

A Translational Perspective on Clozapine: Clinical Utility



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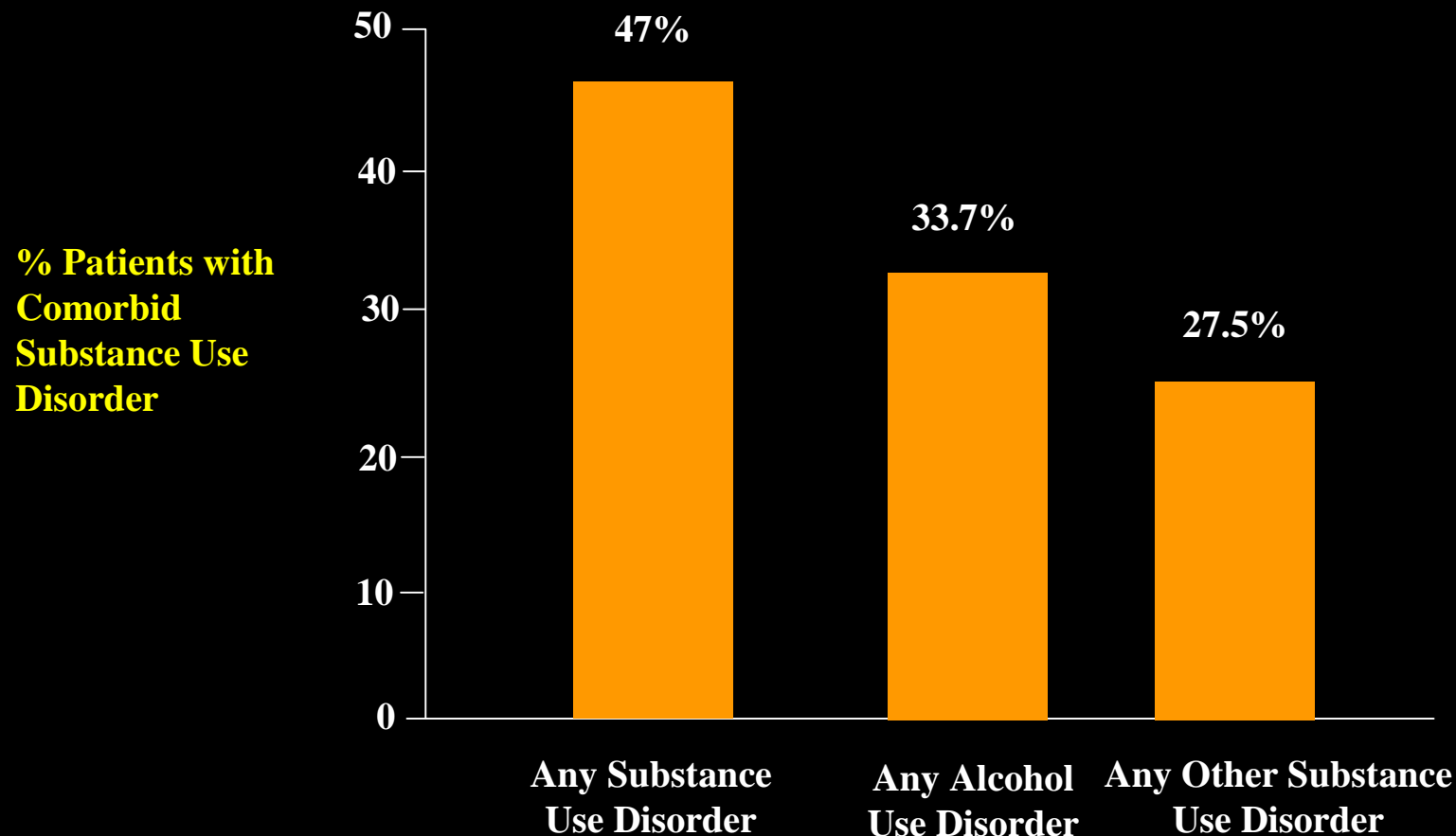
CINP Edinburgh

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Disclosure

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

Lifetime Prevalence of Substance Use Disorder in Patients With Schizophrenia



Regier et al. JAMA 1990; 264-2511.

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

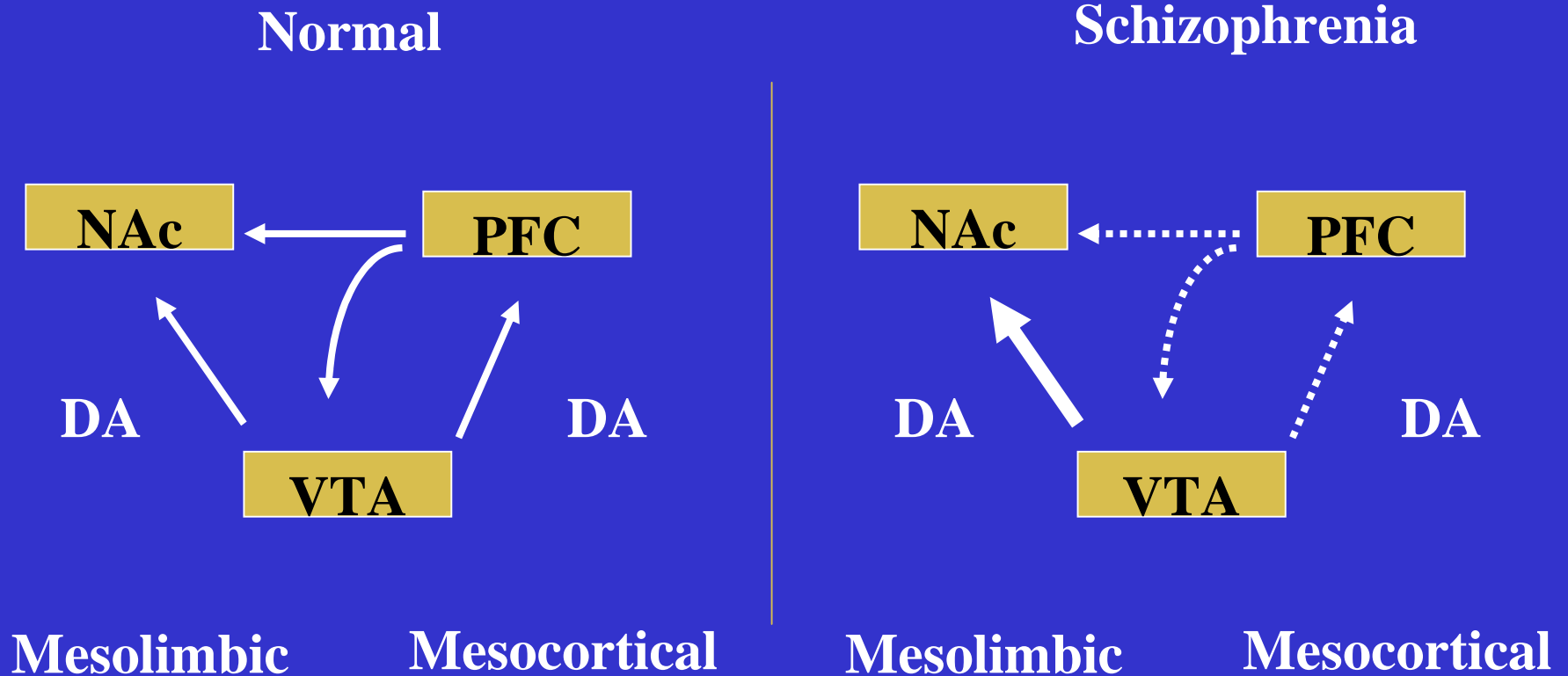
§ Self-medication?

§ Biologic predisposition to substance abuse?

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**

Mesocorticolimbic Dopamine System



NAc: Nucleus Accumbens
PFC: Prefrontal Cortex

VTA: Ventral Tegmental Area
DA: Dopamine

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.**

Antipsychotic Dose Ratio vs. Chlorpromazine

Drug	Dose Ratio
Chlorpromazine (Thorazine)	100
Thioridazine(Mellaril)	95.3
Prochlorperazine (Compazine)	14.3
Perphenazine (Trilafon)	8.9
Fluphenazine (Prolixin)	1.2
Fluphenazine (Prolixin deconate)	0.67
Trifluoperazine (Stelazine)	2.8
Acetophenazine (Tindal)	23.5
Mesoridazine (Serentil)	55.3
Haloperidol (Haldol)	1.6

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

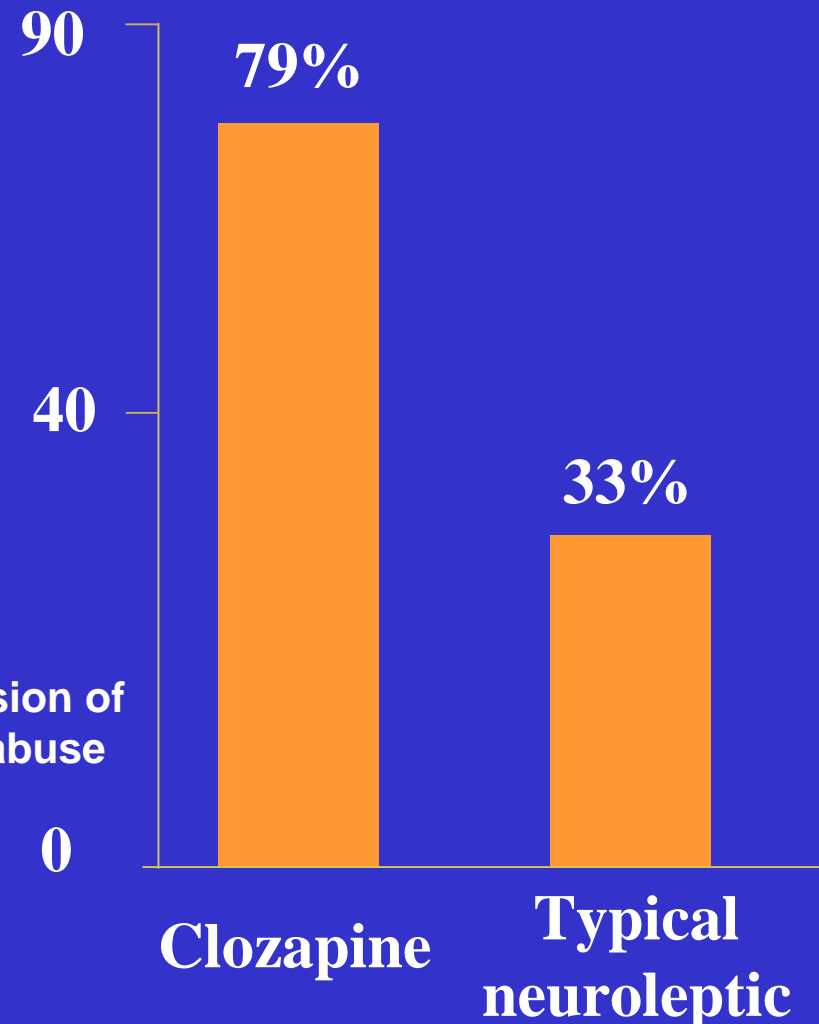
- **Yovell Y and Opler LA (1994) – clozapine associated with decreased craving for cocaine and 1 dual diagnosis case**
- **Marcus P, Snyder R (1995) – clozapine decreased smoking/substance use (N=13)**
- **McEvoy J (1995) – clozapine decreased smoking (N=12)**
- **George TP et al. (1995) – clozapine 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).**
- **10 year follow-up for patients achieving remission: relapse with CLOZ = 8% vs. 40% with other antipsychotics.**

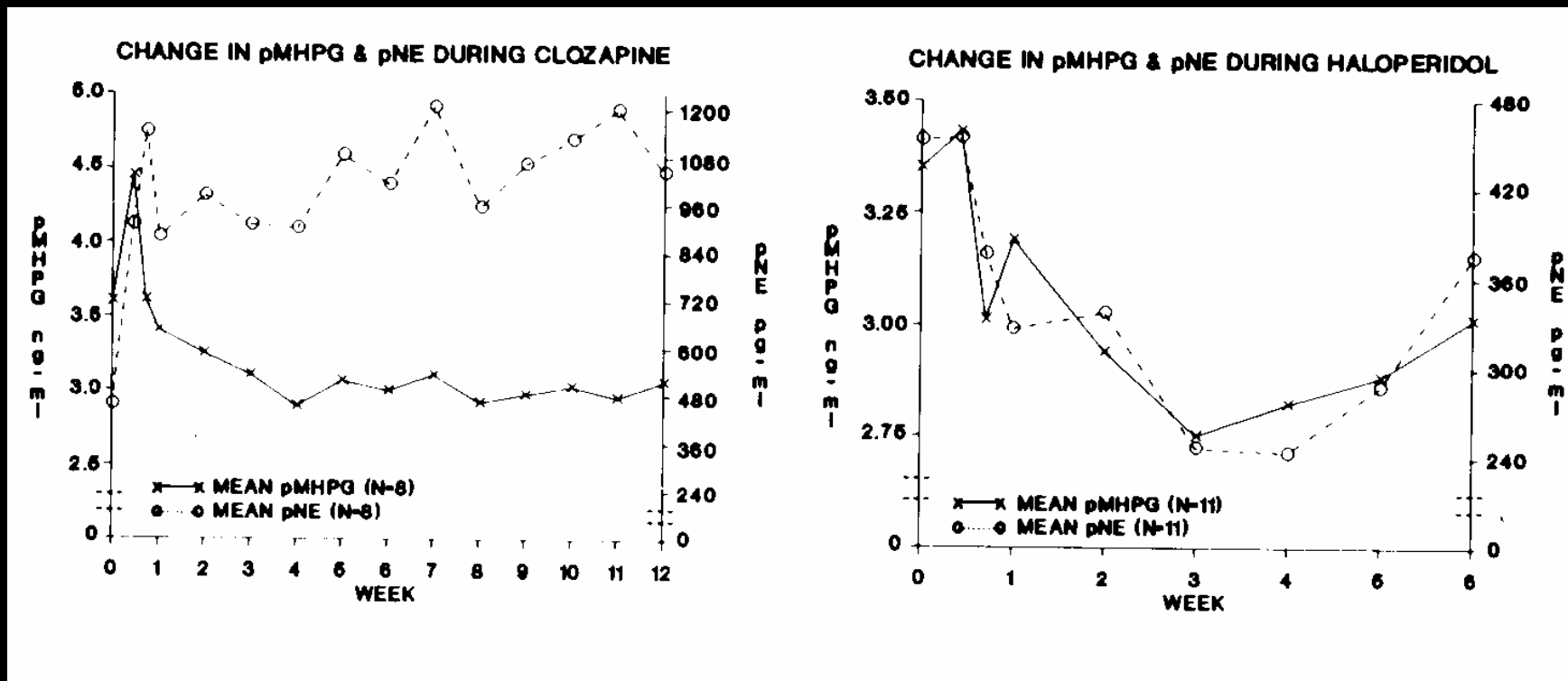
Pharmacotherapy of Substance Use Disorder -- Clozapine

- **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**

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



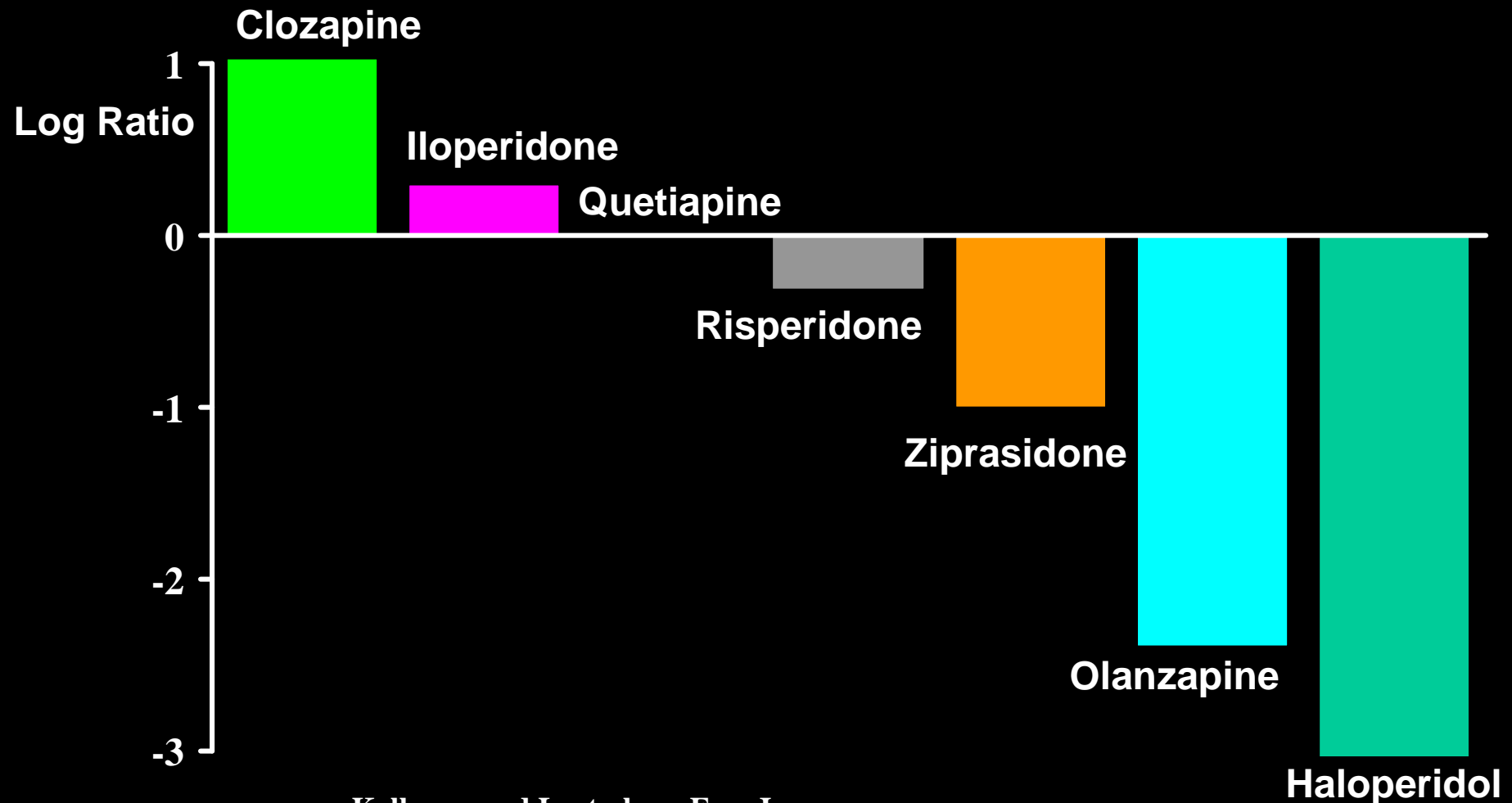
Green et al, 1993

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 release in brain) coupled with potent 5-HT₂ and weak D₂ antagonism may be linked to actions of clozapine

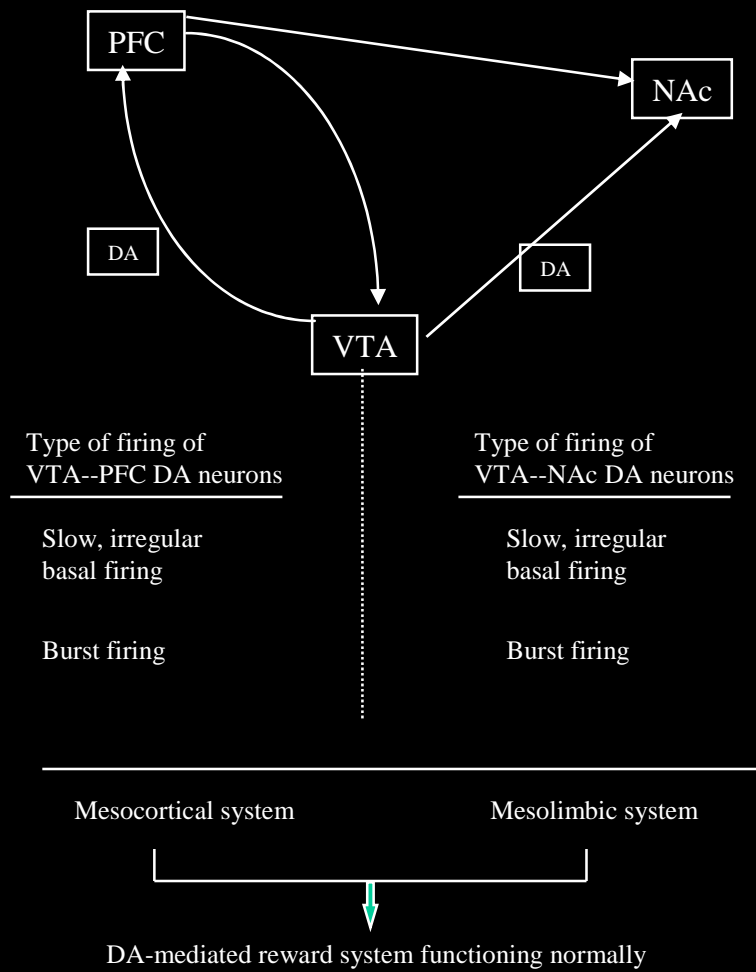
Svensson TH, et al. 1995; Litman et al, 1996; Green AI, et al. 1999; Linner et al, 2002; Svensson, 2003

Comparison of α_{2C}/D_2 ratios

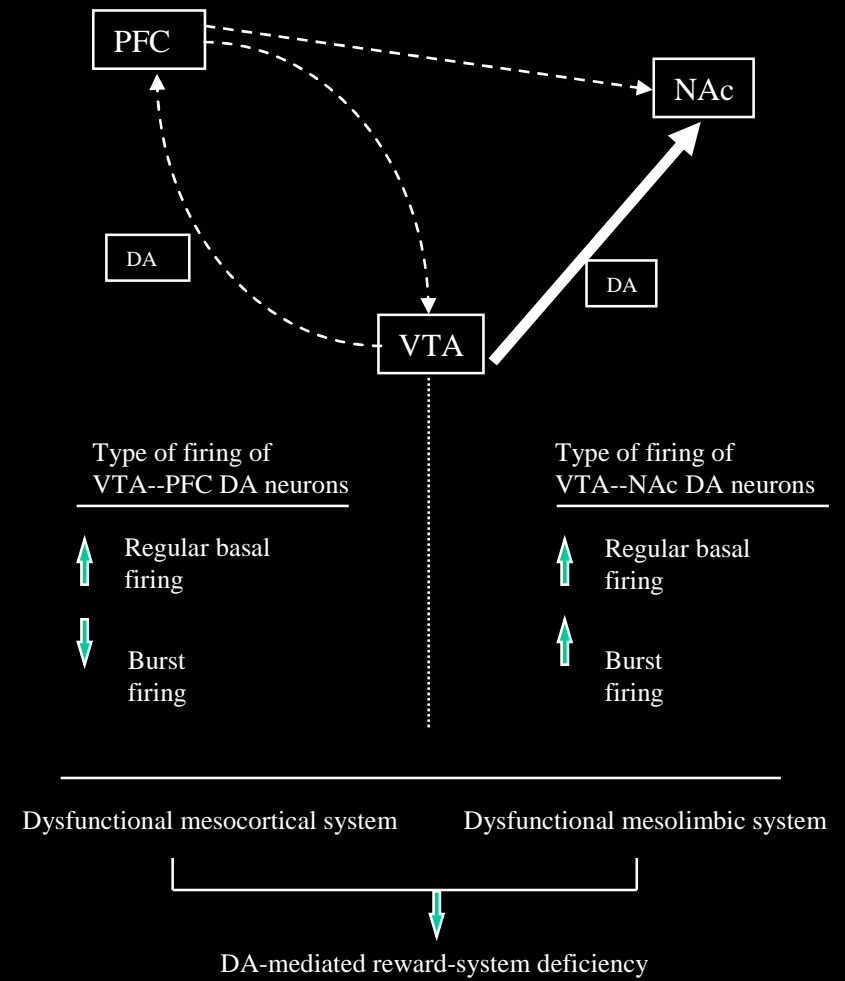


Kalkman and Loetscher, Eur. J. Pharm., 2003

Normal



Schizophrenia ?



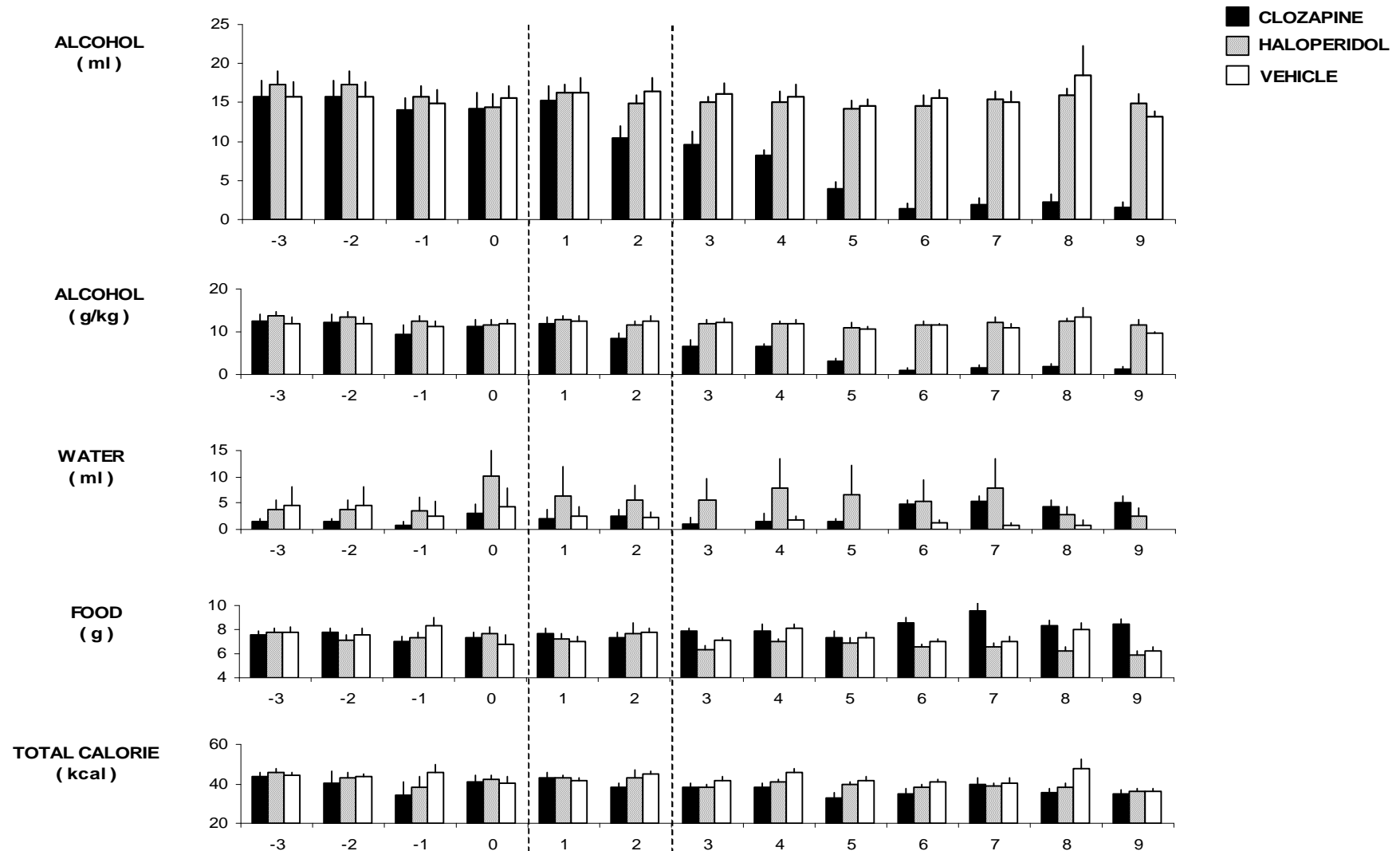
Syrian Golden Hamster

- **Outbred animal that consumes little water**
- **With 15% ethanol, increases consumption of liquid**
- **Maintains constant ethanol consumption**
 - At a steady rate during the night (1.5 g/kg/hr)
 - 10-15 g/ kg/day
 - High alcohol metabolism
 - Steady blood alcohol level (7-13 mg%)
- **Does not demonstrate signs of withdrawal from chronic alcohol consumption**
- **Does not demonstrate alcohol deprivation effect (i.e., binging following alcohol deprivation)**

Alcohol-Preferring P Rat

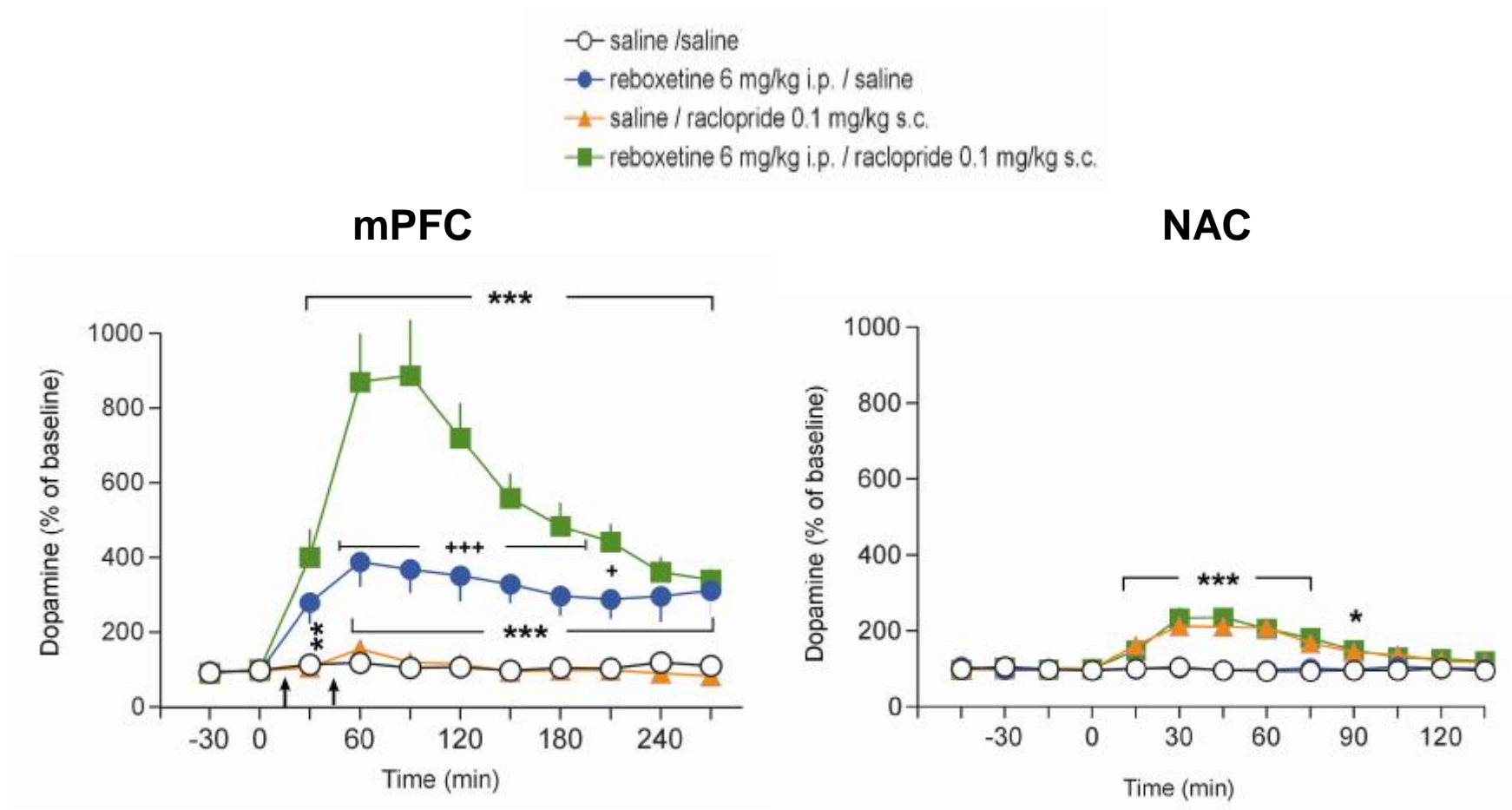
- **Selectively bred, genetic line of rodent used to:**
 - **Study the neurobiology of alcohol abuse & dependence**
 - **Assess medications for treatment of alcoholism**
- **Voluntarily consumes alcohol (5-8 g/kg/day)**
- **Demonstrates high BAL (50-200 mg%)**
- **Develops physical withdrawal from chronic alcohol drinking**
- **Demonstrates alcohol deprivation effect**

Clozapine and Haloperidol on Alcohol Drinking in Hamsters



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

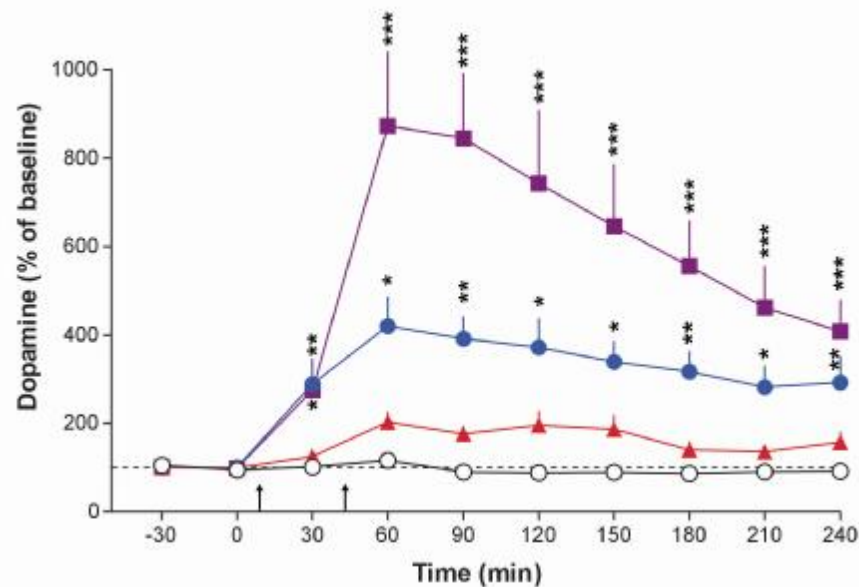
Reboxetine enhances the dopamine outflow induced by a D₂ antagonist preferentially in the PFC



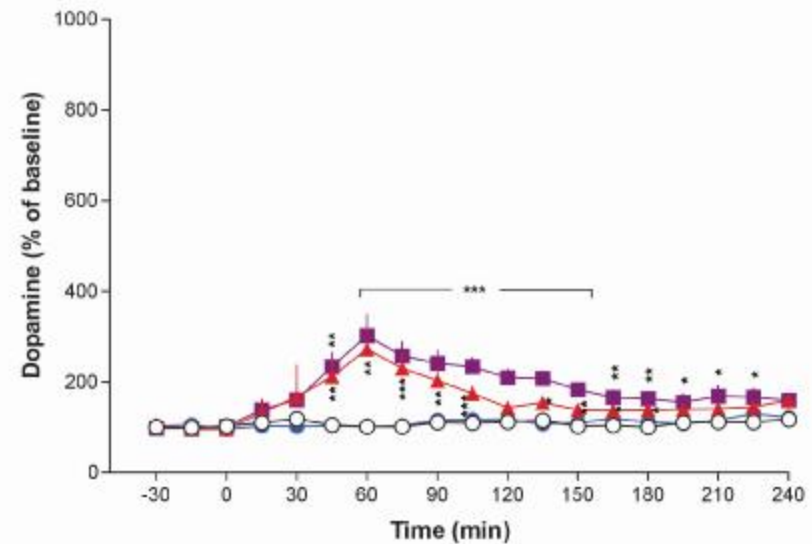
Reboxetine enhances the dopamine outflow induced by olanzapine preferentially in the PFC

- saline / vehicle
- ▲ saline / olanzapine 1.25 mg/kg i.p.
- reboxetine 6 mg/kg i.p. / vehicle
- reboxetine 6 mg/kg i.p. / olanzapine 1.25 mg/kg i.p.

mPFC



NAC



Summary

- CLOZ appears to decrease alcohol abuse in patients with schizophrenia
- Studies in alcohol preferring rodents demonstrate:
 - 1) CLOZ decreases alcohol drinking
 - Raclopride added to CLOZ impairs this effect of CLOZ
 - 2) HAL and RISP have modest effects on alcohol drinking
 - Idazoxan increases ability of HAL to decrease alcohol drinking
 - 3) Studies in alcohol preferring rodents suggest that CLOZ's ability to decrease alcohol drinking may relate to its:
 - 1) weak D2 receptor antagonism
 - 2) α 2 antagonism
 - 3) other effects on the noradrenergic system?

Collaborators

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