Facts in favor of limited alcohol consumption concept

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Immersed in a sea of risk

Leading 12 selected risk factors as causes of disease burden

NCD = noncommunicable disease

■ = *Major NCD risk factors*

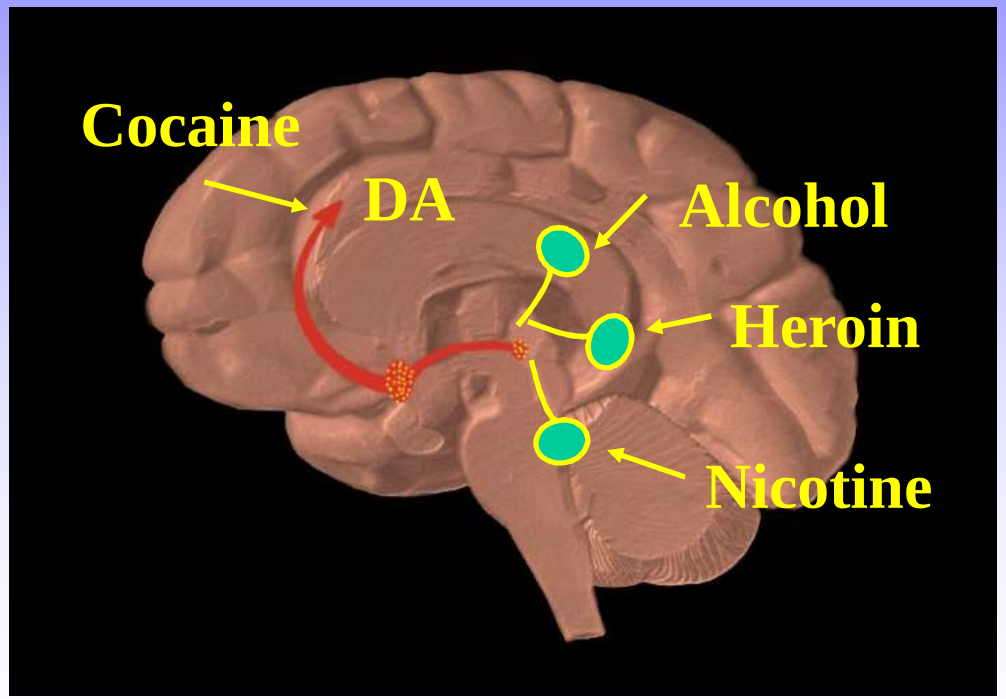
	High Mortality Developing Countries	*Low Mortality Developing Countries*	*Developed Countries*
1	Underweight	Alcohol	Tobacco
2	Unsafe sex	Blood pressure	Blood pressure
3	Unsafe water	Tobacco	Alcohol
4	Indoor smoke	Underweight	Cholesterol
5	Zinc deficiency	Body mass index	Body mass index
6	Iron deficiency	Cholesterol	Low fruit & veg. intake
7	Vitamin A deficiency	Low fruit & veg intake	Physical inactivity
8	Blood pressure	Indoor smoke - solid fuels	Illicit drugs
9	Tobacco	Iron deficiency	Unsafe sex
10	Cholesterol	Unsafe water	Iron deficiency
11	Alcohol	Unsafe sex	Lead exposure
12	Low fruit & veg intake	Lead exposure	Childhood sexual abuse

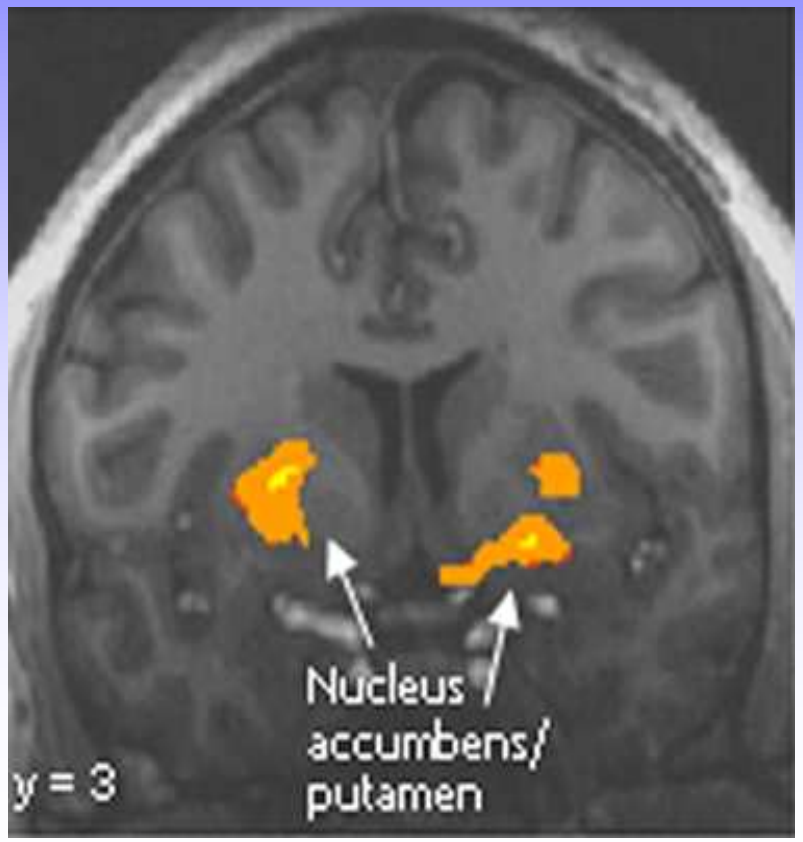
Similar to other drugs, alcohol <u>can</u> activate brain reward circuitry

(Gilman et al. J Neurosci 2008)

Addiction is a brain disease

Alcohol dependence is relapsing, chronic disease

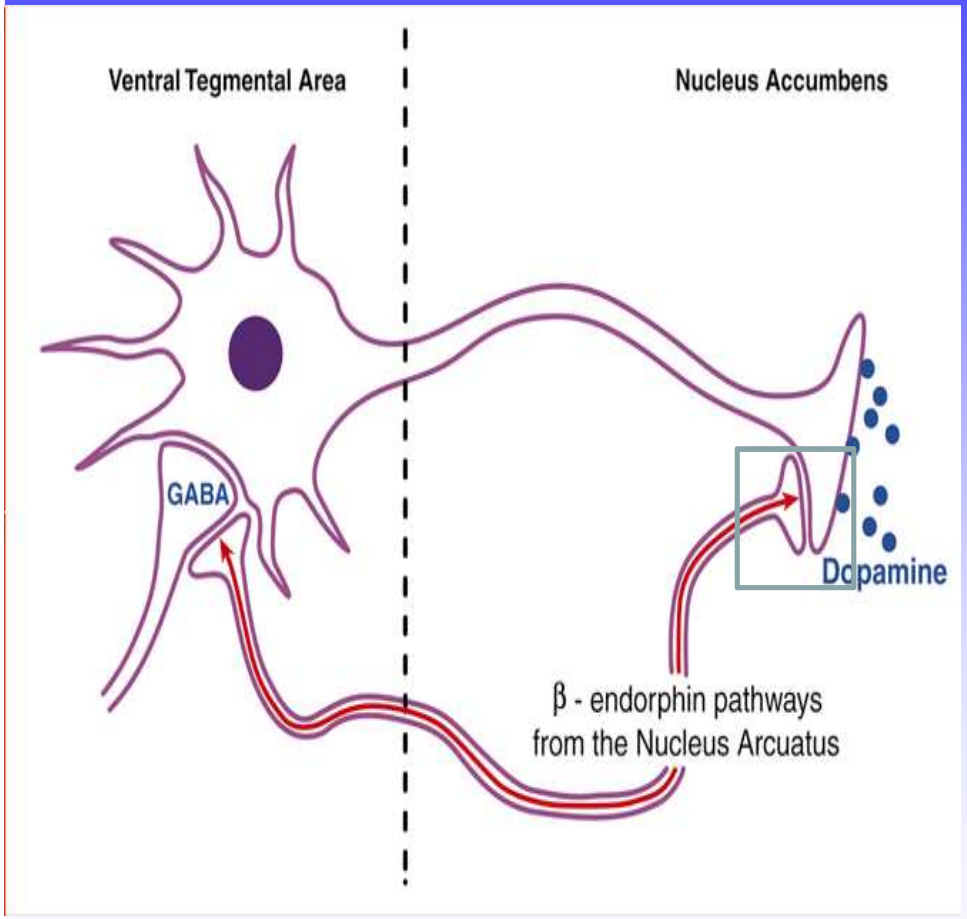




Alcohol dependence, background

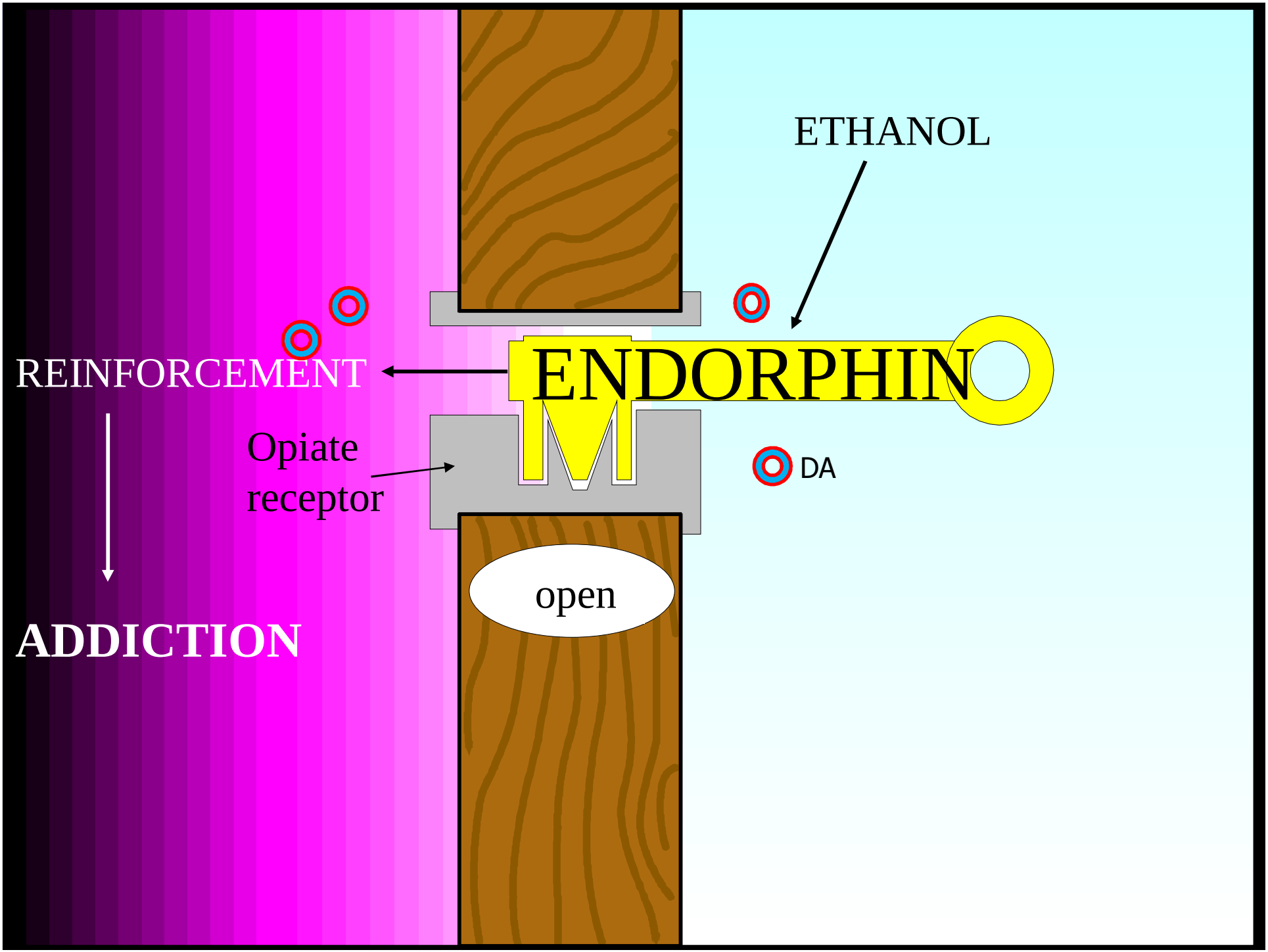
- Psychosocial and pharmacological treatments help many alcoholics to reduce their drinking or achieve abstinence; however, 40 % to 70 % of these individuals relapse within 1 year (Swift et al. 1999)
  - A new concept that can enhance and prolong the effectiveness of these treatments is clearly needed
- Does the limited alcohol consumption and targeted medication concept (taken before alcohol or craving situation) have neuropharmacological bases ?
- Is the reduction of alcohol consumption and preventing relapse prevention an acceptable and effective treatment goal ??

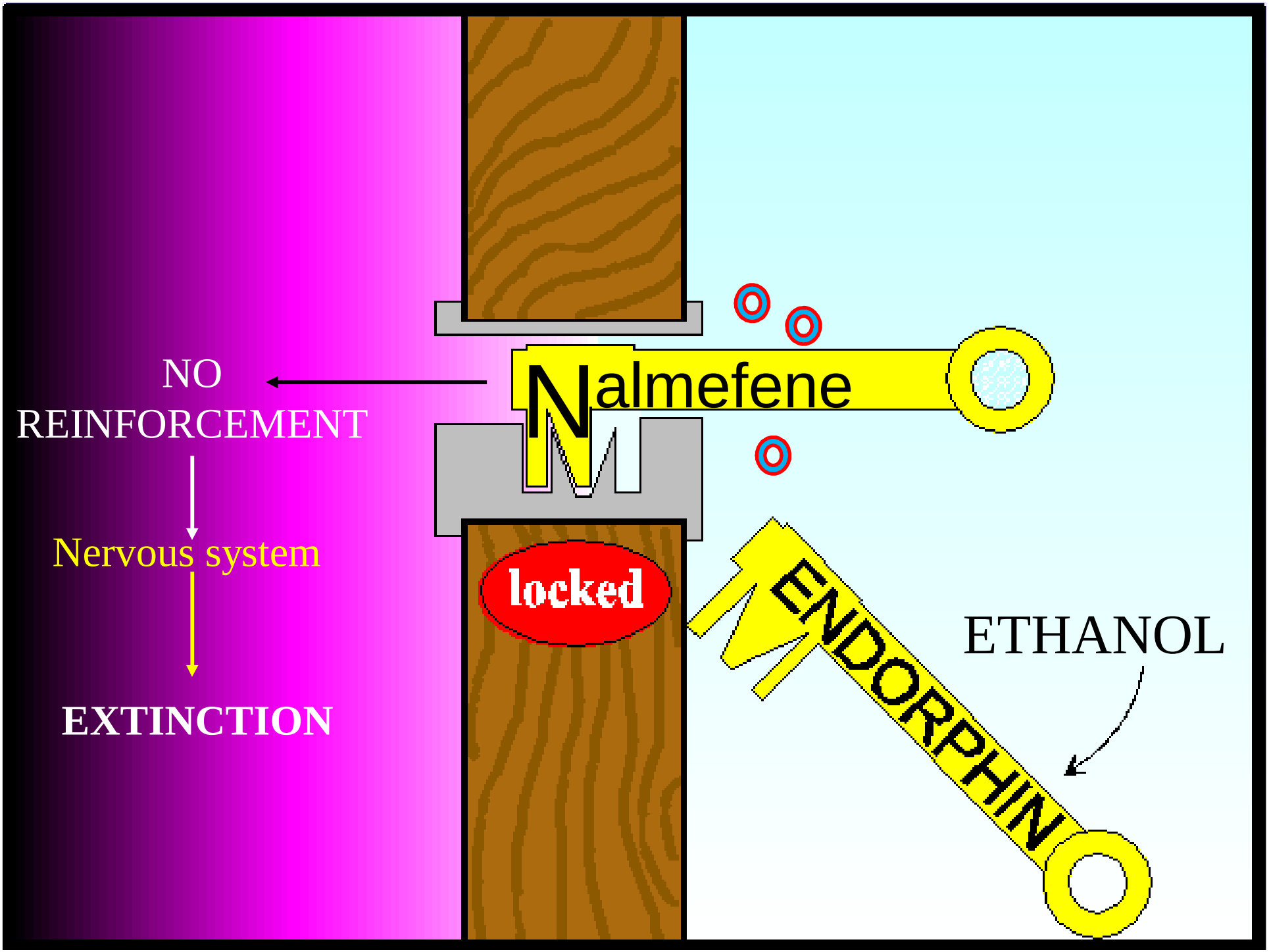
I, Opioid antagonists - basic science



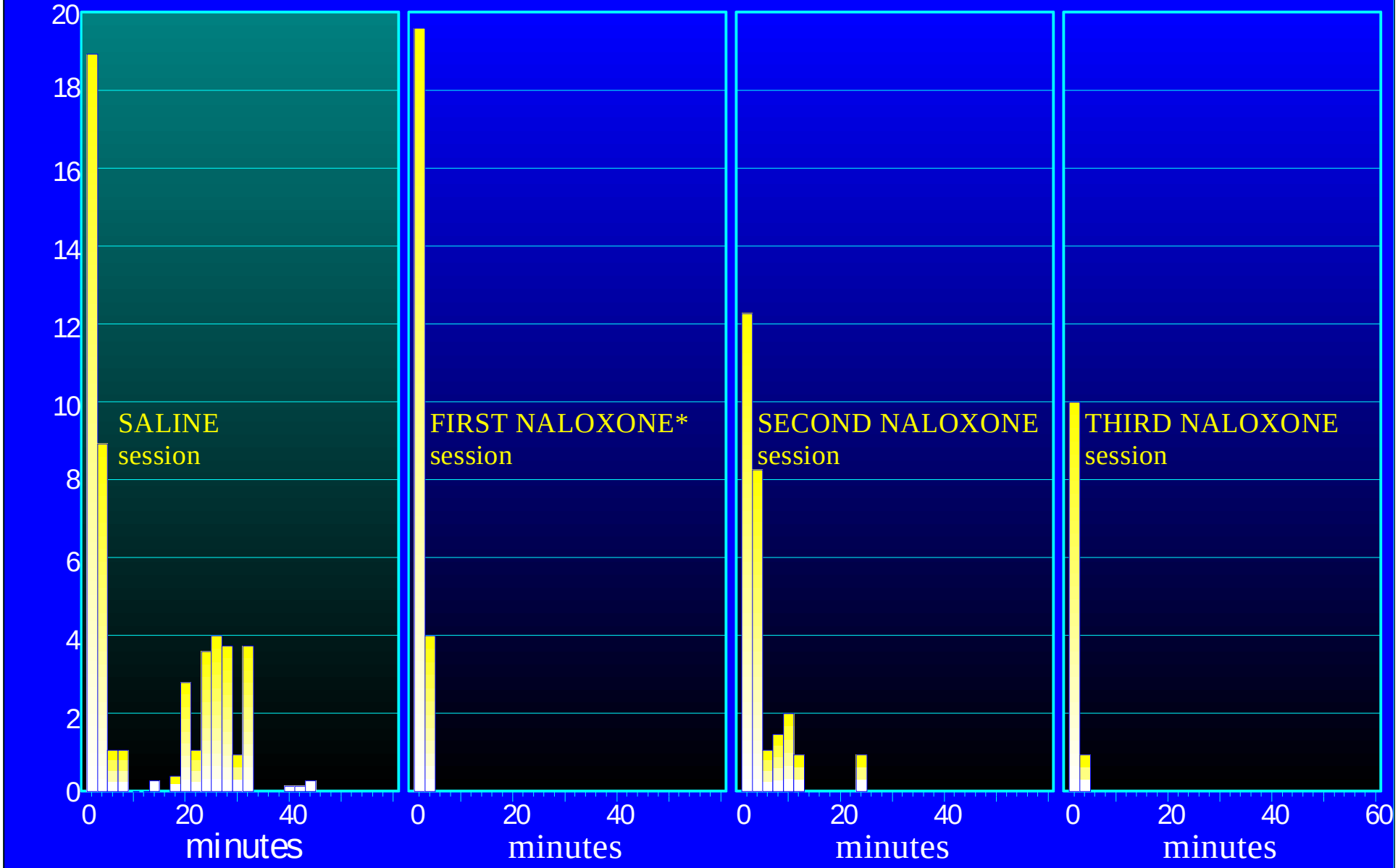
Embellished from Gianoulakis 1998

- Alcohol consumption increases the production, release, and activity of endogenous opioid peptides (Herz, 1997)
- Endogenous opioid peptides mediate some of alcohol's rewarding effects perhaps by enhancing midbrain dopamine release (Weise 1987, Herz 1997)
- Opioid antagonists naltrexone and nalmefene suppress alcohol-induced reward (Swift,1999) and general consummatory behaviors (Boyle et al. 1998)


ETHANOL
REINFORCEMENT
ENDORPHIN
Opiate
receptor
DA
open
ADDICTION


NO
REINFORCEMENT
Nervous system
EXTINCTION
Nalmefene
locked
ENDORPHIN
ETHANOL

Progressive decrease in lever pressing for alcohol induced by naloxone



Data from Petri Hyytiä, 1994

* 1 mg/kg , 30 min before alcohol access

Alcoholism is..

learning to press a “bar” to get alcohol,

and learning, and learning, and learning

and learning, and learning, and learning, and learning

and learning, and learning, and learning, and learning, and learning,

and learning, and learning, and learning, and learning, and learning, and learning

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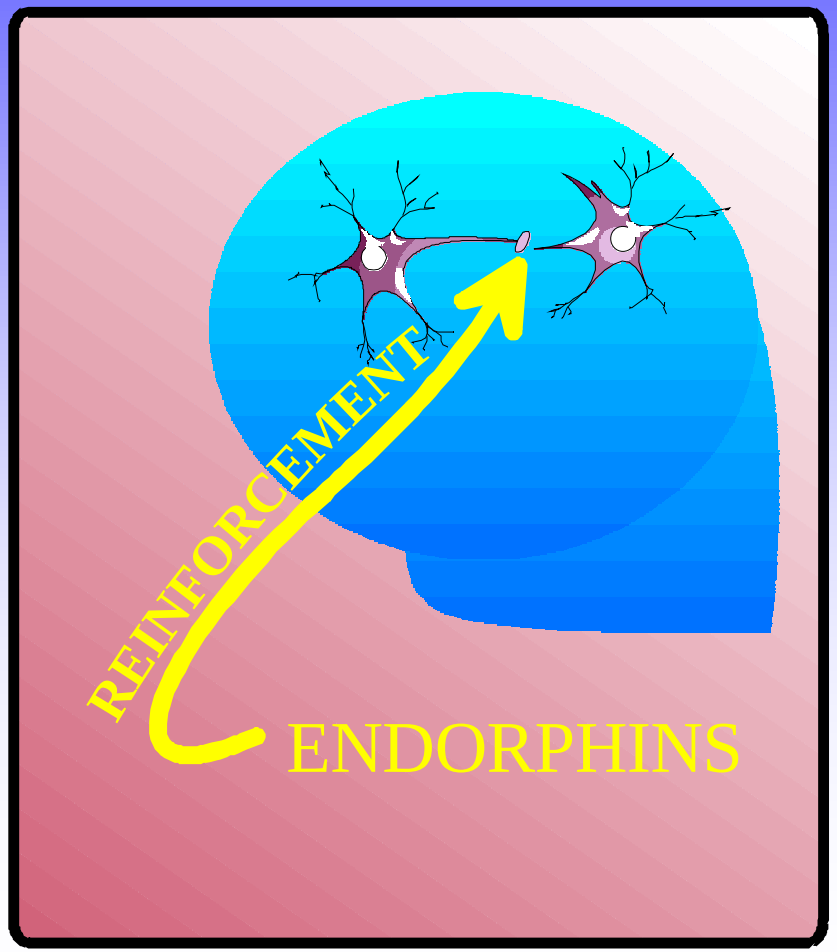
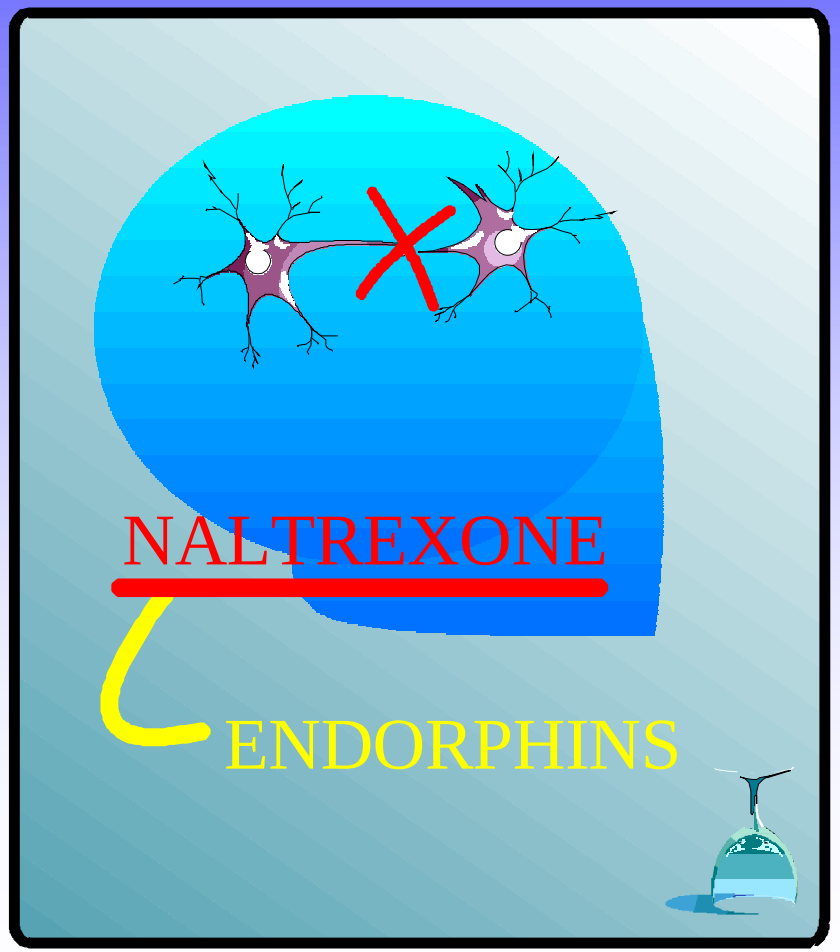
Two processes in information systems

LEARNING



EXTINCTION



Summary

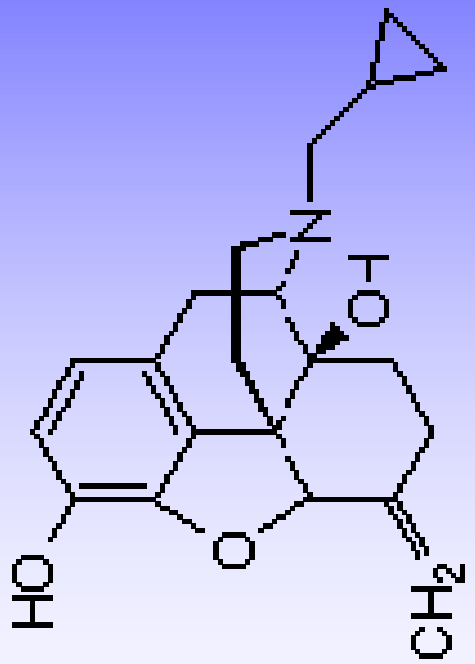
- Alcohol dependence is partially learned behavior
- The nervous system removes learned behaviors with a mechanism called extinction
- Extinction removes behaviors that are made and then don't produce reinforcement: *extinction is Nature's way of "removing" mistakes*
- Extinction does not touch behaviors that are not made

THEREFORE

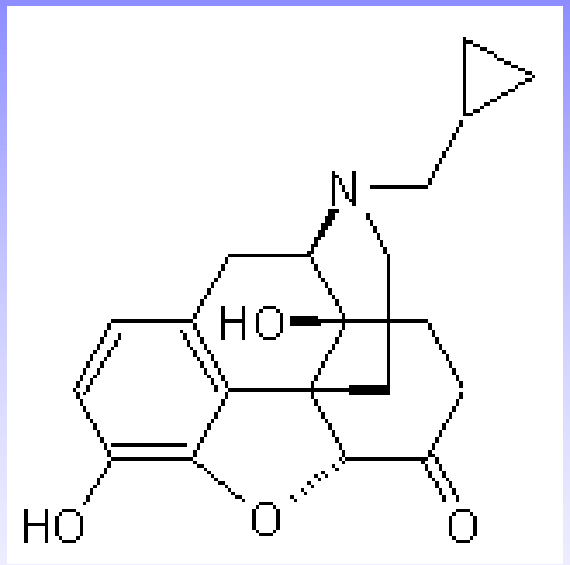
- Thus the reduced alcohol consumption and targeted medication (taken before alcohol consumption or craving situation) have neuropharmacological bases
- Any clinical evidence ??

Chemical formula of Nalmefene and naltrexone

Nalmefene

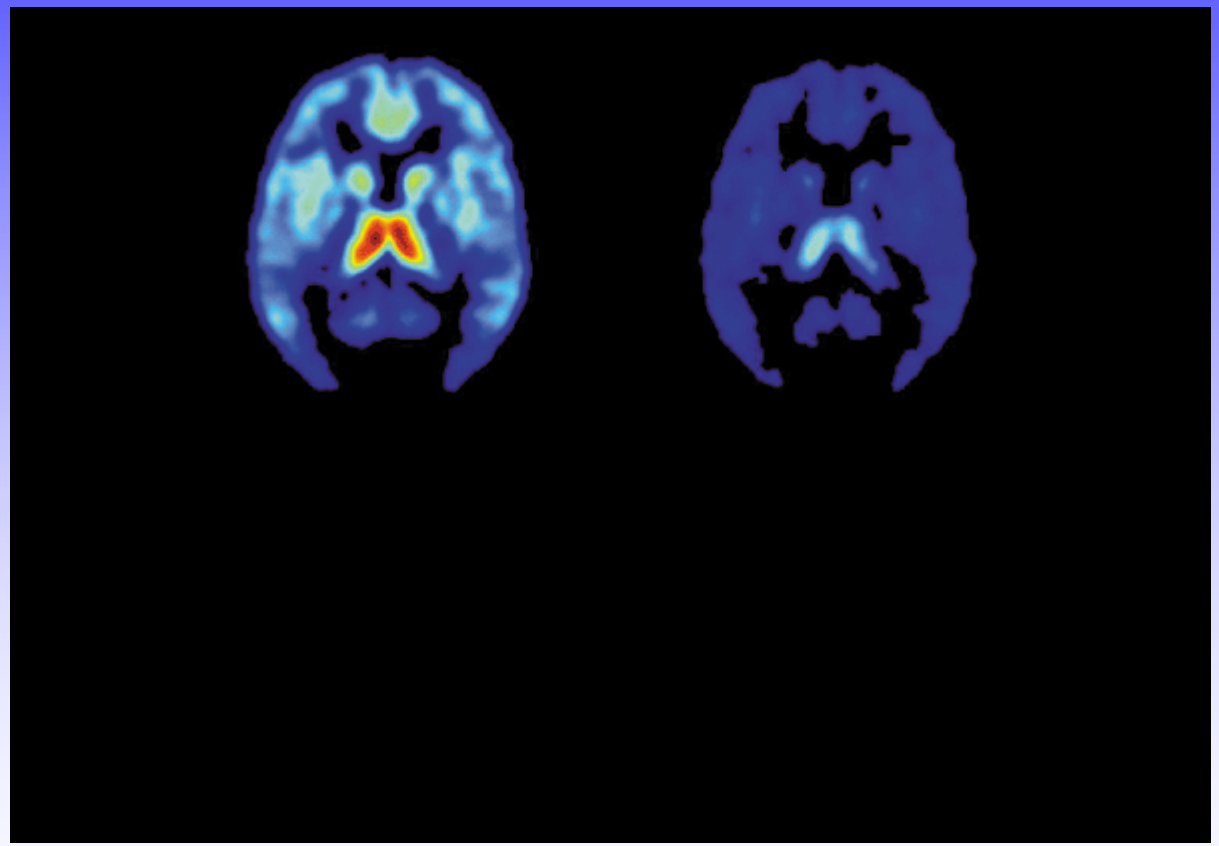


Naltrexone



Binding of [^{11}C]-carfentanil (morphine)

before **after** **nalmefene (20 mg, 3 h)**



Neuropsychopharmacology, 2005, 30, 2245-2253

Comparison of nalmefene and naltrexone

• Binds to μ opiatereceptors	• Same
• Has greater affinity to the κ and δ receptors than naltrexone and naloxone	• **Lower**
• Antagonist at μ and δ receptors	• Same
• Partial agonist at κ receptors	• Same
• Very low affinity to cholinergic, histaminergic, serotonergic and alpha-receptors	• Same

Comparison of nalmefene and naltrexone

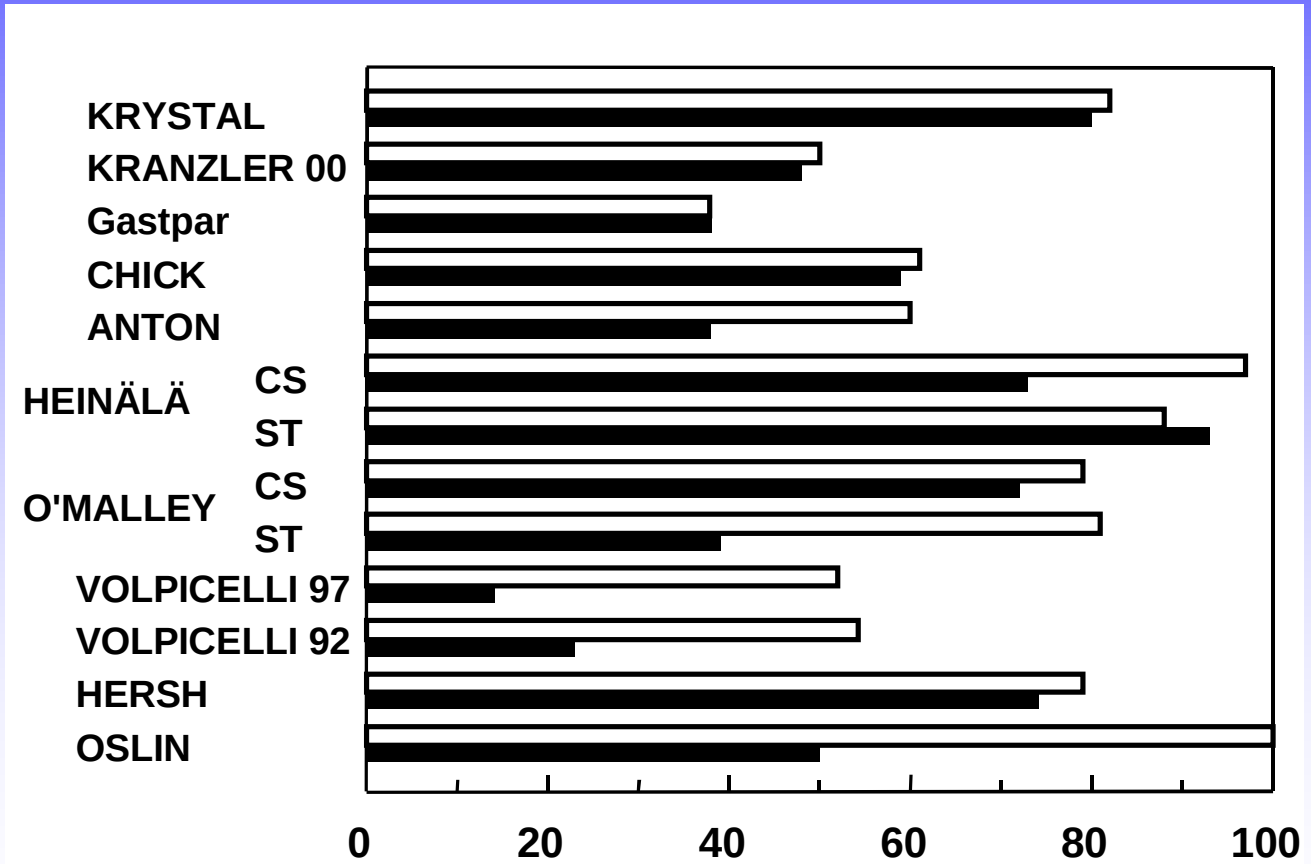
- t_{max} 0.5-3 h
- Oral availability >50%
- $T_{½}$ 8-11 h
- Effect of food unlikely to be clinically significant
- Hepatic impairment
  - Moderately and severely impaired patients had 50% increase in AUC following iv administration

- Same
- **5** - 60 %
- **1 – 9 h**
- **Some**

- Same

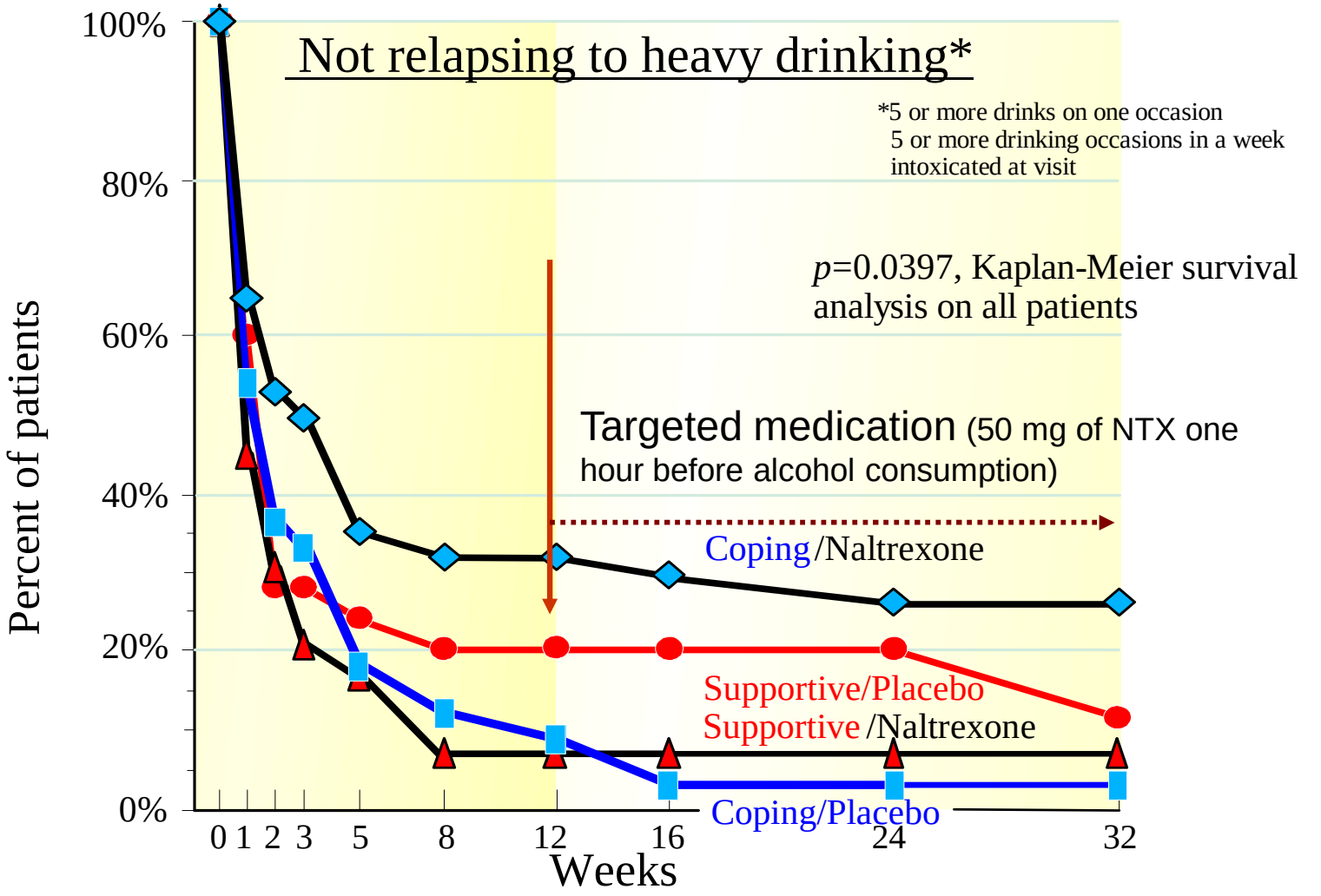
Naltrexone, Clinical science

Relapse Rates (> 60 g aa / day)



K. Mann, CNS-Drugs 2004

Targeted NTX treatment



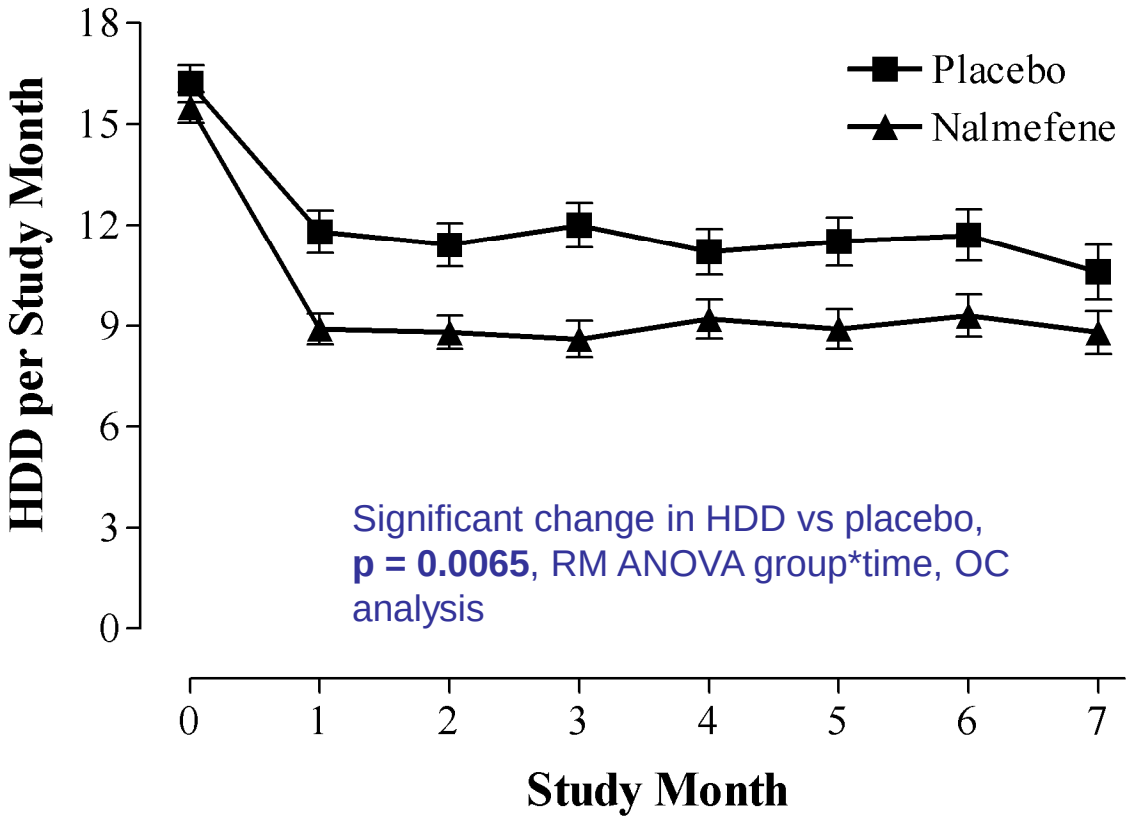
*Heinälä, P., H. Alho, et al.. Targeted use of naltrexone without prior detoxification in the treatment of alcohol dependence: A factorial double-blind placebo-controlled trial. Journal of Clinical Psychopharmacology: **21**(3): 287-292, 2001.*

Nalmefene - clinical science

- Reduction of heavy drinking: two positive studies (Mason et al. 1999, Karhuvaara et al., 2007), one negative study (Anton et al., 2004) in preventing heavy drinking and relapsing
- Large scale RCT multicenter study with ample power is ongoing in EU (n =600)

Nalmefene, efficacy results

Randomised: 403 patients, NMF:242, PBO:161



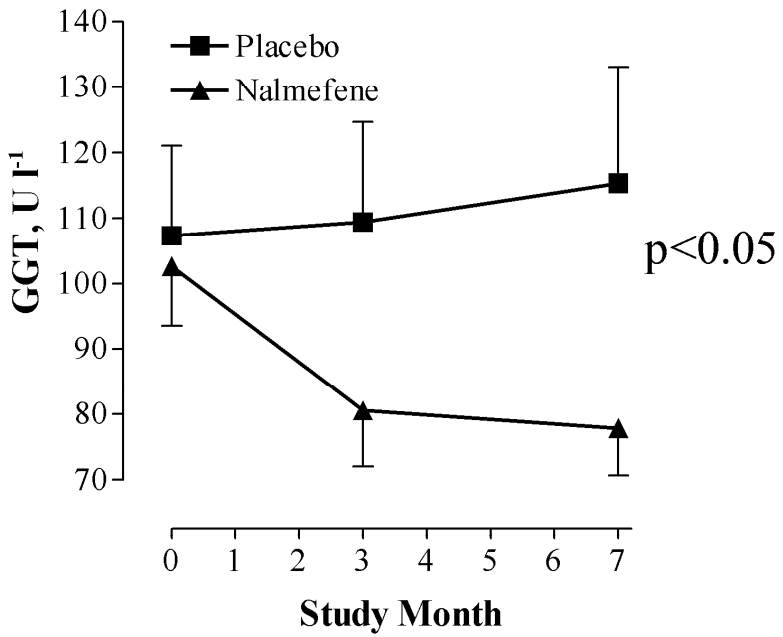
Significant results on:

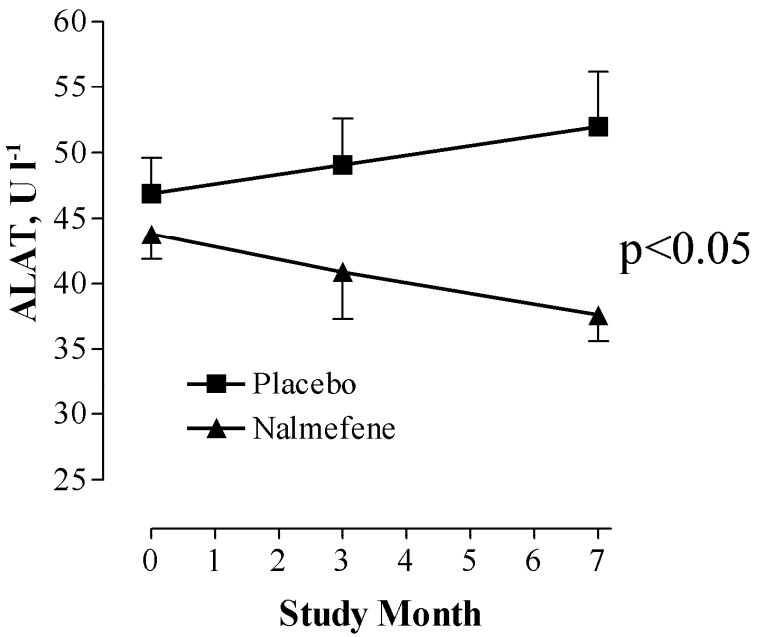
- HDD
- Total Consumption
- Liver enzymes

*Karhuvaara et al., **Targeted nalmefene** with simple medical management in the treatment of heavy drinkers: a randomized double-blind placebo-controlled multicenter study. Alcohol Clin Exp Res. 2007 Jul;31(7):1179-87*

Nalmefene, efficacy results-II

Karhuvaara et. Al., 2007





GGT=Gamma-glutamyl transpeptidase
ALAT=Alanine-aminotransferase

Strategies to improve the naltrexone/nalmefene treatment efficacy

Variation in the μ-opioid receptor gene sequence 118a → g *(Bond et al. 1998)*

```
   1 cggatgagcc tctgtgaact actaaggtgg gaggggcta tacgcagagg agaatgtcag
  61 atgctcagct cggtcccctc cgcctgacgc tcctctctgt ctcagccagg actggtttct
 121 gtaagaaaca gcaggagctg tggcagcggc gaaaggaagc ggctgaggcg cttggaaccc
 181 gaaaagtctc ggtgctcctg gctacctcgc acagcgtgcc cgcccggccg tcagtaccat
 241 ggacagcagc gctgccccca cgaacgccag caattgcact gatgccttgg cgtactcaag
 301 ttgctcccca gcacccagcc ccggttcctg ggtcaacttg tcccacttag atggcaa
 361 gtccgaccca tgcggtccga accgcaccga cctgggcggg agagacagcc tgtgccctcc
 421 gaccggcagt ccctccatga tcacggccat cacgatcatg gccctctact ccatcgtgtg
 481 cgtggtgggg ctcttcggaa acttcctggt catgtatgtg attgtcagat acacca
 541 gaagactgcc accaacatct acattttcaa ccttgctctg gcagatgcct tagcca
 601 taccctgccc ttccagagtg tgaattacct aatgggaaca tggccatttg gaacca
 661 ttgcaagata gtgatctcca tagattacta taacatgttc accagcatat tcaccc
 721 caccatgagt gttgatcgat acattgcagt ctgccaccct gtcaaggcct tagatt
 781 tactccccga aatgccaaaa ttatcaatgt ctgcaactgg atcctctctt cagcca
 841 tcttcctgta atgttcatgg ctacaacaaa atacaggcaa ggttccatag attgta
 901 aacattctct catccaacct ggtactggga aaacctgctg aagatctgtg ttttca
 961 cgccttcatt atgccagtgc tcatcattac cgtgtgctat ggactgatga tcttgc
1021 caagagtgtc cgcatgctct ctggctccaa agaaaaggac aggaatcttc gaagga
1081 caggatggtg ctggtggtgg tggctgtgtt catcgtctgc tggactccca ttcaca
1141 cgtcatcatt aaagccttgg ttacaatccc agaaactacg ttccagactg tttctt
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1321 gcaacaaaac tccactcgaa ttcgtcagaa cactagagac cacccctcca cggcca
1381 agtggataga actaatcatc agctagaaaa tctggaagca gaaactgctc cgttgc
1441 acagggtctc atgccattcc gaccttcacc aagcttagaa gccaccatgt atgtgg
1501 aggttgcttc aagaatgtgt aggaggctct aattctctag gaaagtgcct gctttt
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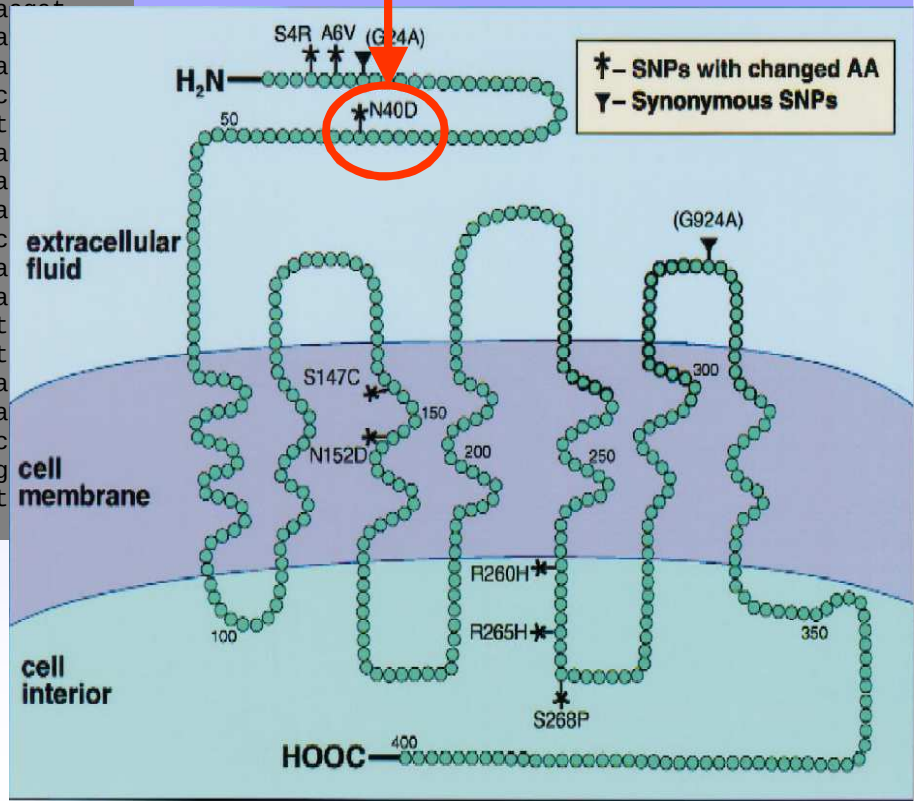
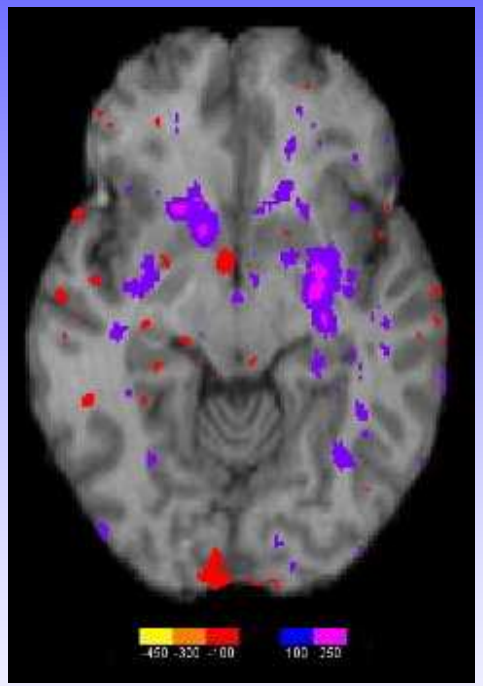
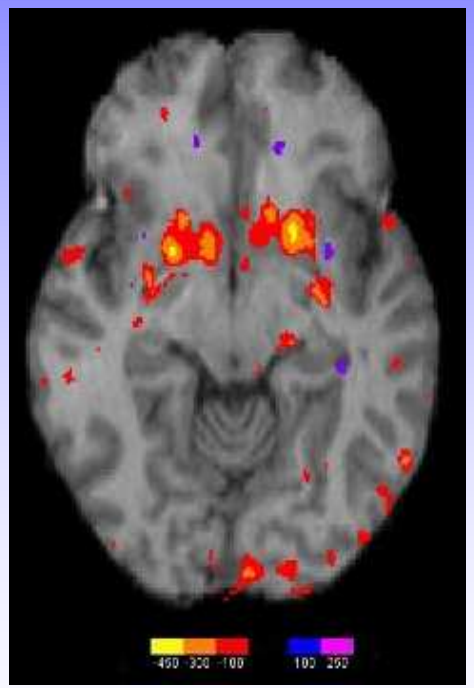


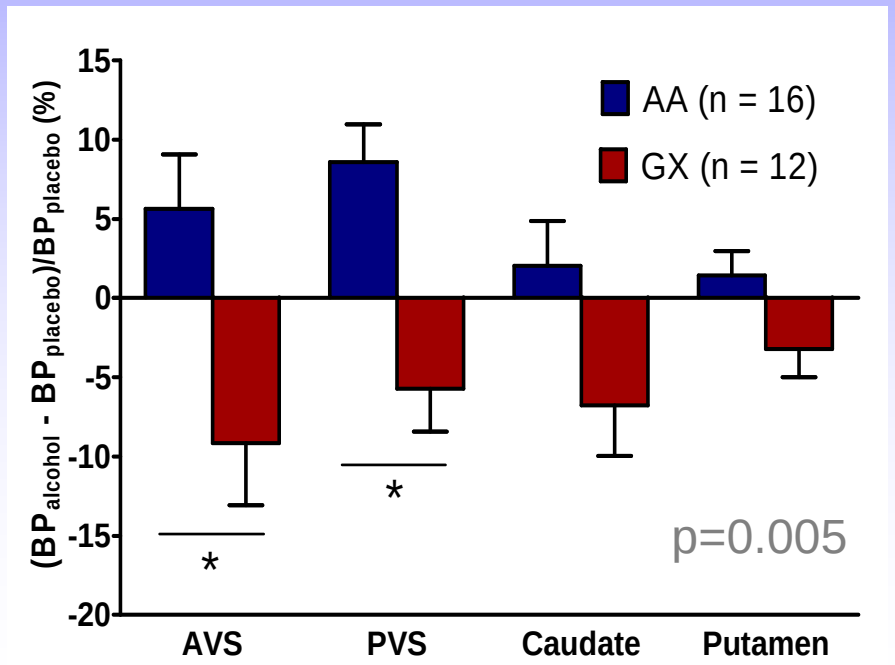
Significant alcohol induced dopamine release in ventral striatum occurs only in 118G carriers (Heilig et al., unpublished2010)



AA

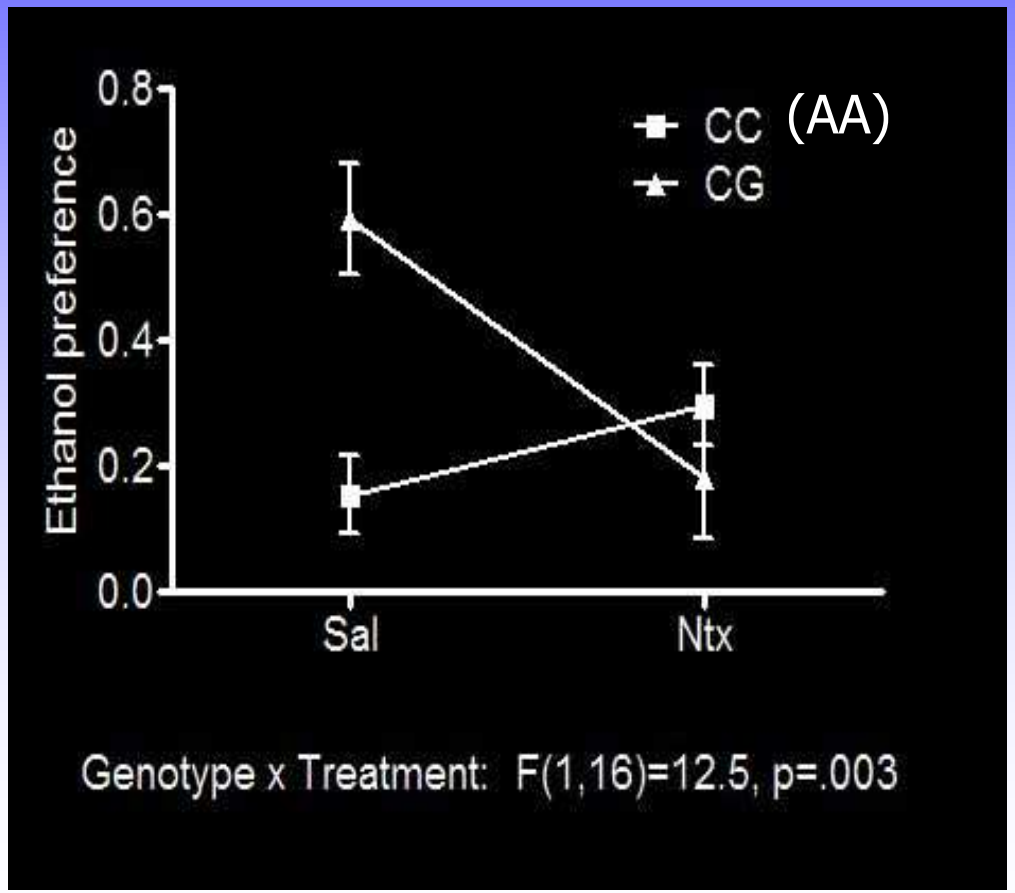


GX

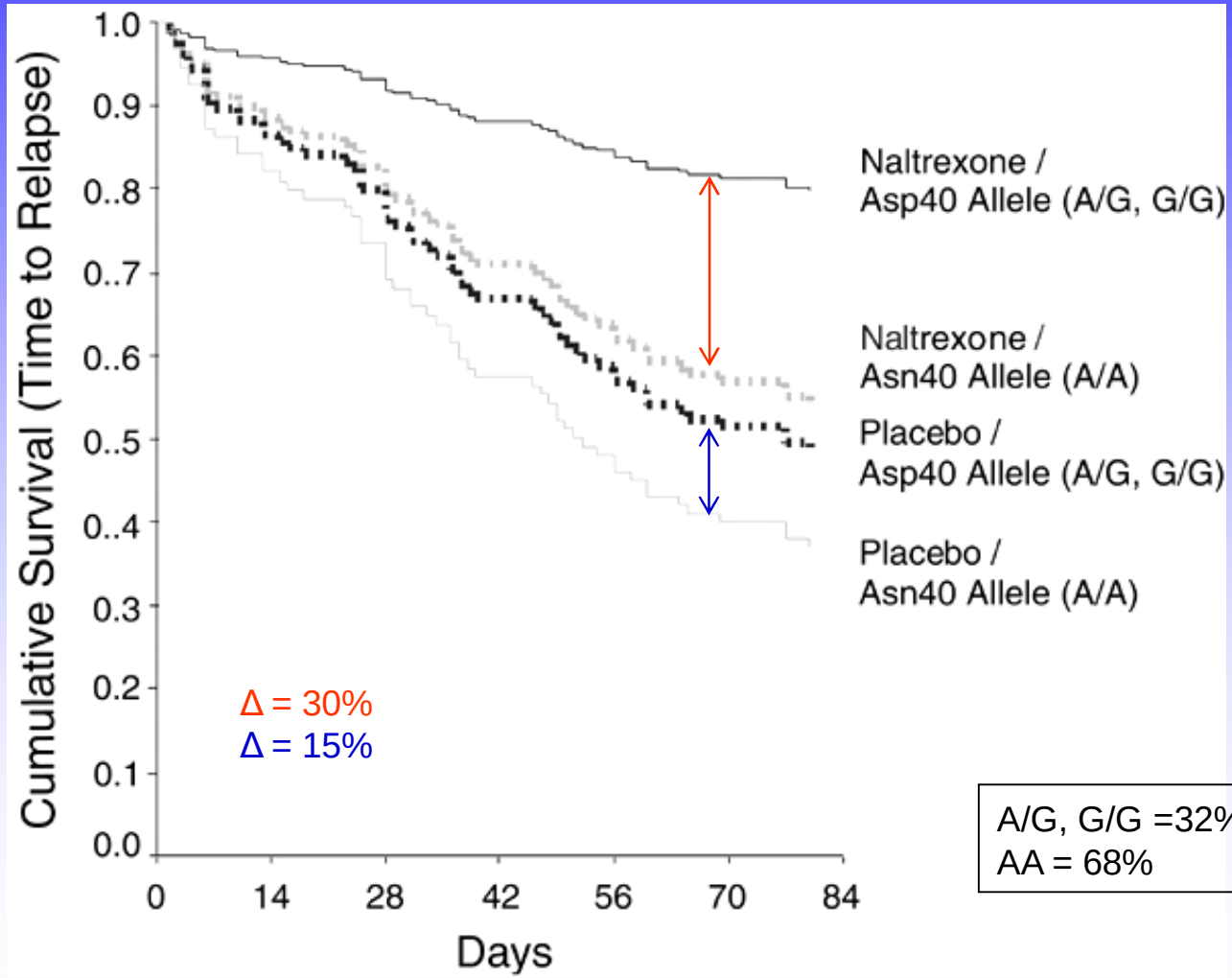


Only carriers of rhesus variant μ-opioid receptor are sensitive to naltrexone

(Barr et al. In press, Biol Psychiat)



Naltrexone Pharmacogenomics



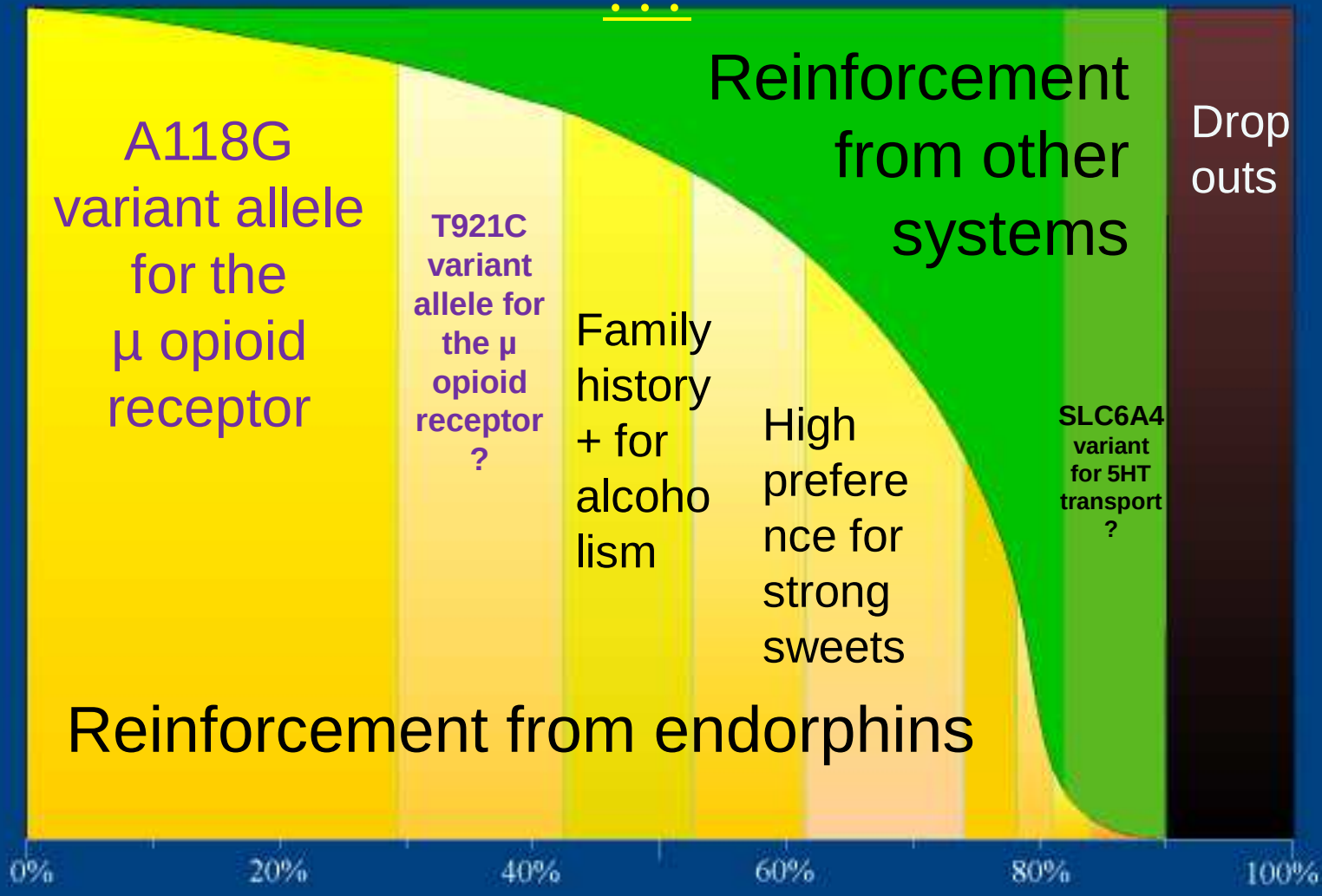
A/G, G/G =32%
AA = 68%

Oslin et al. Neuropsychopharmacology 2003

Strategies to improve the naltexone treatment efficacy

- Targeted use
  - Associated to drinking, extinction
  - Associated to genes/polymorphism
- Predictors
  - Predict study by Mann et al
    - Defining subtypes of alcoholics and exploring their response to individualized pharmacotherapy
      - Genotyping, fMRI, PET, CBI in relapsers, Health economics
- Long acting NTX microspheres ?

Which alcoholics may benefit most from naltrexone ???



Summary: Opioid antagonists

- Well-documented pharmacological evidence to treat alcohol dependence and reduce heavy drinking and relapsing is found for opioid antagonists naltrexone and nalmefene
- They significantly reduces alcohol abuse and particularly the relapse to heavy drinking:
  - 1) The antagonist blocks endogenous opioids and the "first-drink effect"; i.e., it reduces the duration of a binge that has already started
  - 2) The antagonist paired with drinking extinguishes the craving for alcohol and drinking

Conclusions

- Strong preclinical and clinical evidence support the new concept in reducing alcohol consumption
  - the targeted use of opioid antagonist is an effective method in reducing alcohol consumption and relapse prevention
- As a treatment goal, the reduction of alcohol consumption and the prevention of relapsing, seems to be as acceptable and effective as abstinence

Disclosure of interests, 2008-10

- Hannu Alho, MD, PhD, Professor of Addiction Medicine, University of Helsinki, Finland
- Secondary Occupations
  - Research Professor, National Institute for Health and Welfare (THL), Helsinki
  - Chief doctor, Unit of Alcoholism, Helsinki University Hospital (HUS)
- Positions of trust in health care
  - Deputation member of A-Clinic Foundation, Helsinki, Finland
- Other positions aiming to guide health care
  - International Society of Addiction Medicine, president elect
  - WHO, consultant for Guidelines for the Psychosocially Assisted Pharmacological Treatment of Opioid Dependence
- Owner or stockholder in health care business or pharmaceutical industry
  - none
- Other commitments
  - Paid expert lectures by Lundbeck AS, MSD and Schering-Plough


Thank you for your attention

Table 1. RCTs wiht naltrexone (16) ja nalmefene (3)*

Clinical Trial	Therapy	Effect
Karhuvaara et al,2007 *	MT	+
Anton et al., 2004 *	MT	--
Mason et al 1999*	(CBT)	+
Latt et al., 2002	MT	+
Volpicelli et al. 1992,	(CBT)	+
Vollpicelli et al. 1997	(CBT)	+
Oslin et al. 1997	CBT	+
Anton et al. 1999,	CBT	+
Rubio et al. 2001	CBT	+
Morris et al., 2001	(CBT)	+
Monti et al., 2001	CBT	+
O'Malley et al. 1992	CBT Support	+ --
O'Malley et al. 1996	CBT Support	+ --
Baldin et al.1997	CBT Support	+ --
Heinälä et al. 2001	CBT Support	+ --
Knox et al., 1999	Support	--
Kranzler et al.2000	Support	--
Krystal et al., 2001	Support	--
Chick et al. 2000	Multiple	--

CBT = cognitive behavioral therapy

Support = abstinence aiming supportive therapy

MT = minimal therapy or no therapy