

Schizophrenia and Substance Abuse: Approaching Pharmacotherapy



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Disclosure

- Grants: NIMH, NIAAAA, NIDA, NARSAD, Janssen, Lilly, AstraZeneca, Bristol Myers, Cyberonics, Lundbeck
- Advisory Board/Consultant: Lilly, AstraZeneca, Janssen
- Stock Ownership: Pfizer, Mylan
- Patent Pending: Treatment for substance abuse

Course of Schizophrenia

Functioning

Course



Premorbid

Prodrome

First episode

Illness
begins

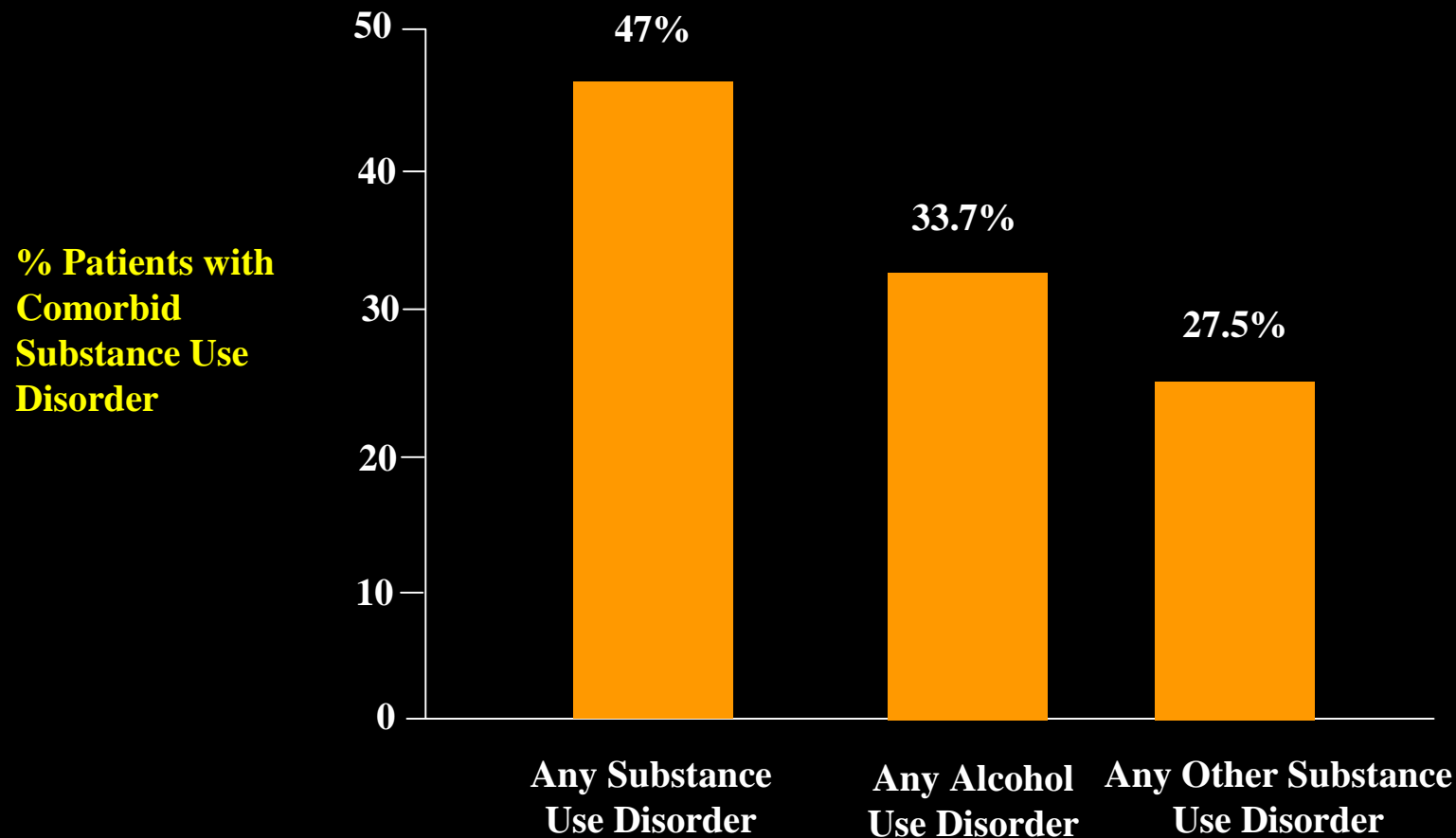
Onset
psychosis

Early Intervention

Domains of Schizophrenia

- § Positive Symptoms
- § Negative Symptoms
- § Disorganization
- § Cognitive Function

Lifetime Prevalence of Substance Use Disorder in Patients With Schizophrenia



Regier et al. JAMA 1990; 264-2511.

First Episode Schizophrenia and Substance Abuse

- **Cannabis most common**
- **SUD is up to 50%**
- **Associated with increased positive symptoms**
- **Associated with poor treatment response**

Complications of Substance Use in Schizophrenia

- § Earlier onset of schizophrenia**
- § Increased relapse**
- § Treatment non-compliance**
 - Poorer overall response to antipsychotic medication**
 - More hospitalizations**
 - Increased risk for violence**
 - Increased medical costs**

Nature of Substance Abuse in Schizophrenia

- **Use of substances (other than tobacco) is modest**
- **Abuse is more common than dependence**
- **Even modest use worsens primary symptoms of schizophrenia**

Basis of Comorbidity of Substance Use Disorder and Schizophrenia

§ Vulnerability to schizophrenia

– Substance abuse → early-onset schizophrenia

§ Self-medication?

§ Biologic predisposition to substance abuse?

Cannabis and Psychosis

- **Delta-9-THC injected into healthy individuals:**
 - **positive/negative symptoms**
 - **altered perception, increased anxiety**
 - **euphoria**
 - **decreased immediate, delayed word recall**
 - **increased plasma cortisol**

Cannabis and Schizophrenia

- **Causal? 8% of risk of schizophrenia?
Arsenault et al, 2004**
- **Could it precipitate “schizophrenia” in non-vulnerable populations? Arsenault et al, 2004**
- **Adolescent cannabis use risk for schizophreniform disorder in COMT val/val polymorphism -- Caspi et al, 2005**
- **Earlier age of onset of schizophrenia in cannabis users; Green et al, 2004.**

Basis of Comorbidity of Substance Use Disorder and Schizophrenia

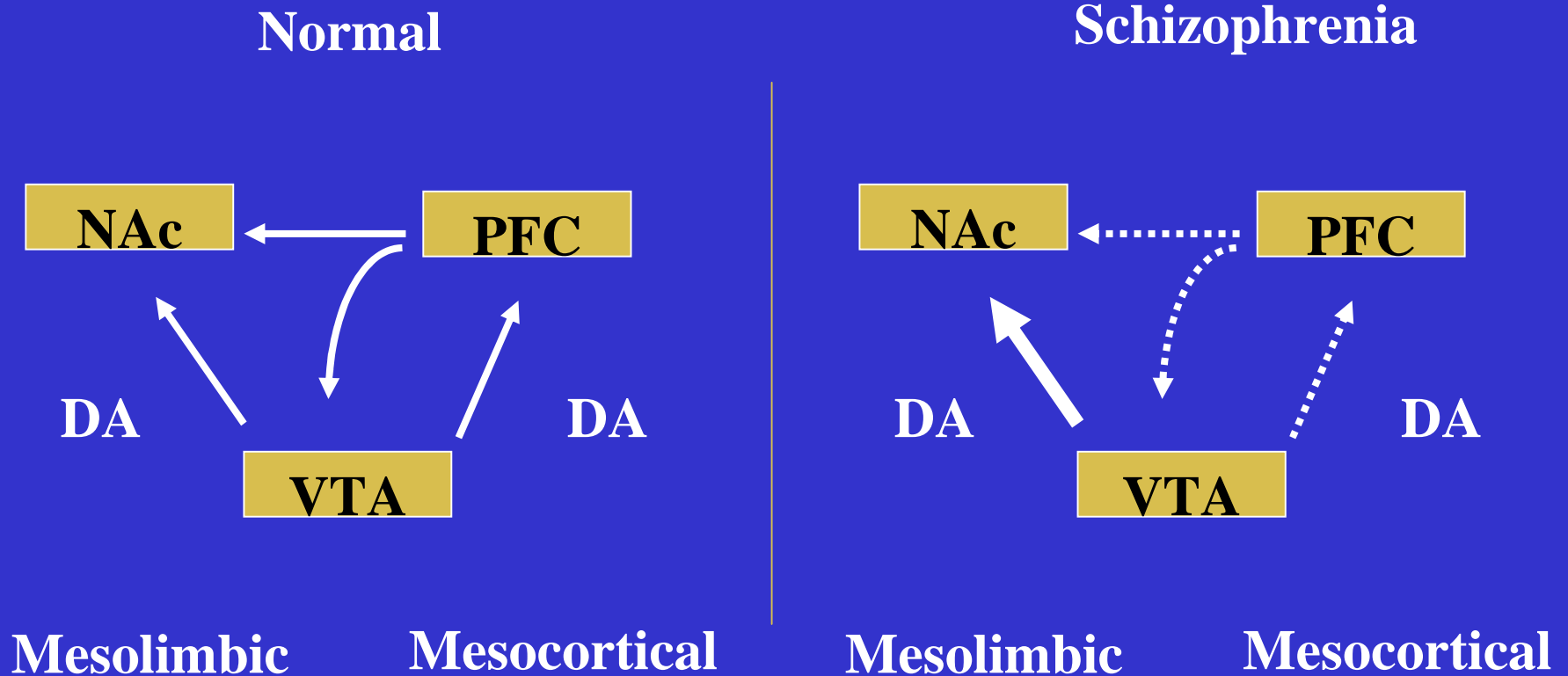
§ Vulnerability to schizophrenia

– Substance abuse → early-onset schizophrenia

§ Self-medication?

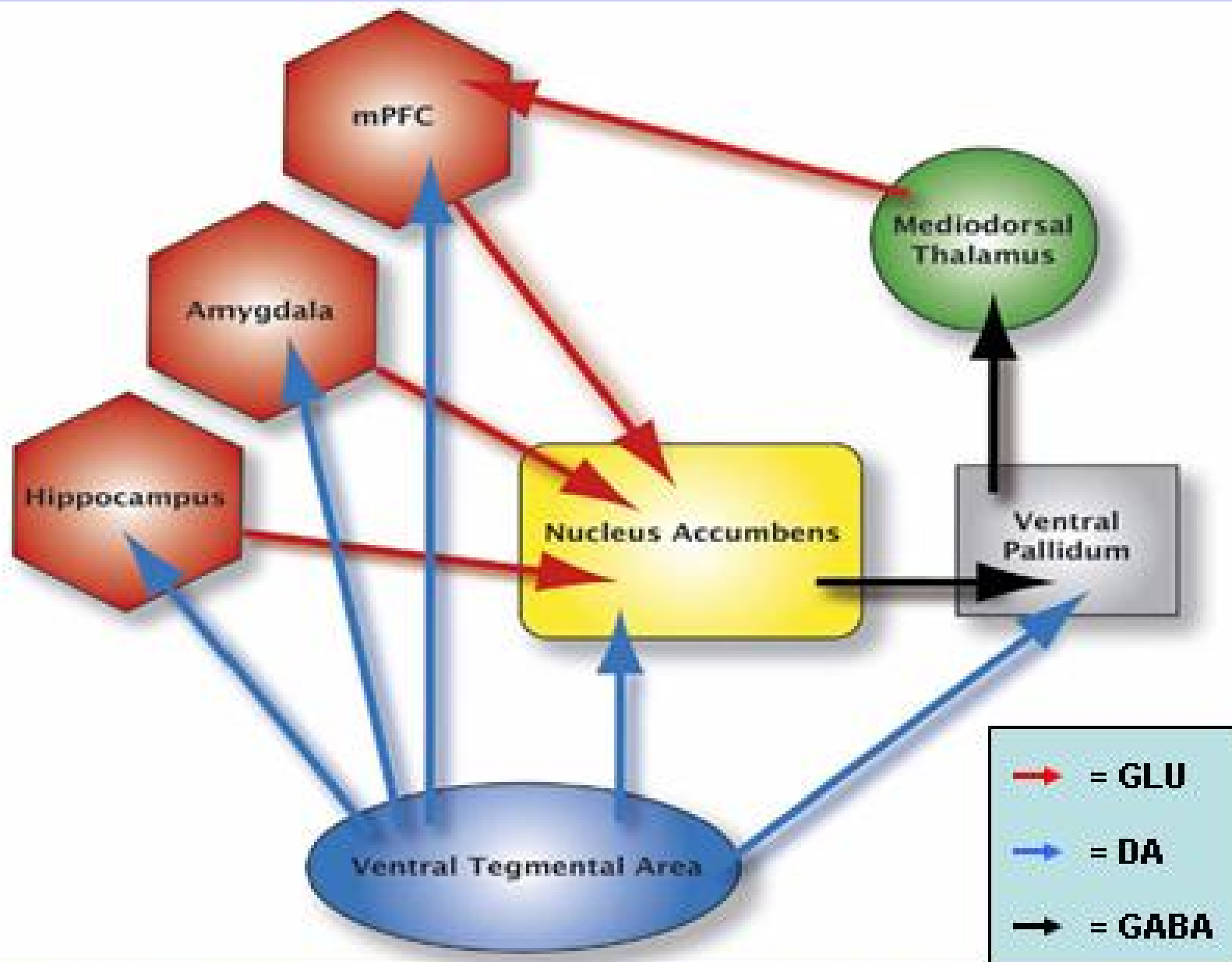
§ Biologic predisposition to substance abuse?

Mesocorticolimbic Dopamine System



NAc: Nucleus Accumbens
PFC: Prefrontal Cortex

VTA: Ventral Tegmental Area
DA: Dopamine



Pierce RC & Kumaresan V. *Neurosci Biobehav Rev.* 2006; 30(2): 215-238.

Biologic Predisposition to Substance Abuse in Patients with Schizophrenia?

- § Patients with schizophrenia have mesocorticolimbic dopamine system dysfunction**
- § Do patients with schizophrenia have a reward system deficit? – Green et al, 1999; Chambers et al, 2001**
- § Substances of abuse potentiate dopamine functions**
- § However, substances of abuse also have detrimental effects in patients with schizophrenia**

Brain Reward Circuitry

§ First demonstrated in animal self-stimulation experiments

§ Functional MRI studies used to investigate BRC in humans

§ Discrete neural circuitry activated by expectancy or consumption of rewards

§ Brain reward dysfunction postulated for substance abuse, schizophrenia, pathological gambling, depression, ADHD and obesity.

Do Patients with Schizophrenia Have a Brain Reward Deficiency?

§ *Some Probes of Brain Reward Circuitry:*

ü Beautiful faces

ü Pain

ü Olfaction

ü Monetary paradigms

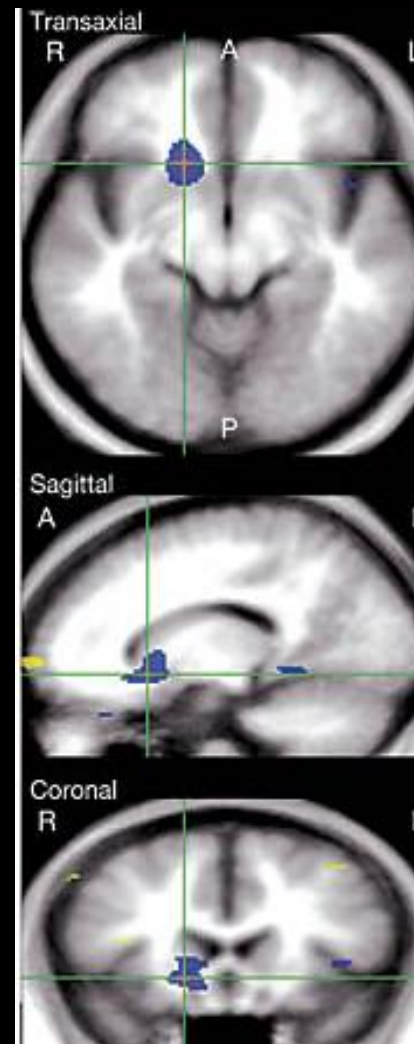
ü Substances of abuse

Olfactory Stimulation

§ PET activation to pleasant and unpleasant odors in schizophrenia - *Crespo-Facorro et al. (2001)*

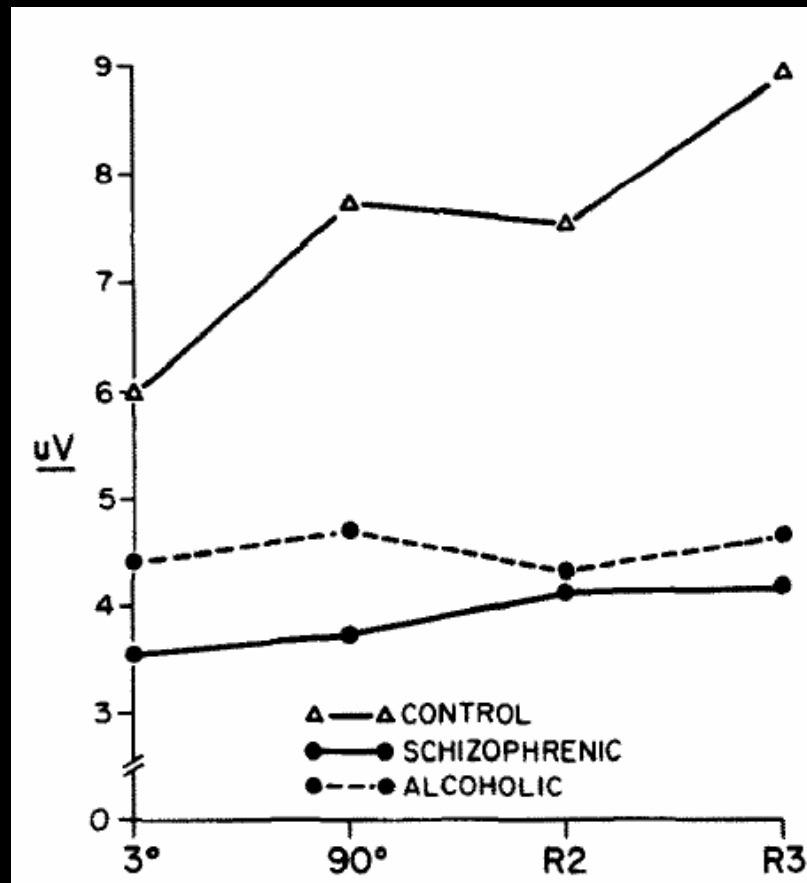
ü Behaviorally, patients showed impaired experience of pleasant odors

ü On PET, patients showed a prominent decrease of activation in the nucleus accumbens



Monetary Reward

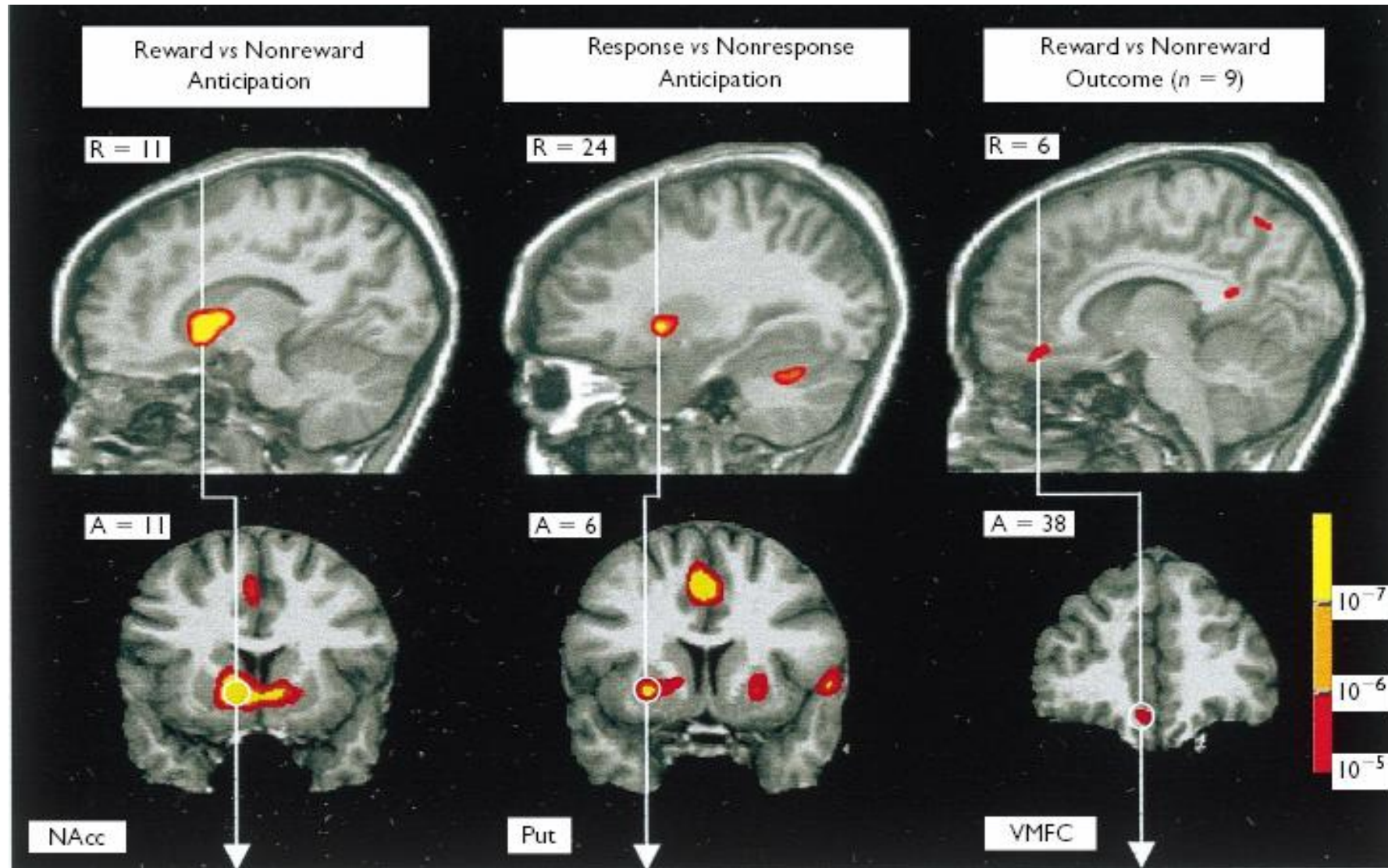
§ Patients with alcohol use disorder and patients with schizophrenia both show reduced P300 amplitude in response to monetary reward in odd-ball paradigm



Last three conditions: \$1 for each correct response

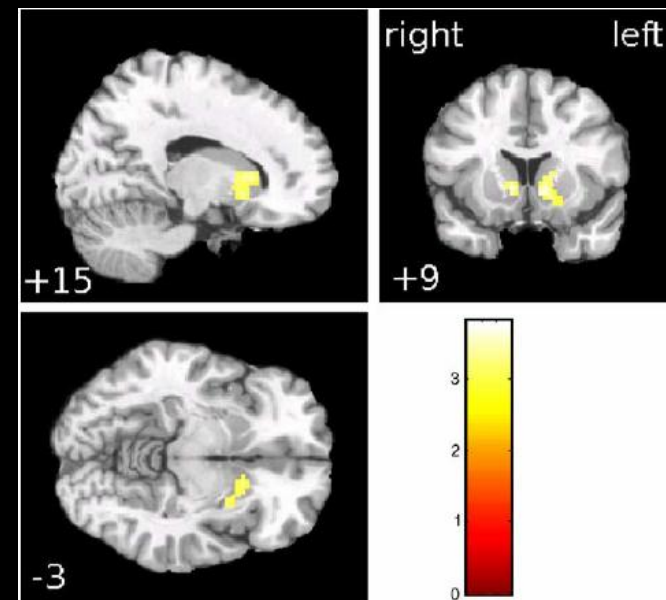
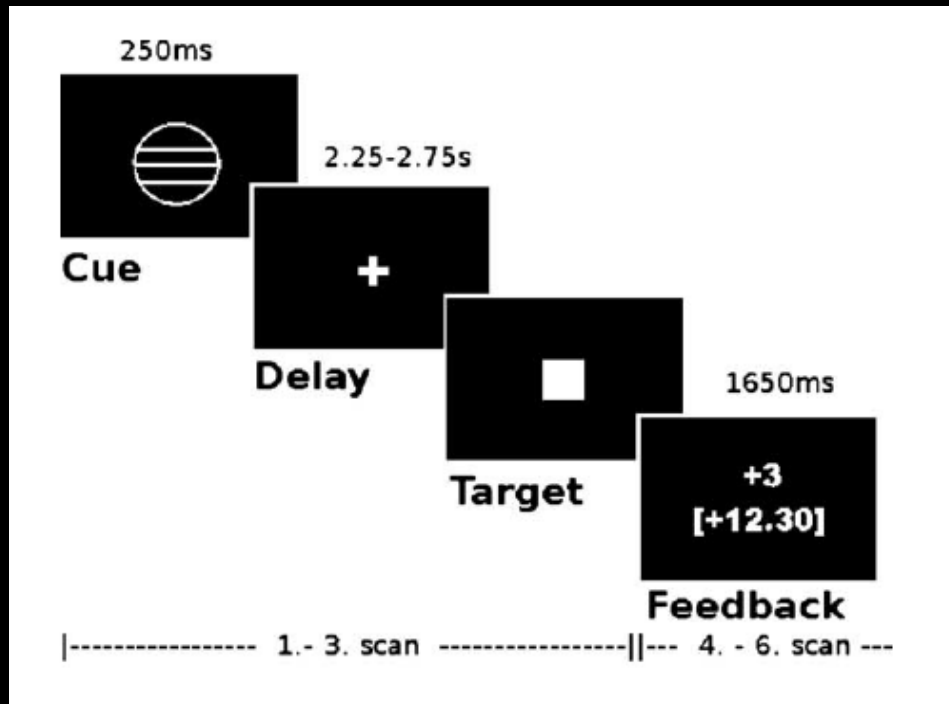
Brecher et al., 1987

Brain reward circuitry fMRI activation to anticipation and consumption of reward



Knutson et al. (2001)

Decreased activation during anticipation of monetary reward in 10 unmedicated patients with SCZ vs. 10 healthy control subjects

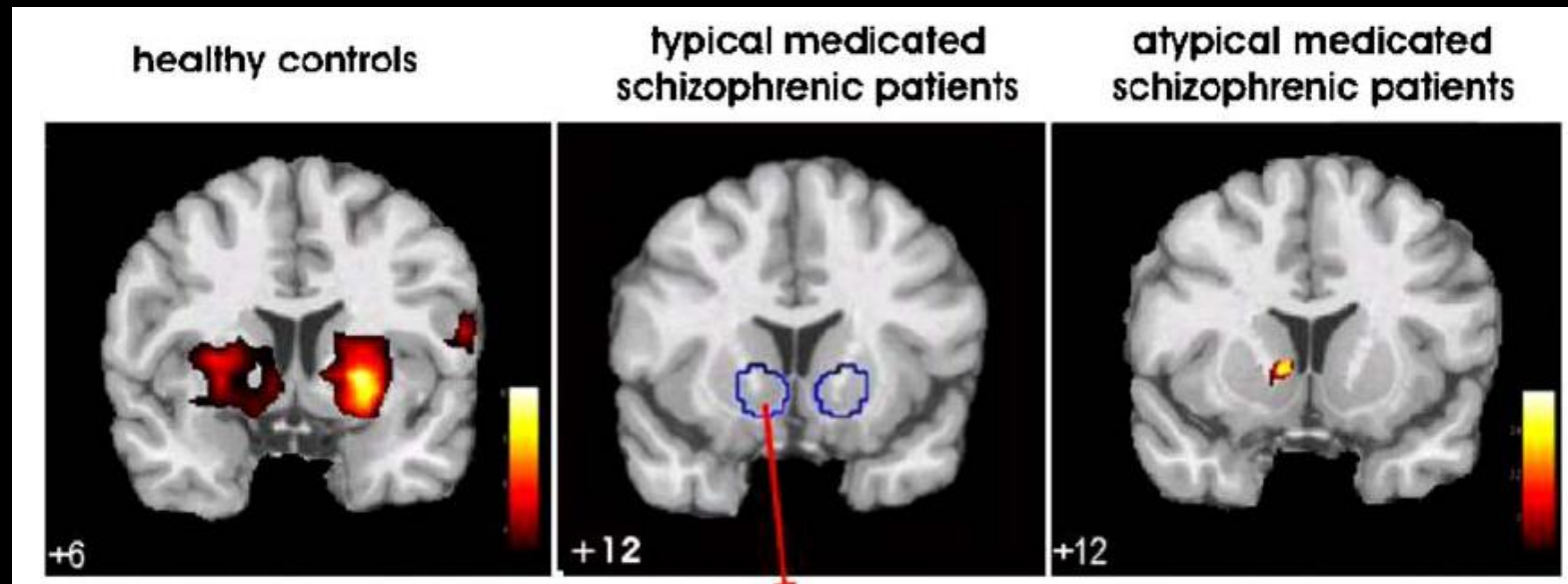


Juckel et al, 2005

fMRI activation to anticipation of monetary reward and medication type in schizophrenia

- § 10 patients with schizophrenia on typical antipsychotics
- § 10 patients with schizophrenia on atypical antipsychotics
- § 10 healthy controls

4 flupentixol (12±4)	4 risperidone (5±1)
4 haloperidol (10±5)	4 olanzapine (19±6)
2 fluphenazine (12±4)	1 aripiprazole (30)
	1 amisulpride (300)



fMRI activation during treatment with olanzapine

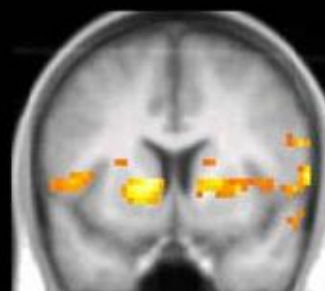
§10 patients with schizophrenia pre and post olanzapine

§10 healthy controls

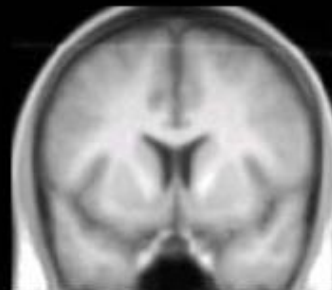
Controls at
time point T1



Controls at
time point T2



Patients with
typical NL



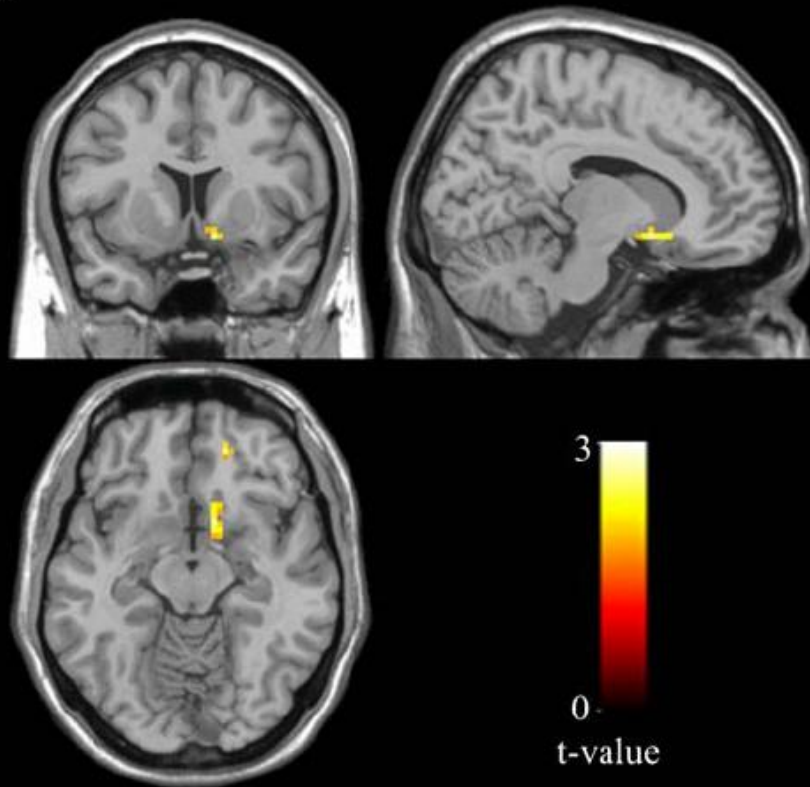
Patients with
olanzapine



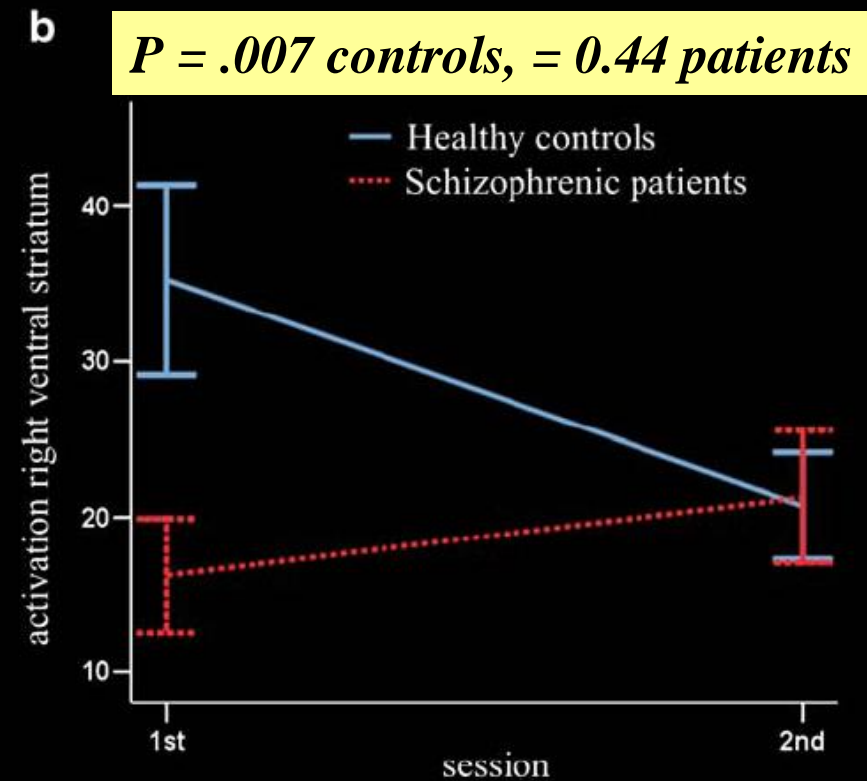
fMRI activation during treatment with olanzapine

§ Interaction Effect (Group X Time) in Right ventral striatum

a



b



Treatment Principles

- **Hybrid programs have been created – combining psychiatric and substance abuse treatment approaches – specialized treatment of both disorders.**
- **“Integrated Dual Diagnosis Treatment Programs”:** Coordinated treatment, with individualized treatment designs
- **One treatment team delivers medication management, as well as substance abuse and psychosocial treatment services.**

Pharmacotherapy for Comorbid Cannabis Use in Patients With Schizophrenia

- **Typical antipsychotics**
 - **Poor response in comorbid patients¹**
 - **EPS effects of typical antipsychotics**
 - **Minimal improvement in negative symptoms**
 - **High rate of substance use in patients treated with these agents**
 - **Haloperidol increases rate of smoking²**
 - **Conclusion: typical antipsychotics appear to be of limited value for controlling substance use in these patients**

Novel antipsychotic drugs

clozapine
risperidone
olanzapine
quetiapine
ziprasidone
aripiprazole
paliperidone

risperidone Consta

Pharmacotherapy of Comorbid SUD – Clozapine

- **Albanese MJ, et al. (1994) – in 2 patients with psychosis and alcohol use disorder, clozapine use associated with decreased psychosis and abstinence**
- **Buckley PF, et al. (1994) – in 29 treatment refractory patients with comorbid SUD, clozapine produced a good response; retrospective survey indicated decreased substance use.**

Pharmacotherapy of Comorbid SUD – Clozapine

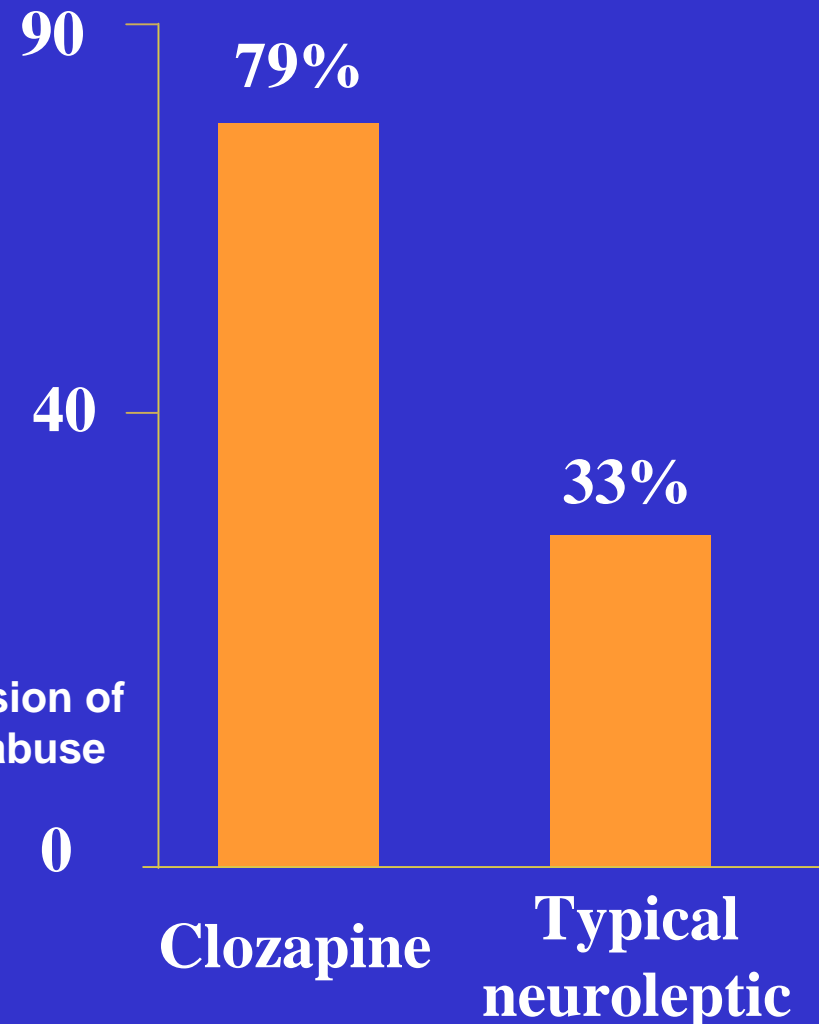
- **Yovell Y and Opler LA (1994) – clozapine associated with decreased craving for cocaine and 1 dual diagnosis case**
- **Marcus P, Snyder R (1995) – clozapine decreased smoking/substance use (N=13)**
- **McEvoy J (1995) – clozapine decreased smoking (N=12)**
- **George TP et al. (1995) – clozapine decreased smoking (N=29)**

Pharmacotherapy for Comorbid Substance Use Disorder in Patients with Schizophrenia

§ Naturalistic longitudinal study (N=101)

- Dual-diagnosis, treatment-refractory patients
- 36 patients given clozapine on clinical basis
- All patients prospectively assessed

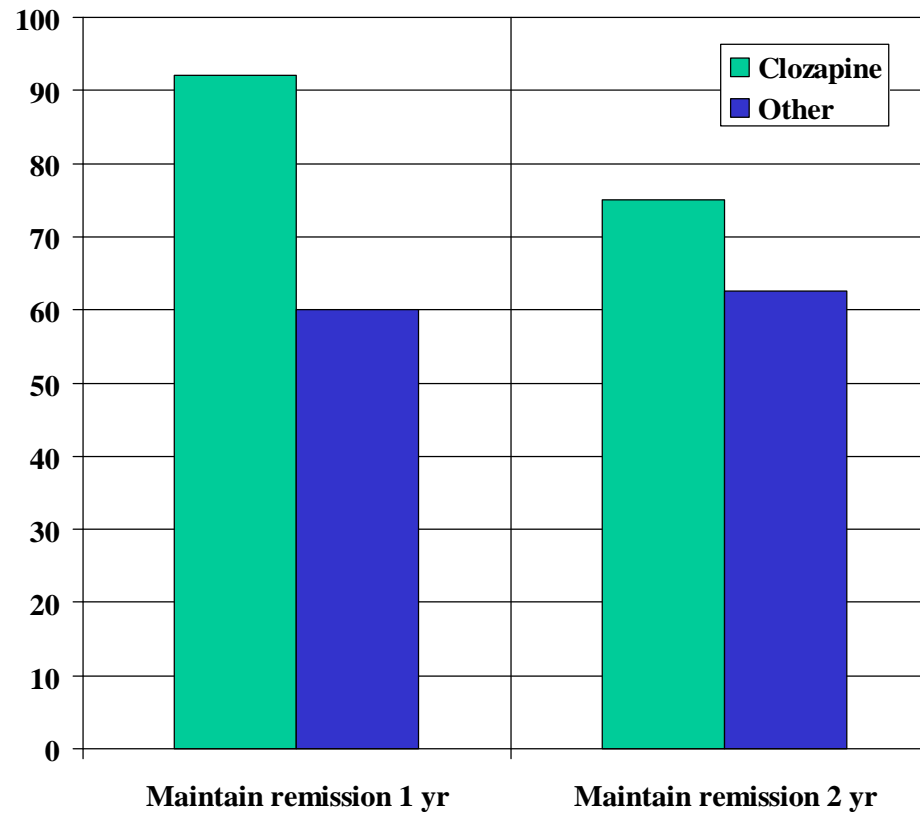
% remission of alcohol abuse



Pharmacotherapy for Substance Use Disorder in Schizophrenia

- **Same study demonstrated effect of CLOZ in cannabis use disorder, compared to typical antipsychotics – 67% (6/9) vs. 32% (12/37).**

Clozapine associated remission and lower rates of relapse



Brunette et al, 2004

Pharmacotherapy of Substance Use Disorder -- Clozapine

- **Retrospective survey of 36 patients with schizophrenia and active substance (primarily alcohol or cannabis) use disorder treated with clozapine.**
- **85% of patients had a decrease in substance use and 72% achieved abstinence during treatment. Zimmet et al, 2000**
- **Clozapine treatment associated with decrease in substance use patients with psychosis and comorbid SUD -- Buckley PF, et al. 1999; Lee et al, 1998**

Comorbid Substance Use Disorder

Risperidone

- **Risperidone treatment associated with good response in patients with bipolar disorder and comorbid SUD --**
Albanese MJ, 2000
- **Risperidone treatment associated with decreased drop out and decreased craving in patients with schizophrenia and comorbid cocaine UD --** *Smelson et al, 2002*
- **Risperidone (or olanzapine) did not decrease substance use in large retrospective VA survey –** *Petrakis et al, 2006*
- **Risperidone “Consta” associated with decreased cocaine use as compared with depot zuclopenthixol –**
Rubio et al, 2006

Comorbid Alcohol/Cannabis Use Disorder: Risperidone vs. Clozapine

- **Boston Continuing Care Service study**
- **41 comorbid patients treated with RISP or CLOZ for at least one year with alcohol/cannabis use at initiation of treatment**
- **32 patients in whom information was available about cessation of substance use during first year of treatment**
- **Abstinence rate was 54% for CLOZ (N=24) and 12.5% for RISP (N = 8), $p < .05$.**

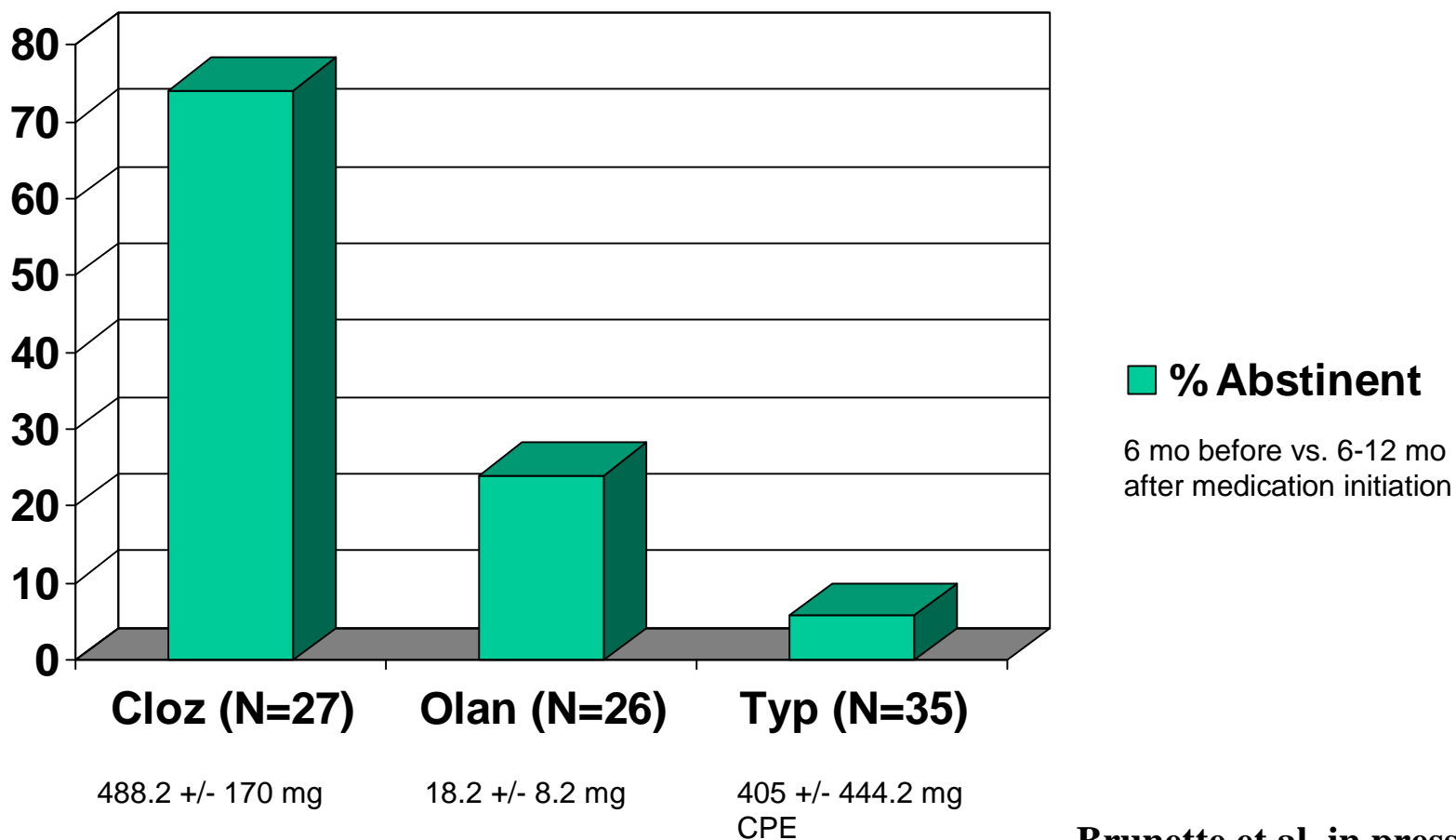
Green AI et al, Schiz. Res., 2003

Pharmacotherapy of Comorbid SUD

- § **Olanzapine:** Data mixed -- can be useful in co-occurring disorder patients, but appears to have **limited ability to decrease alcohol/substance use.** *Conley et al, 1998; Noordsy et al, 2001; Tsuang et al, 2002; Longo et al, 2002; Littrell et al, 2001; Smelson et al, 2006; Sayers et al, 2006, Petrakis et al, 2006..*
- § **Quetiapine:** Suggestion that it may limit stimulant or substance use in co-occurring disorder patients. *Brown et al, 2001; 2004; Potvin et al, 2006.*
- § **Aripiprazole:** Two open-label studies (N=10; N=26) of co-occurring patients, decreased craving for cocaine and alcohol, decreased positive urine screens or no change in cocaine use. *Beresford et al, 2005; Jeffress et al, 2006.*

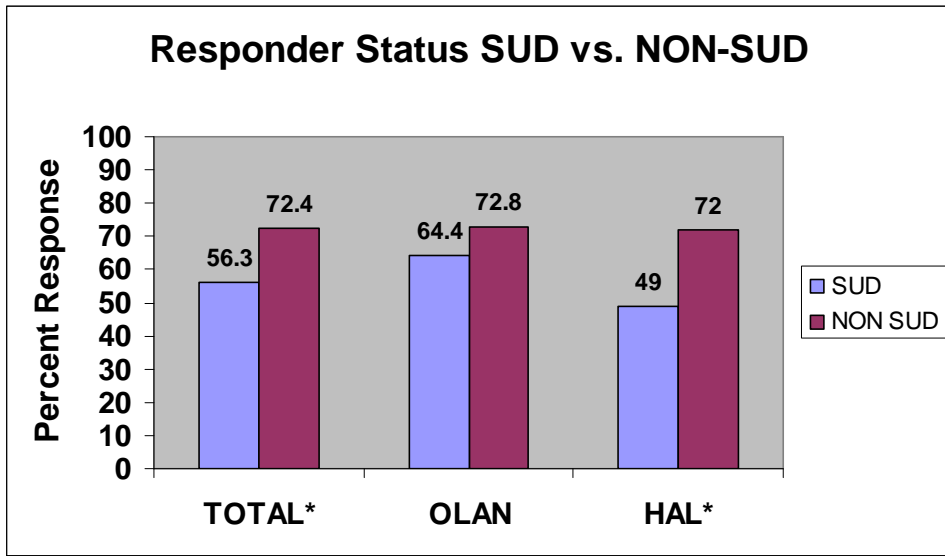
Schizophrenia with co-occurring AUD

Retrospective chart review



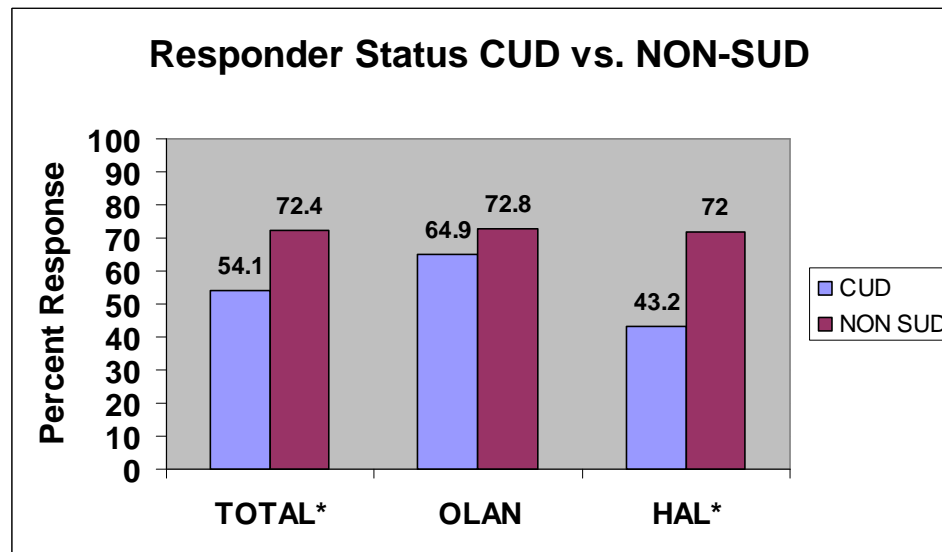
Brunette et al, in press

First Episode Study: Responder Status over two years



N = 262
11 sites

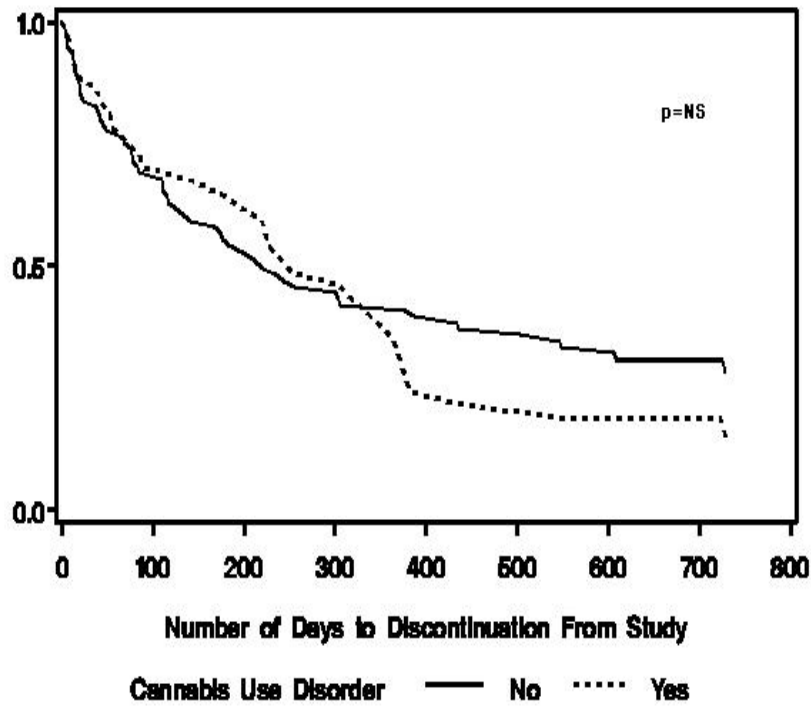
* p < 0.05



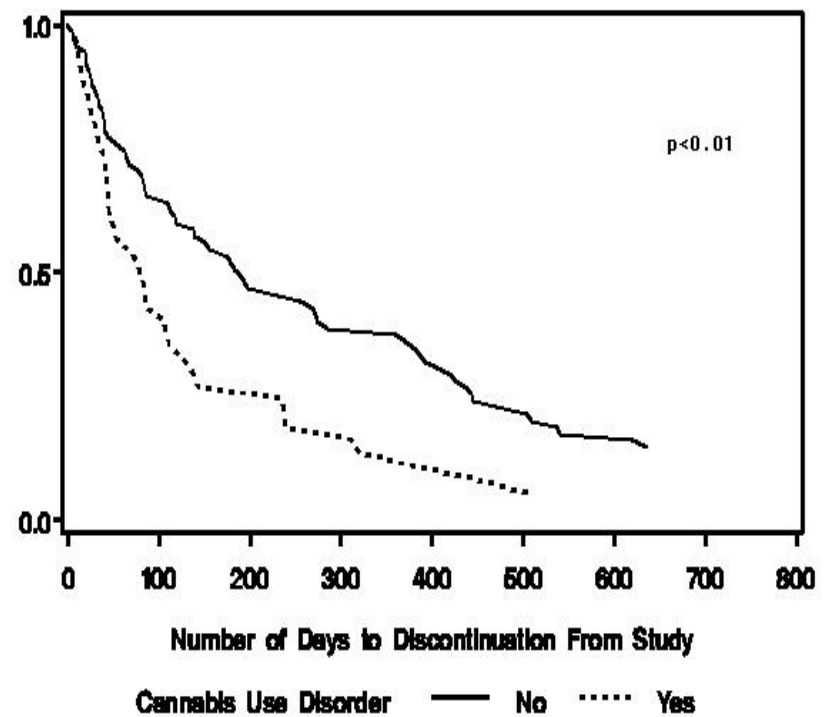
* p < 0.05

First Episode Study: Time to Discontinuation

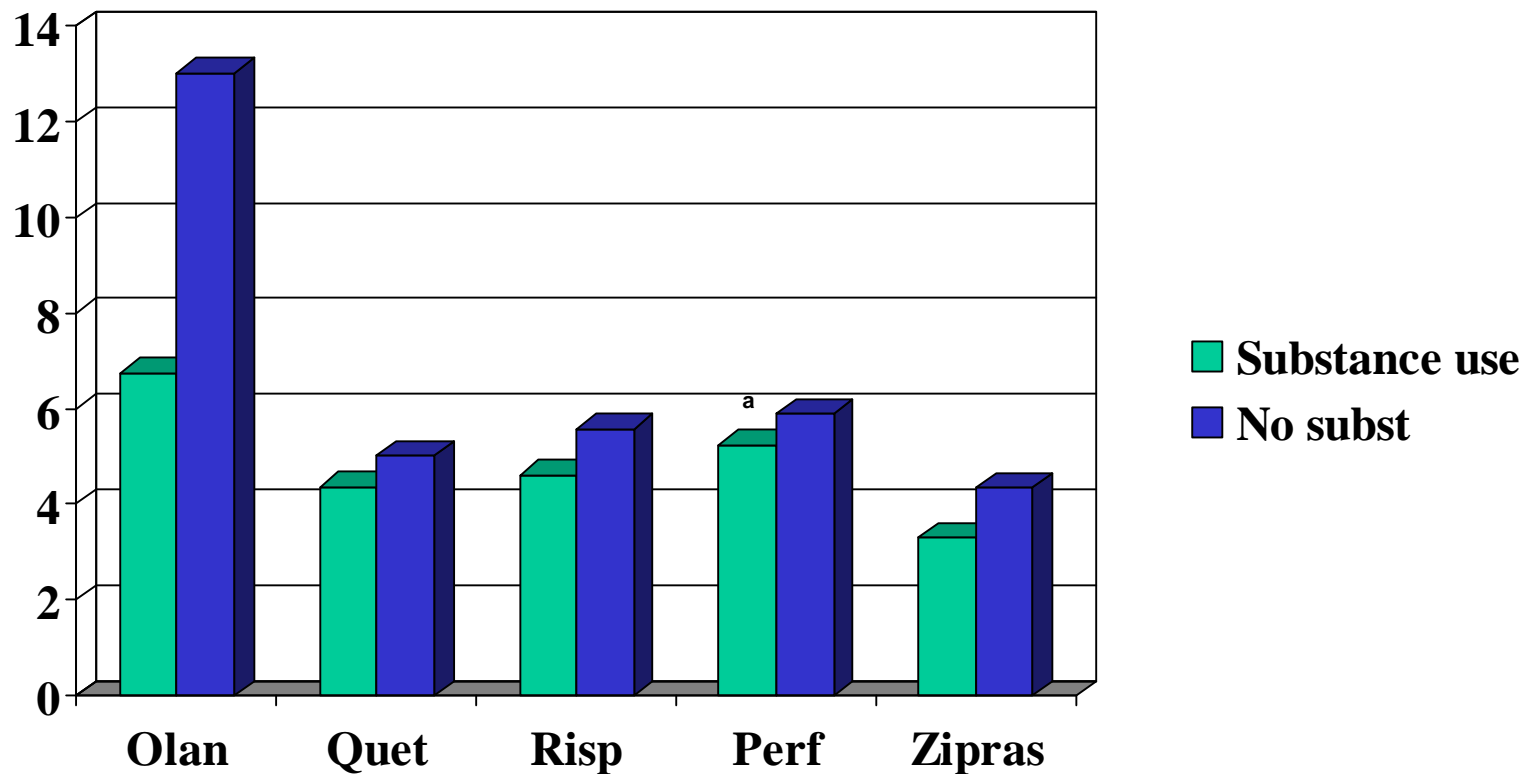
OLAN



HAL



CATIE - Time to discontinuation with and without SUD



Swartz et al, 2008

Potential Adjunctive Agents

- **Imipramine****
 - **Flupenthixol ****
 - **Bromocriptine**
 - **Naltrexone ****
 - **Acamprosate**
 - **Valproic acid**
- Desipramine ****
 - Topiramate**
 - Bupropion ****
 - Disulfiram ****
 - Ondansetron?**
 - Fluoxetine?**

Berger PA, et al. 1986; Siris SG, et al. 1988; Ziedonis D, et al. 1992, 1996;
Wilkins JM, et al. 1997; Maxwell and Shinderman, 1997; Dougherty, 1997;
Johnson et al, 2003; Petrakis et al, 2004; Salloum et al, 2005; Cornelius et al, 2005;
Petrakis et al, 2006

Potential Adjunctive Agents

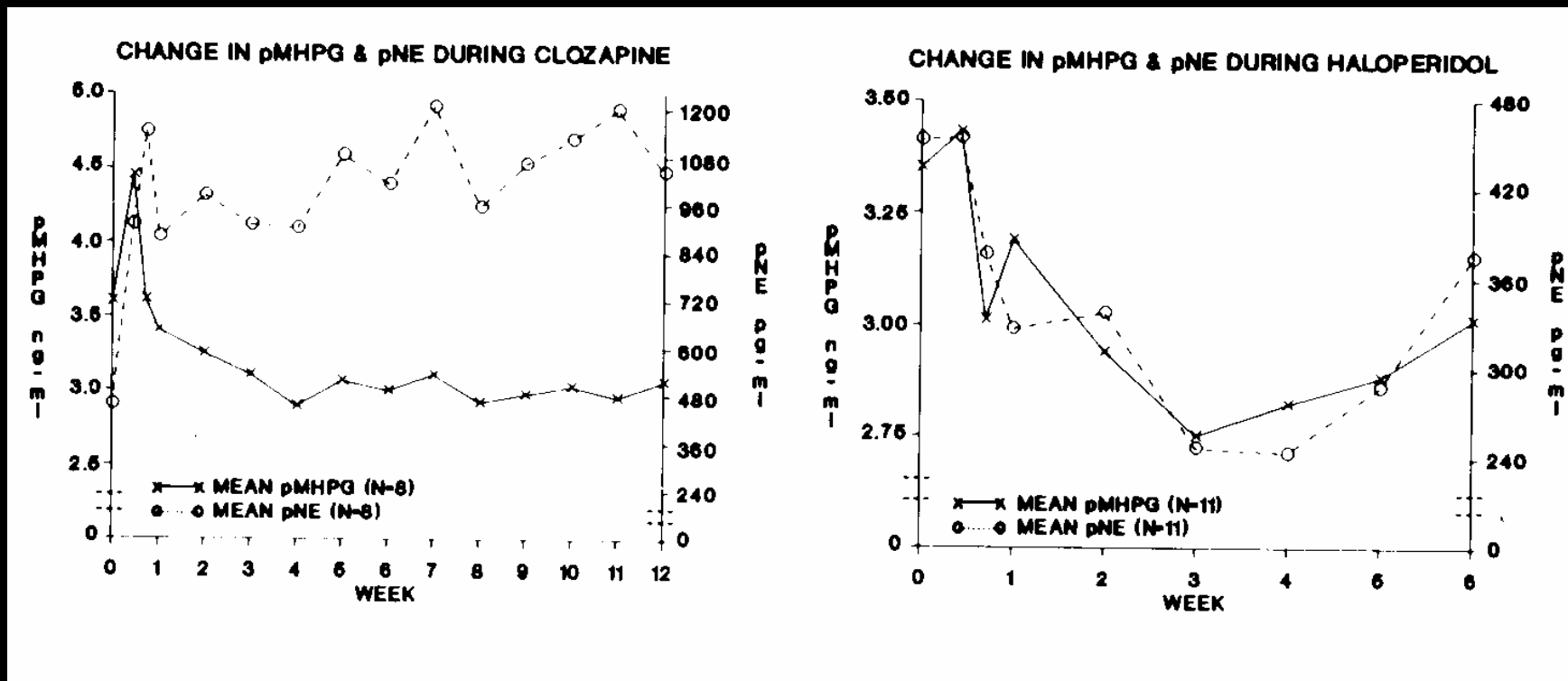
Naltrexone:** Decreased drinking days, heavy drinking days when used as an adjunct to antipsychotic in schizophrenia (N = 31 naltrexone vs. placebo). *Petrakis et al, 2004*

Naltrexone and disulfiram: Both able to reduce alcohol use in patients (N=66) with alcohol dependence and psychotic-spectrum disorders. *Petrakis et al, 2006*

What Makes an Antipsychotic Atypical?

- Weakness of D2 blockade?
- 5 HT2/D2 ratio?
- Displacement from D2 receptor?
- Alpha 1, alpha 2 blockade; NE release?
- Alpha 2c/D2 ratio?

Kalkman et al, 2000; Kapur et al, 2000; Meltzer et al, 1989; Svensson, 2003

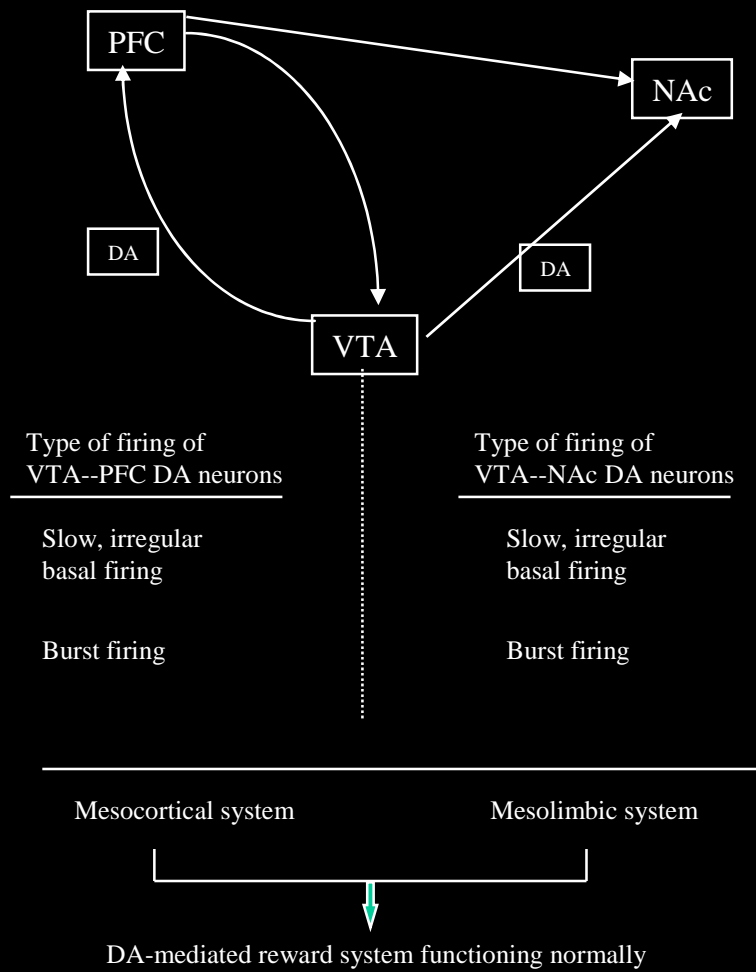


Potential Role of Noradrenergic Activity in Action of Clozapine

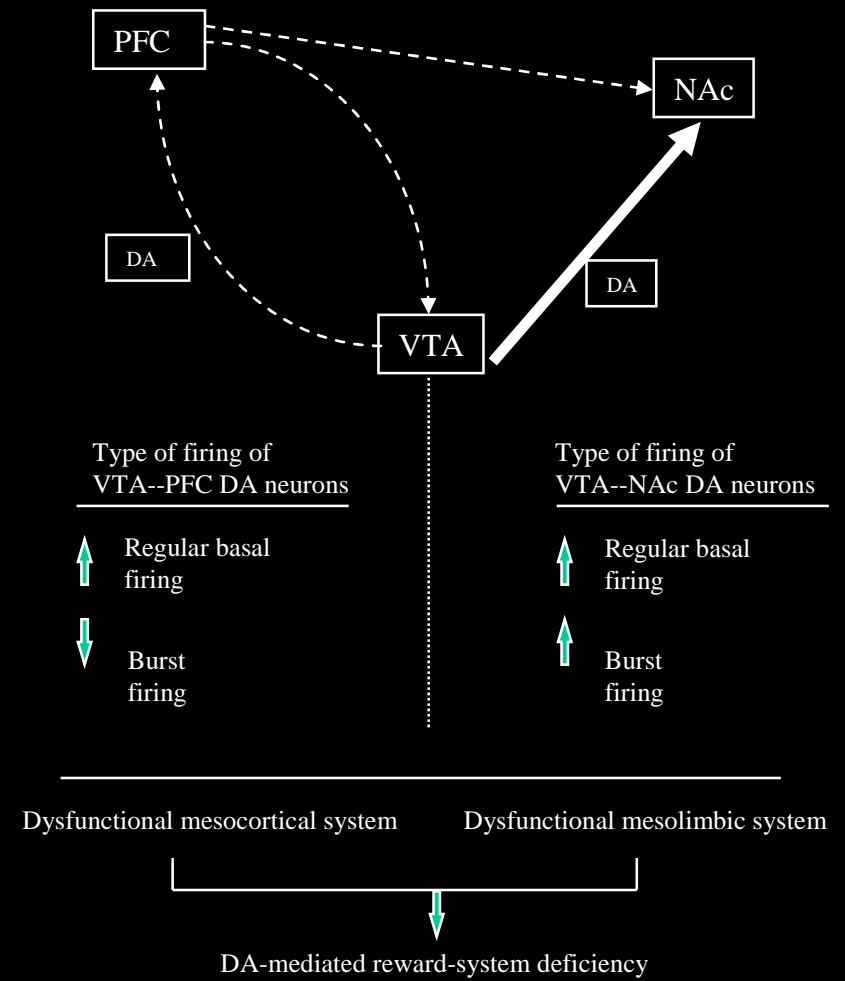
- Clozapine treatment associated with dramatic increase in plasma norepinephrine
- In animal models, α_2 antagonists increase efficiency of firing patterns in DA neurons in brain reward system; decrease symptoms in patients with typical APD
- Noradrenergic effects (α_2 , α_1 antagonism, NE reuptake blockade) coupled with potent 5-HT₂ and weak D₂ antagonism may be linked to actions of clozapine?

Svensson TH, et al. 1995; Litman et al, 1996; Green AI, et al. 1999; Linner et al, 2002; Svensson, 2003, 2009

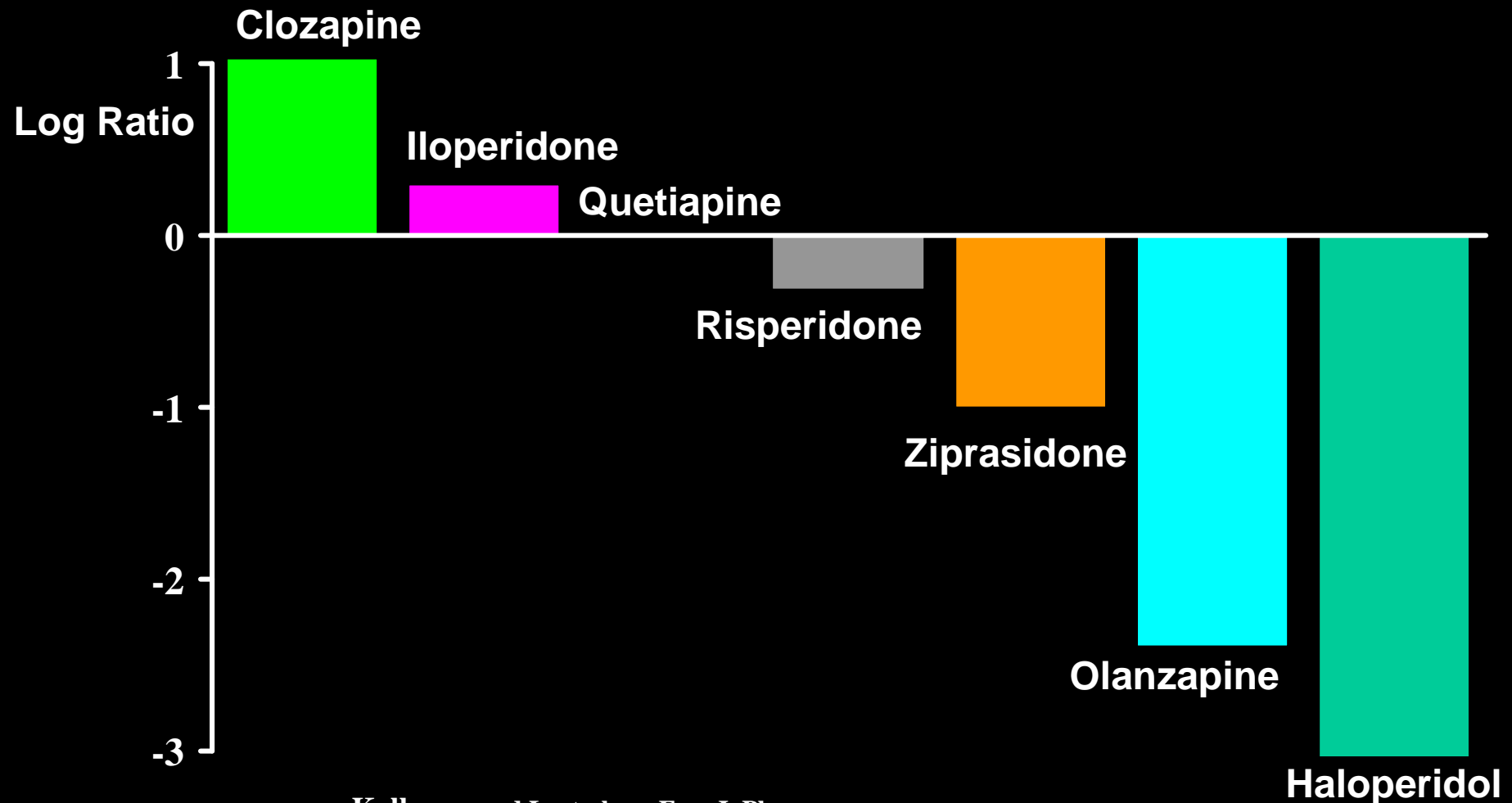
Normal



Schizophrenia ?

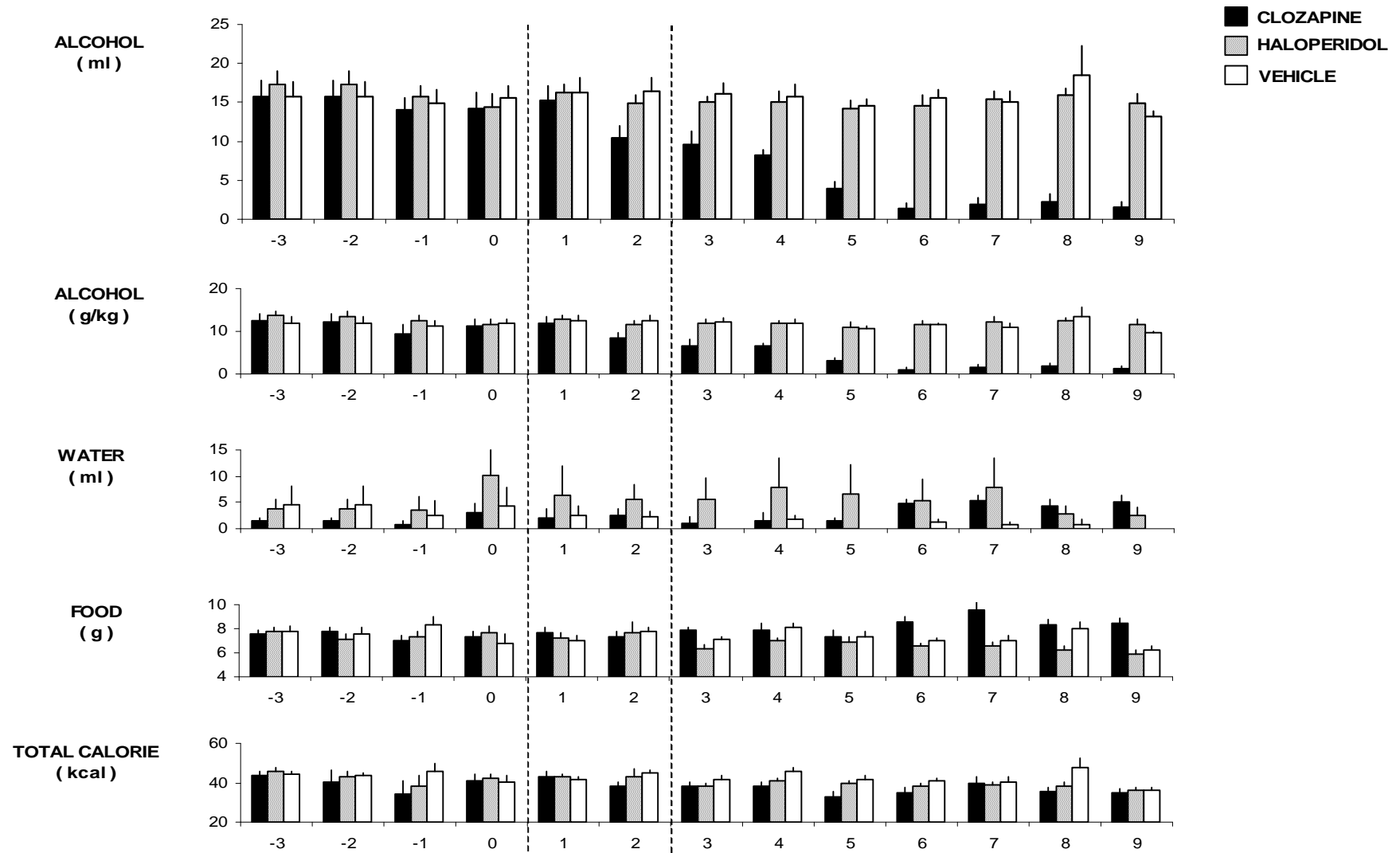


Comparison of α_{2C}/D_2 ratios



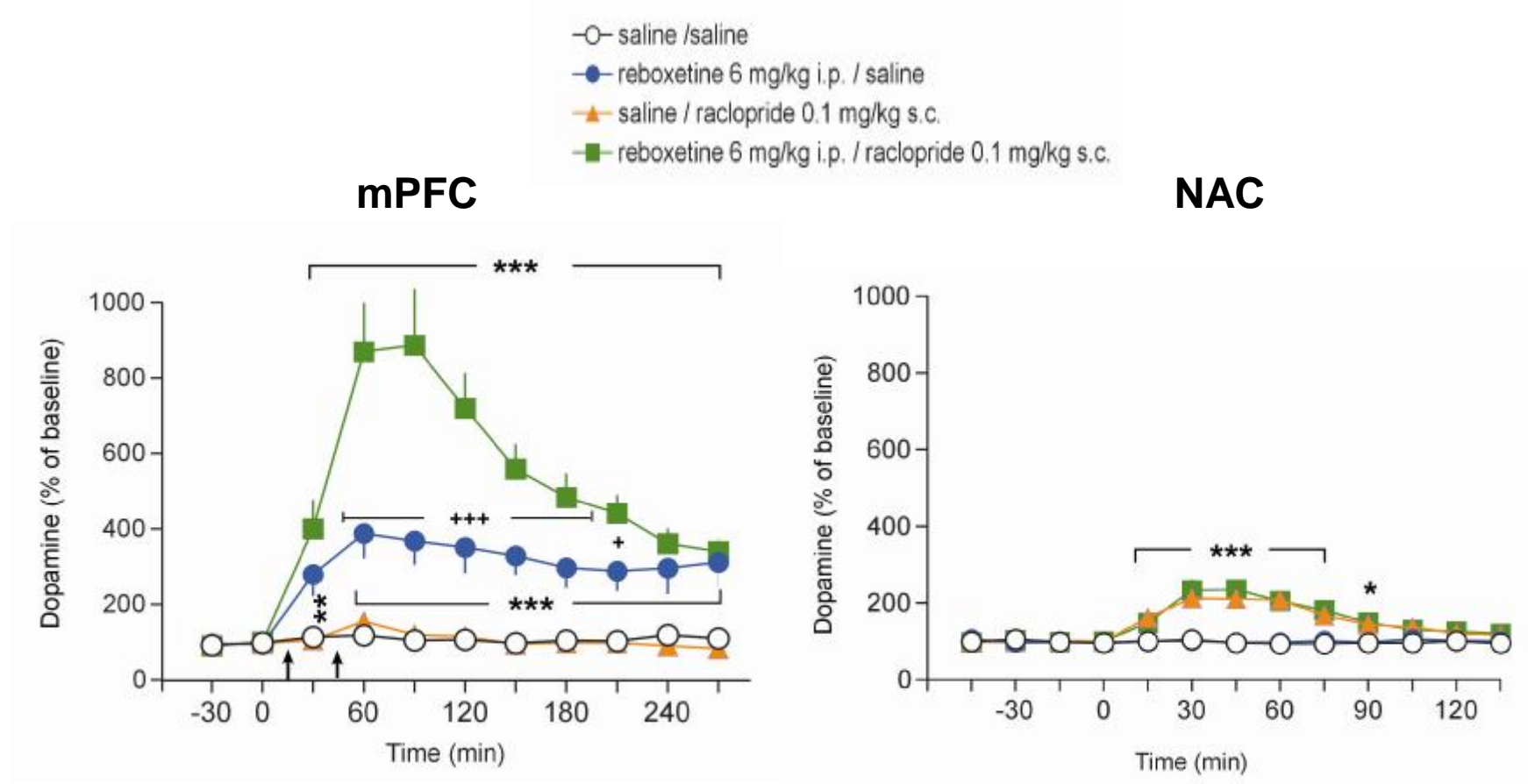
Animal Models of Alcohol Drinking

- **Syrian Golden Hamster**
- **Alcohol-preferring P rat**
- **HAD rat**
- **Sardinian alcohol preferring (sP) rat**

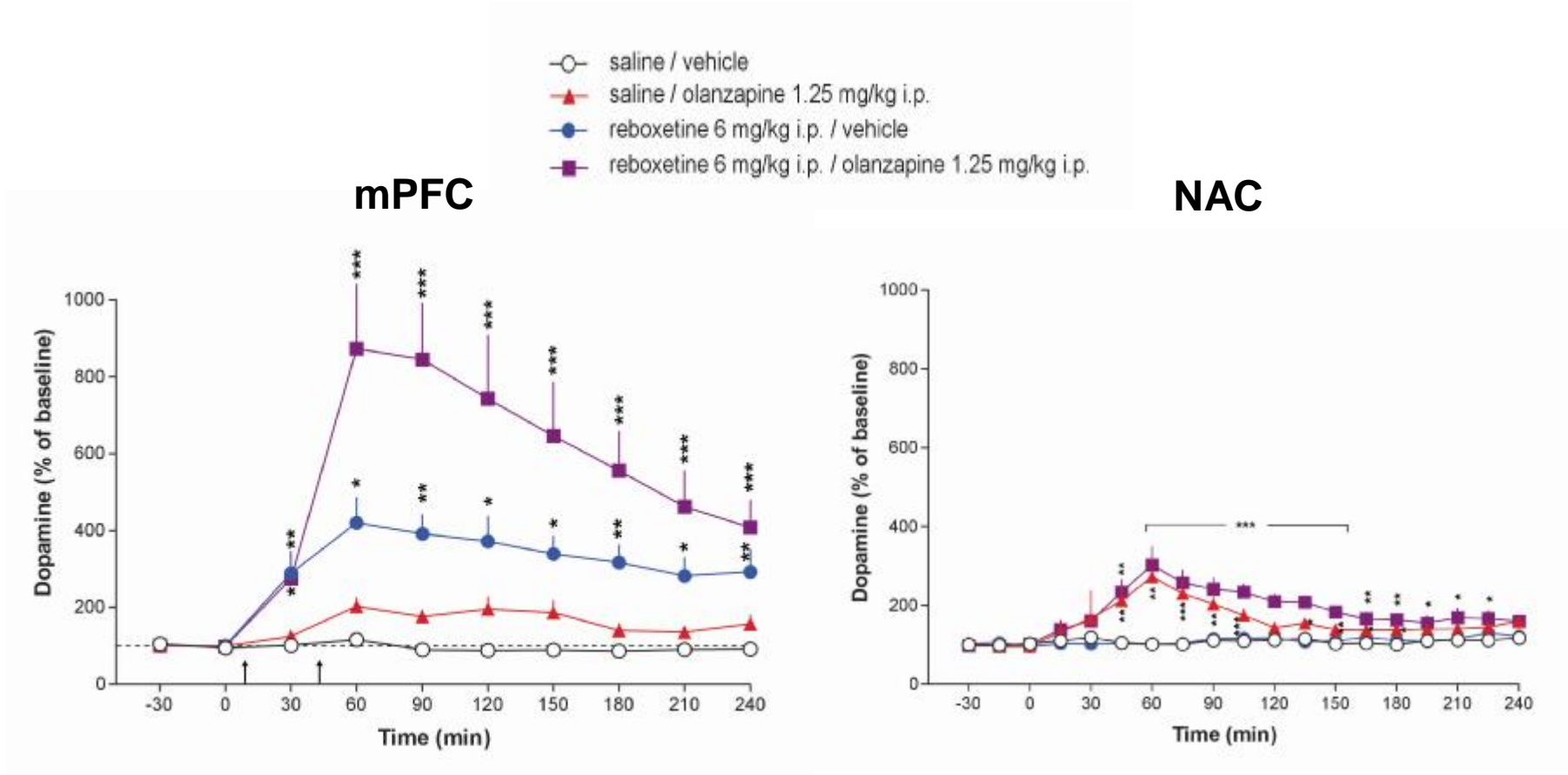


CLOZ		2 mg/kg/day	4 mg/kg/day
HAL		0.2 mg/kg/day	0.4 mg/kg/day
	Baseline Days	Treatment Days	

Reboxetine enhances the dopamine outflow induced by a D₂ antagonist preferentially in the PFC



Reboxetine enhances the dopamine outflow induced by olanzapine preferentially in the PFC



Summary

- **SUD common in patients with SCZ, and increases morbidity of SCZ**
- **TYP antipsychotics of limited value in decreasing SU in SCZ**
- **ATP antipsychotics, especially CLOZ, appear to be of more value**
- **SUD in SCZ related to BRC dysfunction?**
- **Treatment to target BRC dysfunction?**
- **CLOZ's role of DA/NE actions, particularly, to improve BRC dysfunction?**

Collaborators

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