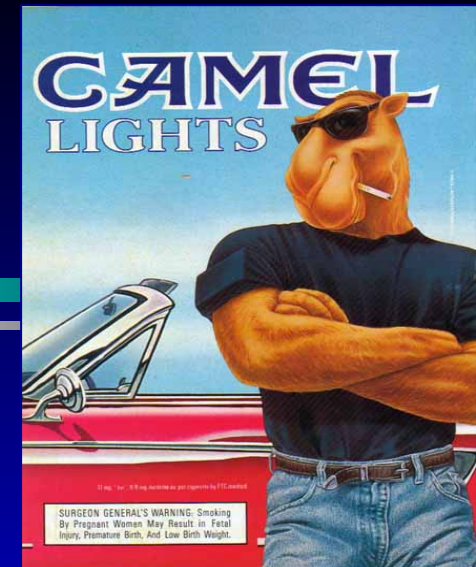


Highlights from Pharmacogenetics



Tyndale Laboratory

Ewa Hoffmann
Sharon Miksys
Helma Nolte
Anna Lee
Eric Sui
Shirley Wong
Meenal Joshi
Jill Mwenifumbo
Viba Maliayandi
Jiang Yue
Qian Zhou
Linda Liu
Nael Al Koudsi
Kerri Schoedel
Aman Mann
Sandy Faheim
Jibran Khokar
Lisa Howard
Manki Ho
Former, Summer and thesis students

SMOKING.
NICOTINE
and the stress of daily living

A bid for closer patient cooperation in adjustments of smoking hygiene

THE pace of modern life leaves its mark on many individuals. Symptoms, though remote, sub-clinical, may be of interest to the physician, perhaps in connection with nicotine intake.* Obviously, the exploration of this potential requires the patient's close cooperation.

In this situation there is an advantage to you in advising slow-burning Camel cigarettes. Millions have changed to Camels for their superior mildness and flavor—the famous Camel “pleasure factor.”

Patient's compliance with your suggestions should lead to improved accuracy in case histories. This may present new clinical opportunities, especially when such records are grouped and studied as a whole.

* J. A. M. A., 92:1128—October 12, 1929
Brüderer, H.—Die Biokemie des Tabaks, 1936
The Military Surgeon, Vol. 49, No. 1, p. 1, July, 1941

“THE CIGARETTE, THE SOLDIER, AND THE PHYSICIAN.” The Military Surgeon, July, 1941. Reprint available. Write Camel Cigarettes, Medical Relations Division, 1 Parkway Square, New York City.

Camel
COSTLIER TOBACCO'S

Dec 1942

390 When you write mention THE TRAINED NURSE, December, 1942

Collaborators

Ed Sellers
Caryn Lerman
Neal Benowitz
Gary Swan
Huijun Ring
Jennifer O'Loughlin
Janet Audrain
Margaret Spitz
John McLaughlin
Tamara Wall
Jeff Jones

Denise Kandel
Jasjit Ahluwalia
Lisa Cox
Ming Tsao
Kolawole Okuyemi
Frank Gonzalez
Mark Myers

Funding From

CIHR: MT-14173; MT-14719, Tobacco research training grants and doctoral awards
Canadian Research Chair in Pharmacogenetics
NCIC: 010271
NIH Pharmacogenetics Network
NIDA: DA06889
Centre for Addiction and Mental Health
Nicogen Research Inc





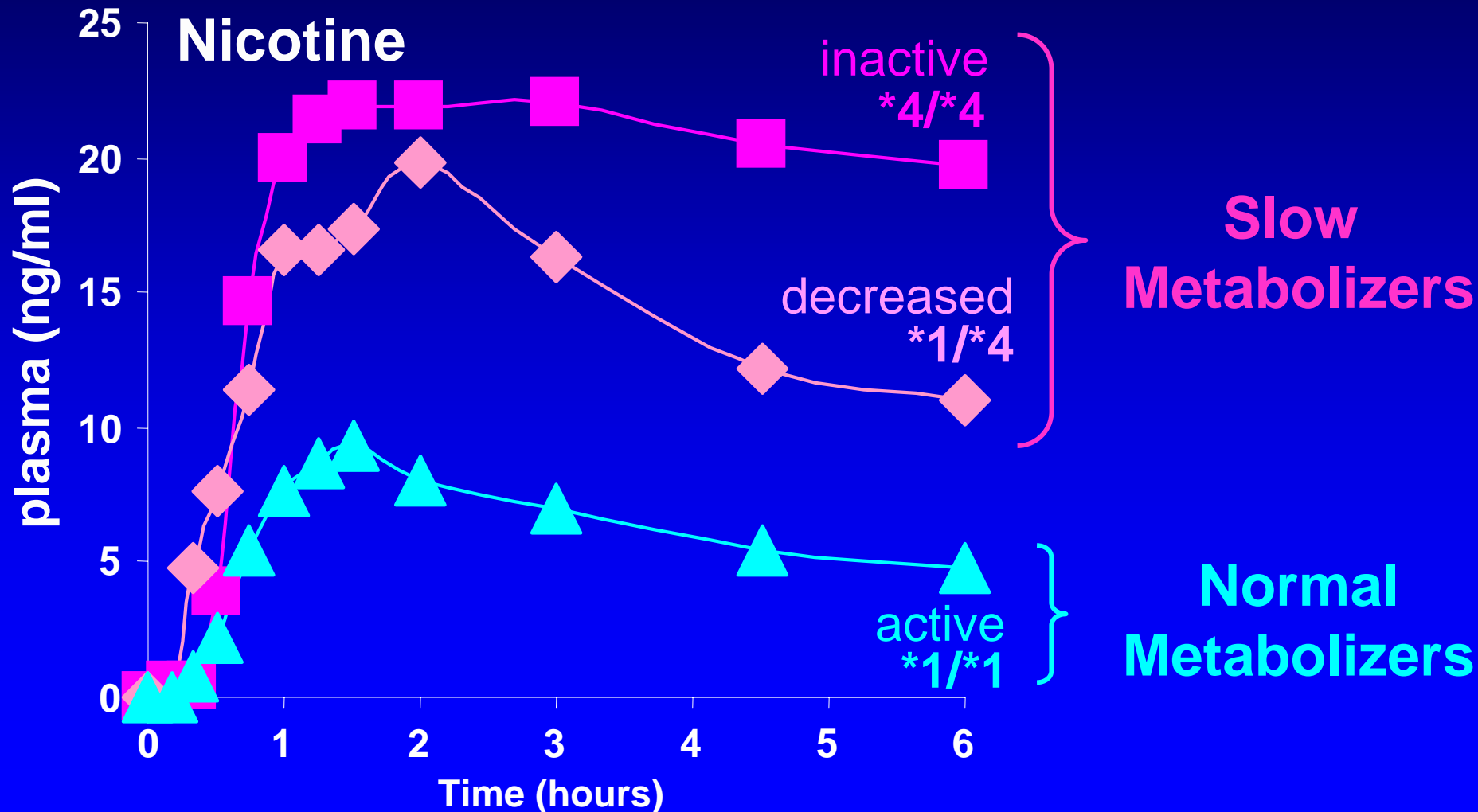
Pharmacogenetics of Treatment

Current treatment: low efficacy

- **Genetic variation in response**
- **Tailor medication to genetic make-up**
- **Discover novel targets for drug development**

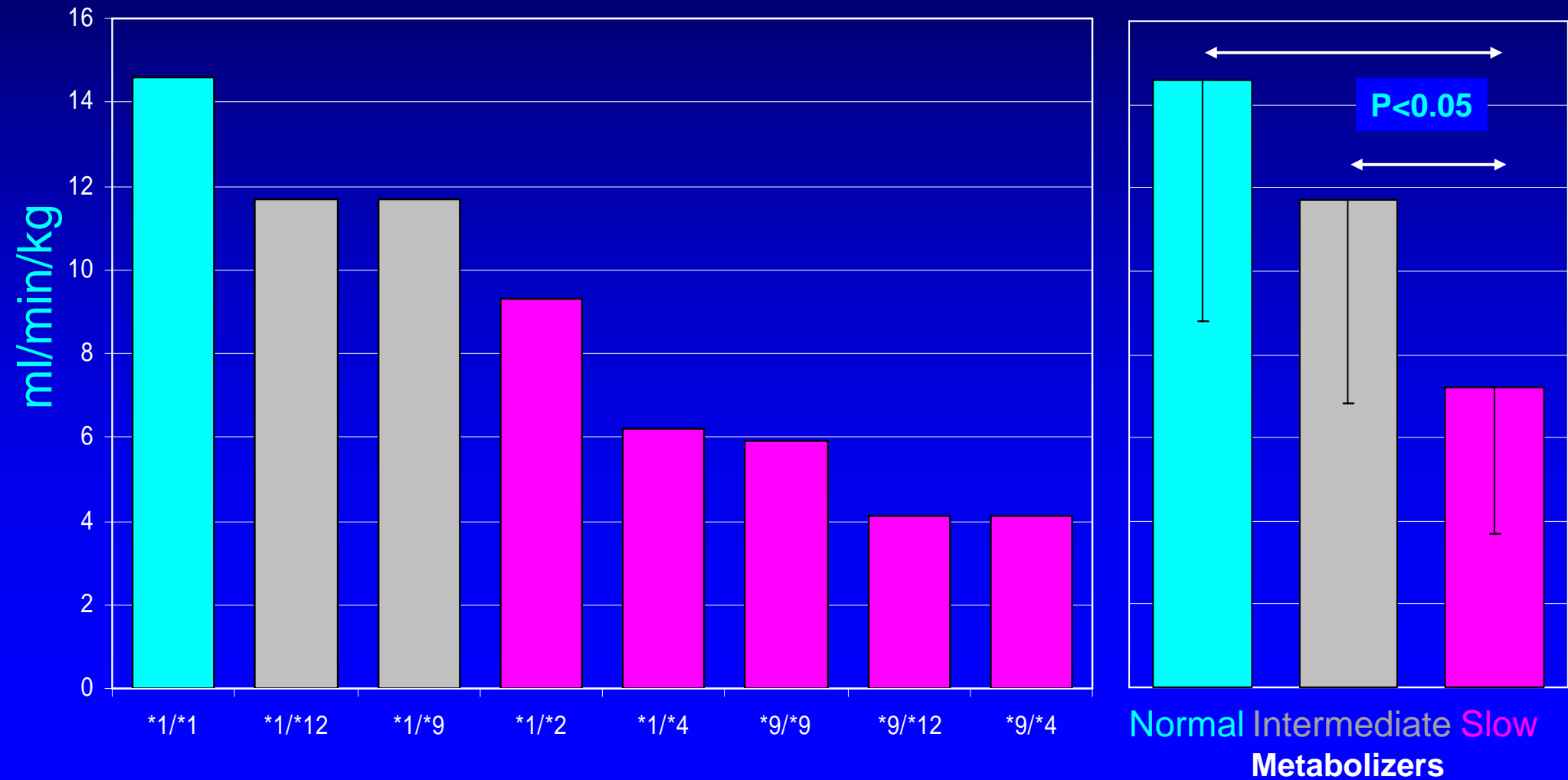
Genetically Reduced CYP2A6 increases nicotine plasma levels

Nicotine 4 mg base, oral Japanese subjects



CYP2A6 Genotype: Fractional Clearance of Plasma NIC to COT

(Twin NIC infusion cohort) *Benowitz CPT In press*

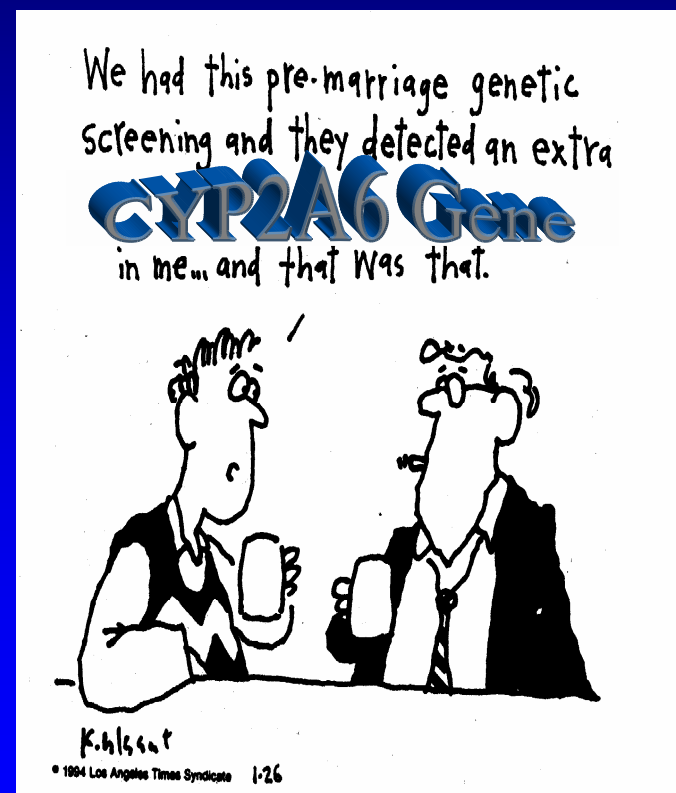


Genetic studies suggest smoking is altered by variable nicotine metabolism:

Other enzymes are not compensating for altered CYP2A6 activity

Decreased CYP2A6 activity :

- ↓ Number of Cigarettes/day
- ↓ Duration Tobacco Dependence
- ↓ Risk to be an adult smoker
- ↑ Success of Quitting
- ↑ Success on Nicotine patch





Slow Metabolism and Nicotine Replacement Therapy Hypotheses:

Slow nicotine metabolizers will have:

➤ **Nicotine Patch**

= use of patch (?)

↑ nicotine levels on the patch (25% higher)

↑ treatment response

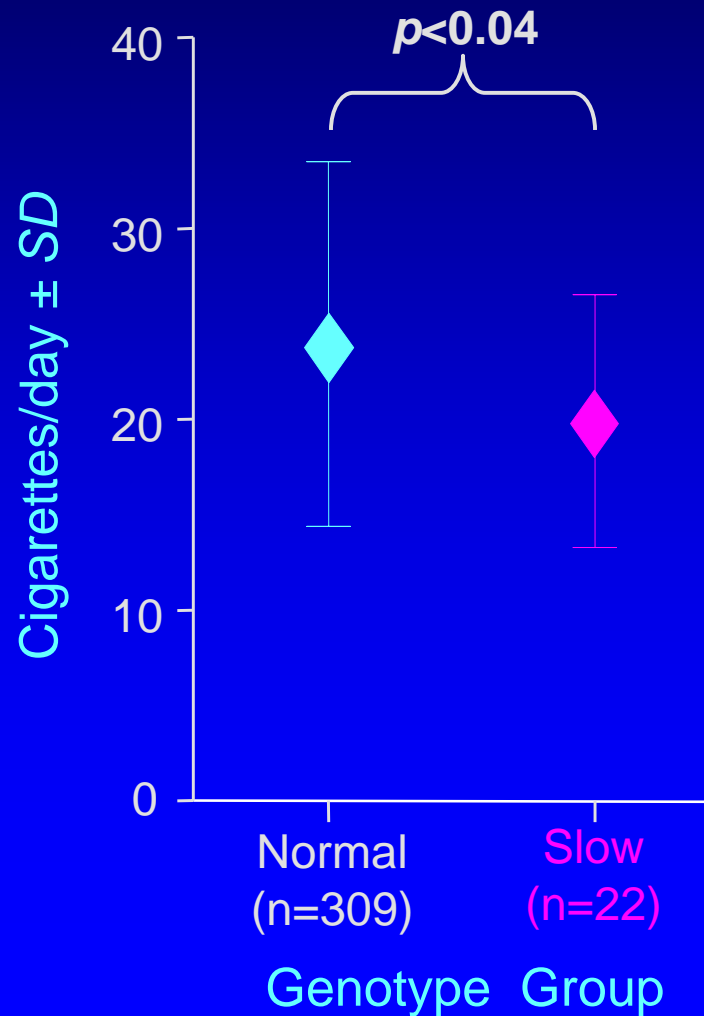
➤ **Nicotine Spray**

= nicotine levels (titration) but will require

↓ doses to achieve this (50% less)

= treatment response

Genetically Slow Metabolizers smoke less per day (treatment seeking population)



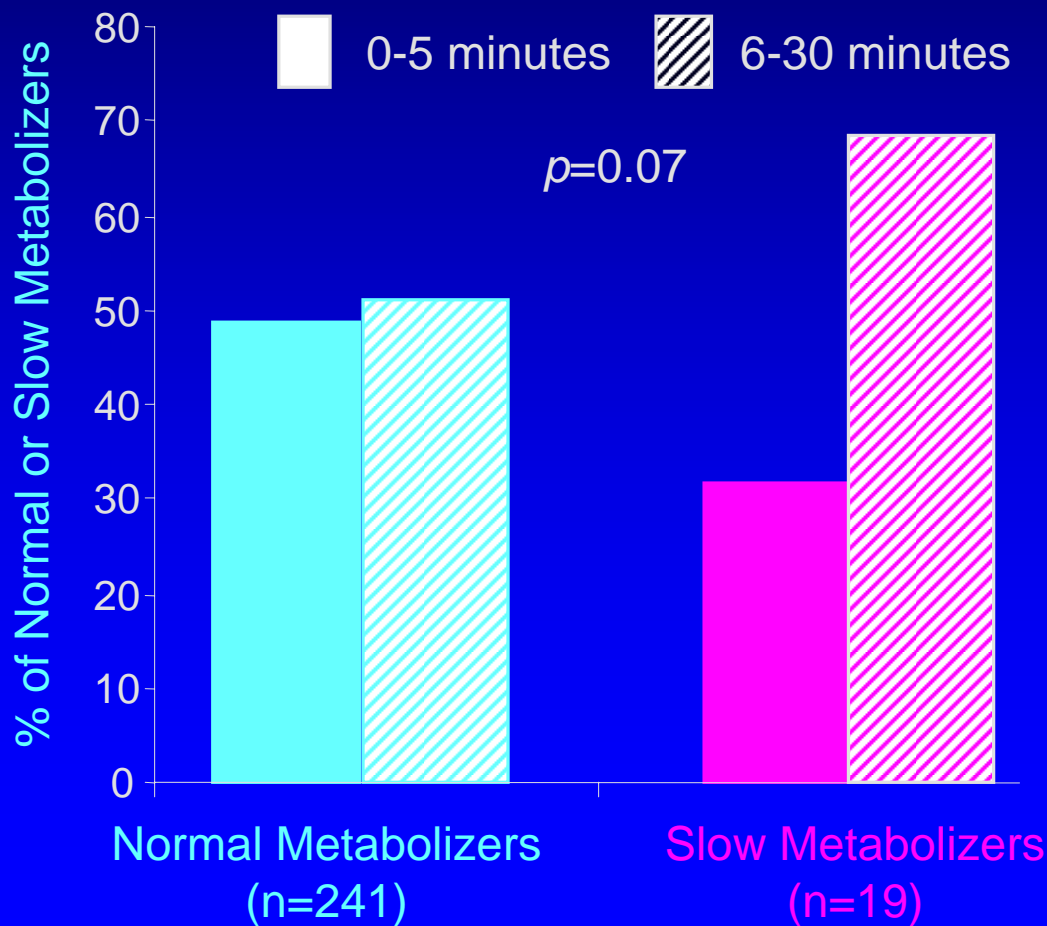
Malaiyandi et al,
Mol Psychiatry 2006

Genetically Slow Metabolism alters smoking

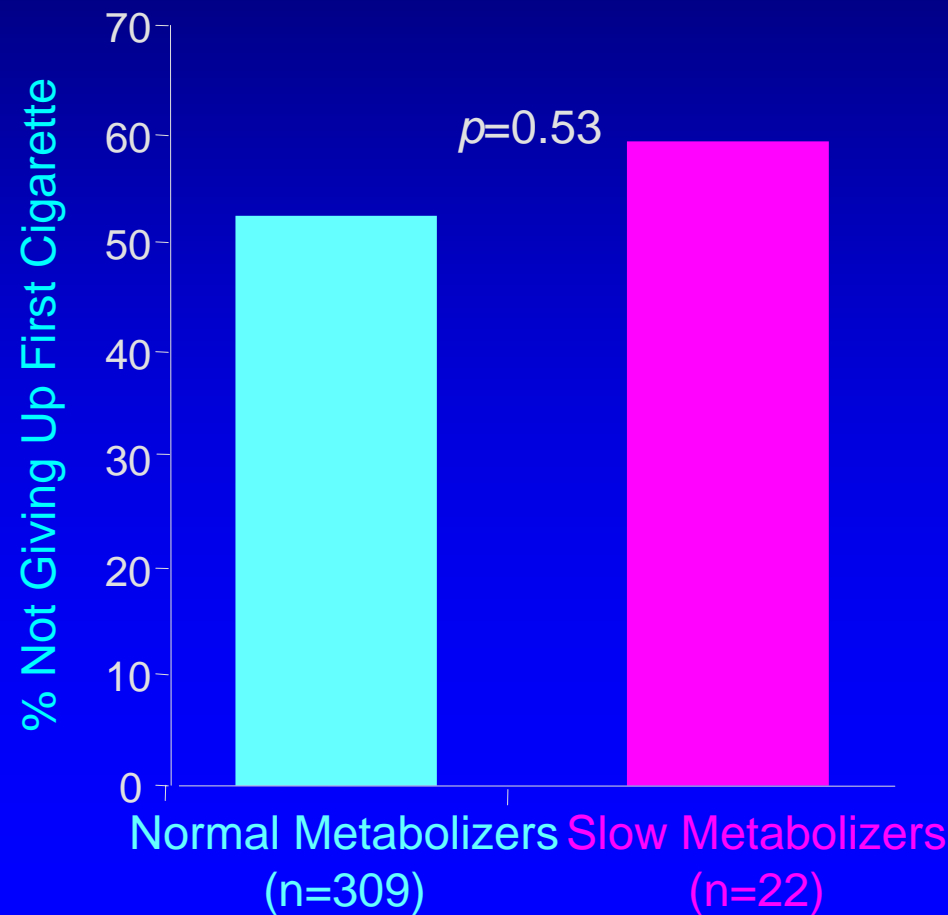
(treatment seeking population)

Malaiyandi et al,
Mol Psychiatry 2006

Time to first cigarette

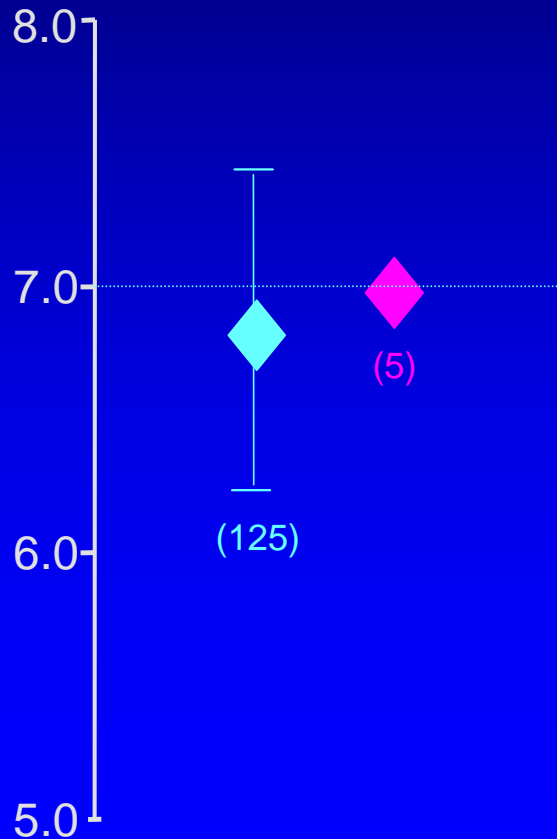


First vs. Other Cigarette

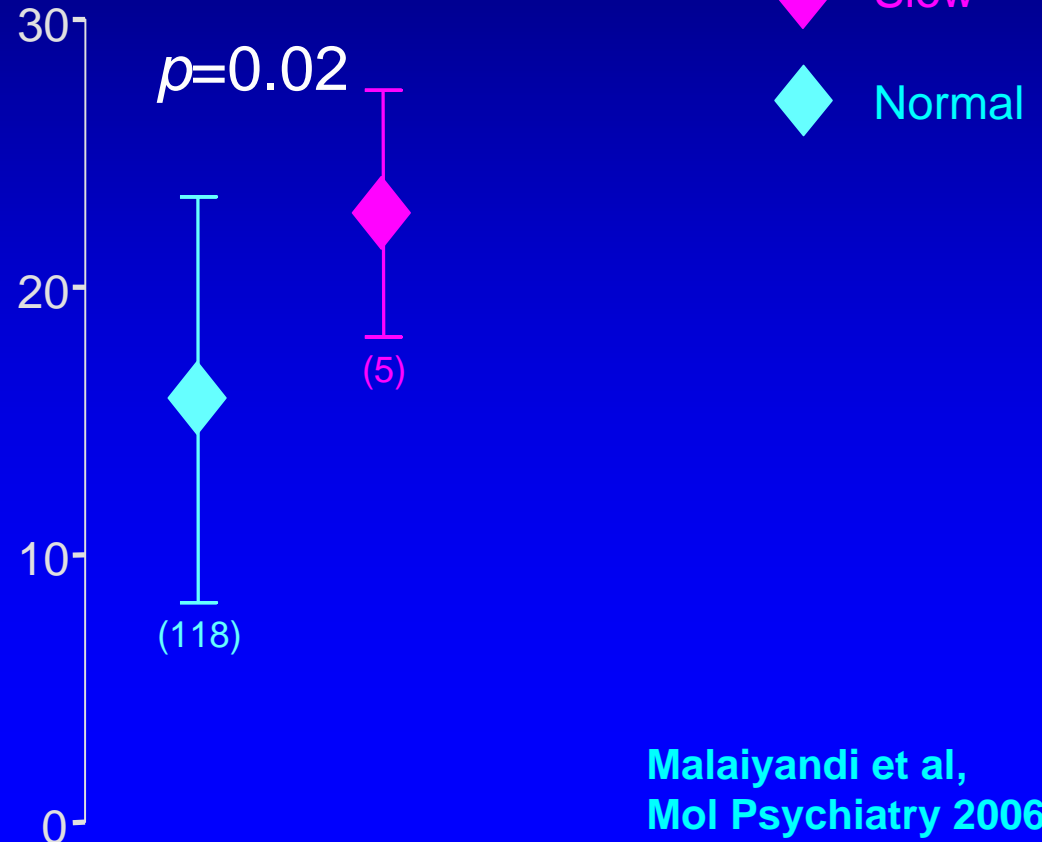


Genetically Slow Metabolizers have higher nicotine on the patch (treatment seeking population)

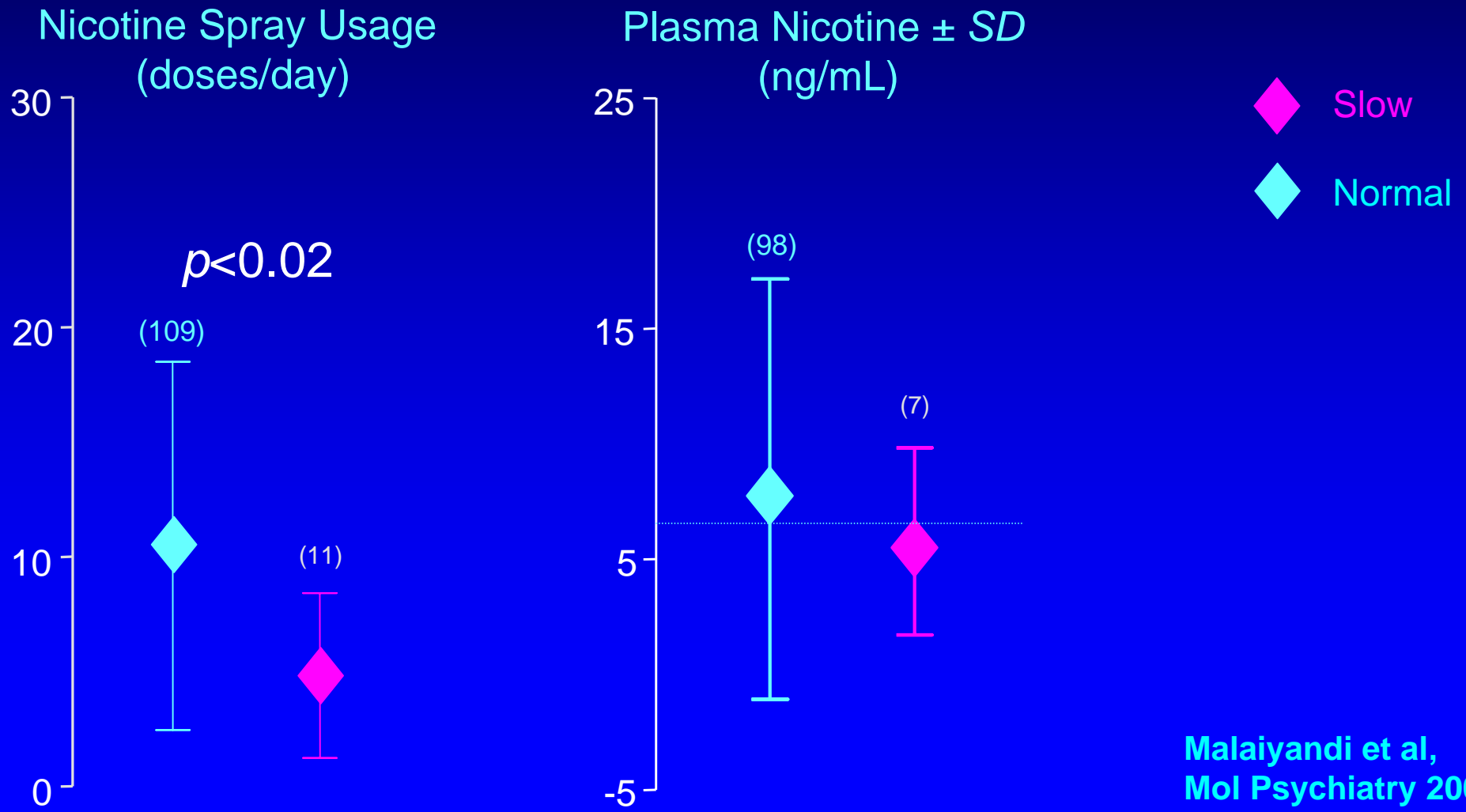
Nicotine Patch Usage
(# days worn)



Plasma Nicotine \pm SD
(ng/mL)



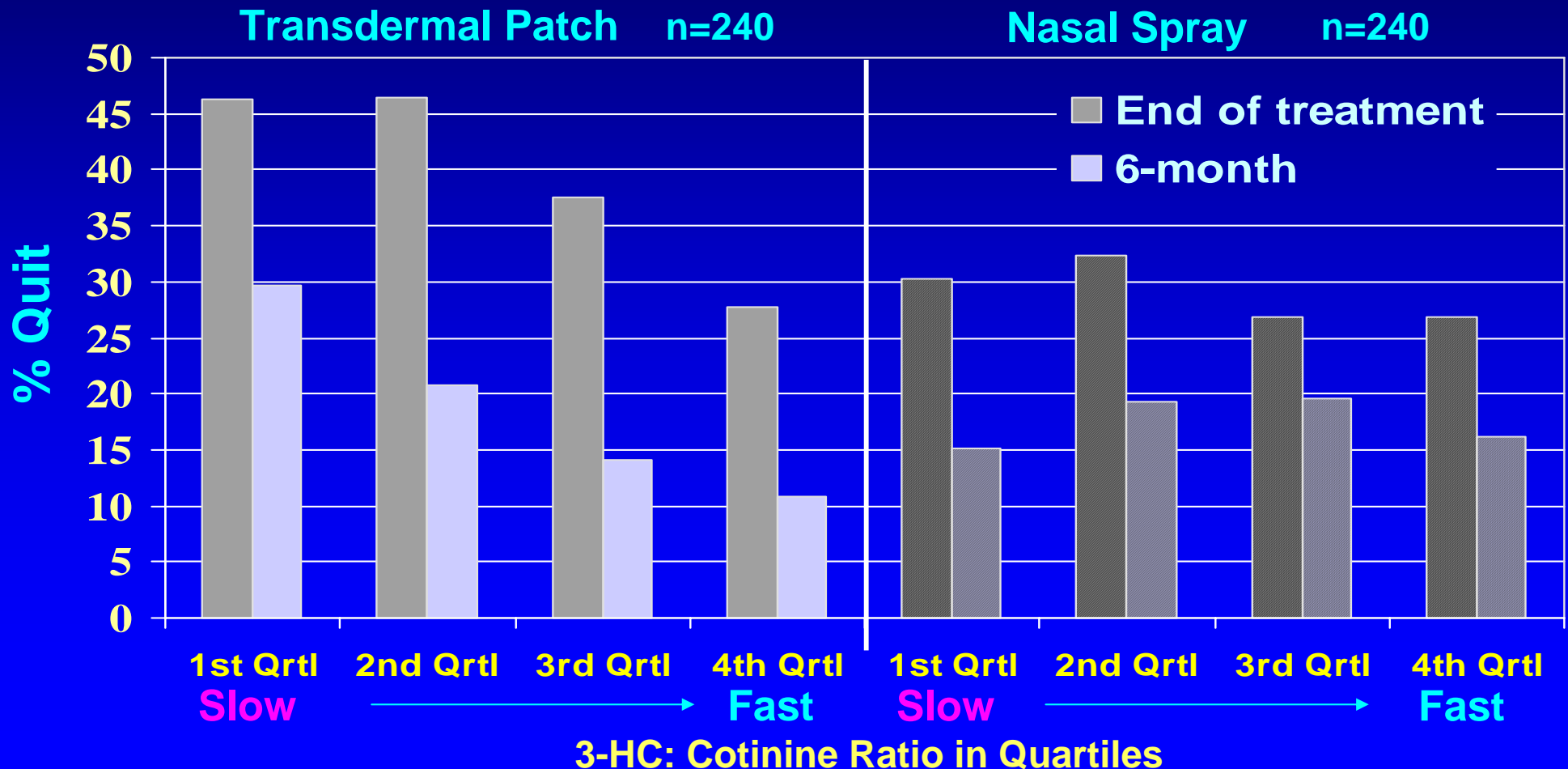
Genetically Slow Metabolizers have lower usage & equal nicotine using the spray (treatment seeking population)




Slow Metabolizers have better treatment with Nicotine Patch but not Spray

Lerman et al., Clin. Pharm. Ther. 2006

Effect of ratio in TP group (p=.005); Wald Test for interaction of ratio by treatment (p=.04)





Pharmacogenetic Impact on Nicotine Replacement Therapy

Maliyandi et al., Mol Psych 2006

Lerman et al., Clin. Pharm Ther. 2006

Slow metabolizers:

Baseline smoking (similar to non-treatment seeking smokers)

↓ Cigs/day (titration)

↑ Time to first cigarette, but = interest in first cigarette

Treatment effects

Patch


↑ Nicotine levels on nicotine patch, = usage

↑ Cessation than on nicotine patch

Spray

= Nicotine levels on nicotine spray, but ↓ usage

= Cessation in spray



Pharmacogenetic Impact on Nicotine Replacement Therapy

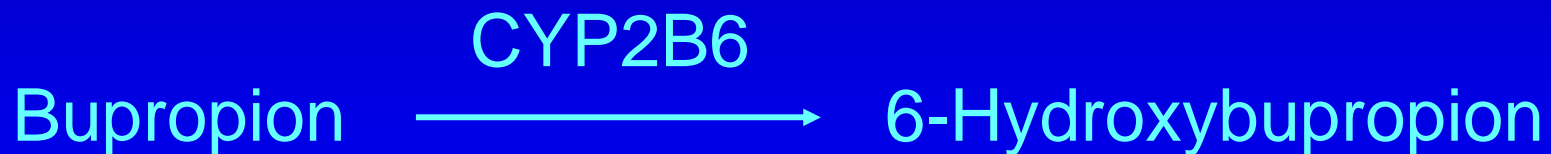
Maliyandi et al., Mol Psych 2006

Lerman et al., Clin. Pharm Ther. 2006

- Identify Fast and Slow metabolizers using
 - 3HC/COT ratio from smoking (blood, saliva, urine)
 - CYP2A6 genotype
- Treatment
 - Fast metabolizers need higher doses of NRT patch
 - Fast metabolizser will titrate spray levels

Bupropion (Zyban[®]) in Smoking Cessation

- Only non-nicotinic drug approved for smoking cessation
- Inhibits norepinephrine and dopamine reuptake; is a nicotinic receptor antagonist
- Bupropion is also Wellbutrin[®] used for depression
- Six month bupropion abstinence rates are 11-15% above placebo rates
- Half-lives: bupropion 19 ± 5 h; active metabolite 21 ± 5 h



Will genetic variants that result in slow *CYP2B6* affect bupropion-mediated smoking cessation?



Clinical Trial Design

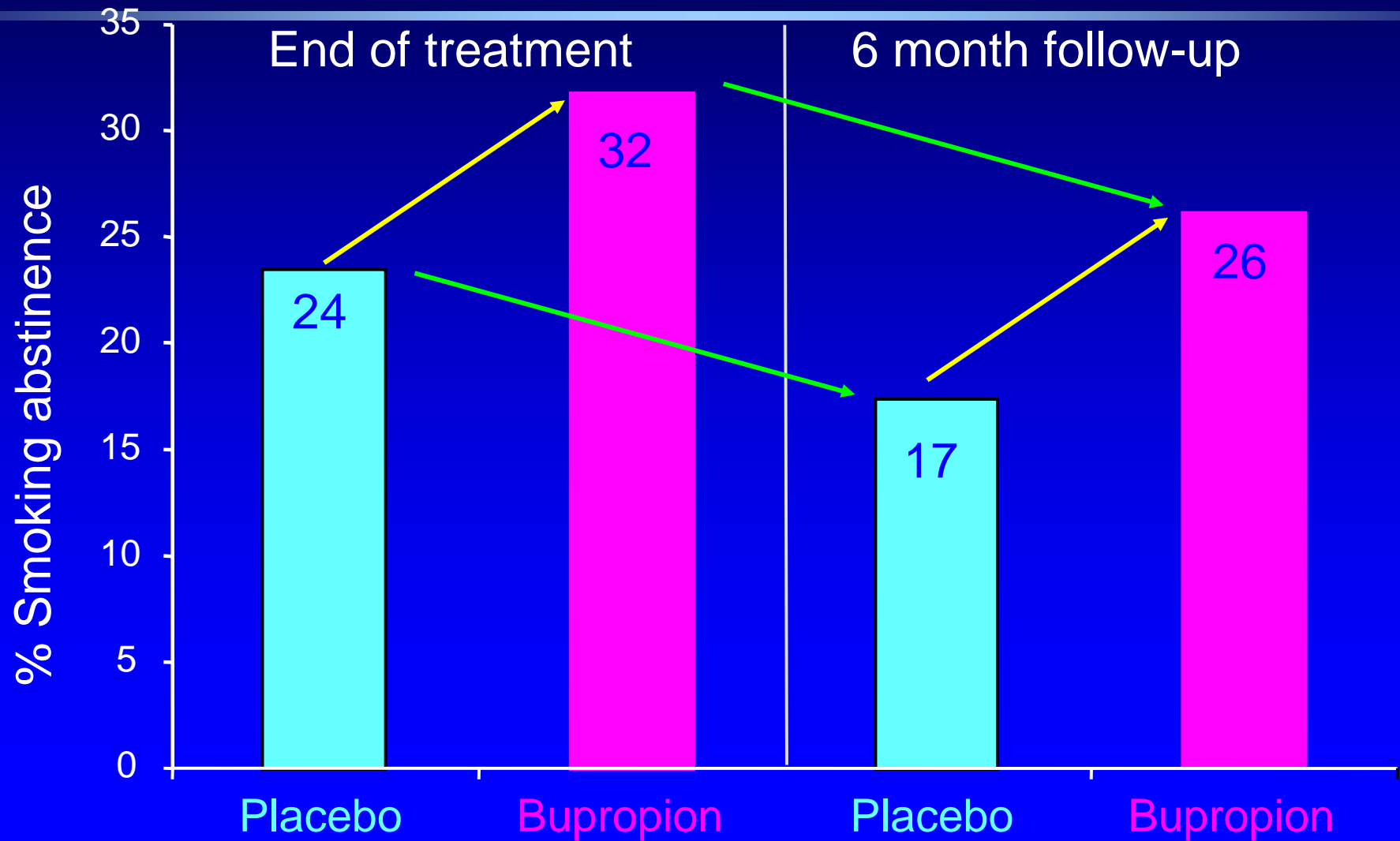
- Bupropion (150 mg bid) or placebo, and behavioural counseling
- Started 2 weeks before target quit date, continued for 8 weeks
- **Inclusion criteria:** minimum 10 cigarettes/day, 18 years old
- **Exclusion criteria:** seizure disorder, psychiatric disorder, brain tumor, diabetes, alcoholism, other drug addictions, pregnancy


Main outcomes:

- Abstinence at EOT (measured 8 weeks after quit date)
- Abstinence at 6 month follow-up



Bupropion improves cessation; cessation reduced at 6 month





Population restricted to *CYP2B6*1* or *CYP2B6*6*, and Caucasians

<i>CYP2B6</i> genotypes	N=324 (% of population)	Activity groups
<i>*1/*1</i>	Total 177 (55%) 78 on placebo 99 on bupropion	<i>CYP2B6*1</i> group (<i>CYP2B6*1/*1</i>) predicted normal activity
<i>*1/*6</i> & <i>*6/*6</i>	Total 147 (45%) 70 on placebo 77 on bupropion	<i>CYP2B6*6</i> group (<i>CYP2B6*1/*6</i> & <i>CYP2B6*6/*6</i>) predicted decreased activity



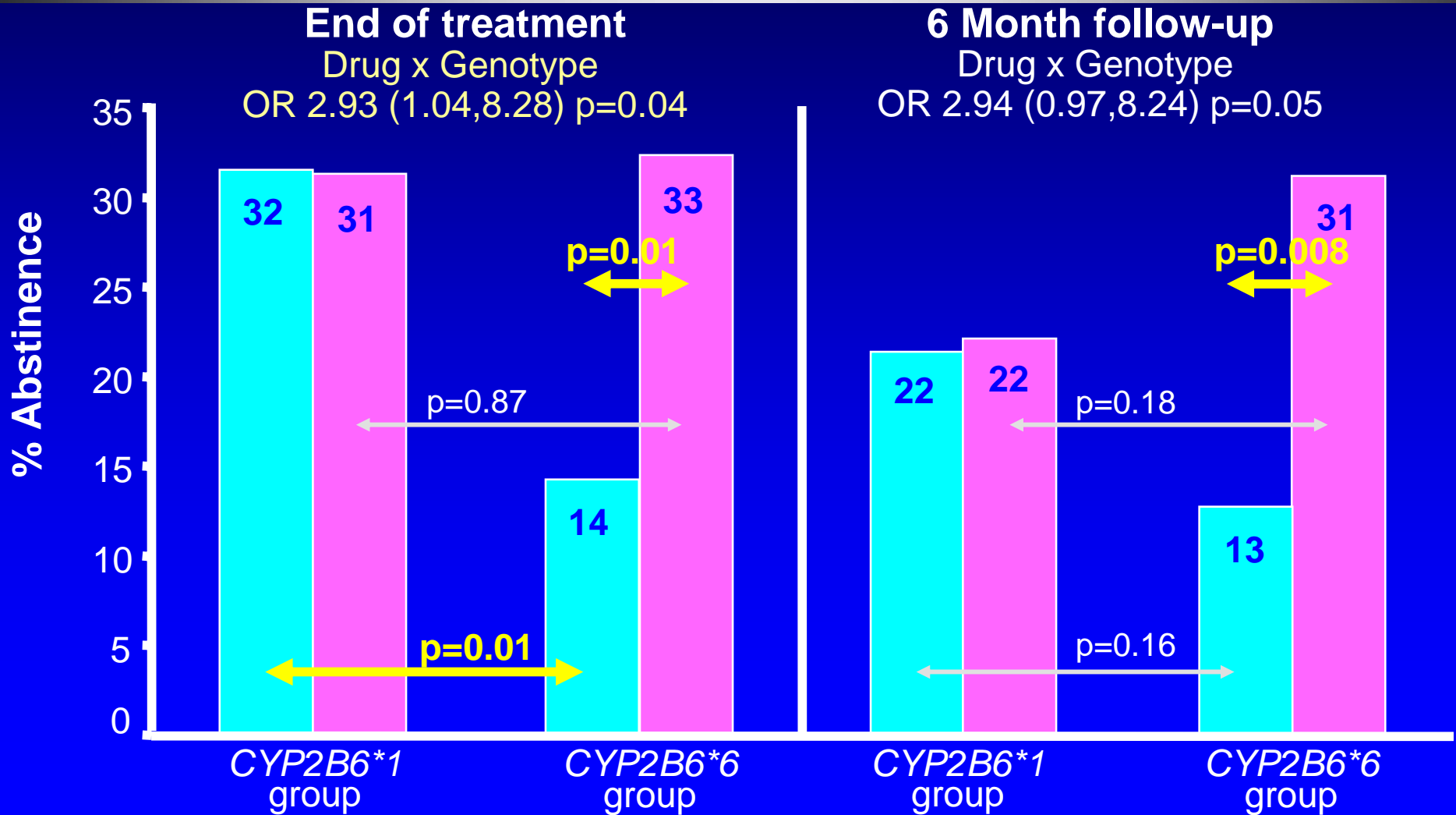
No differences in baseline variables between genotype groups split by treatment

Baseline Variable	<i>CYP2B6</i> *1 placebo	<i>CYP2B6</i> *1 bupropion	<i>CYP2B6</i> *6 placebo	<i>CYP2B6</i> *6 bupropion	p
Cigarettes per day	23.1 ± 12.2	21.7 ± 9.0	21.4 ± 6.7	20.8 ± 8.0	0.50
Nicotine dependence (FTND)	5.2 ± 2.5	5.4 ± 2.0	5.3 ± 2.0	5.2 ± 2.1	0.91
Age of smoking initiation (years)	16.3 ± 3.4	16.9 ± 3.2	16.6 ± 3.1	17.7 ± 4.4	0.08
Withdrawal and craving score	30.1 ± 7.9	31.3 ± 7.4	31.0 ± 7.2	32.2 ± 7.7	0.42
Urge to smoke score	6.1 ± 1.2	6.3 ± 1.2	6.3 ± 1.5	6.4 ± 1.4	0.61

Genetic variation in CYP2B6 alters Bupropion Efficacy

Placebo
Bupropion

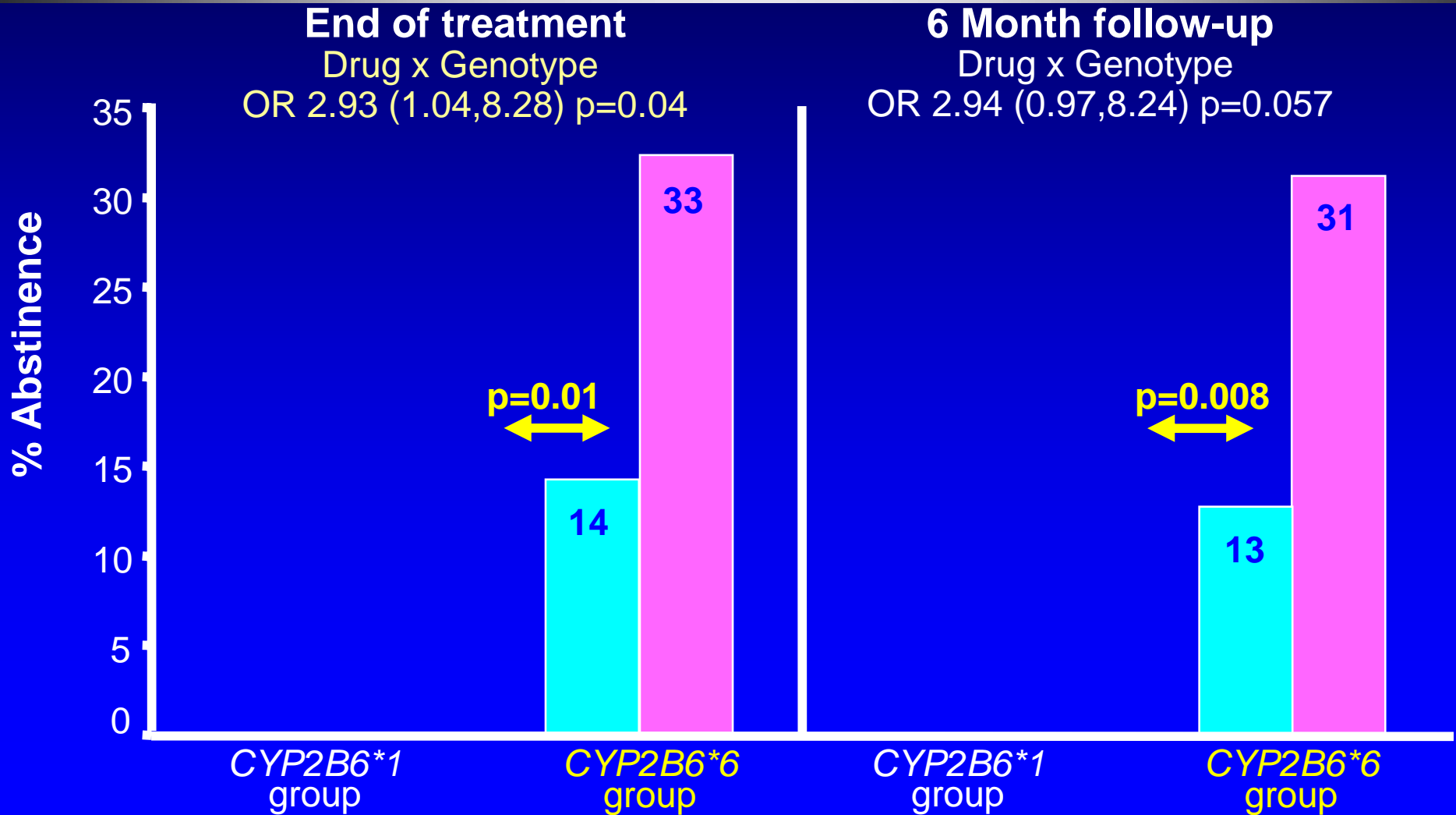
Lee et al. Biological Psychiatry 2006



Genetic variation in CYP2B6 alters Bupropion Efficacy

Placebo
Bupropion

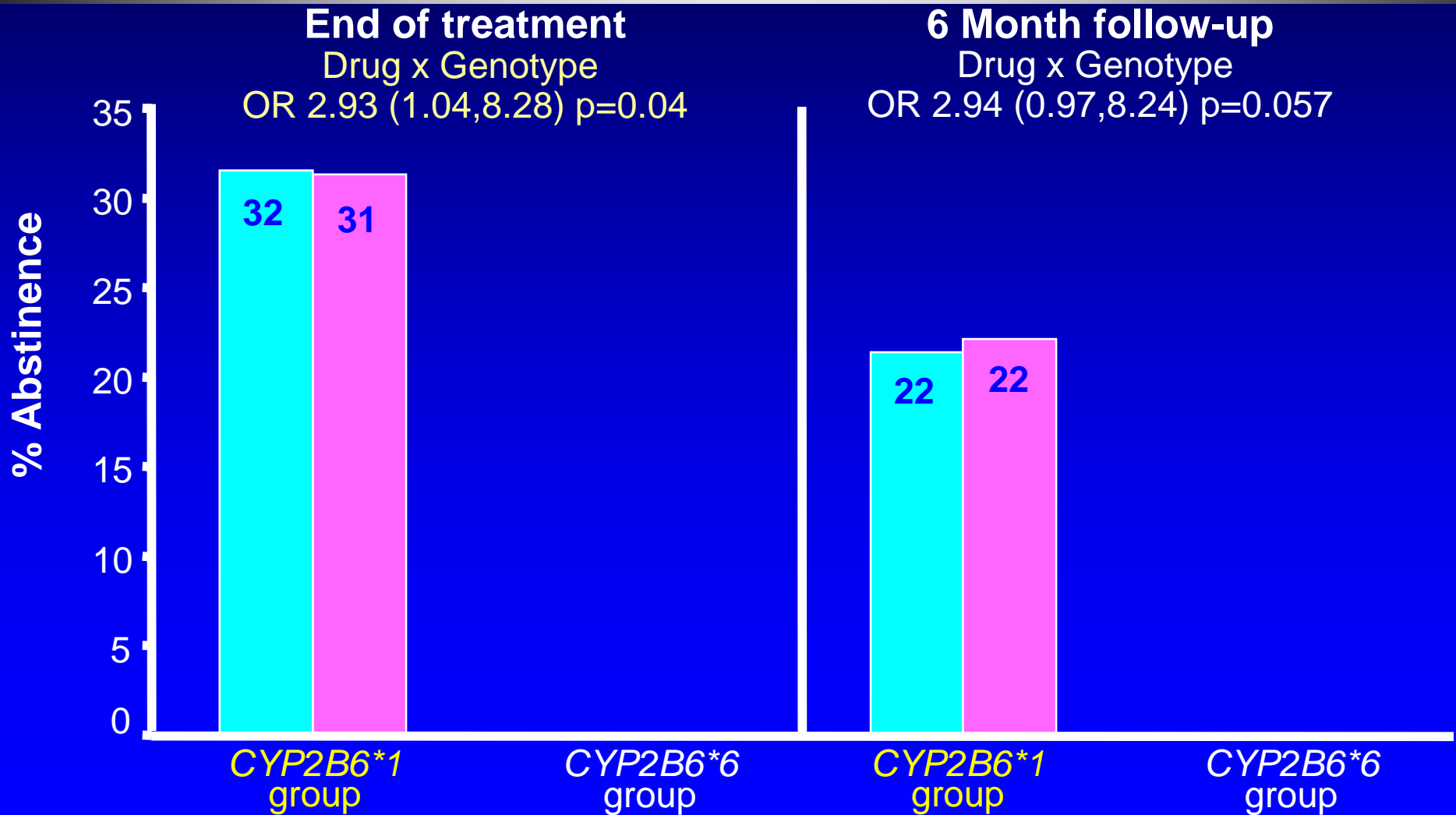
Lee et al. Biological Psychiatry 2006




Genetic variation in CYP2B6 alters Bupropion Efficacy

Placebo
Bupropion

Lee et al. Biological Psychiatry 2006





CYP2B6 genotype affects bupropion treatment outcomes

*CYP2B6*6 group vs CYP2B6*1*

- benefited more from bupropion over placebo
- bupropion abstinence rates were maintained at 6 months
- should be treated with bupropion, increases and maintains abstinence rates at 6 months (45% of pop.)

*CYP2B6*1 group vs CYP2B6*6*

- had high *placebo* abstinence rates
- did not benefit with bupropion over placebo (55% of pop.)