Biological Subtype ofAlcoholism with specific treatment

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Disclosures

Consultant to

Embera (Research)

Alkermes (Depot Naltrexone)

Astra (drug development)

Alcohol: desired drink

- Common Disorder, 10-15% prevalence
- Barely covered in medical school

- 50-60% genetic
- Polygenic
- 223 Billion costs per year
- 90,000 deaths
- 30% of liver transplants
- Should be diagnosed and treated in PRIMARY CARE

Ethanol:
a drug with complex effects on multiple neurotransmitter systems

Alcohol reward

Partial list

- **GABA**
- **Serotonin**
- **AMPA, Glu-rec**
- **NMDA**
- **Neuropeptide Y**
- **Glycine**
- **Opioid- μ, k, ∂**

Treatment of Alcoholism in USA

<10% receive treatment

- Medications only for treatment of withdrawal
- Relapse prevention medication rare
- Relapses very common

FDA Approved Medications

- Disulfiram (Antabuse)
- Naltrexone (generic)
- Acamprosate (Campral)
- Depot Naltrexone (Vivitrol)
- Nalmefene (approved in Europe)
- Topiramate (used off label)

DETOXIFICATION IS NOT TREATMENT

Arguments against medications

- They are just a “crutch”
- You have to work the program yourself – no chemical aids
- They get in the way of the 12 steps
- I’ve been sober for 10 years and I never took medication
- They have side effects
- You’ll become addicted to them
- Etc…

True Translational Story: Naltrexone for Alcoholism

- Animal lab
  to
- Randomized clinical trials
  to
- FDA approval for clinical practice
  to
  ?? Standard practice

Endogenous Opioid System

Opiate Receptors

Simon 1973

Pert & Snyder 1973

Terenius 1973

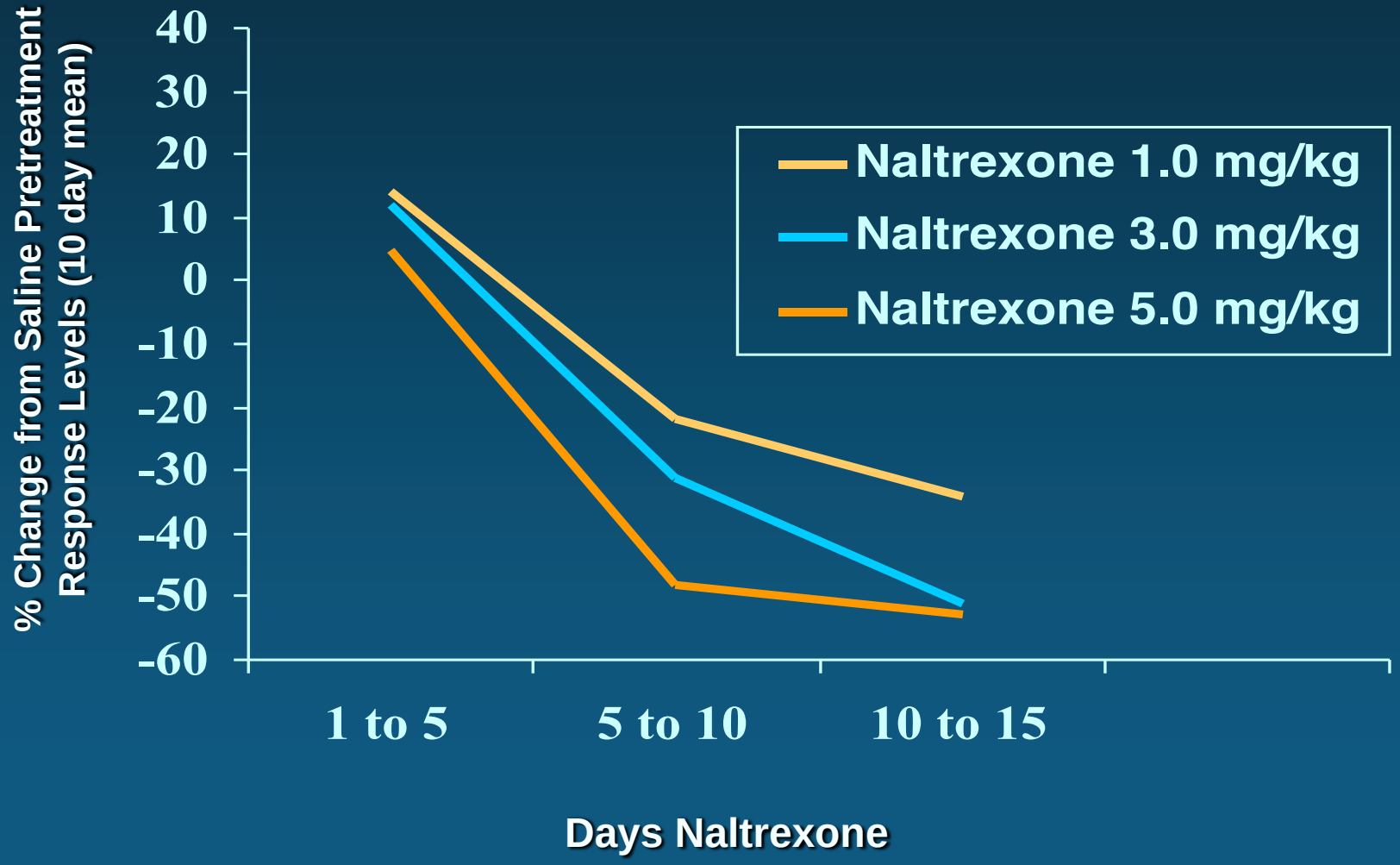
Enkephalin 1975 ∂

B-Endorphin μ

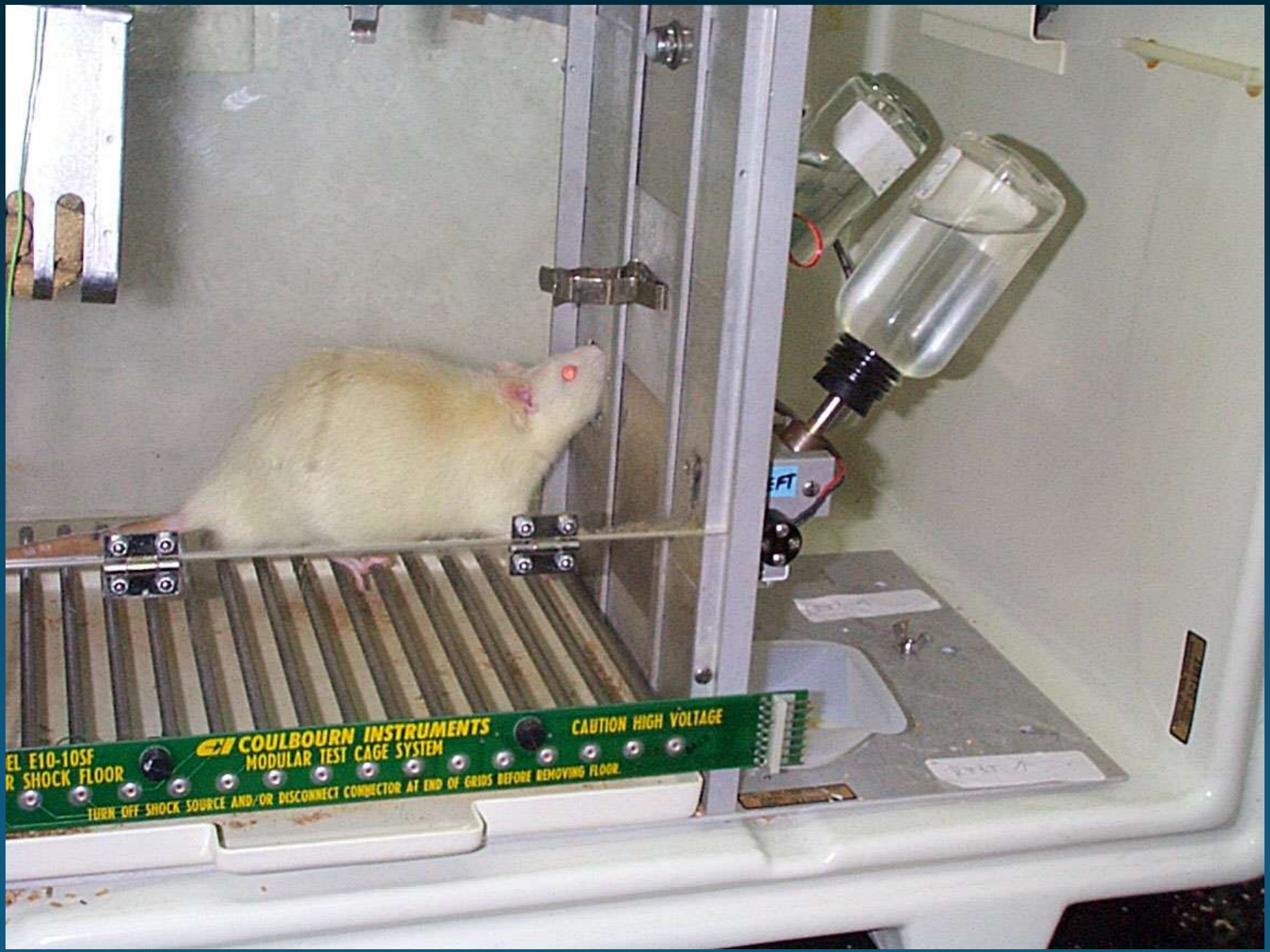
Dynorphin k

Nociceptin OFQ/NOC 1990s

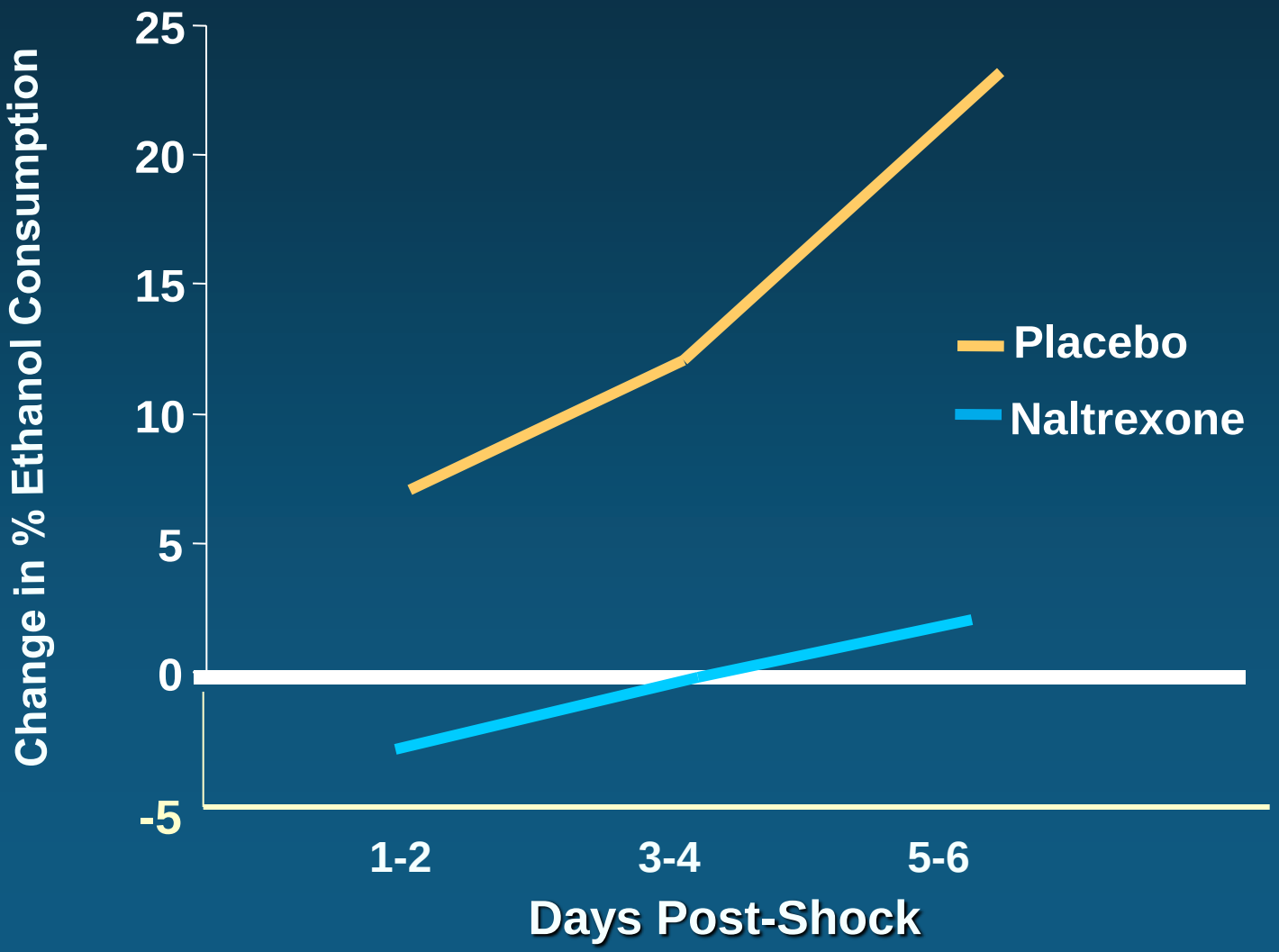
Naltrexone decreases Alcohol preference*



* Altshuler 1980

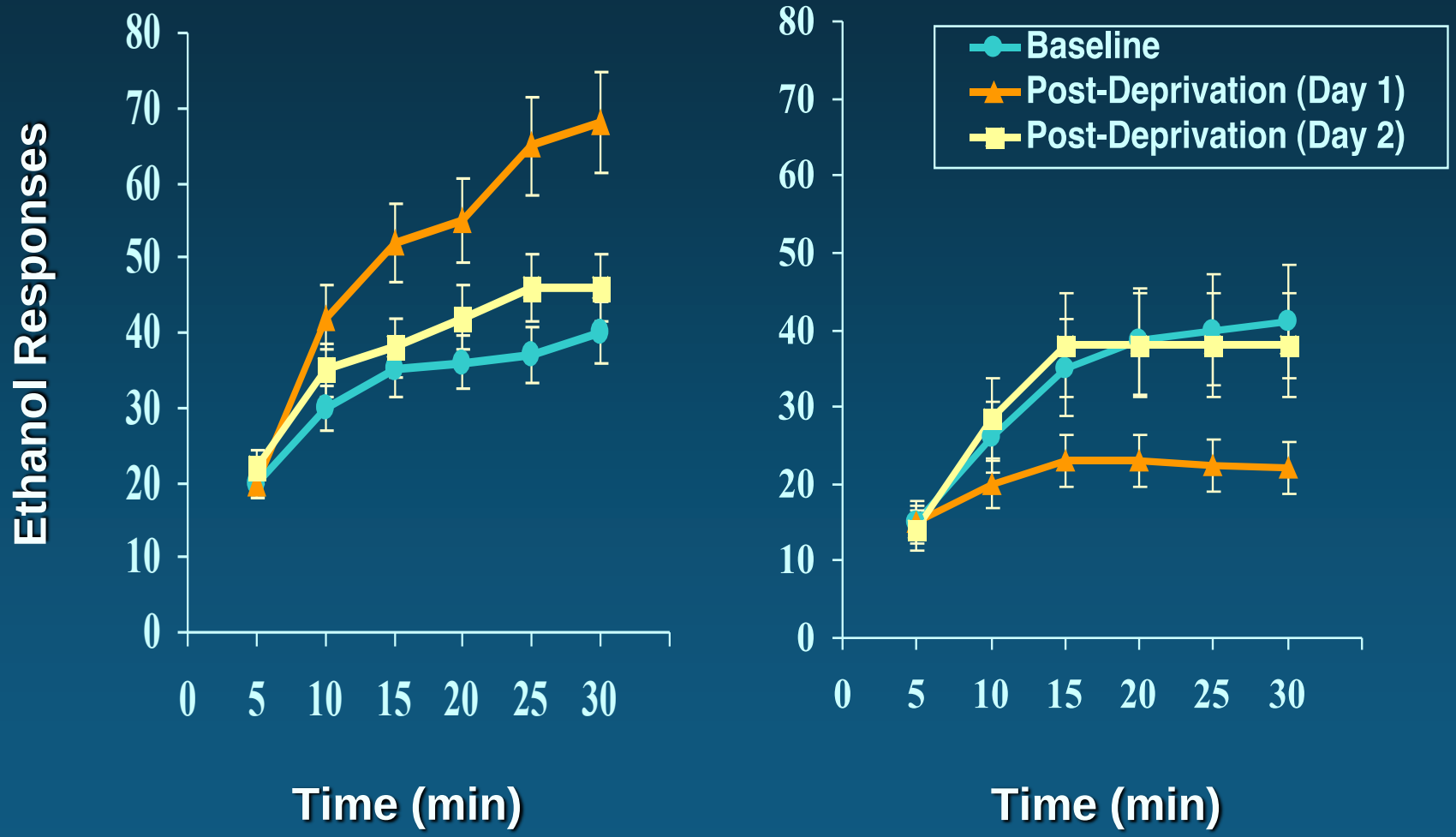

COULBOURN INSTRUMENTS
MODULAR TEST CAGE SYSTEM
CAUTION HIGH VOLTAGE
TURN OFF SHOCK SOURCE AND/OR DISCONNECT CONNECTOR AT END OF GRIDS BEFORE REMOVING FLOOR.

Post-Shock Drinking



Saline

.25 mg/kg Naltrexone



Hypothesis: alcohol releases endogenous opioids

In vivo evidence: only indirect evidence in brain, direct evidence in plasma

In vitro evidence: direct measures in lymphocyte cultures, HIV effects of alcohol blocked by naltrexone.

Wen Ze Ho et al, 2006

Molecular mechanism unknown

IND 1983

Open studies

Range of doses

Minimal side effects

IRB approval

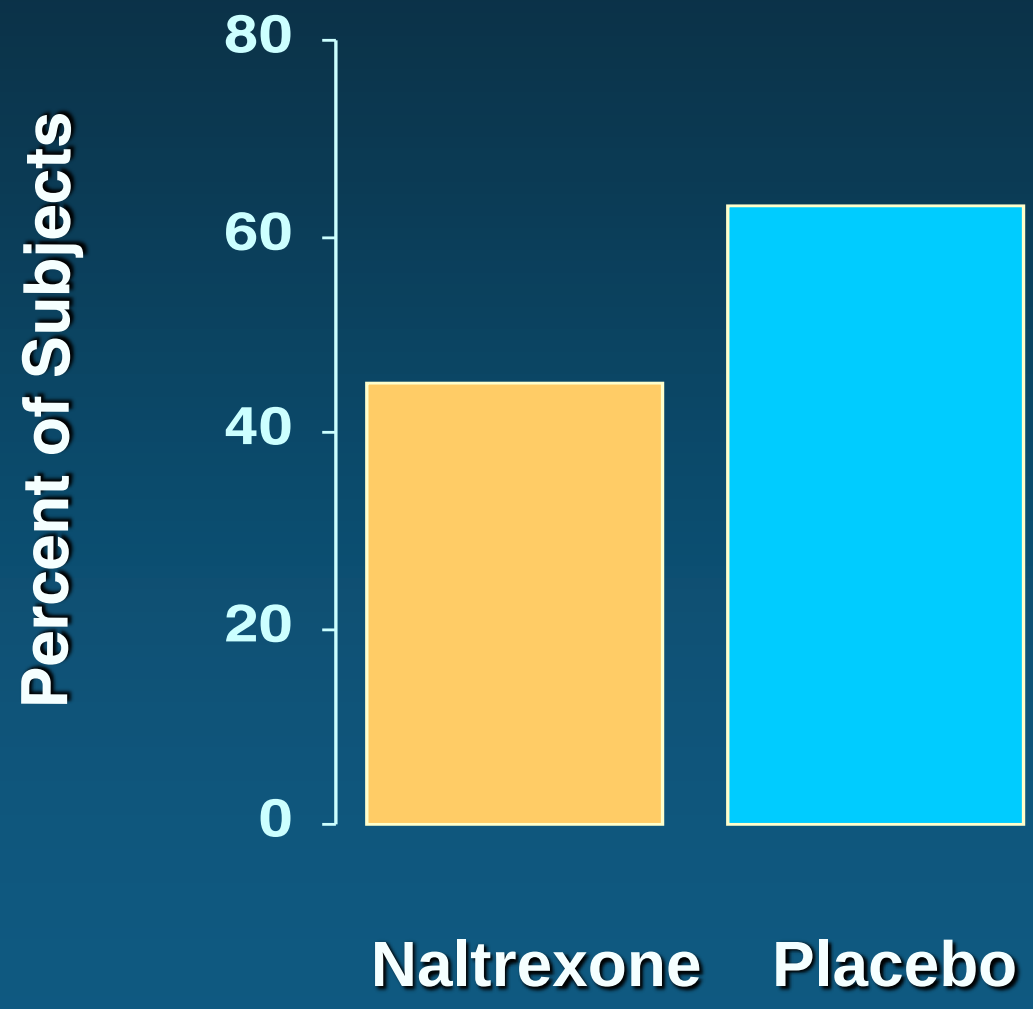
Protocol 1986

Self report + breathalyzer 5x per week
Endpoint = Relapse to heavy drinking
“Slips” recorded, not as endpoint
Craving recorded
RECRUITMET OBSTRUCTIONS
Joe Volpicelli started fellowship

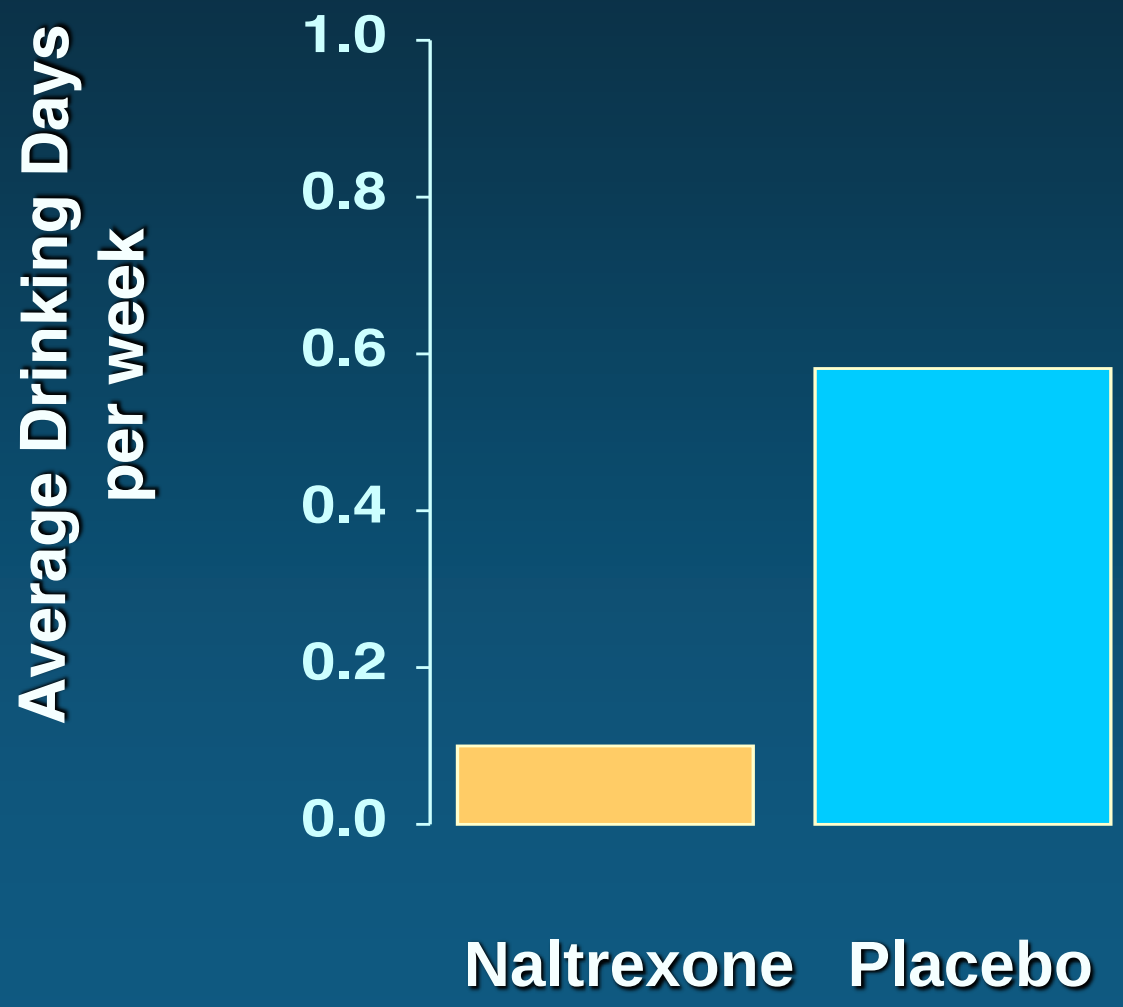
Series of Lucky Coincidences

- 1. Altshuler poster at CPDD
- 2. Joe Volpicelli decides on Fellowship

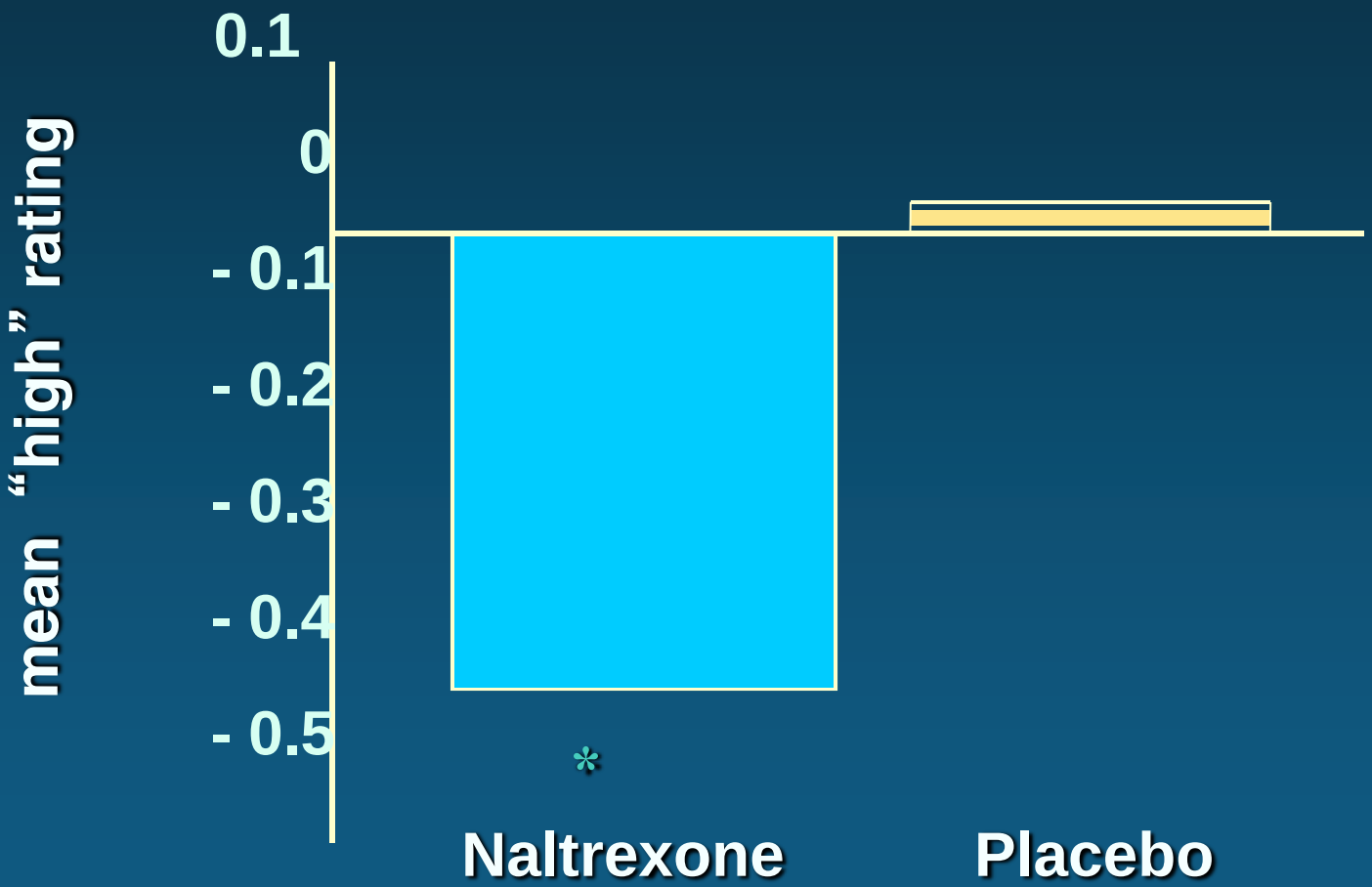
Any Alcohol Drinking



Days Drinking

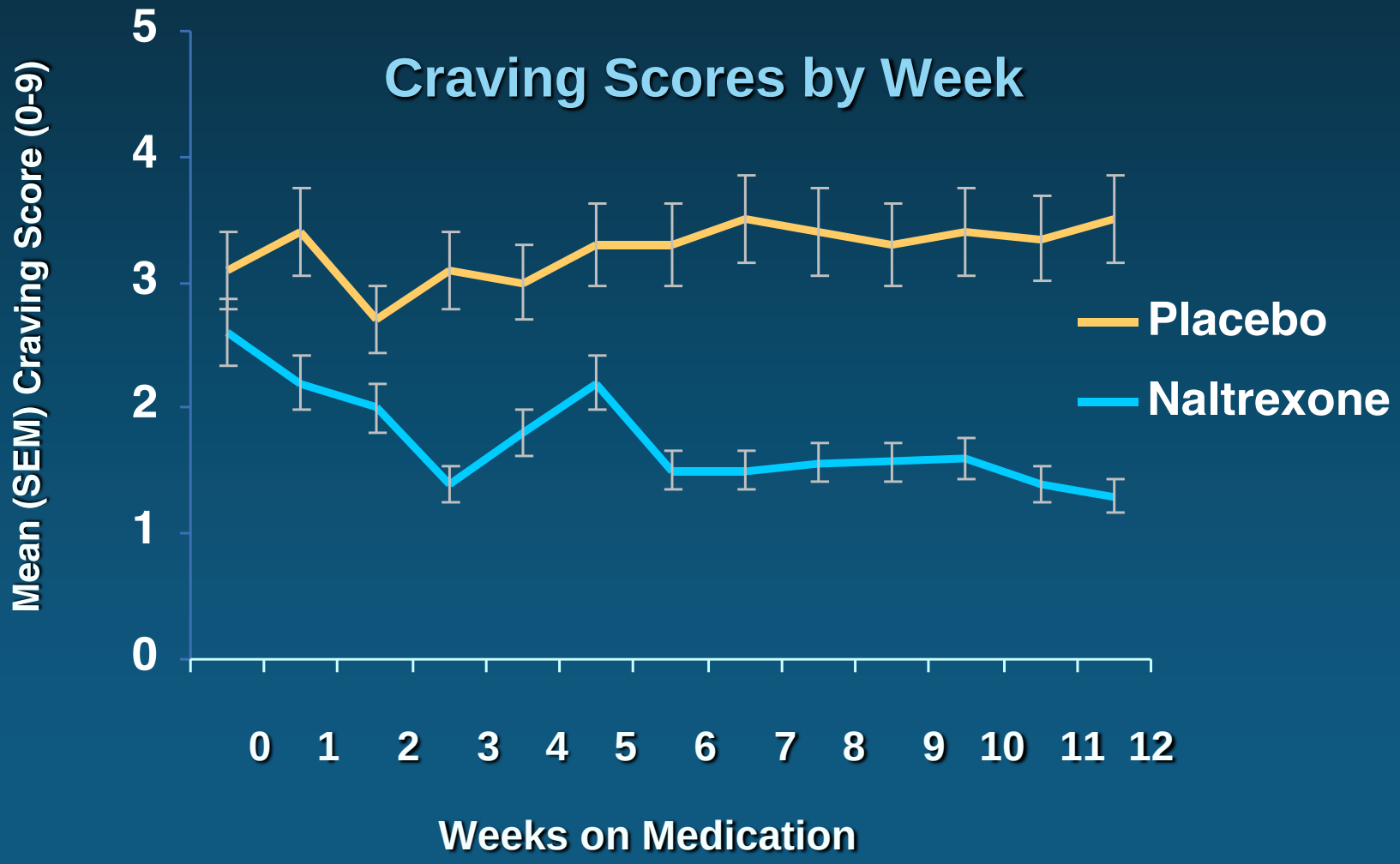


Subjective “high” in Naltrexone and Placebo Subjects



* p<.05

Pharmacological Treatments for Alcoholism



Alcohol Relapse

A. coming to treatment appointment with a blood alcohol concentration > 100 mg%

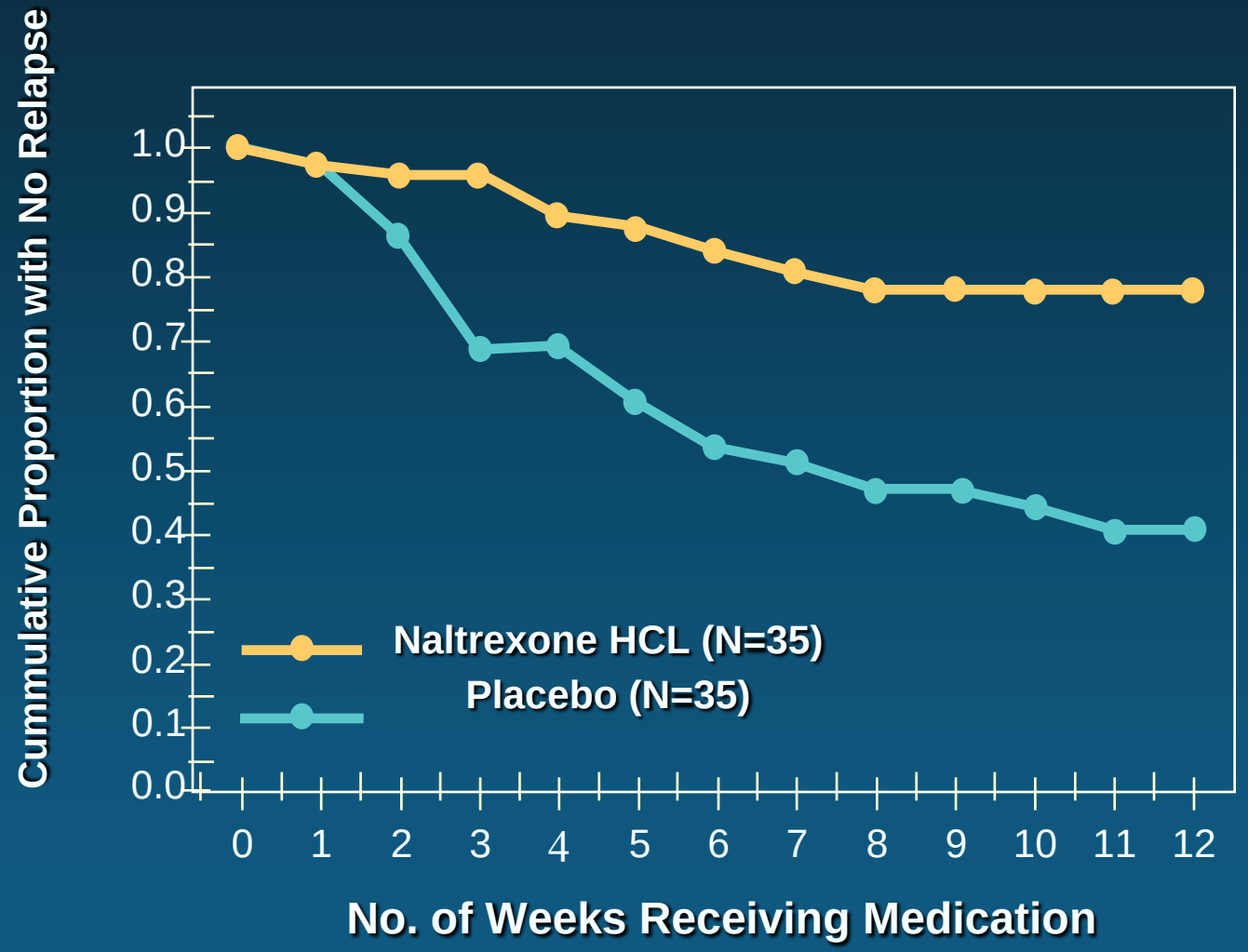
or

B. self report of drinking five or more days within one week

or

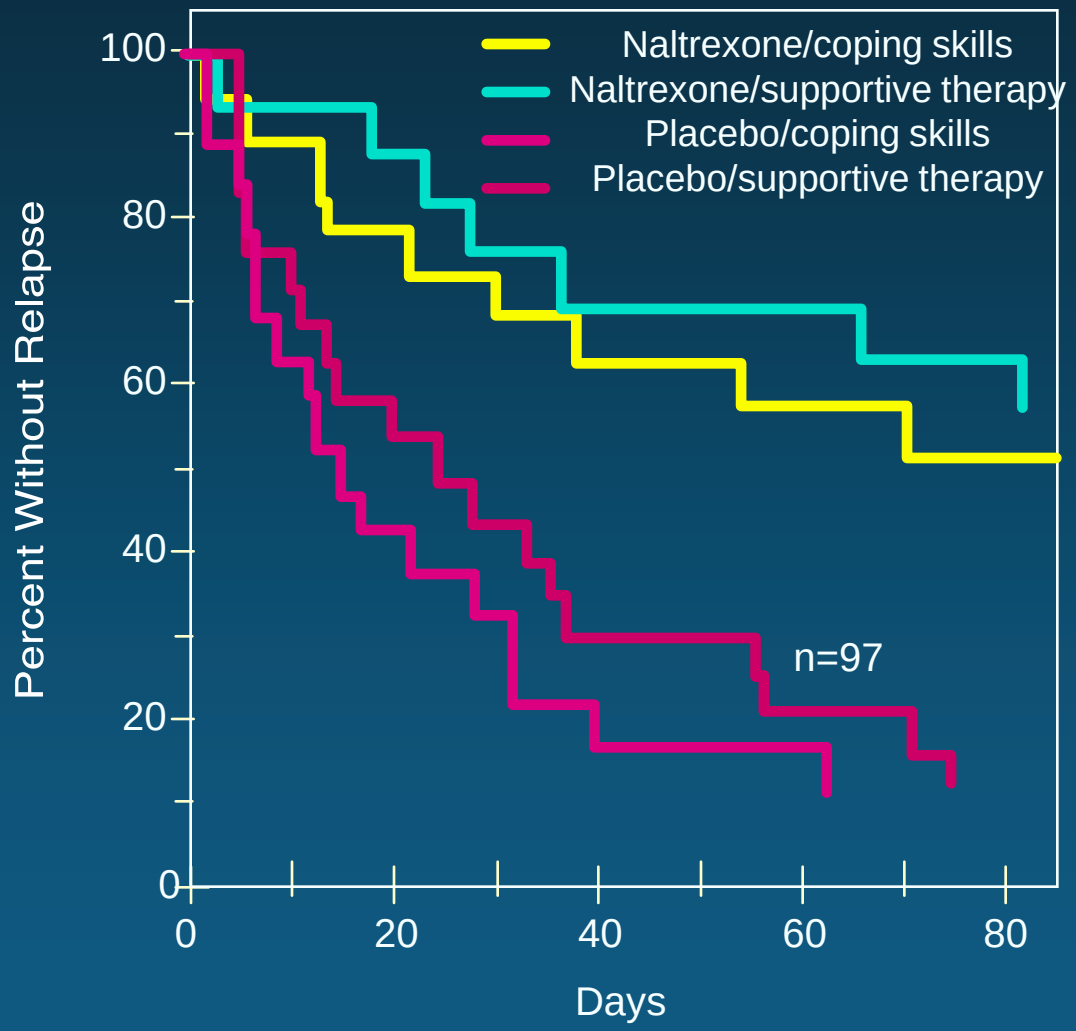
C. self report of five or more drinks during one drinking occasion

Non-relapse “Survival”



Volpicelli et al, Arch Gen Psychiatry, 1992; 49: 876-880

Rates of Never Relapsing According to Treatment Group (n=97)



O'Malley et al, *Arch of Gen Psychiatry*, Vol 49, Nov 1992

Studies supporting efficacy

Study	# Ss	Notes
Volpicelli, et al 1992	70	None
O'Malley, et al 1992	97	None
Mason, et al 1994 [Nalmefene]	21	None
Oslin, et al 1997	44	Elderly
Volpicelli, et al 1997	97	None
Mason, et al 1999 [Nalmefene]	105	None
Kranzler, et al 1998	20	Depot
Anton, et al 2000	131	None
Chick, et al 2000 (UK)	169	Adherence
Monterosso, et al 2001	183	None
Morris, et al 2001 (Australia)	111	None
Heinala, et al 2001 (Finland)	121	Nonabstinent
Lee, et al 2001 (Singapore)	53	None
Kiefer et al 2003 (Germany)	160	None

Studies not supporting efficacy

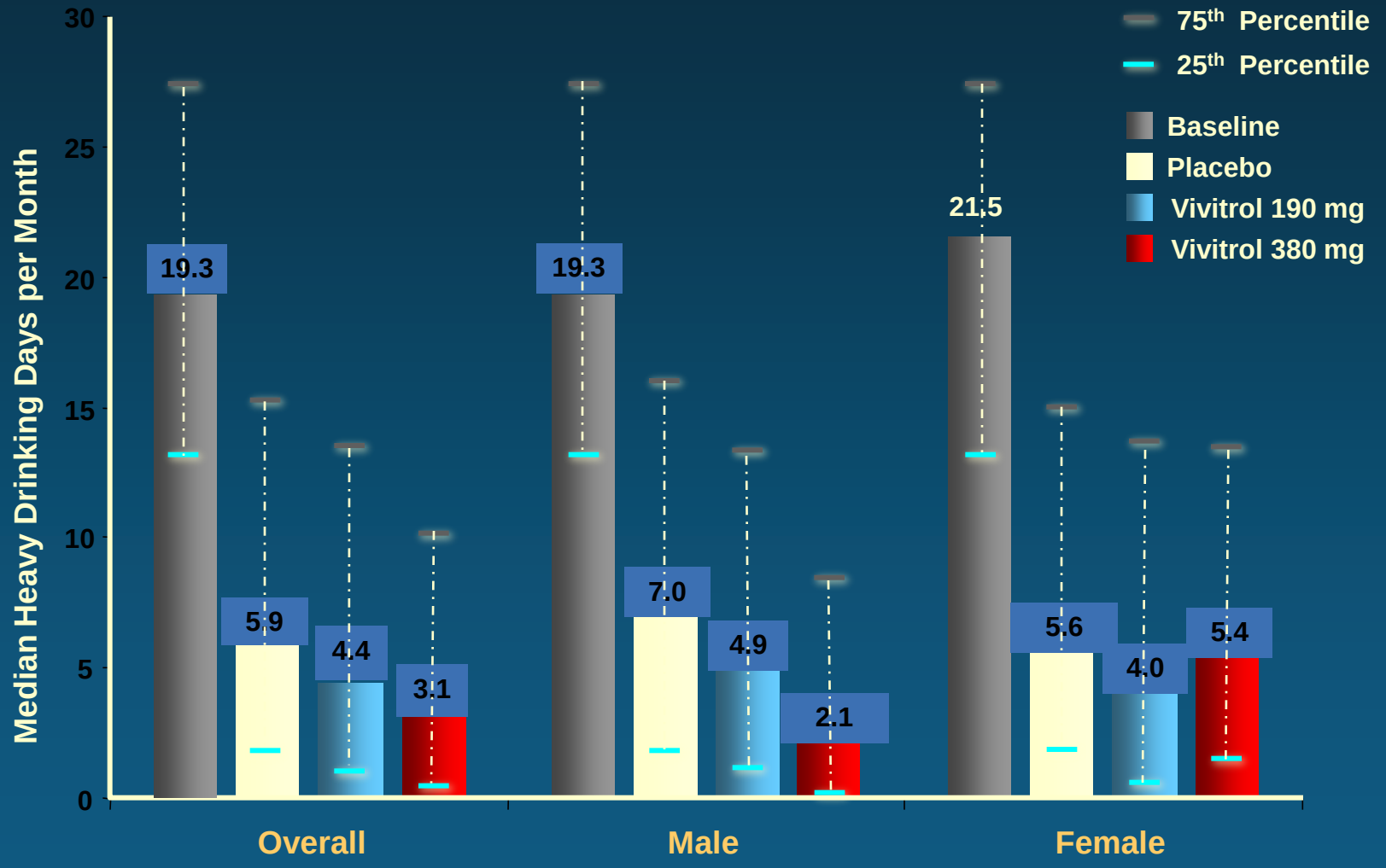
Study	# Ss	Notes
Kranzler, et al 1999	183	None
Krystal, et al 2002	627	None

Studies supporting efficacy			Studies not supporting efficacy		
Study	# Ss	Notes	Study	# Ss	Notes
Latt et al 2002	107	Family Prac			
Balldin et al 2003	118	None			
Feeney et al 2001	50	Hist. cont			
Rubio et al 2001	157	v. Acamp.			
Rubio et al 2002	30	Cont. Drink.			
Gastpar et al 2002	105	Neg. in self report Pos. GGT	Gastpar et al 2002	105	Neg. in self report Pos. GGT
Guardia et al 2002	202	Relapse			
Kranzler et al 2003	153	Heavy drinkers			
O'Malley et al 2002	18	Human lab			
Anton et al 2006	1383	RCT, depot			

Compliance Improved

- Extended release depot preparation
- Injection q 30-40 days
- Pharma sets price at $800 per injection

Results: Heavy Drinking Days



Europe 2012

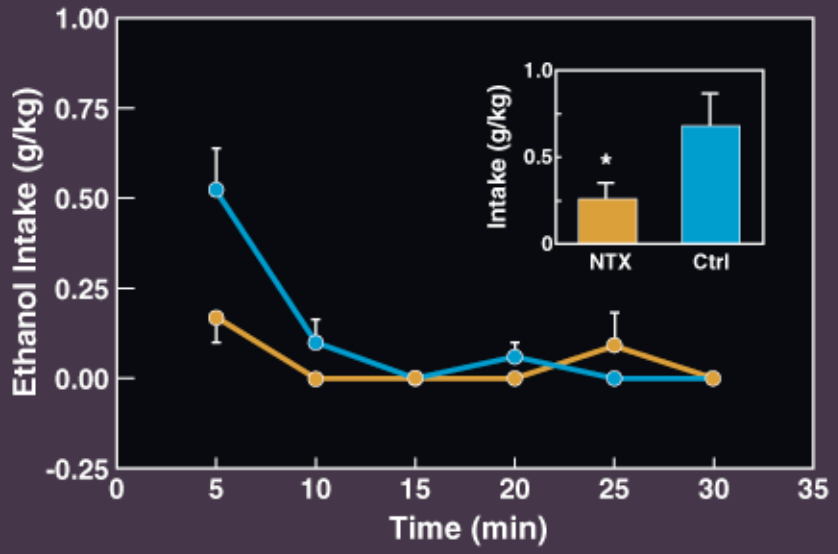
- 3 Large clinical trials
- ~1,000 alcoholics each
- Nalmephene v placebo

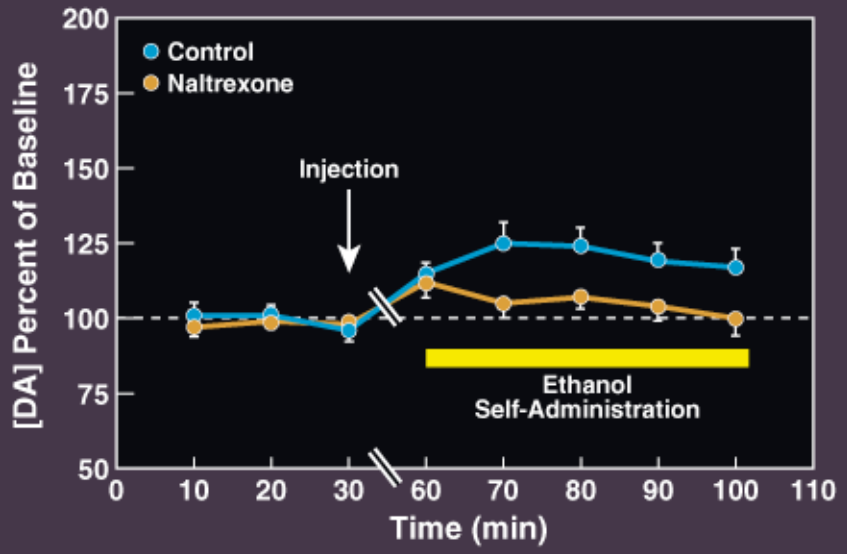
prn

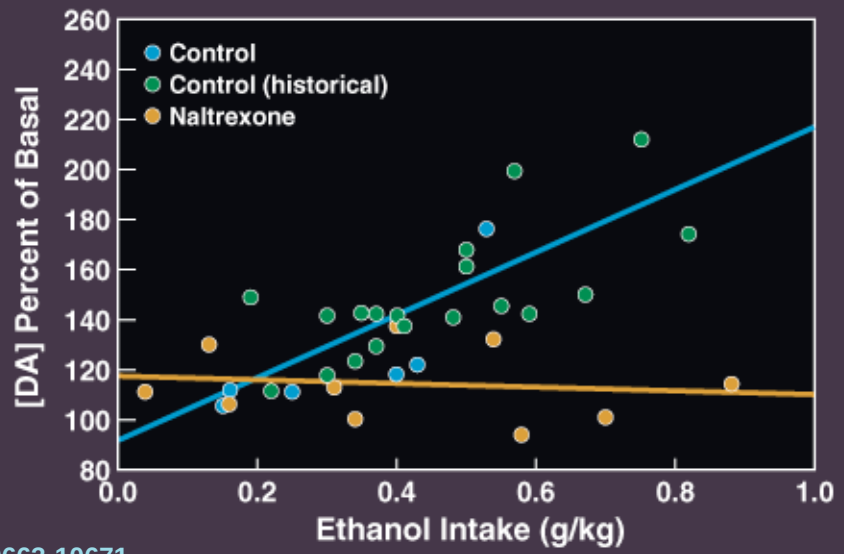
- All positive
- Approved 2013: EMA

Assumption: alcohol causes the release of endogenous opioids which are “required” for DA release in response to alcohol?

Naltrexone Concurrently Antagonizes EtOH-Induced Accumbal DA Release and EtOH Self-Administration



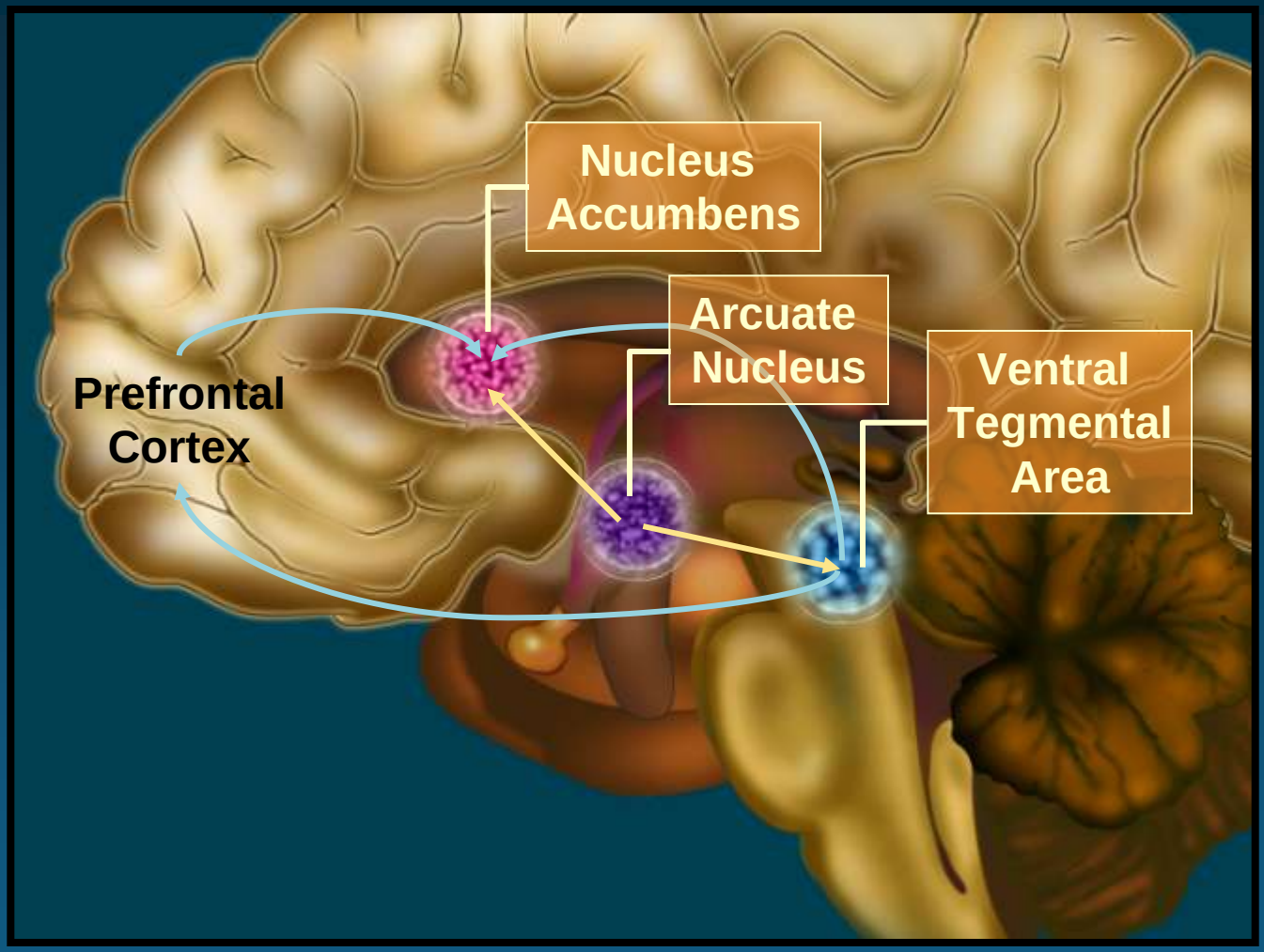




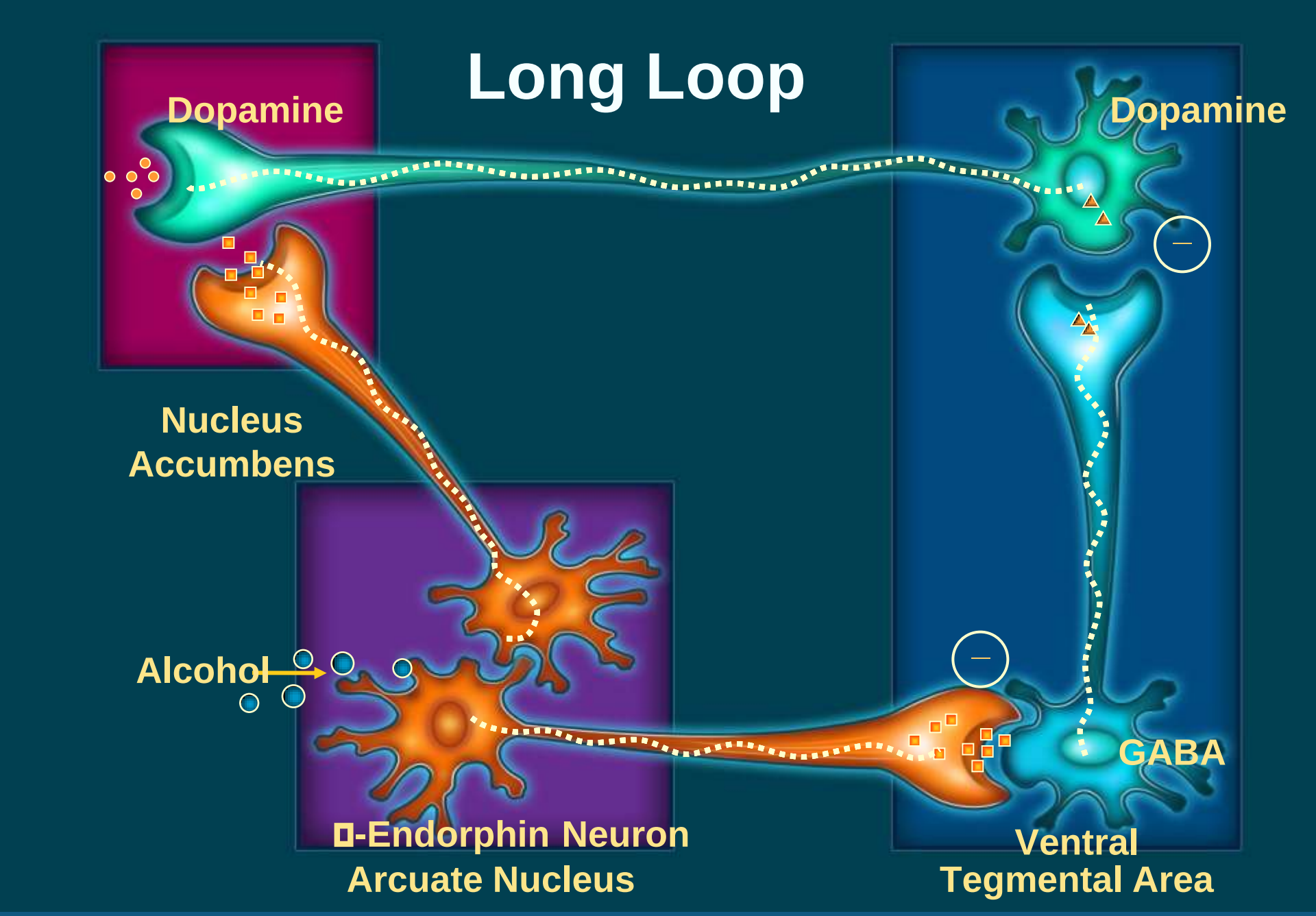
Gonzales & Weiss (2002) *J Neurosci* 18:10663-10671

Assumption: alcohol causes the release of endogenous opioids which are “required” for DA release in response to alcohol?

Brain Reward System

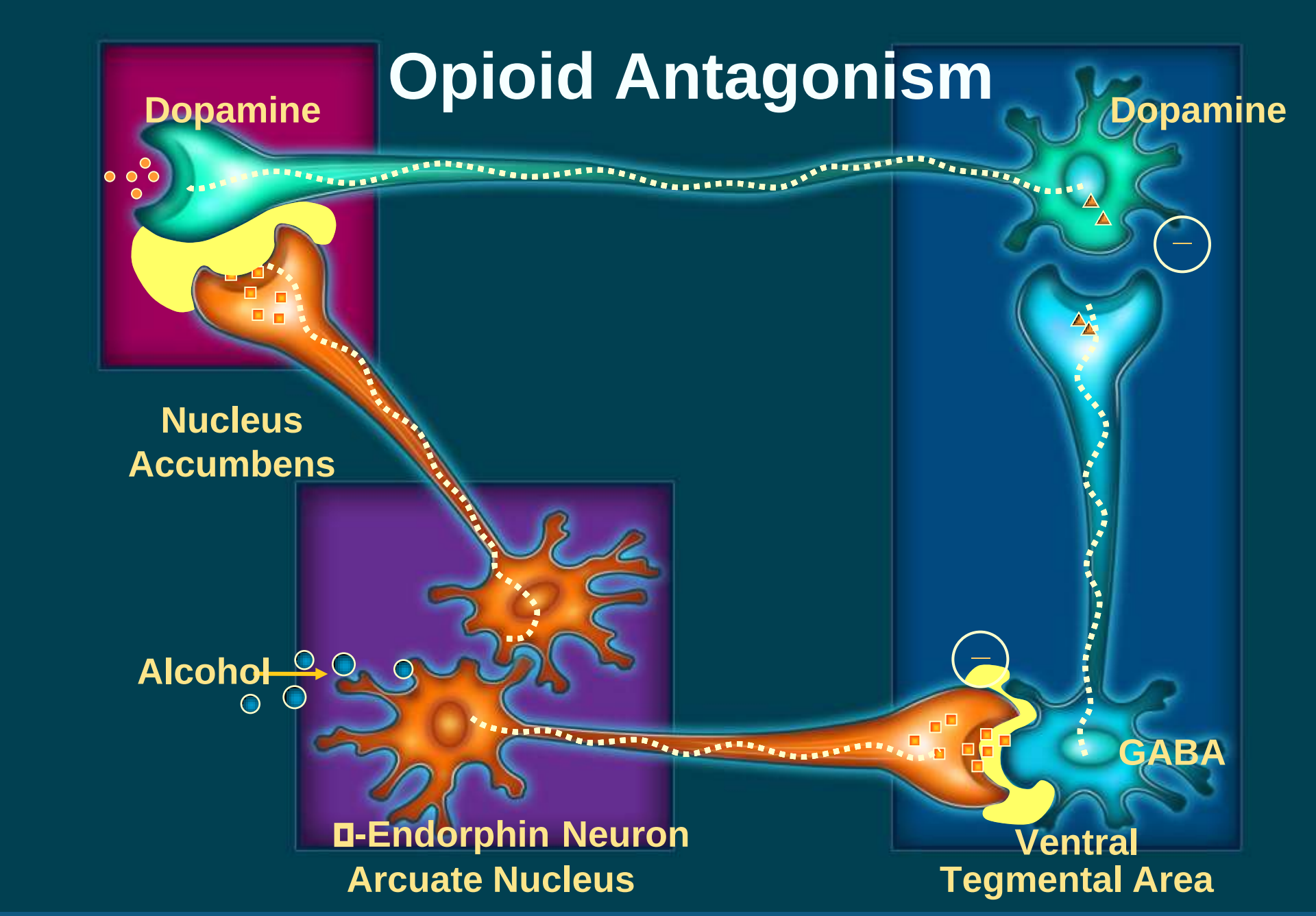


Nestler and Malenka. The Addicted Brain. Scientific American. March, 2004.



Gianoulakis. Alcohol-Seeking Behavior: The Roles of the Hypothalamic-Pituitary-Adrenal Axis and the Endogenous Opioid System. Alcohol Health and Research World. 1998;22(3).

Opioid Antagonism

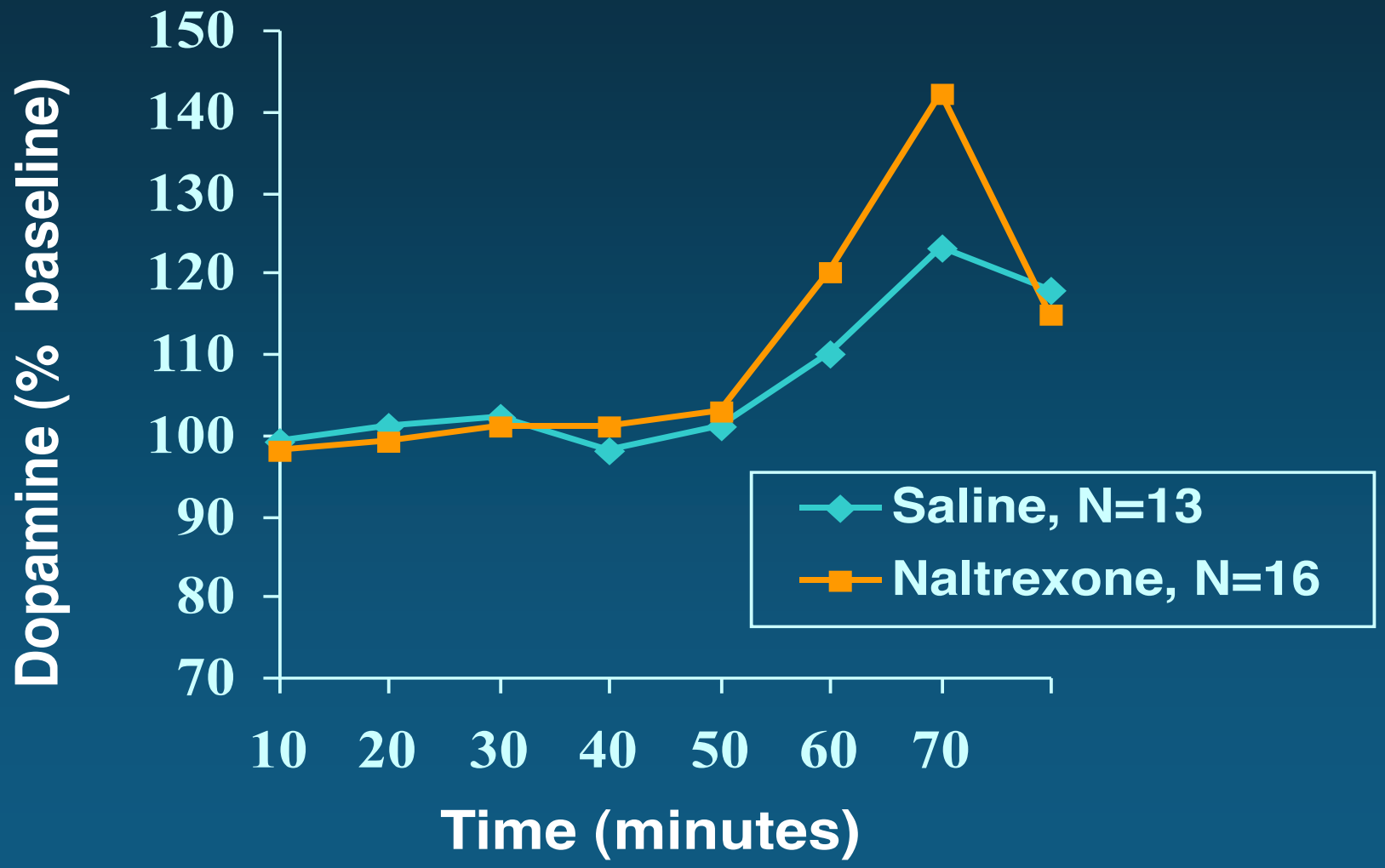


Gianoulakis. Alcohol-Seeking Behavior: The Roles of the Hypothalamic-Pituitary-Adrenal Axis and the Endogenous Opioid System. Alcohol Health and Research World. 1998;22(3).

Alcohol effects become conditioned to environmental cues

Naltrexone blocks cue induced relapse better than stress induced

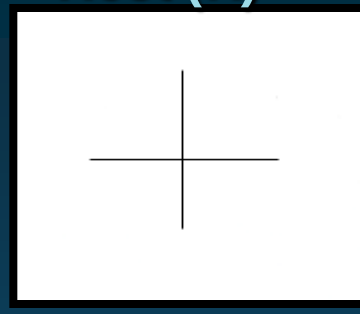
Pre-Alcohol “Craving”



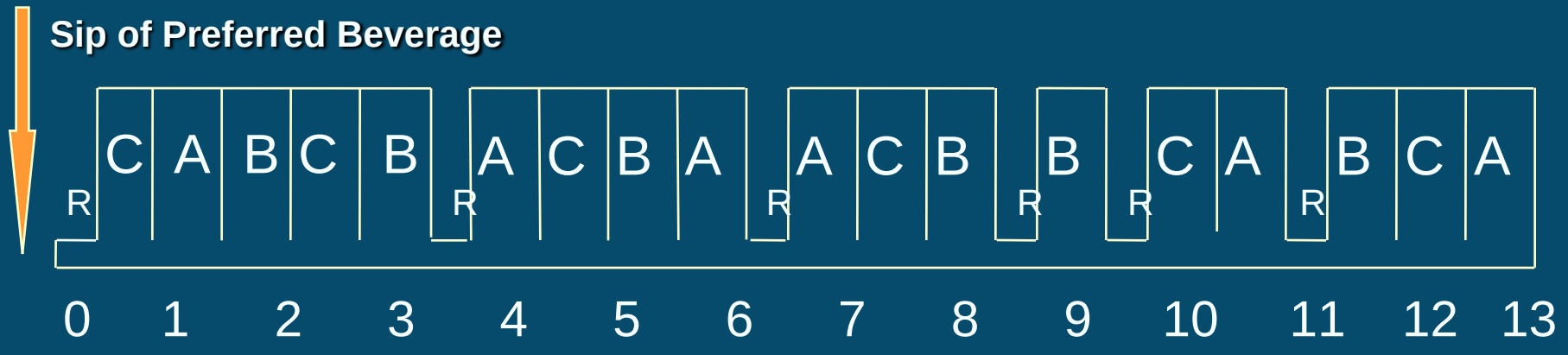
Examples of the various visual cues from Normative Appetitive Picture System (NAPS)

Alcohol (A) | Beverage (B) | Visual Control (C) | Rest (R)



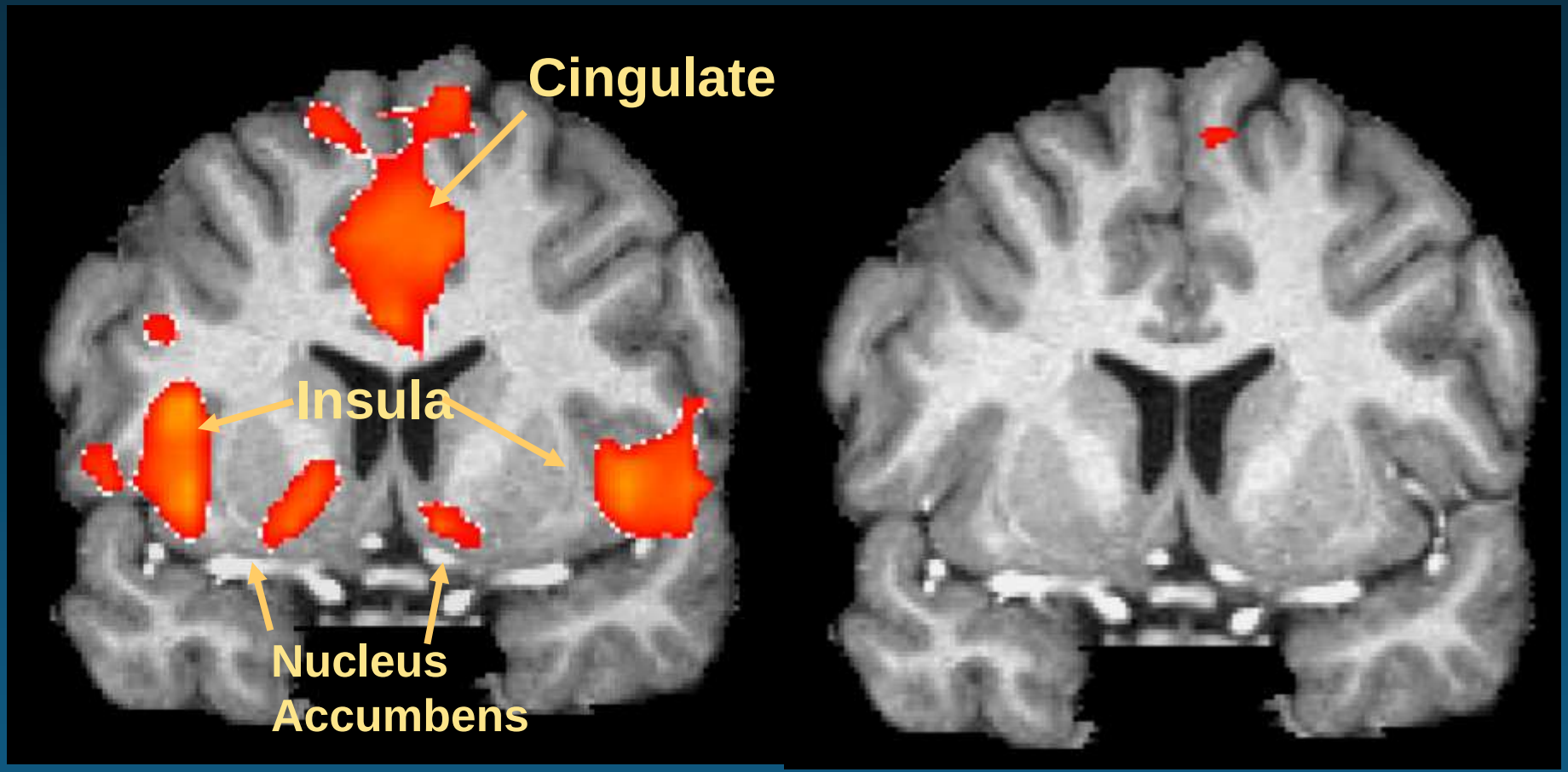
Time Course of the Presentation of Stimuli During fMRI



* Craving rated after each block

Comparisons:			
Alcohol	- Beverage	Beverage - Vis Ctrl
Alcohol	- Vis Ctrl	Beverage - Rest
Vis Ctrl	- Rest	

Alcohol - Beverage Condition

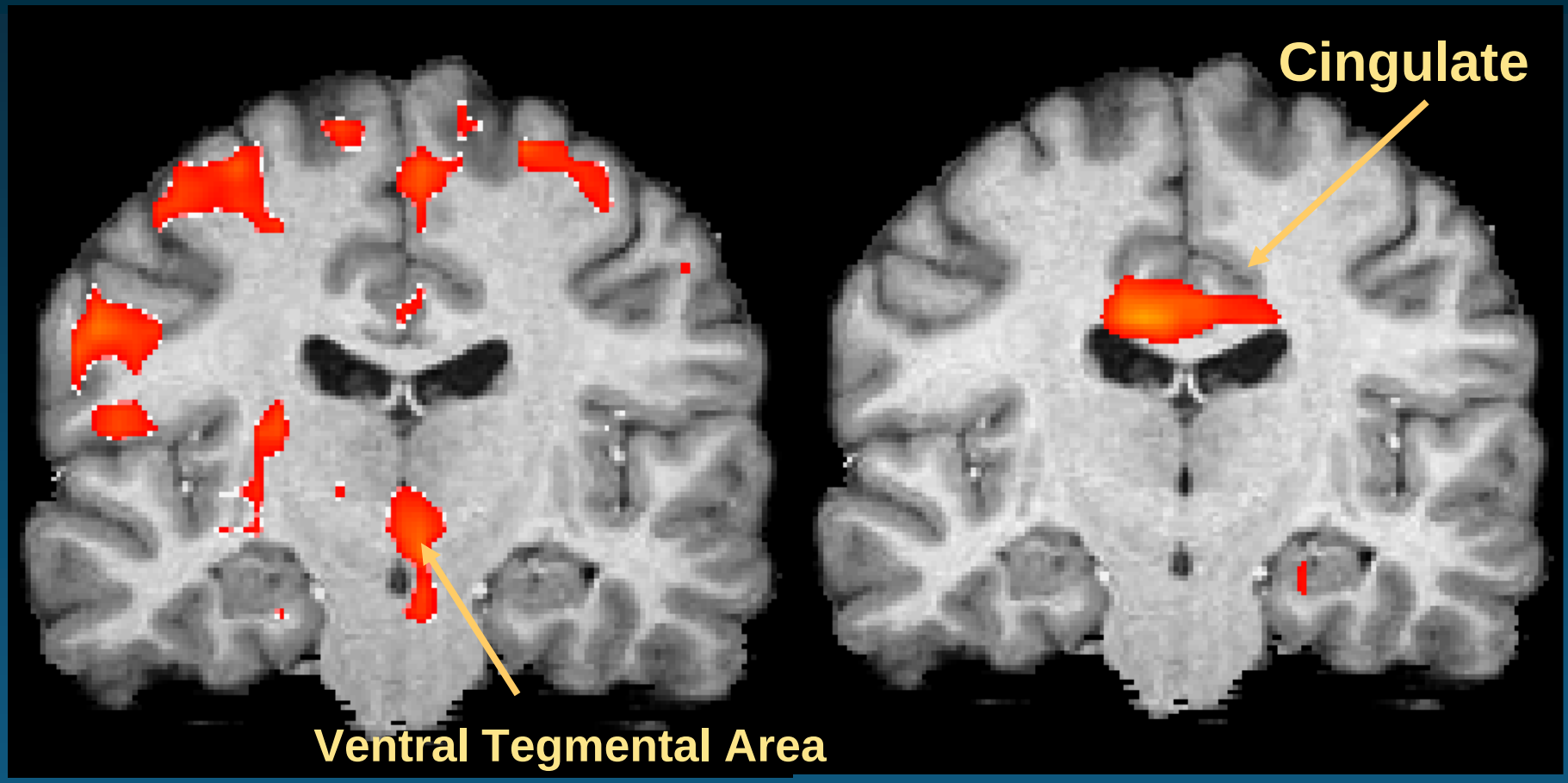


Alcoholics (n=10)

Controls (n=10)

Z=1.645 Ex .05

Alcohol - Beverage Condition



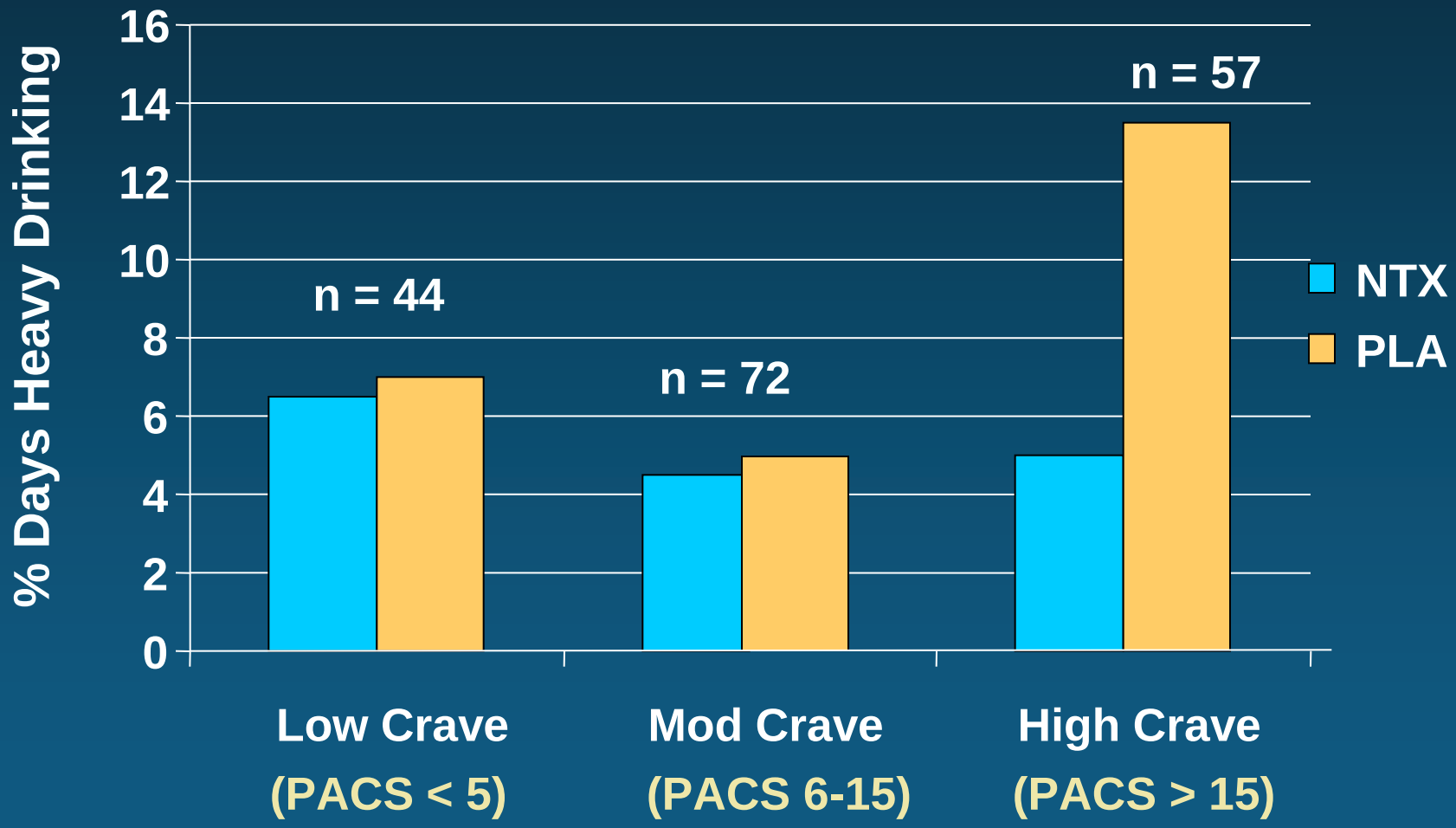
Alcoholics (n=10)

Controls (n=10)

Z=1.645 Ex .05

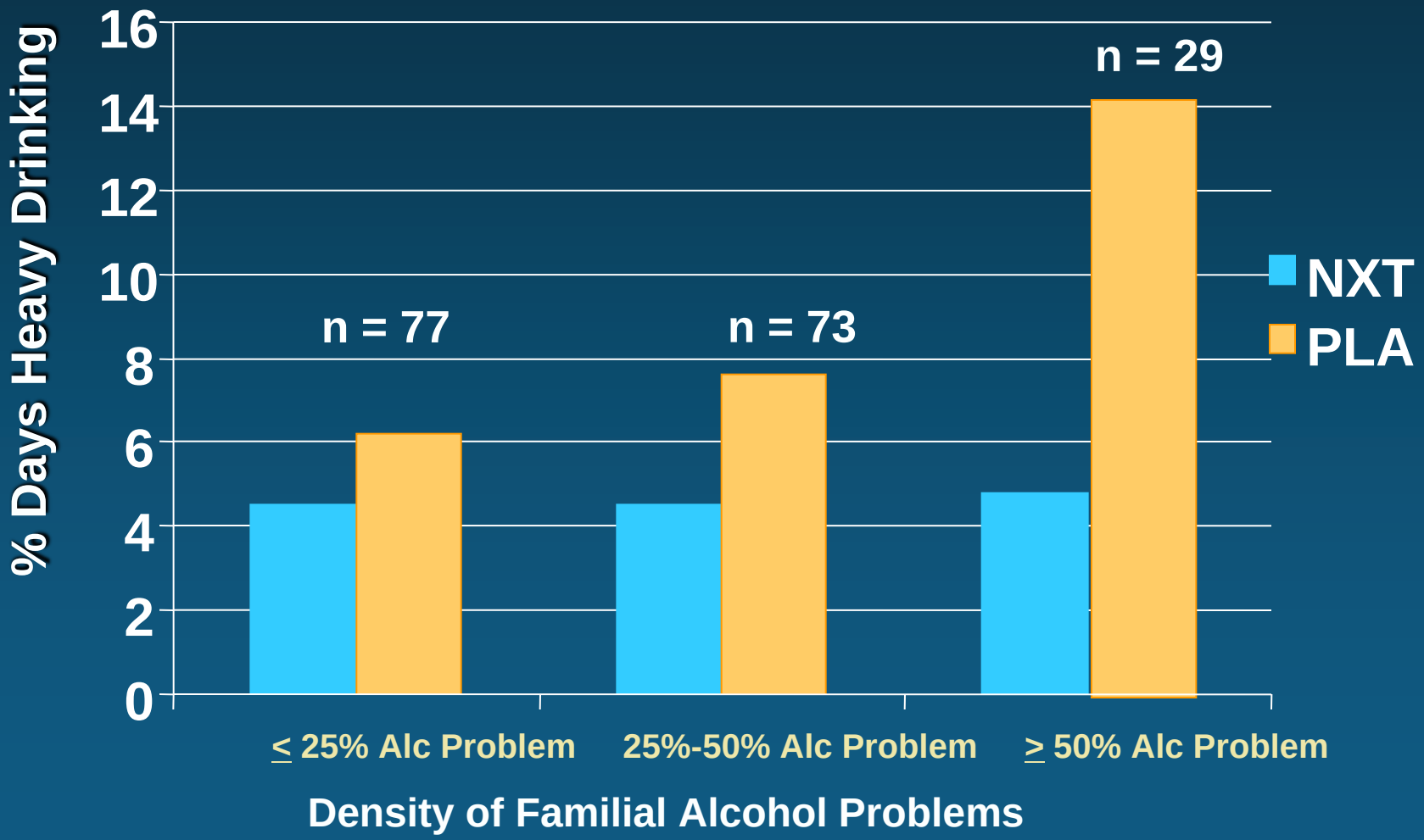
Why do many alcoholics respond to naltrexone, but others show no response?

Baseline Craving Scores

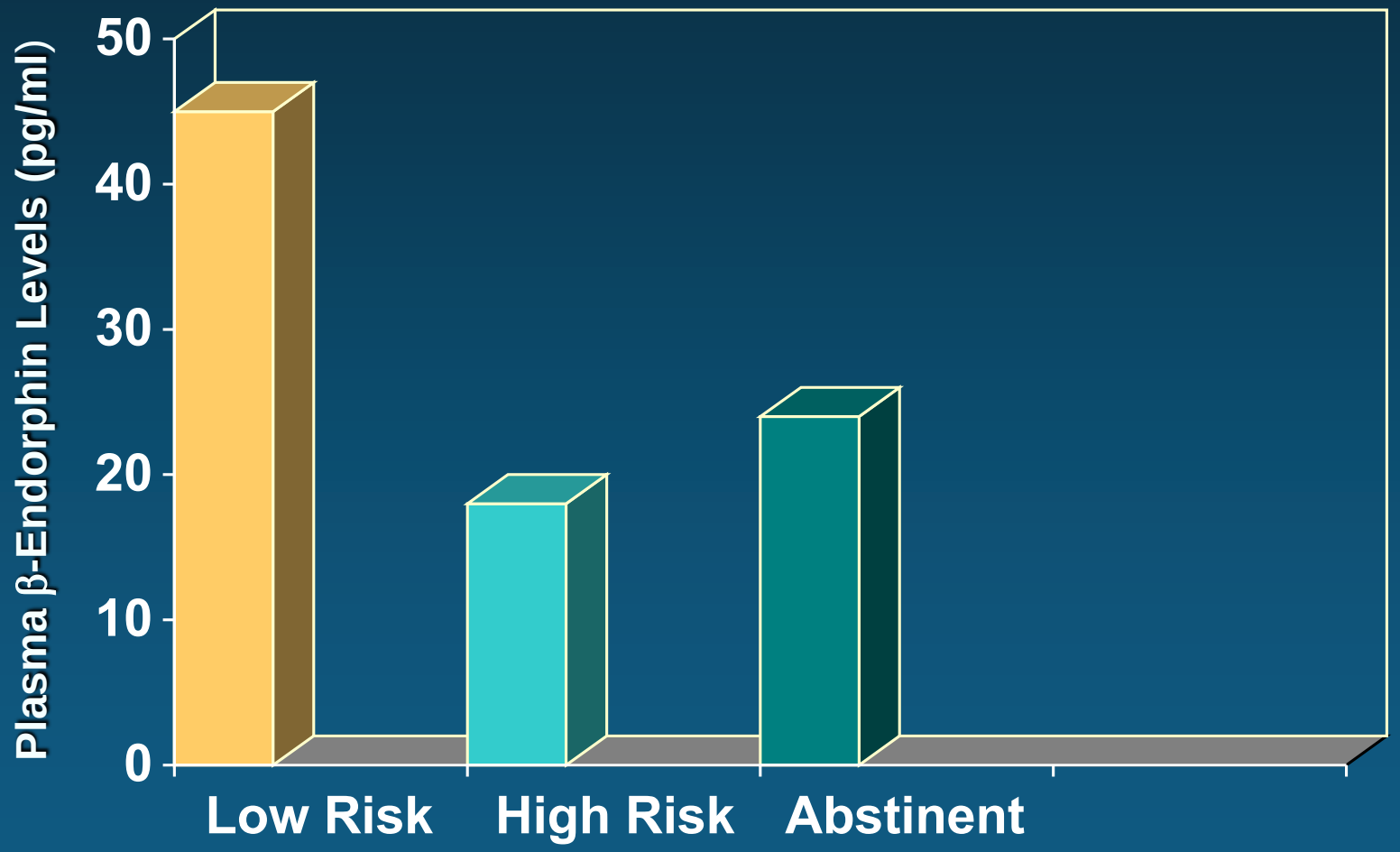


PACS = Penn Alcohol Craving Scale

Family History and Naltrexone Efficacy

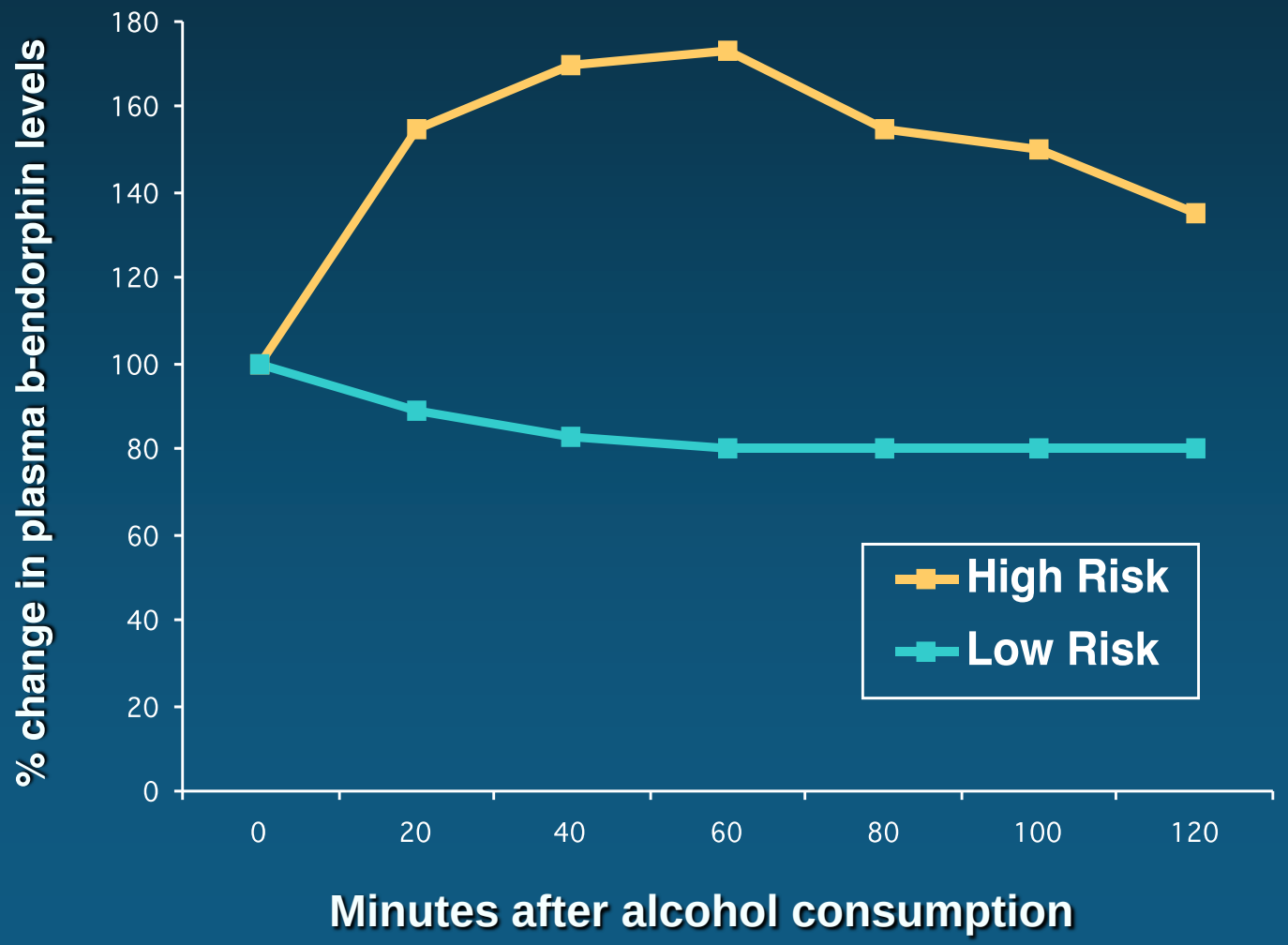


Baseline b-Endorphin Levels in Low- and High-Risk, and Abstinent Alcoholic Patients

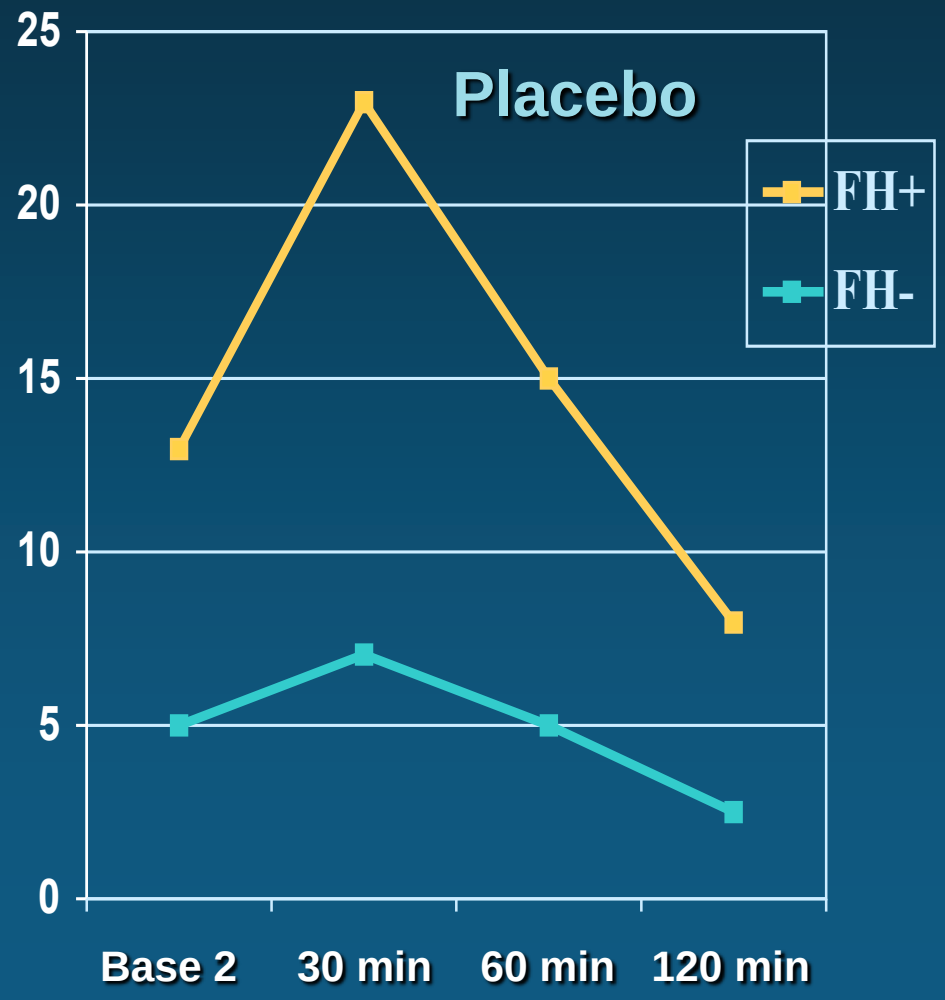


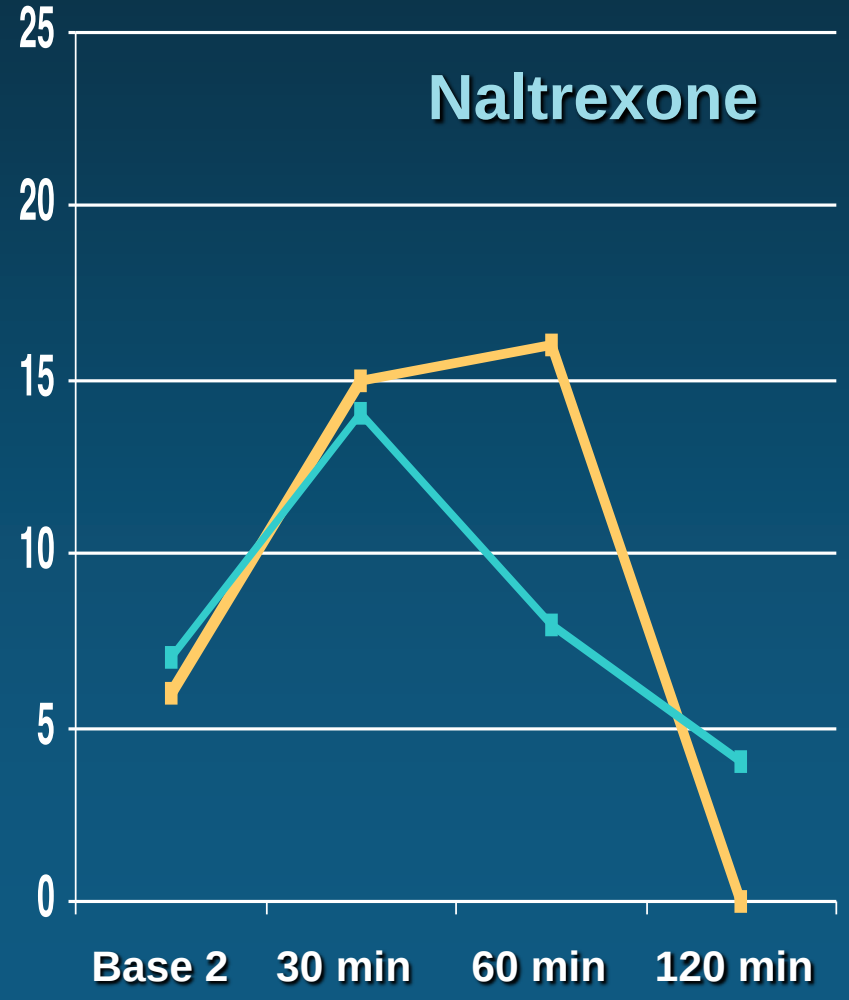
Gianoulakis. *Eur J Pharmacol.* 1990;180:21-29

Change in b- Endorphin Levels after Alcohol Consumption



BAES Stimulation Scores Among FH+ and FH Subjects

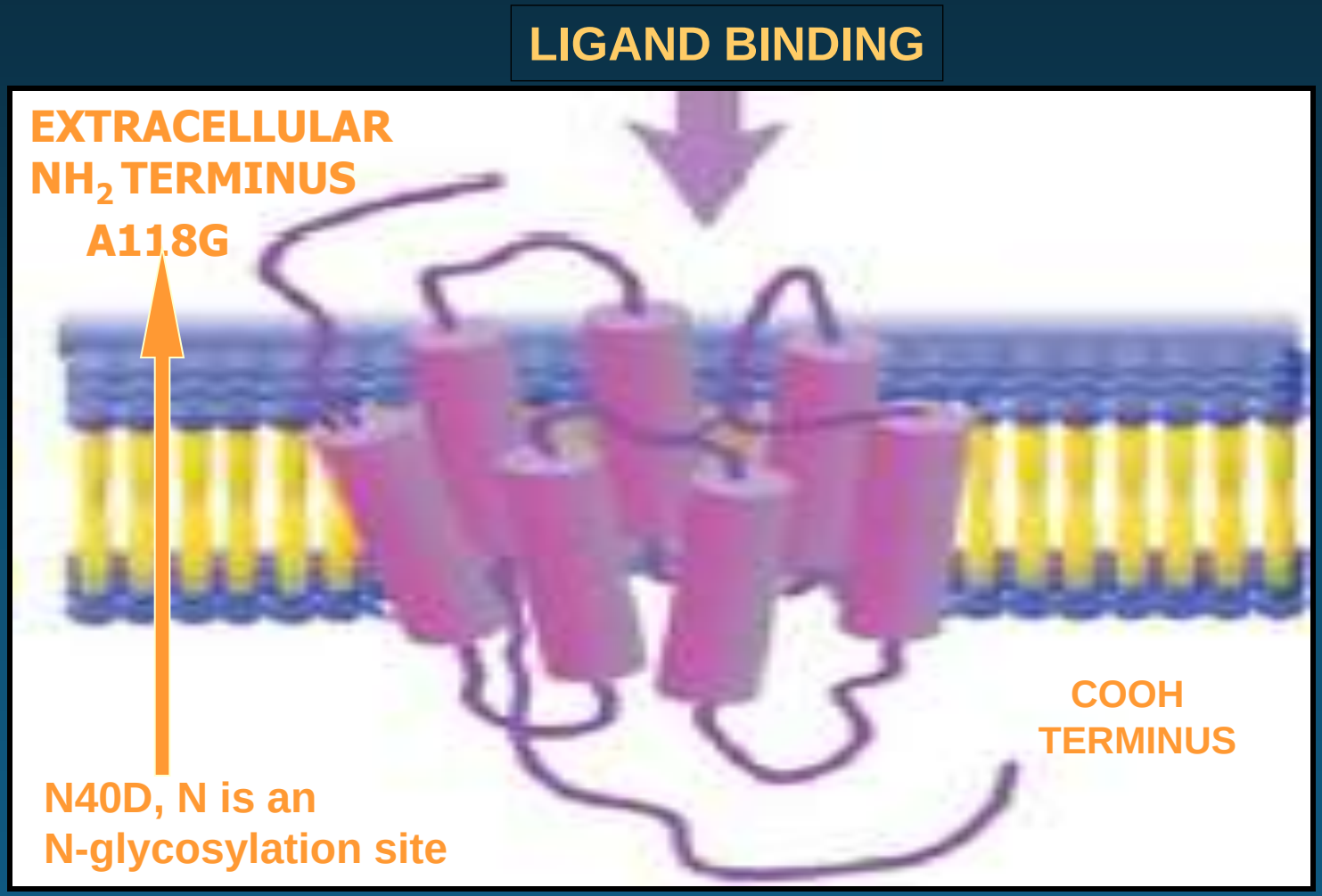




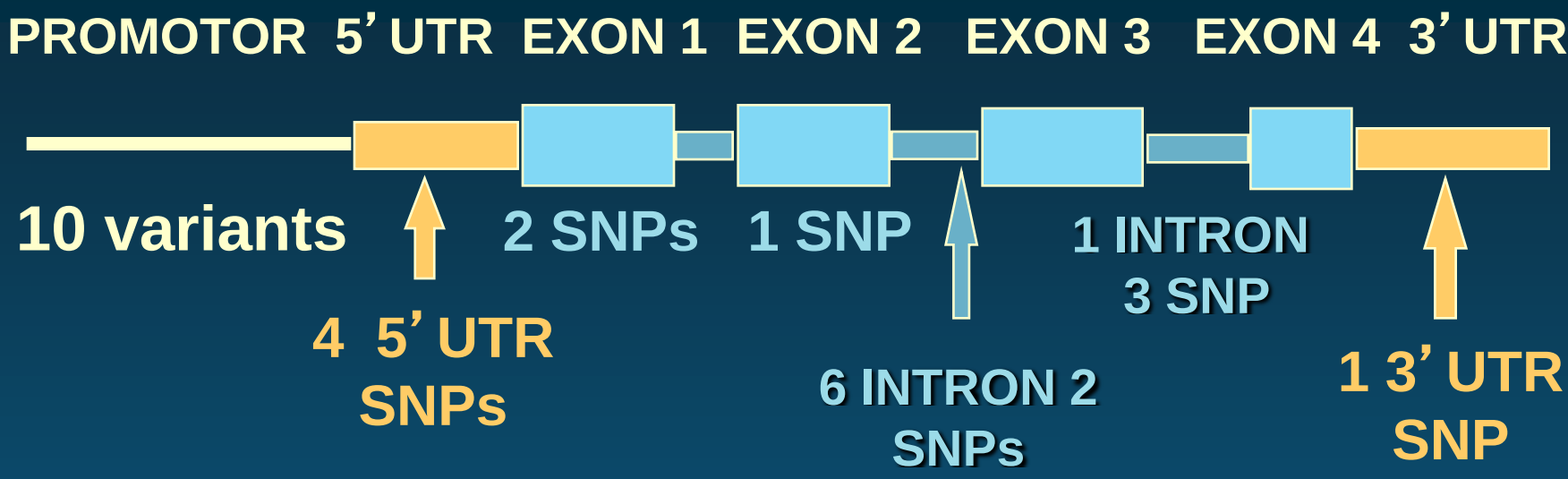
Key effect: Sensitivity of Endogenous Opioid system to alcohol

One source of individual variability in response to ethyl alcohol

OPRM1 PROTEIN STRUCTURE



Human Mu Opioid Receptor Gene



6.6 kb of OPRM1 gene sequence was determined in ~200 persons; 25 variants occurred at a frequency >1%.

The 118 A>G exon 1 SNP increases OPRM1 affinity for beta-endorphin. The functional significance of other variants remains unknown.

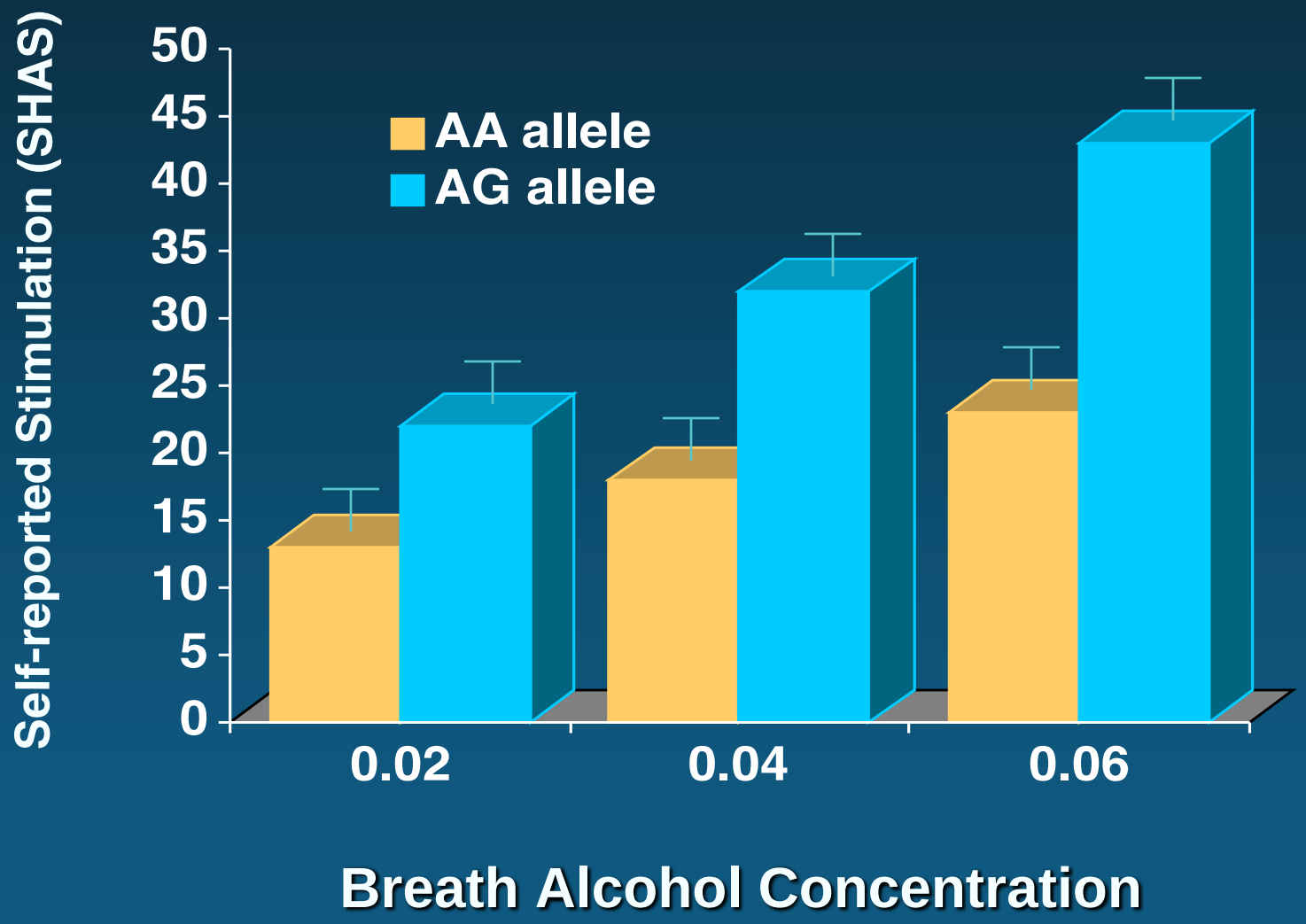
Functional Allele

Increase

and

Decrease

Alcohol effects by genotype



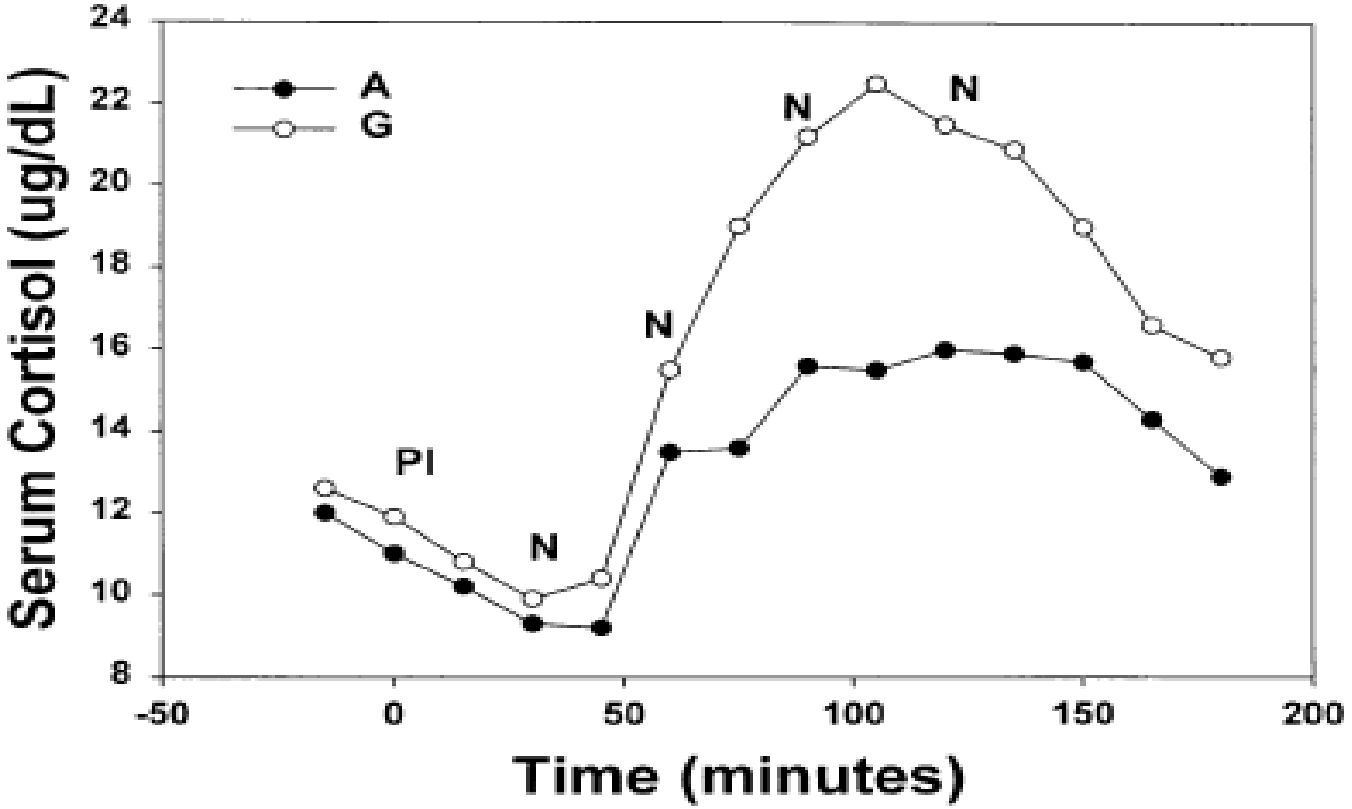


Figure 3. Cortisol responses to Naloxone by mu-opioid receptor genotype. Pl denotes time of placebo (saline) administration. N denotes times of incremental Naloxone administration.

Wand et al, *Neuropsychopharm* 26:106–114, 2002

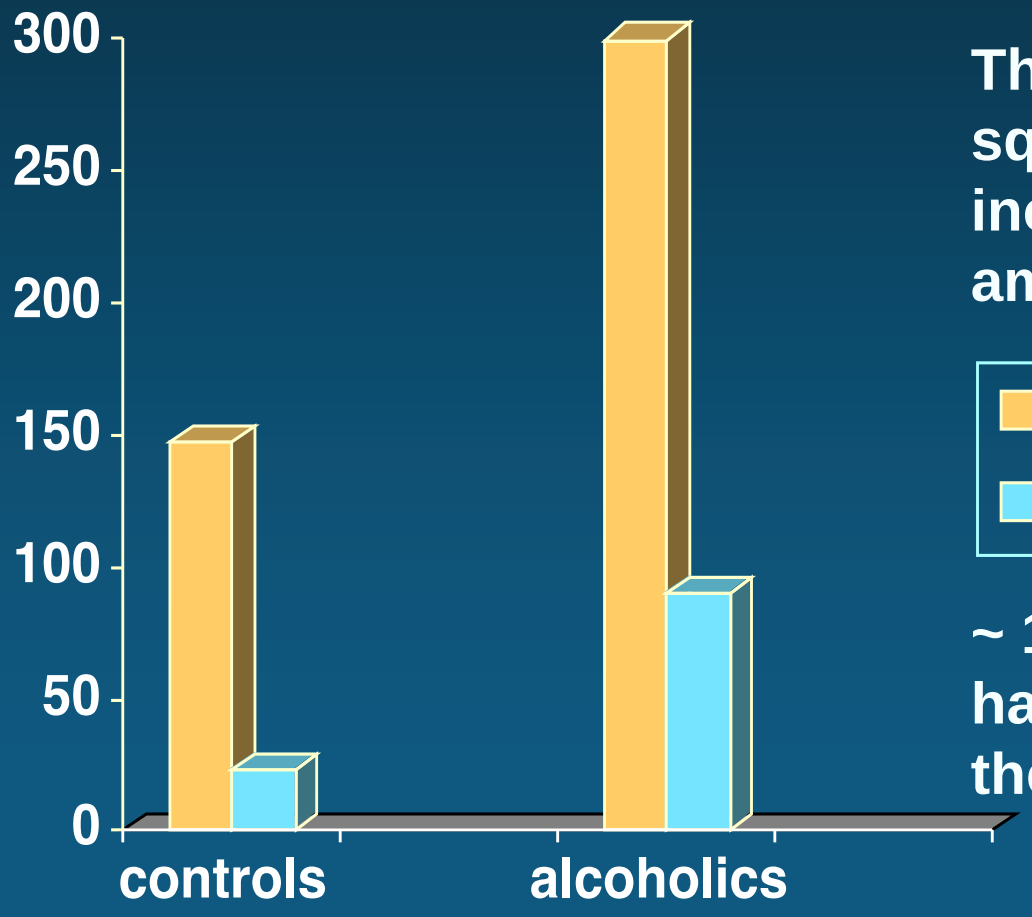
Ethnicity & A118G Allele Frequency

- Based on multiple studies, allele frequencies differ markedly across ethnicities for the A118G SNP in the mu opioid receptor gene. It arose after the out-of-Africa migration.
- Crowley et al, 2003
- Gelernter et al, 1999
- Tan et al, 2003
- Bart et al, 2004

ETHNICITY	f(G)	ETHNICITY	f(G)
African	1%	Koreans	31%
African-American	3%	Chinese	35%
Swedish	17%	Malaysian	45%
European-origin US	15%	Indian	47%

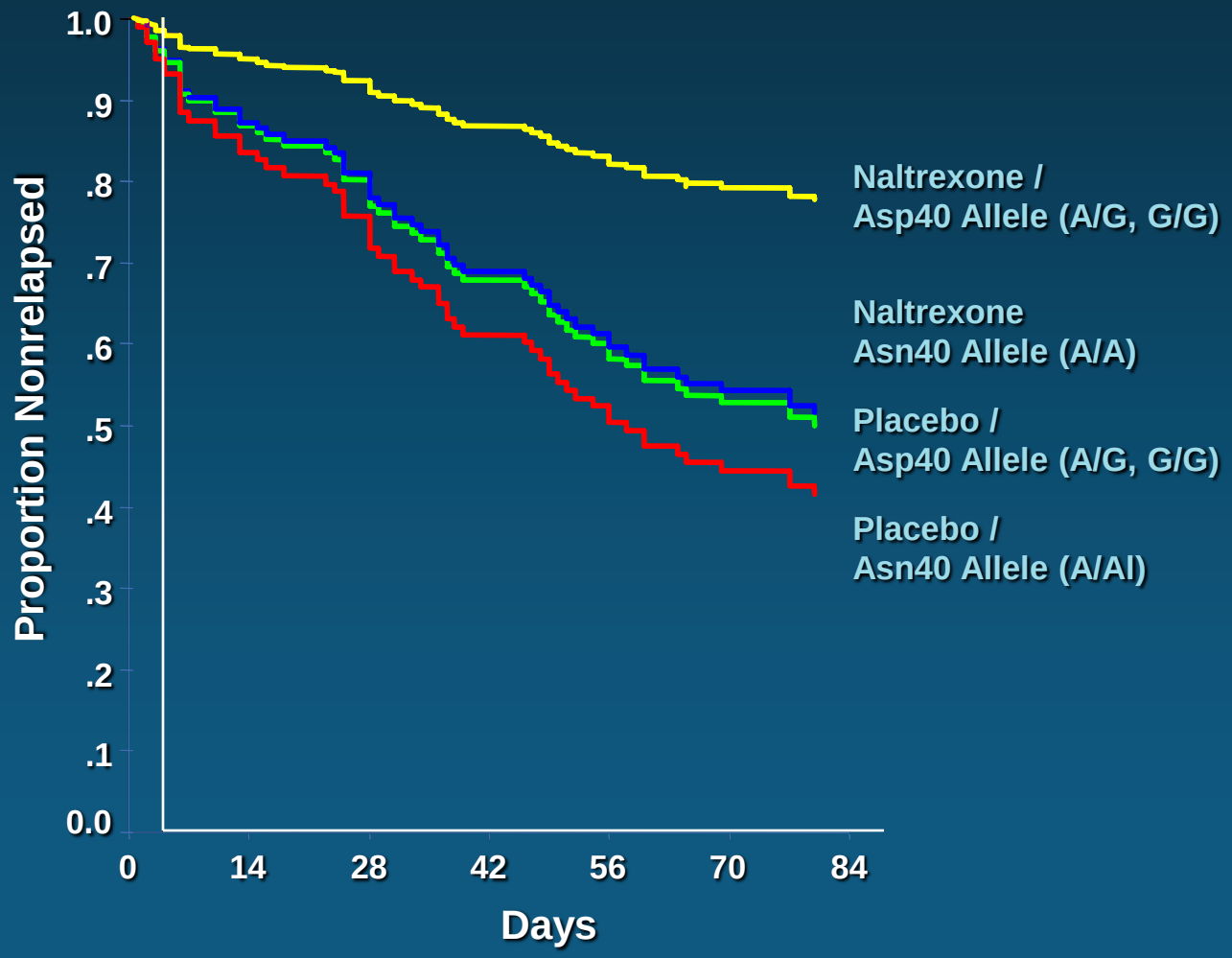
OPRM1 A118G and Alcoholism

Bart et al (Neuropsychopharmacol, 2005) studied alcoholics in Sweden for the A118G.



There was a significant (Chi squared = 7.2, p = 0.007) increase in A/G, G/G genotype among alcoholics. In this study the attributable risk for the G allele is ~ 11%, suggesting that ~ 11% of Swedish alcoholics have disease in part due to the G allele.

Relapse Rate by Genotype



COMBINE Study

- N = 1383; 9 randomized groups
  - MM + Placebo
  - MM + Naltrexone
  - MM + Acamprosate
  - MM + Naltrexone + Acamprosate
    - CBI only
- At least 4 days abstinence at baseline
- Endpoints
  - Percent days abstinent
  - Time to first heavy drinking day

+/- CBI

Anton et al. *JAMA*. 2006;295:2003.

CBI = cognitive behavioral intervention;
MM = medical management

Combine: NIAAA Good Outcome

Nalt	A/G, GG	95%	N = 28
Nalt	A/A	73%	N = 86
Plac.	A/G, GG	63%	N = 60
Plac.	A/A	65%	N = 205

Odds ratio, nalt good regs, GVA = 10.25 (95% CI 1.31 - 80.0 P= .03)

*VA multi-site study: sample size with G allele small

Rhesus model

Ortholog of A118G allele in humans

(OPRM1C77G)

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increased sensitivity to alcohol

increased alcohol preference

greater effect in males (Barr et al)

Sub-sample of VA coop. study

Those who gave blood for DNA

Naltrexone sig. better than placebo, but no genetic association.

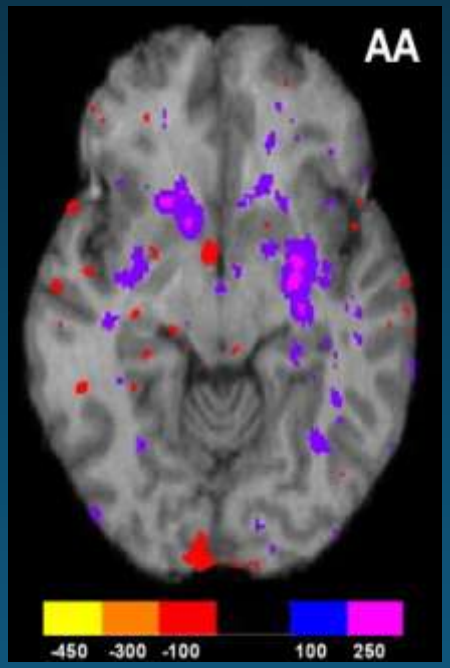
Finnish study with Nalmefene- Naltrexone superior to placebo, but no genetic association

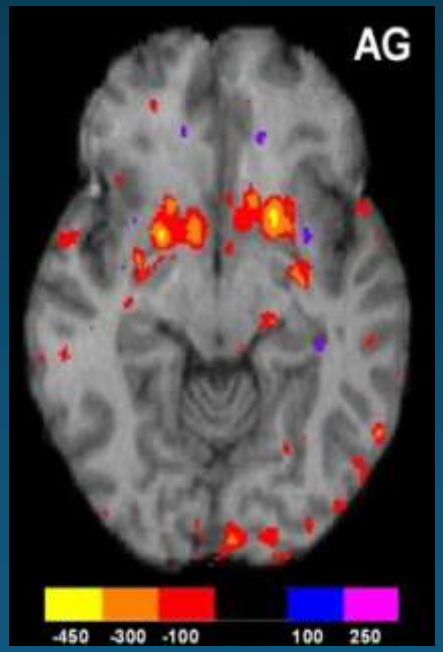
PROSPECTIVE study in progress

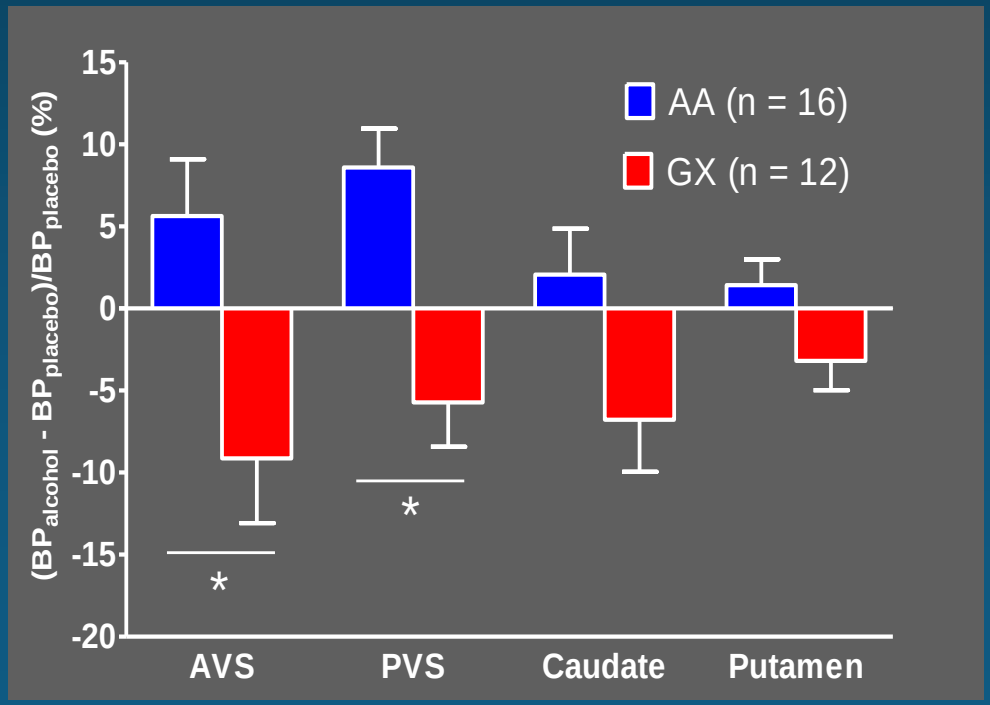
Slow release version of naltrexone

Alcohol-induced dopamine release in ventral striatum is restricted to OPRM1 - 118G carriers

(Ramchandani et al., Mol Psychiat 2010)







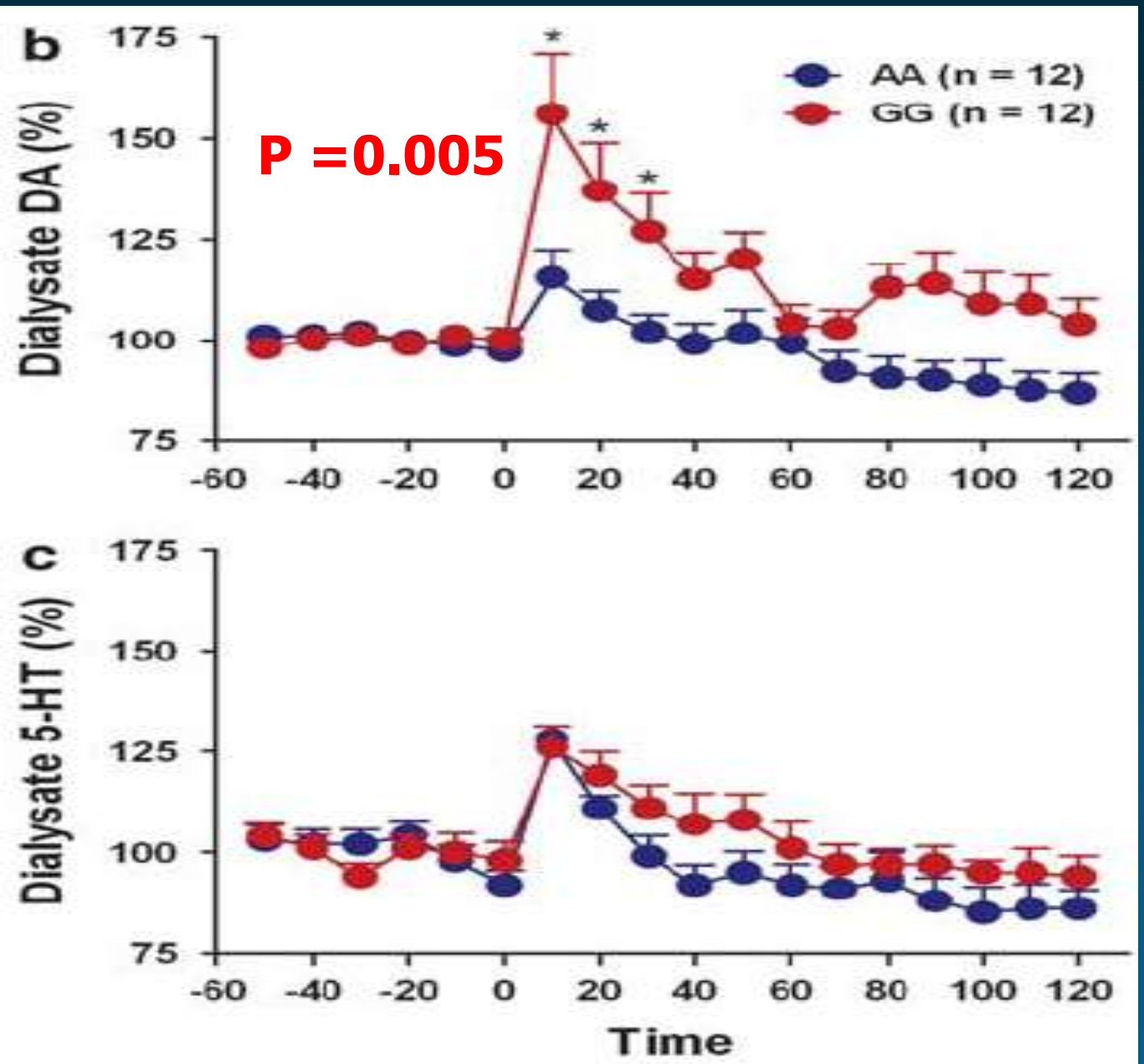
Mouse models: “knock-in” human OPRM-1

2 Labs A/A and G/G versions of μ receptor gene, 4x inc DA release in response to ethanol in G/G mice, increased ethanol Self Adm

Penn: Blendy inc DA response

- Rhesus, functionally equivalent allele (77G variant13) produces sensitivity to alcohol-induced psychomotor stimulation.

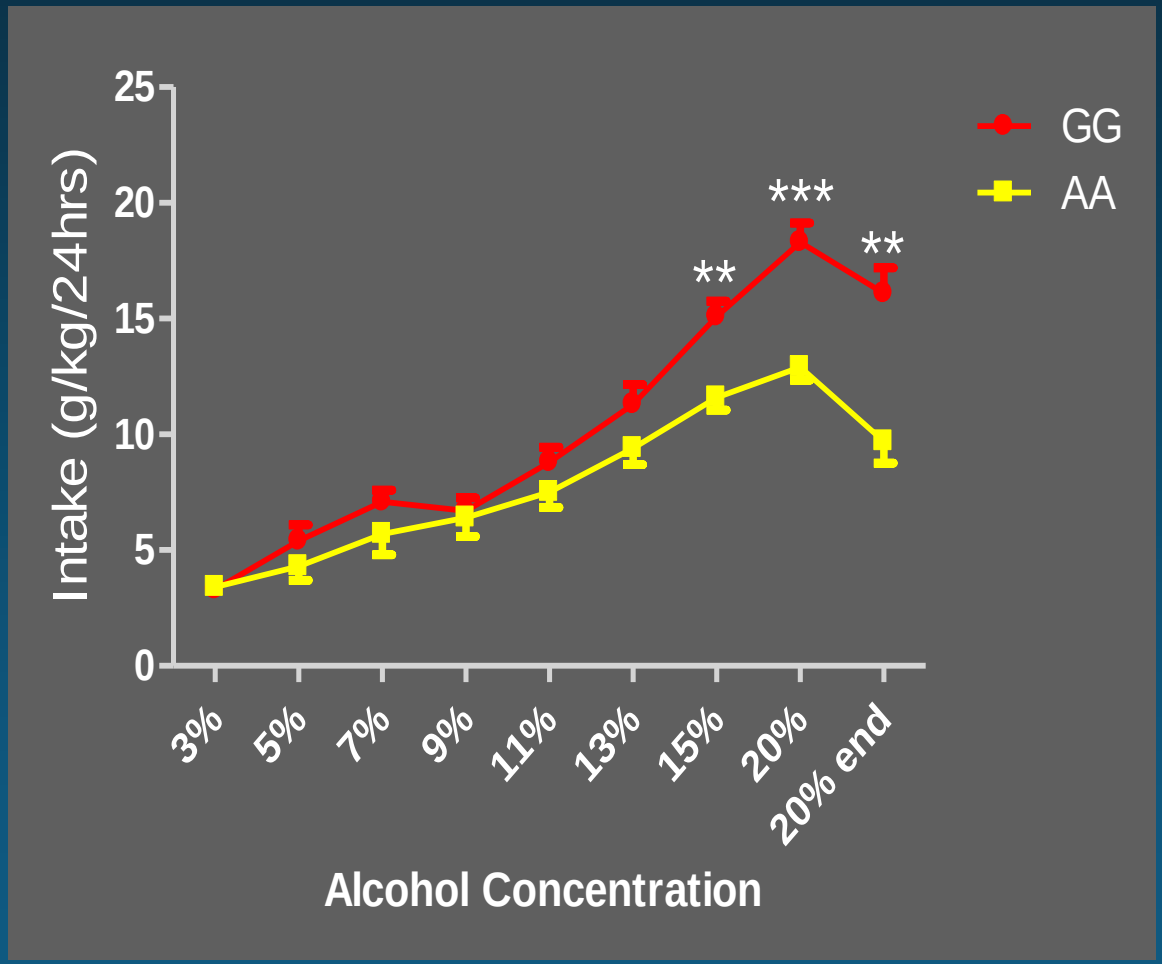
Animal Models for A118G: Mouse



OPRM 118 AA & GG mice were given ethanol 2 g/kg, during *in vivo* microdialysis. GG mice showed a significant dopamine elevation in striatum after the ethanol, while AA mice did not. No change was seen in striatum for the 5HT levels.

(Ramchandani et al Mol Psychiatry, 2010)

Increased alcohol-induced DA-release in 118GG mice is associated with increased voluntary alcohol intake (Thorsell et al, in preparation)



Treatment of Alcoholism in USA

How to prescribe oral natrexone
Very low dose to begin
Try to convince patient to continue at least 3-4 months before giving up
Duration depends on results- years
Slow release depot
Q 30 days
Most success, few side effects, best continuity of care. This is a chronic disease.

Cost-Benefit studies

Cost of Treatment 6 months prior to admission compared to 6 months later

Fewer visits to Emergency Room

Co-Morbidity

2 new placebo controlled trials

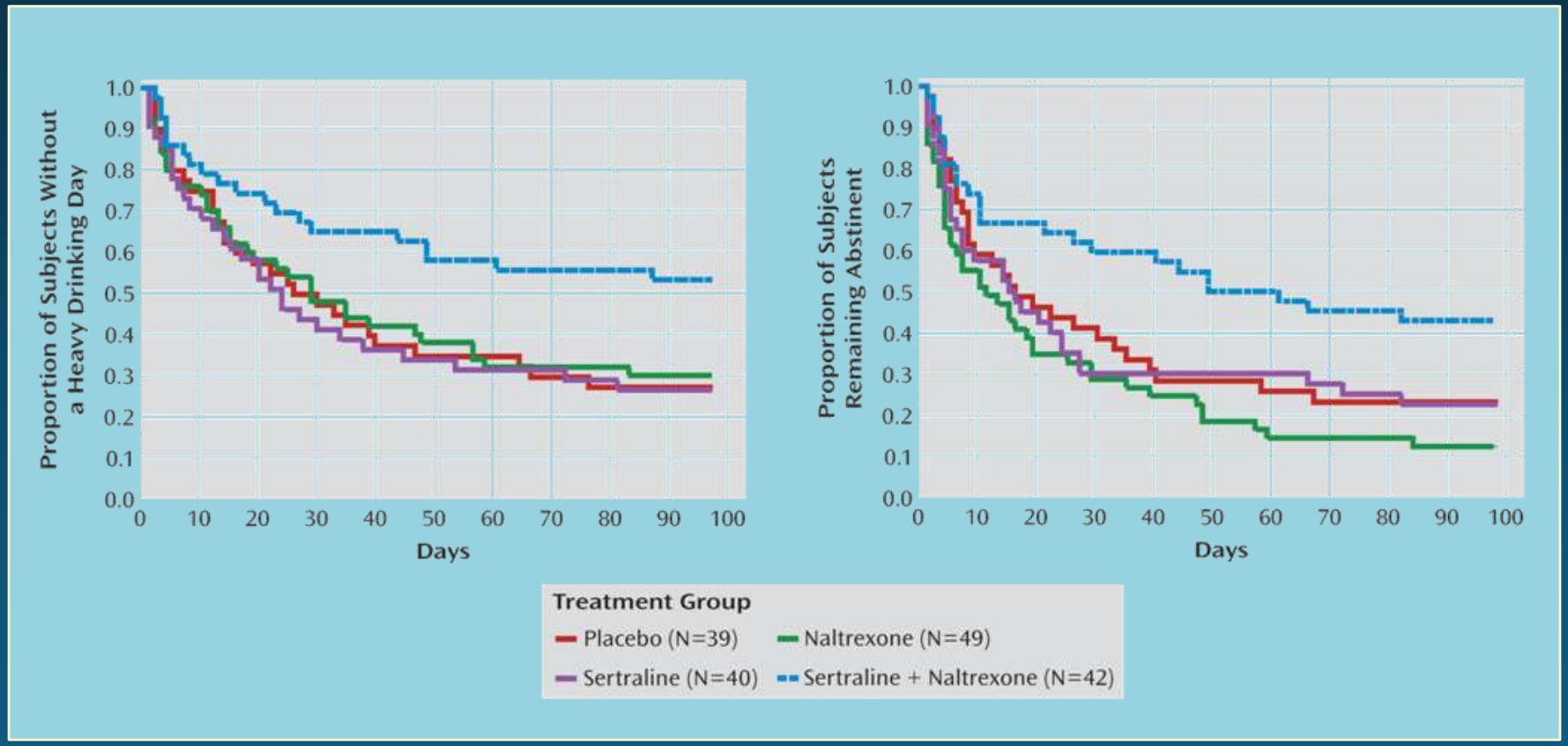
Alcoholism + Depression (Pettinati 2010)

Naltrexone + Sertraline

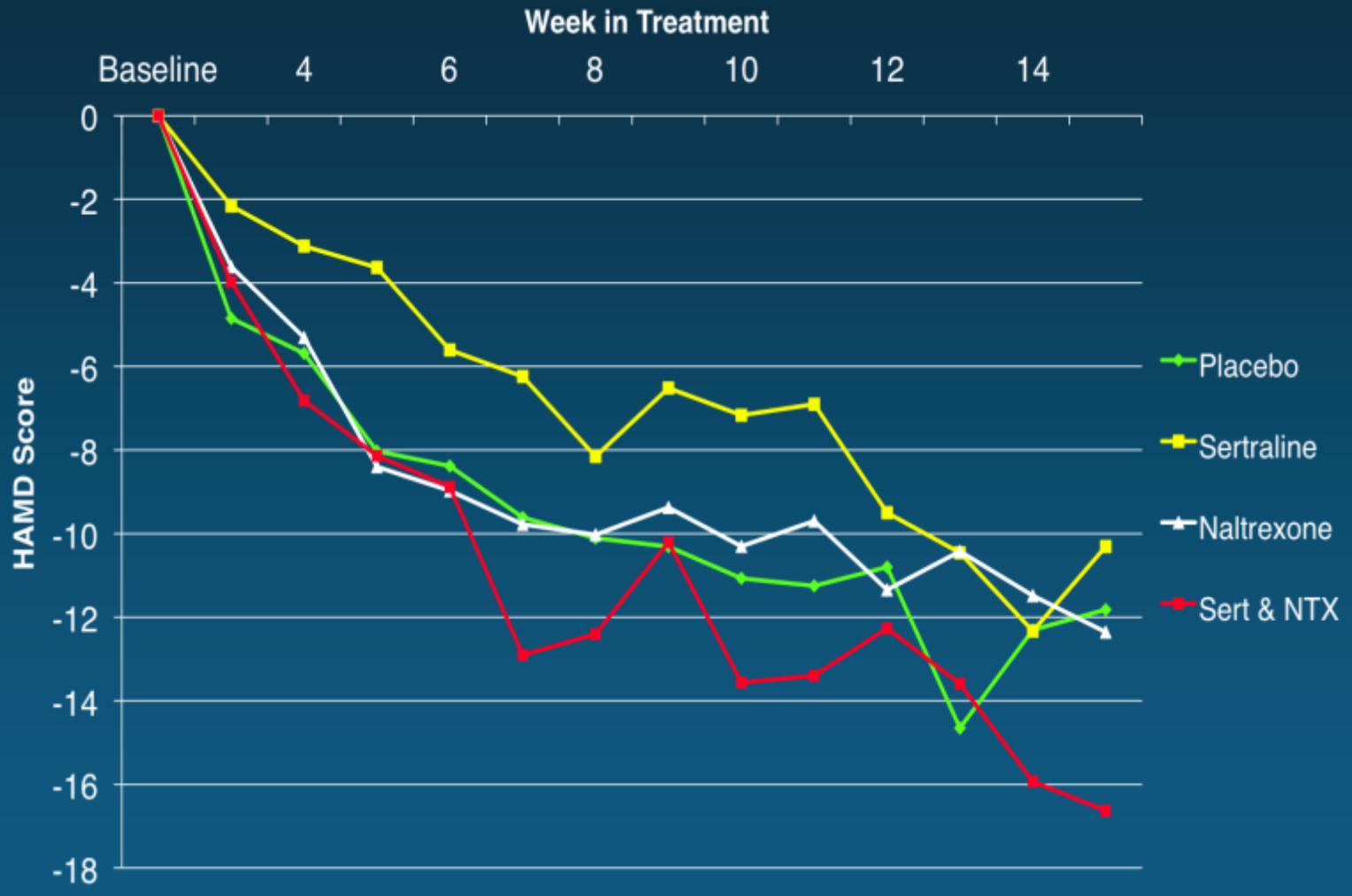
Alcoholism + PTSD (Foa 2012)

Naltrexone + Exposure Therapy

Time to First Heavy Drinking Day and Time to First Drinking Day in Depressed Alcohol-Dependent Patients Randomly Assigned to Medication Treatment or Placebo



Hamilton Score Change From Baseline



CNN Special
Addiction: Life on the edge

5 patients followed for one year
Different parts of country

- Admissions
- Graduations
- Relapses
- Interviews with counselors at famous programs

GUPTA: And so he tried again. He checked himself into an experimental program run by Brown University. **This time he got counseling once a week and a daily pill, a medicine called naltrexone. About two months into it, Walter Kent suddenly noticed the world around him looked and felt different.**

KENT: And I had just turned around and I said, this is really something **for the first time in my life that I never had this sensation where I didn't want a drink.** And this, to me, was like a godsend because of the fact that for someone who had to have a drink, now all of a sudden I don't need that -- I don't have that feeling anymore.

GUPTA: **He hasn't had a drink in more than eight years.** Even after his doctor stopped the medication. **He's healthy, back at work, fixing up carburetors.** And now he's part of a running debate. Is addiction an illness you can treat with a pill or a character flaw to be tackled with therapy and self-help?

Addiction: Life on the Edge – CNN Correspondent Dr. Sanjay Gupta aired April 19, 2009

GUPTA: **Despite the evidence, most fancy rehab centers use medication only rarely, if at all. The focus is much more on therapy.**

Head Counselor Minnesota: **With the health care professional staff here at Hazelden, our experience tells us having that network of support in recovery is what really makes the difference.**

GUPTA: More so than medication?

CLARK: More so than just medication, exactly.

GUPTA: And that's the conventional wisdom.

Addiction: Life on the Edge – CNN Correspondent Dr. Sanjay Gupta aired April 19, 2009

California Program

GUPTA: **What about medications?**

Head Counselor California Program: **We do not use them at the Betty Ford Center.**

No comment from the interviewer, no follow up questions.

Addiction: Life on the Edge – CNN Correspondent Dr. Sanjay Gupta aired April 19, 2009

FOR MORE INFORMATION

http://www.med.upenn.edu/csa/or

obrien@upenn.edu

Endophenotype
Endorphin Dependent Alcoholism

- Alcohol → Endogenous Opioids
- Euphoria/Stimulation
- Sensitive μ Receptors
- Family History
- Alcohol Craving

Best Treatment

- **Medications**

  Plus

- **Psychosocial Intervention**

Penn/VA Center Team

Joe Volpicelli
Wade Berrettini
John Cacciola
Anna Rose Childress
James Cornish
Charles Dackis
Ronald Ehrman
Teresa Franklin
Kyle Kampman
James McKay
A. Thomas McLellan
David Metzger
David Oslin
Helen Pettinati
Michael Stromberg
Elmer Yu
George Woody
Arthur Alterman

FOR MORE INFORMATION

http://www.med.upenn.edu/csa/or

obrien@mail.trc.upenn.edu

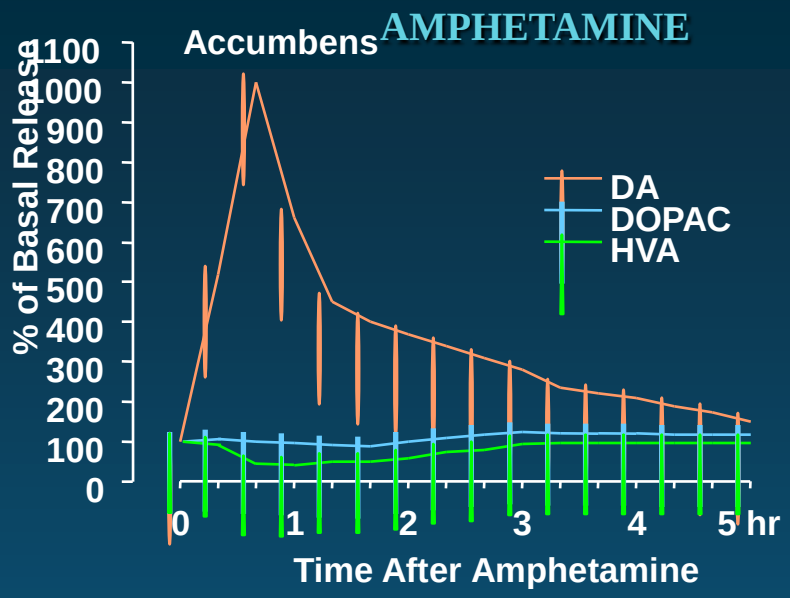
Possible Gender Effect

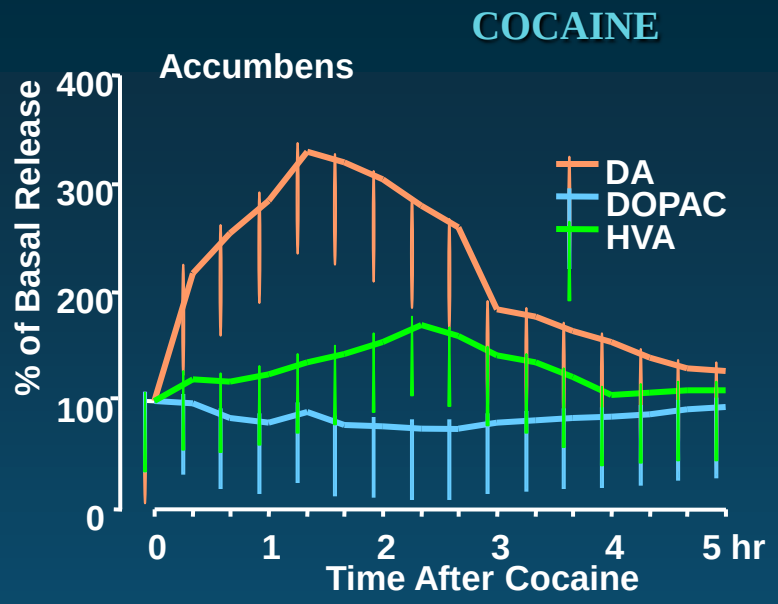
Males more responsive in only study with large number of women

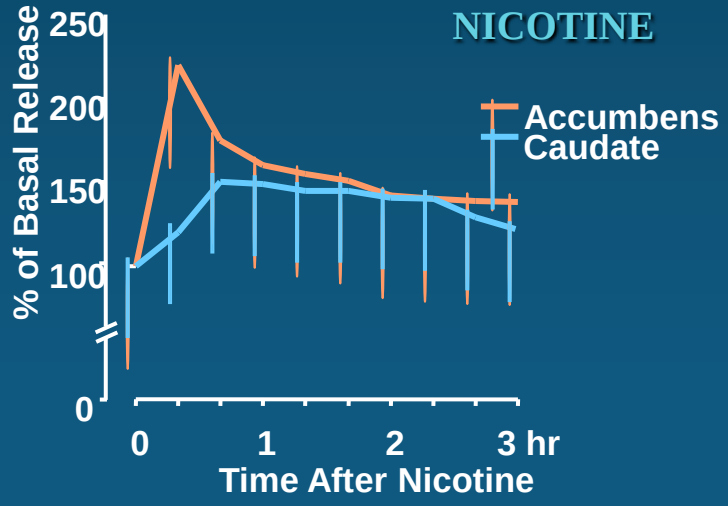
Medications

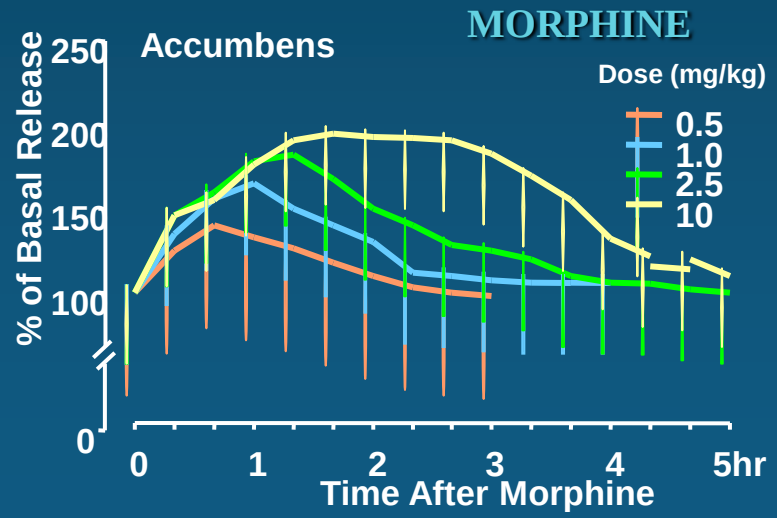
- Nicotine
  - Nicotine patch, gum, nasal spray
  - Bupropion
  - Varenicline
  - Rimonabant*
- Opiates
  - Methadone
  - Buprenorphine
  - Naltrexone
- Stimulants
  - Modafinil
  - Topiramate
  - Baclofen
  - Disulfiram
  - Propranolol
  - Vigabatrin (clinical trials)
- Alcohol
  - Disulfiram
  - Naltrexone
  - Acamprosate
  - Topiramate

Effects of Drugs on Dopamine Levels









Source: Di Chiara and Imperato

Learning Objectives

- Describe the data supporting a new subtype or endophenotype of alcoholism.
- Describe the relative merits of the various medications available for the treatment of alcoholism.
- Describe the range of specific psychosocial treatments for alcoholism.

Use

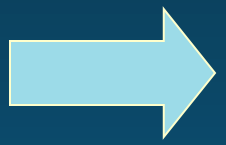
Use

Use

Use

Use

Abuse
(declarative)



Addiction
(automatic)

Abuse

Dependence (Addiction)

DSM-IV

- Tolerance
- Withdrawal
- More use than intended
- Unsuccessful efforts to cut down
- Spends excessive time in acquisition
- Activities given up because of use
- Uses despite negative effects

Possible Changes

DSM-V

- Addiction instead of Dependence?
- Abuse? necessary
- Severity?
- Substance and non-substance addictions
  - Gambling addiction
  - Internet gaming?
  - Food? Sex? Shopping?

Risk of Addiction

	Ever Used (%)	Dependence (%)	Risk (%)
Tobacco	75.6	24.1	31.9
Cocaine	16.2	2.7	16.7
Heroin	1.5	0.4	23.1
Alcohol	91.5	14.1	15.4
Cannabis	46.3	4.2	9.1

Source: Anthony et al, 1994.

Types of Genetic Studies

Family
Twin
Adoption
Large population: COGA
Candidate gene studies

Level Of Response To Alcohol

- Observe less response when tested with alcohol
- Self-report of more drinks for an effect
- IV alcohol clamp to control level

Response

- Genetically influenced (heritability ≥40%)
- Low LR in animals, twins, 1° relatives, 40% offspring of alcoholics

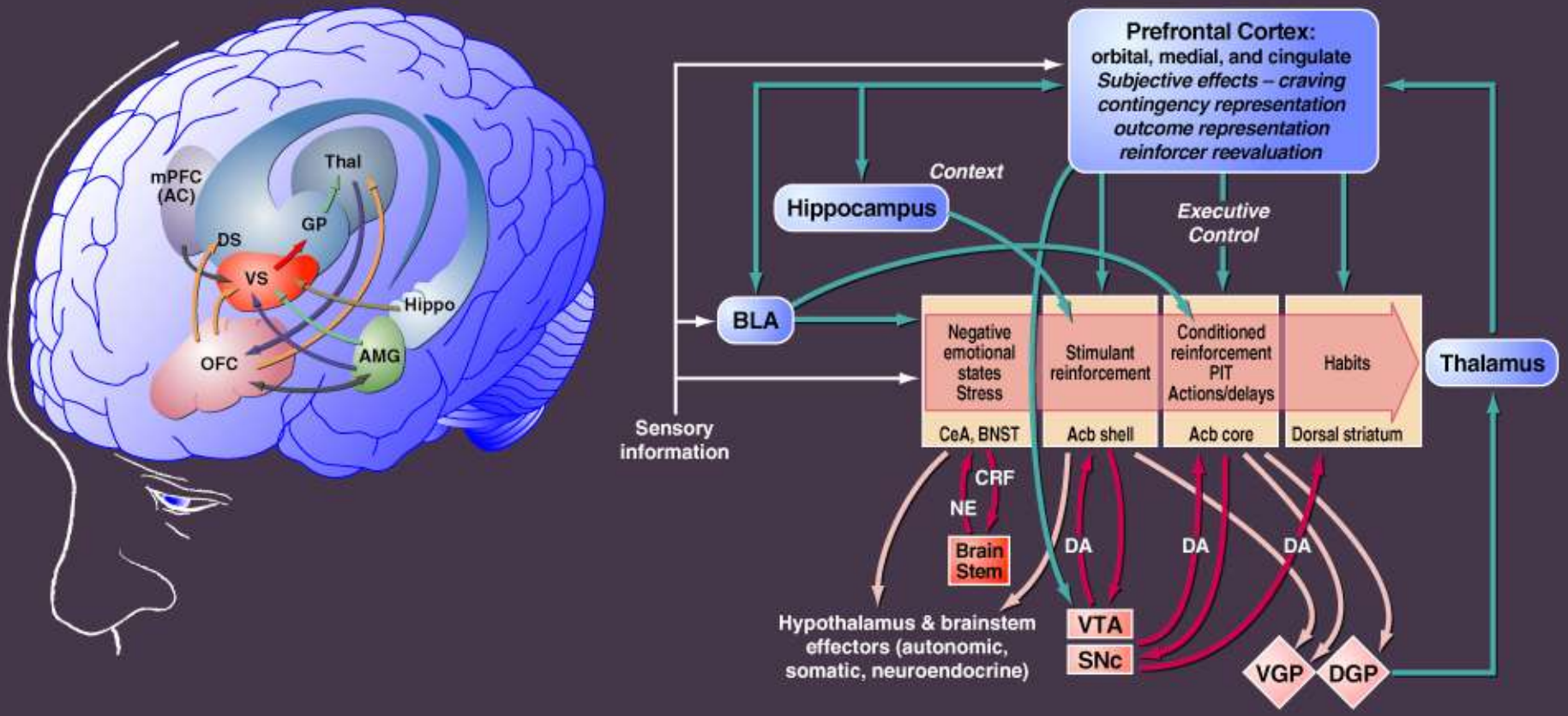
Low response Predicts Alcoholism 4-20 Years Later

- If response low at age 20
- And FH positive
- 60% men developed alcohol use disorder by age 30

Drugs of Abuse all Activate Reward System

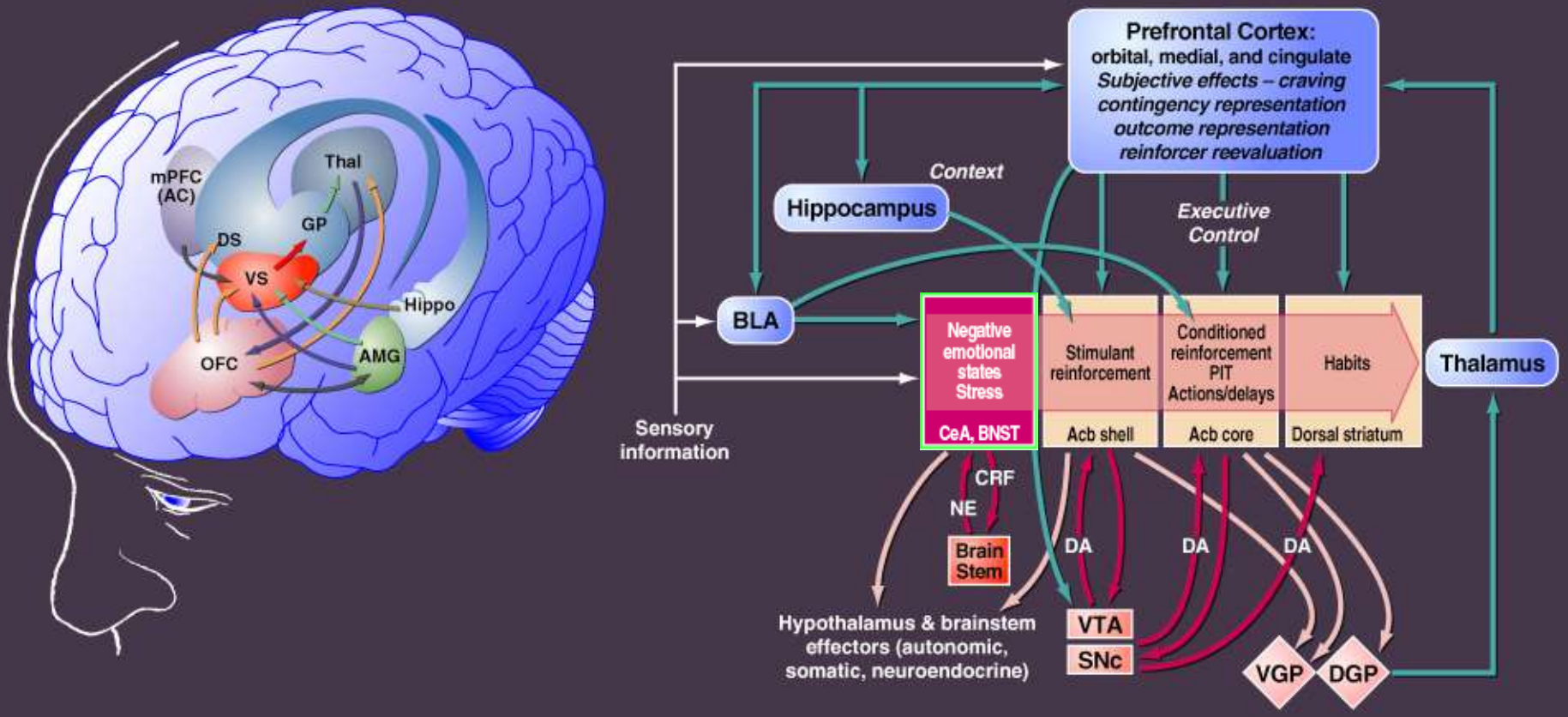
- Cues associated with drugs become conditioned stimuli

Key Elements of the Neurocircuitry of Addiction



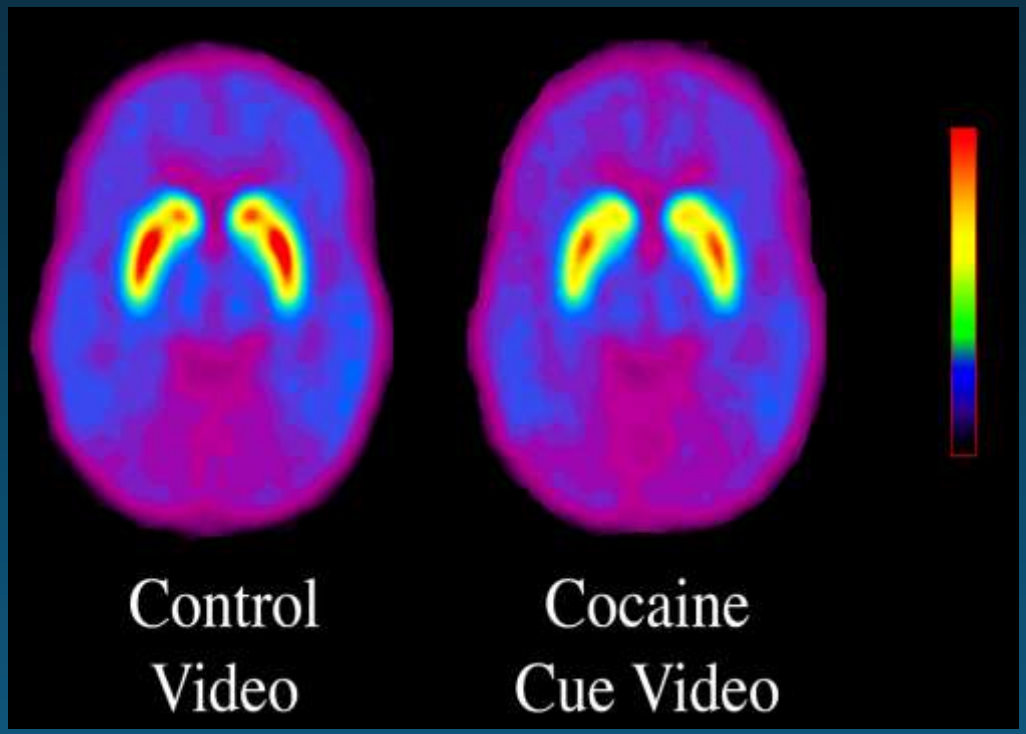
From: Koob G, Everitt, B and Robbins T, Reward, motivation and addiction. In: Fundamental Neuroscience, in press.

Key Elements of the Neurocircuitry of Addiction



From: Koob G, Everitt, B and Robbins T, Reward, motivation and addiction. In: Fundamental Neuroscience, in press.

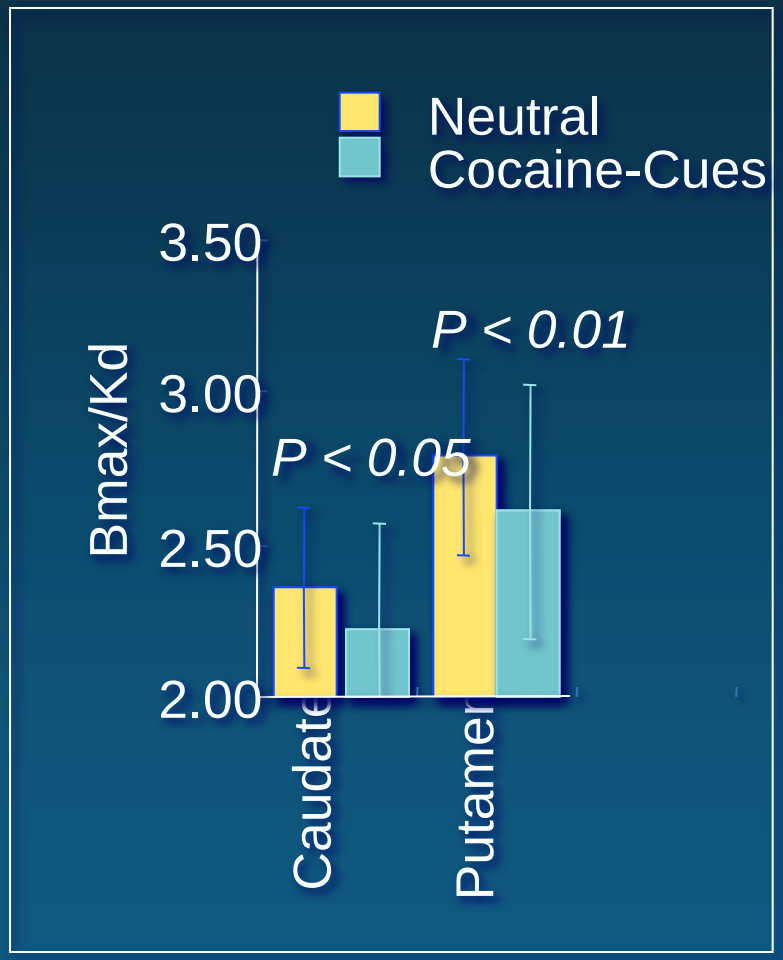
[^{11}C]Raclopride Binding In Cocaine Abusers (n=18) Viewing a Neutral and a Cocaine-Cue Video

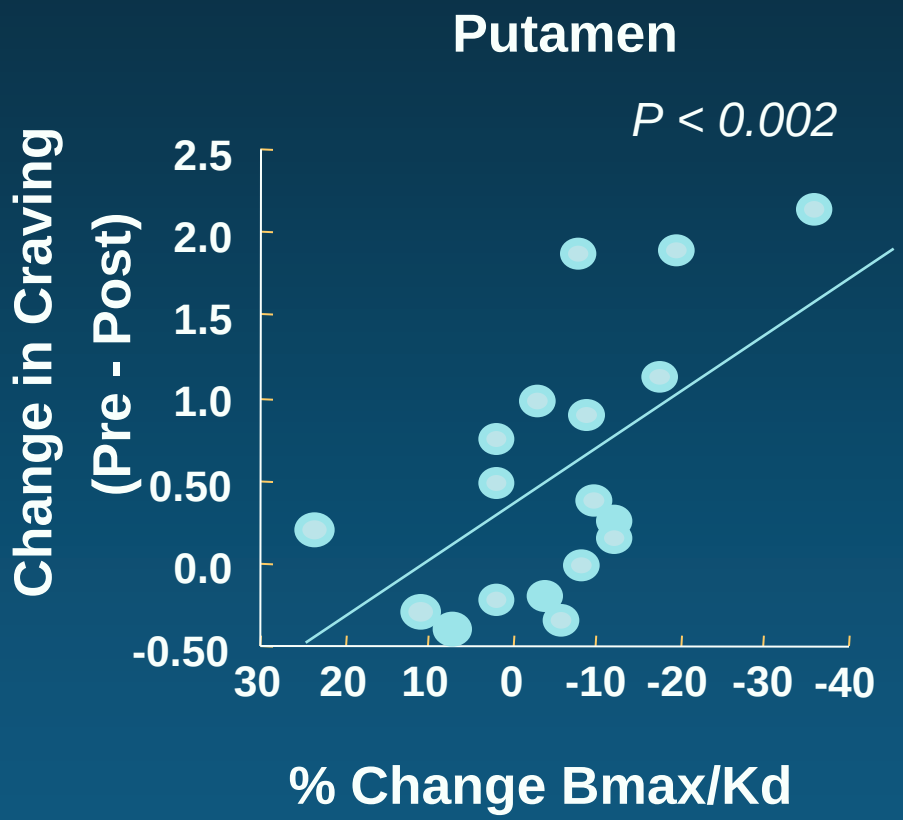


Viewing a video of cocaine scenes decreased specific binding of [11C]raclopride presumably from DA increases

Volkow et al J Neuroscience 2006

Relationship between Cue-Induced Decreases in [11C]raclopride Binding and Cocaine Craving





Volkow et al J Neuroscience 2006

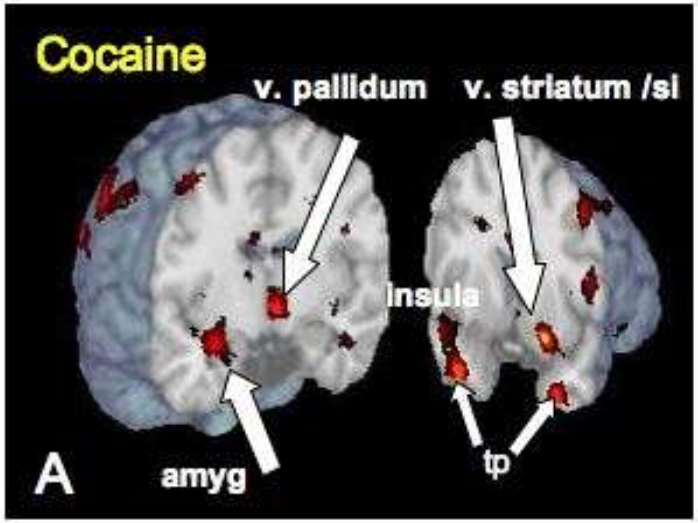
Cue-induced increases in DA were associated with craving

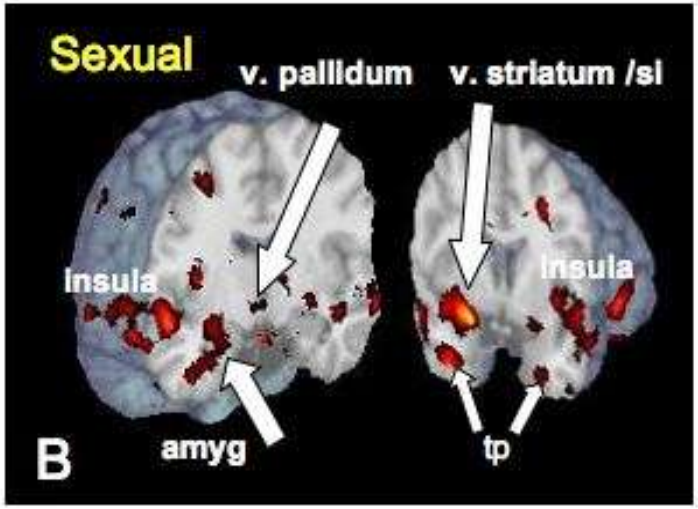
"Unseen" Cue Paradigm

33 msec targets

467 msec "masks"

Activations





"Unseen" Reward Cues

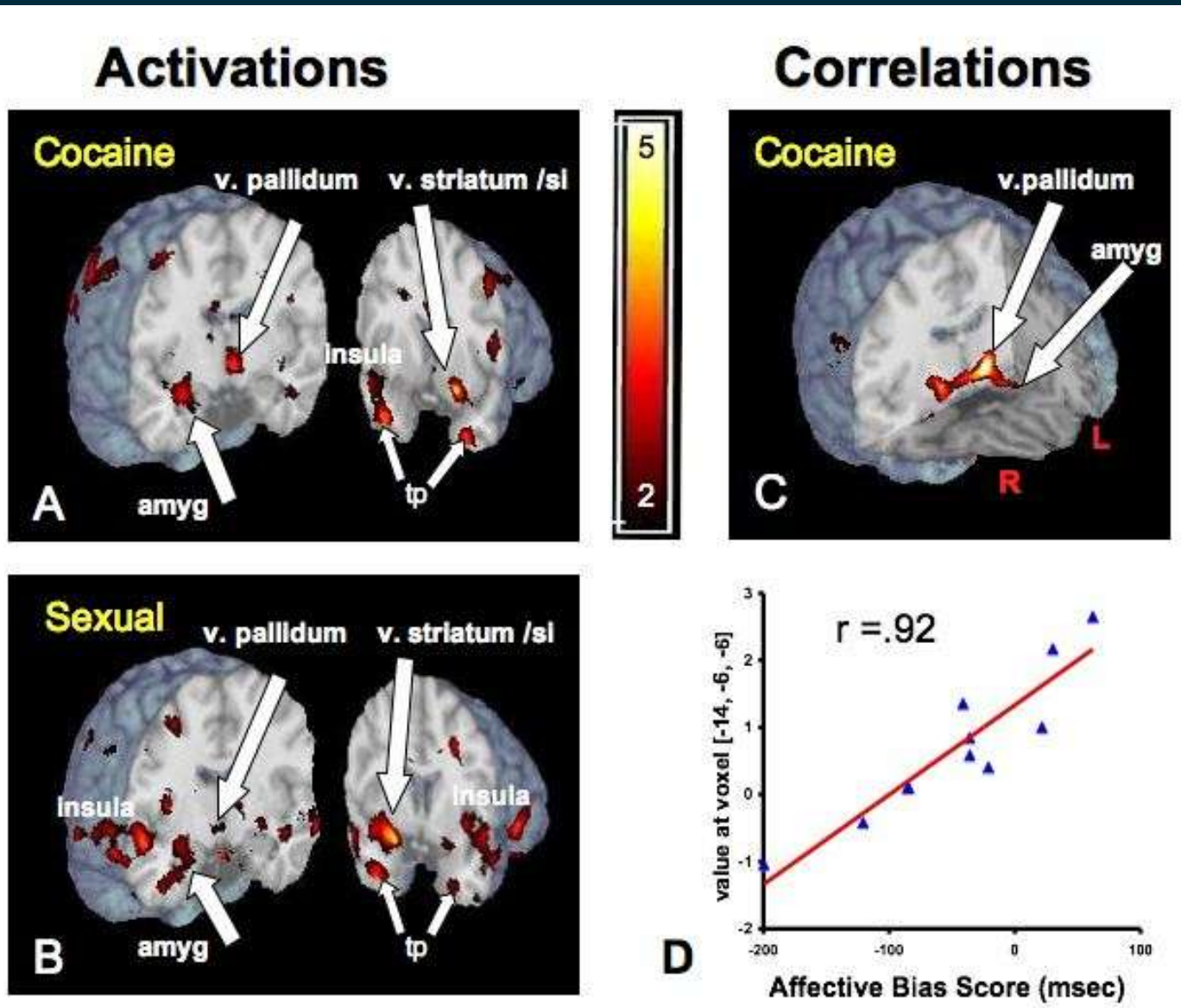
activate

amygdala

v. striatum

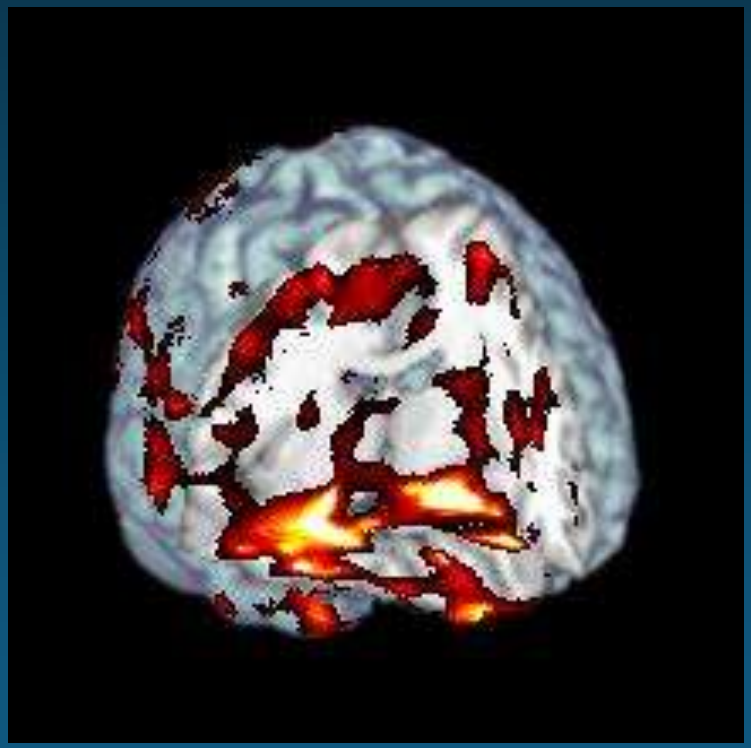
v. pallidum

Insula

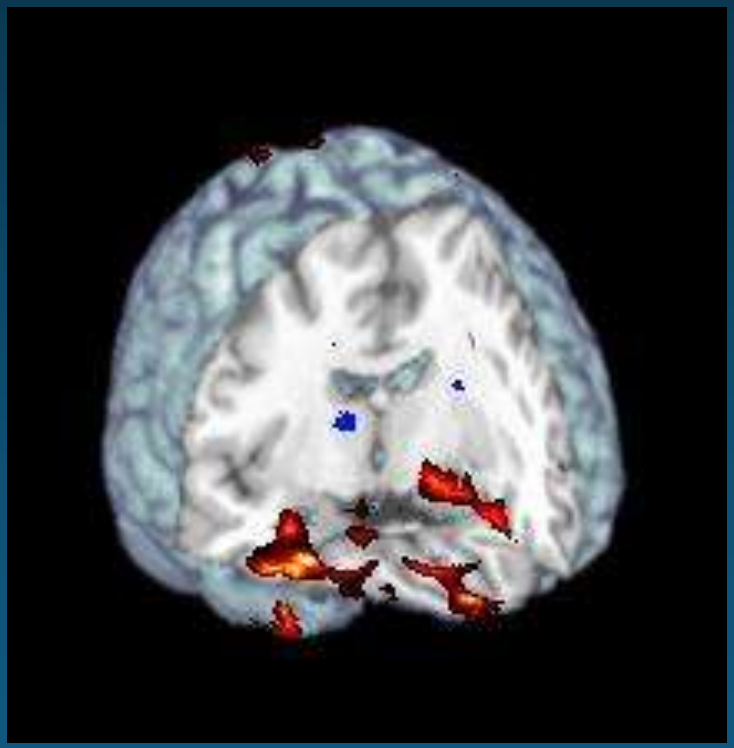

Activations
Correlations
Cocaine
v. pallidum
v. striatum /si
insula
amyg
tp
A
5
2
Cocaine
v.pallidum
amyg
L
R
C
Sexual
v. pallidum
v. striatum /si
insula
insula
amyg
tp
B
r =.92
value at voxel [-14, -6, -6]
3
2
1
0
-1
-2
-200
-100
0
100
Affective Bias Score (msec)
D

Baclofen blunts Amygdala Connectivity during 500 msec “SEEN” Cocaine Cues

Placebo



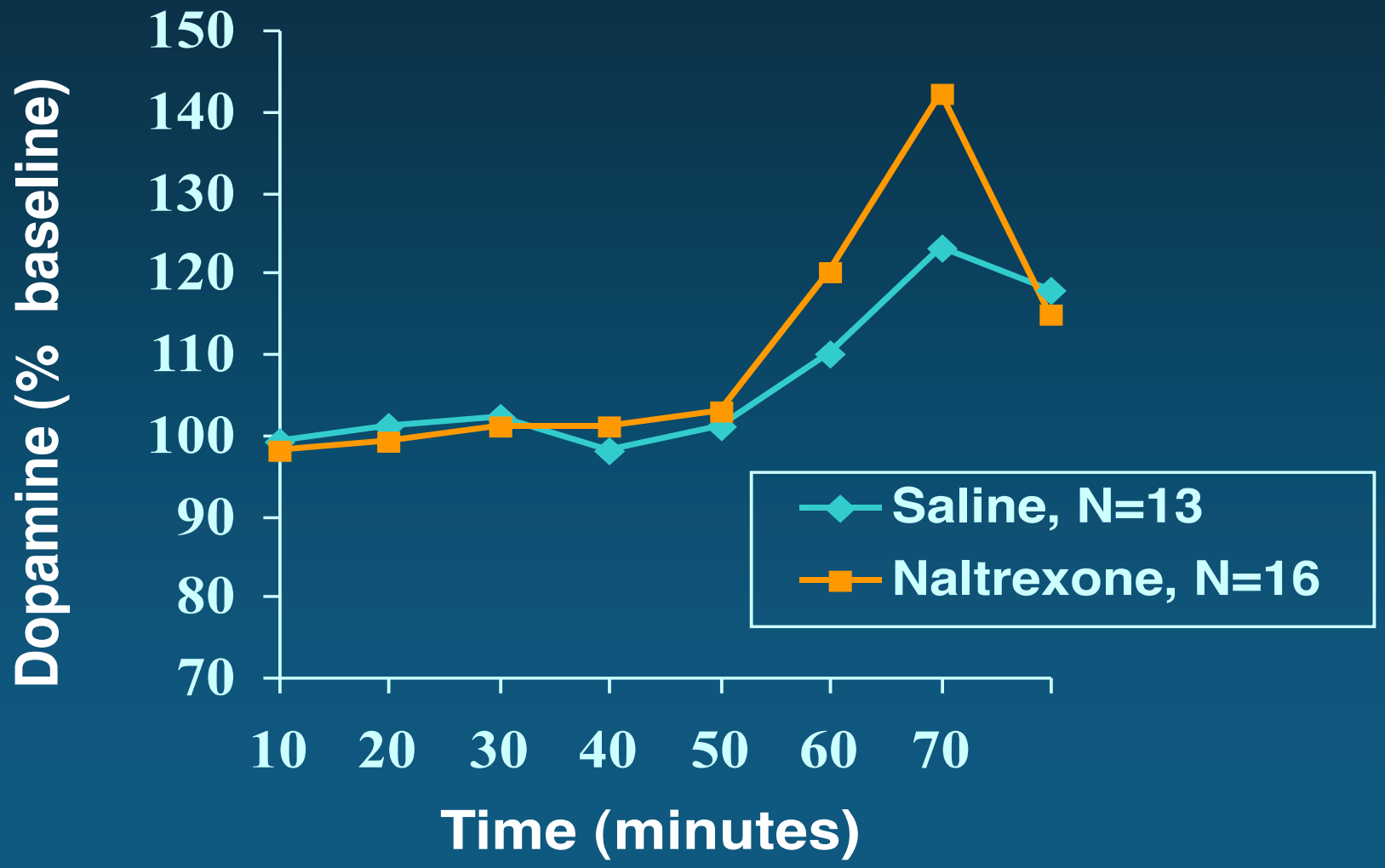
Baclofen



Second half of the task

[Drug 2; placebo n = 9; baclofen n =10]

Pre-Alcohol “Craving”



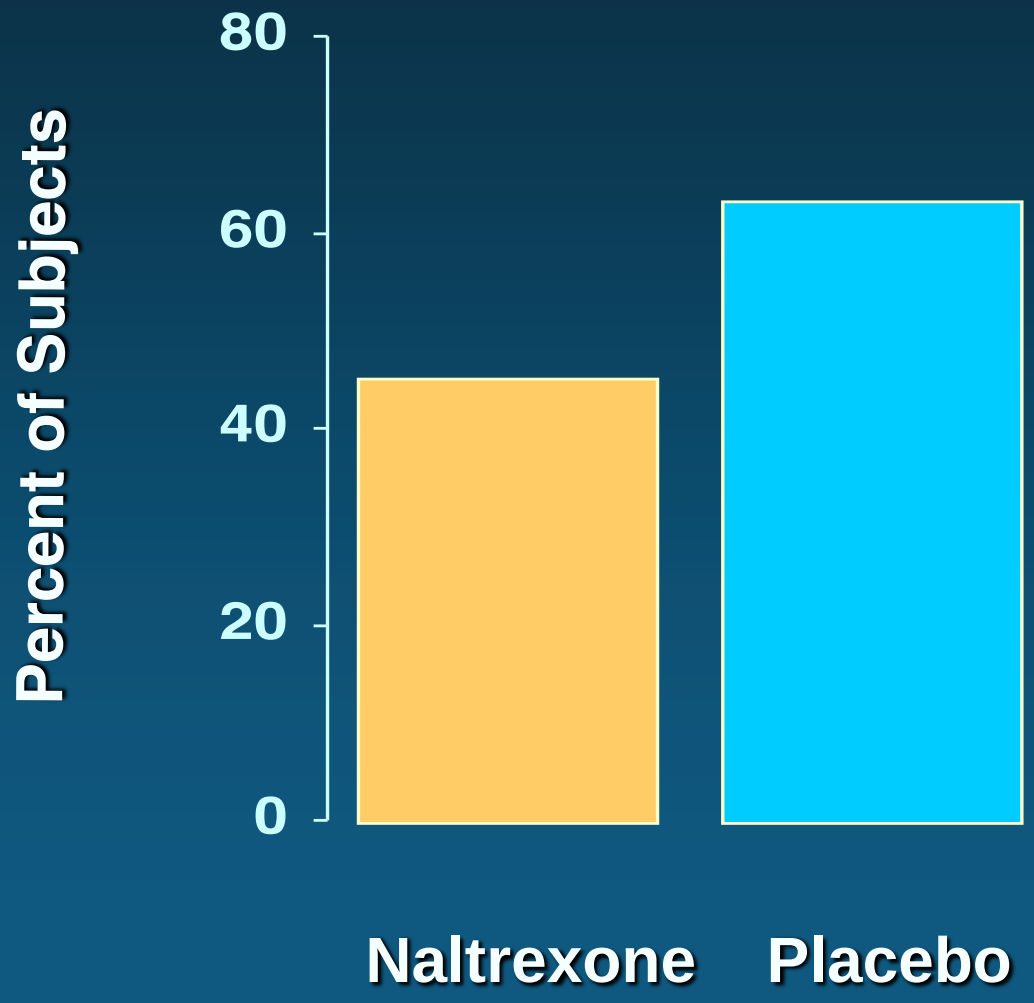
What is Transducer?

- Alcohol releases Beta endorphin in
  - Plasma (pituitary)
  - Lymphocyte cultures (HIV infectivity blocked by naltrexone
  - ? CNS

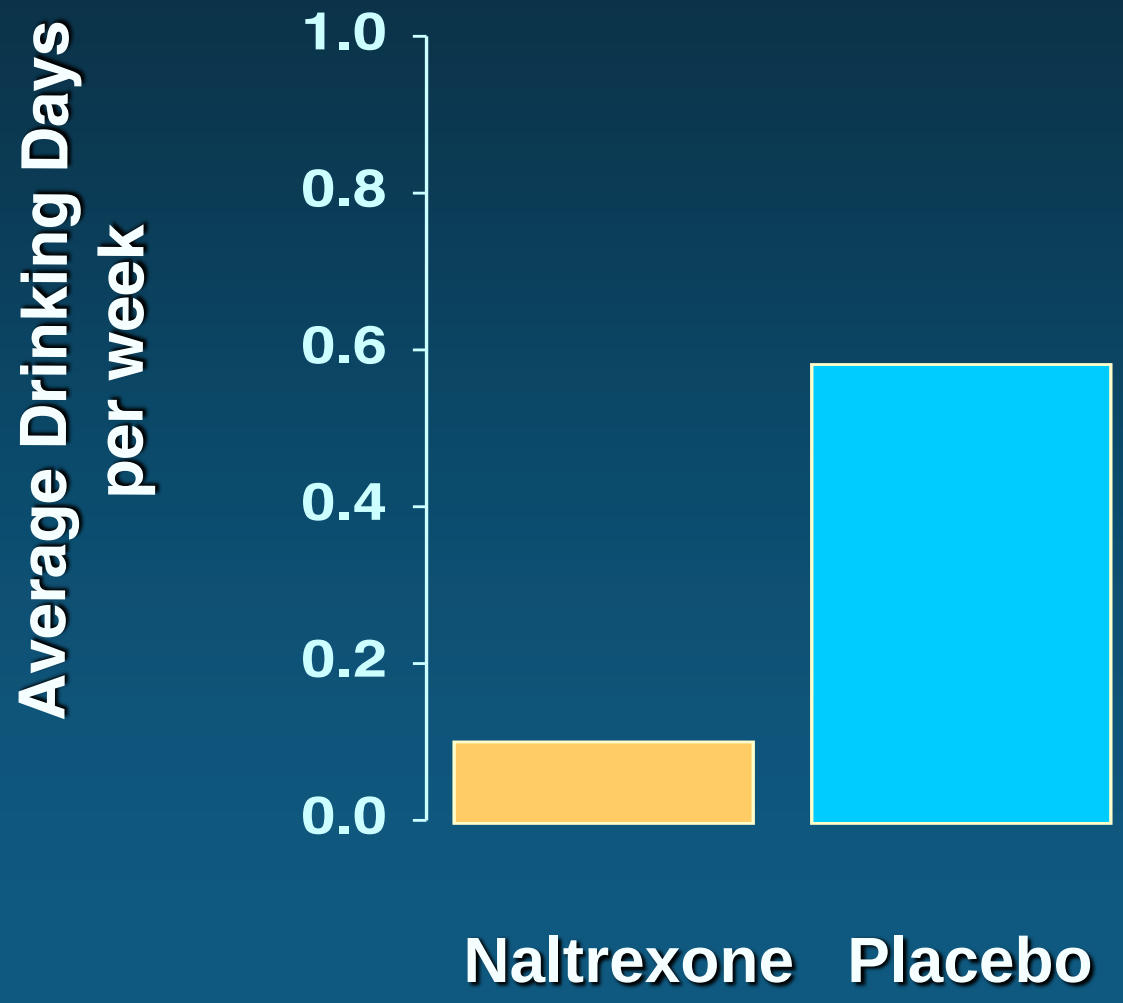
Post-Docs

- Tom Aronson, MD
- ✓Joseph Volpicelli, MD, PhD

Any Alcohol Drinking



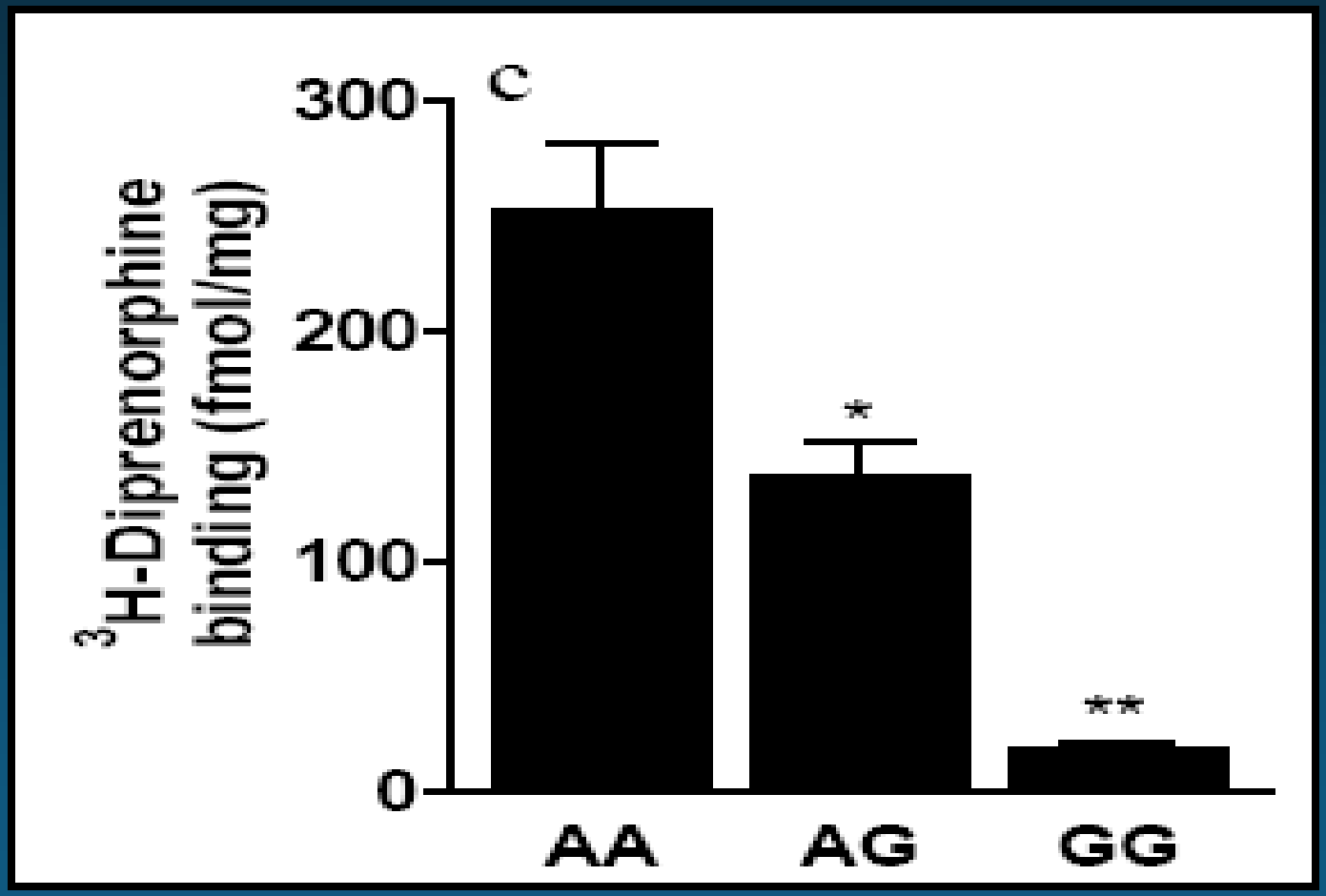
Days Drinking



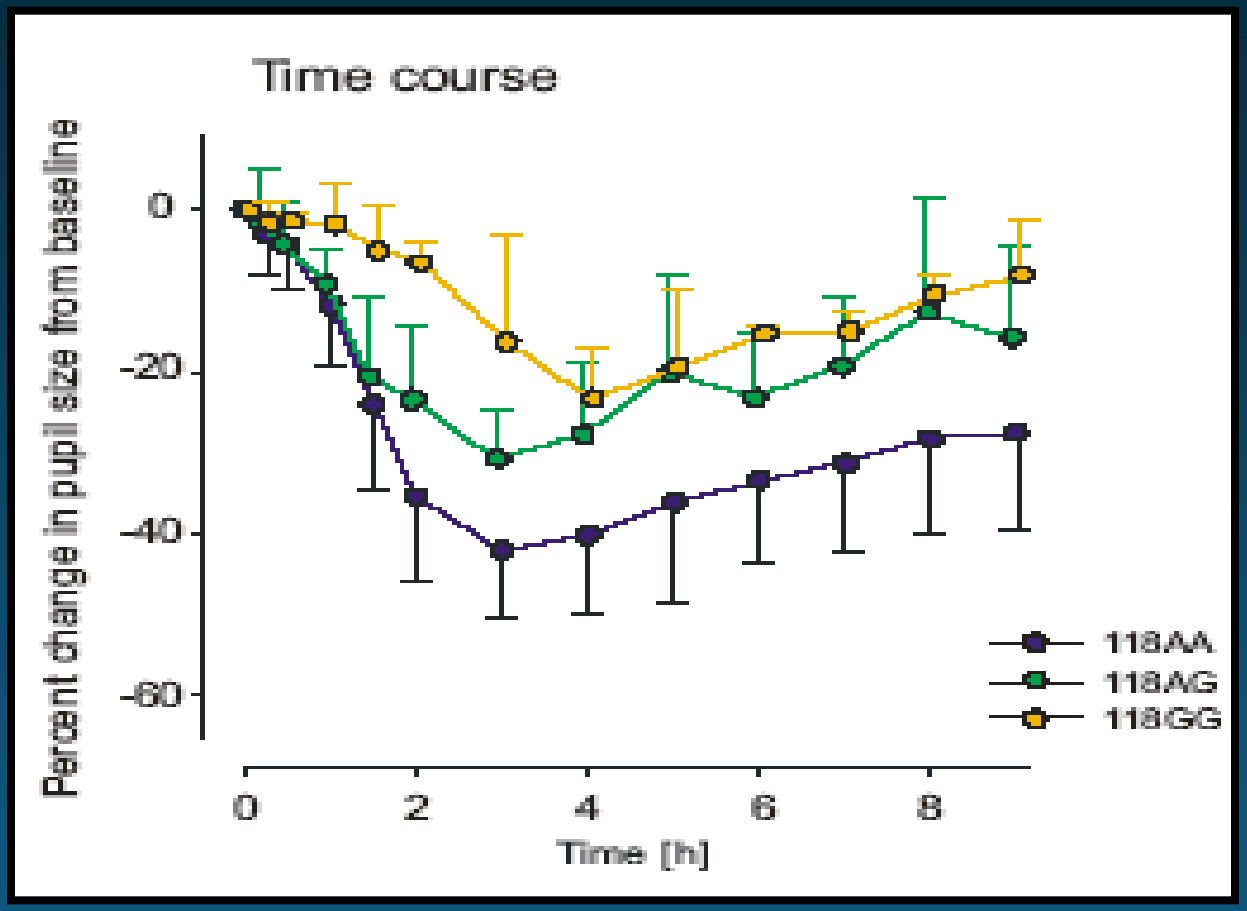
Measures of Craving

- 100 mm Visual Analog Scale
- Anton's Obsessive Compulsive Drinking Scale
- Alcohol Urge Questionnaire
- Penn Alcohol Craving Scale

OPRM1 A118G EFFECT ON TRANSLATION



Zhang et al, JBC, 2005



Lotsch et al, 2006

Naltrexone Affinity at Opioid Receptor Subtypes

	Receptor Binding Ki (nM)		
	Mu	Delta	Kappa
Antagonist:			
Naltrexone	0.37	9.4	4.8
Agonists:			
Morphine (m)	38	510	1,900
DADL-enke (d)	150	1.8	>10,000
(-)-EKC (k)	2.3	5.2	2.2

Schmidt, W.K., et al., *Drug Alcohol Depend*, 1985;14:339-362.

Receptor Blockade with Naltrexone (50mg)

Study	Naltrexone Dose	Time (hr)	Receptor Blockade (%)
Lee et al, 1988*	50 mg	48	91
		72	80
		120	48
		168	30

* Lee, MC, et al *J Nuc Med,* 1988, 29(7) 1207-1211

Receptor Blockade with Naltrexone in Alcoholics (50mg)

93% blockade of μ receptors, 24 hours, all SS
C ^{11} carfentanil

Variable (22.8 +/- 12%) blockade of ∂ receptors
C ^{11} N methyl naltrindole, 24 hrs.

* McCaul et al 2004

Alcohol Relapse

A. coming to treatment appointment with a blood alcohol concentration > 100 mg%

or

B. self report of drinking five or more days within one week

or

C. self report of five or more drinks during one drinking occasion

Possible Families of Risk Factors

- Level of response (LR)
- P3/disinhibition/ASPD/type 2/B
- Independent axis II disorders
- Endogenous Opioid System
- Alcohol metabolizing enzymes

Alcohol reward

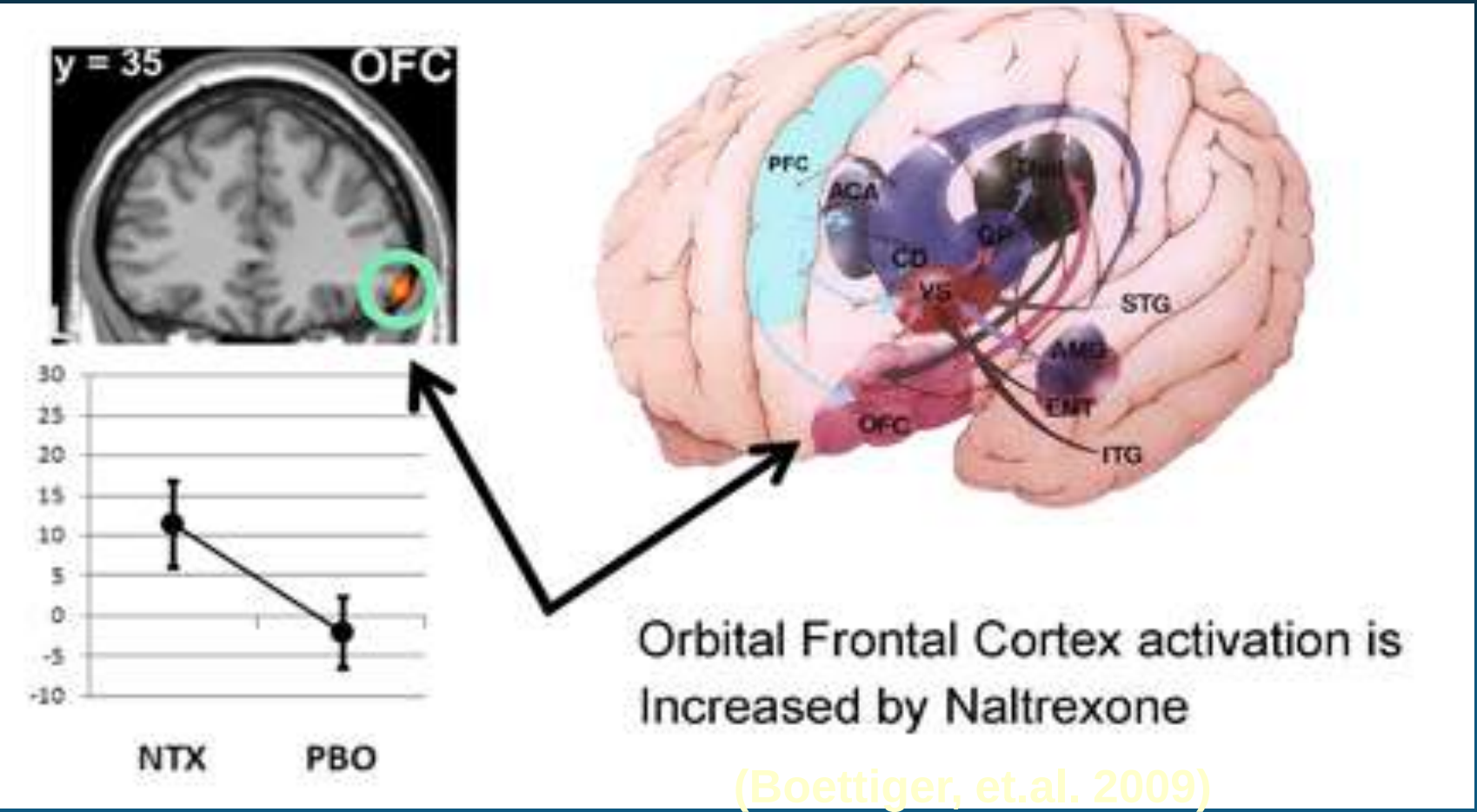
Sedating drug, facilitates GABAergic meds, no specific receptor

“dirty” drug- affects numerous receptor systems, directly or indirectly

Variable response to alcohol

- Alcohol seeking
  - 10 of 22 Rhesus (Altshuler)
  - 15% Vervets
  - 10-15% H. sapiens
- Less variable in rodents
- μ receptor knock outs will not self administer alcohol

Addiction Therapy may be related to activation of Frontal Cortex



(Crews and Boettiger et.al. 2009)

Alcohol - gene associations

genome scans - Phenotype association

Genotype - Behavior, (DSM IV)
1940s categories
- Endophenotype –
biological-
alcohol
response, imaging

Propose an RCT of an opiate antagonist in human alcoholics because of animal data ??

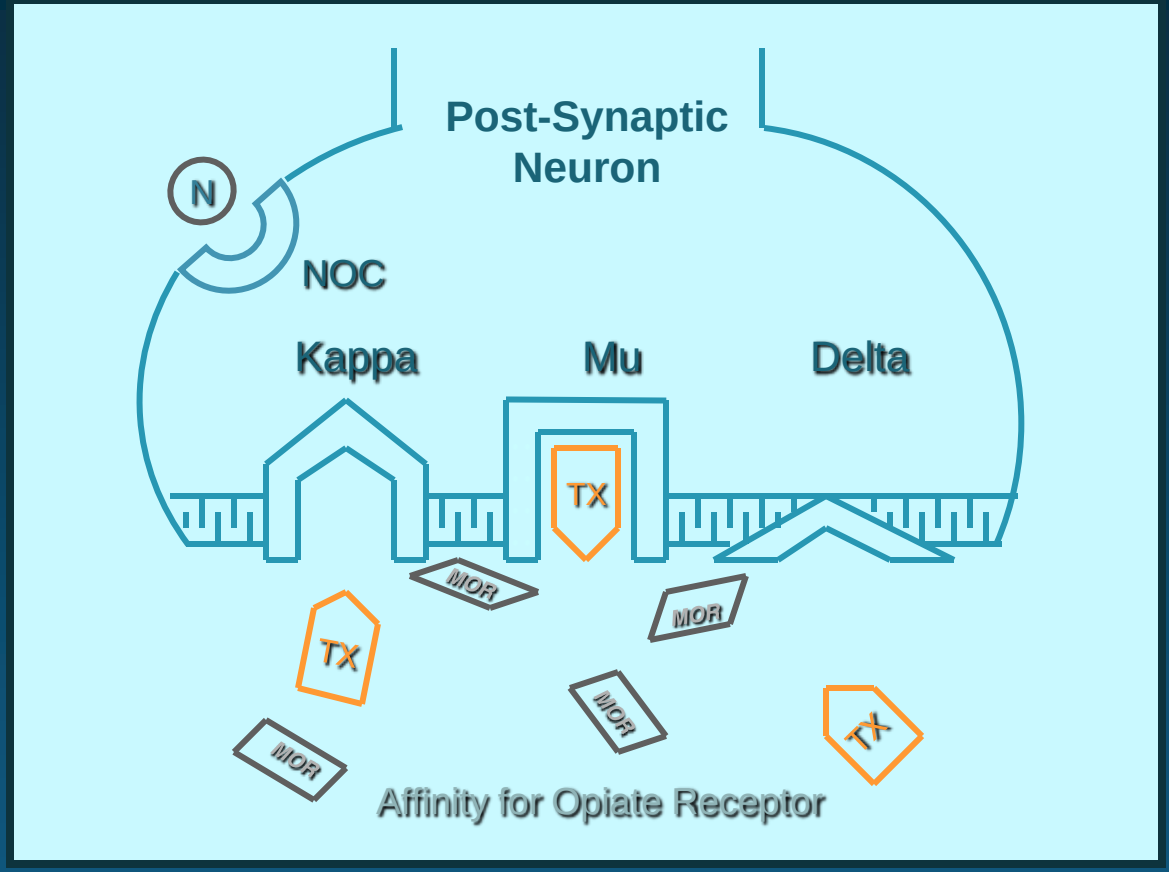
IND 1983

Begin open studies

50 mg dose based on experience with heroin

Philadelphia VA Hospital

Opiate Receptors

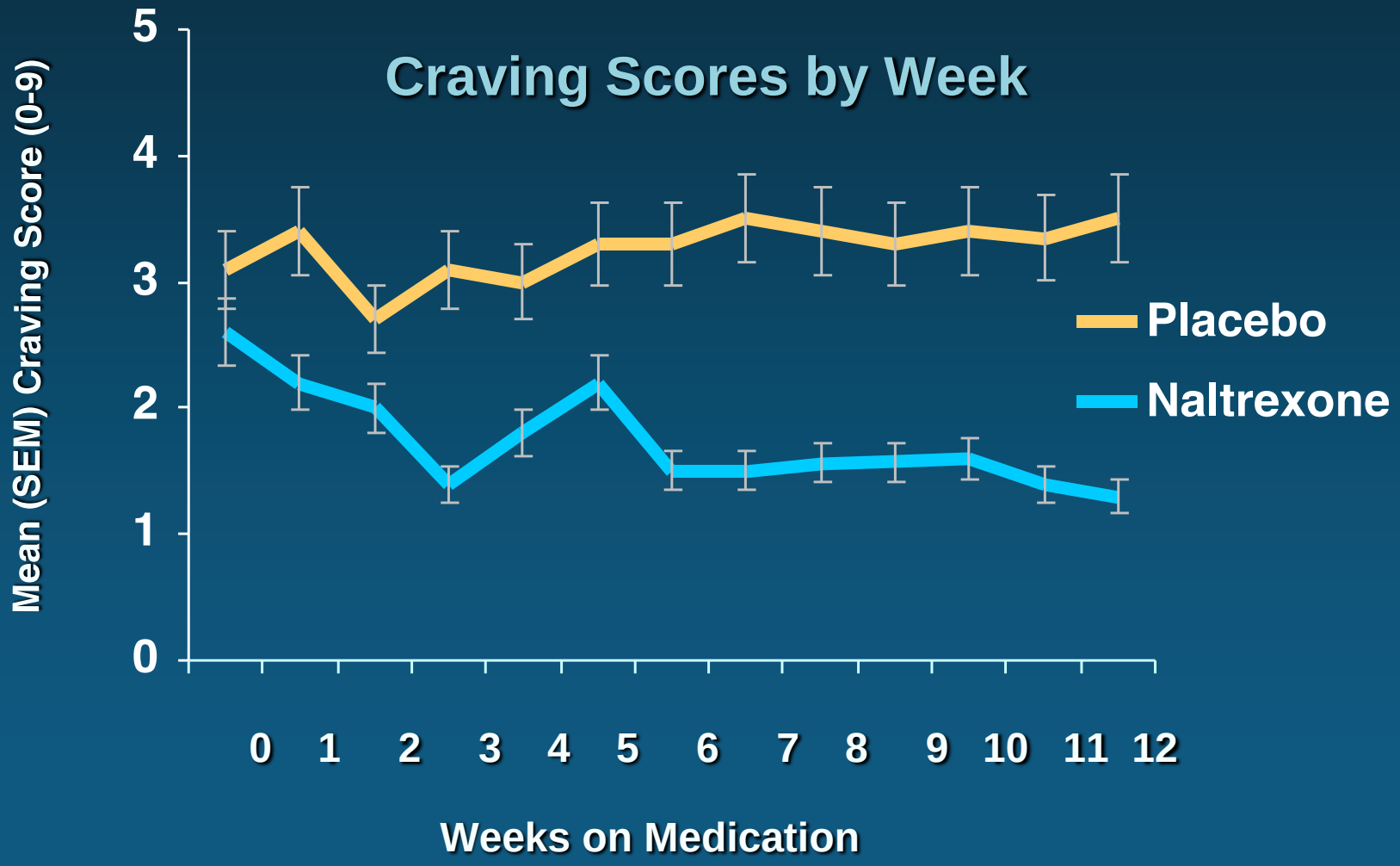


	Kappa	Mu	Delta
Naltrexone	406	108	54
Morphine	1	1	1

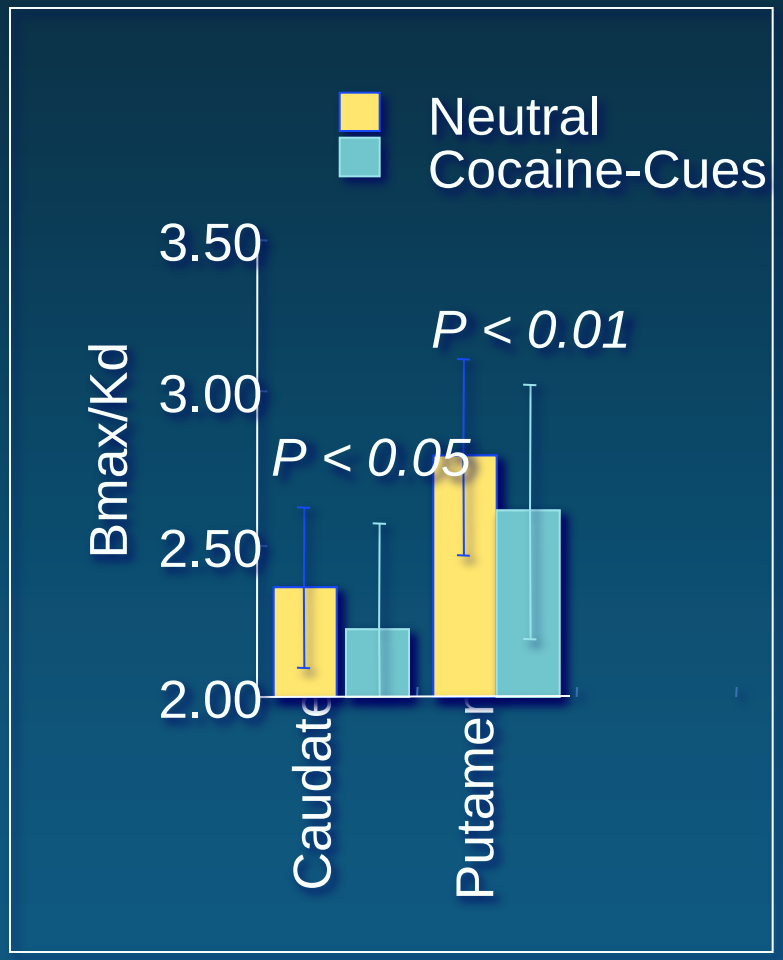
Double blind design

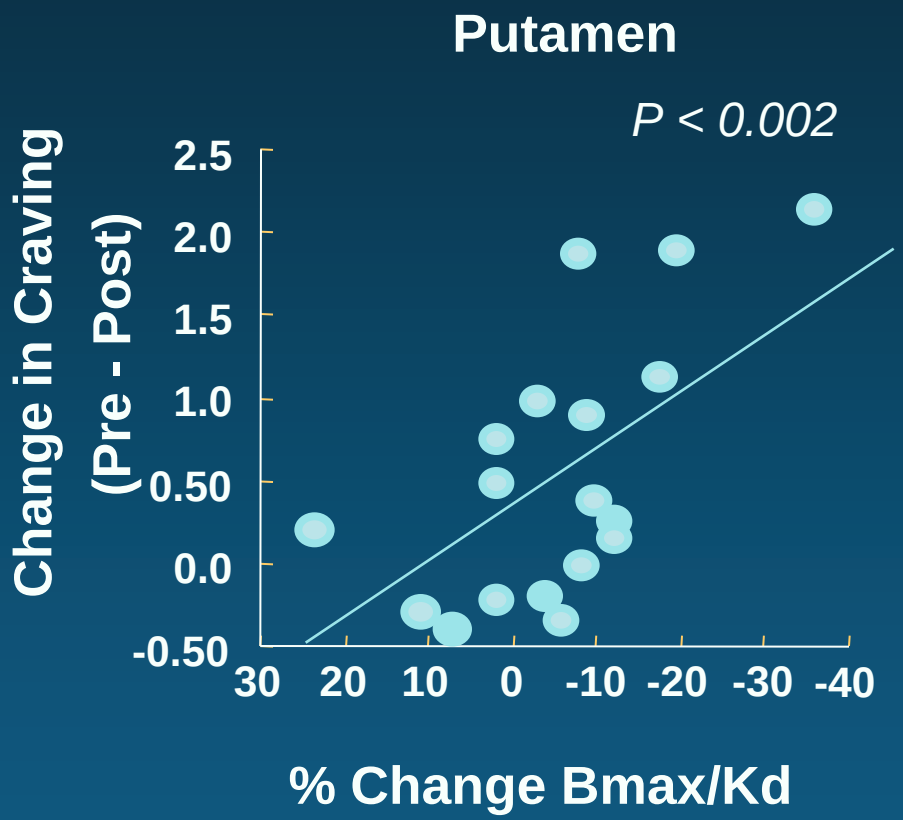
- 70 chronic alcoholics
- All received intensive day hospital, AA, psychotherapy
- Half received Naltrexone 50 mg/day
- Half received identical placebo
- Weekly craving scores
- “slips” measured (not a relapse)
- Relapse defined

Pharmacological Treatments for Alcoholism



Relationship between Cue-Induced Decreases in [11C]raclopride Binding and Cocaine Craving

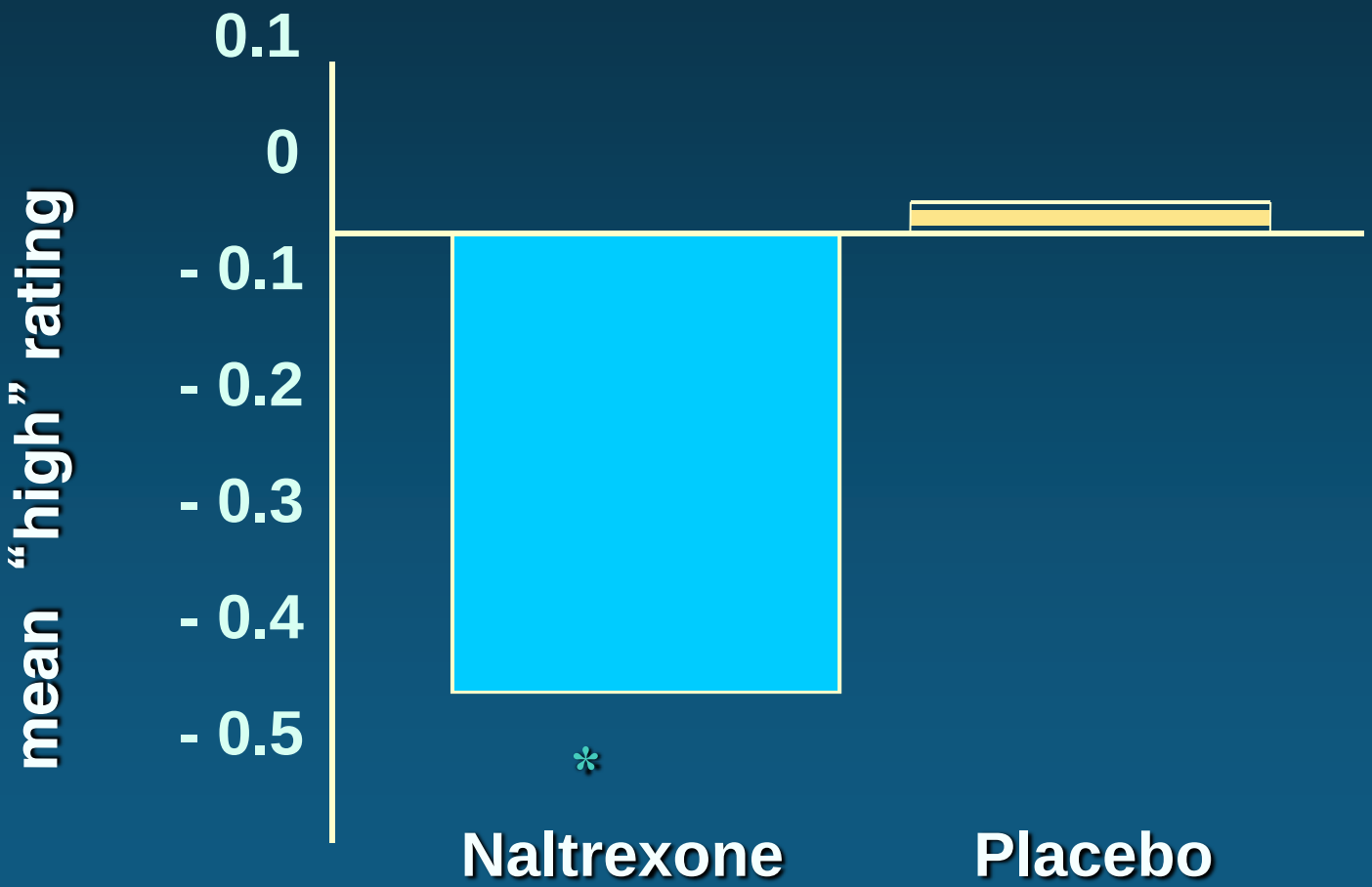




Volkow et al J Neuroscience 2006

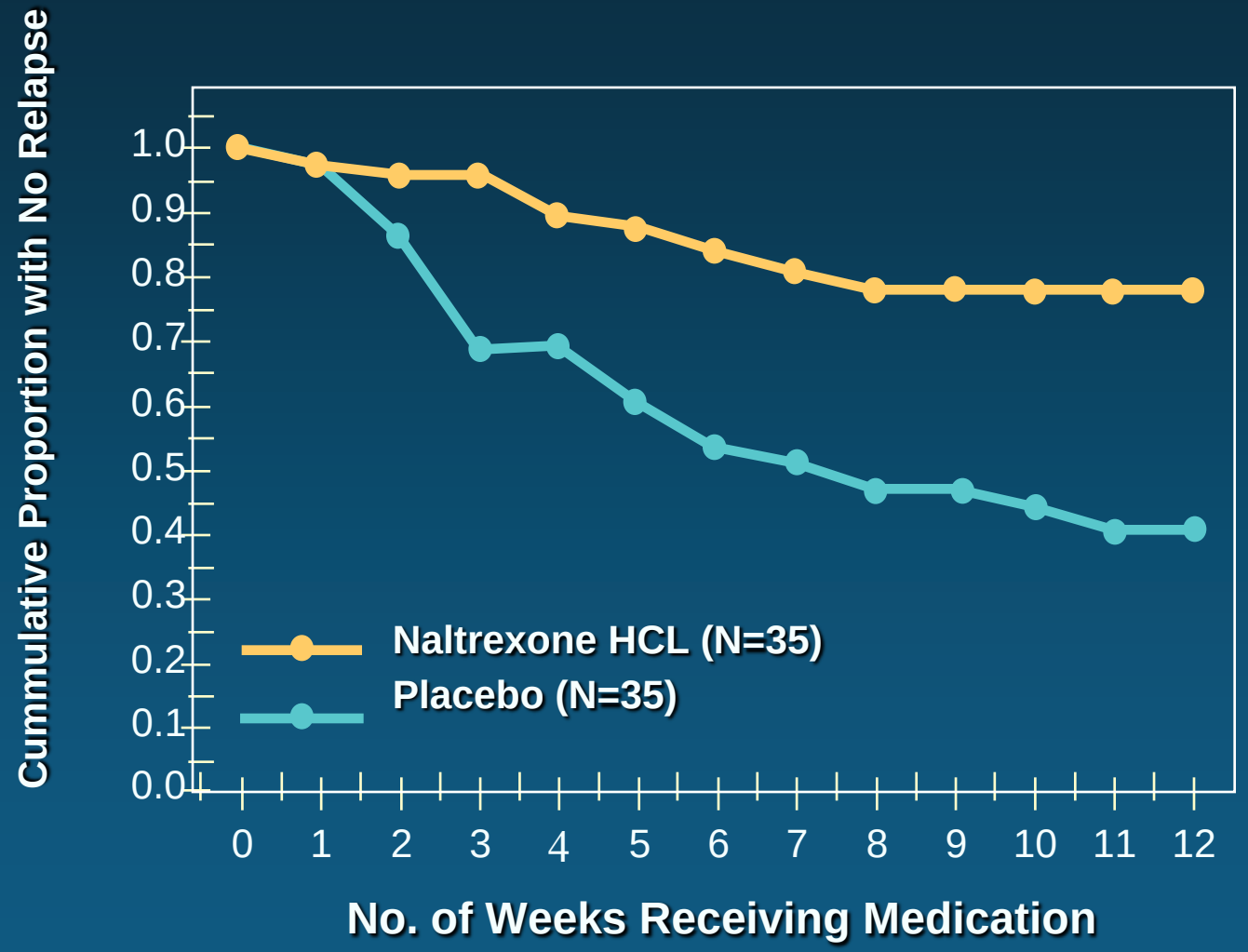
Cue-induced increases in DA were associated with craving

Subjective “high” in Naltrexone and Placebo Subjects



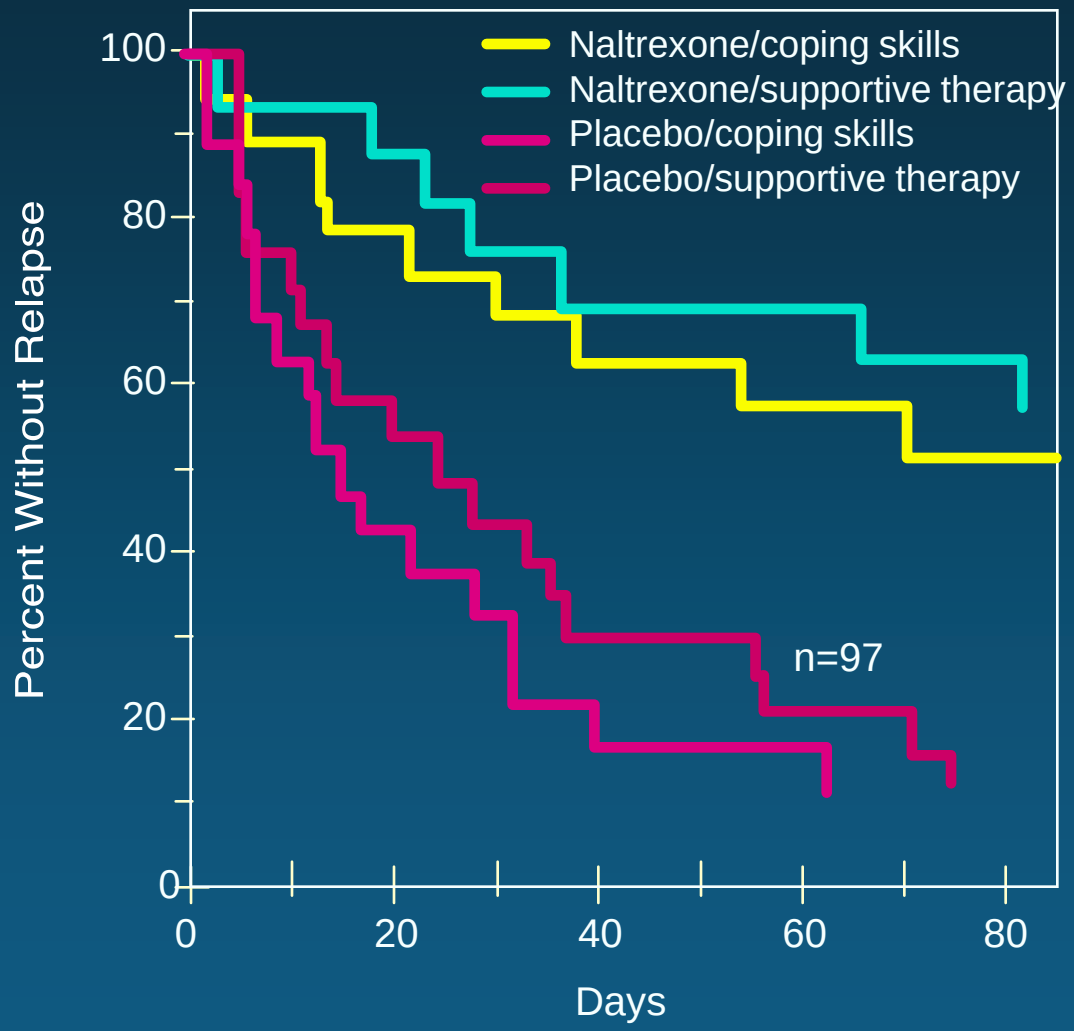
* p<.05

Non-relapse “Survival”



Volpicelli et al, Arch Gen Psychiatry, 1992; 49: 876-880

Rates of Never Relapsing According to Treatment Group (n=97)

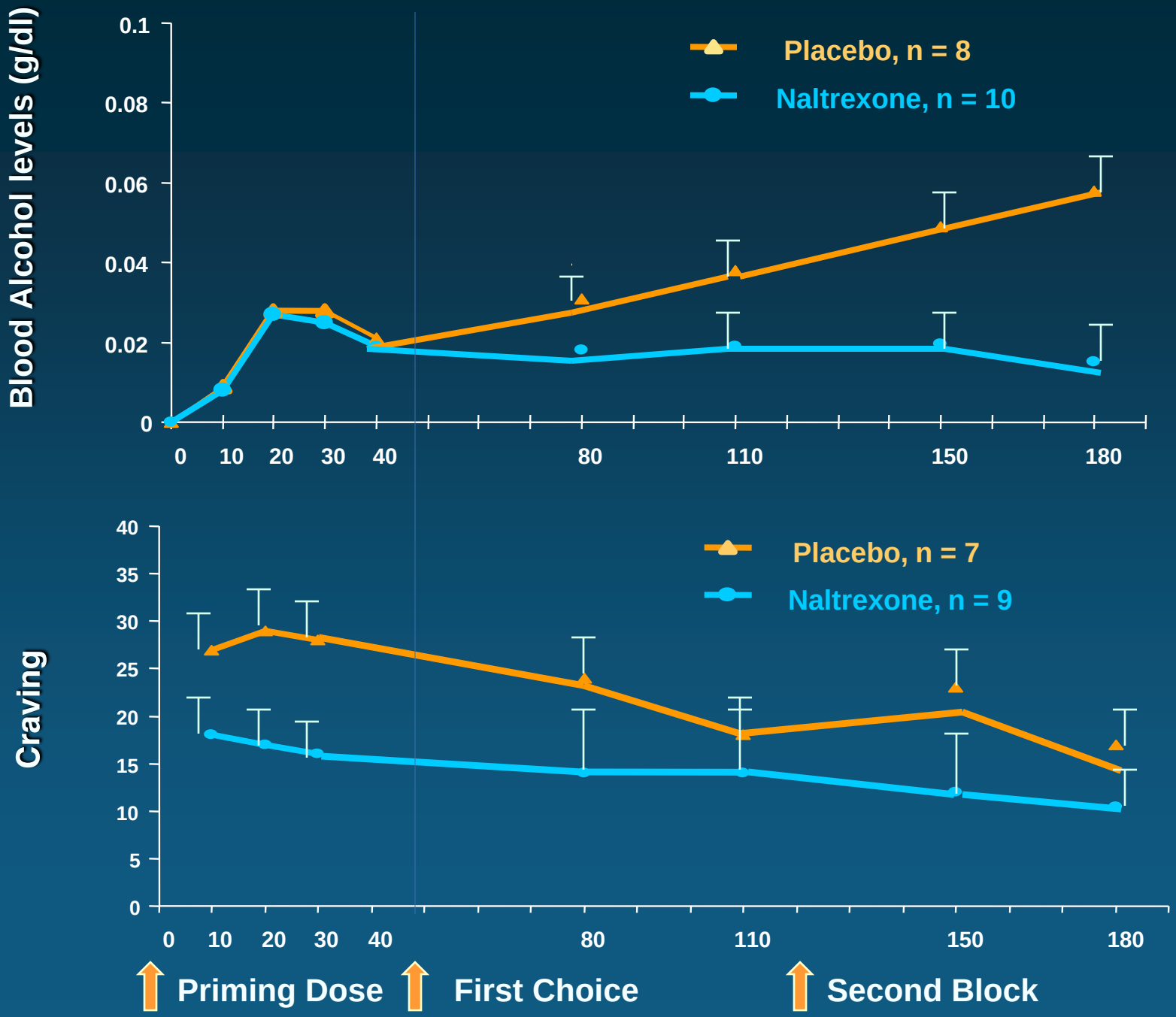


O'Malley et al, *Arch of Gen Psychiatry*, Vol 49, Nov 1992

Alcohol “PRIMING” in human, non-treatment seeking Alcoholics

O’ Malley et al

From the animal laboratory back to the clinic


Blood Alcohol levels (g/dl)
0.1
0.08
0.06
0.04
0.02
0
Placebo, n = 8
Naltrexone, n = 10
0
10
20
30
40
80
110
150
180
Craving
40
35
30
25
20
15
10
5
0
Placebo, n = 7
Naltrexone, n = 9
0
10
20
30
40
80
110
150
180
Priming Dose
First Choice
Second Block

Possible mechanisms of naltrexone effects

1. Block reward via endogenous opioid system
   - alcohol activates E.O.
   - Extinction of alcohol self-administration

2. Reduction in craving
   does not require extinction
   some treated alcoholics do not test by drinking

3. Direct effect of naltrexone on frontal executive fx
   Inc activity in r.lat.orbital gyrus during decision making (delay of reward) & decreased selection of immediate reward. (Boettiger et al 2009)

Studies supporting efficacy

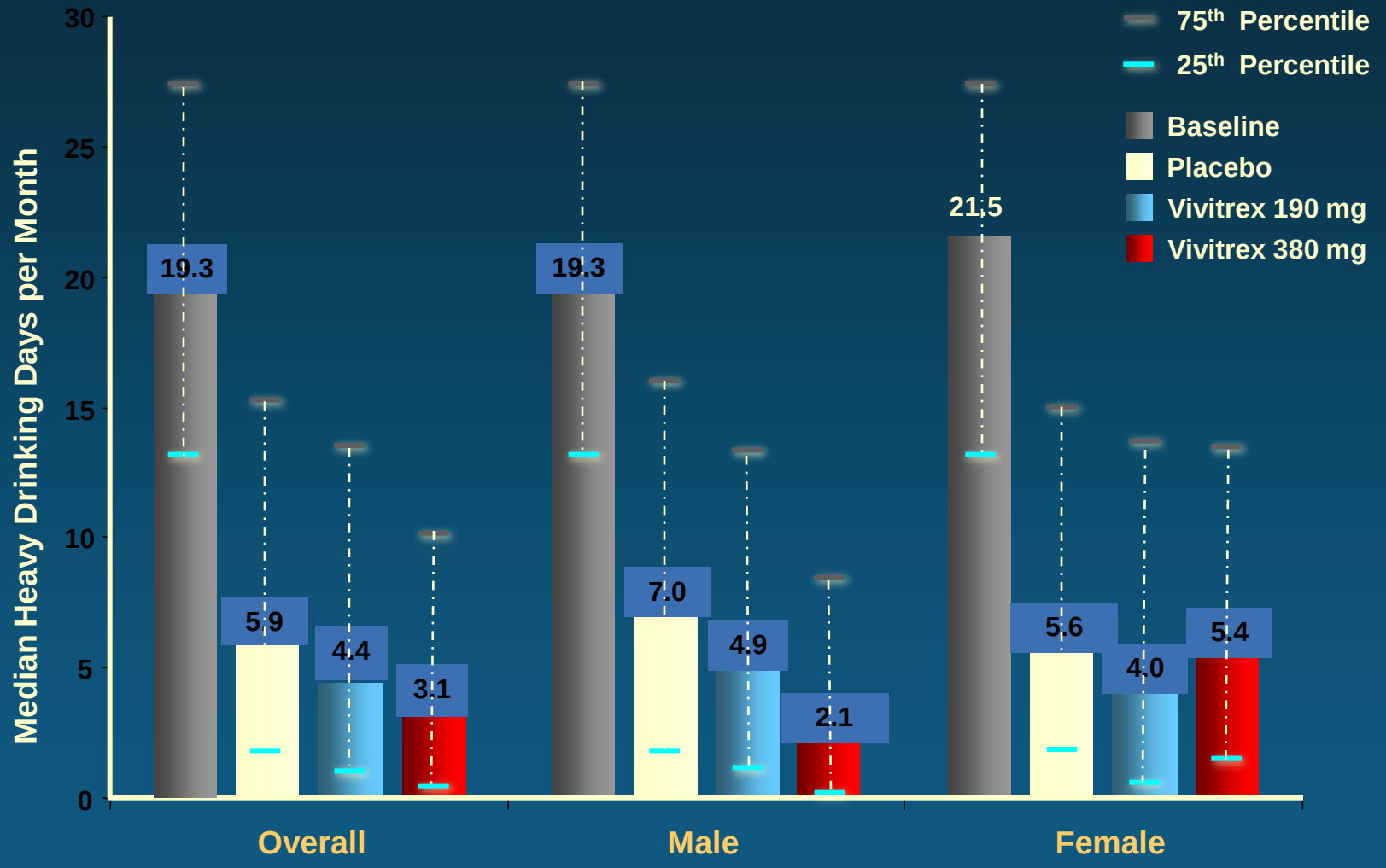
Study	# Ss	Notes
Volpicelli, et al 1992	70	None
O'Malley, et al 1992	97	None
Mason, et al 1994 [Nalmefene]	21	None
Oslin, et al 1997	44	Elderly
Volpicelli, et al 1997	97	None
Mason, et al 1999 [Nalmefene]	105	None
Kranzler, et al 1998	20	Depot
Anton, et al 2000	131	None
Chick, et al 2000 (UK)	169	Adherence
Monterosso, et al 2001	183	None
Morris, et al 2001 (Australia)	111	None
Heinala, et al 2001 (Finland)	121	Nonabstinent
Lee, et al 2001 (Singapore)	53	None
Kiefer et al 2003 (Germany)	160	None

Studies not supporting efficacy

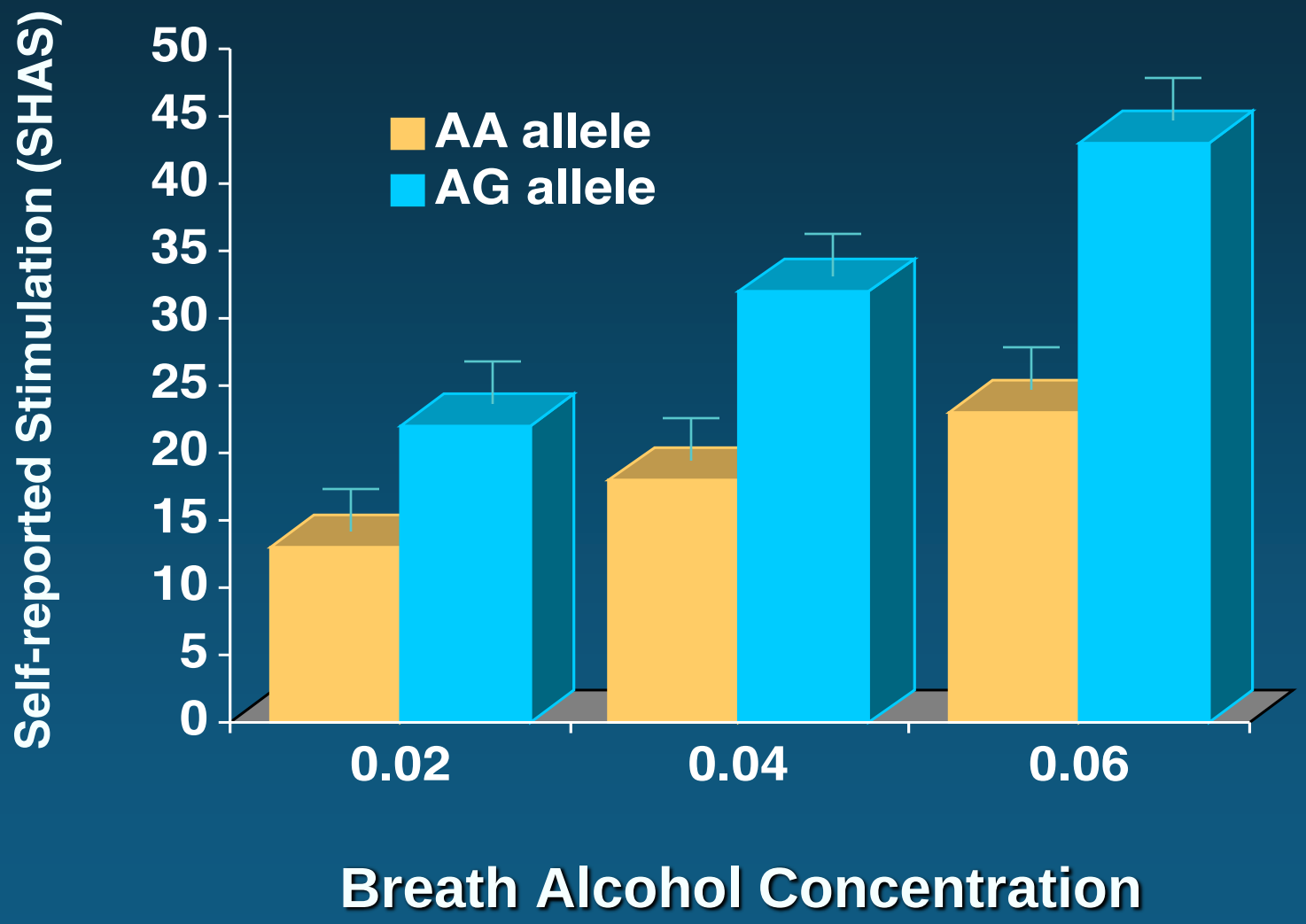
Study	# Ss	Notes
Kranzler, et al 1999	183	None
Krystal, et al 2002	627	None

Studies supporting efficacy			Studies not supporting efficacy		
Study	# Ss	Notes	Study	# Ss	Notes
Latt et al 2002	107	Family Prac			
Balldin et al 2003	118	None			
Feeney et al 2001	50	Hist. cont			
Rubio et al 2001	157	v. Acamp.			
Rubio et al 2002	30	Cont. Drink.			
Gastpar et al 2002	105	Neg. in self report Pos. GGT	Gastpar et al 2002	105	Neg. in self report Pos. GGT
Guardia et al 2002	202	Relapse			
Kranzler et al 2003	153	Heavy drinkers			
O'Malley et al 2002	18	Human lab			
Anton et al 2006	1383	RCT, depot			

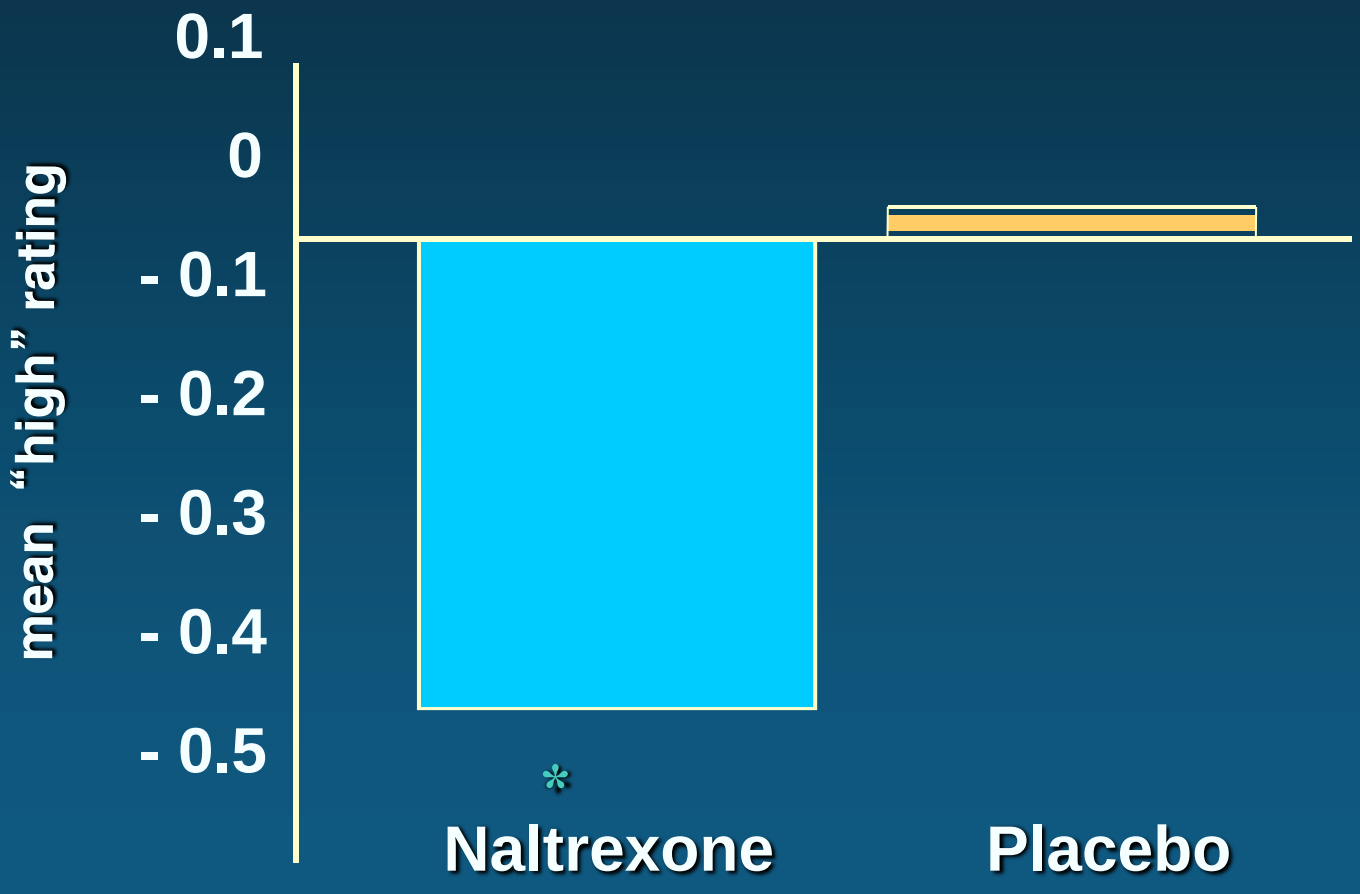
Results: Heavy Drinking Days



Alcohol effects by genotype



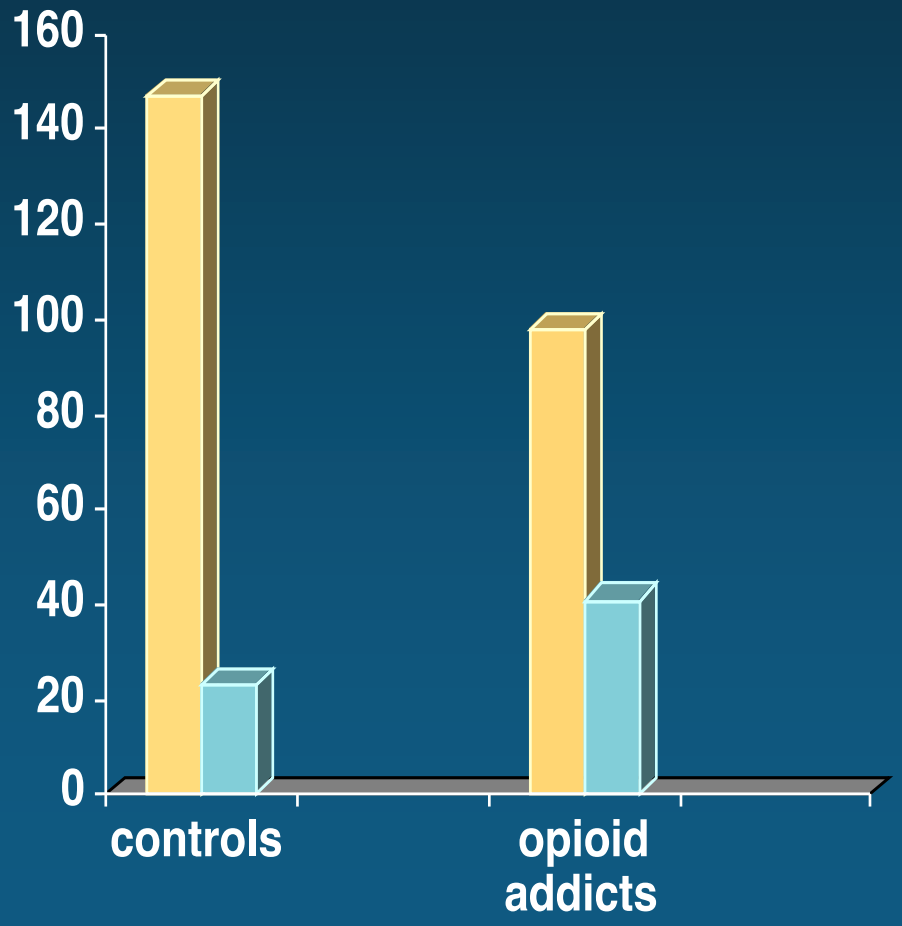
Subjective “high” in Naltrexone and Placebo Subjects



* p<.05

OPRM1 A118G and Opioid Dependence

Bart et al (Mol Psychiatry 9:547, 2004) studied opioid addicts in Sweden for A118G.



There was a significant (Chi squared = 13, p = 0.00025) increase in A/G, G/G genotype among opioid addicts.

The attributable risk for the G allele is ~ 18%, suggesting that ~ 18% of Swedish opioid addicts have disease in part due to the G allele.

Genetic Variables

Risk	Increase	Decrease
Low LR	+	
High LR		-
ASP	+	
ALDH2		-
G-Allele-μ op. (Stimulation)	+	
Environment	+	-