From Ignoring to Disease: Prospects for the Future

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Addiction

- Still largely ignored
- Dutch leadership: Flexible, visionary
- Much credit to Jan van Ree, reviews for medical students, role of endogenous opioids
- Animal models: Projection to clinic
- from Monkey, Rat, Mouse models to FDA approved treatment

Endogenous Opioid System

Opiate Receptors

- Simon 1973
- Pert & Snyder 1973
- Terenius 1973

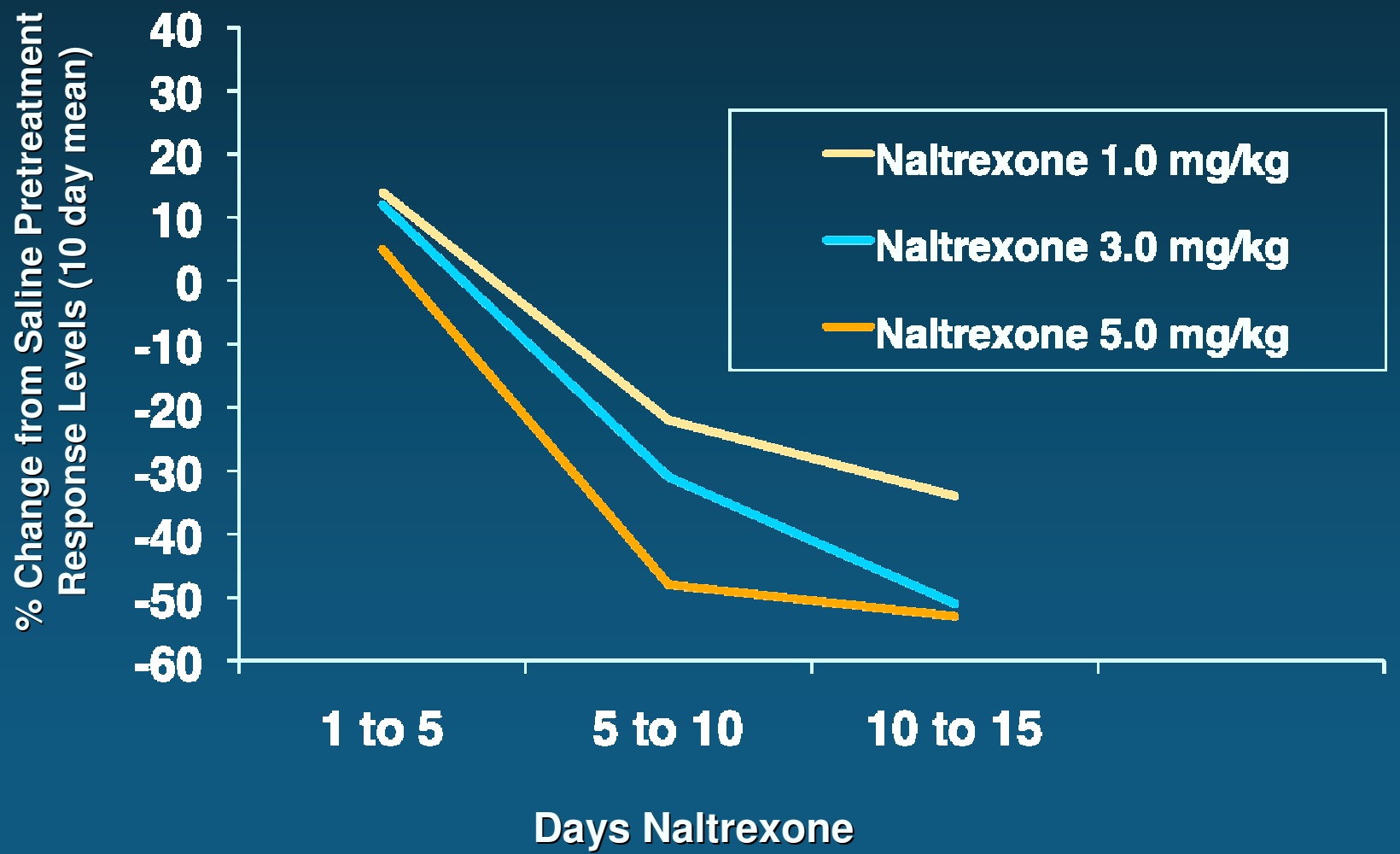
Enkephalin 1975 ∂

B-Endorphin μ

Dynorphin k

Nociceptin OFQ/NOC 1990s

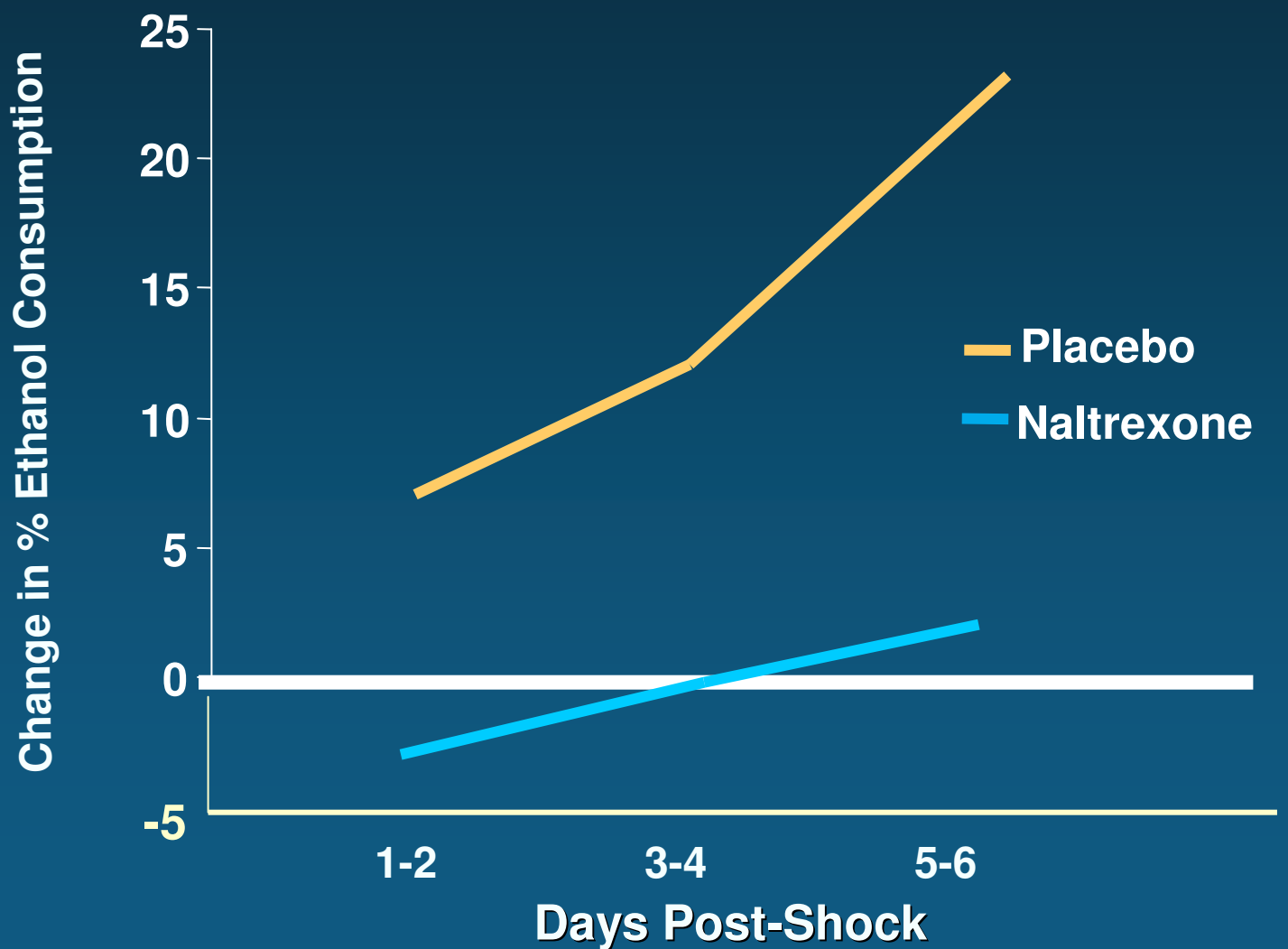
Naltrexone decreases Alcohol preference*



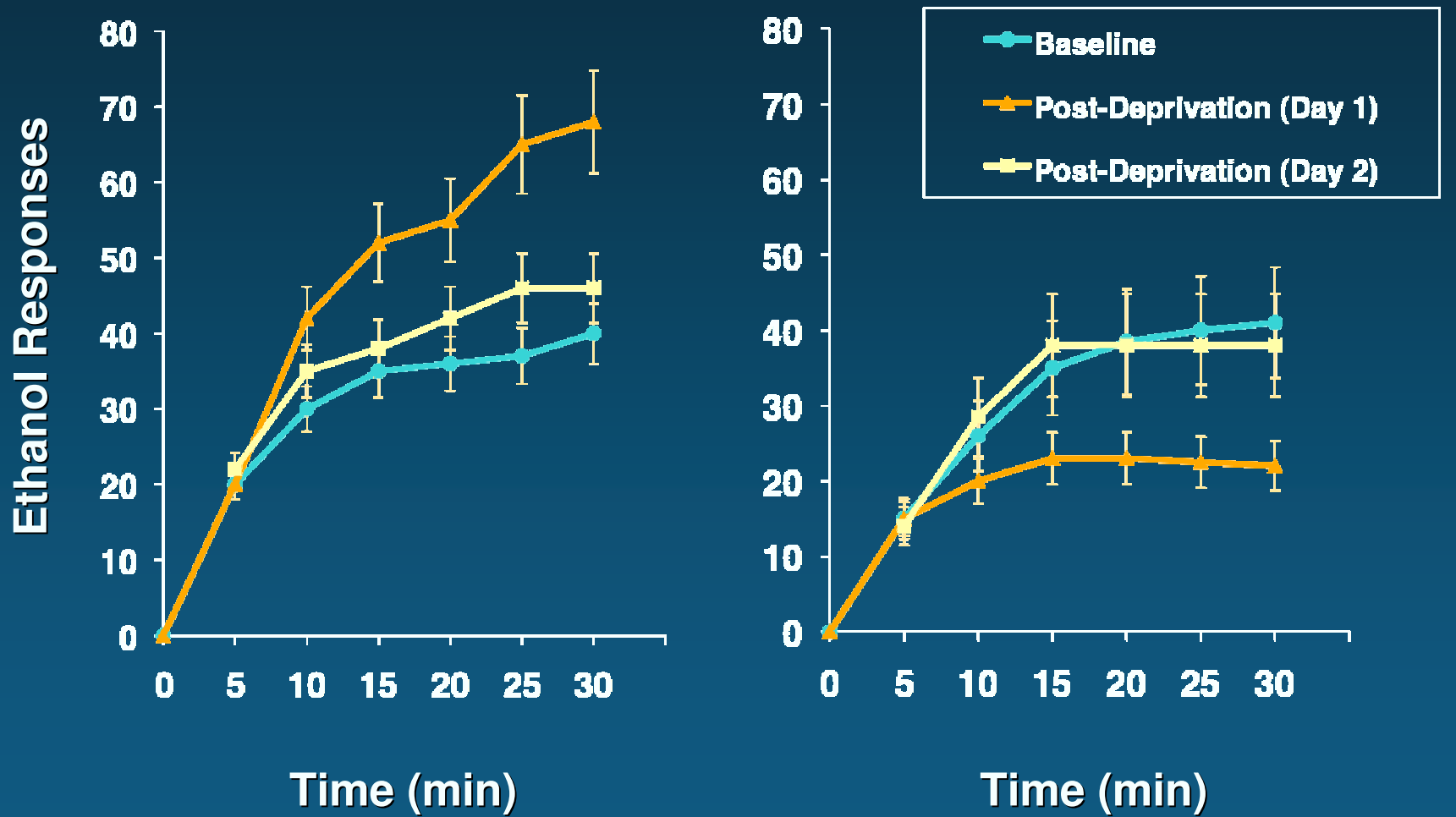
* Altshuler 1980


EL E10-10SF
R SHOCK FLOOR
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



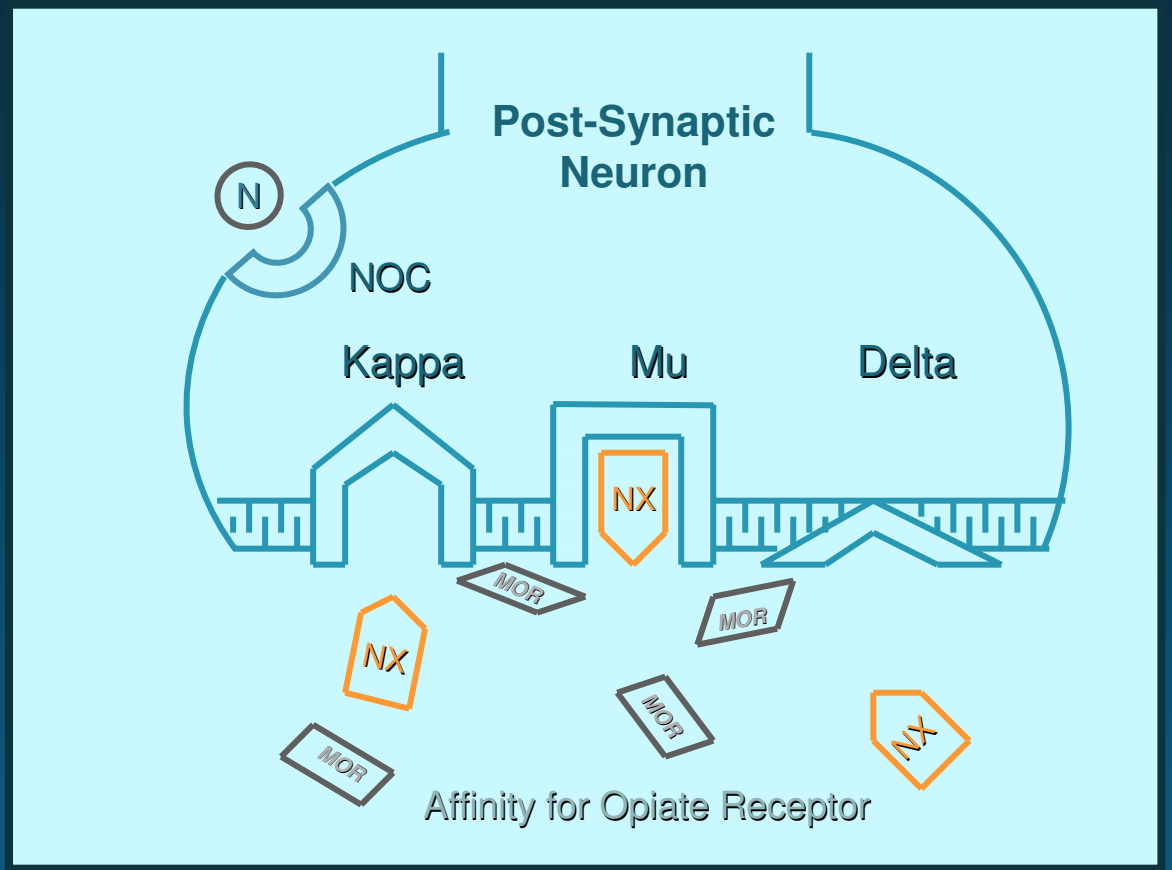
Saline .25 mg/kg Naltrexone



Hypothesis:

alcohol causes the release of endogenous opioids which are "required" for DA release (assoc. Reward) in response to alcohol

Opiate Receptors



Naltrexone Affinity at Opioid Receptor Subtypes

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

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

Propose an RCT of Heroin med in human alcoholics because of animal data ??

IND 1983

Begin open studies (1983-85)

50 mg dose based on experience with heroin

VA Medical Research Center Grant

Not supported by Pharma or by NIAAA

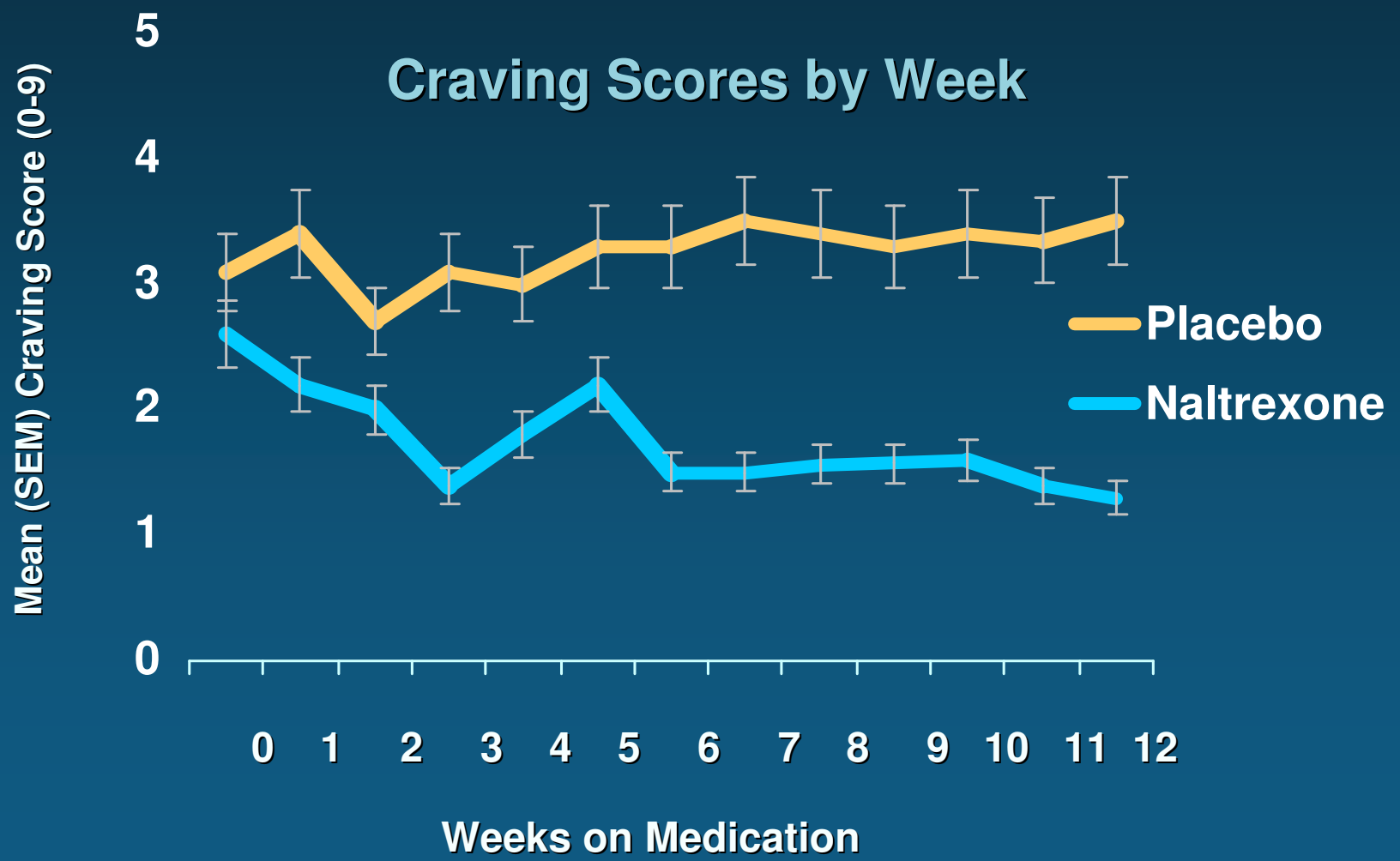
1986 Begin VA Trial

- Based solely on animal data
- Resident and postdoctoral fellow
- Joe Volpicelli

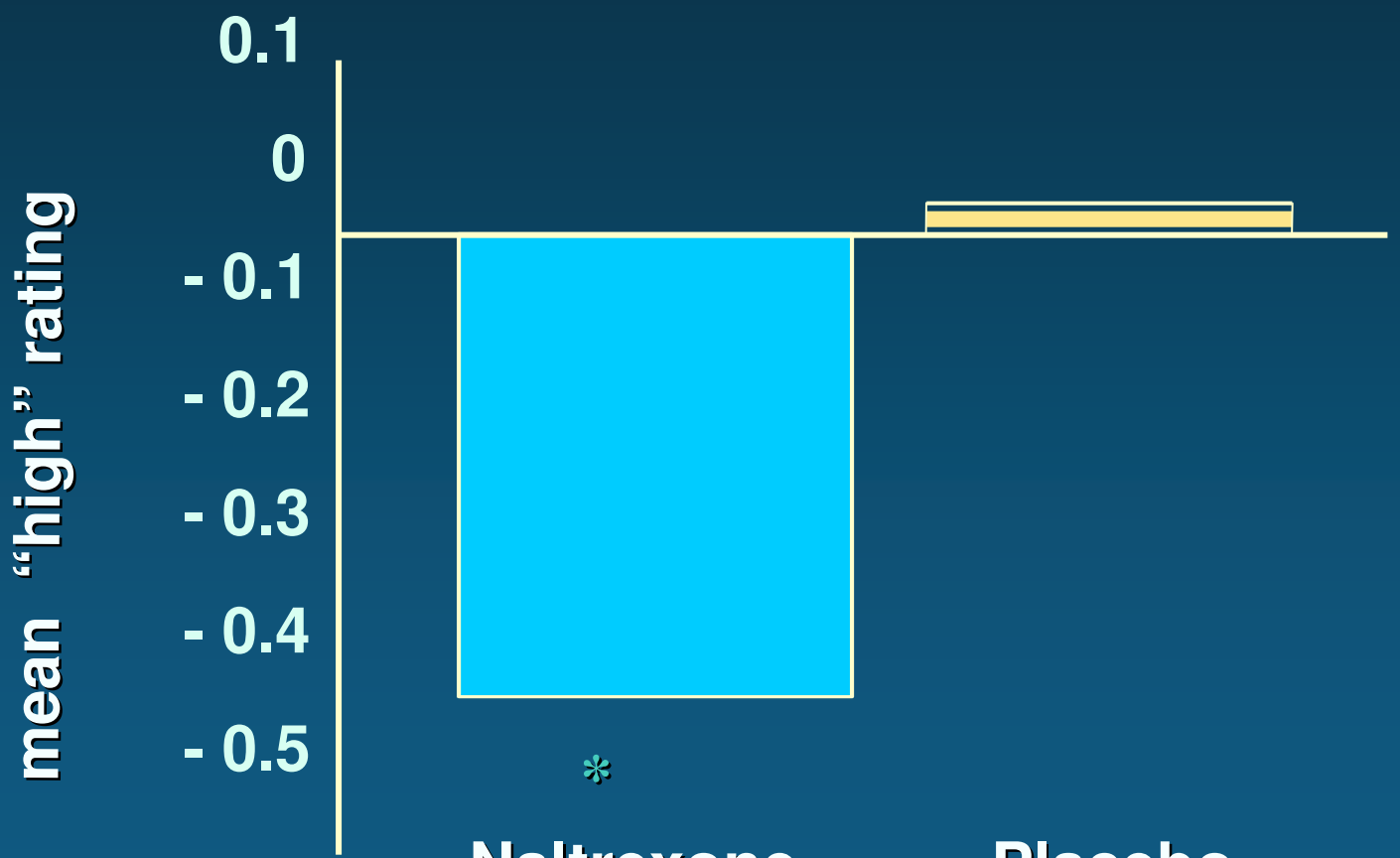
Double blind design

- 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



Subjective "high" in Naltrexone and Placebo Subjects



* p<.05

Alcohol Relapse

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

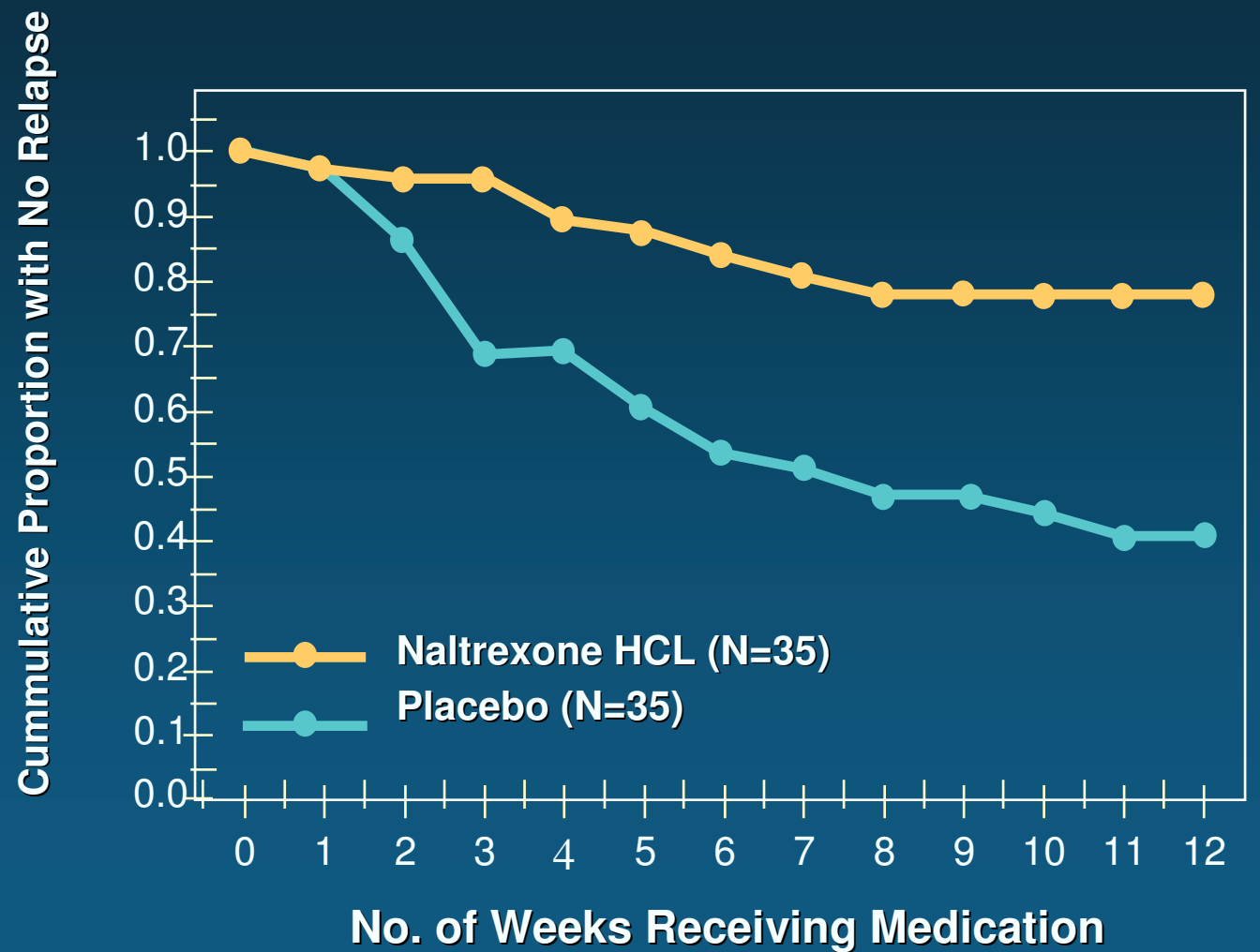
or

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

or

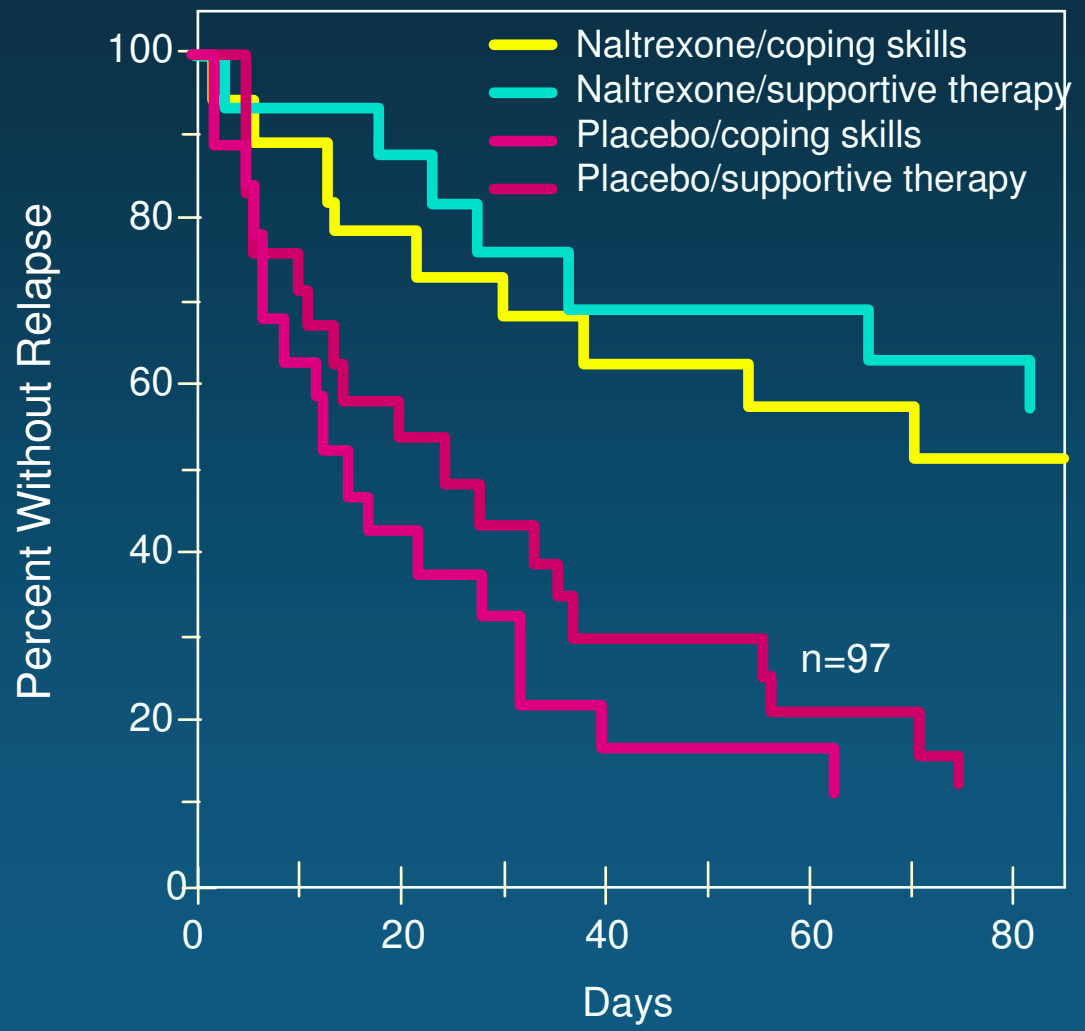
C. self report of five or more drinks during one drinking occasion

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

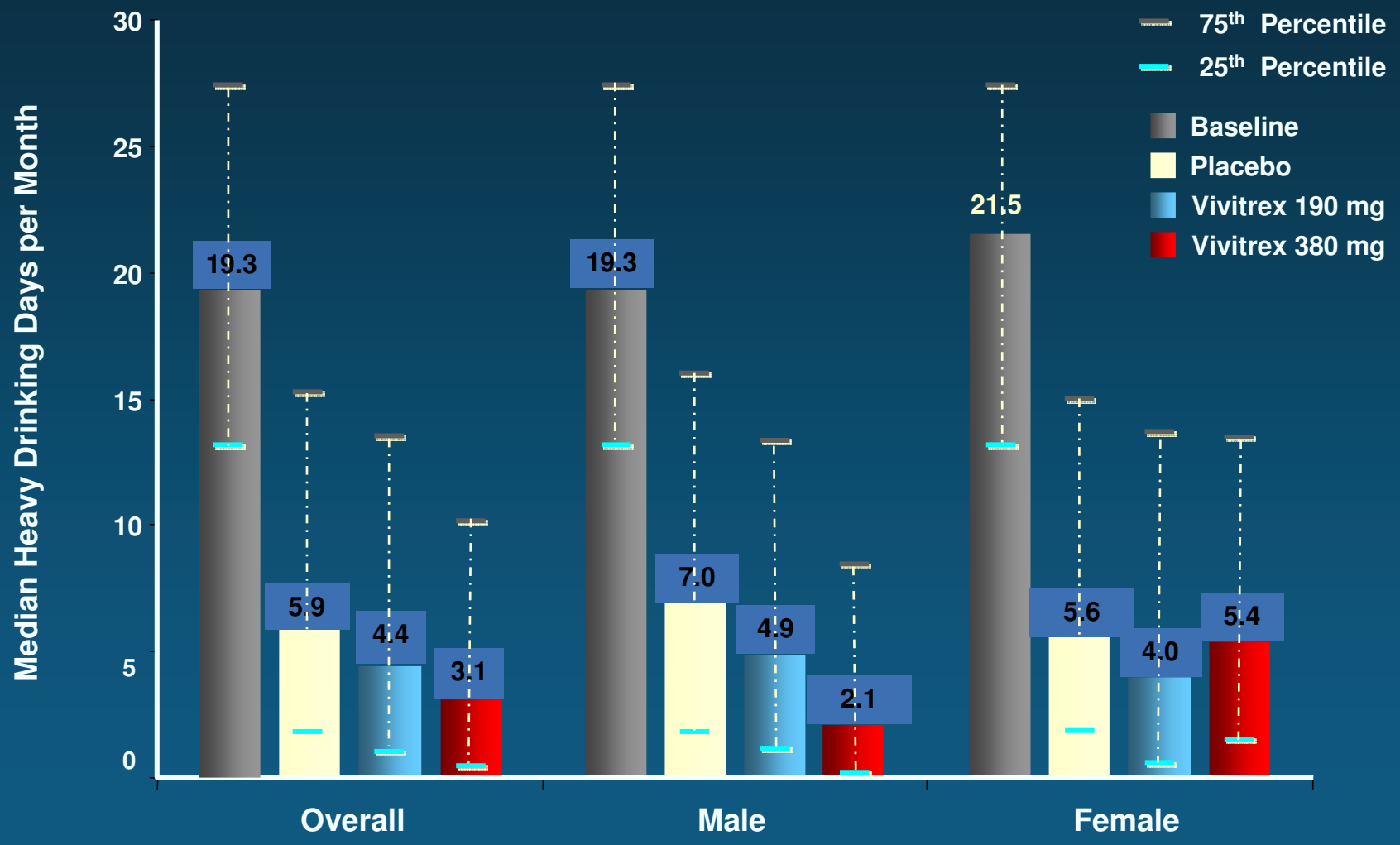
Study	# Ss	Notes
Volpicelli, et al 1992	70	None
O'Malley, et al 1992	97	None
Mason, et al 1994 [Nalmefene]	21	None
Oslin, et al 1997	44	Elderly
Volpicelli, et al 1997	97	None
Mason, et al 1999 [Nalmefene]	105	None
Kranzler, et al 1998	20	Depot
Anton, et al 2000	131	None
Chick, et al 2000 (UK)	169	Adherence
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

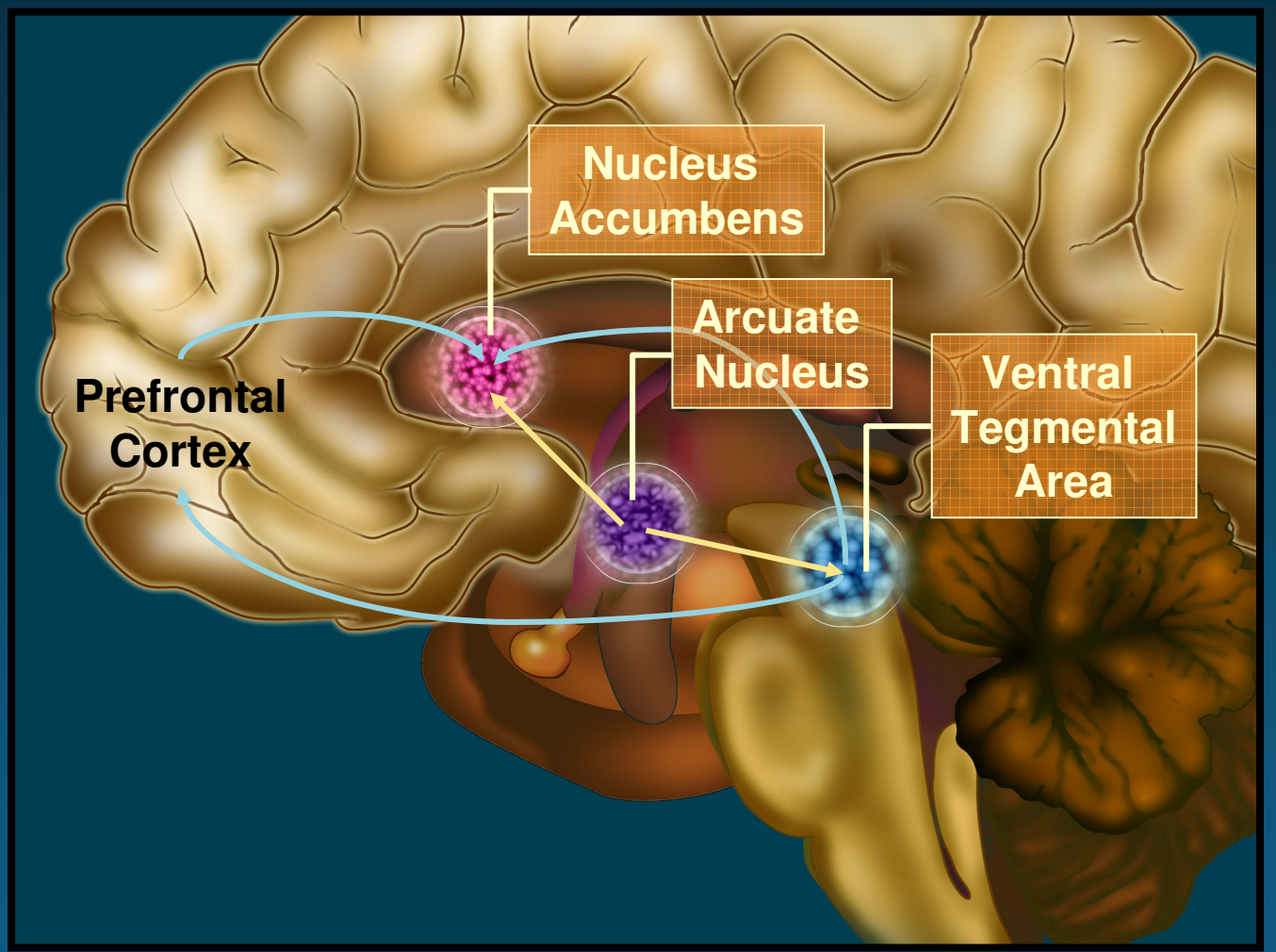
Study	# Ss	Notes
Kranzler, et al 1999	183	None
Krystal, et al 2002	627	None

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			

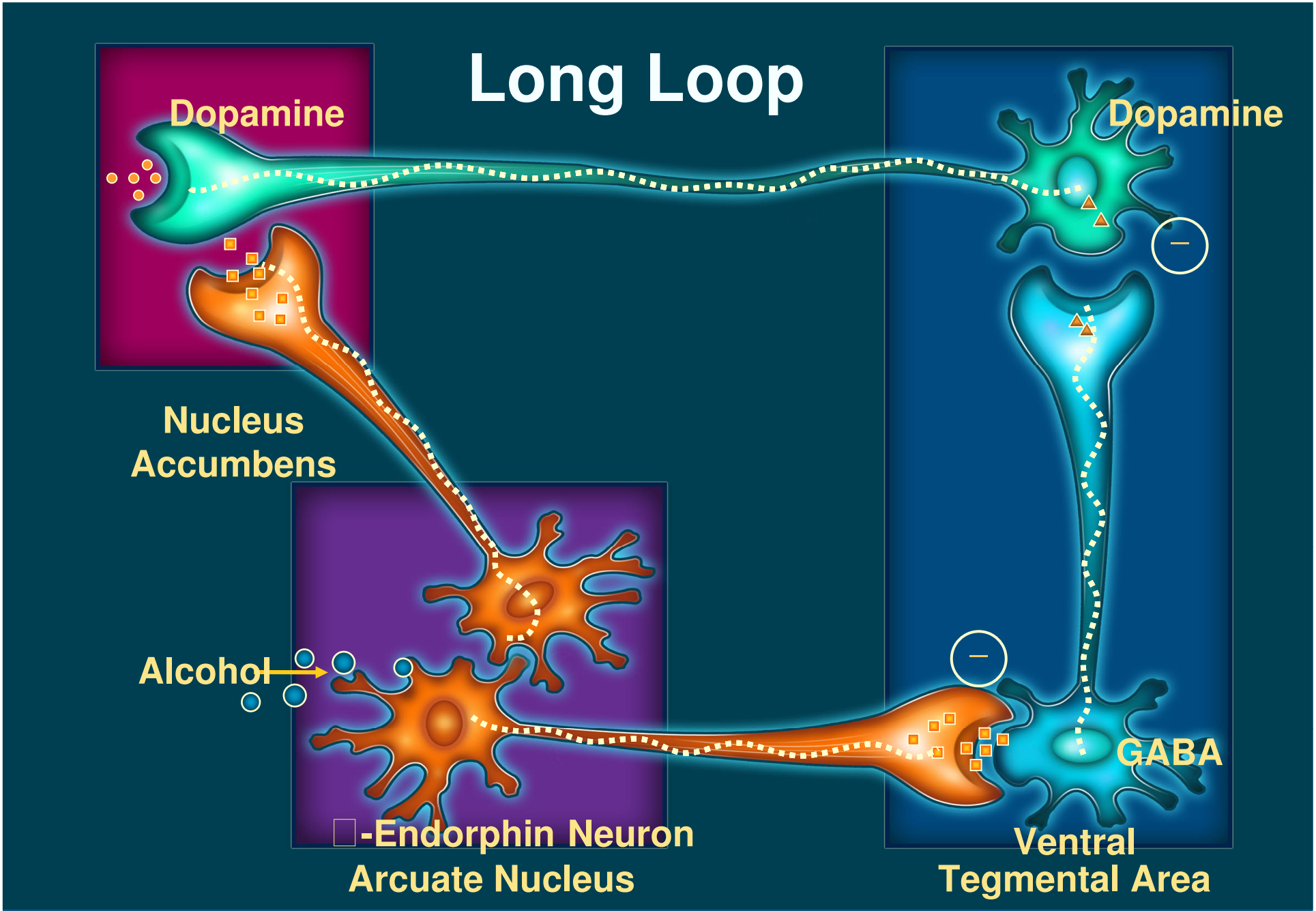
Depot Naltrexone



Brain Reward System

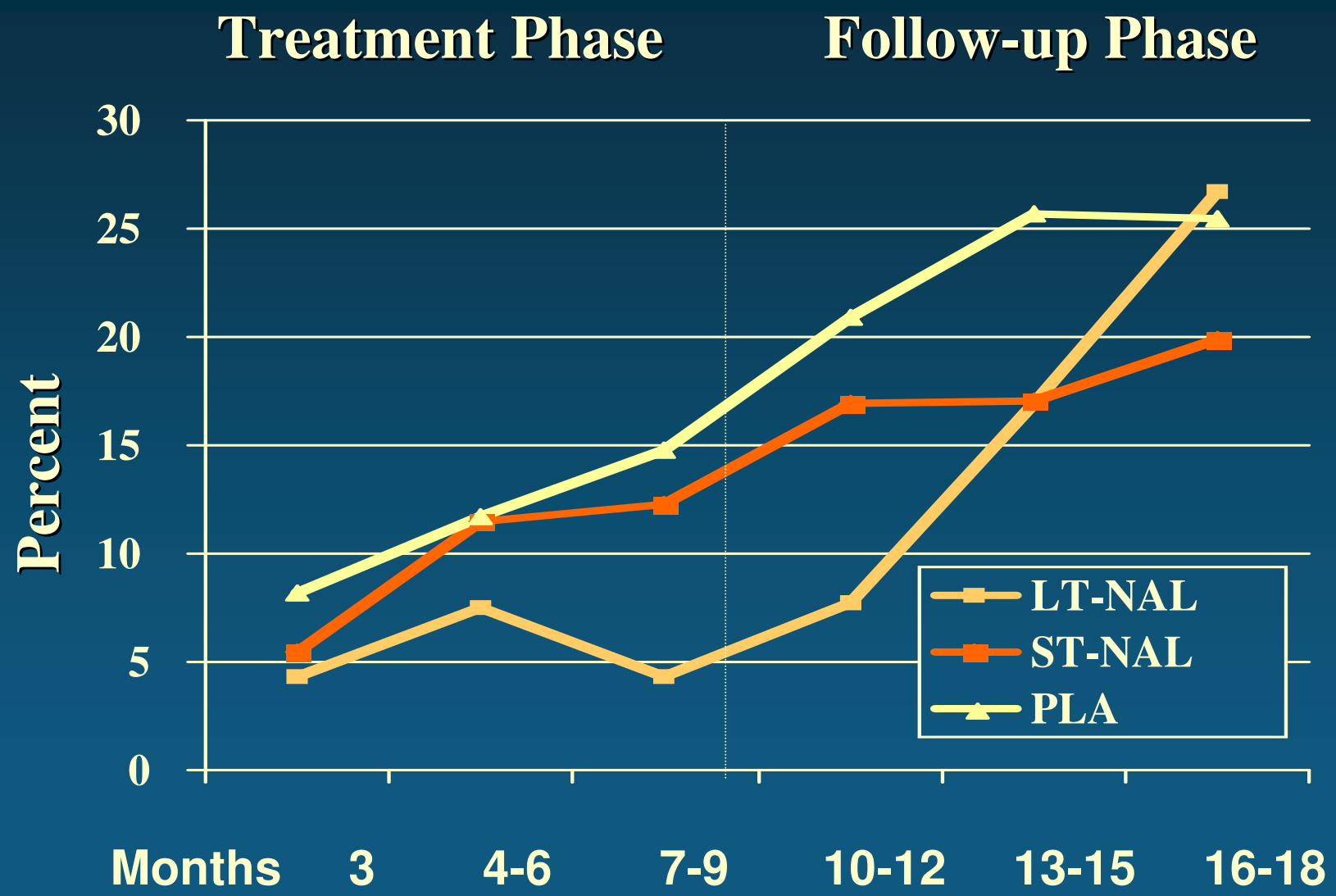


Nestler and Malenka. The Addicted Brain. Scientific American. March, 2004.



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).

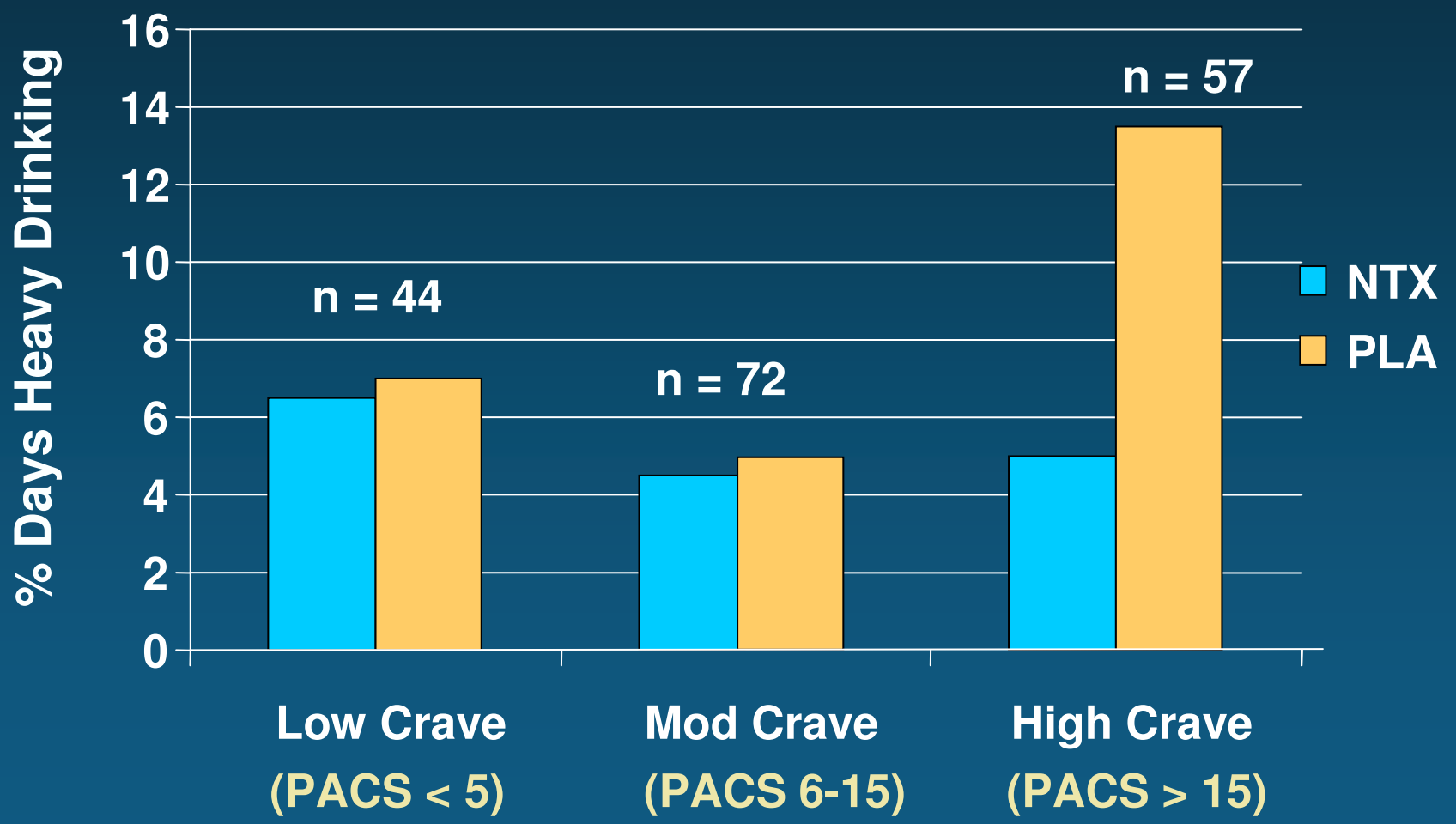
Days of Clinically Significant Drinking



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

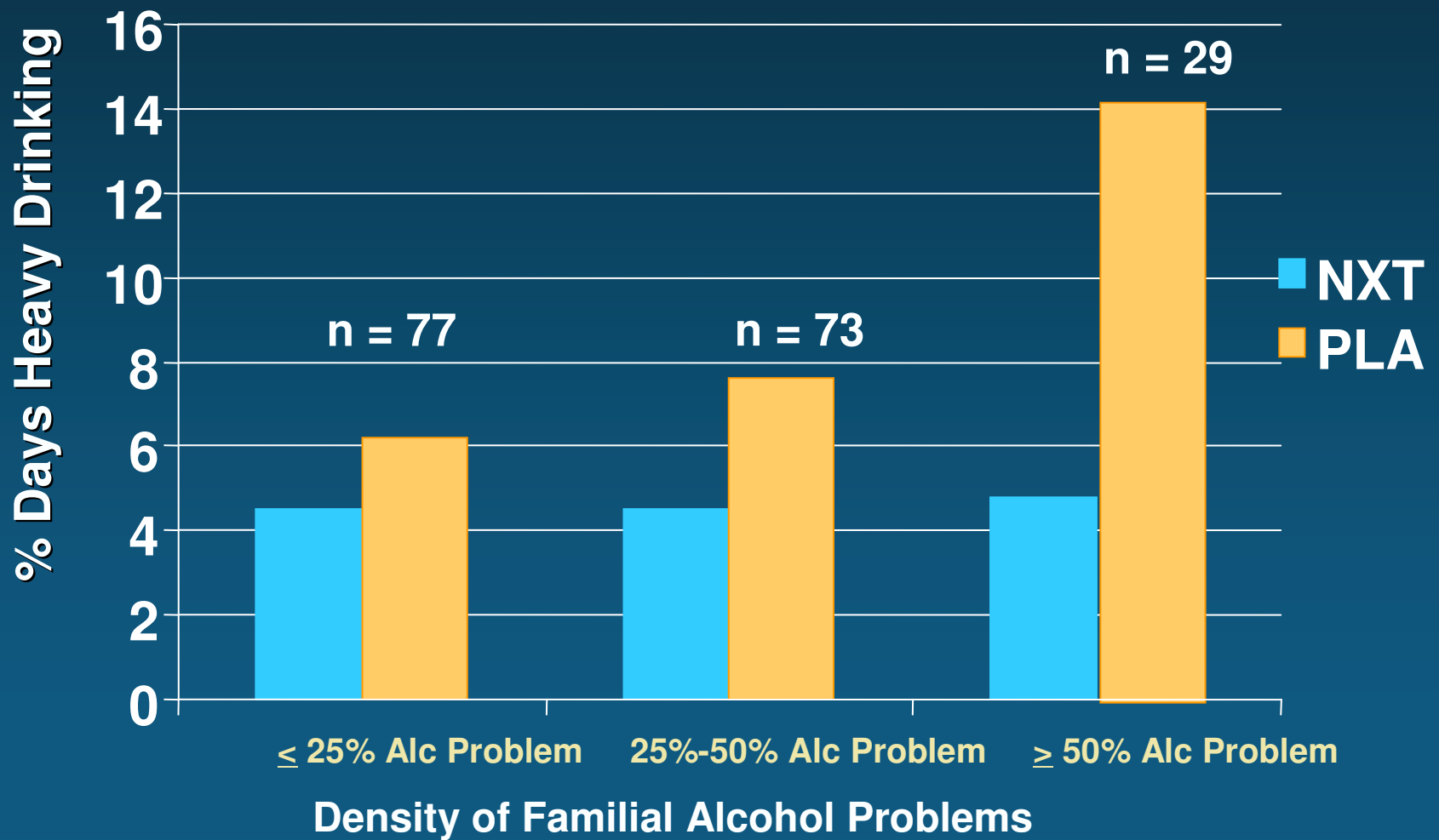
Assumption in clinical trials:
All patients alike
Average effect size: medium

Baseline Craving Scores

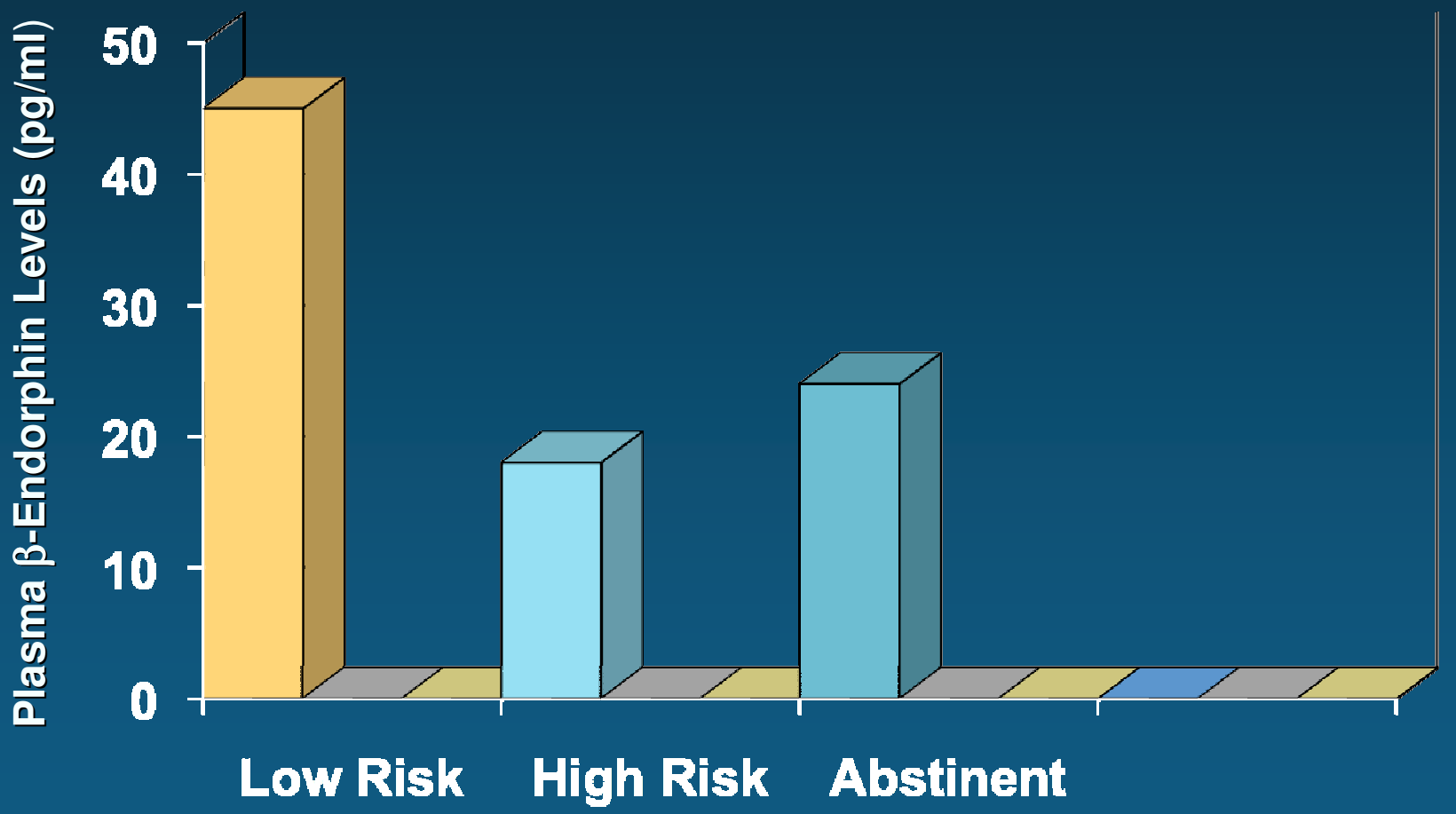


PACS = Penn Alcohol Craving Scale

Family History and Naltrexone Efficacy

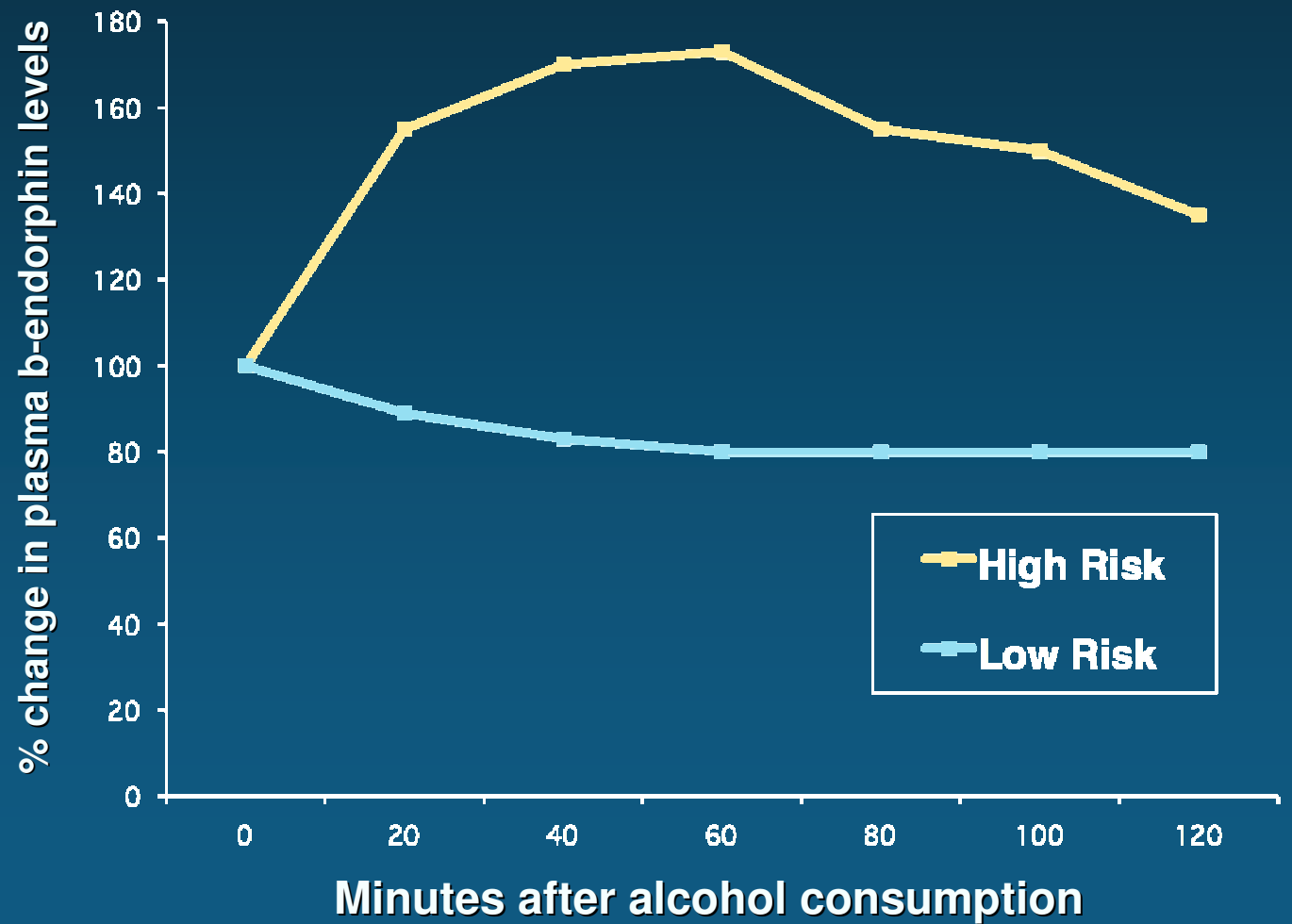


Baseline b-Endorphin Levels in Low- and High-Risk, and Abstinent Alcoholic Patients

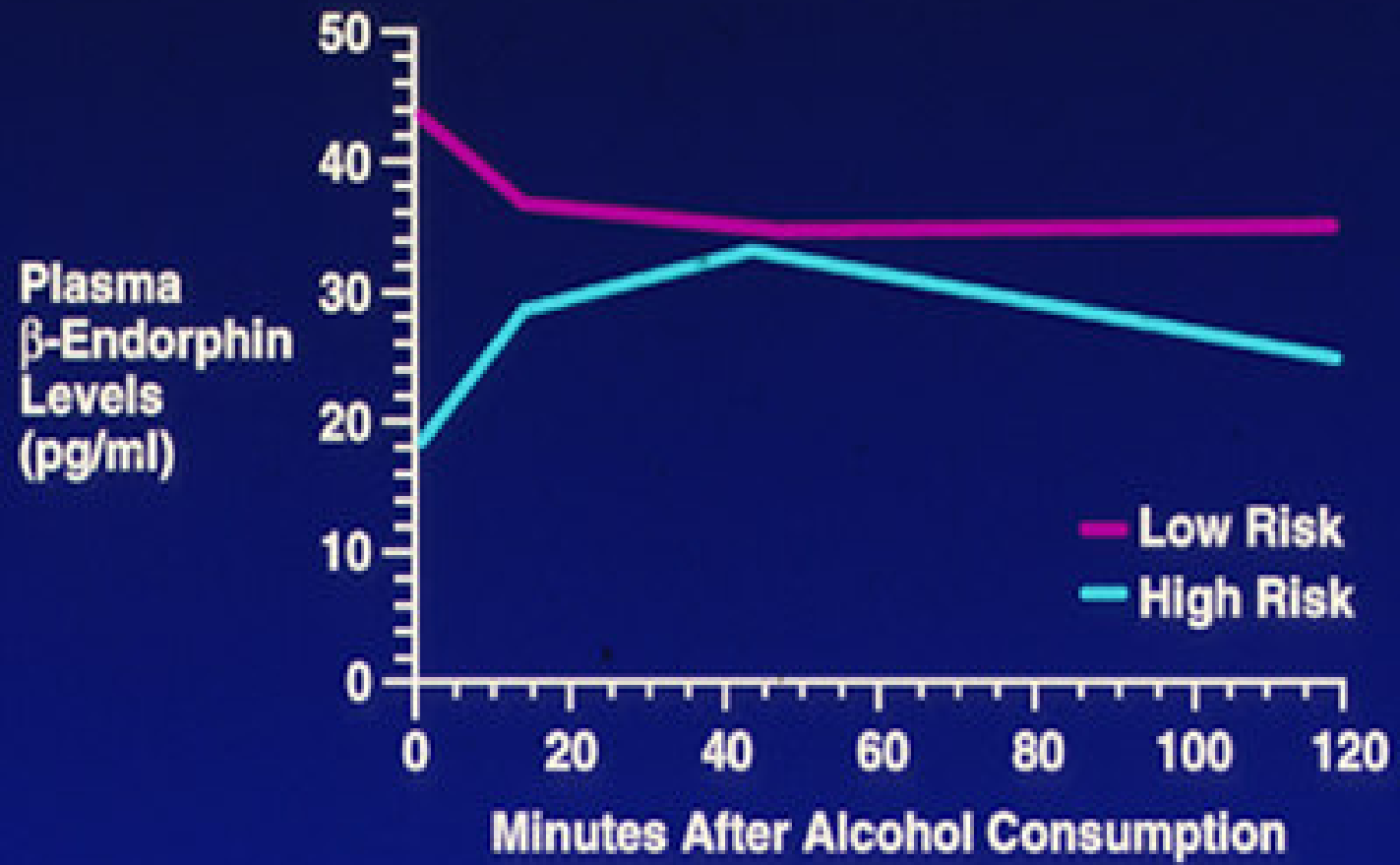


Gianoulakis. *Eur J Pharmacol.* 1990;180:21-29.

Change in β Endorphin Levels after Alcohol Consumption

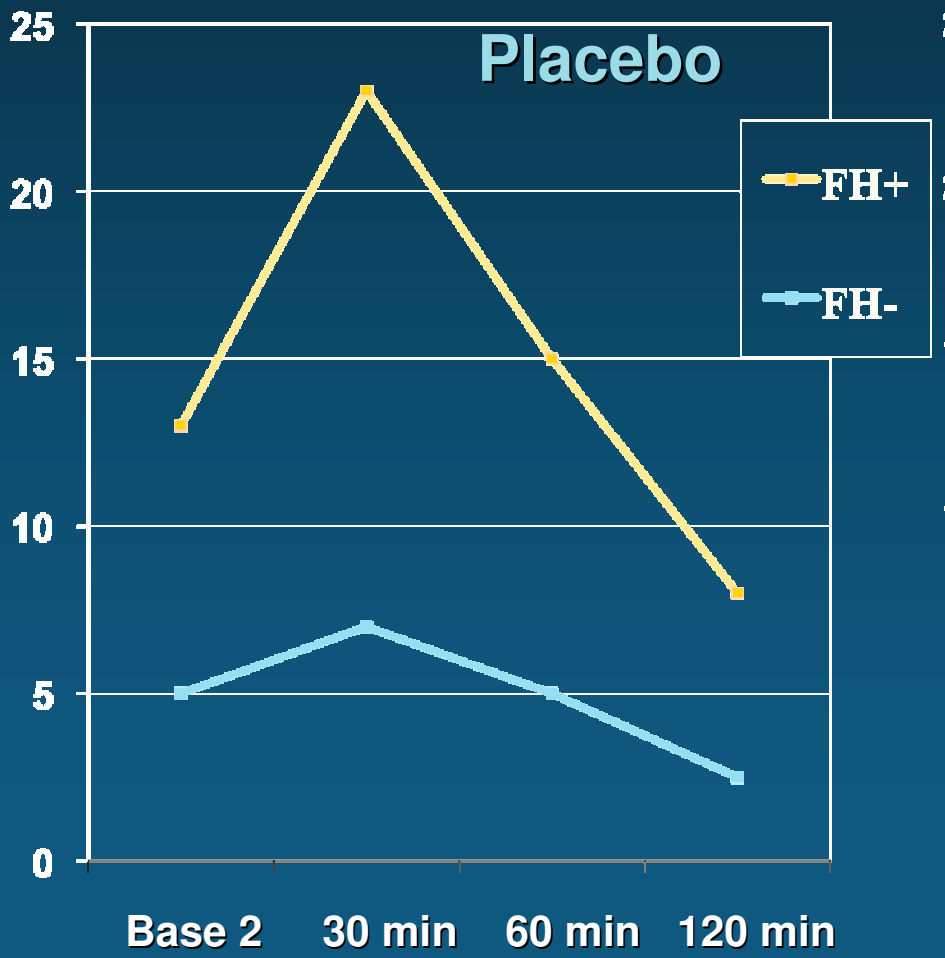


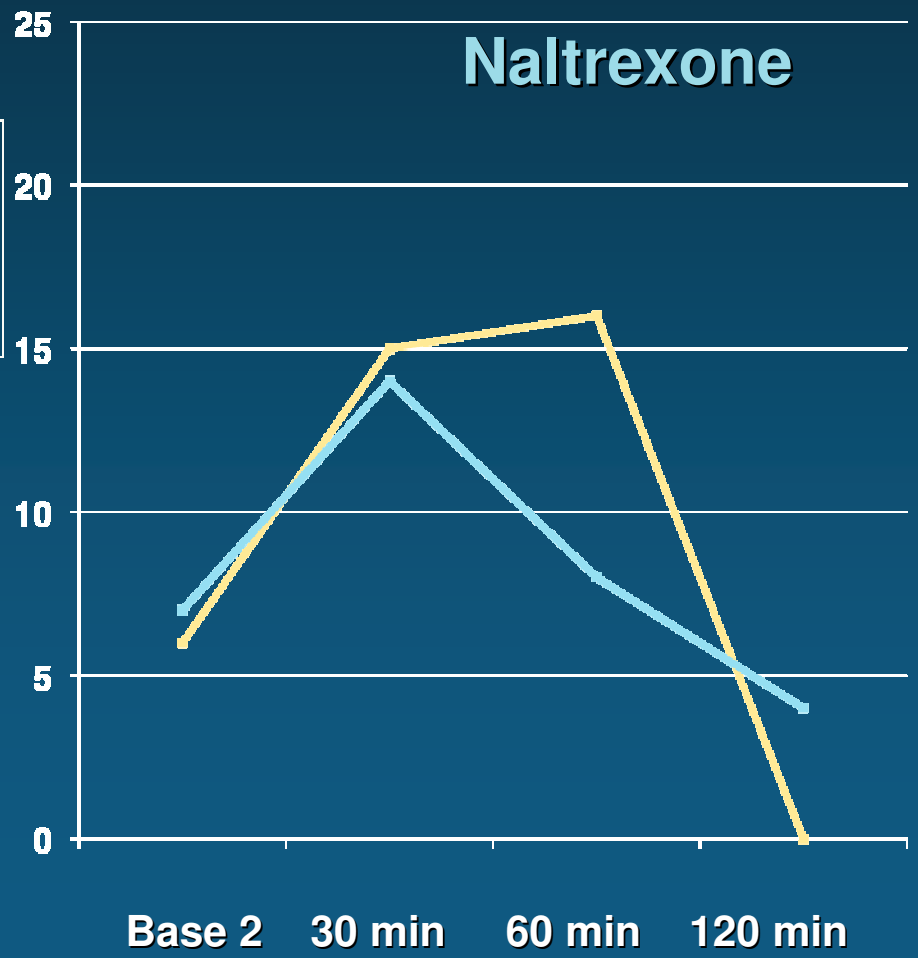
β-Endorphin Levels After Alcohol Consumption



Cipponlakis C. Eur J Pharmacol 1990; 180:21-29

BAES Stimulation Scores Among FH+ and FH Subjects





Key effect: Sensitivity of Endogenous Opioid system to alcohol

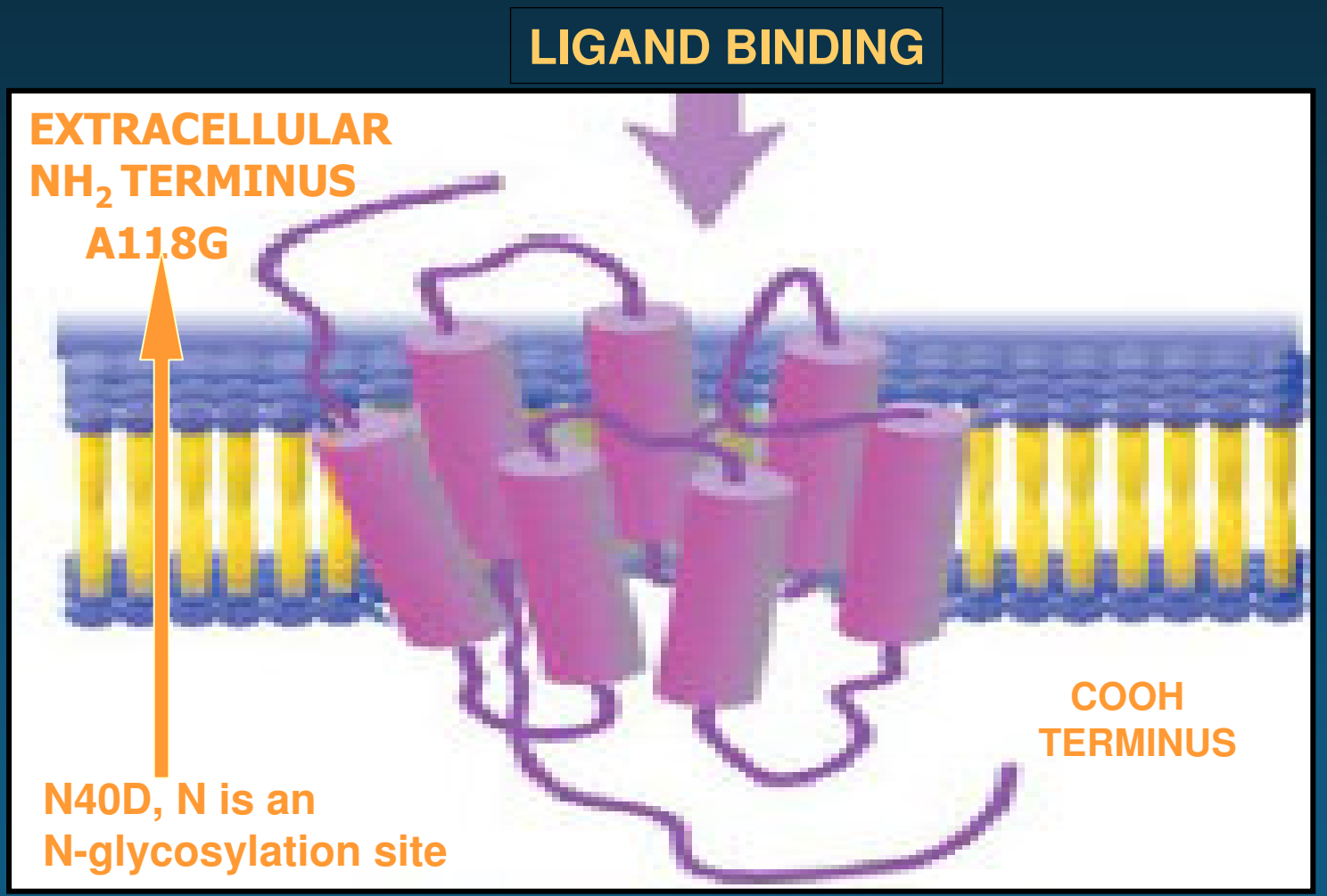
One source of individual variability in response to ethyl alcohol: opioid receptors

Hunt for Candidate Genes!

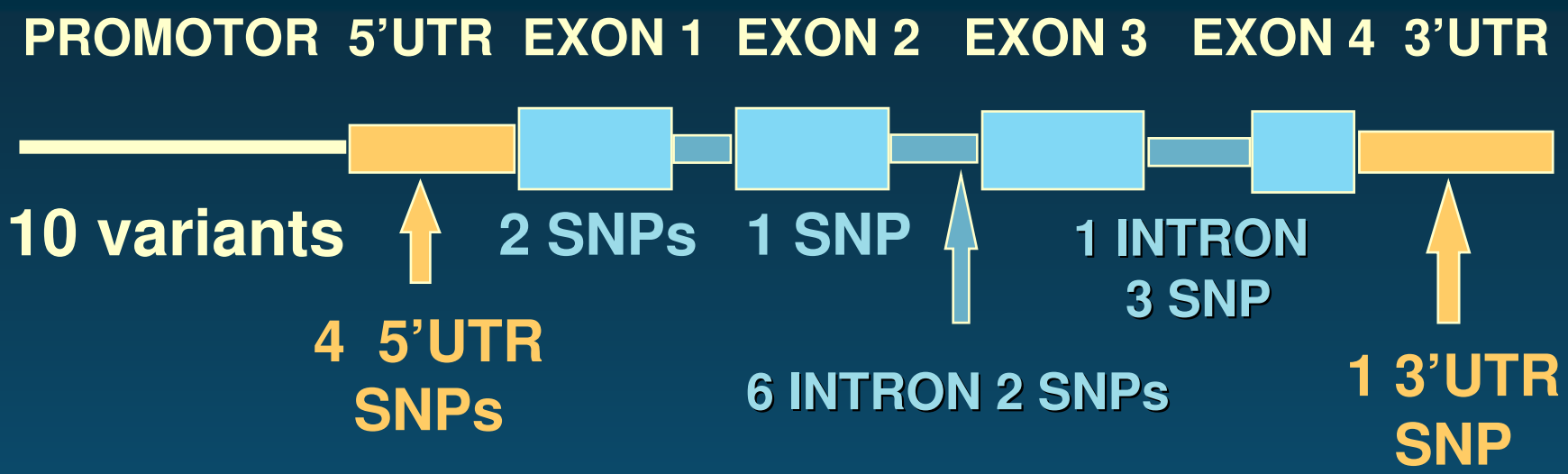
David Oslin, MD

Wade Berrettini, MD, PhD

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%.

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

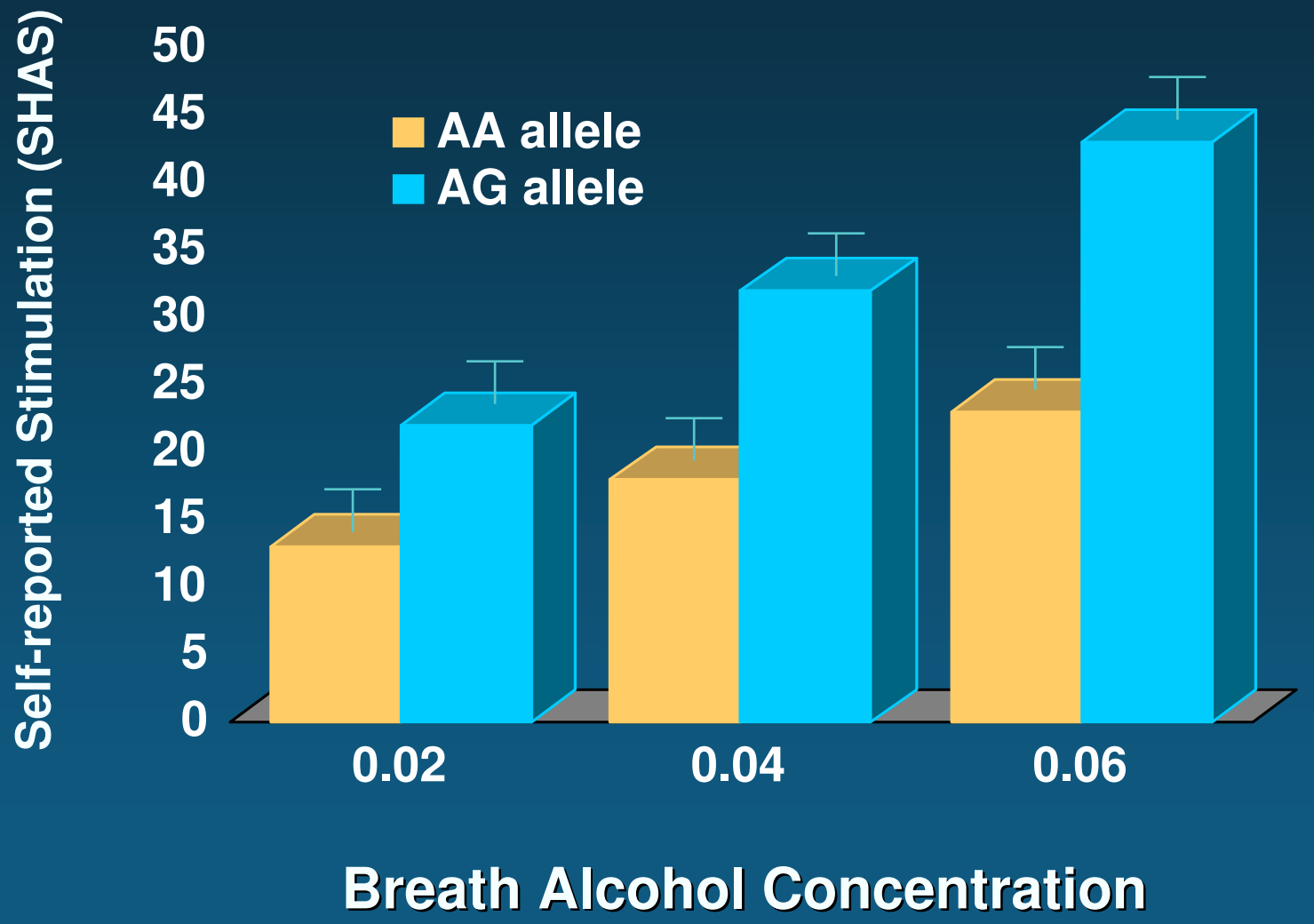
Functional Allele

Increase

and

Decrease

Alcohol effects by genotype



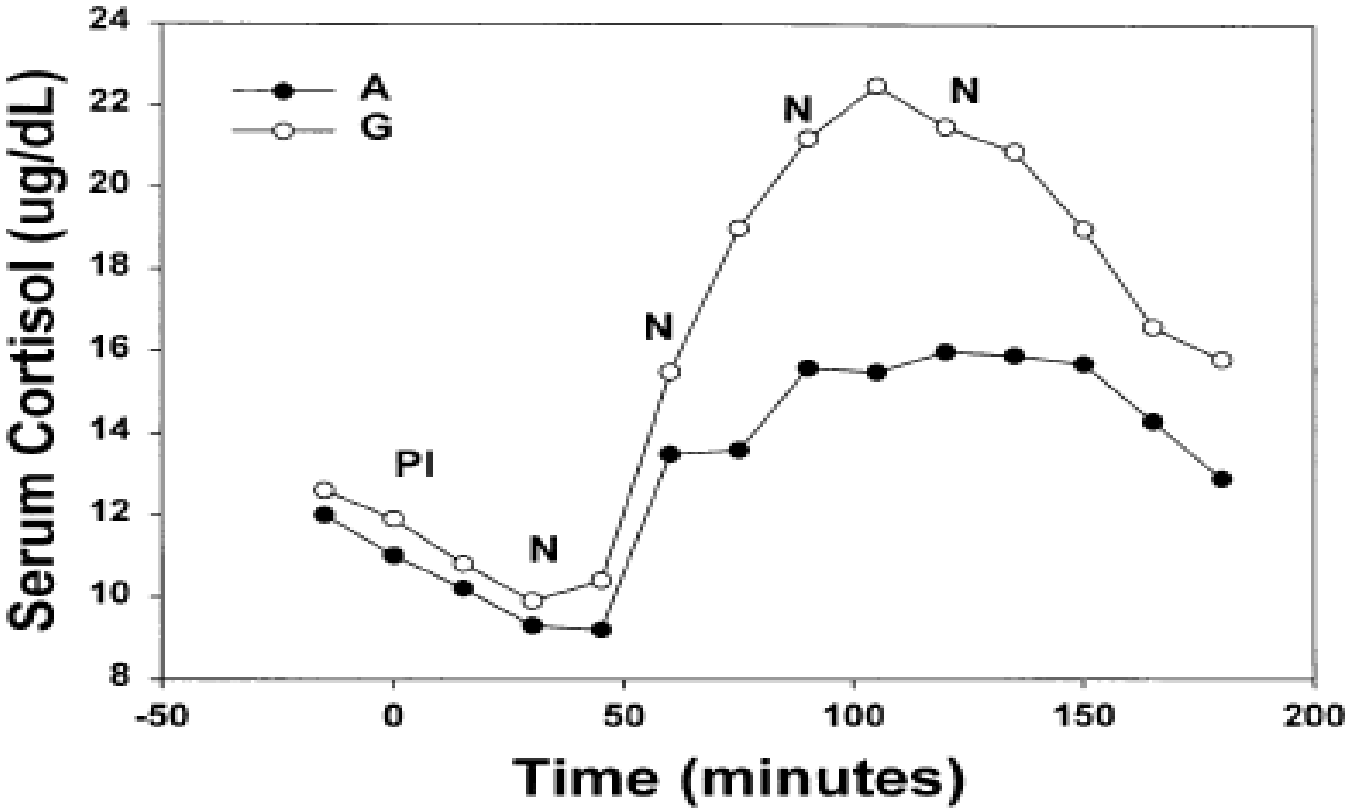


Figure 3. Cortisol responses to Naloxone by mu-opioid receptor genotype. Pl denotes time of placebo (saline) administration. N denotes times of incremental Naloxone administration.

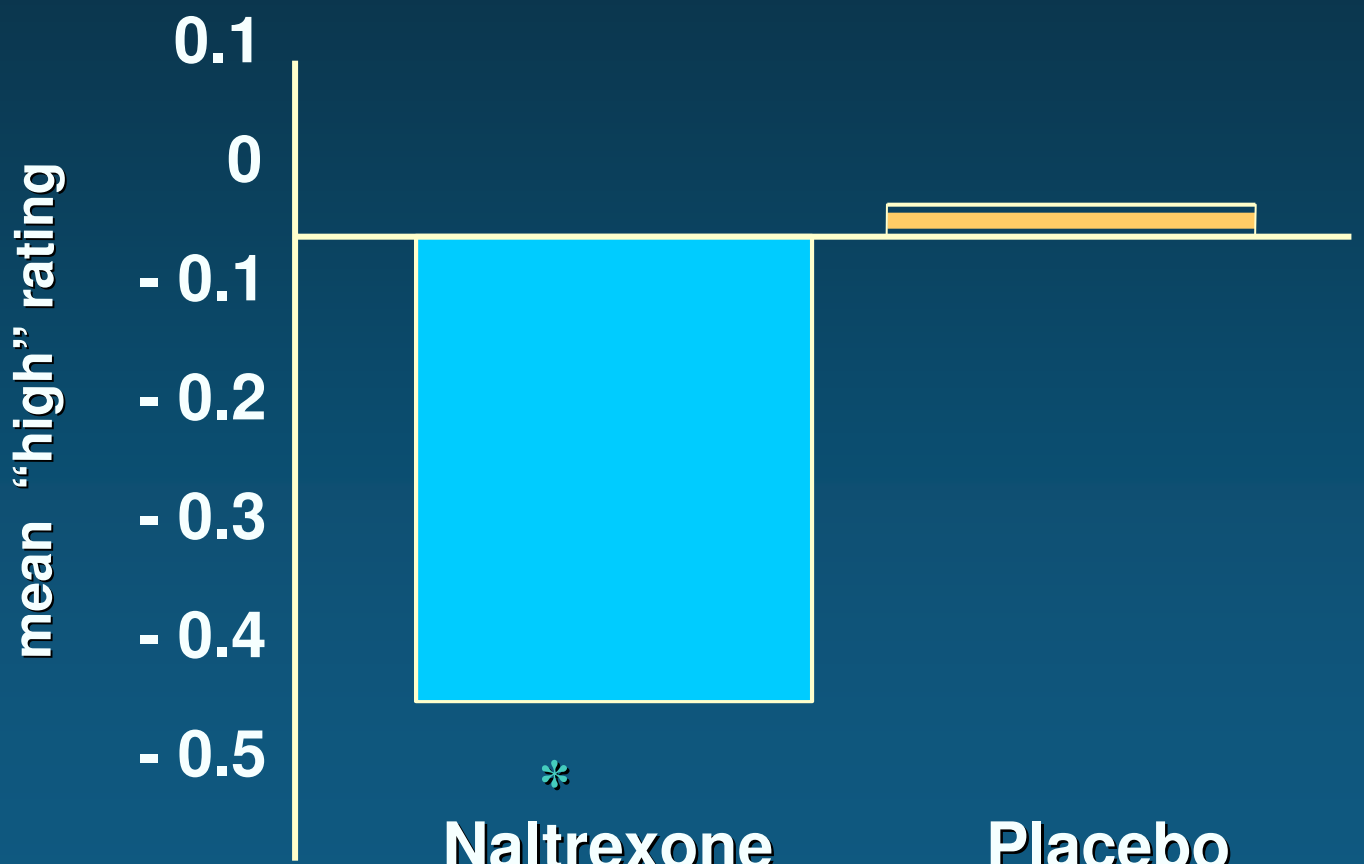
Wand et al, *Neuropsychopharm* 26:106–114, 2002

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%

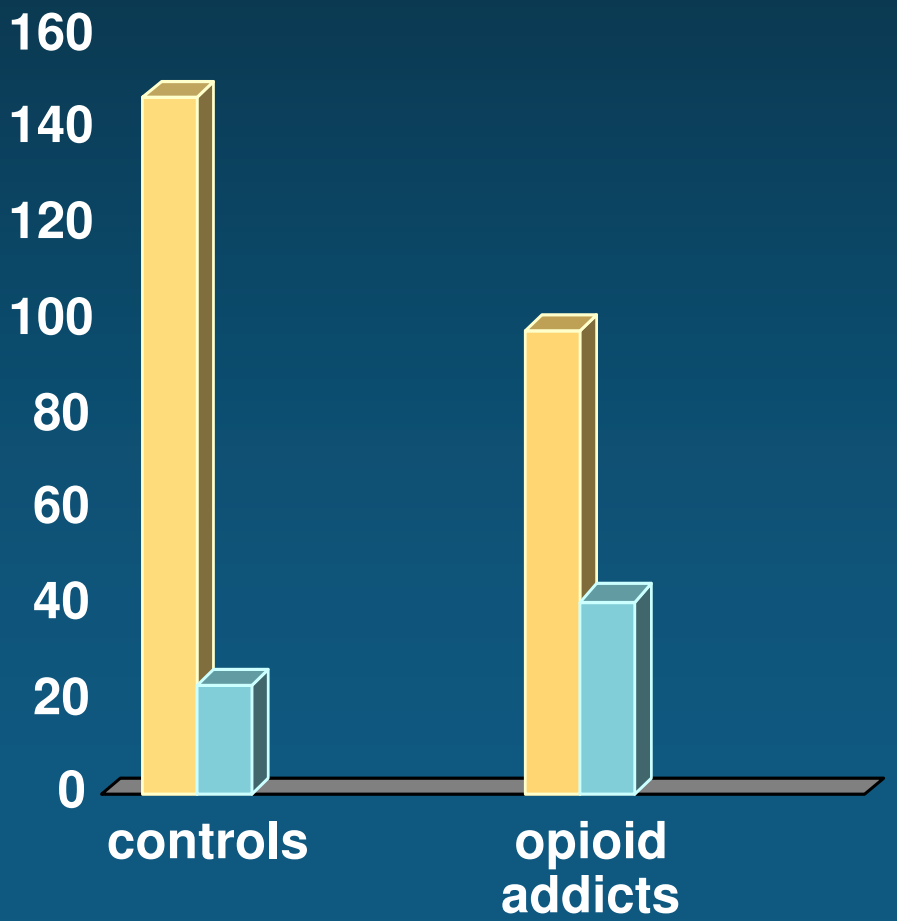
Subjective "high" in Naltrexone and Placebo Subjects



* p<.05

OPRM1 A118G and Opioid Dependence

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

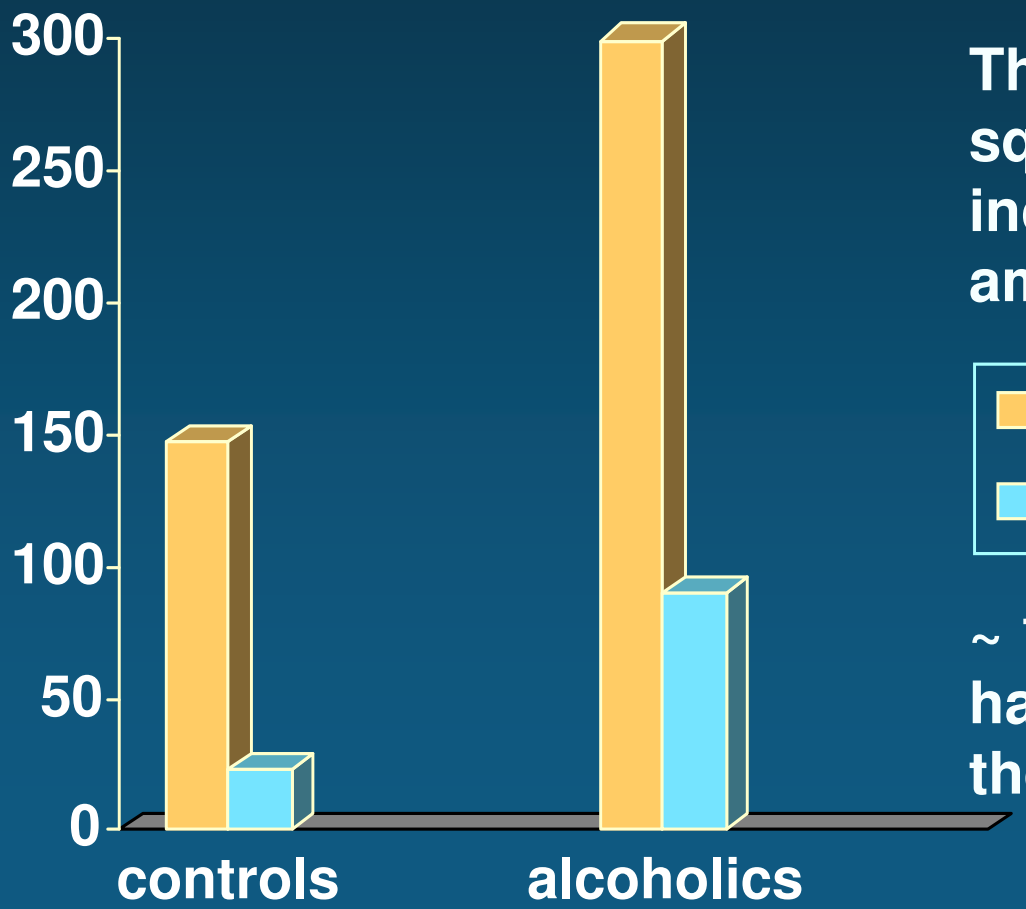


There was a significant (Chi squared = 13, p = 0.00025) increase in A/G, G/G genotype among opioid addicts.

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.

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.

Genetic Variables

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

Rhesus model

Ortholog of A118G allele in humans

(OPRM1C77G)

---

increased sensitivity to alcohol

increased alcohol preference

greater effect in males (Barr et al)

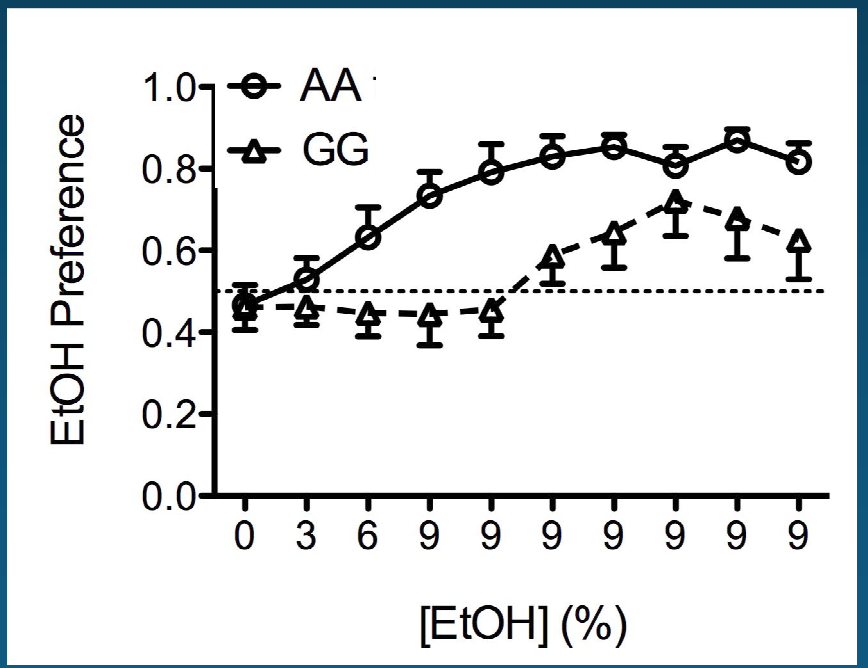
Humanized (knock in mouse C57/B) OPRM1- AA v. GG

Increased DA response to given dose of alcohol in GG animals compared to AA

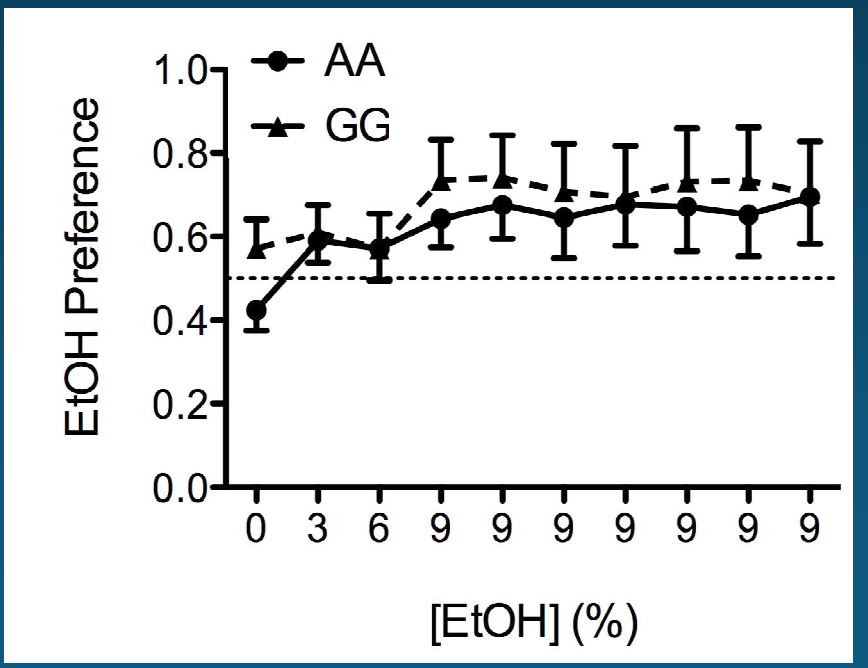
μ Knockouts do not self-administer alcohol

G/G females demonstrate decreased alcohol reward

Female



Male

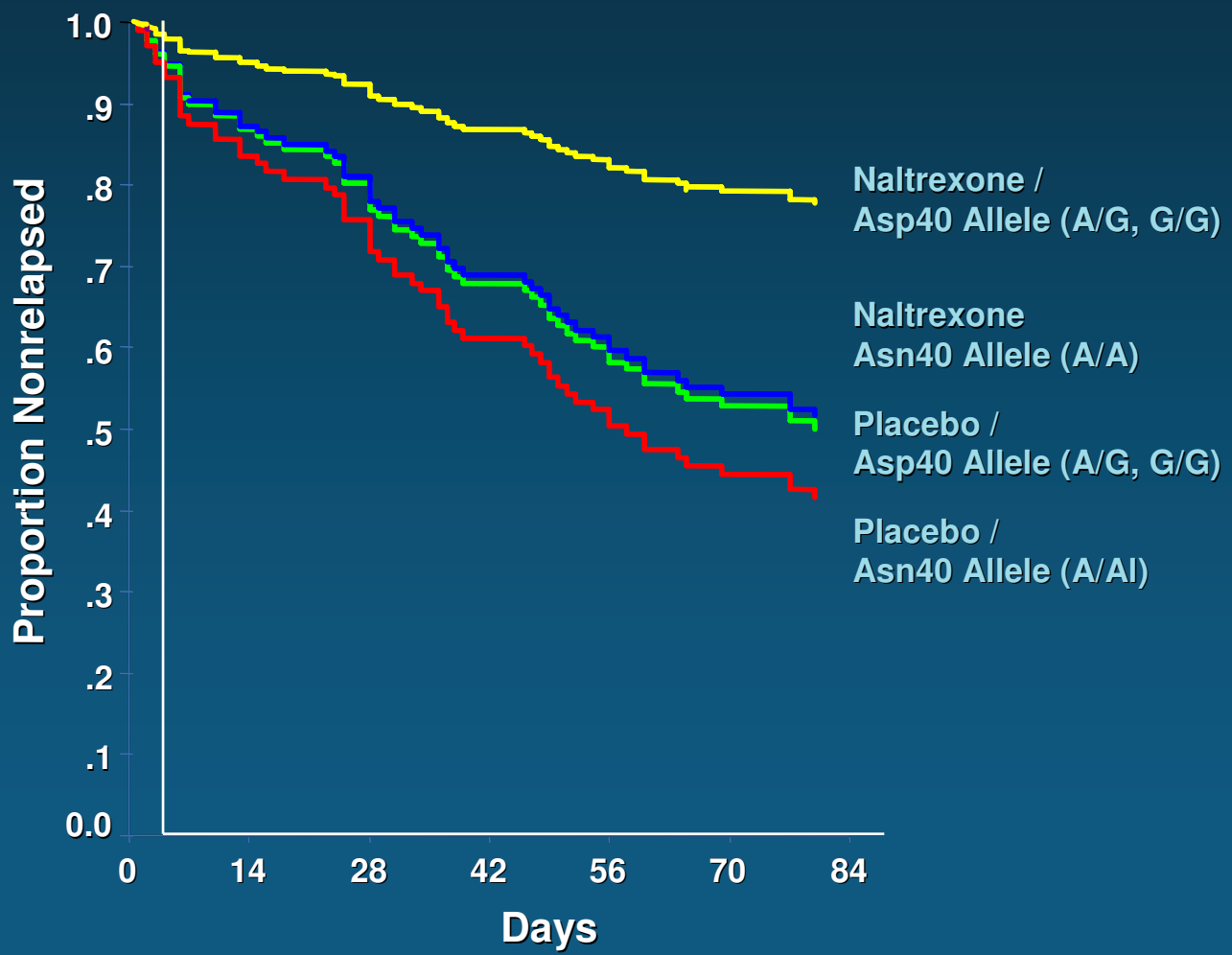


Mague, Kahn and Blendy, unpublished results

Un-published PET studies in Human males AA v AG

Increased DA response to given dose of alcohol measured by displacement of C11 labeled raclopride in AG participants

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

Sub-sample of VA cooperative 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

Pharmacogenetic Trial oral naltrexone

400 Alcoholics **80% AA** **N = 320**

20%AG, GG **N = 80**

Randomize:

	Placebo	Naltrexone
A/G, GG	**40**	**40**
A/A	**40**	**40**

A/A not used: 240

Endophenotype
Endorphin Dependent Alcoholism

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

Penn/VA Center Team

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

Summary

1. DA release in alcohol reward depends on opioidergic mechanism
2. Sub categories of alcoholism with sensitive endogenous opioid system
3. SNP of μ receptor gene predicts opioid sensitivity and treatment response to naltrexone
4. SNP predicts greater DA response in mouse model

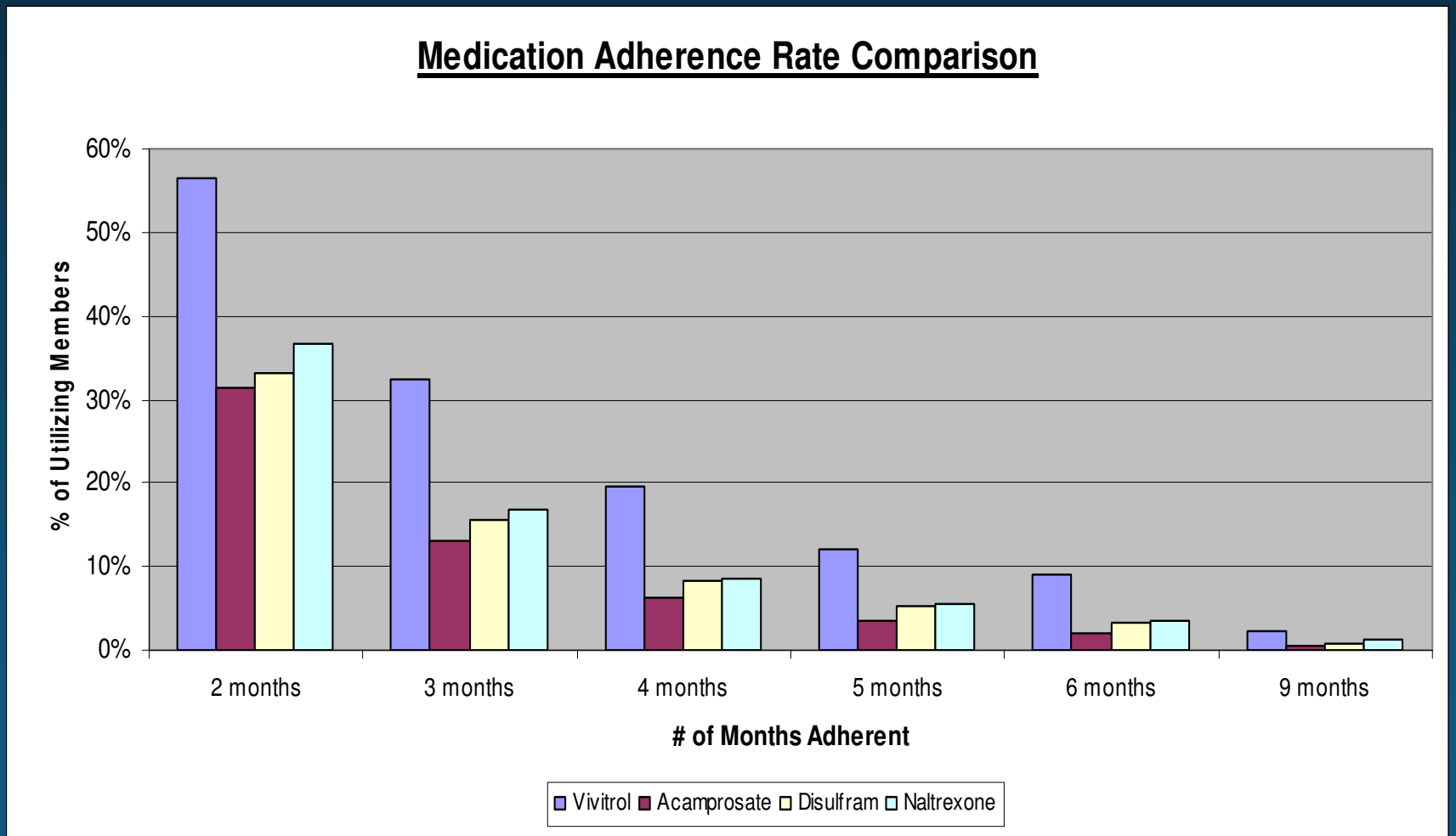
Pharma Opposition

- “Our medication works for everybody”
- Personalized medicine is coming whether or not the pharma industry supports it

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…

Persistence of medication assisted treatment



Utilization pattern changes (6 months pre and post medication initiation)

	Vivitrol	Acamprosate	Disulfram	Naltrexone
BH IP Days/1000	-30%	-33%	-38%	-31%
Medical IP Days/1000	-76%	-57%	-49%	-67%
BH IOP Days/1000	29%	97%	42%	48%
Psychiatrist Visits/1000	41%	130%	36%	133%
Psychotherapy Visits/1000	93%	56%	49%	85%
ER Visits/1000	-13%	12%	0%	12%

Summary of Aetna Findings

Summary:

- **Low utilization of medication assisted treatment**
- **Low persistence rate overall but best with Vivitrol**
- **Inpatient behavioral health and medical bed days reduction**
- **Increased outpatient behavioral health utilization**
- **Vivitrol related reduction in ER visits**

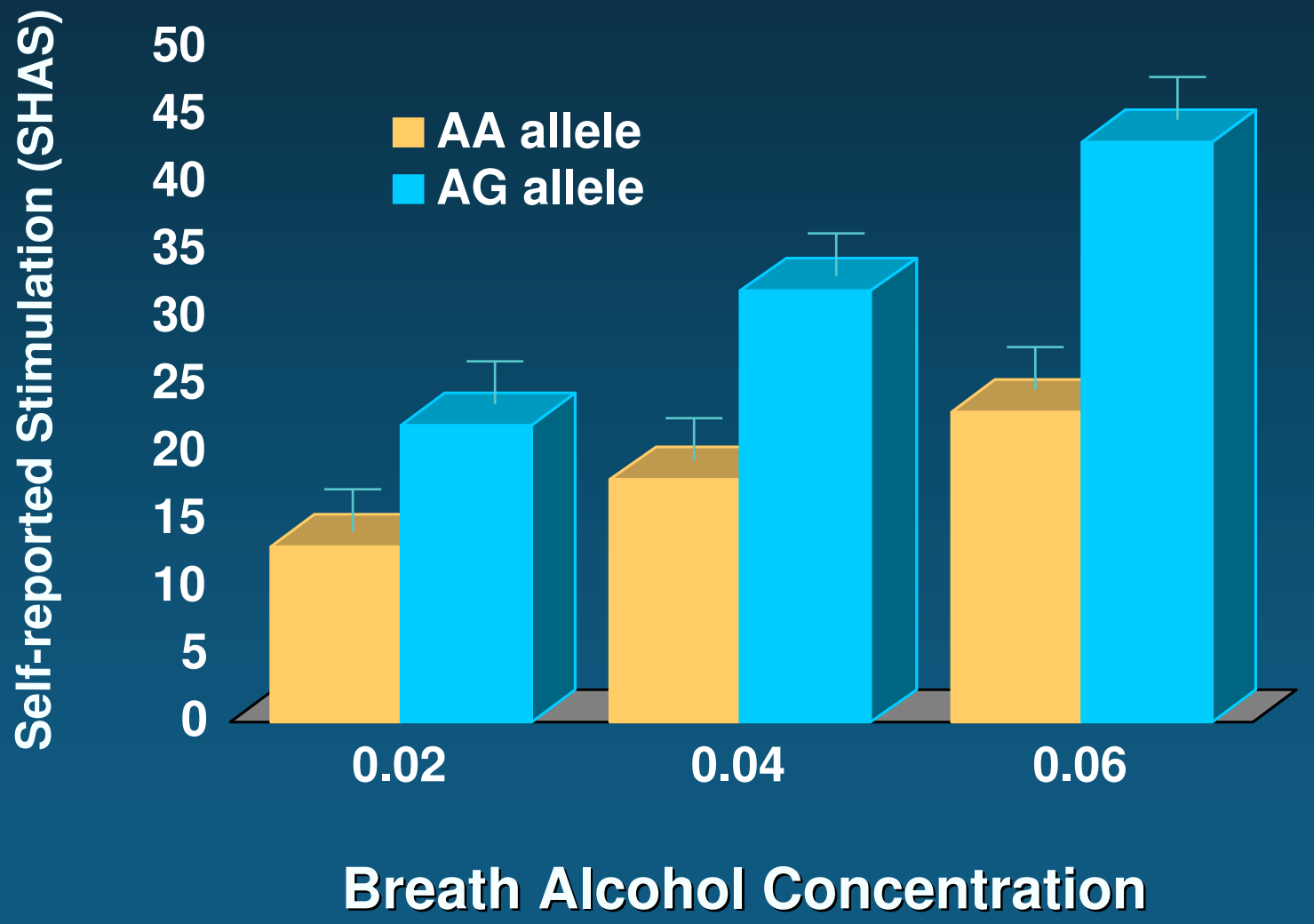
Limitations:

- **Early naturalistic observations without controls or case mix adjustment**
- **Small sample sizes**

Top Health Advances of 2009

- Time Magazine, 12/1/2009
- Depot naltrexone (Vivitrol) for ALCOHOLISM

Alcohol effects by genotype



Summary

1. New mechanism for alcohol reward (1990)
   still not fully accepted or used
2. Sub categories of addictive disorders
3. Resistance to use of medication despite
   randomized, placebo controlled trials
4. Early signs of acceptance for alcohol use
   disorder after years of studies

FOR MORE INFORMATION

http://www.med.upenn.edu/csa/o
r
obrien@mail.trc.upenn.edu

Lines of supporting evidence

Monkey	drinking blocked by naltrexone
	genetics (males)
Rat drinking	stress
	deprivation
	cue relapse
	micro dialysis DA
Mouse	Knock out μ opioid receptor
	Knock in A/A v. G/G
Human	clinical trials
	Lab drinking-Stimulation: Family History
	Lab IV alcohol genotype
	PET raclopride-DA response to alcohol by genotype
	Treatment outcome-retrospective
	Treatment outcome- PROSPECTIVE IN PROGRESS**

To Clinicians Without Pharma Support

Avg. cost: 800 Million Dollars

Penn/VA studies: 1983-1990

First pub	1990
Roger Meyer	1988
Two pubs Archives	1992
Leonard Cook, PhD	Retirement golf day- Dupont Merck

Directive to buy data from Penn & Yale

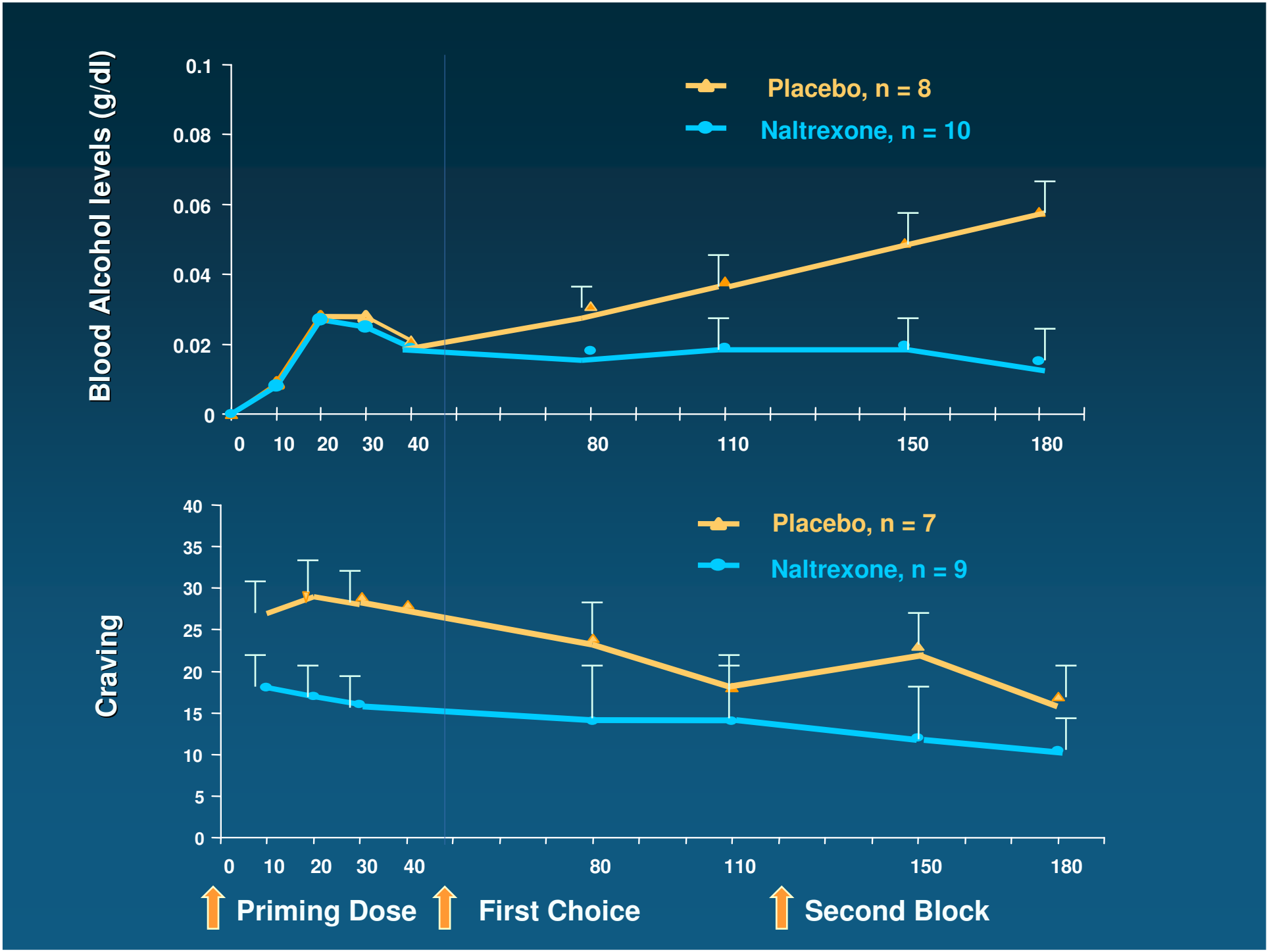
FDA approval 1995 (Alcoholism added to indications)

FDA approval 2006 Depot version (Vivitrol)

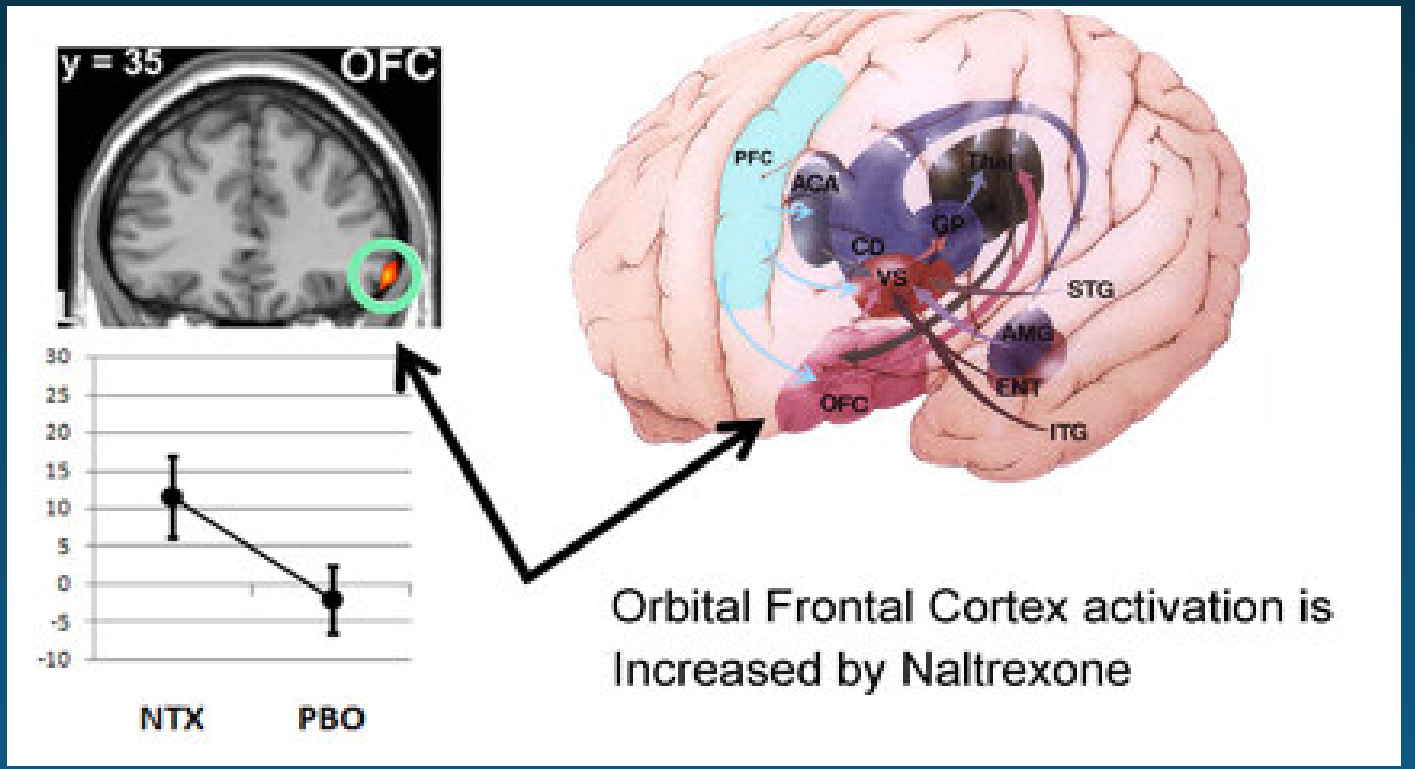
Alcohol “PRIMING” in human, non-treatment seeking Alcoholics

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

Addiction Therapy may be related to activation of Frontal Cortex

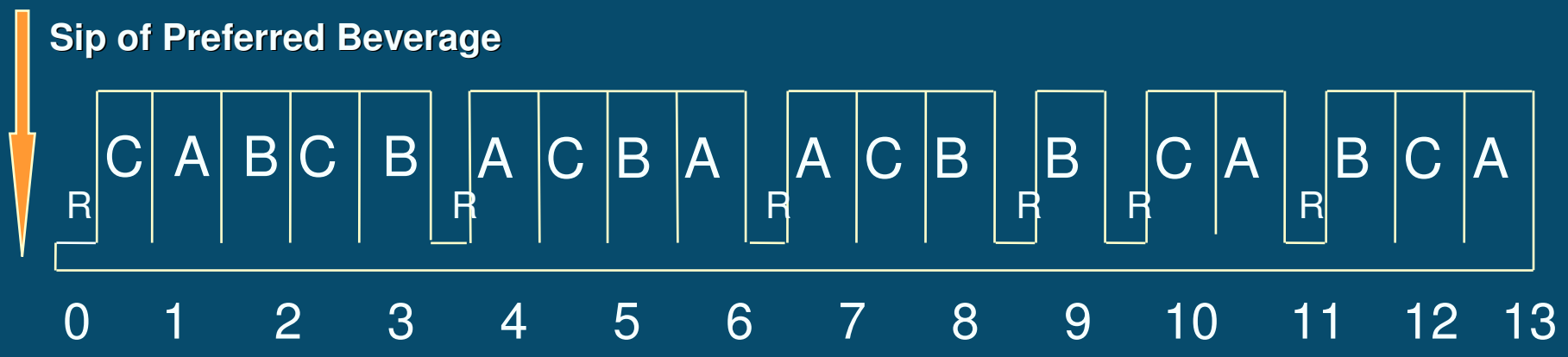


(Boettiger, et.al. 2009)
(Crews and Boettiger et.al. 2009)

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

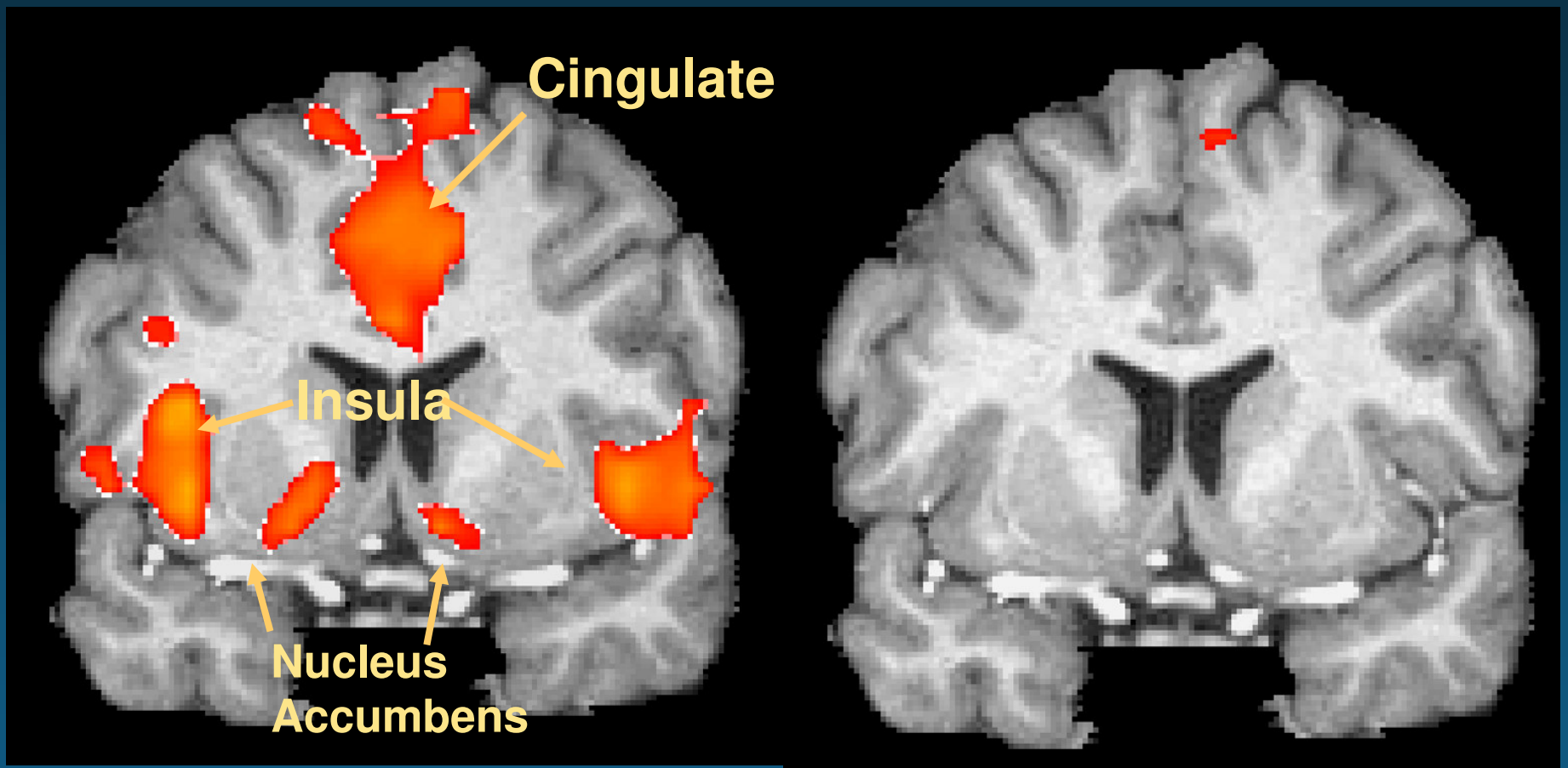


* Craving rated after each block

Comparisons:

- Alcohol - Beverage
- Alcohol - Vis Ctrl
- Vis Ctrl - Rest
- Beverage - Vis Ctrl
- Beverage - Rest

Alcohol - Beverage Condition

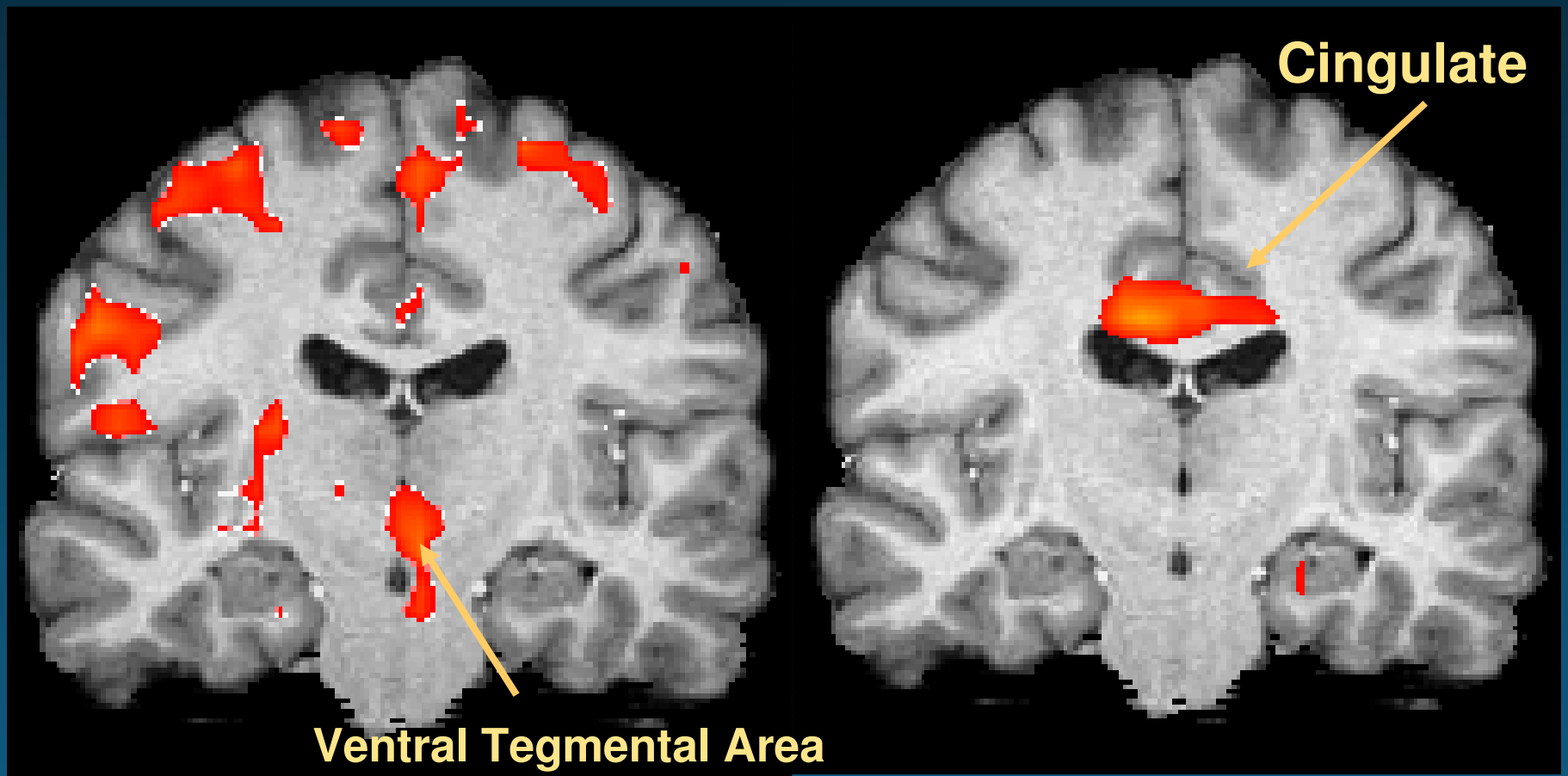


Alcoholics (n=10)

Controls (n=10)

Z=1.645 Ex .05

Alcohol - Beverage Condition



Alcoholics (n=10)

Controls (n=10)

Z=1.645 Ex .05

True Translational Story: Naltrexone for Alcoholism

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

?? Standard practice

Fundamental nature of alcoholism

Goal of NIH Support

- Improved understanding of addiction
- Development of new medications
- Acceptance of new treatments is a less well understood issue

Opiates & Alcohol 1960s-1970s

? Opiate condensation product Salsolinol

tetrahydroisoquinoline (TIQ) alkaloids

“alcohol becomes morphine-like”

Disclosures

Consultant to

- Embera (Research)
- Abbott (drug development)
- Pfizer (2 years ago)
- Alkermes (3 years ago)

Extinction of Heavy Drinking

David Sinclair

- Encourage drinking while on naltrexone
- Weaken impulsive drinking
- Target craving, give naltrexone when craving

Return of symptoms when medication stopped (HBP, Diabetes, etc)