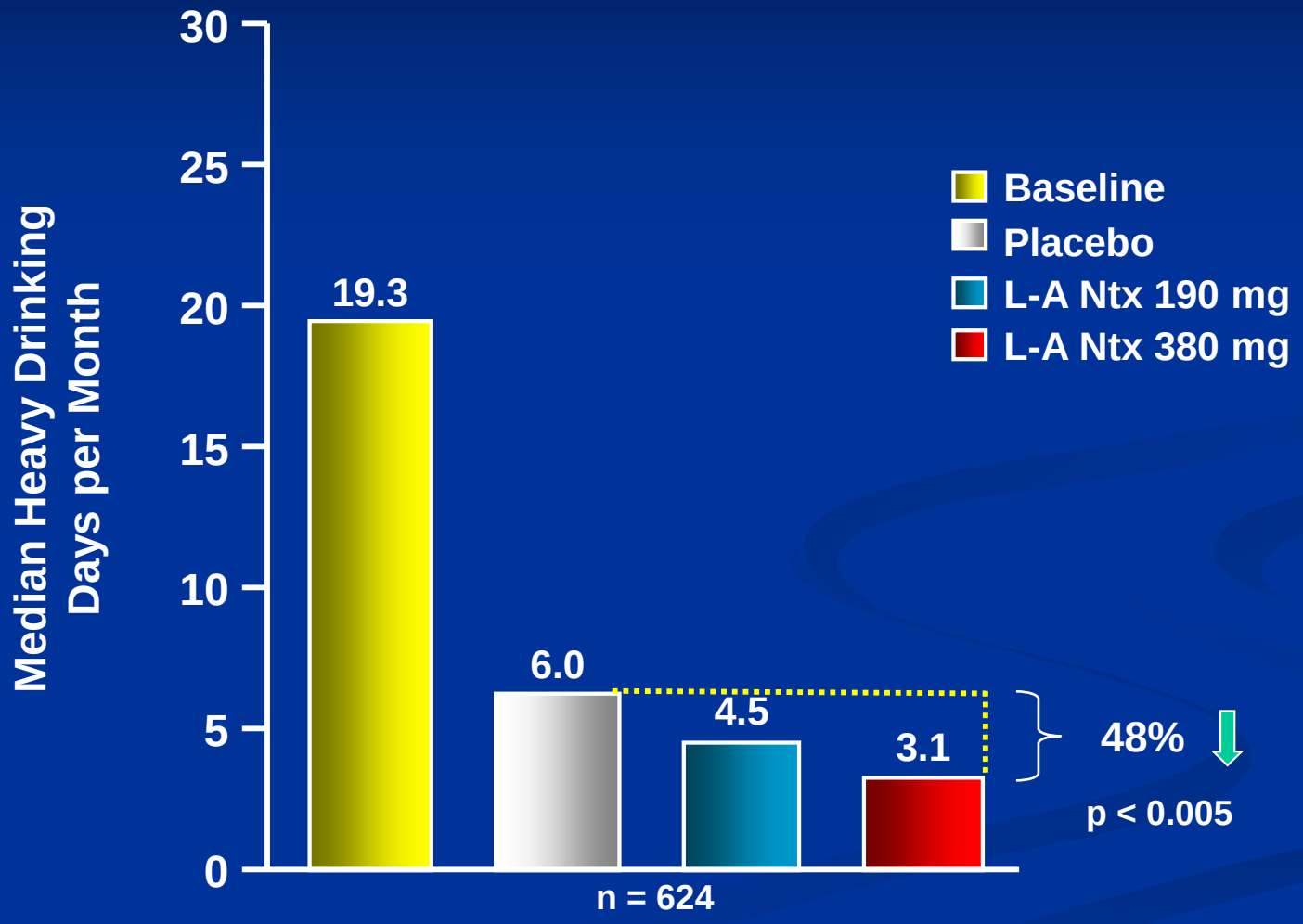
Long-Acting Naltrexone Results: Median Heavy Drinking Days



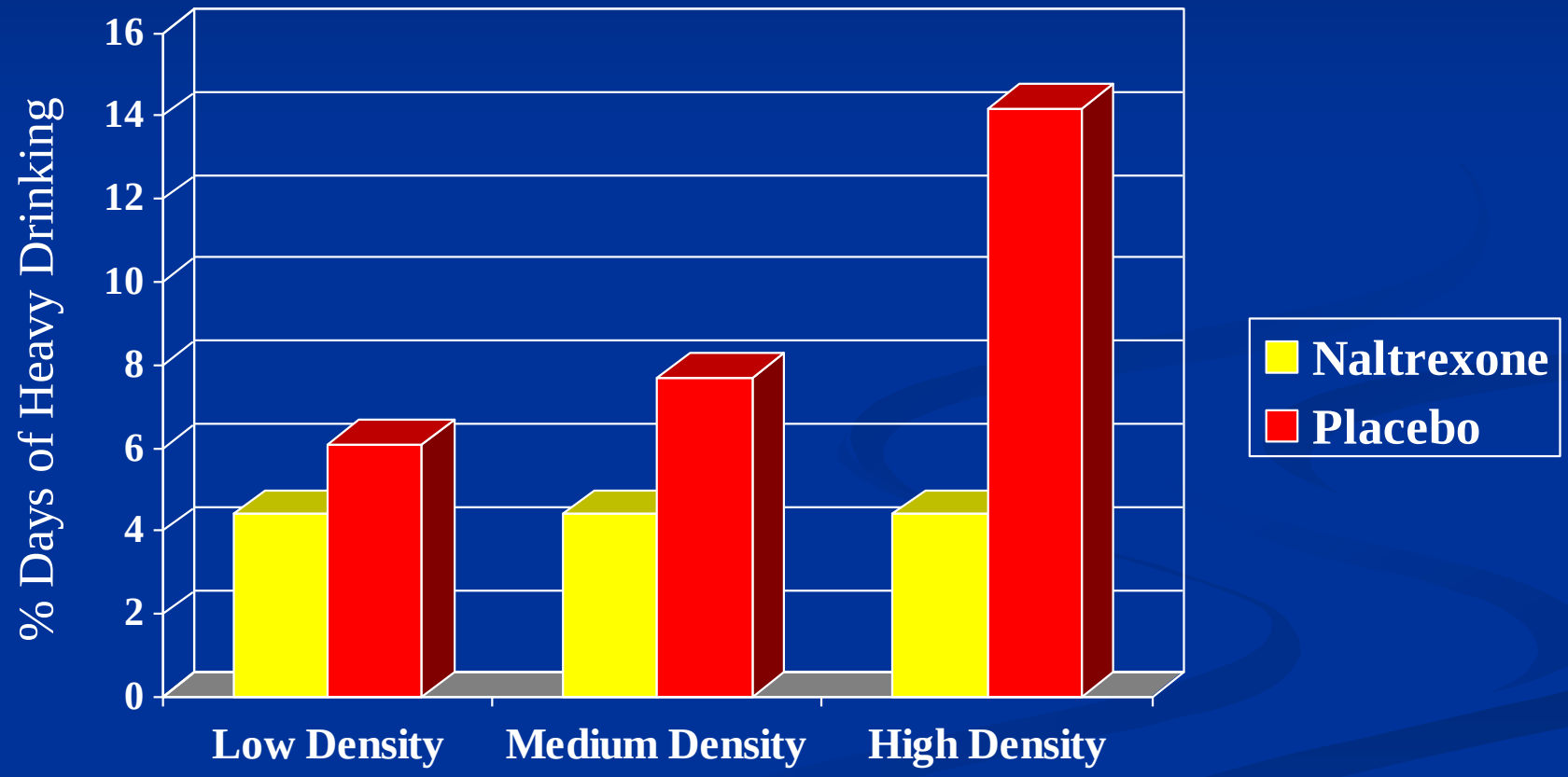
For Whom?

- 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:

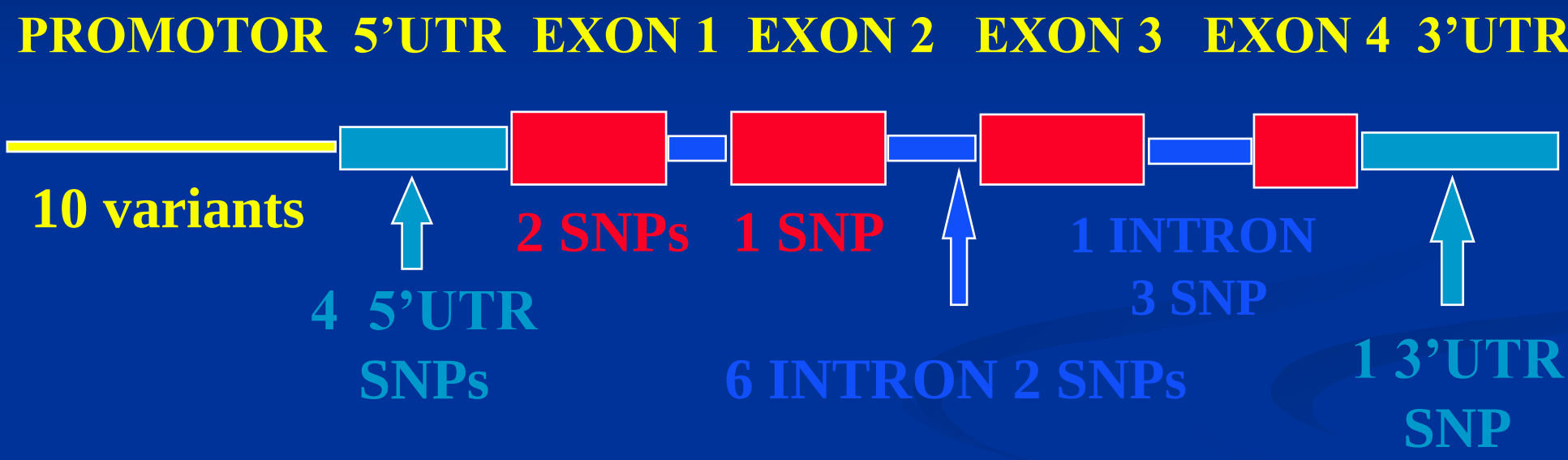
- Prior treatment failure
- High level of interest in biomedical therapies
- Low level of interest in traditional psychosocial therapies
- Cognitive impairment
- In most alcohol-dependent patients
- Consider depot formulation for added adherence

Effects of Family History on Naltrexone Response



Monterosso et al 2001

Human Mu Opioid Receptor Gene



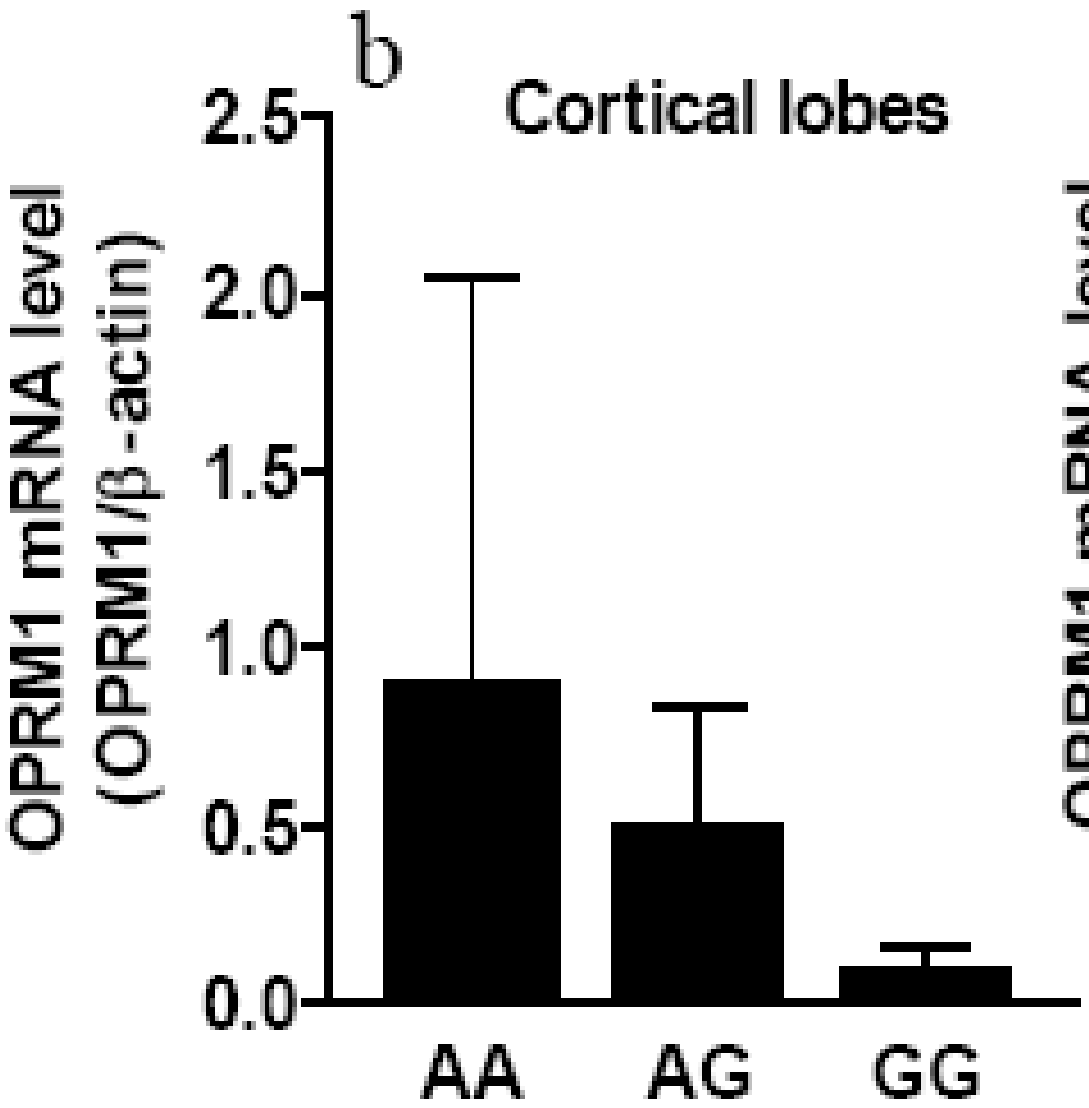
OPRM1 gene is estimated to span at least 90 kb in the chromosome 6q24-25 region. Four coding exons are separated by 3 introns.

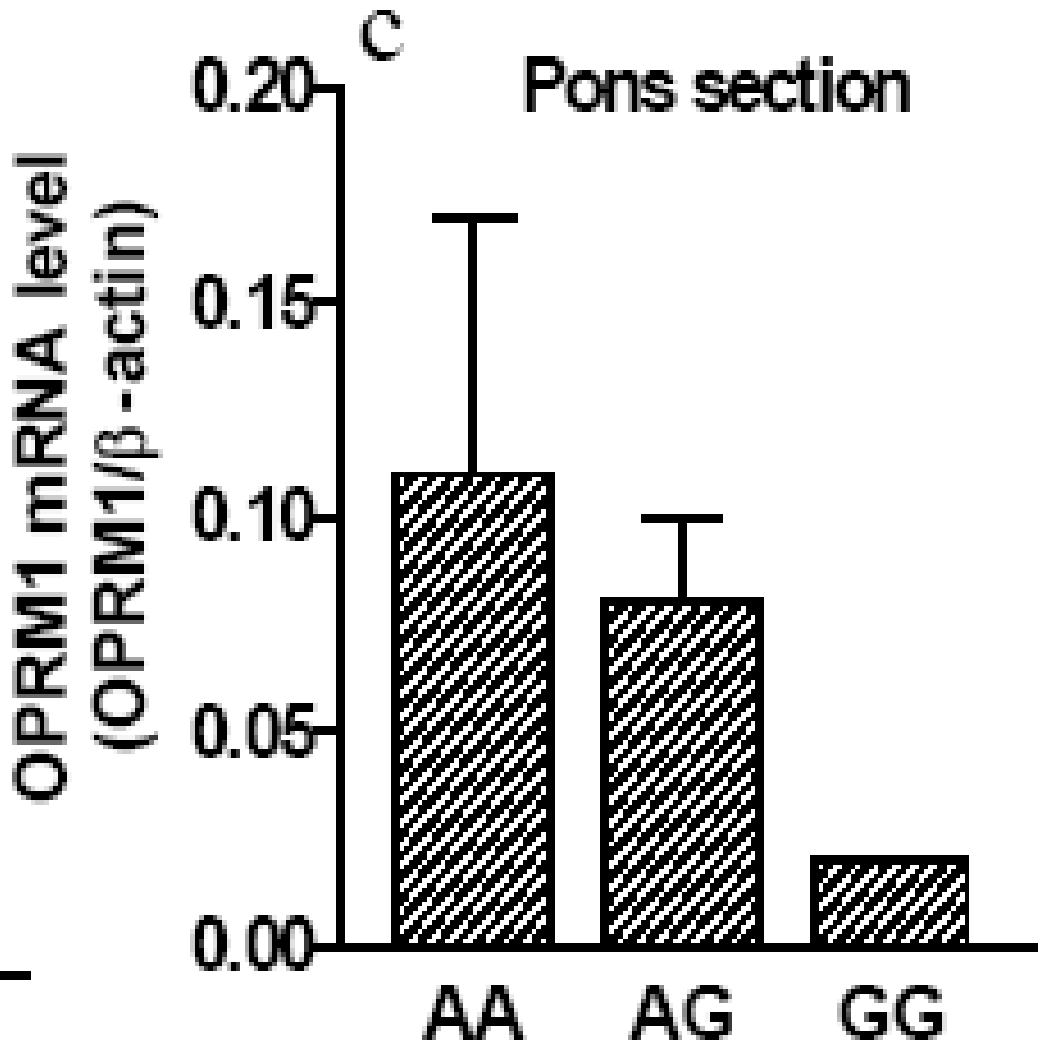
A+118G (Asn40Asp)

- 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

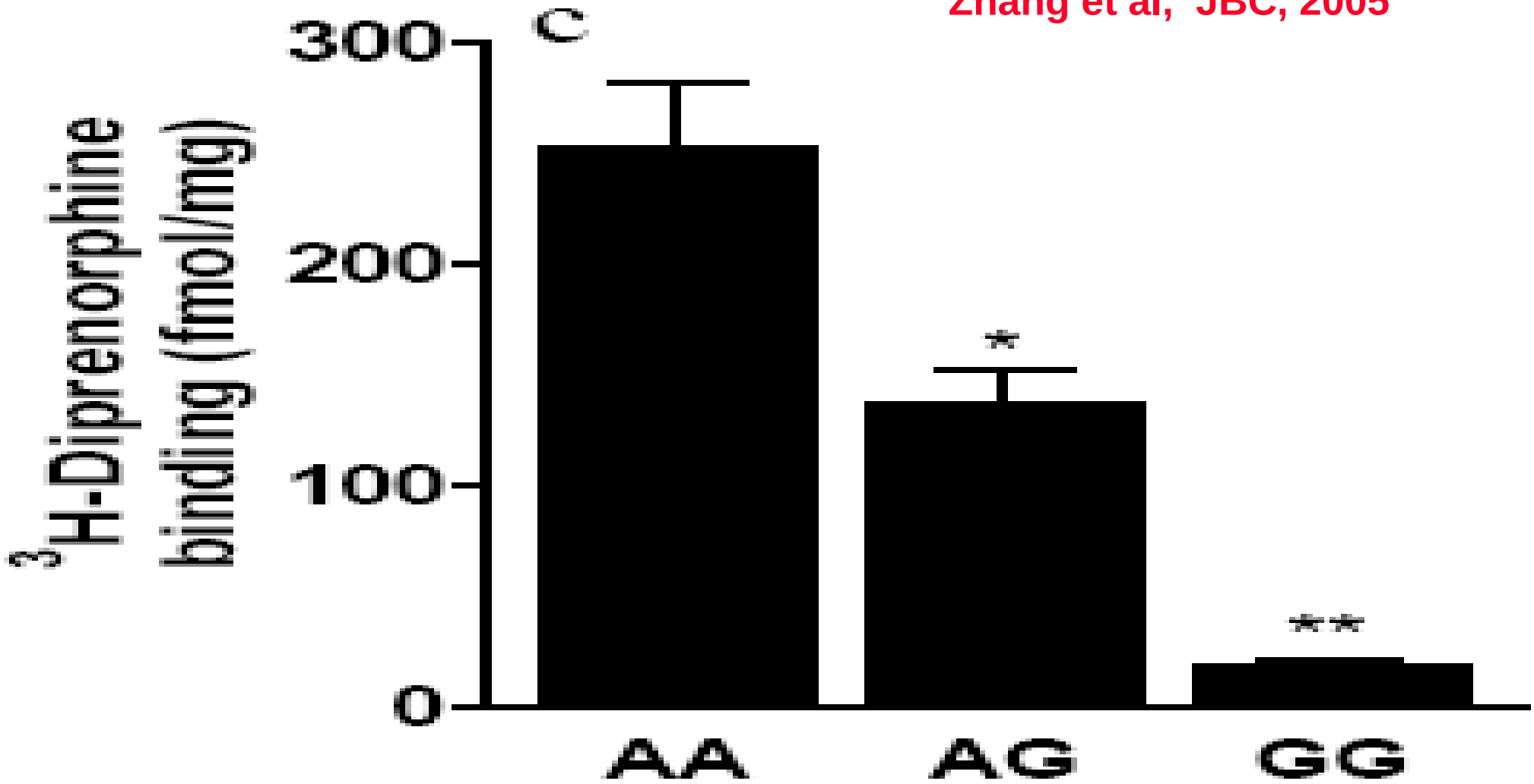
Zhang et al, JBC, 2005



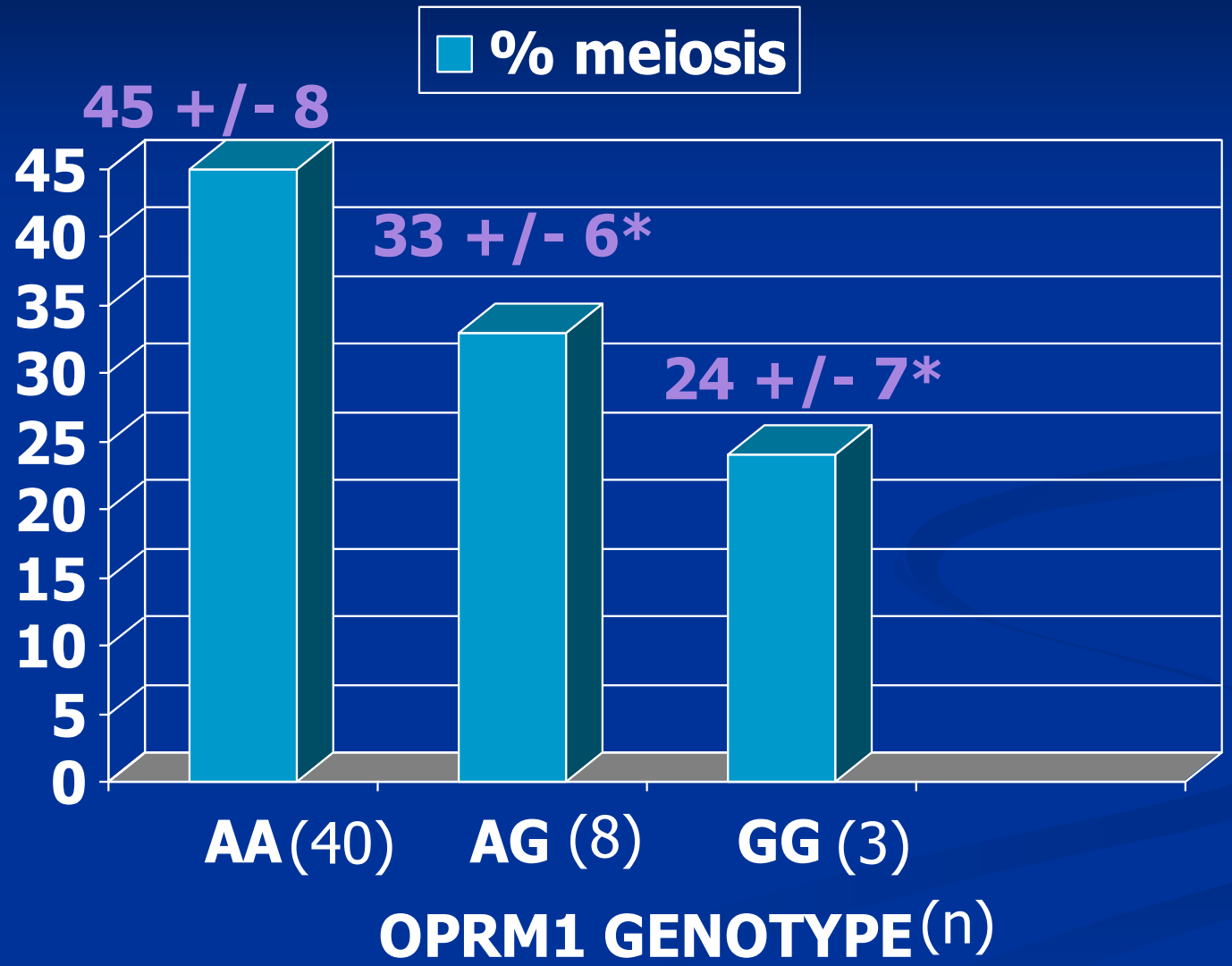


OPRM1 A118G EFFECT ON TRANSLATION

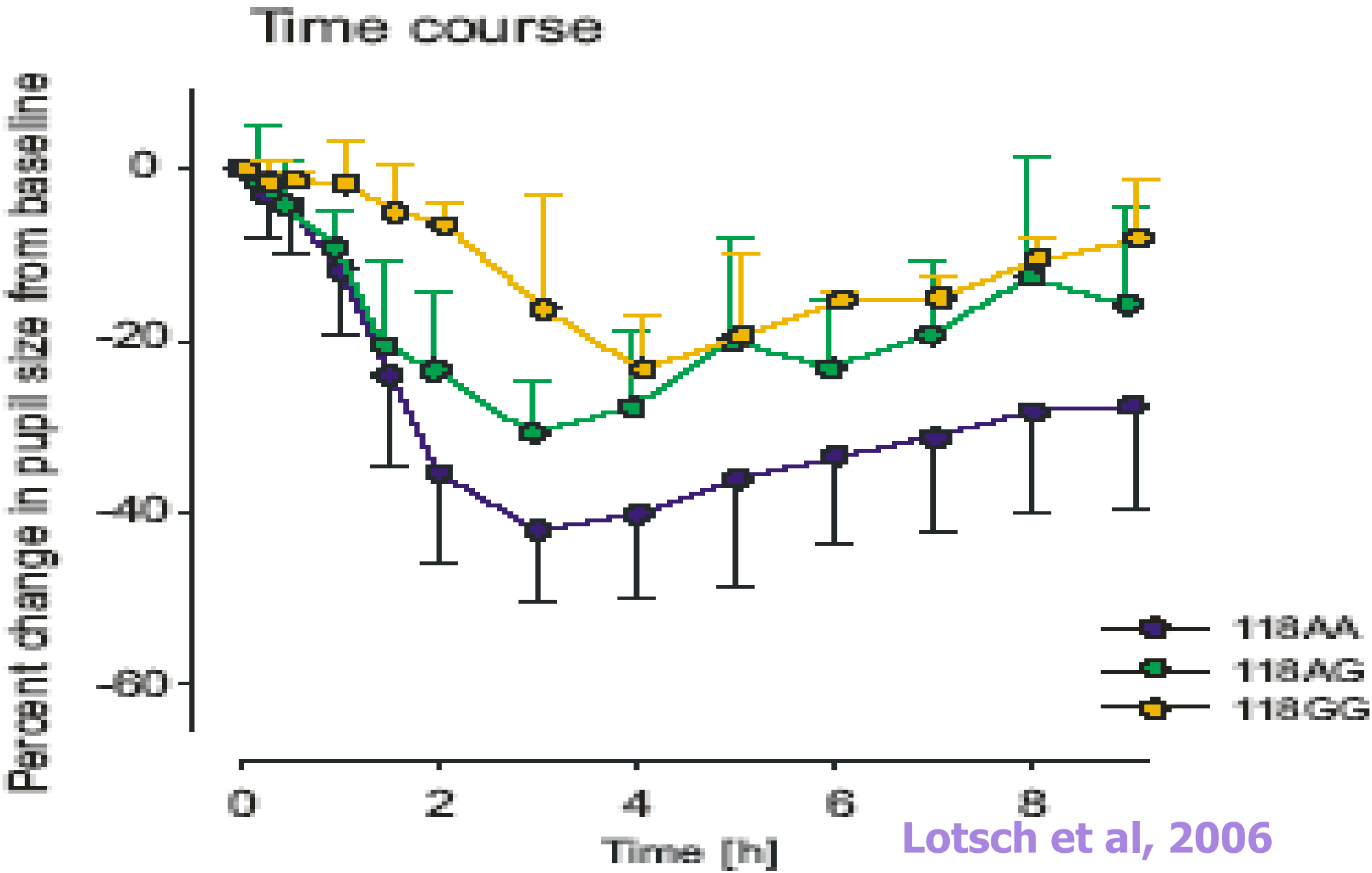
Zhang et al, JBC, 2005



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



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

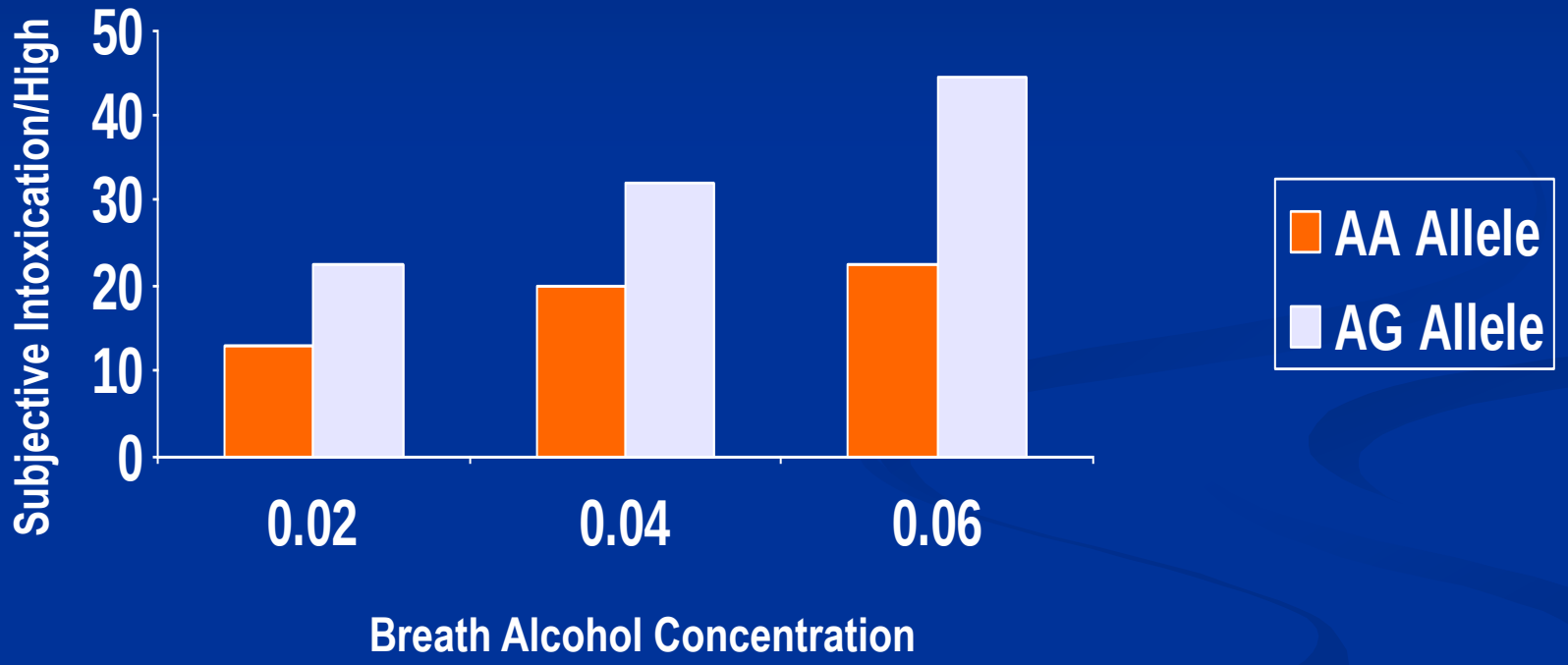


Lotsch et al, 2006

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



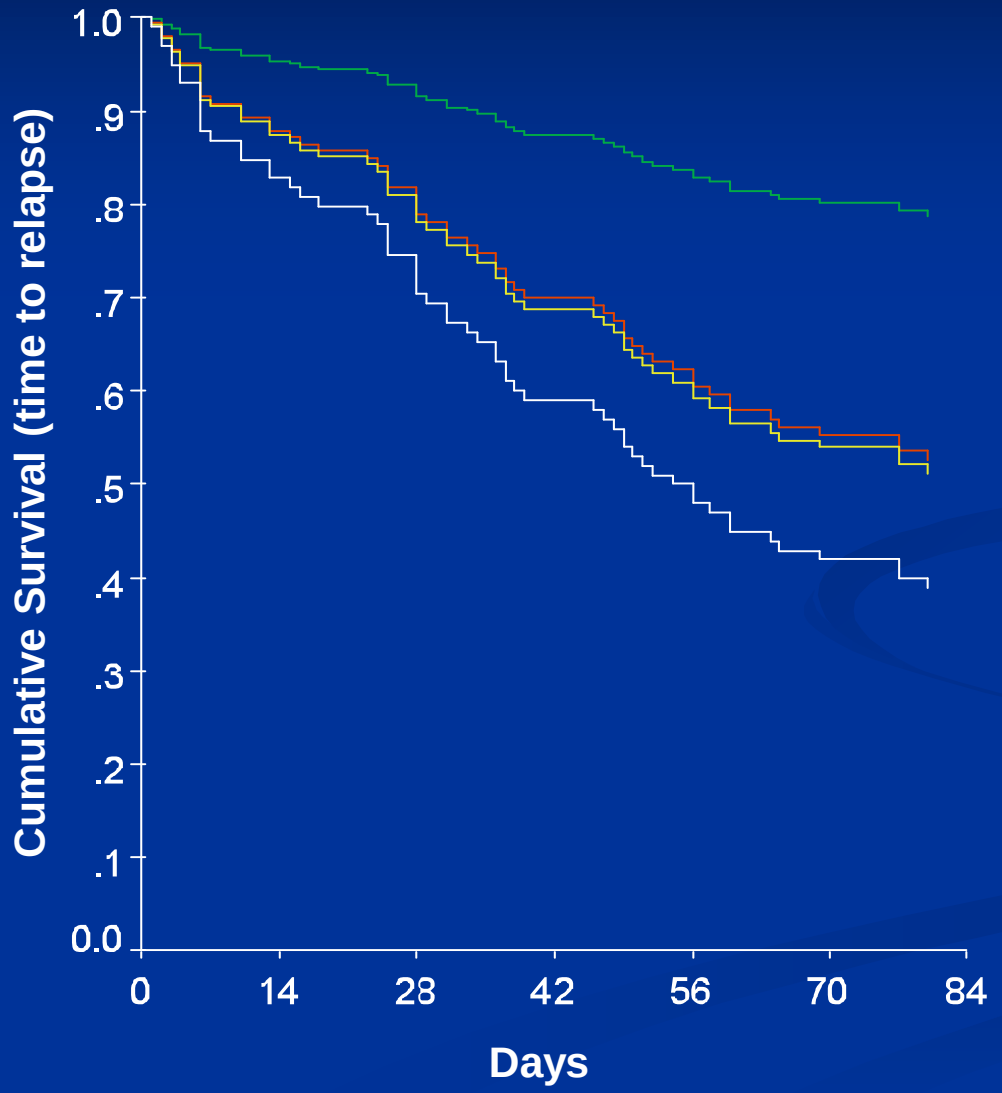
- Ray and Hutchinson, 2004

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