Alcoholism and Naltrexone

David W. Oslin, MD
Associate Professor
University of Pennsylvania, School of Medicine
And
Philadelphia, VAMC

Hazelden Research Co-Chair on Late Life Addictions

Question # 1

- True or False: The annual cost for the consequences of alcoholism in the US exceeds the annual cost of the Iraq war.

Question # 2

Which of the following diseases requires a lifestyle change for adequate treatment:

1. Diabetes
2. Heart disease
3. Alcoholism
4. Arthritis
5. All of the above

Question # 3

Naltrexone

1. Is a mu opioid receptor agonist
2. Reduces heavy drinking days more than placebo
3. Has a long acting injectable formulation that is free of serious side effects
4. Works best in patients who drink to self-medicate stress or mood symptoms
5. Works least well in familial forms of alcoholism

Question # 4

The opioid receptor gene has alleles that

1. Are associated with increased pain sensitivity
2. Are associated with a greater likelihood of intoxication after drinking a given amount of alcohol
3. When present in alcoholics are associated with response to naltrexone
4. 1, 2, and 3 are correct

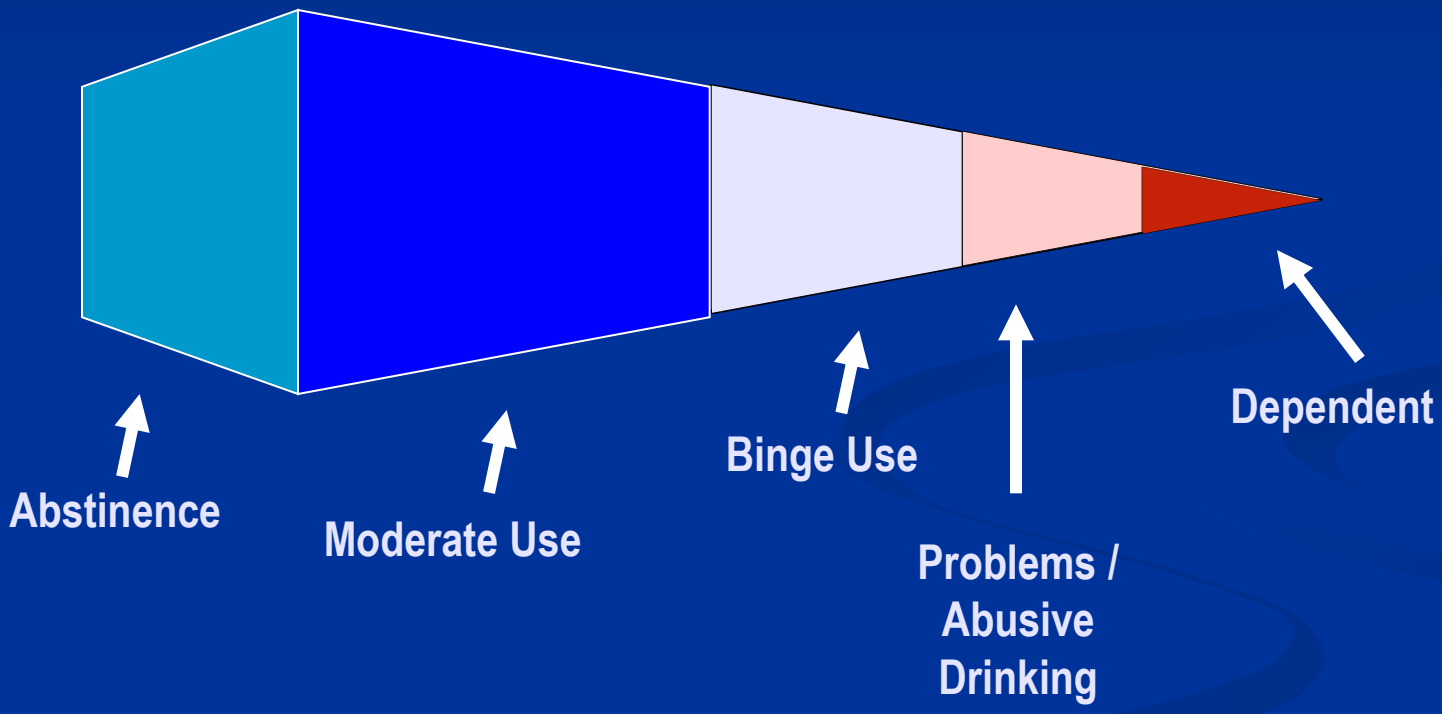
Lecture Outline

- General review of diagnosis and impact of alcoholism
- Opioid antagonists and alcoholism – basic science
- Efficacy of naltrexone and depot naltrexone
- Genetics of the mu-opioid receptor and alleles
- Genetic influences on naltrexone efficacy
- Conclusions

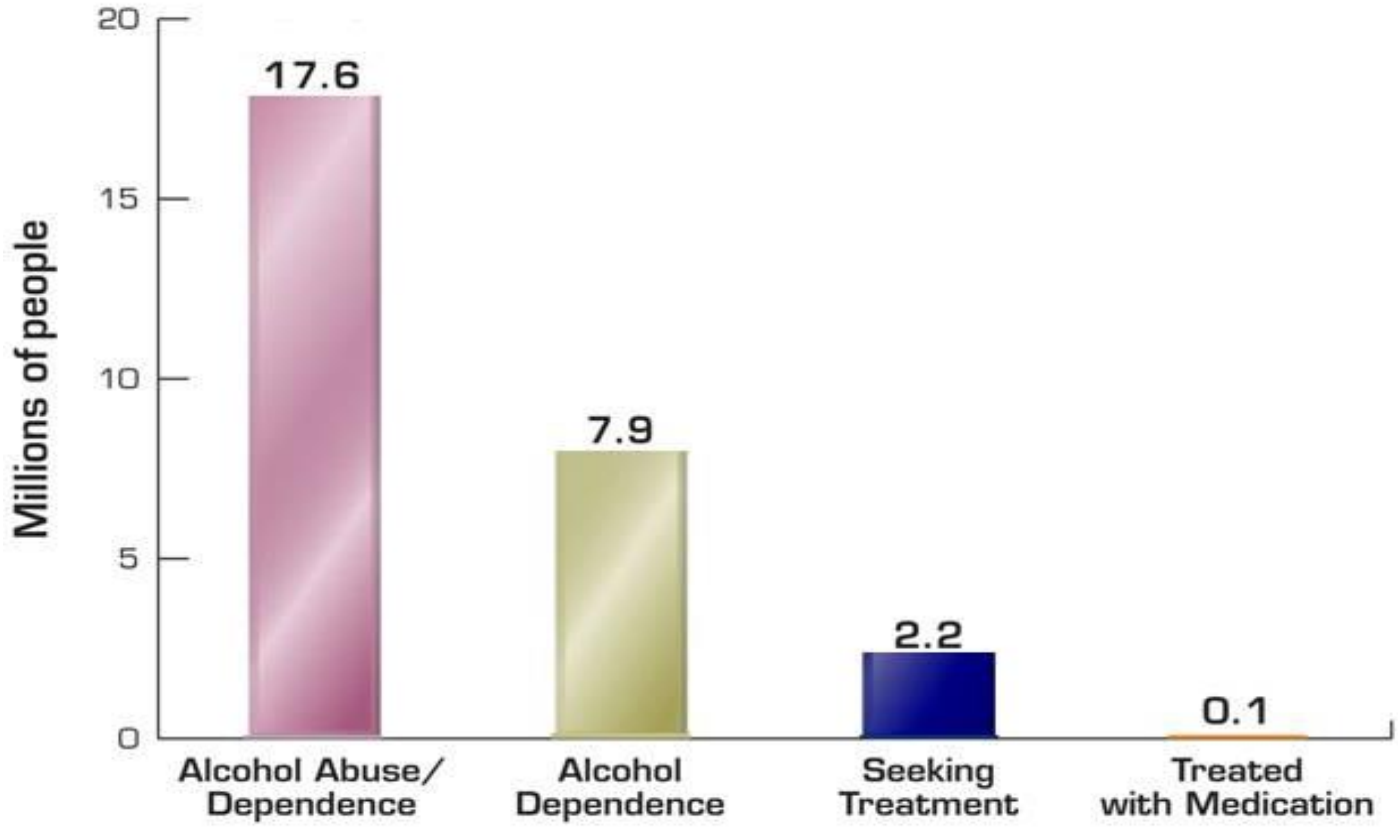
Introduction

- Alcoholism costs the nation $150 Billion / annum in the US. As such it is the most expensive addictive disorder.
- Alcoholism leads to increased mortality and morbidity
- Alcoholism is common with about 7 million Americans afflicted
- Worldwide alcoholism is the 7th leading cause of disability

Alcohol Use


Abstinence
Moderate Use
Binge Use
Problems / Abusive Drinking
Dependent

Undertreatment of Alcohol Use Disorders



Defining Alcohol Dependence

- a person's maladaptive pattern of alcohol use leads to clinically important distress or impairment
- 3 of the following in a 12-month period
  - Tolerance
  - Withdrawal
  - More time or larger amounts than desired
  - Desire or effort to cut down
  - Time spent obtaining or recovering
  - Social, occupational or recreational effects
  - Drinking despite consequences

Alcoholism: A Chronic Disease

Alcoholism is often compared to traditional illnesses

Asthma, diabetes, heart disease and arthritis

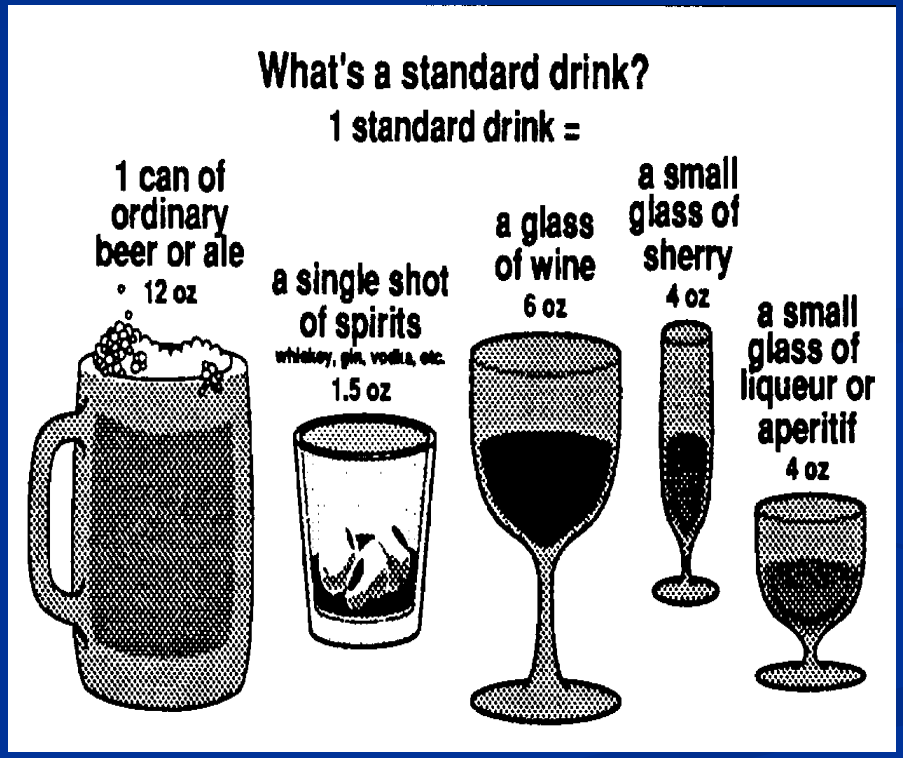
- Progressive, relapsing disease
- Genetic factors are important
- Symptoms show with advanced disease
- Treatment requires lifestyle changes

What Are the Terms?

Social/Moderate Drinker

- Generally defined as drinking no more than 2 drinks per day
  - No binge drinking
  - Modified for women (1 drinks per day)
  - Modified for older adults (1 drinks per day)

What is a Drink?

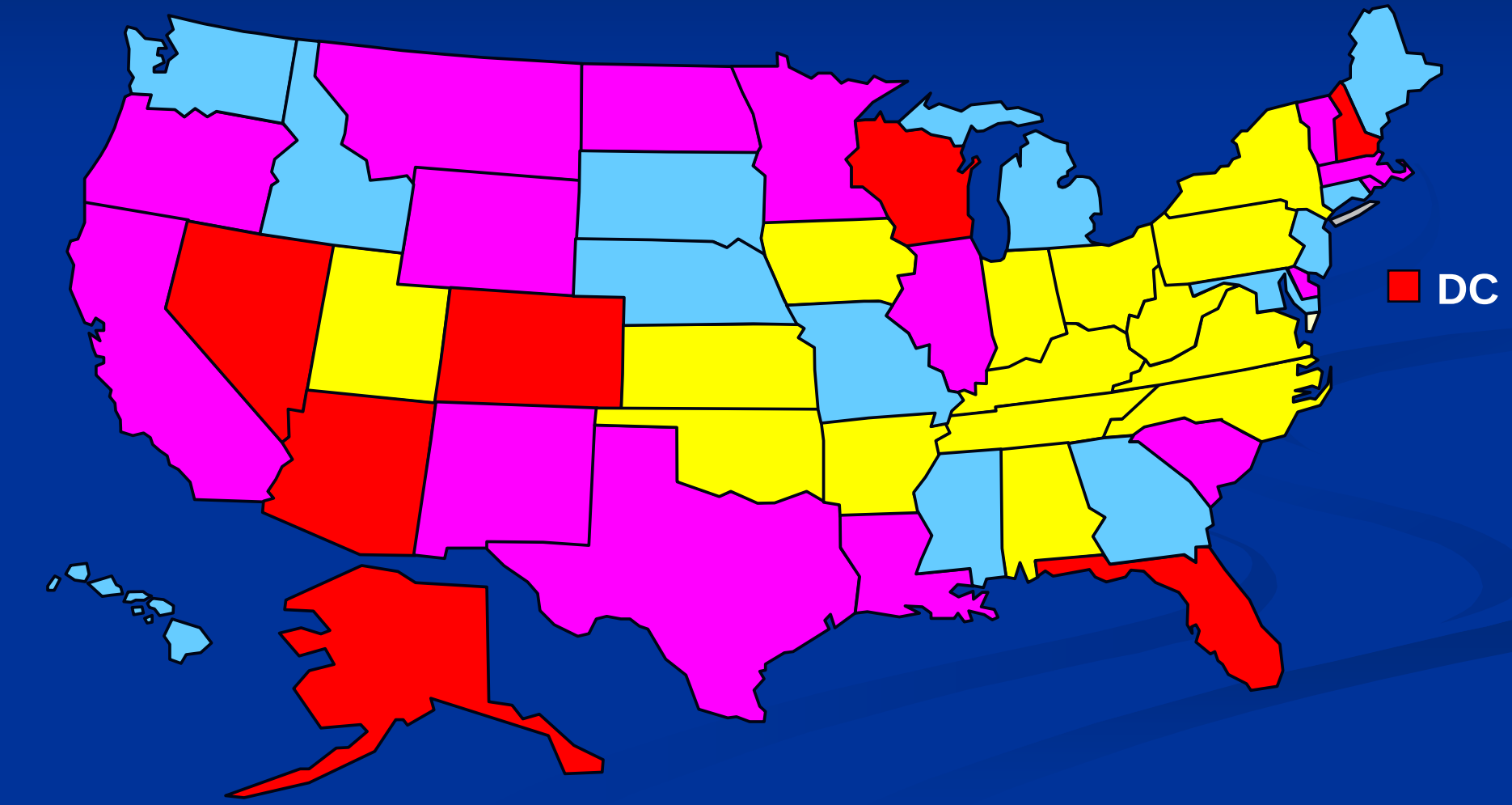


Factors Modifying the Ethanol Elimination Rate

- There is a 3-4 fold variability in the rate of ethanol elimination by humans because of genetic and environmental factors, including
  - Sex / genetic factors
  - Age
  - Race
  - Food
  - biological rhythms
  - Exercise
  - Alcoholism
  - Drugs / medications

Know Your State's Consumption

U.S. Total = 2.18



Clinical Components

- Withdrawal (acute and subacute)
- Tolerance
- Social devastation
- Medical consequences
  - CNS – depression, cognition
  - Non-CNS – liver, heart, renal, PNS, pancreas, etc

Risks vs. Benefits

	Risks	Benefits
Abstinence	▪Cardiovascular	▪Social
Moderate	▪Medication interactions	▪Social ▪Cardiovascular
At-Risk	▪Psychological distress ▪Suicide risk ▪Fractures ▪Adherence	▪Social
Abuse	▪Social ▪Legal	▪None
Dependence	▪All aspects of health / functioning	▪None

Barriers to Recognition and Treatment

- Patient factors
- Health professional factors
- Healthcare system factors
- Society factors
- Treatment factors

Treatment Options

- Brief therapies
- Self-help groups (AA, ACOA, etc.)
- Individual therapy
- Family therapy
- Psychoeducational activities
- Hypnosis
- Activities therapy
- Group therapy (elder specific)
- Psychopharmacology

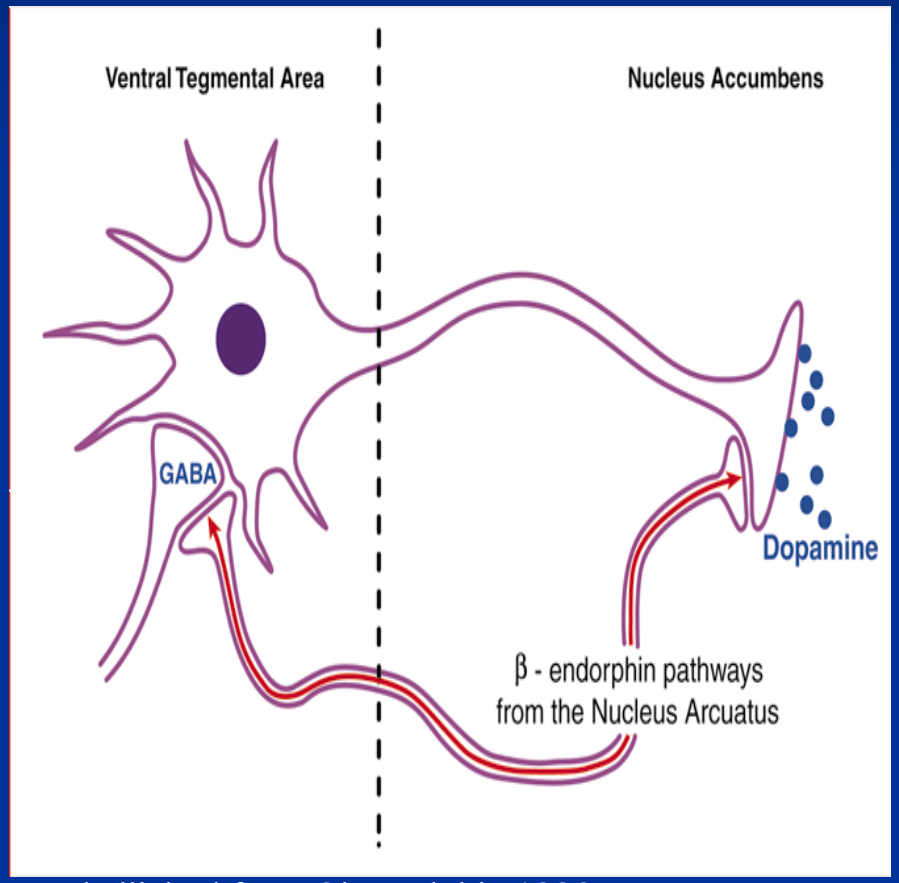
Caveats About Treatment

- Addiction treatment is not one size fits all. There are many options—use them
- Compliance with treatment is important. Continually support treatment
- Treatment is not a "carve out" available only in select settings
- While abstinence is often the goal, it is not the only goal

How does Alcohol work at the cellular level?

- Older hypotheses suggesting that ethanol has very generalized, non-specific actions on many neuronal systems seem unlikely
- At intoxicating concentrations, ethanol has some very specific actions on a number of membrane proteins
- Certain kinds of ligand-gated ion channels (i.e., postsynaptic receptors) appear to be an important target for ethanol action
- Experimental strategies need to be developed to determine which actions of ethanol are relevant to specific behavioral effects

Opioid antagonists - basic science



Embellished from Gianoulakis 1998

- Alcohol consumption affects the production, release, and activity of opioid peptides (Herz, 1997)
- Opioid peptides mediate some of alcohol's rewarding effects by enhancing midbrain dopamine release
- Opioid antagonists suppress alcohol-induced reward (Swift,1999) and general consummatory behaviors (Boyle et al. 1998)
- Genetic high-risk / FH+ individuals have an exaggerated alcohol-induced rise in β-endorphin level, and are more responsive to naltrexone treatment (Gianoulakis et al. 1996; King et al. 1997)

Naltrexone

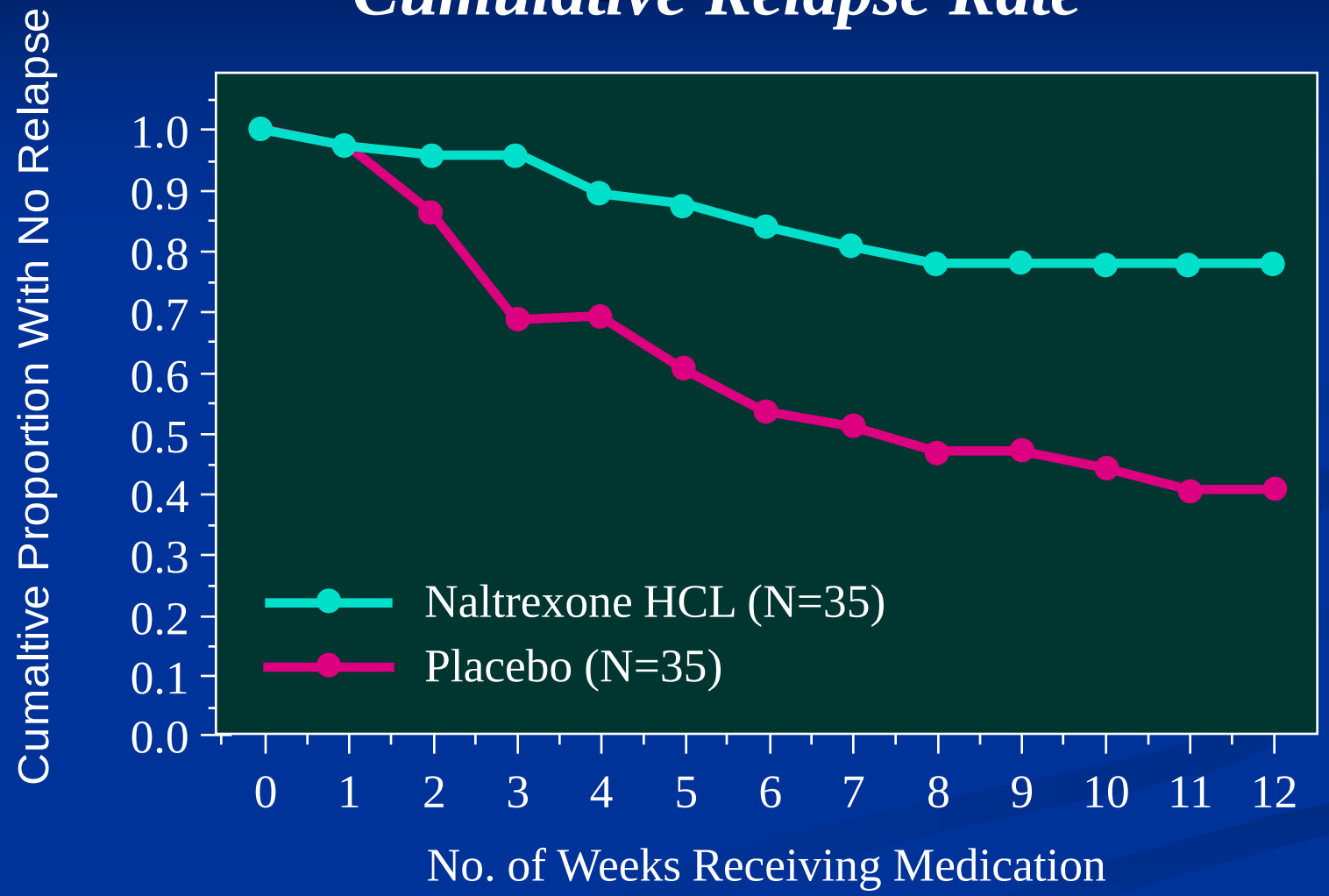
- Functions as an opioid receptor antagonist (mu >> delta or kappa)
- Development was an example of bench to bedside translational science (opioid effects on reward pathways)

Randomized Placebo Controlled Naltrexone Trials

Studies supporting efficacy			Studies not supporting efficacy		
Study	# Ss	Notes	Study	# Ss	Notes
Volpicelli et al 1992	70	None	Oslin et al 1997	44	Older
O'Malley et al 1992	97	None	Kranzler et al 2000	183	None
Volpicelli et al 1997	97	None	Krystal et al 2001	627	VA only
Kranzler et al 1998	20	Depot	Lee et al 2001 (Singapore)	53	None
Anton et al 1999	131	None	Gastpar et al 2002 (Germ.)	171	None
Chick et al 2000 (UK)	169	Adherence	Kranzler et al 2004	315	Depot
Monterosso et al 2001	183	None	Killeen et al 2004	145	None
Morris et al 2001 (Australia)	111	None	Oslin et al in press	240	None
Heinala et al 2001 (Finland)	121	Nonabst.			
Latt et al 2002 (Australia)	107	None			
Ahmadi and Ahmadi 2002 (Iran)	116	None			
Guardia et al 2002 (Spain)	202	None			
Balldin 2003	118	None			
Kiefer et al 2003 (Germany)	160	None			
Kranzler et al 2003	153	None			
Kranzler et al 2004	315	For drinking not relapse			
Anton et al 2004	270	None			

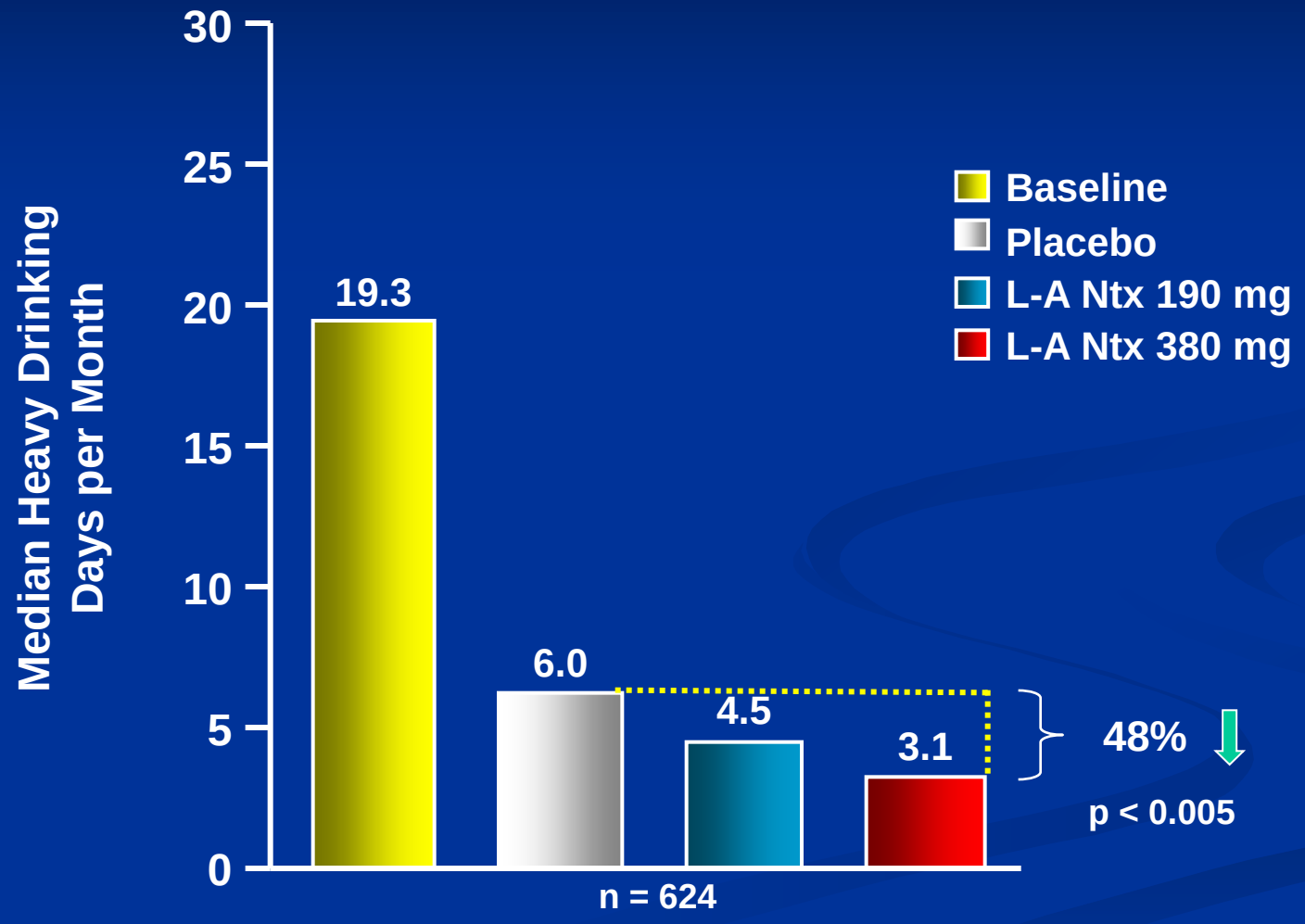
Naltrexone in the Treatment of Alcohol Dependence

Cumulative Relapse Rate



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

Long-Acting Naltrexone Results: Median Heavy Drinking Days



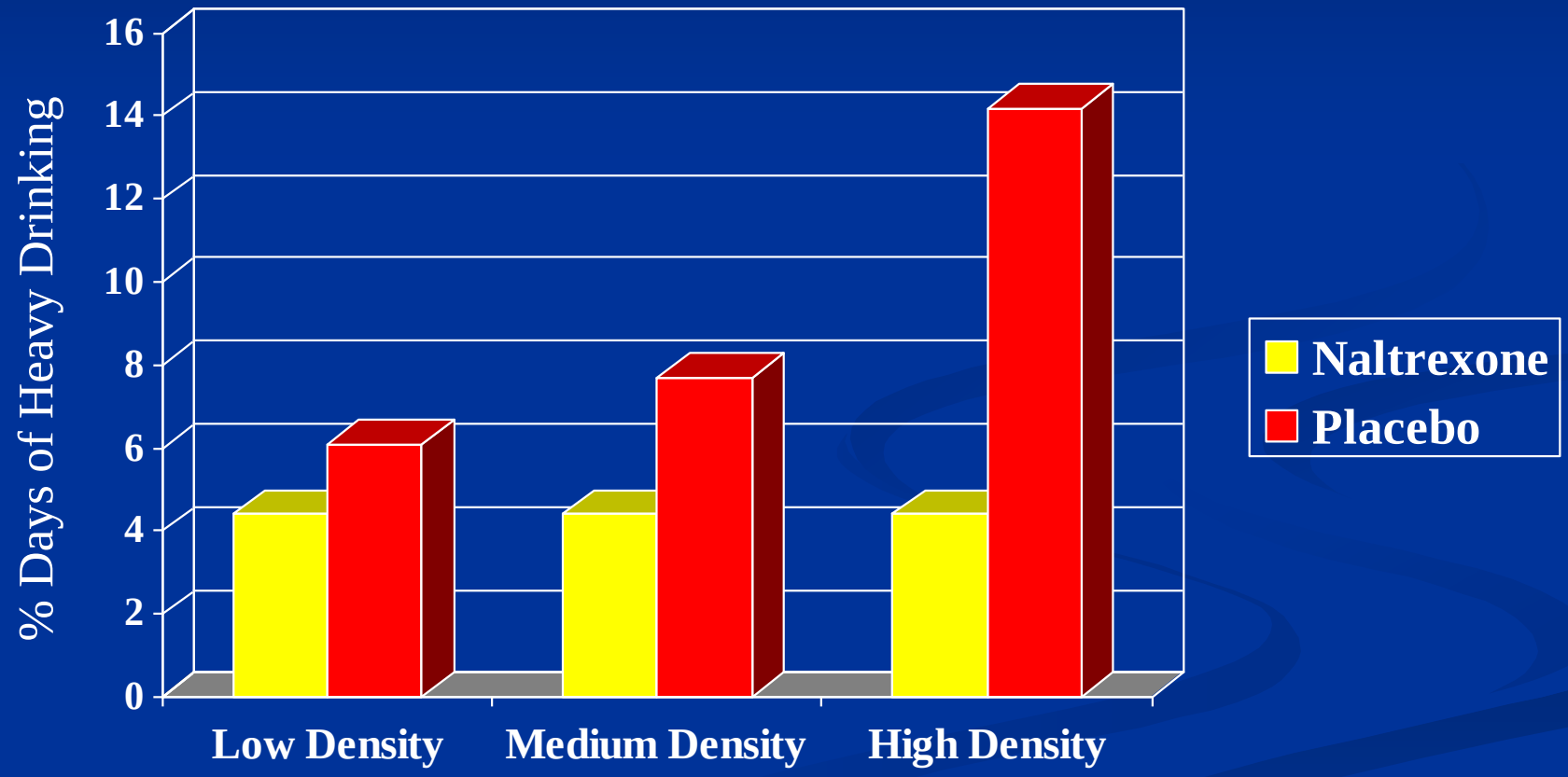
For Whom?

- Under what conditions and for which patients will naltrexone have the greatest impact?
- Treatment variance is common
  - High levels of craving that improves after treatment: better response
  - Alcoholics who use alcohol to treat anxiety and distress respond less well than those who use it to satisfy craving
  - Adherence
  - Gender / Race
  - Pharmacokinetics
  - Pharmacodynamics

Naltrexone Should Be Used for Patients With:

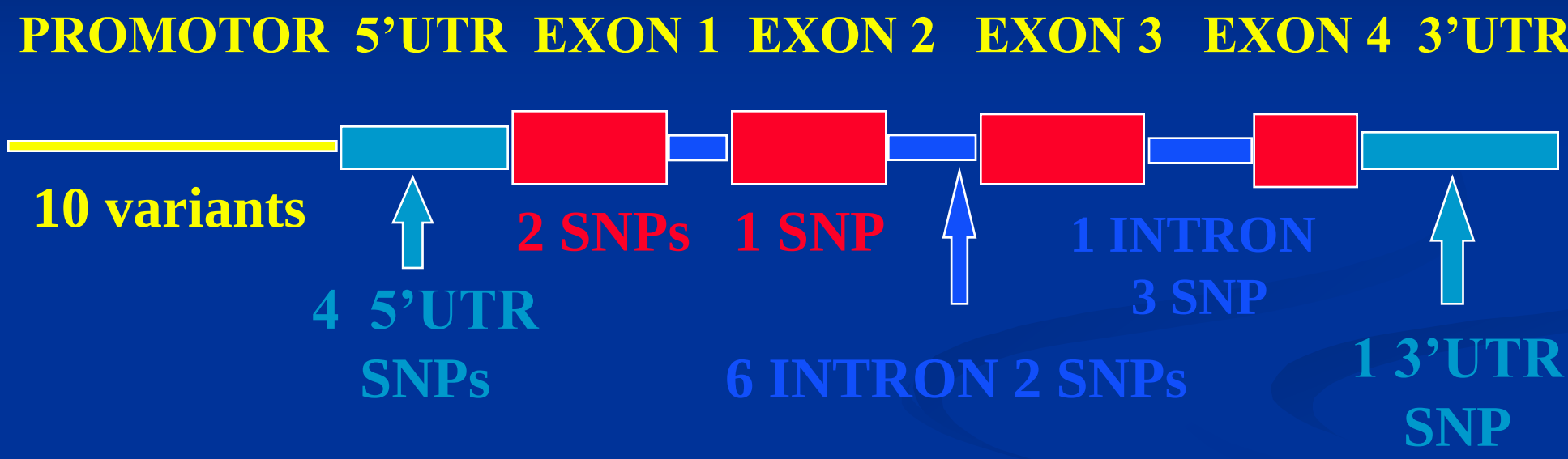
- Prior treatment failure
- High level of interest in biomedical therapies
- Low level of interest in traditional psychosocial therapies
- Cognitive impairment
- In most alcohol-dependent patients
- Consider depot formulation for added adherence

Effects of Family History on Naltrexone Response



Monterosso et al 2001

Human Mu Opioid Receptor Gene



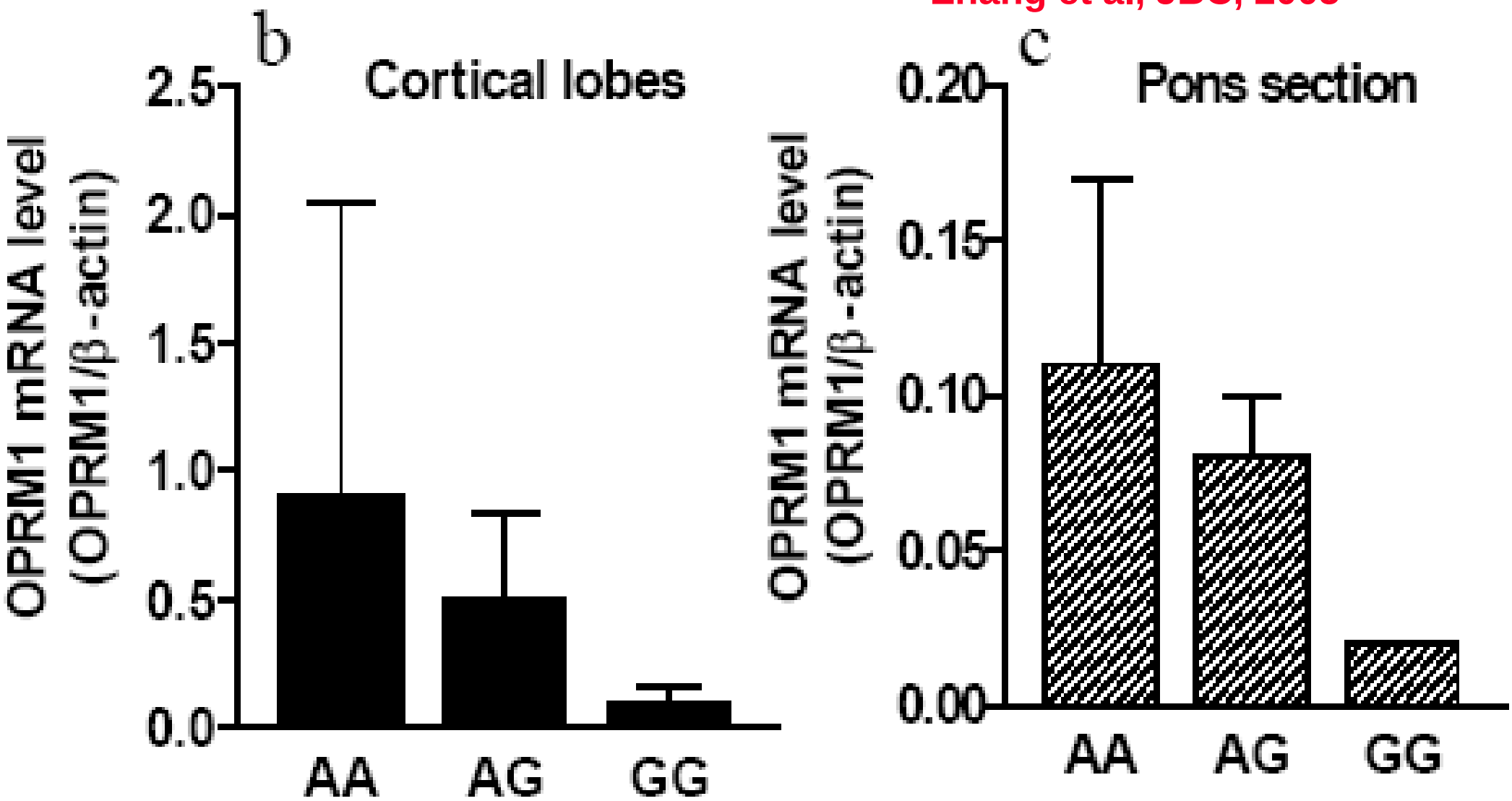
OPRM1 gene is estimated to span at least 90 kb in the chromosome 6q24-25 region. Four coding exons are separated by 3 introns.

A+118G (Asn40Asp)

- Asp40 allele frequency of 13-20% (24.3 – 36% of European Americans have at least one copy)
- Functional Significance:
  - Asp40 variant binds beta-endorphin and activates G- protein coupled protein potassium ion channels with 3 times greater potency
  - Naloxone challenge alters CRF secretion in those with the Asp40 variant
  - Asp40 variant appears to be transcribed less efficiently than Asn40
  - Asp40 increases pain sensitivity

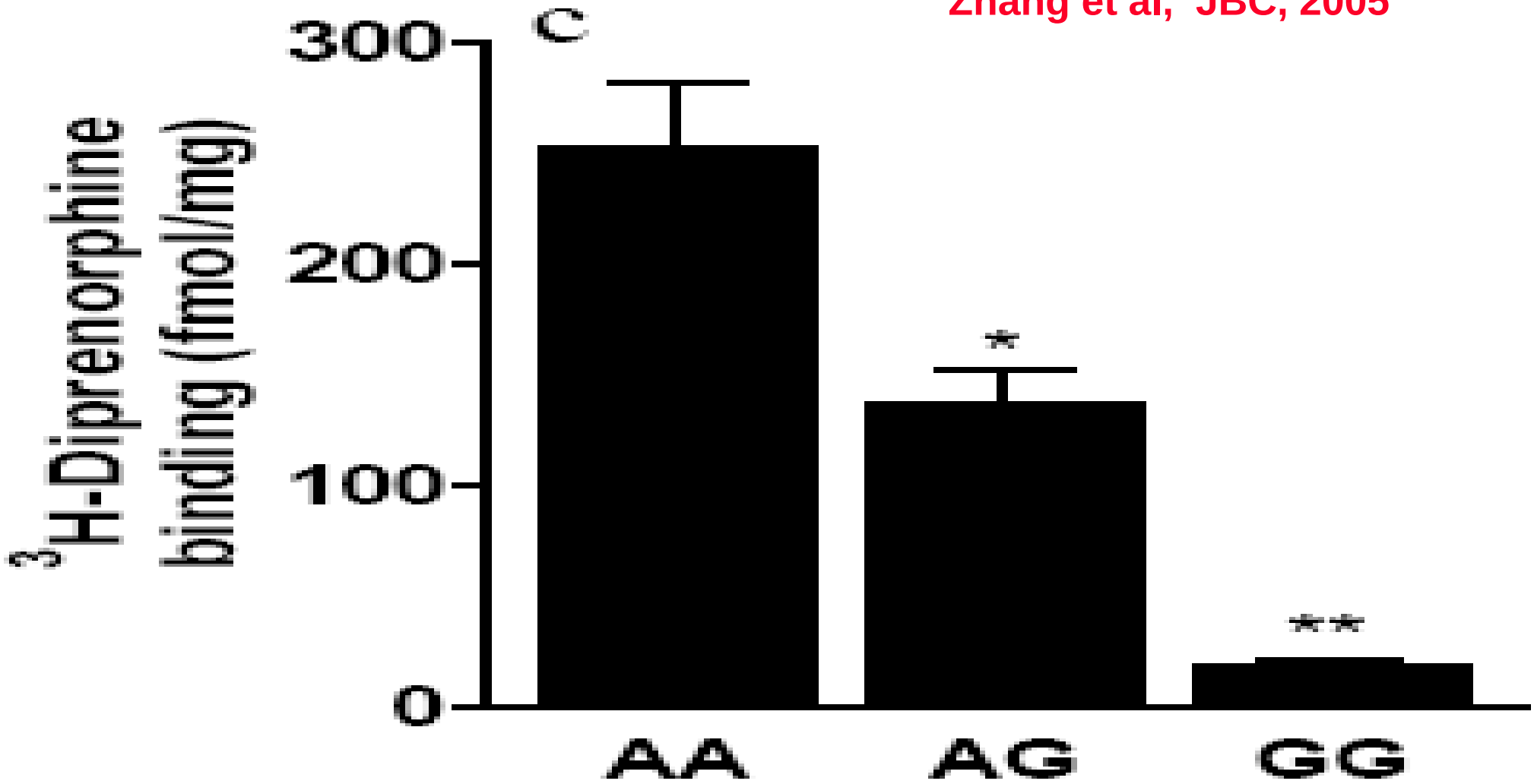
OPRM1 A118G EFFECT ON TRANSCRIPTION

Zhang et al, JBC, 2005

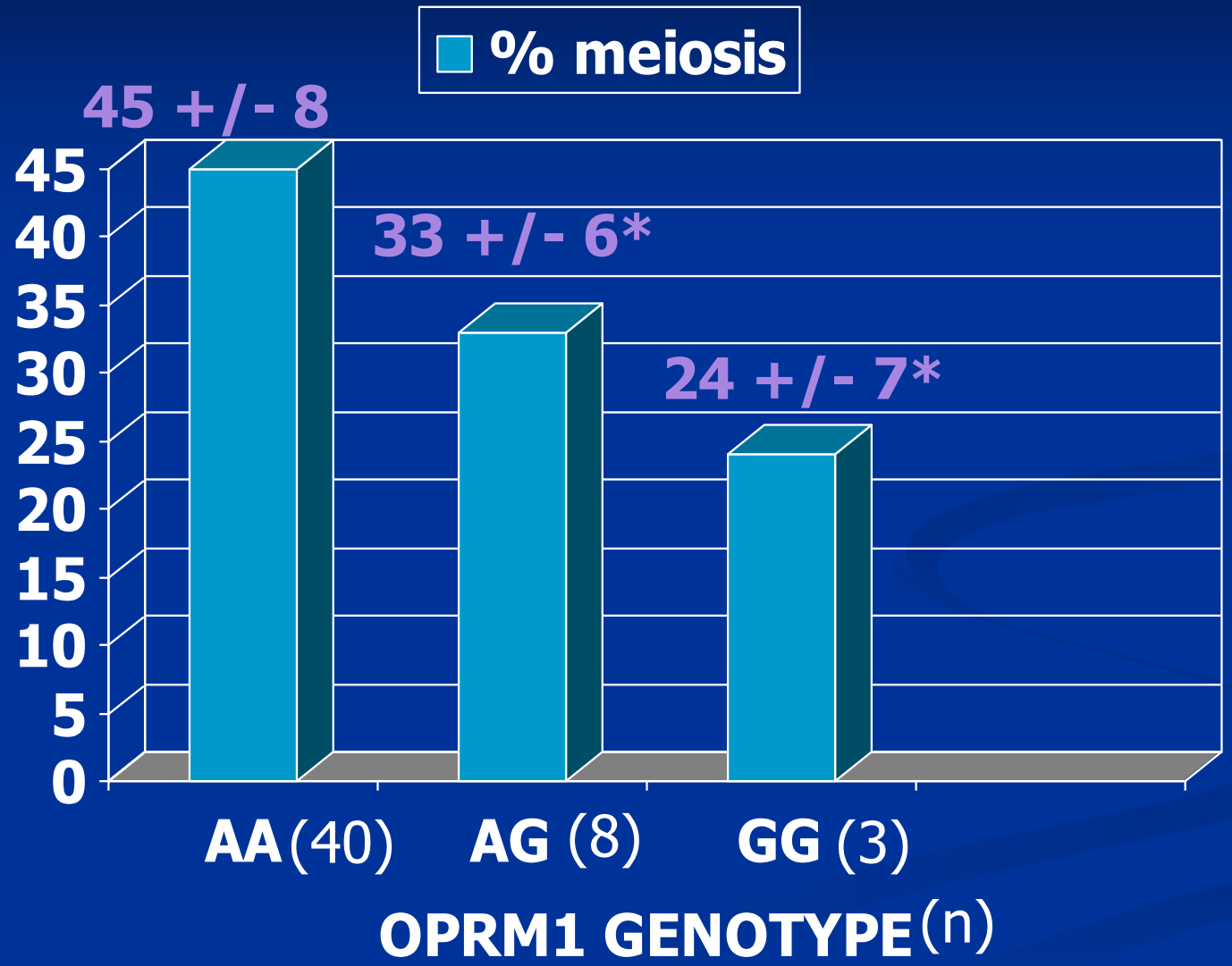


OPRM1 A118G EFFECT ON TRANSLATION

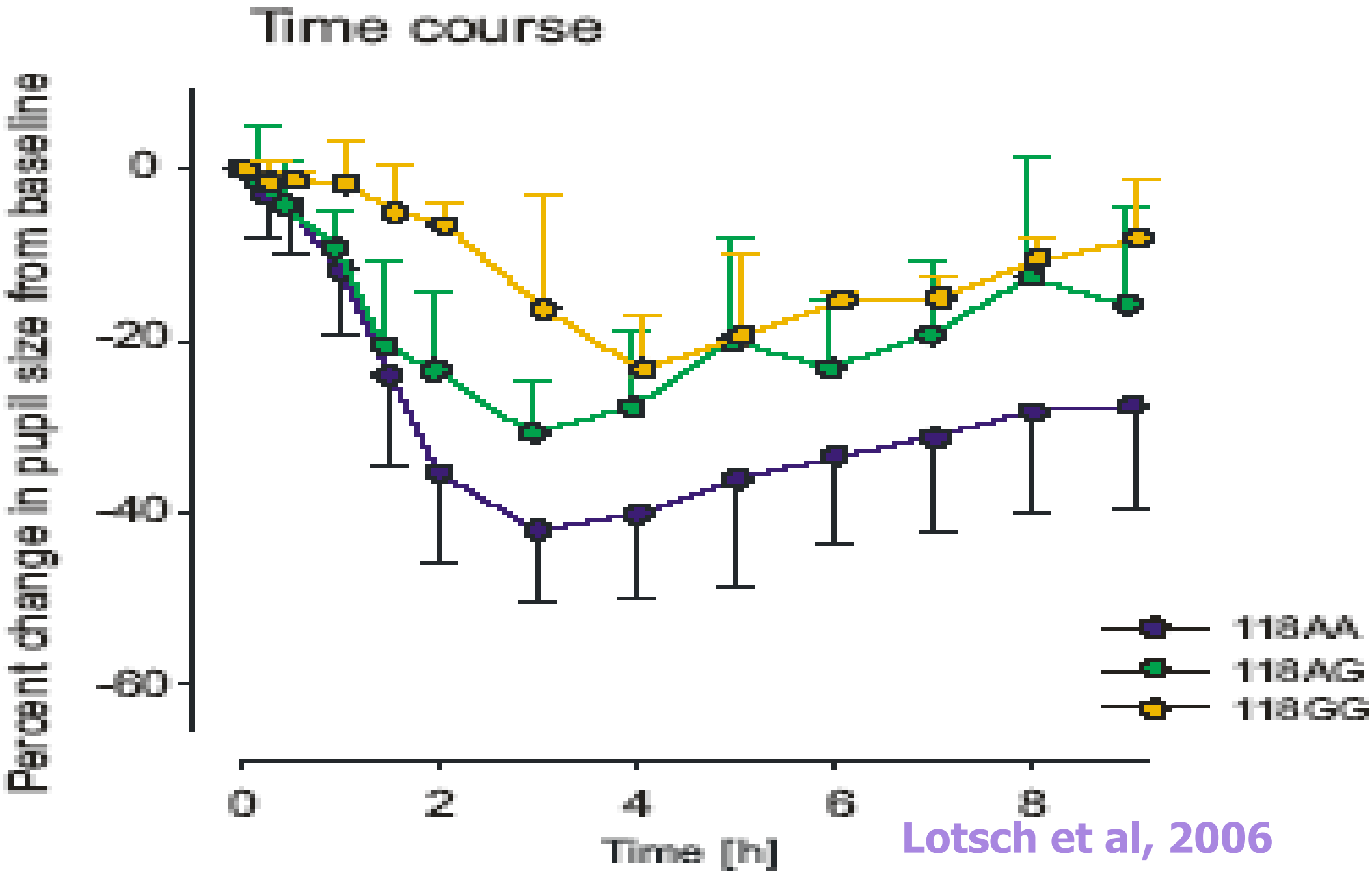
Zhang et al, JBC, 2005



in vivo A118G Effects in Response to a mu Opioid Receptor Agonist



- p<0.001 AA vs AG/GG Lotsch et al, 2006

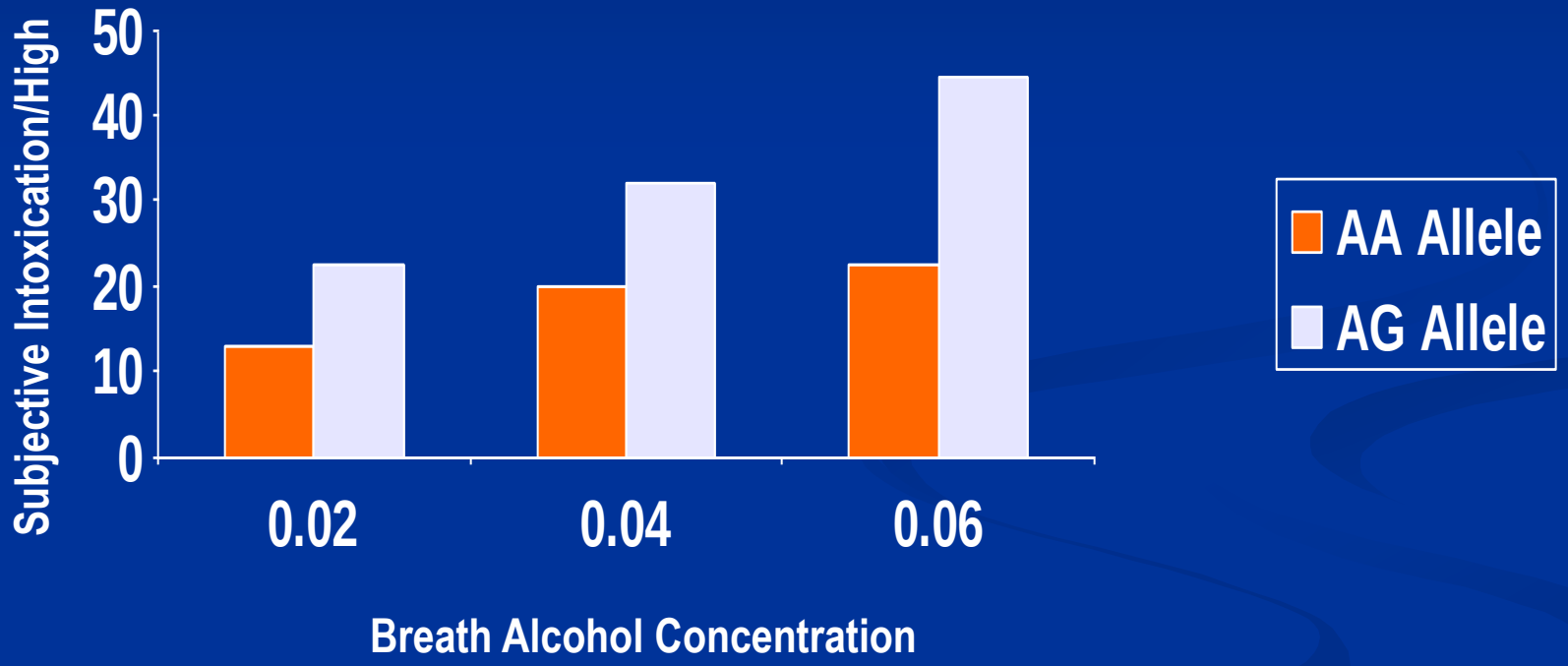


Lotsch et al, 2006

G Allele Carriers Hyporesponsive to mu Opioid Receptor Agonists

- Romberg et al. Polymorphism of mu-opioid receptor gene (OPRM1:c.118AG) does not protect against opioid-induced respiratory depression despite reduced analgesic response. Anesthesiology 2005;102:522-30.
- Klepstad et al. The 118 A G polymorphism in the human mu-opioid receptor gene may increase morphine requirements in patients with pain caused by malignant disease. Acta Anaesthesiol Scand 2004;48:1232-9

Alcohol Induced Stimulation



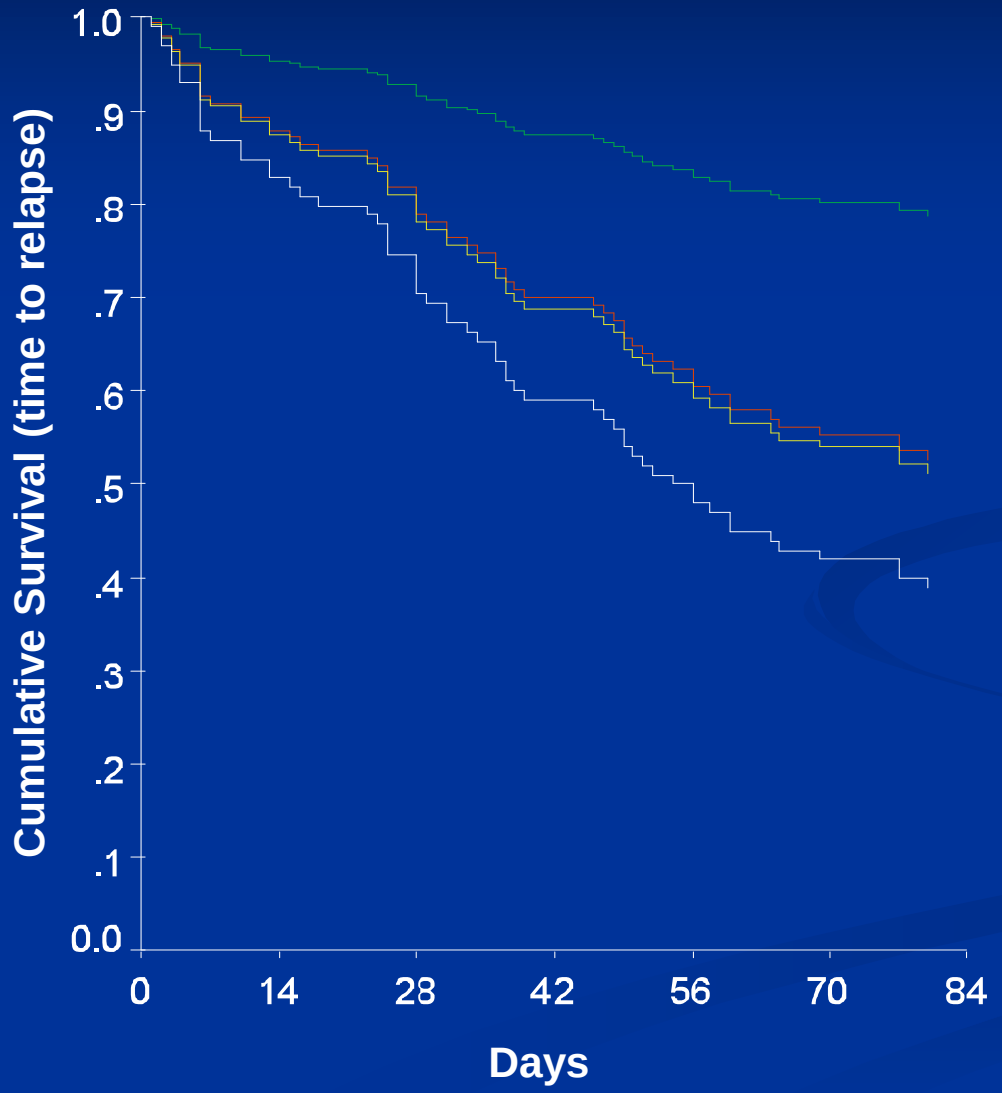
- Ray and Hutchinson, 2004

Does Genotype influence Treatment Response with opioid receptor antagonism?

Data Supporting Genetic Influences

- 4-fold increased risk in close relatives (e.g. children, siblings)
- Identical vs fraternal twins
- Adopted away children still have a 4-fold increase in risk
- Work with genetic animal models

Genetic Polymorphisms and Alcohol Treatment



Naltrexone / Asp40 Allele (A/G, G/G)

Naltrexone Asn40 Allele (A/A)

Placebo / Asp40 Allele (A/G, G/G)

Placebo / Asn40 Allele (A/A)

Oslin DW, et. al. 2003

COMBINE Study

Good Clinical Outcome (%)

	Asn40/Asn40	Asp40
Naltrexone	**73**	**96**
Placebo	**63**	**51**

Relapsed (%)

	Asn40/Asn40	Asp40
Naltrexone	**21**	**4**
Placebo	**29**	**12**

Conclusions

Alcoholism is a major public health problem associated with medical, psychiatric, and economic consequences

Alcoholism is a Brain Disorder

- Activates & dysregulates reward-related circuits
- Important genetic basis
- Responds to Pharmacotherapy

Stigma prevents its proper diagnosis and treatment

Understanding the biological basis of alcoholism will reduce its stigma and improve its prognosis

Question # 1

- True or False: The annual cost for the consequences of alcoholism in the US exceeds the annual cost of the Iraq war.

Question # 2

Which of the following diseases requires a lifestyle change for adequate treatment:

1. Diabetes
2. Heart disease
3. Alcoholism
4. Arthritis
5. All of the above

Question # 3

Naltrexone

1. Is a mu opioid receptor agonist
2. Reduces heavy drinking days more than placebo
3. Has a long acting injectable formulation that is free of serious side effects
4. Works best in patients who drink to self-medicate stress or mood symptoms
5. Works least well in familial forms of alcoholism

Question # 4

The opioid receptor gene has alleles that

1. Are associated with increased pain sensitivity
2. Are associated with a greater likelihood of intoxication after drinking a given amount of alcohol
3. When present in alcoholics are associated with response to naltrexone
4. 1, 2, and 3 are correct

Answers to Questions

- 1. True. Alcoholism costs $150 billion per year and the Iraq war is costing $120 billion (estimate in October, 2008)
- 2. 5
- 3. 2
- 4. 4