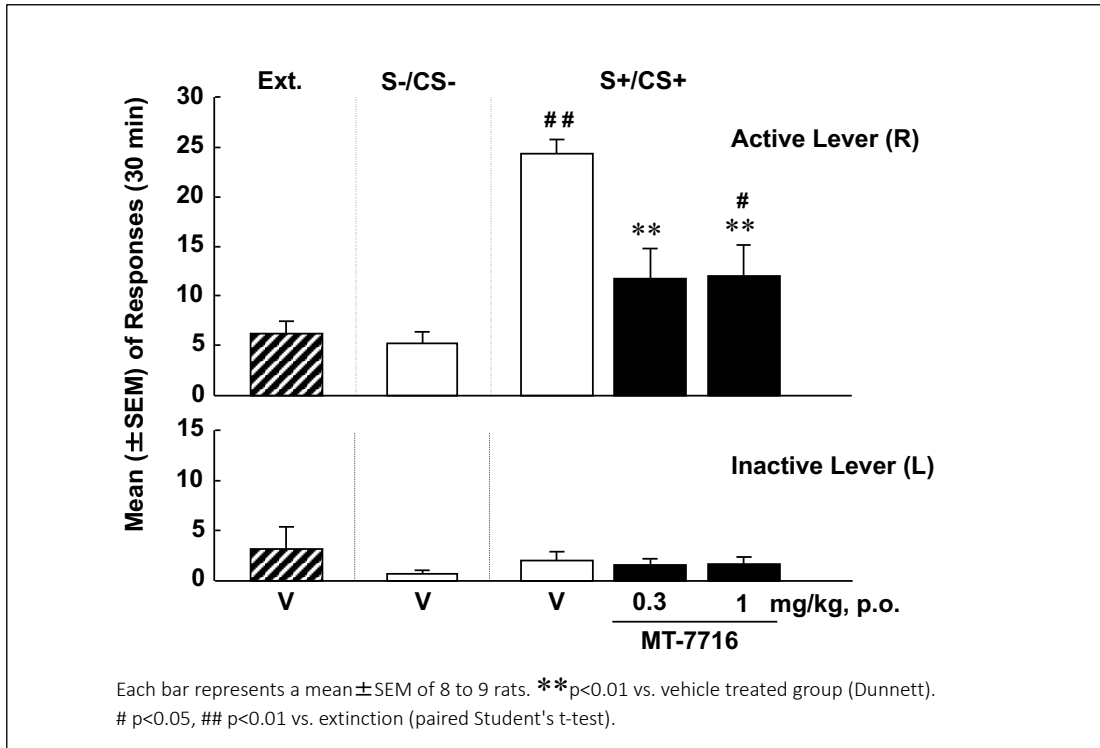
Blockade of Classical Opioid Receptors by Naltrexone Reduces the Motivation for Alcohol in the Rat

A



B





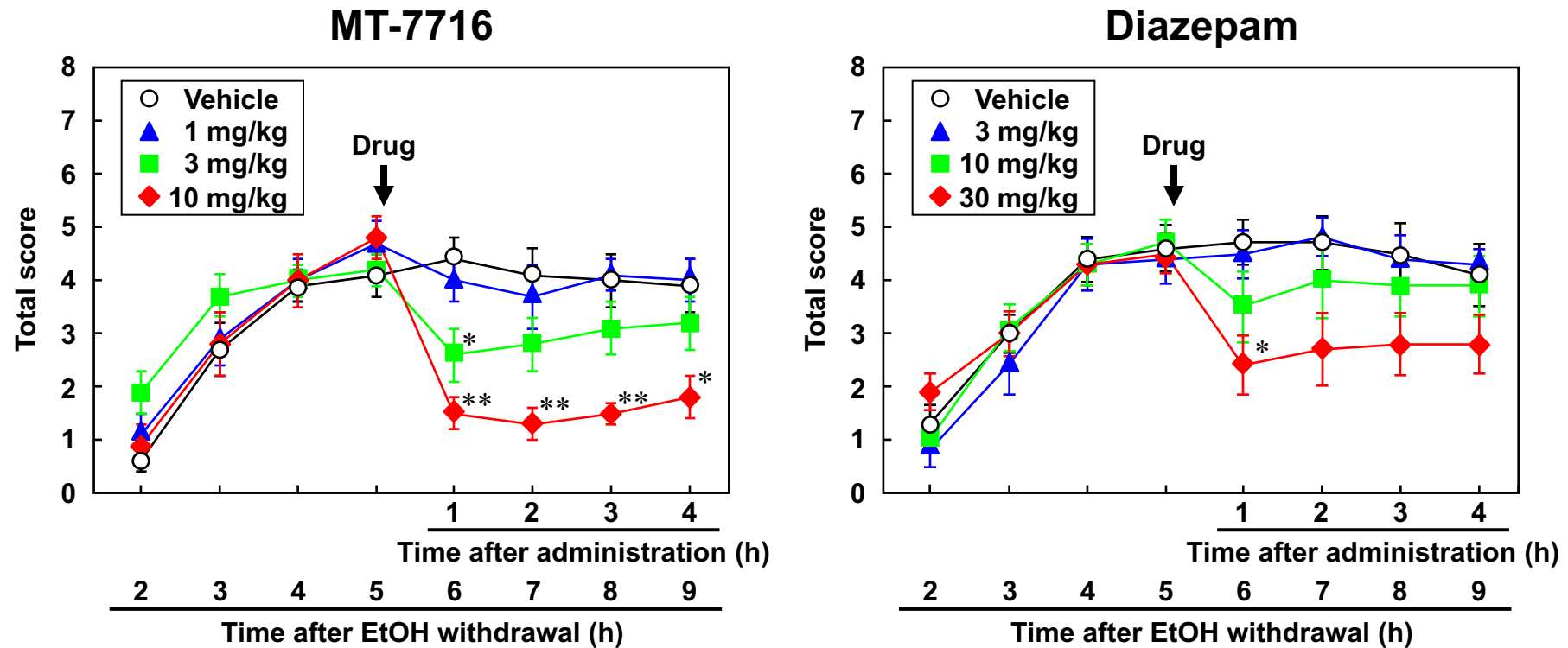
MT-7716 vs Diazepam on Ethanol Withdrawal Symptoms in the Rat

Symptoms:

Vocalization
Ventromedial Limb Retraction
Tail Rigidity
Tail Tremors

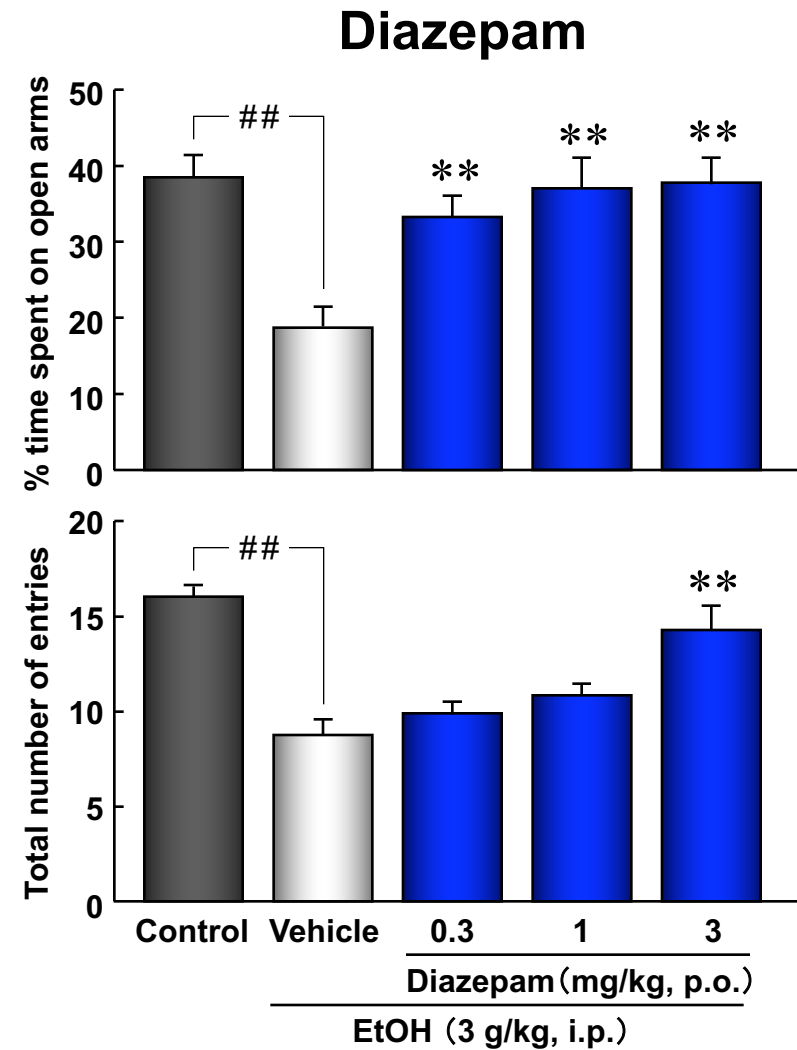
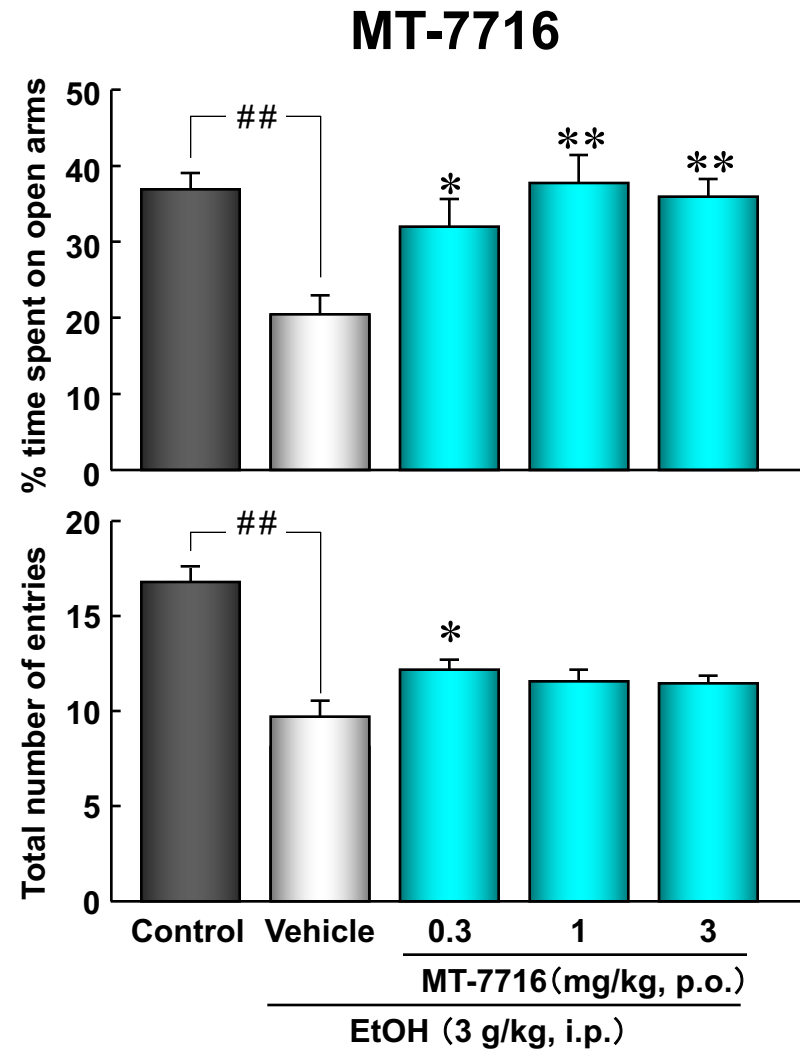
Score - Severity

0 = Mild
1 = Moderate
2 = Severe

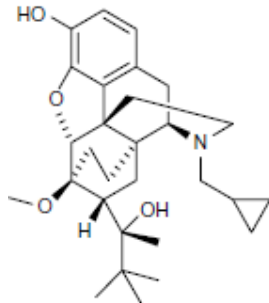


Each data point represents mean \pm S.E.M. of 9 or 10 rats. * $p < 0.05$, ** $p < 0.01$ vs. vehicle (Steel test)

MT-7716 vs Diazepam on Ethanol Induced Hangover Anxiety in the Rat

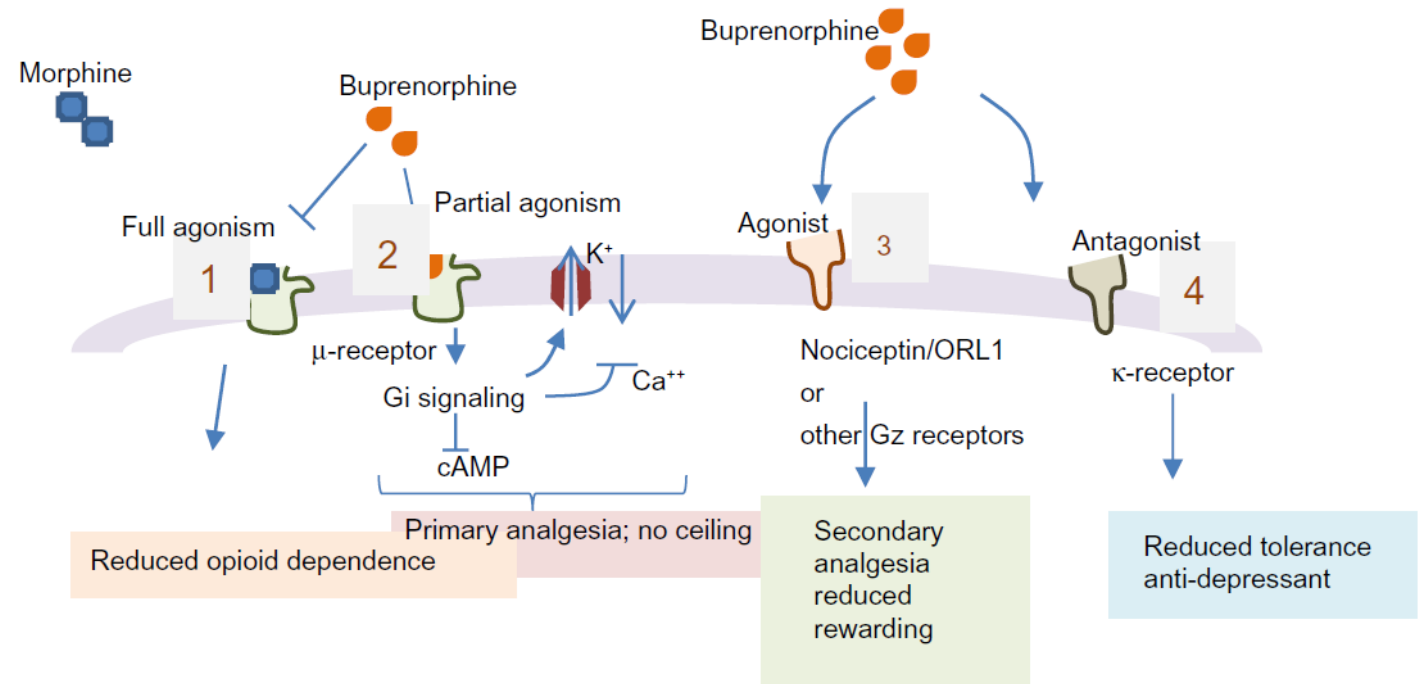


Buprenorphine Receptor Binding Profile



Buprenorphine is a semi-synthetic opioid agent derived from thebaine¹

NOP plays a role in the regulation of reward and motivation pathways related to substance abuse²



Adapted from: Khanna IK *et al. J Pain Res* 2015.

Opioid receptor	K _i (nM)	Agonist/antagonist
μ	1.5	Partial agonist
δ	6.1	Antagonist
κ	2.5	Antagonist
Nociceptin or ORL1	77.4	Agonist

1-year retention and social function after buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a randomised, placebo-controlled trial

Johan Kakko, Kerstin Dybrandt Svanborg, Mary Jeanne Kreek, Markus Heilig

	Baseline	3 months	6 months	9 months	12 months
Somatic morbidity	0.31 (0.66)	0.14 (0.62)	0.22 (0.66)	0.16 (0.60)	0.22 (0.70)
Occupation*	0.94 (0.34)	0.80 (0.20)	0.80 (0.46)	0.73 (0.56)	0.64 (0.50)
Alcohol use	0.06 (0.44)	0.02 (0.16)	0.01 (0.02)	0.01 (0.02)	0.09 (0.50)
Drug use†	0.29 (0.22)	0.09 (0.18)	0.05 (0.16)	0.06 (0.16)	0.03 (0.12)
Criminality‡	0.19 (0.44)	0.07 (0.30)	0.08 (0.36)	0.01 (0.02)	0.02 (0.18)
Family situation	0.20 (0.40)	0.20 (0.46)	0.17 (0.50)	0.11 (0.26)	0.14 (0.38)
Psychiatric morbidity	0.13 (0.42)	0.12 (0.30)	0.12 (0.34)	0.07 (0.18)	0.06 (0.22)

*p=0.0006 for effect over time. †p<0.0001 for effect over time. ‡p=0.02 for effect over time. Data are mean (SD).

Table 3: Composite scores in the seven subscales of the ASI for patients given buprenorphine

High doses (32 mg) of Buprenorphine reduces alcohol consumption in opioid use disorder patients

A Literature Review

Alcohol Use Disorders in Opioid Maintenance Therapy: Prevalence, Clinical Correlates and Treatment

Soyka M. *Eur. Addiction. Research*, 2015

AUD in opioid dependence

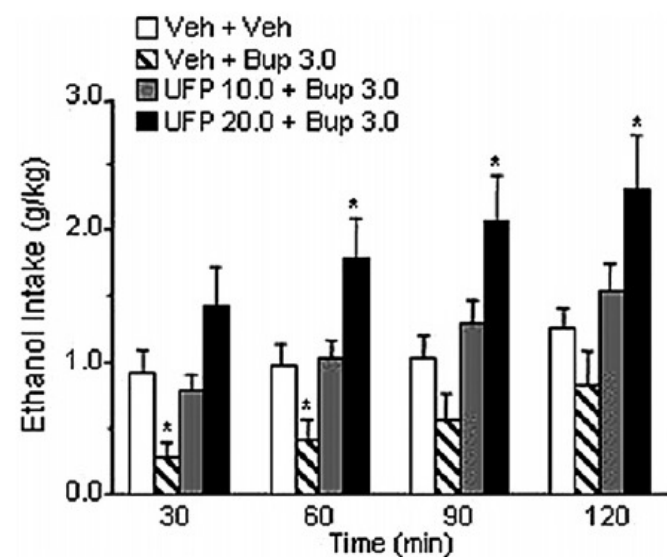
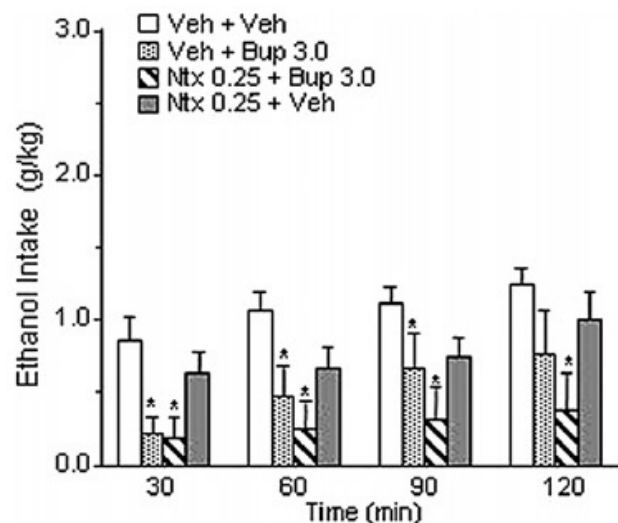
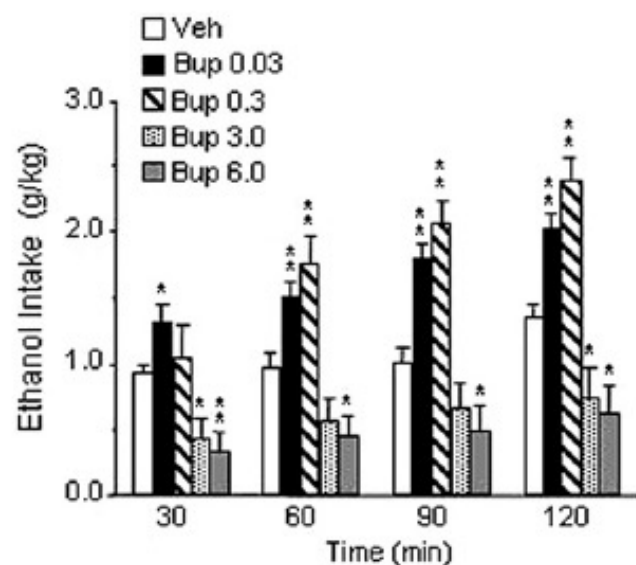
Study	Methods	Key findings
The effect of methadone maintenance treatment on alcohol consumption: a systematic review [8]	Systematic review of 15 studies	Alcohol use: Increased in 3 studies Decreased in 3 studies Did not change in 9 studies
Opioid maintenance therapy suppresses alcohol intake in heroin addicts with alcohol dependence [101]	Open randomized 12-month study, MET (80, 120, 160 and 200 mg) or BUP (8, 16, 24 and 32 mg) (n = 218)	Both treatments suppressed opioid and alcohol consumption (ASI scores) Highest BUP dose better than highest MET dose on alcohol craving and intake
Effects of heroin-assisted treatment on alcohol consumption [99]	Secondary analysis of self-reported alcohol consumption, CDT, ASI scores Randomized trial: heroin vs. MET	Both groups: significant reduction of alcohol use and CDT Heroin group: reduction of ASI score Effect of daily frequency of heroin dispensing (setting effect)?

BUP = Bupropione; CDT = carbohydrate-deficient transferrin; MET = methadone.

PRIORITY COMMUNICATION

Buprenorphine Reduces Alcohol Drinking Through Activation of the Nociceptin/Orphanin FQ-NOP Receptor System

Roberto Ciccocioppo, Daina Economidou, Roberto Rimondini, Wolfgang Sommer, Maurizio Massi, and Markus Heilig

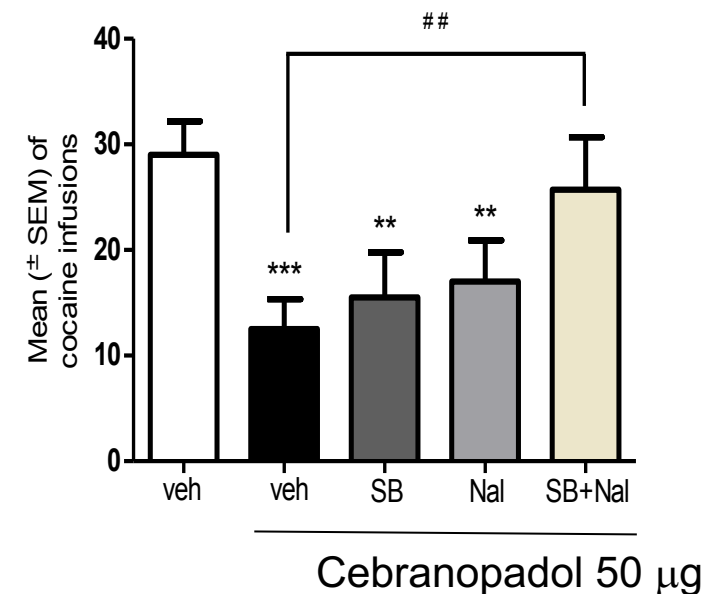
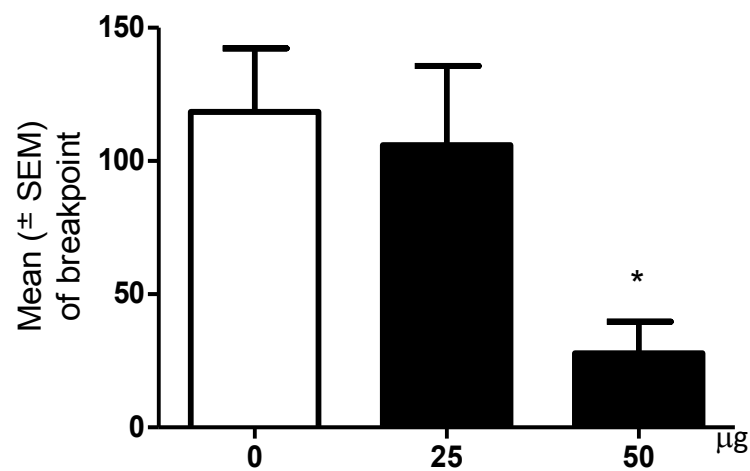
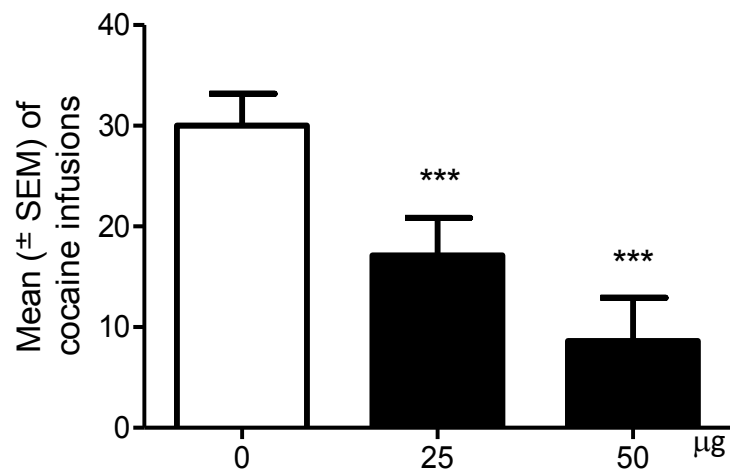


Cebranopadol, a Mixed Opioid Agonist, Reduces Cocaine Self-administration through Nociceptin Opioid and Mu Opioid Receptors

Qianwei Shen¹, Yulin Deng², Roberto Ciccocioppo^{1*} and Nazzareno Cannella¹

Cebranopadol is a high affinity agonist for MOP, NOP and a lower affinity for DOP and KOP. Cebranopadol Reduces Cocaine Self-Administration in Rats

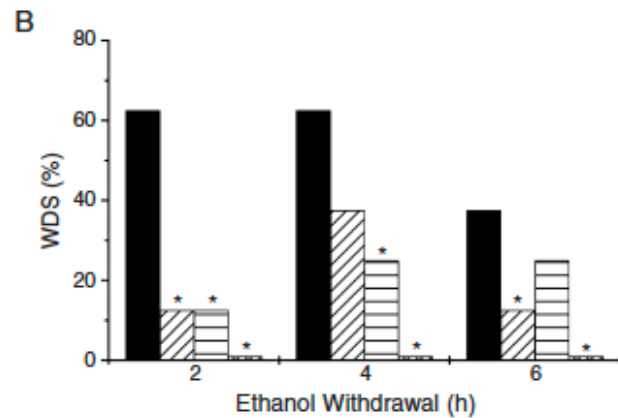
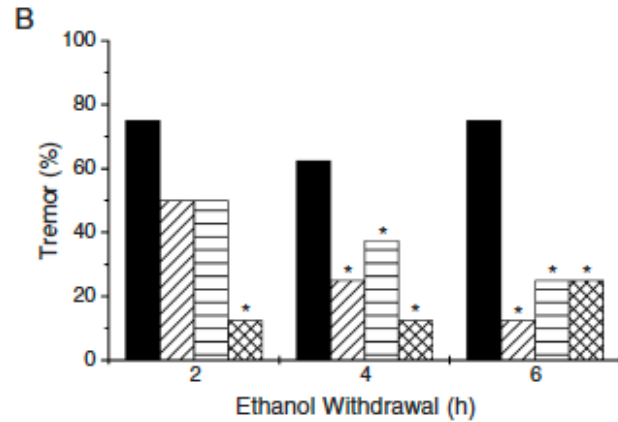
Target	Rat Receptor Subtypes		Human Receptor Subtypes	
	Radioligand Binding		[³⁵ S]GTP γ S Binding	
	K_i	K_i	EC_{50}^a	Relative Efficacy ^b
	<i>nM</i>	<i>nM</i>	<i>nM</i>	%
NOP receptor	1.0 \pm 0.5 (<i>n</i> = 5)	0.9 \pm 0.2 (<i>n</i> = 7)	13.0 \pm 2.0 (<i>n</i> = 5)	88.9 \pm 3.9 (<i>n</i> = 5)
MOP receptor	2.4 \pm 1.2 (<i>n</i> = 4)	0.7 \pm 0.3 (<i>n</i> = 7)	1.2 \pm 0.4 (<i>n</i> = 5)	103.5 \pm 4.7 (<i>n</i> = 5)
KOP receptor	64.0 \pm 11.0 (<i>n</i> = 2)	2.6 \pm 1.4 (<i>n</i> = 7)	17.0 \pm 5.0 (<i>n</i> = 6)	67.2 \pm 5.3 (<i>n</i> = 6)
DOP receptor	N.D.	18.0 \pm 20.0 (<i>n</i> = 11)	110.0 \pm 28.0 (<i>n</i> = 4)	105.0 \pm 8.5 (<i>n</i> = 4)



Acute and chronic tianeptine treatments attenuate ethanol withdrawal syndrome in rats

Tayfun Uzbay^{a,*}, Hakan Kayir^a, Turgay Çelik^a, Nevzat Yüksel^b

Biological Psychiatry 2006

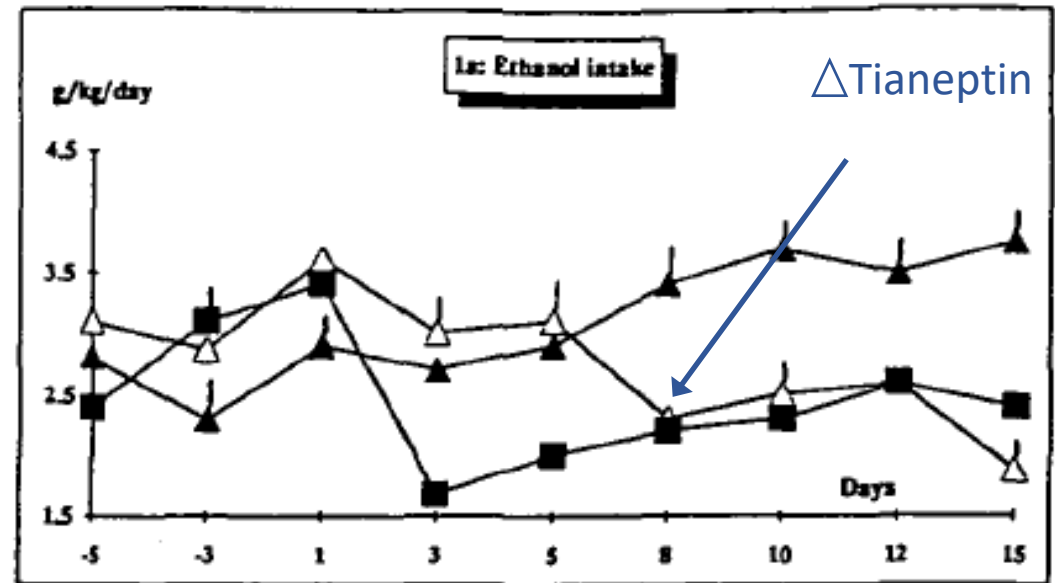


RAPID COMMUNICATION

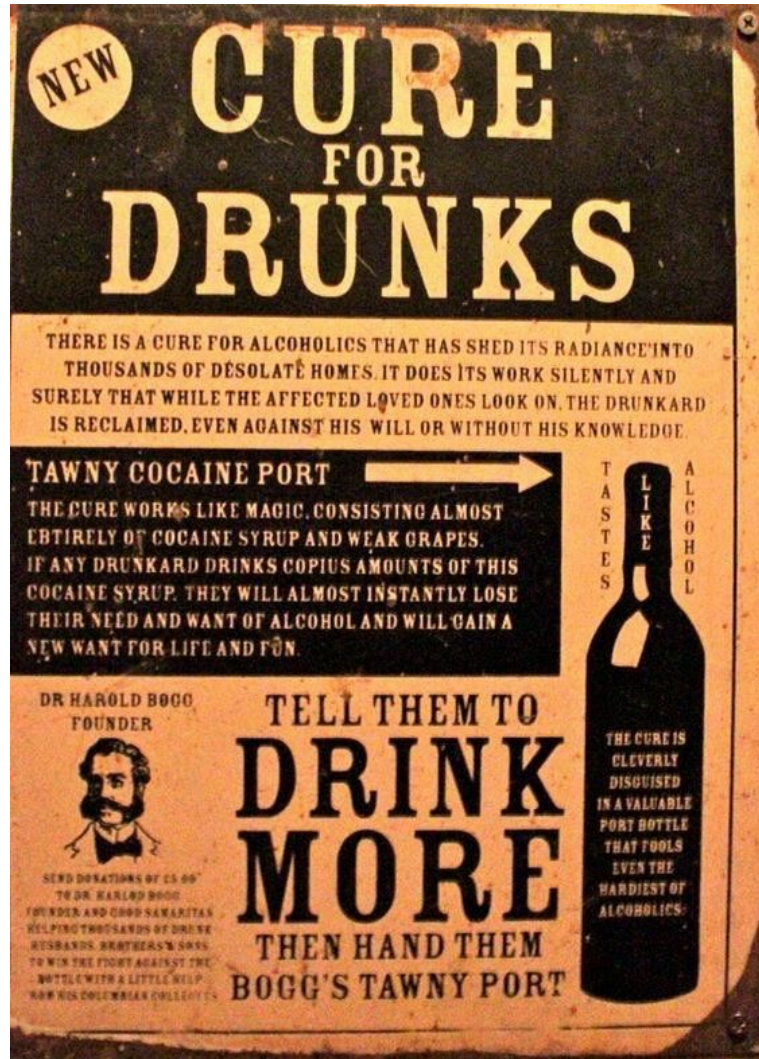
TIANEPTINE, A SPECIFIC SEROTONIN UPTAKE ENHANCER, DECREASES ETHANOL INTAKE IN RATS

M. DAOUST,* P. COMPAGNON,* E. LEGRAND* and E. MOCAËR†

Alcohol and Alcoholism, 1992



Conclusions



THERE IS A CURE FOR ALCOHOLICS THAT HAS SHED RADIANCE INTO THOUSANDS OF DESOLATED HOMES. IT DOES ITS WORK SILENTLY AND SURELY THAT WHILE THE AFFECTED LOVED ONES LOOK ON, THE DRUNKARD IS RECLAIMED, EVEN AGAINST HIS WILL OR WITHOUT HIS KNOWLEDGE

THE CURE WORKS LIKE MAGICIF ANY DRUNKARD DRINKS COPIOUS AMOUNT OF THIS COCAINE SYRUP THEY WILL ALMOST INSTANTLY LOSE THEIR NEED AND WANT OF ALCOHOL AND WILL GAIN A NEW WANT FOR LIFE AND FUN

.....OUR HOPE IS TO FIND TREATMENTS TO MAKE AUD PATIENTS TO FEEL RELIEVED BY RESTORING REWARD HOMEOSTASIS



Eva-Maria and Rutger Hetzler
Foundation