Nicotine-Opioid System Interactions: From Mouse to Man to Medicine

PENN TTURC
Abramson Cancer Center

Nicotine Dependence Treatment

- Despite progress in tobacco control research, almost one quarter of Americans continue to smoke.

- FDA-approved medications, NRT and bupropion, are effective for only a fraction of smokers. As many as 80% of smokers respond poorly or not at all to these therapies.

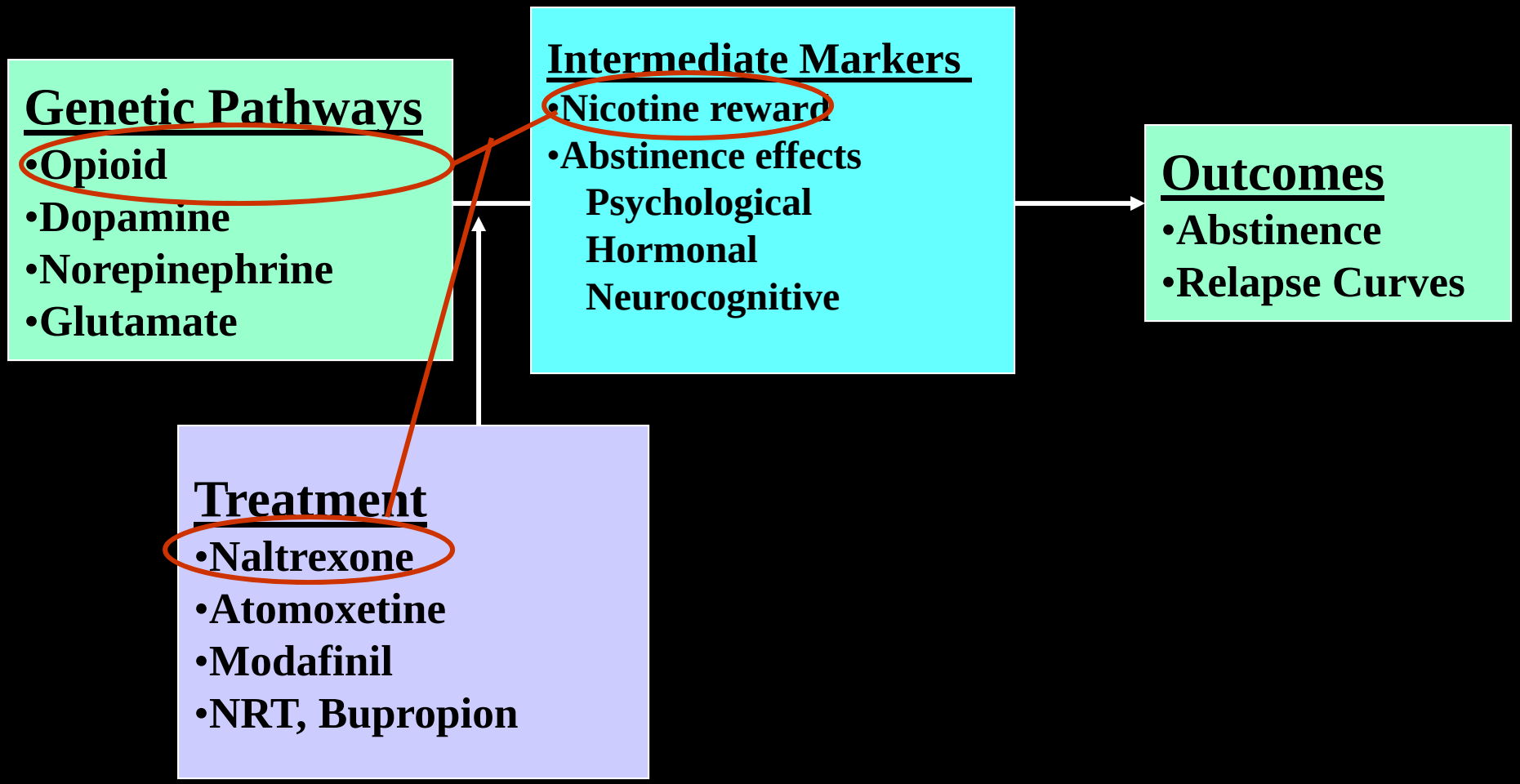
- There is a need to develop new treatment models that can be readily translated to the clinical setting to maximize the effectiveness of nicotine dependence treatment.

TTURC2 Research

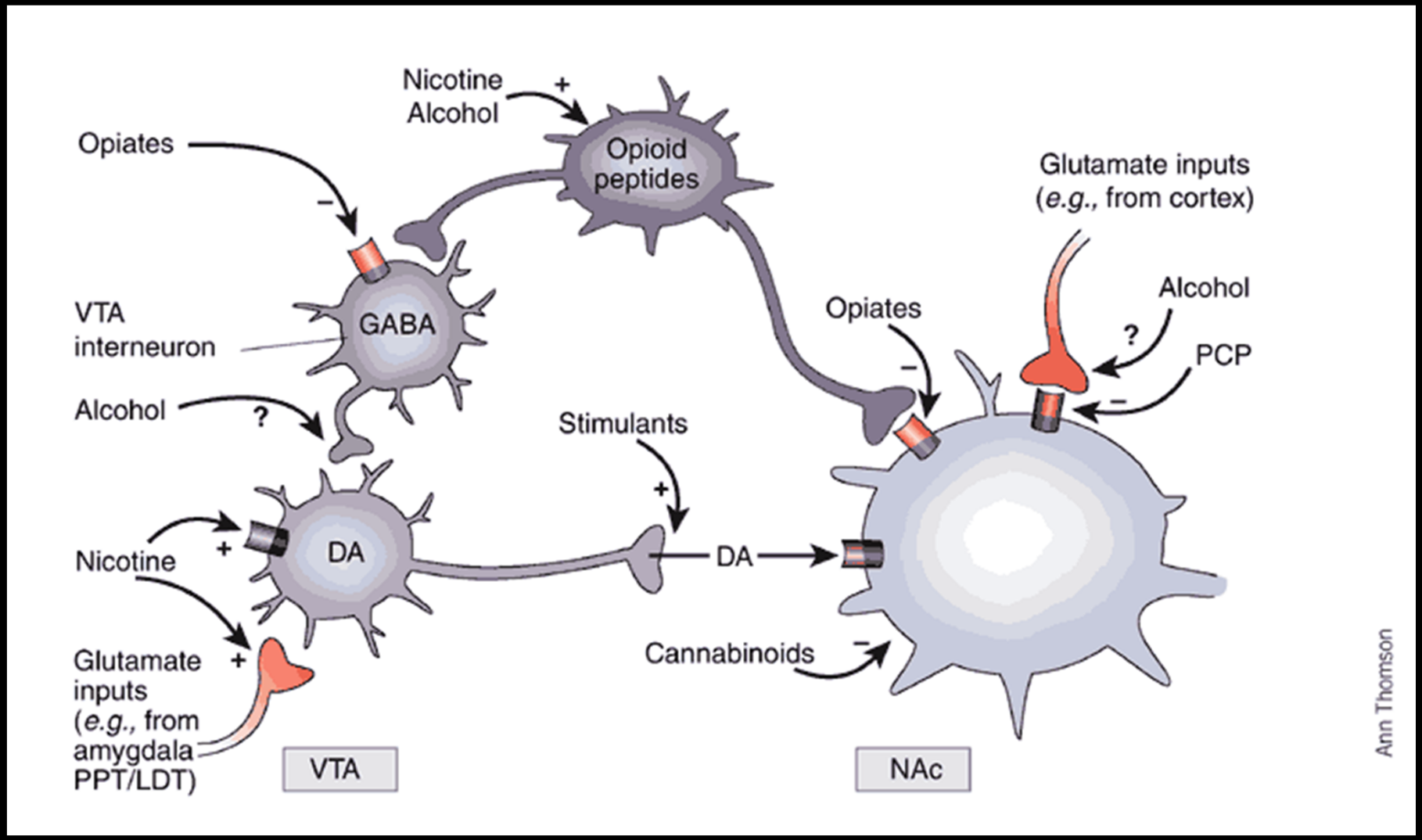
Mission Statement

To translate discoveries in basic neuroscience, pharmacology, genetics, and behavioral science to improve treatment for nicotine dependence.

Pharmacogenetic Model of Nicotine Dependence Treatment



From the Laboratory to the Clinic:
Nicotine-Opioid Interactions



Conditioned Place Preference

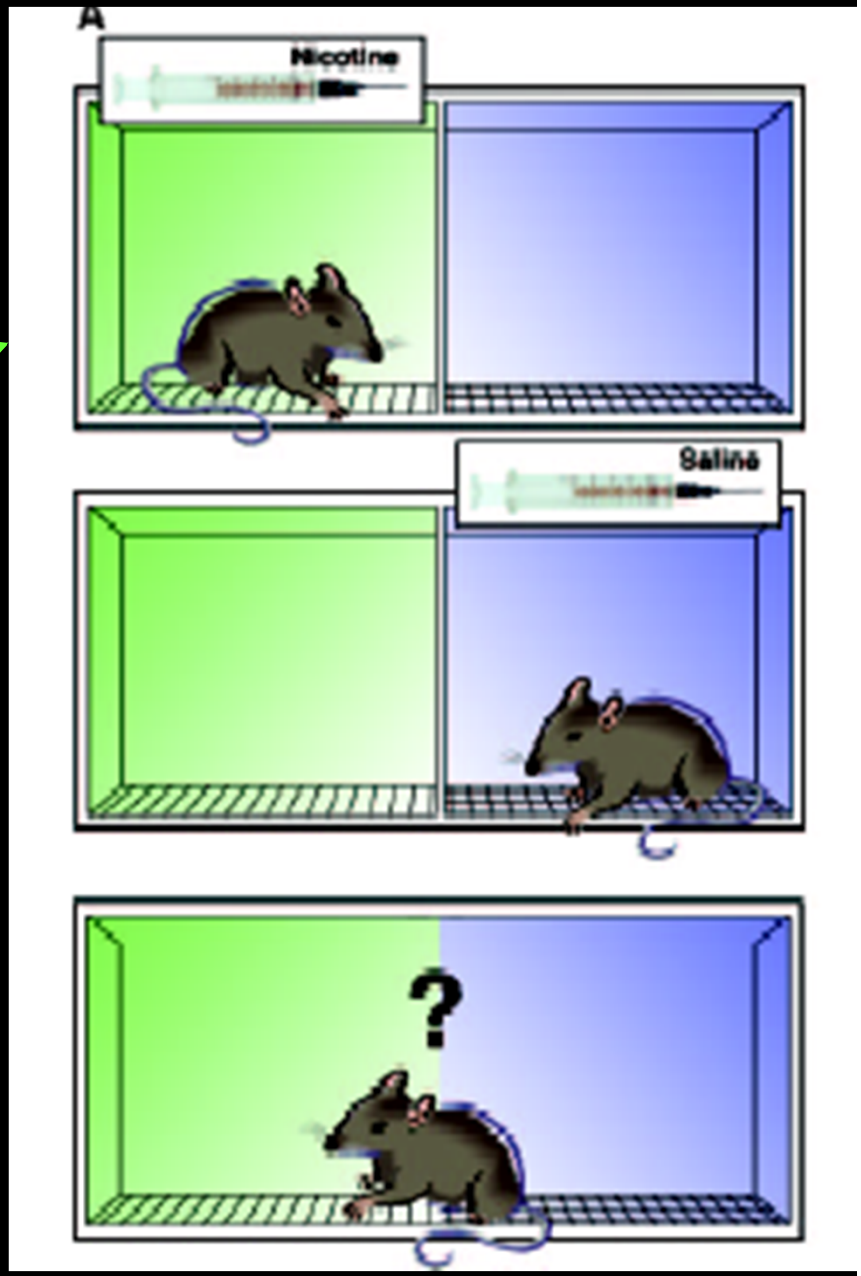
Pre-conditioning day: roam free

Conditioning phase (Days 2-8)

nicotine

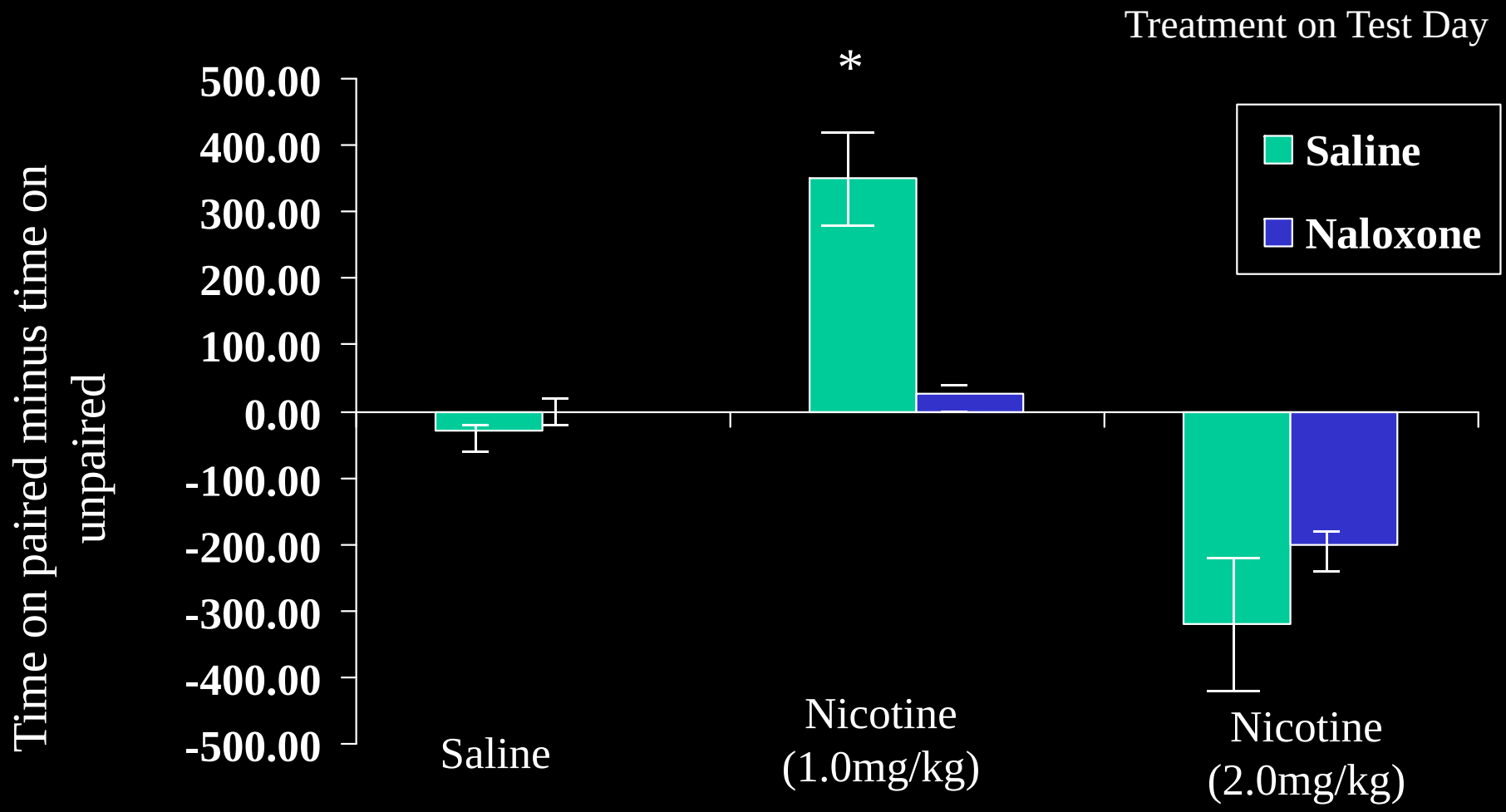
saline

Test Day



Work in Julie Blendy's lab

Naloxone on Test Day Blocks Conditioned Rewarding Effects of Nicotine in 129/C57 B16 Mice



*p<.05

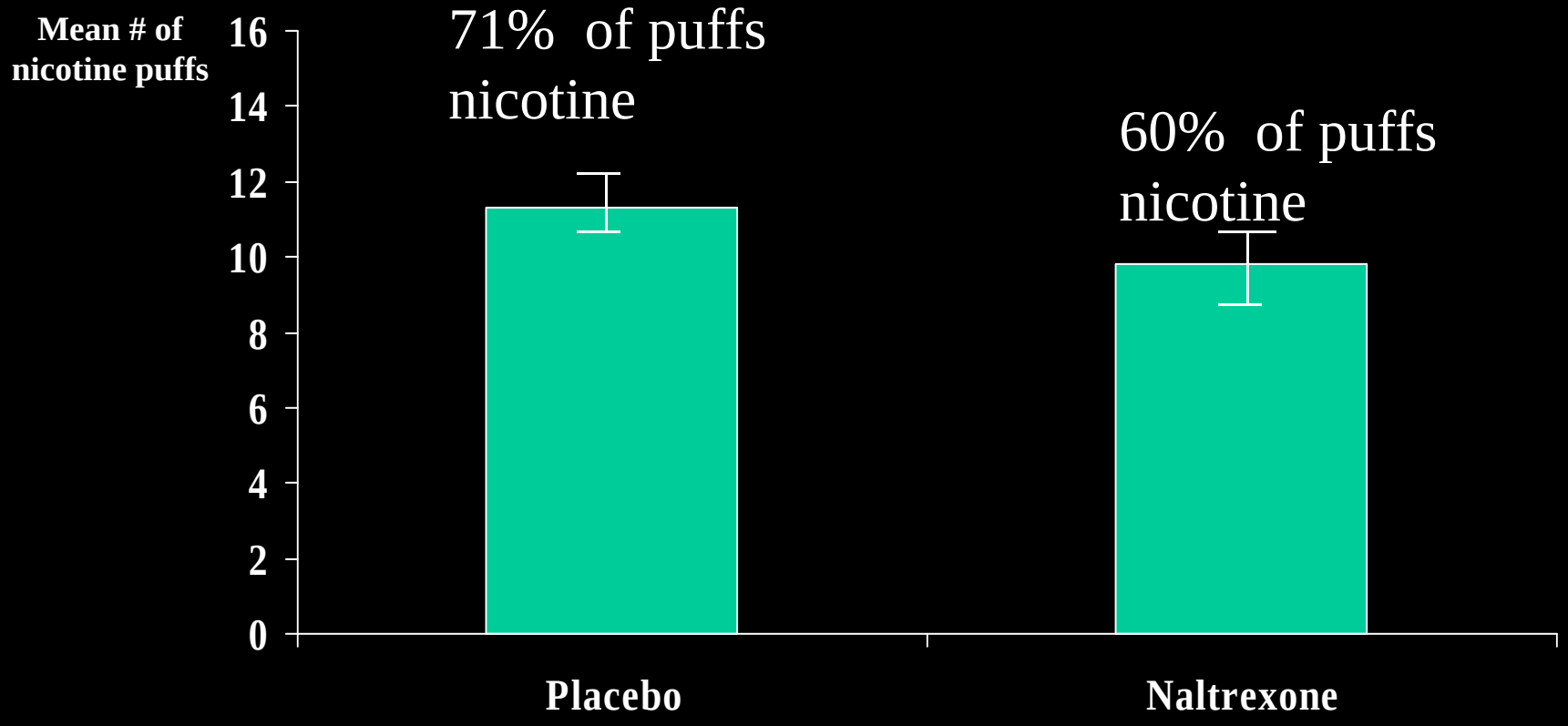
Walters et al, Neuron, 2005

Nicotine Choice Paradigm*

1. **Smoke own brand cigarette following arrival to the clinic**
2. **2 hour deprivation period (to standardize exposure without inducing serious withdrawal symptoms)**
3. **Initial (blinded) exposure to 4 puffs of Quest cigarettes: denic. (.05 mg) vs nic. (.6 mg) with 30-minute interval. Assess subjective effects**
4. **Self-administer 4 puffs from either cigarette at 30 minute intervals over a 2-hour period**
5. **Standardized puffing procedure – no differences in smoking topography**
6. **Outcome measure is number of nicotine puffs chosen out of 16 = relative reinforcing value of nicotine**

**Paradigm validated by Ken Perkins (1996, 1999, 2002). # nicotine choices sensitive to differences in deprivation and predicts abstinence*

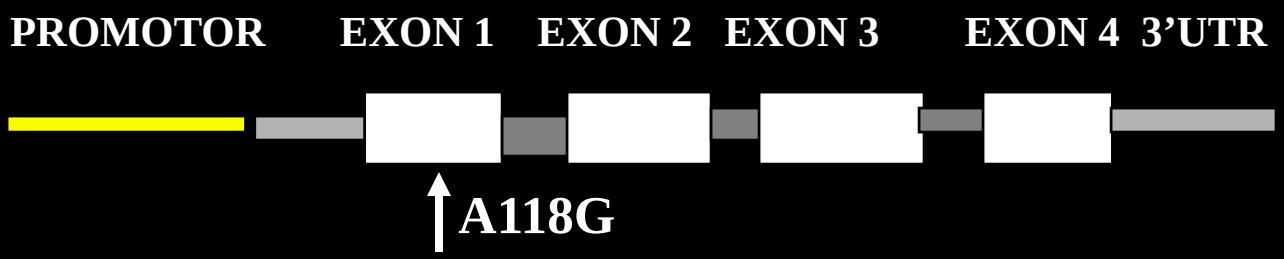
Effects of Naltrexone Single Acute Dose 50mg on the Relative Reinforcing Value of Nicotine:



Within Subject Mixed Effects Model (p=.03)

Rukstalis et al, Psychopharm, 2005

The Human OPRM1 Gene

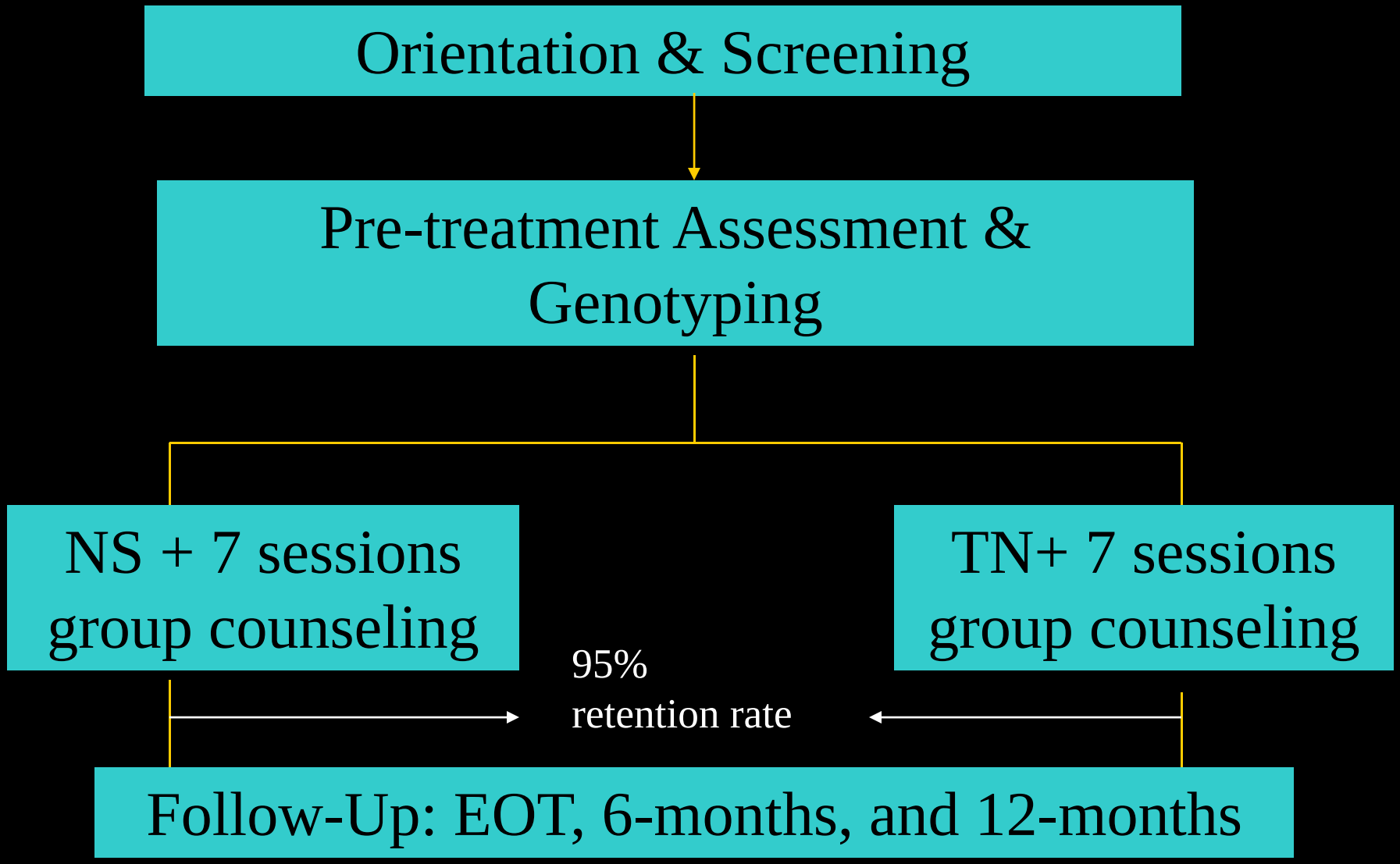


- **The human OPRM1 gene includes a common Exon 1 Asn40Asp (A118G) mis-sense single nucleotide polymorphism (SNP).**

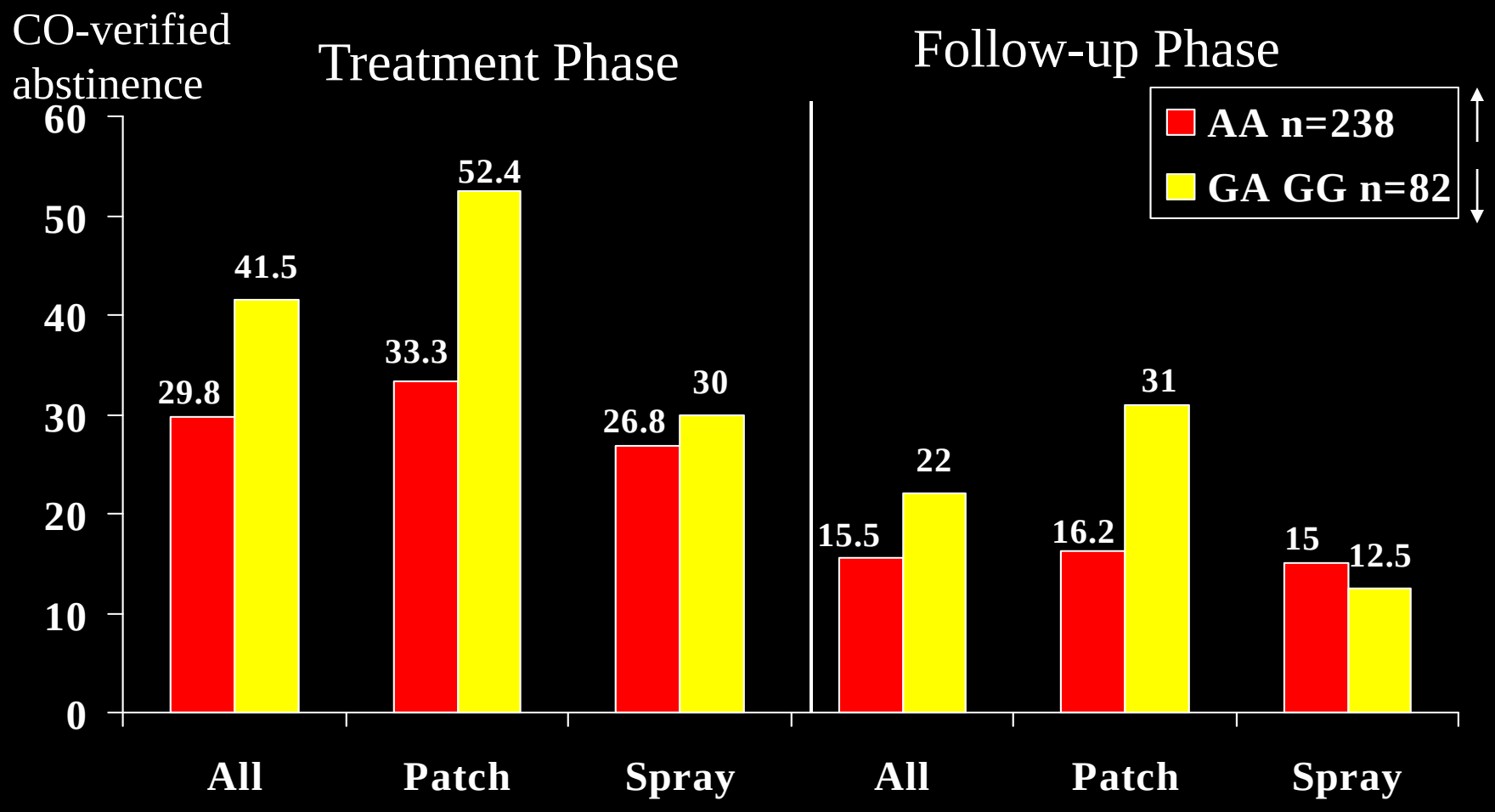
- **G allele associated with reduced mRNA expression and protein levels (Zhang et al., 2005) and is present in 25-30% of persons of European ancestry.**

Hypothesis: Smokers with G allele will have a lower liability to relapse in smoking cessation treatment

Open Label Trial of Nicotine Patch vs. Nicotine Nasal Spray (n=600)



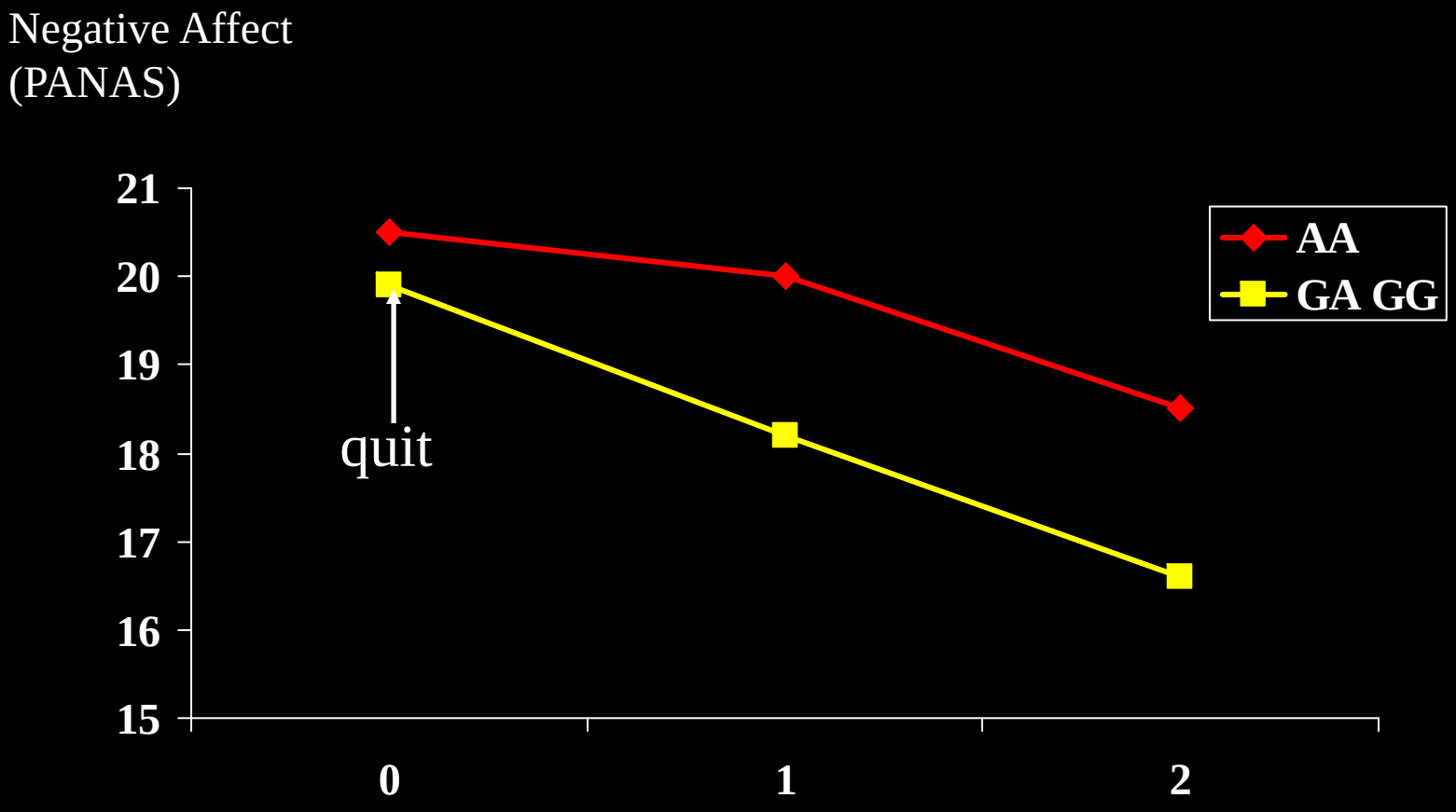
OPRM1 Asn40Asp Variant is Associated with Response to Nicotine Replacement Therapy



OR= 1.9, p=.01

Lerman et al., Pharmacogenomics J, 2004

Smokers with Asp40 Variant Report Greater Reductions in Negative Affect During NRT

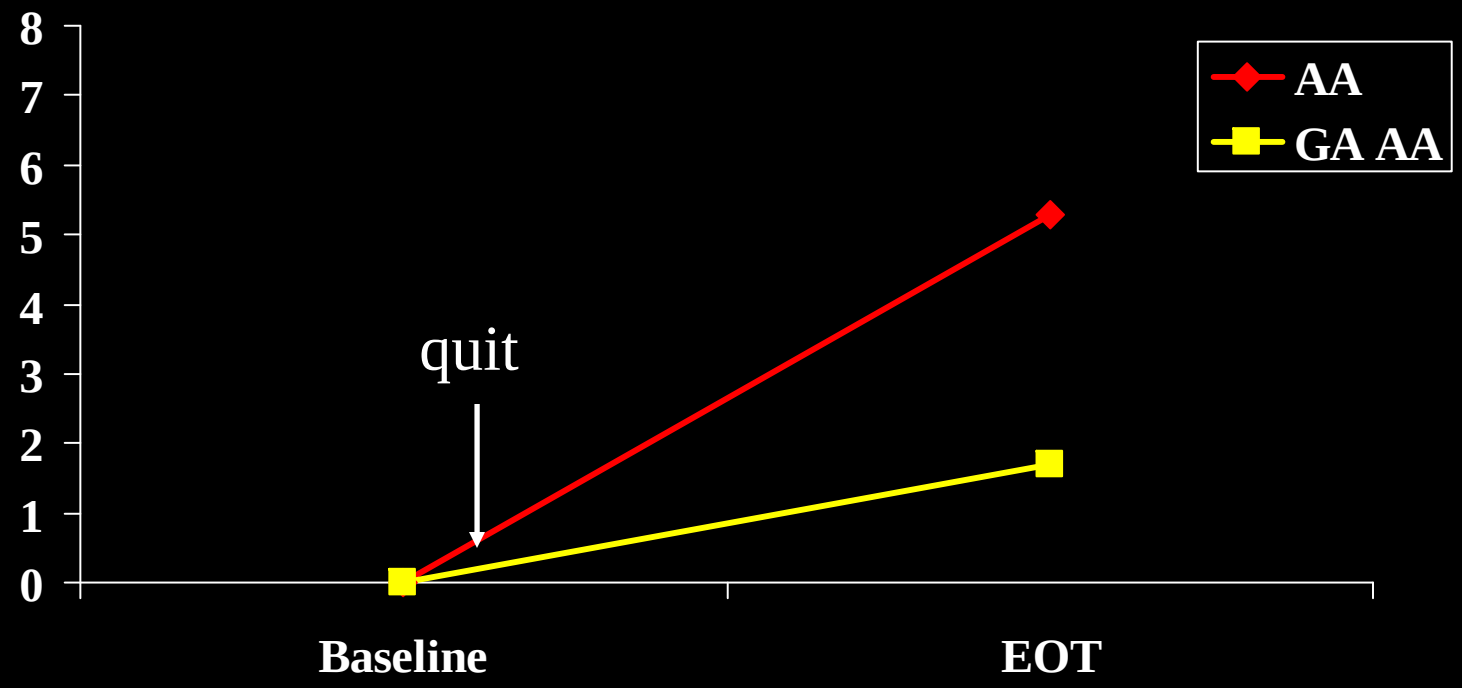


p=<.001 in linear regression model

Lerman et al., Pharmacogenomics J, 2004

Smokers with Asp40 Variant Gain Less Weight During NRT

Weight gain in lbs.



p=<.05 in linear regression model, controlling for sex, treatment, and baseline BMI and cotinine

Lerman et al., Pharmacogenomics J, 2004

Summary of Findings

- **Pharmacologic blockade of the mu opioid receptor is associated with reduction in nicotine reward in rodent and human models.**

- **The low activity OPRM1 G allele is associated with a greater ability to quit smoking.**

- **The mu opioid receptor and interacting proteins may be important targets for medication development, as well as for tailored treatment based on genotype.**

Ultimate Objectives

- **Identify novel targets for the development of nicotine dependence treatments**
- **Improve the delivery of nicotine dependence treatment by targeting therapy to smokers based on biological profiles**
- **Facilitate effective and ethical diffusion of new models of treatment delivery to the clinic and to the public**

Acknowledgements!

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