

# Pharmacology of Antipsychotic Drugs

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# Disclosures

*Neither I nor my spouse has a financial relationship with  
a commercial Interest to disclose*

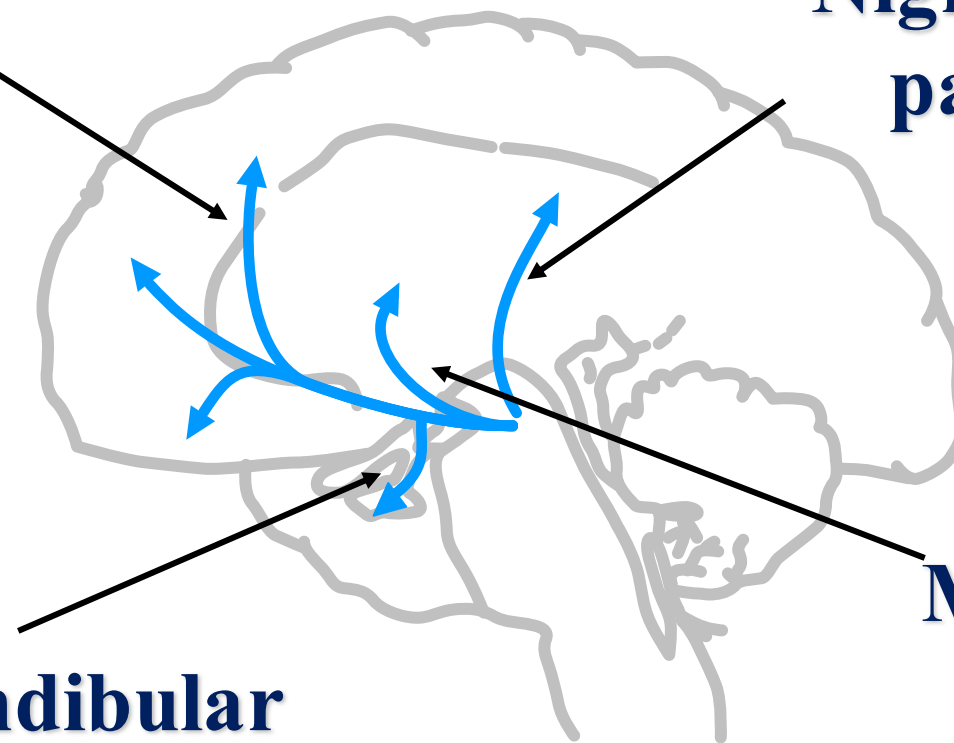
# Major Dopaminergic Pathways in Mammalian Brain

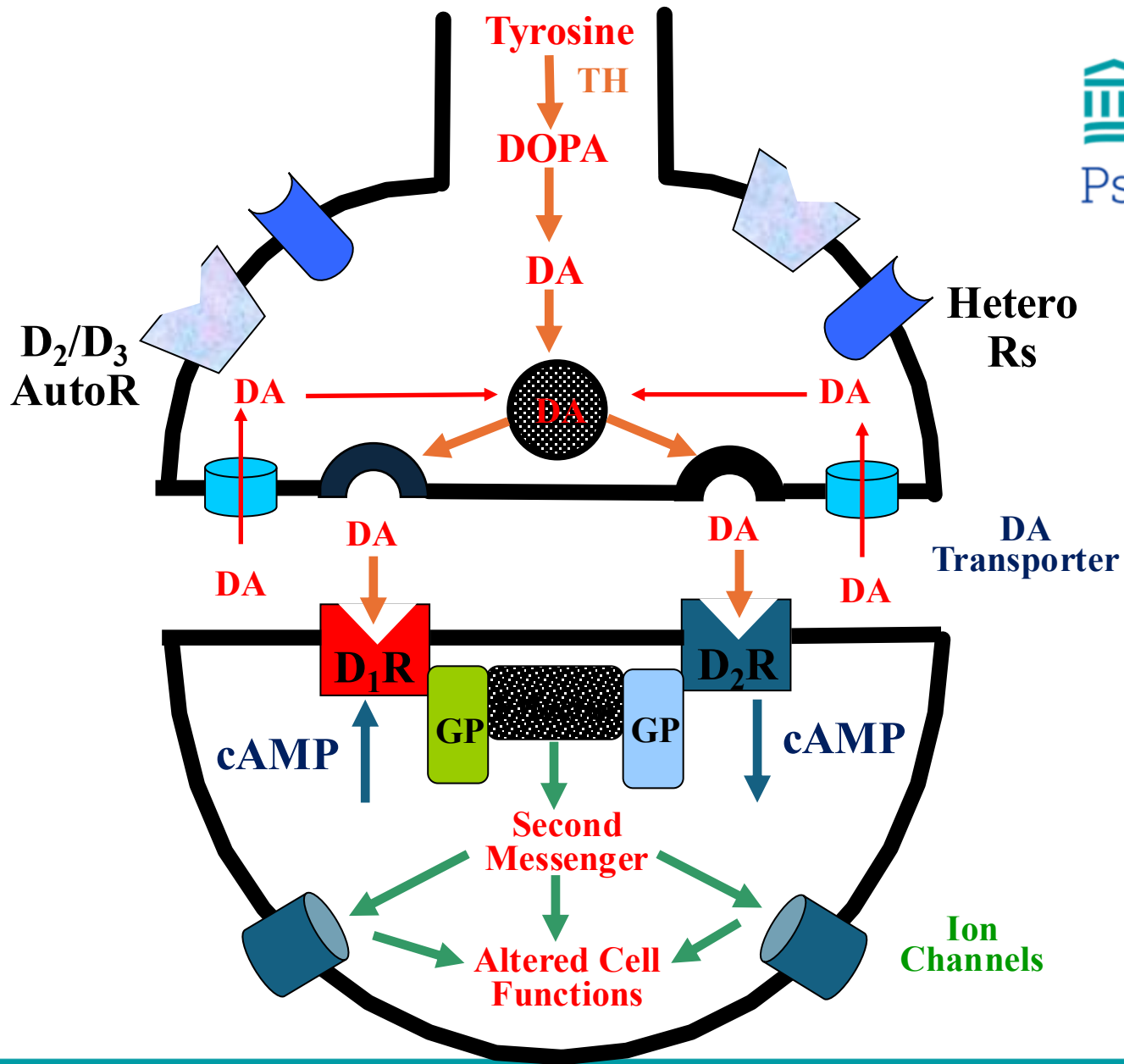
**Mesocortical  
pathway**

**Nigrostriatal  
pathway**

**Tuberoinfundibular  
pathway**

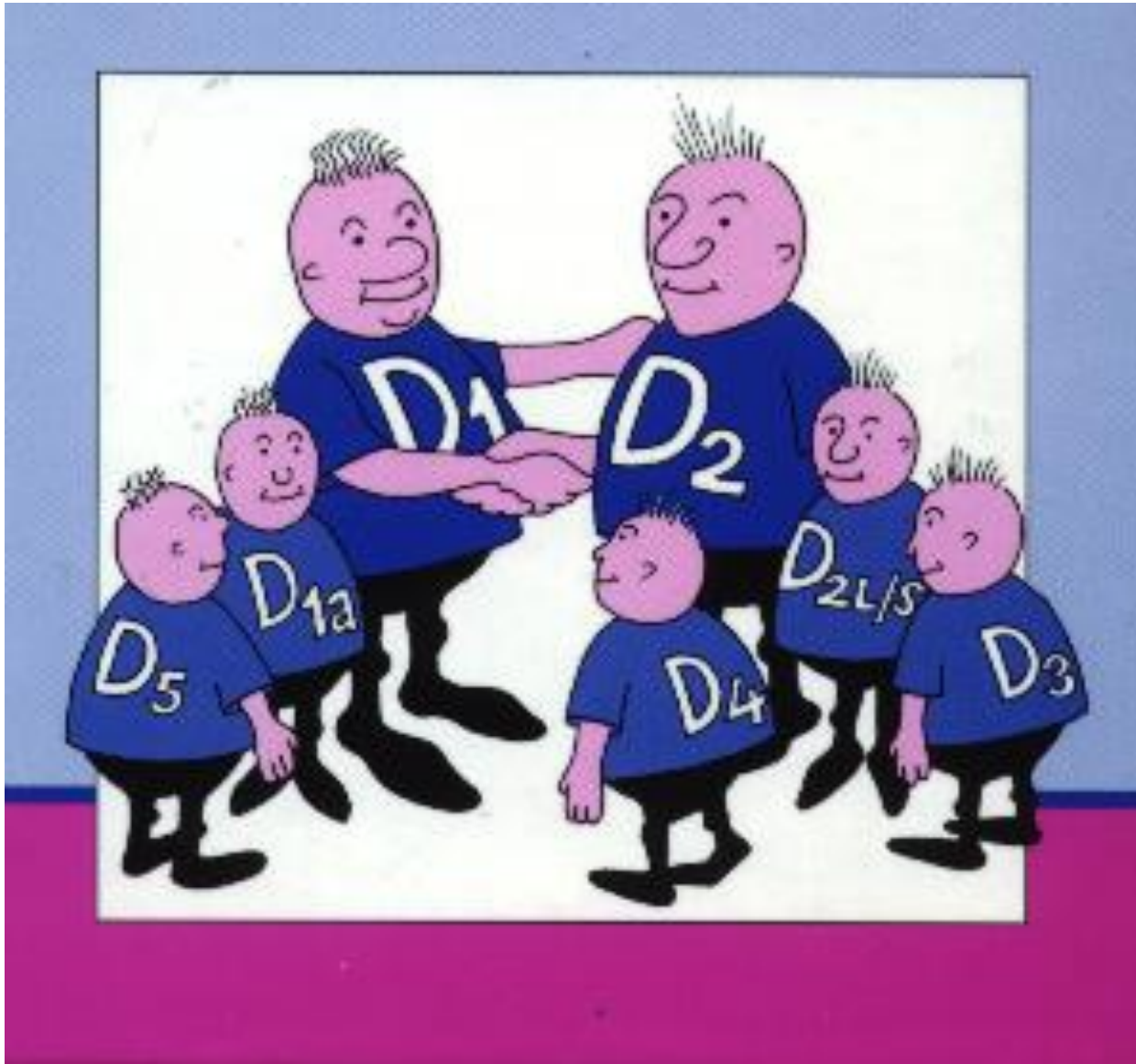
**Mesolimbic  
pathway**



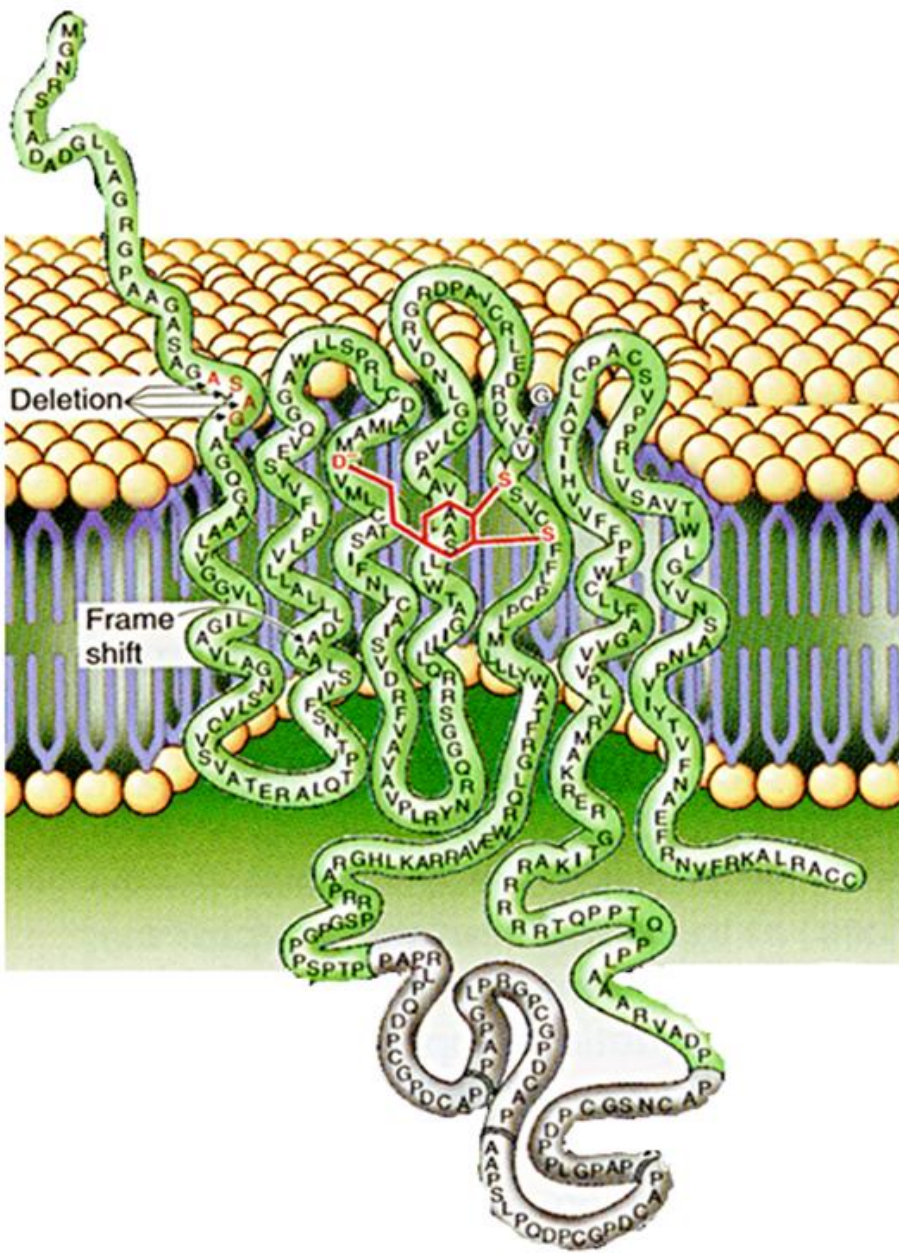


## *Organization of a Dopaminergic Synapse*

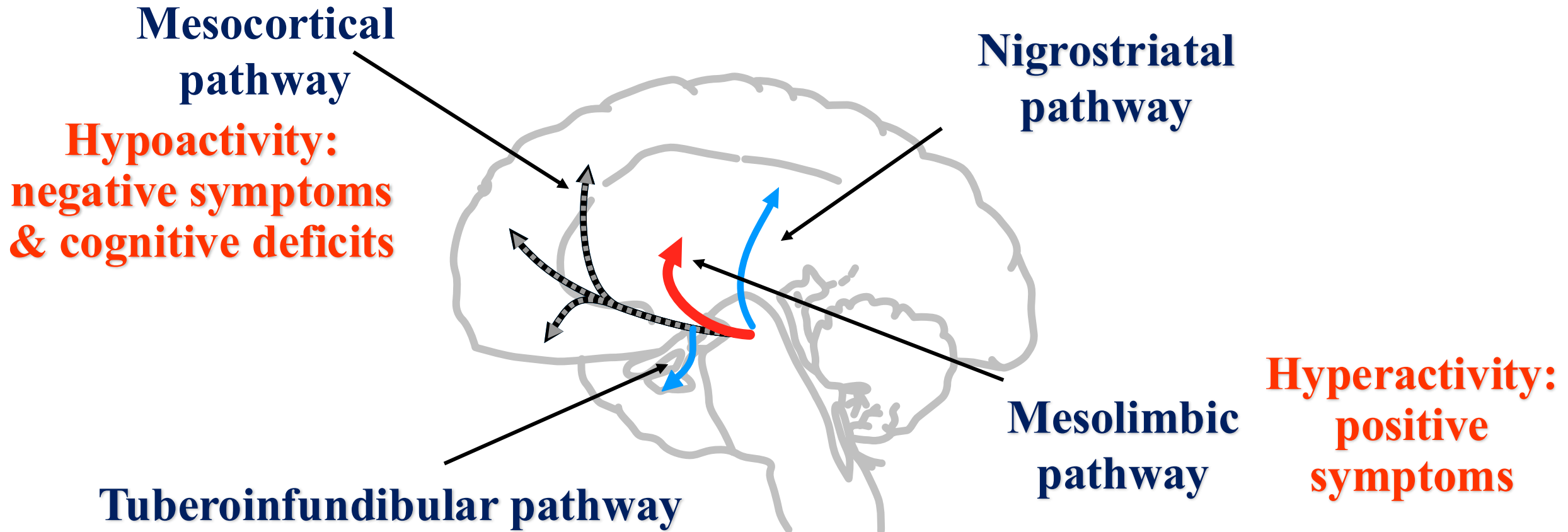
# Dopamine Receptor Superfamily



# Dopamine D<sub>2</sub> Receptors



# Dopamine Hypothesis of Schizophrenia



# *The Journey of Antipsychotic Drugs*

**50s**

**60s**



**Chlorpromazine  
(1954)**

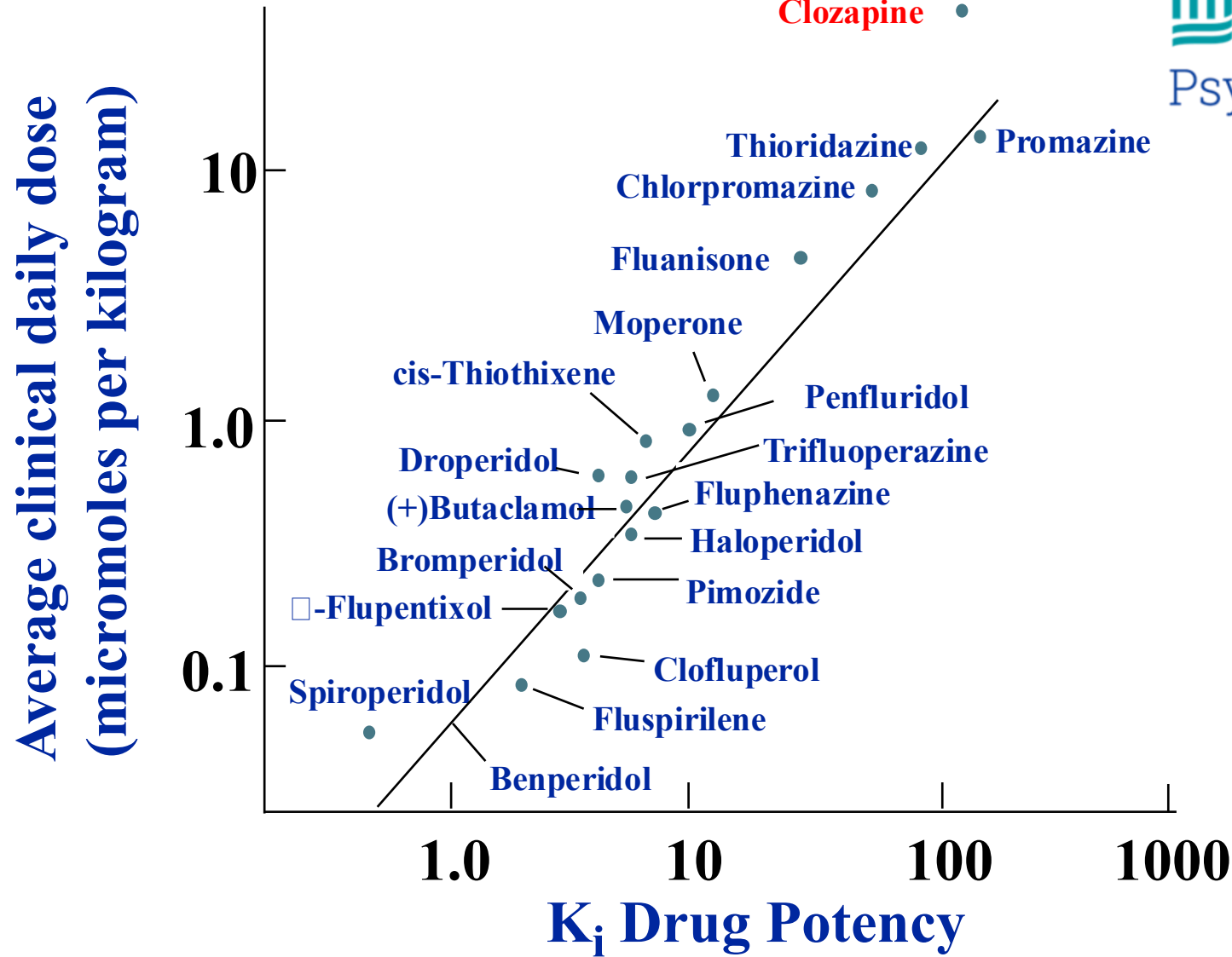
**Perphenazine (1957)**  
**Fluphenazine (1959)**  
**Thioridazine (1959)**  
**Haloperidol (1967)**

**Typical Antipsychotics**

# Pharmacology of Typical Antipsychotic Drugs

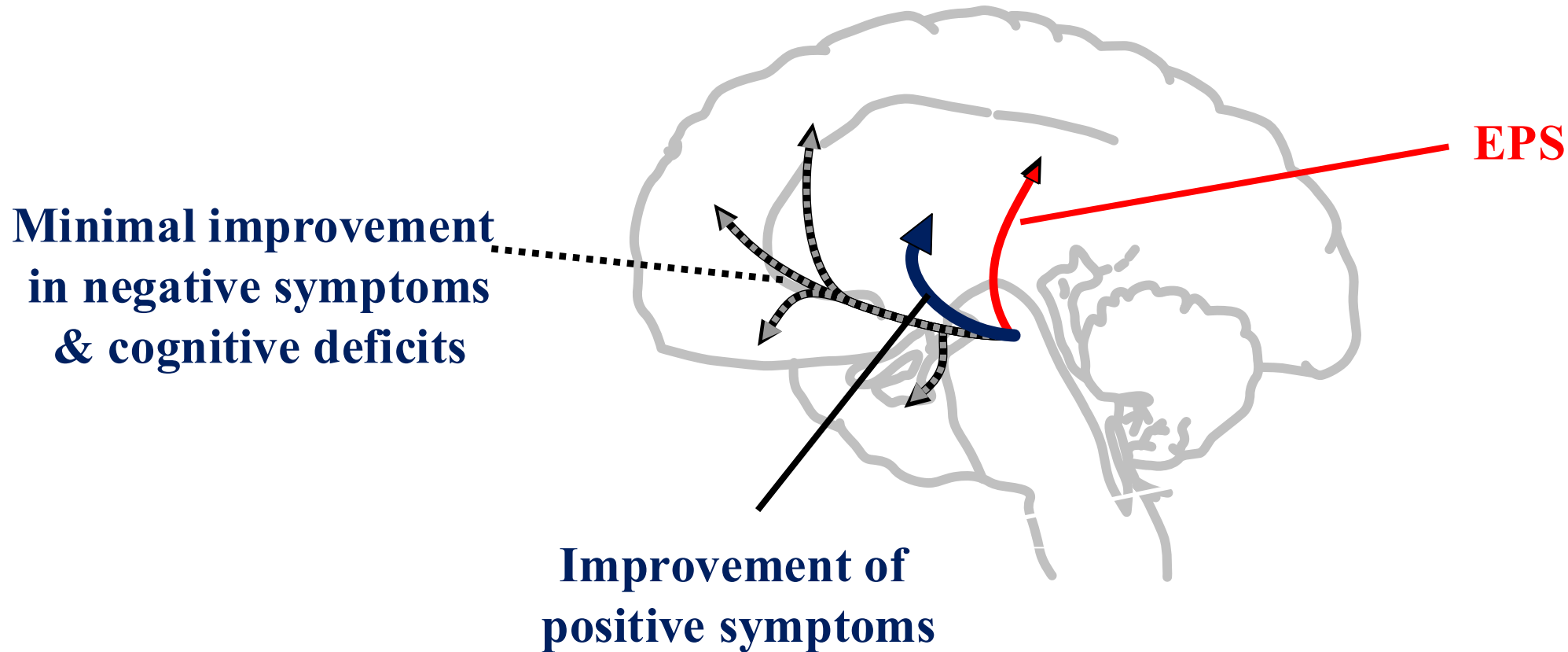
| Drugs                | D <sub>2</sub> | 5HT <sub>2A</sub> | ACh <sub>m</sub> | α <sub>1</sub> | α <sub>2</sub> | H <sub>1</sub> |
|----------------------|----------------|-------------------|------------------|----------------|----------------|----------------|
| <i>Thiothixene</i>   | <b>0.45</b>    | 130               | 2,600            | 11             | 200            | 6              |
| <i>Fluphenazine</i>  | <b>0.8</b>     | 19                | >5,000           | 9              | 1,540          | 21             |
| <i>Haloperidol</i>   | <b>4.0</b>     | 36                | >5,000           | 6.3            | 3,850          | 1,900          |
| <i>Clorpromazine</i> | <b>19</b>      | 1.4               | 25               | 2.6            | 770            | 9.1            |
| <i>Thioridazine</i>  | <b>26</b>      | 22                | 2.7              | 5              | 830            | 16             |

# Dopamine D<sub>2</sub> Receptors



*Creese et al. Science 1976; 192:481*

# Dopamine D<sub>2</sub> Antagonism: Positive Symptoms and Side Effects



# **Extrapyramidal Side Effects (EPS)**

## **Associated with Typical Antipsychotics**

### **Reaction**

### **Features**

**Acute Dystonia**

**Muscle spasms: tongue, face, neck**

**Parkinsonism**

**Rigidity, variable tremor**

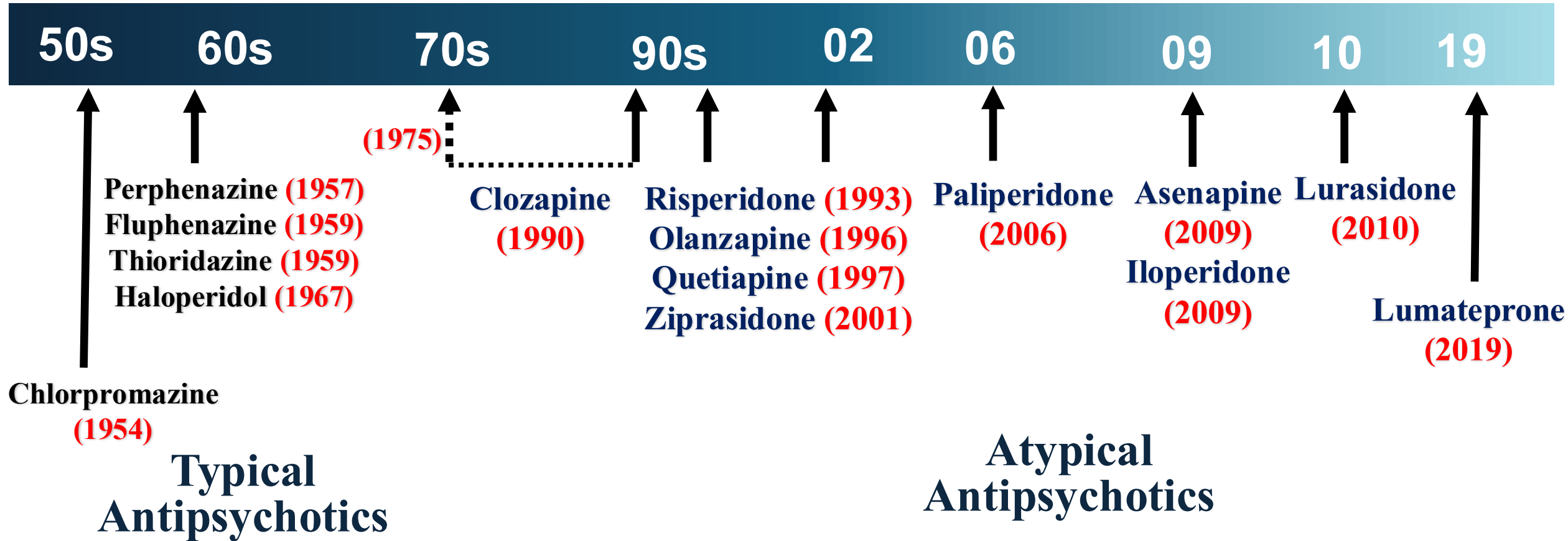
**Akathisia**

**Motor restlessness with anxiety and agitation**

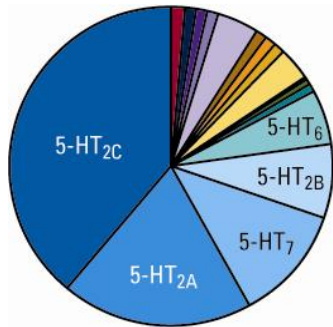
**Tardive Dyskinesia**

**Hyperkinetic movement of orofacial and limbic muscles. Often irreversible**

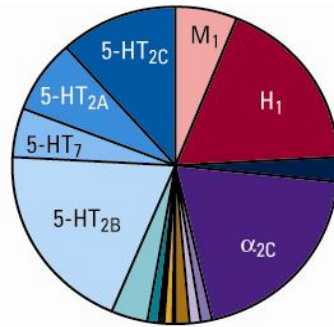
# *The Journey of Antipsychotic Drugs*



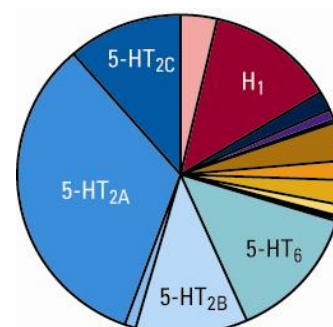
# Receptor profile of atypical antipsychotic drugs



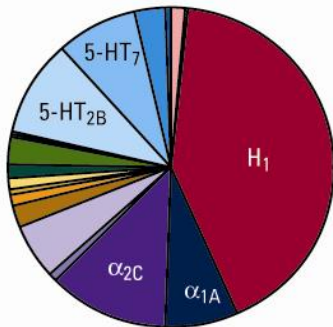
Asenapine



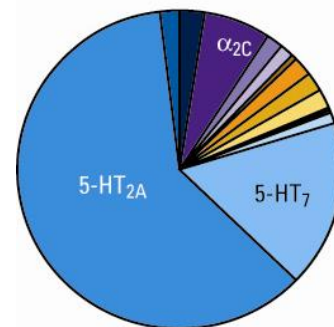
Clozapine



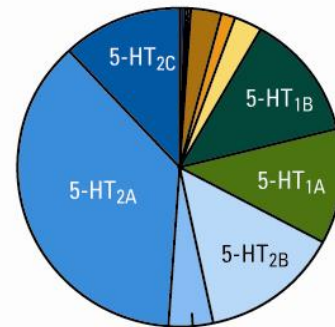
Olanzapine



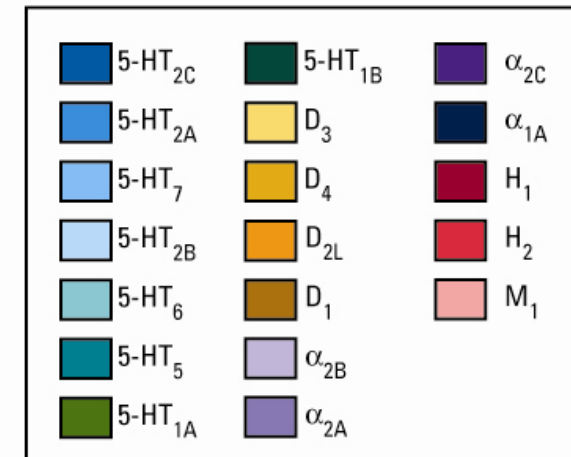
Quetiapine



Risperidone



Ziprasidone



*Bymaster et al. Neuropsychopharmacology. 1996;14(2):87*

# Receptor profile of atypical antipsychotic drugs

## *Clozapine*

$$5\text{-HT}_{2A} = 5\text{-HT}_{2C} > H_1 > M_1 > D_4 > \alpha_1 > D_2$$

## *Olanzapine*

$$5\text{-HT}_{2A} = M_{1-5} > H_1 > D_2 = D_3 = D_4 > D_1 = \alpha_1 > \alpha_2$$

## *Risperidone*

$$5\text{-HT}_{2A} > D_2 > D_3 = D_4 > \alpha_1 > \alpha_2 = H_1$$

## *Quetiapine*

$$H_1 > 5\text{-HT}_{2A} = \alpha_1 = \alpha_2 > D_2 = D_3 > D_4 > D_1 = M$$

## *Ziprasidone*

$$5\text{-HT}_{2A} > D_2 = D_3 > D_4 > \alpha_1 > \alpha_2 > H_1$$

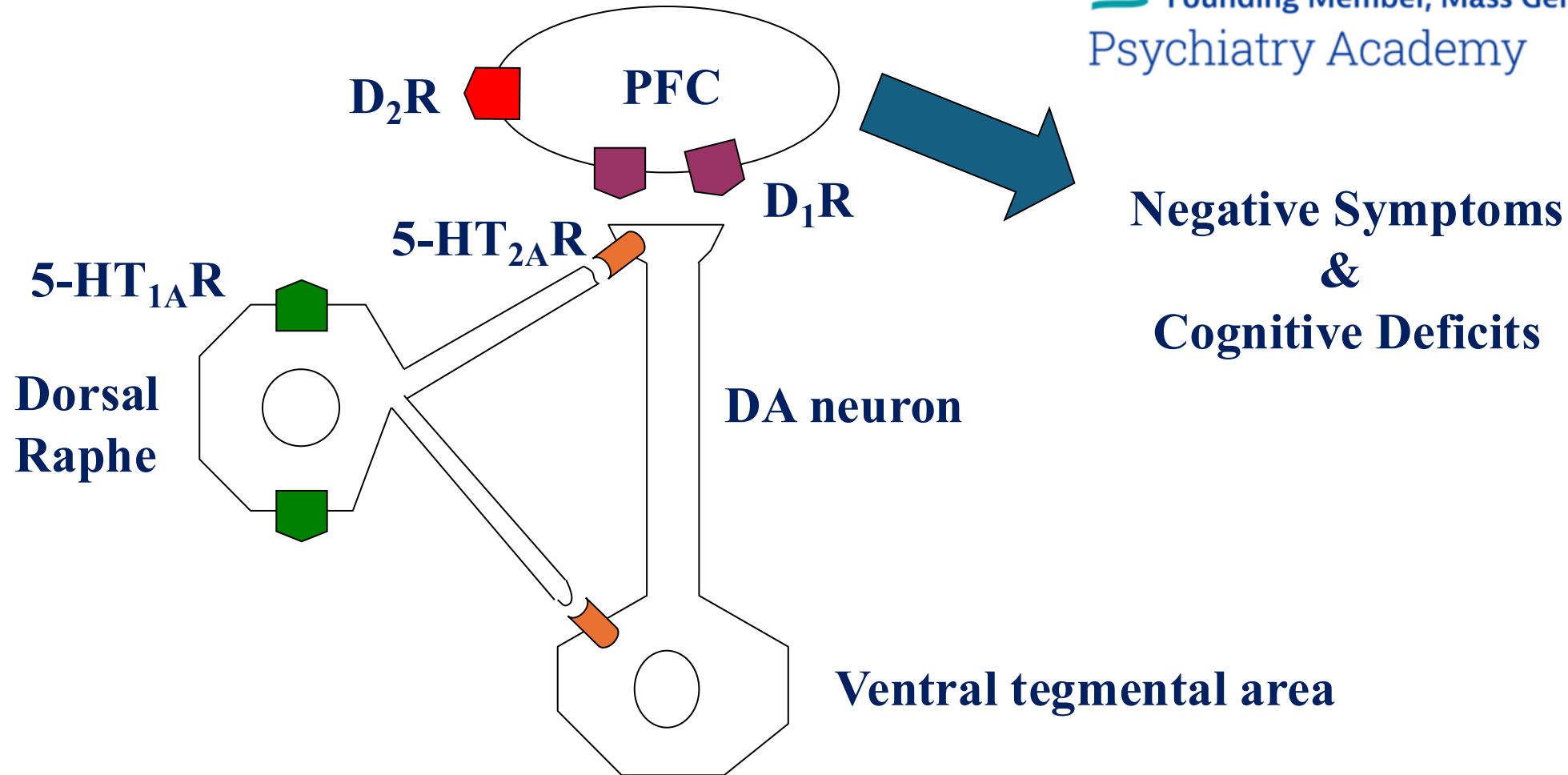
*Baldessarini & Tarazi. Goodman and Gilman's  
The Pharmacological Basis of Therapeutics, 2001*

# Emergence of 5-HT<sub>1A</sub> receptors

**Antipsychotics with mixed  
5HT<sub>1A</sub> agonist/5HT<sub>2A</sub> antagonist activity**

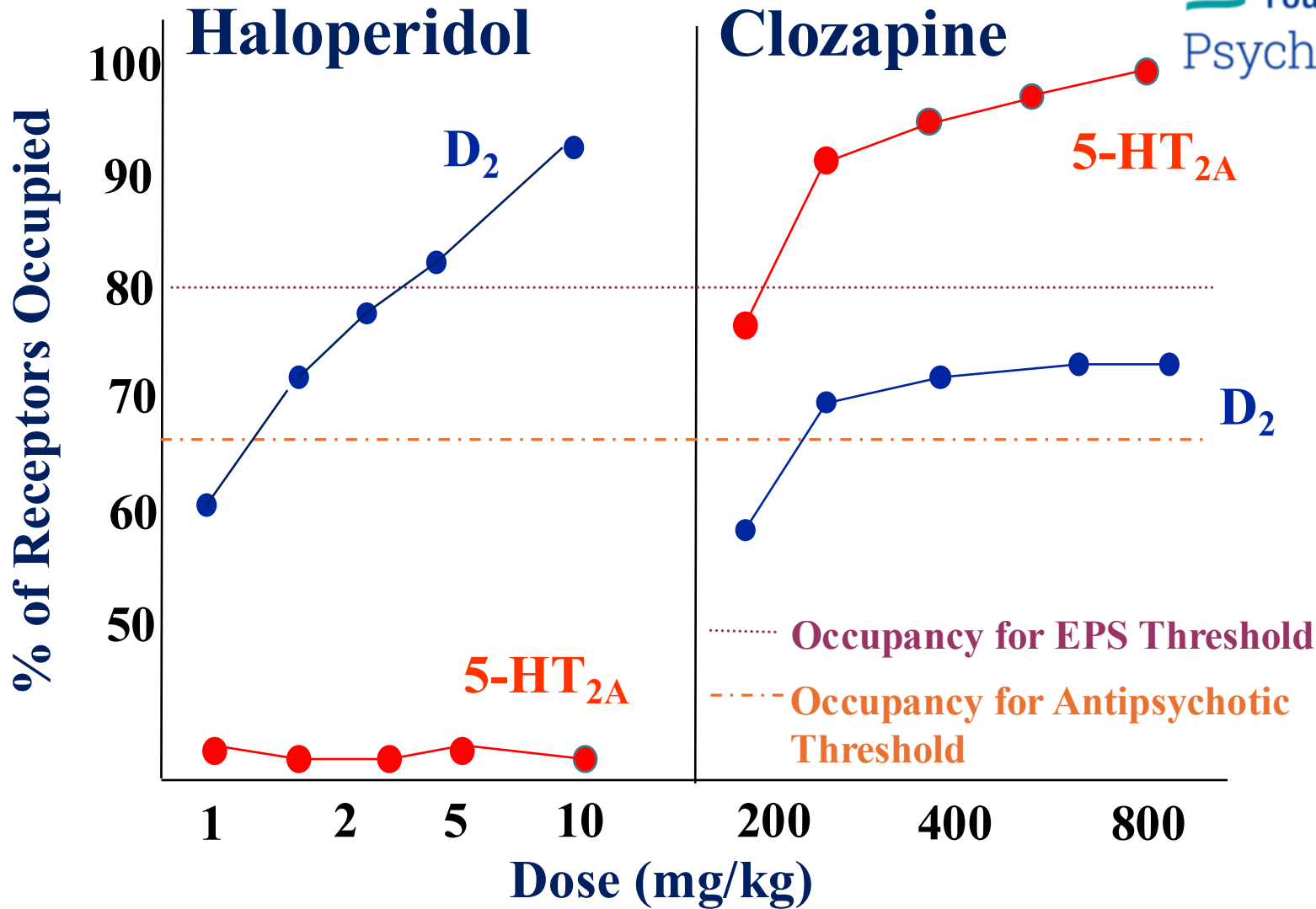
**Clozapine  
Quetiapine  
Ziprasidone  
Lurasidone**

# Interactions between DA and 5-HT systems in prefrontal cortex

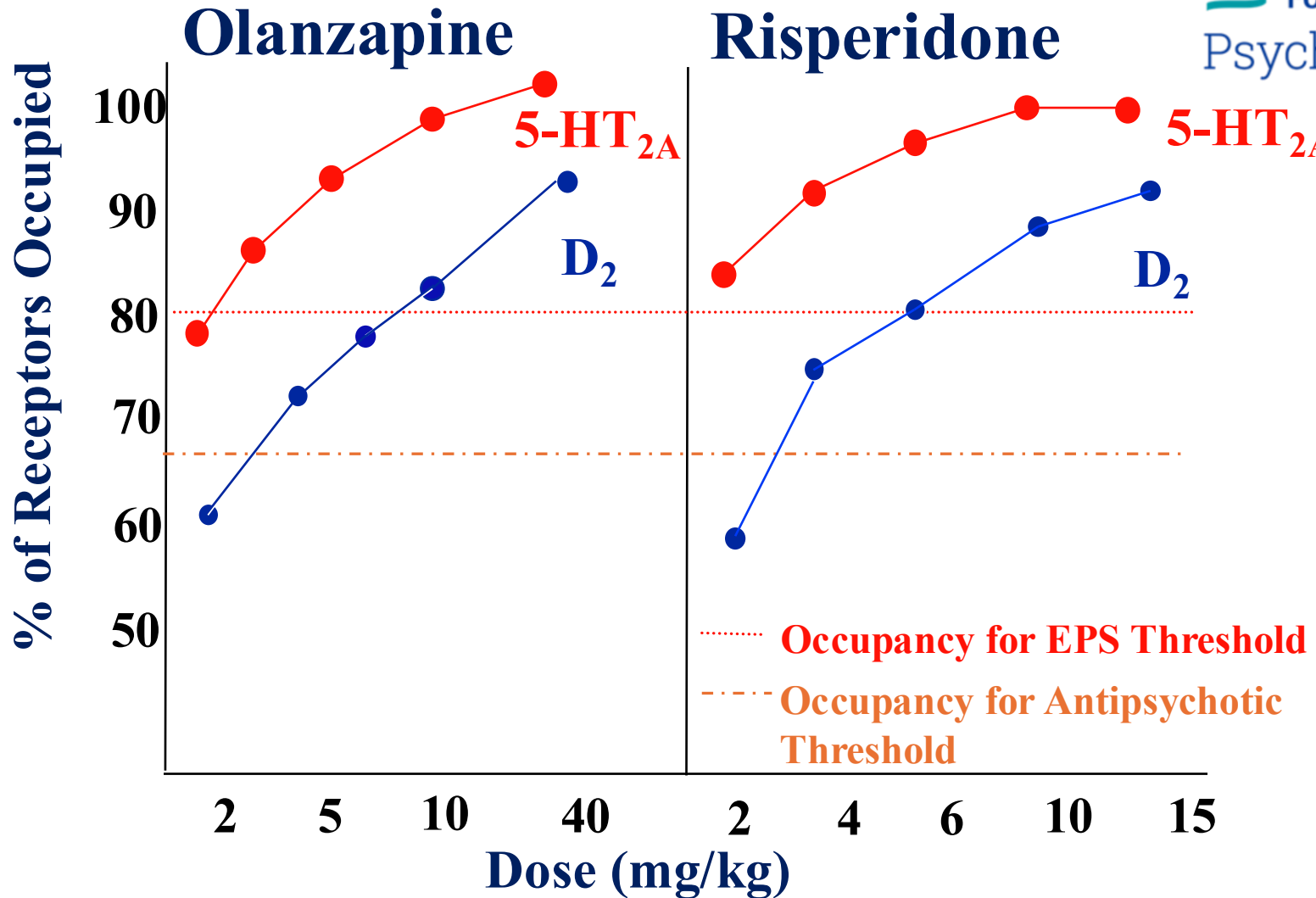


**5HT<sub>1A</sub> Agonists and 5HT<sub>2A</sub> Antagonists increase DA levels in prefrontal cortex**

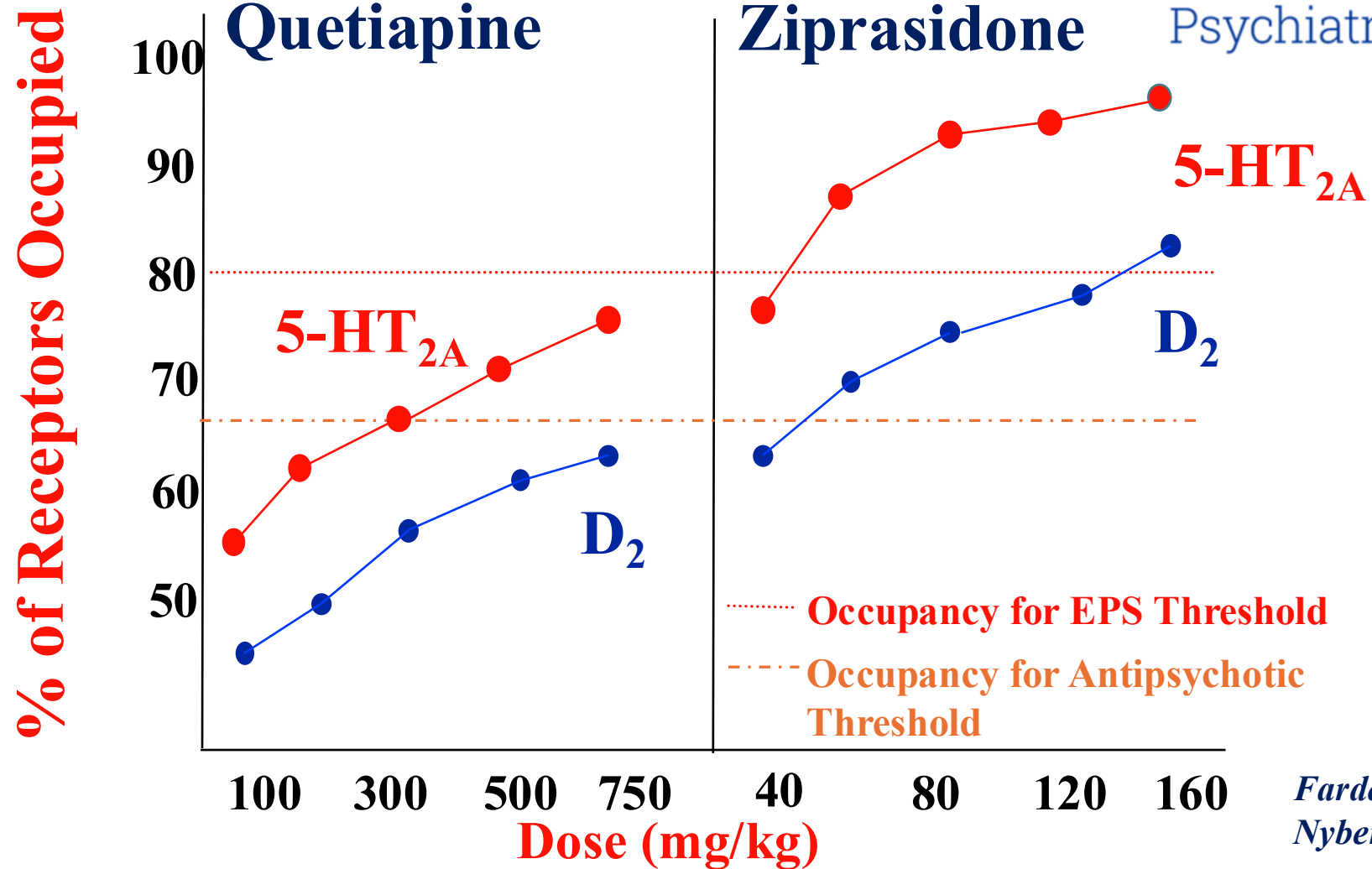
# **Relation of Threshold for Clinical Response to Receptor Occupancy as determined by PET studies**



*Farde et al. Arch Gen Psychiatry. 1992;49:538*  
*Nyberg et al. Psychopharmacology. 1993;110:265*



*Farde et al. Arch Gen Psychiatry. 1992;49:538*  
*Nyberg et al. Psychopharmacology. 1993;110:265*



*Farde et al. Arch Gen Psychiatry. 1992;49:538*  
*Nyberg et al. Psychopharmacology. 1993;110:265*

# Clozapine & Quetiapine: “Fast-Off Kinetics”

| Drug                   | D <sub>2</sub> binding characteristic        | Clinical implication                                                        |
|------------------------|----------------------------------------------|-----------------------------------------------------------------------------|
| Clozapine              | Very fast D <sub>2</sub> dissociation        | Transient D <sub>2</sub> occupancy → very low EPS and prolactin elevation   |
| Quetiapine             | Fast D <sub>2</sub> dissociation             | Transient D <sub>2</sub> occupancy → relatively low EPS/prolactin liability |
| Typical antipsychotics | Generally slower D <sub>2</sub> dissociation | More sustained D <sub>2</sub> blockade → greater EPS/prolactin risk         |

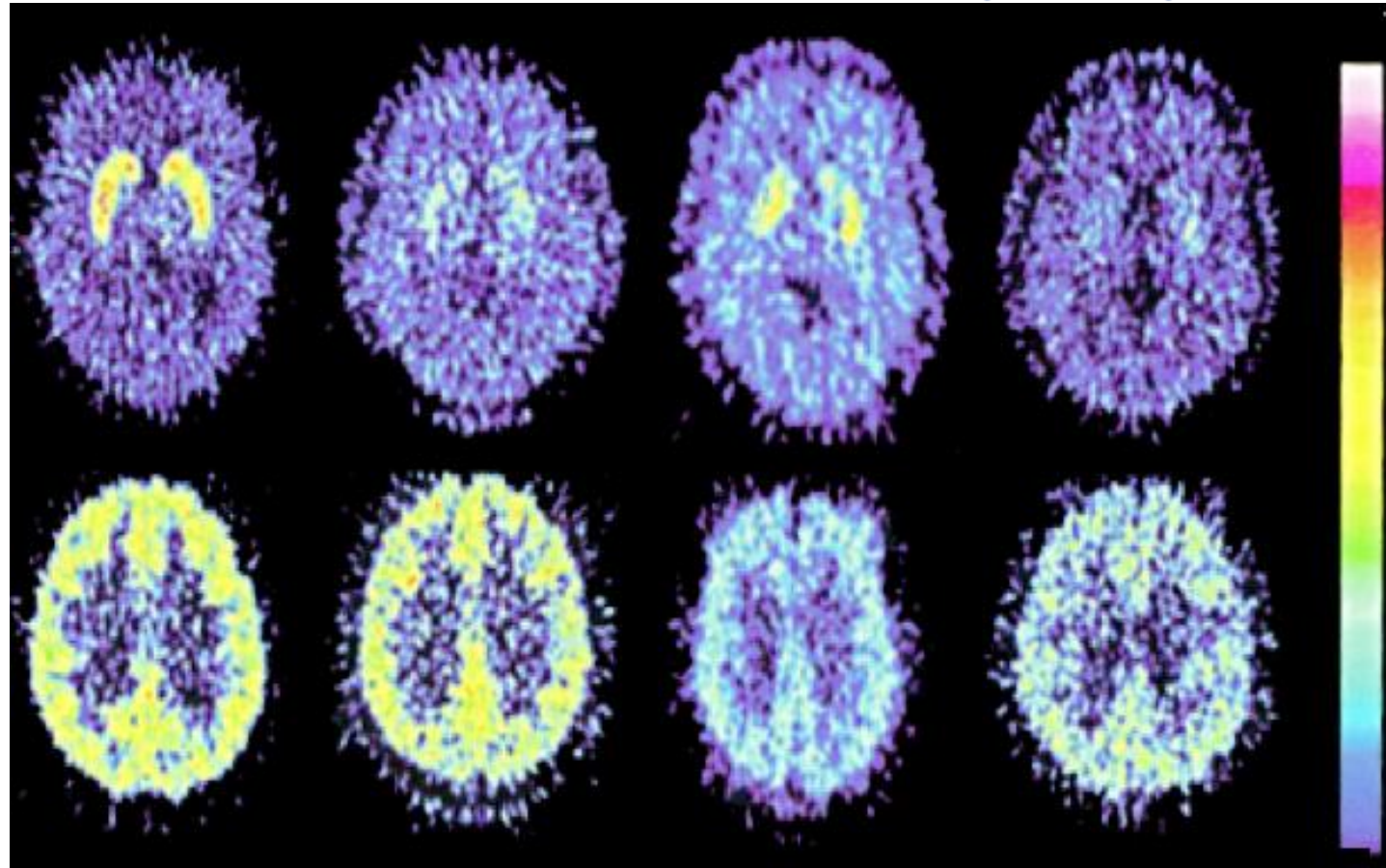
**Clozapine and quetiapine exhibit rapid D<sub>2</sub>-receptor dissociation (“Fast-Off” kinetics), producing transient D<sub>2</sub> occupancy and contributing to their low risk for EPS and hyperprolactinemia.**

*Kapur & Seeman. Am J Psychiatry 2001;158:360*

# Occupancy of Human D<sub>2</sub> and 5-HT<sub>2A</sub> Receptors by Antipsychotic Drugs

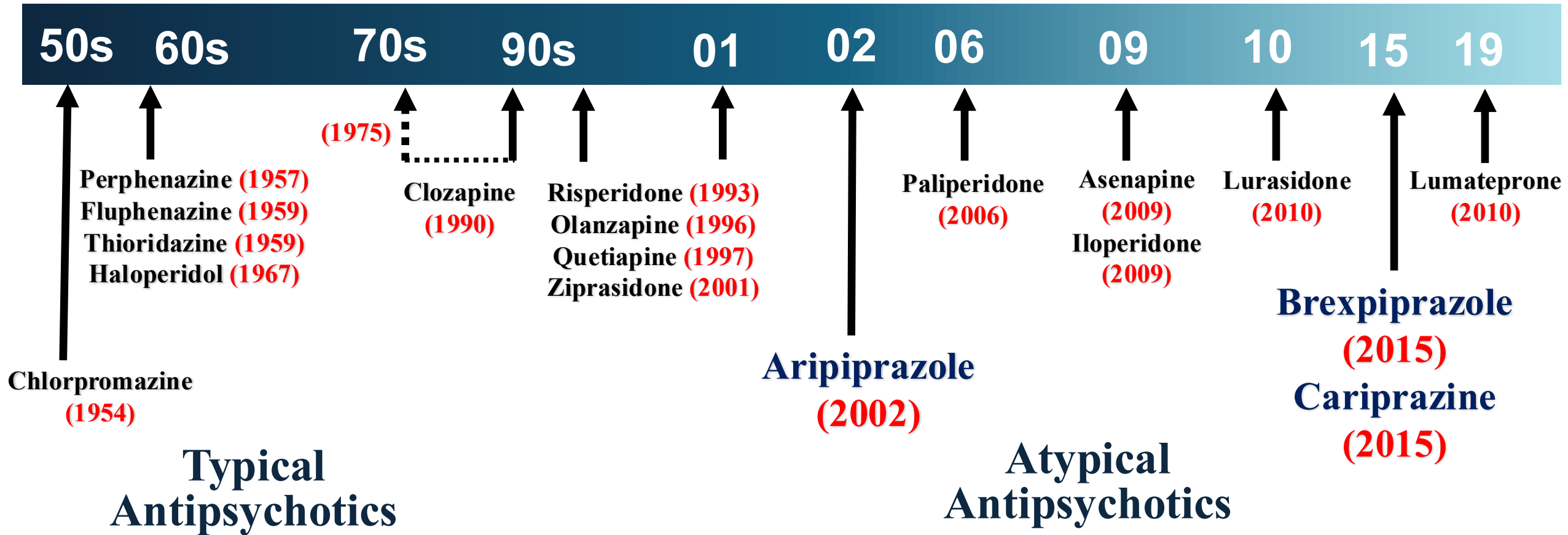
**[<sup>11</sup>C]Raclopride**  
**D<sub>2</sub> receptor**

**[<sup>11</sup>C]NMSP**  
**5-HT<sub>2A</sub> receptor**



**Control   Haloperidol   Clozapine   Risperidone**

# *The Journey of Antipsychotic Drugs*



## Aripiprazole, Brexpiprazole, Cariprazine: Dopamine-Serotonin System Stabilizers

- **Partial agonist** at D<sub>2</sub> receptors
- **Agonist** at 5-HT<sub>1A</sub> receptors
- **Antagonist** at 5-HT<sub>2A</sub> receptors

*Burris et al. J Pharmacol Exp Ther. 2002;302:381*

# Defining Pharmacology Terms

## Affinity vs Intrinsic Activity

### Affinity

How well does a drug bind to the receptor? (*in vitro* binding studies)

low affinity  $< 10$  nM

Medium affinity (10 nM- 1 mM)

High affinity  $> 1$  mM

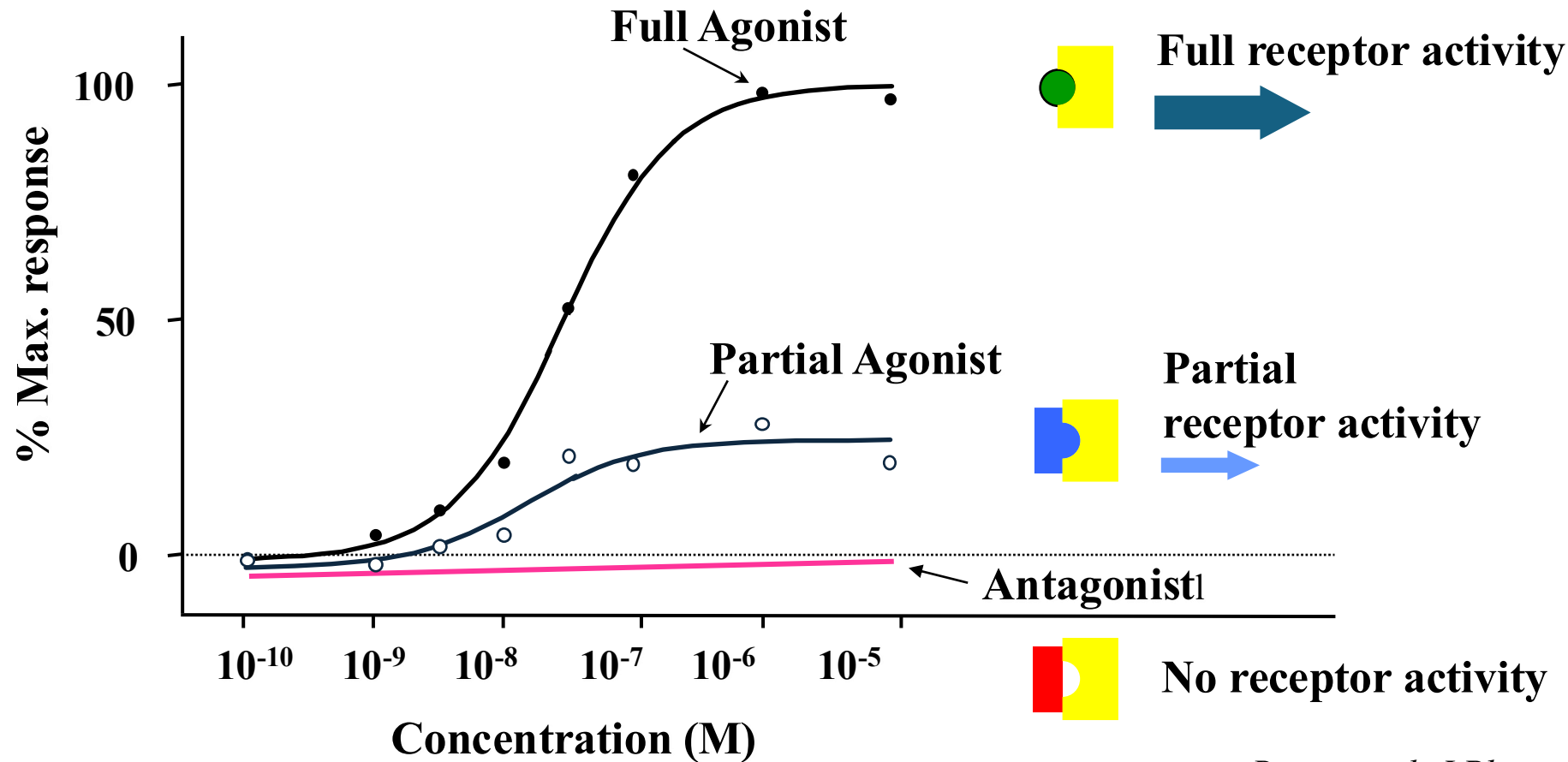
### Intrinsic activity

**Agonist** interacts with the receptor and initiates maximal cellular response.

**Antagonist** blocks the receptor and inhibits receptor stimulation by endogenous ligand or by selective agonists.

**Partial agonist** binds to and activates a receptor but produces less than the maximal response, even when it occupies all available receptors.

# Activity of Agonists, Antagonists and Partial Agonists at D<sub>2</sub>Rs

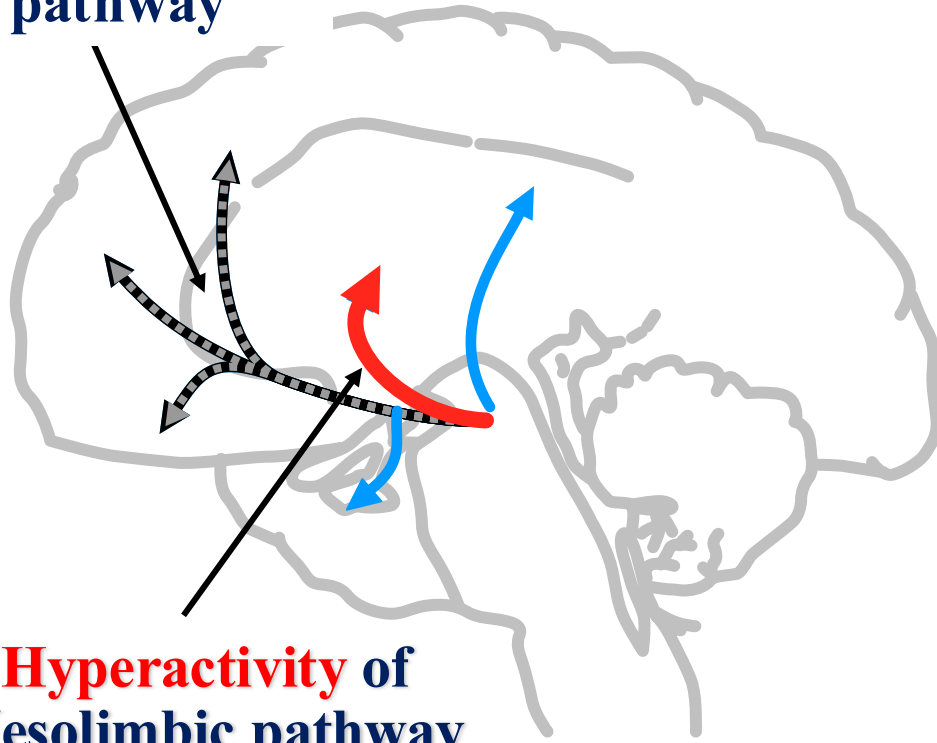


*Burris et al. J Pharmacol Exp Ther. 2002;302:381*

# Dopamine Neurotransmission Before and After treatment with a DA/5HT Stabilizer

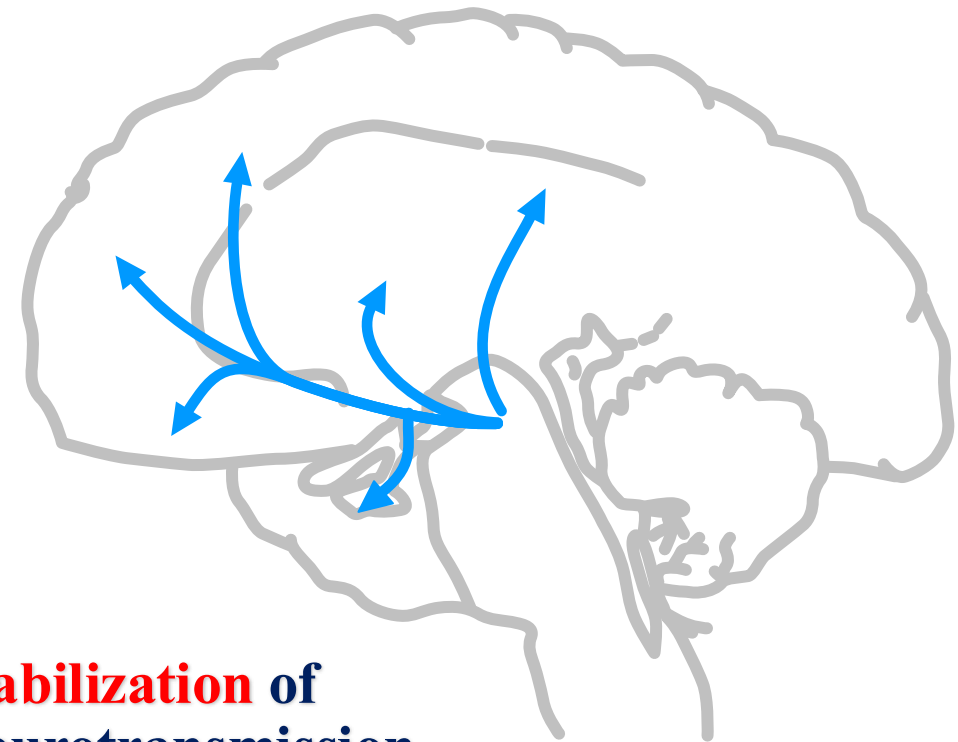
**Hypoactivity of  
Mesocortical  
pathway**

**Before**

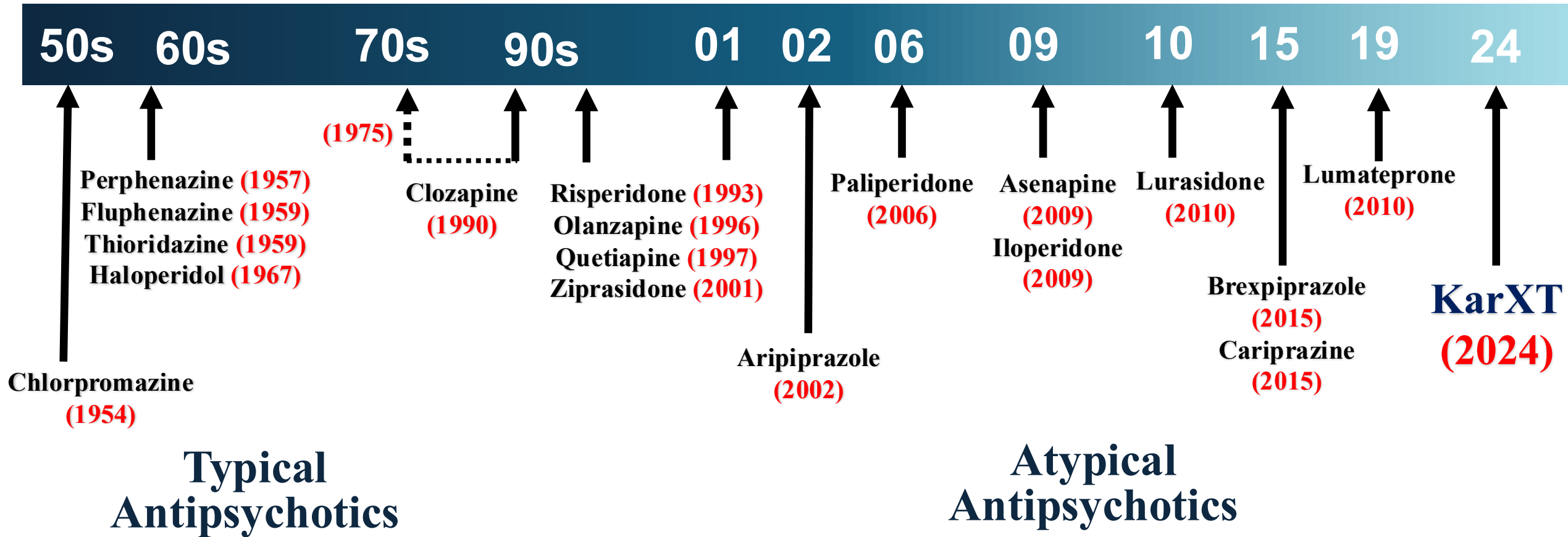


**After**

**Stabilization of  
DA neurotransmission**

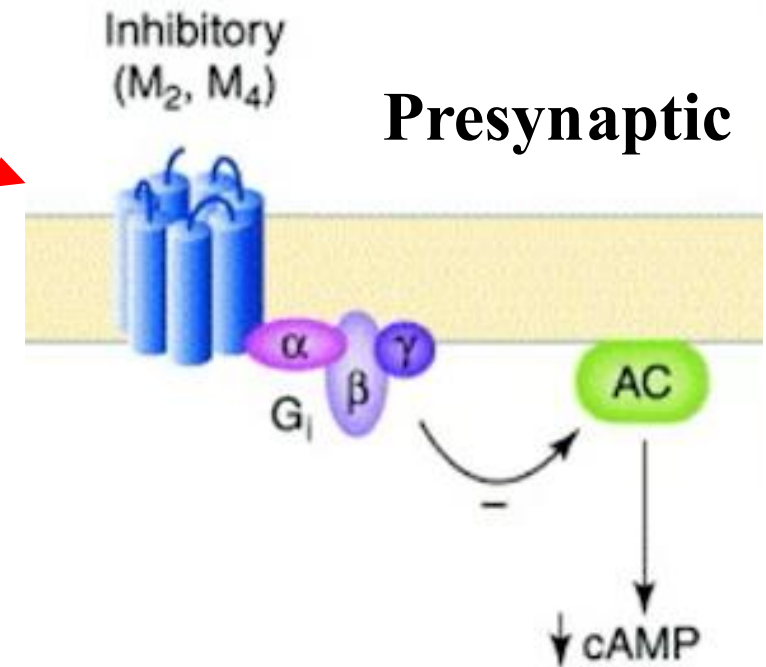
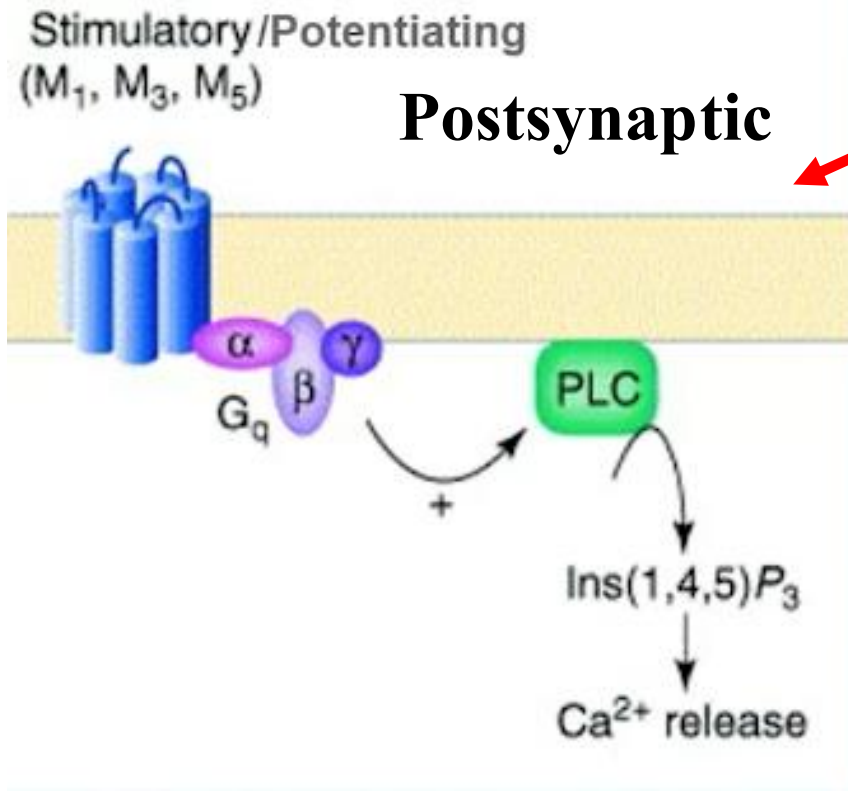


# *The Journey of Antipsychotic Drugs (70 Years in the Making)*



# Muscarinic Receptors: Novel Targets for Antipsychotics Beyond DA-Rs

## Five Different Receptor Subtypes

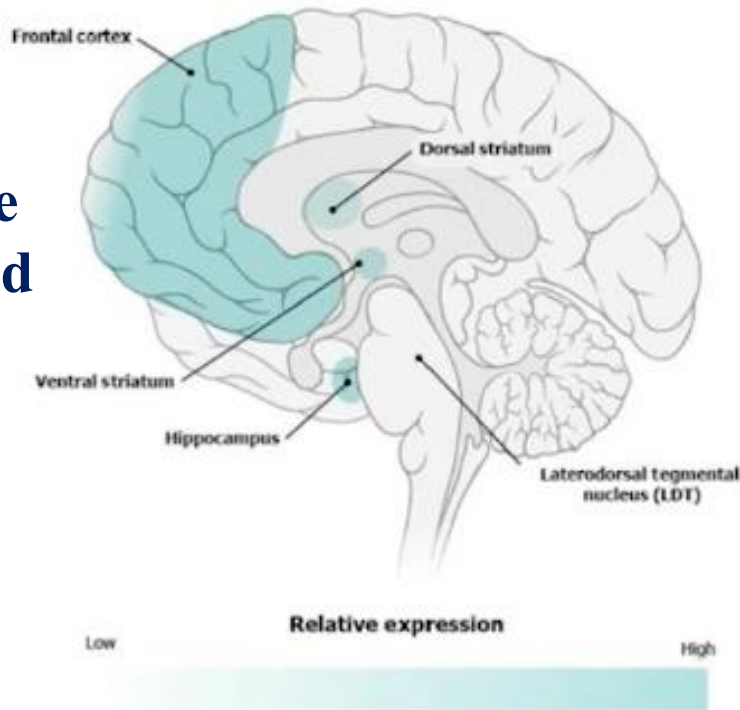


*Yohn et al. Trends Pharmacol Sci 2022; 43:1098*

# Anatomical Distribution of $M_1/M_4$ Receptors

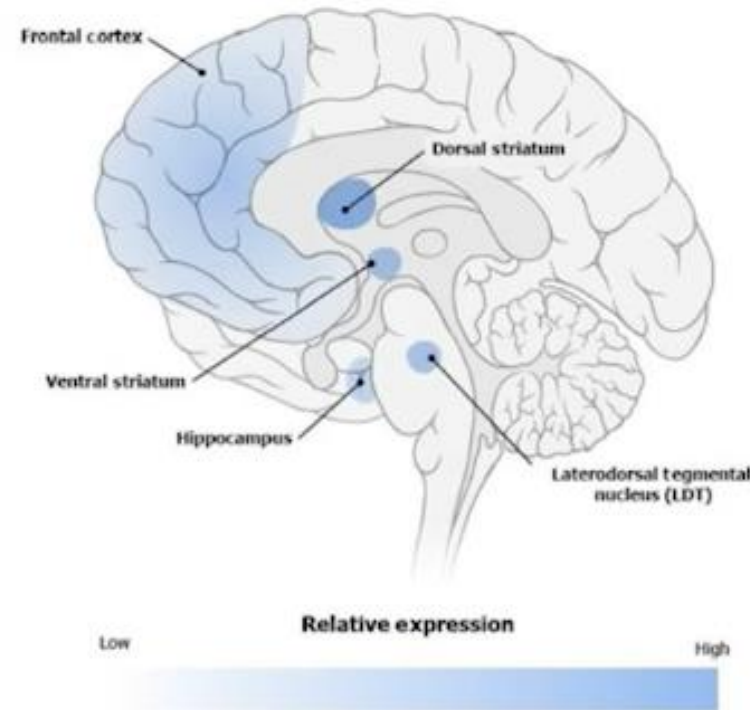
## $M_1$ Receptor Expression

**$M_1$  is more prominent in the frontal cortex and Hippocampus**



## $M_4$ Receptor Expression

**$M_4$  is more prominent in the striatum and LDT**



*Yohn et al. Trends Pharmacol Sci 2022; 43:1098*

# Functions of M<sub>1</sub>/M<sub>4</sub> Receptors

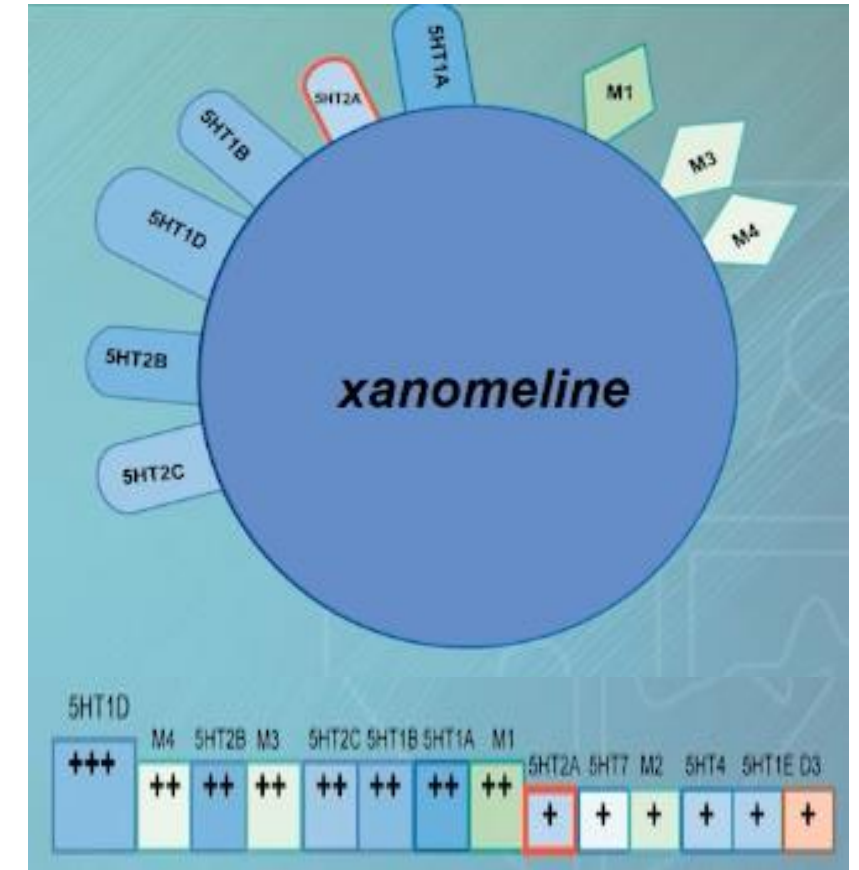
- **M<sub>1</sub> receptor activation** can improve cognitive functions and may also contribute to reducing psychotic symptoms.
- Preclinical studies suggest that M1 activation modulates glutamate and dopamine neurotransmission, which contribute to the pathophysiology of schizophrenia
- **M<sub>4</sub> receptor activation** modulates dopamine neurotransmission
- Preclinical studies show that M4 activation decreases psychosis in animal models

*Langmead et al. Pharmacol Ther 2008; 117:232*

*Dean et al. Curr Mol Med 2015; 15:221*

# KarXT (Xanomeline/Trospium)

- $M_1/M_4$  Agonist
- Decreases DA release in the associative striatum, resulting in reduced positive symptoms
- Increases extracellular DA levels in the prefrontal cortex, potentially improving negative symptoms and cognitive deficits
- Trospium blocks peripheral muscarinic receptors and does not cross the BBB to minimize peripheral cholinergic side effects

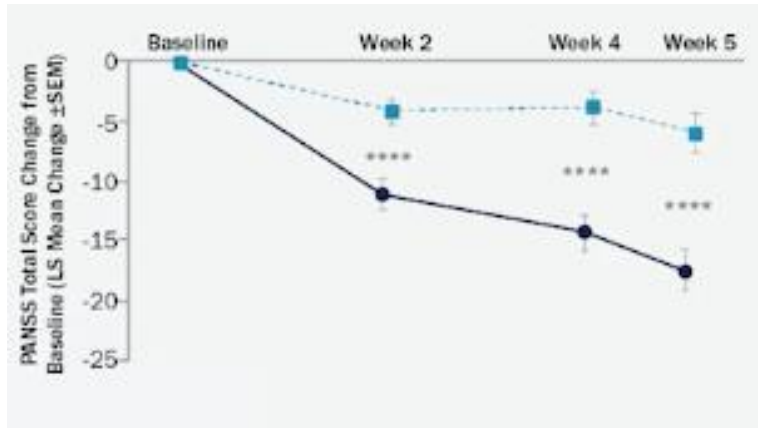


*Stahl's Essential Psychopharmacology; 5<sup>th</sup> Ed, 2021*

# KarXT (Xanomeline/Trospium)

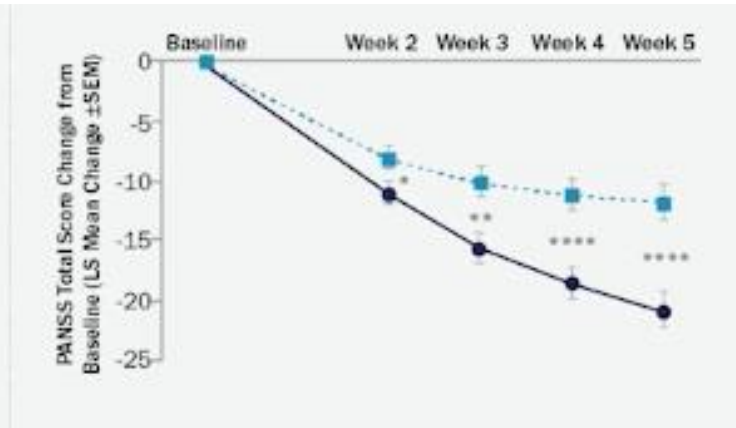
## *Efficacy Data*

**EMERGENT I (Phase 2)**



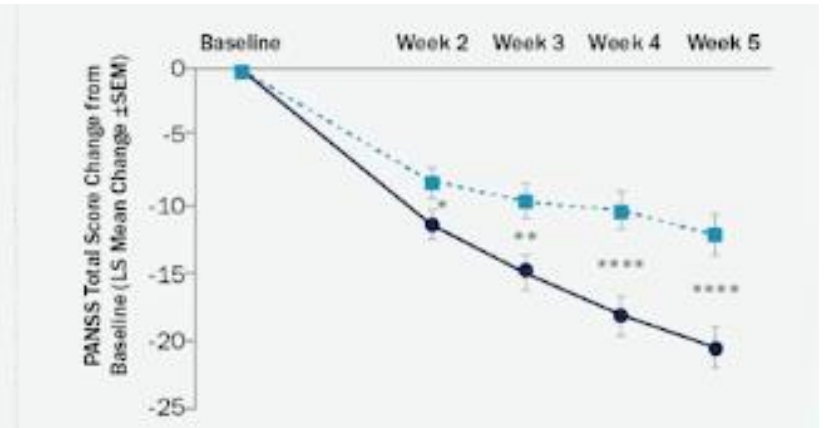
**11.6-point reduction at week 5**

**EMERGENT II (Phase 3)**



**9.6-point reduction at week 5**

**EMERGENT III (Phase 3)**



**8.4-point reduction at week 5**

\* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\*\* $p < 0.0001$

*Brannan et al. N Engl J Med 2012; 384:717*  
*Kaul et al. Lancet 2024; 403:160*

# KarXT (Xanomeline/Trospium)

## Safety Data

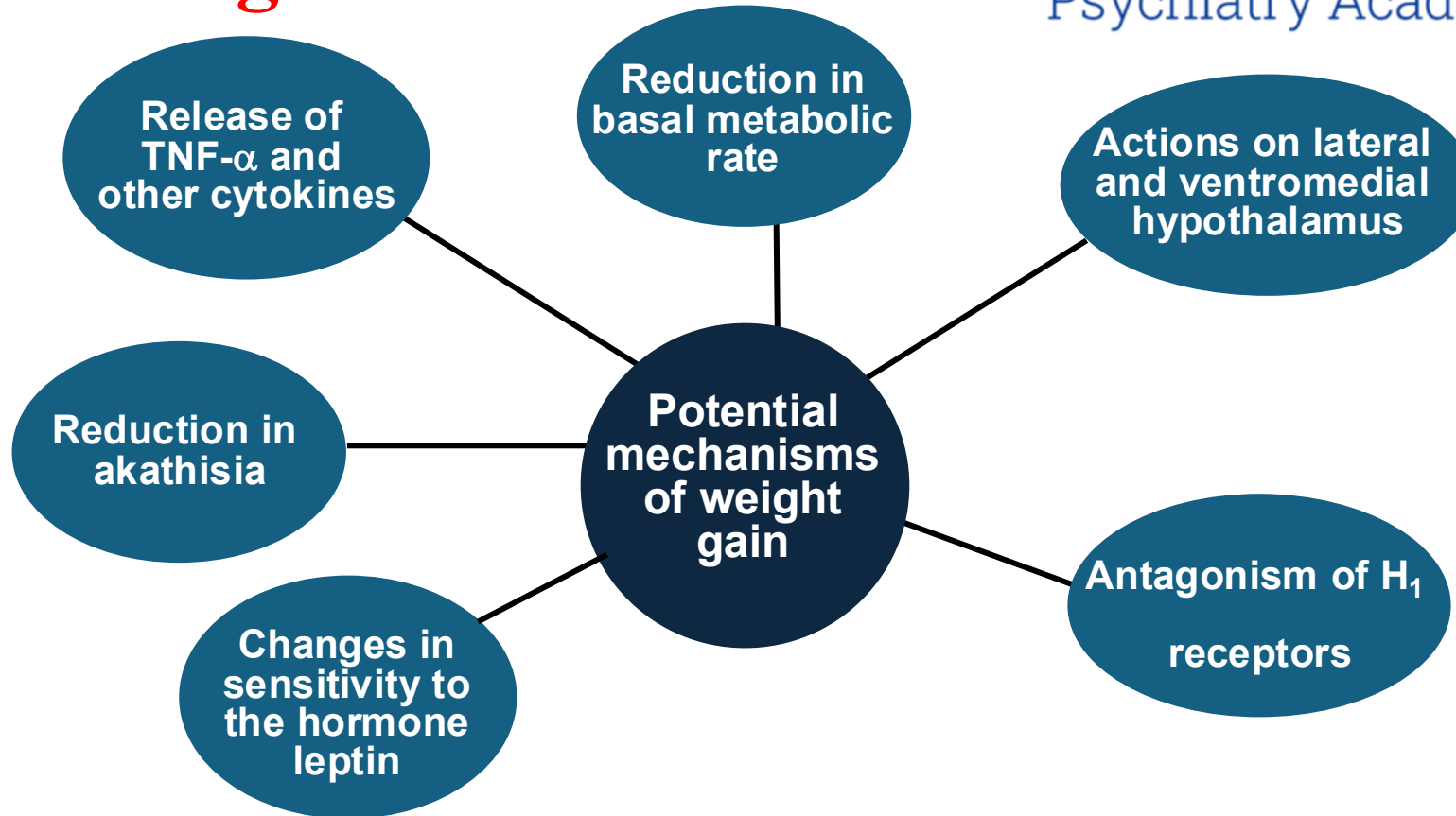
| Variable                                                                           | KarXT (n=340)        | Placebo (n=343)      |
|------------------------------------------------------------------------------------|----------------------|----------------------|
| Any TEAE, n (%)                                                                    | 231 (67.9)           | 176 (51.3)           |
| Serious TEAE, n (%)                                                                | 4 (1.2) <sup>a</sup> | 2 (0.6) <sup>b</sup> |
| TEAE leading to discontinuation, n (%)                                             | 19 (5.6)             | 16 (4.7)             |
| TEAE occurring in ≥5% of people in the KarXT group, n (%)                          |                      |                      |
| → Nausea                                                                           | 63 (18.5)            | 13 (3.8)             |
| → Constipation                                                                     | 58 (17.1)            | 21 (6.1)             |
| → Dyspepsia                                                                        | 54 (15.9)            | 16 (4.7)             |
| → Vomiting                                                                         | 46 (13.5)            | 6 (1.7)              |
| Headache                                                                           | 37 (10.9)            | 35 (10.2)            |
| Hypertension <sup>c</sup>                                                          | 29 (8.5)             | 6 (1.7)              |
| Abdominal pain                                                                     | 20 (5.9)             | 10 (2.9)             |
| Dry mouth                                                                          | 17 (5.0)             | 5 (1.5)              |
| Tachycardia                                                                        | 17 (5.0)             | 8 (2.3)              |
| Body weight (kg), mean change from baseline to week 5 ±SD                          | 1.41±3.18            | 1.94±5.00            |
| Body weight: ≥7% increase from baseline to week 5, n/N (%)                         | 13/245 (5.3)         | 30/264 (11.4)        |
| Simpson-Angus Scale score: mean change from baseline to week 5, ±SD                | -0.1±0.62            | -0.1±0.63            |
| Barnes Akathisia Rating Scale score: mean change from baseline to week 5, ±SD      | -0.1±0.90            | -0.1±0.84            |
| Abnormal Involuntary Movement Scale score, mean change from baseline to week 5 ±SD | 0.0±0.66             | 0.0±0.15             |

*Brannan et al. N Engl J Med 2012; 384:717*  
*Kaul et al. Lancet 2024; 403:160*

## Scorecard of Atypical Antipsychotics

- Cognitive deficits: *much room to improve*
- Persistent negative symptoms: *marginal efficacy*
- GI side effects: *selective agents*
- Akathisia: *it still occurs*
- Dystonias, parkinsonism and TD: *much improved*
- Neuroleptic Malignant syndrome: *rarer, harder to recognise*
- Weight-gain & metabolic deficits: *major public health problem*
- Hyperprolactinemia: *selective agents*
- Cardiovascular issues: *some QT prolongation*

# Potential Mechanisms of Weight Gain



*Baptista. Acta Psychiatr Scand 1999; Mercer et al. J Nutr 1994; Stanton. Schizophr Bull 1995; Tecott et al. Nature 1995; Reynolds et al. Lancet 2002;*

# Weight Gain: Focus on 5-HT<sub>2C</sub> receptors

**Clozapine  
Olanzapine**



**Inverse Agonist**



**Asenapine  
Ziprasidone**



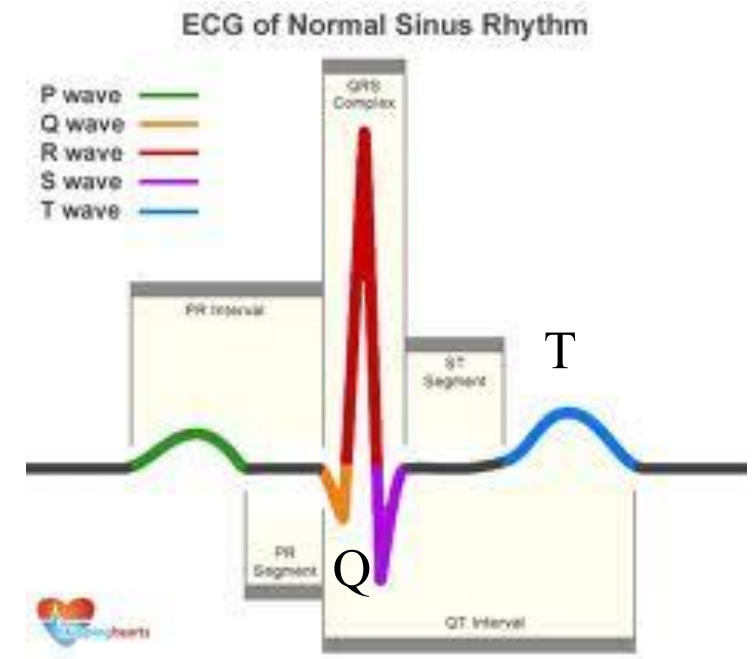
**Antagonist**

*Tecott et al. Nature 1995*

# Cardiovascular QT Elongation

- QT interval is a measure of the time b/w start of Q wave and end of T wave
- Should not exceed 500ms
- Prolonged QT is a risk factor for ventricular arrhythmias and sudden death
- **hERG (the human Ether-à-go-go Related Gene) is most common target for QT elongation**
- **hERG codes for a Kv11.1 potassium ion channel that coordinates the heart's beating**

*Thioridazine, Chlorpromazine, Iloperidone and Ziprasidone are potent blockers of hERG*



# Hyperprolactinemia

## Atypical Antipsychotics



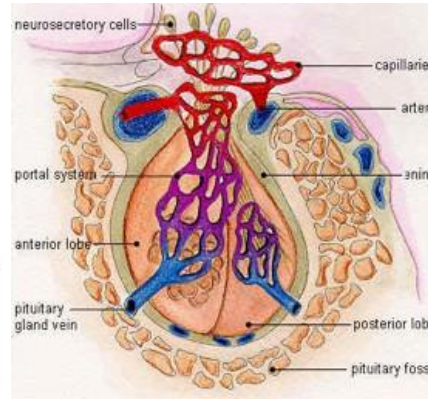
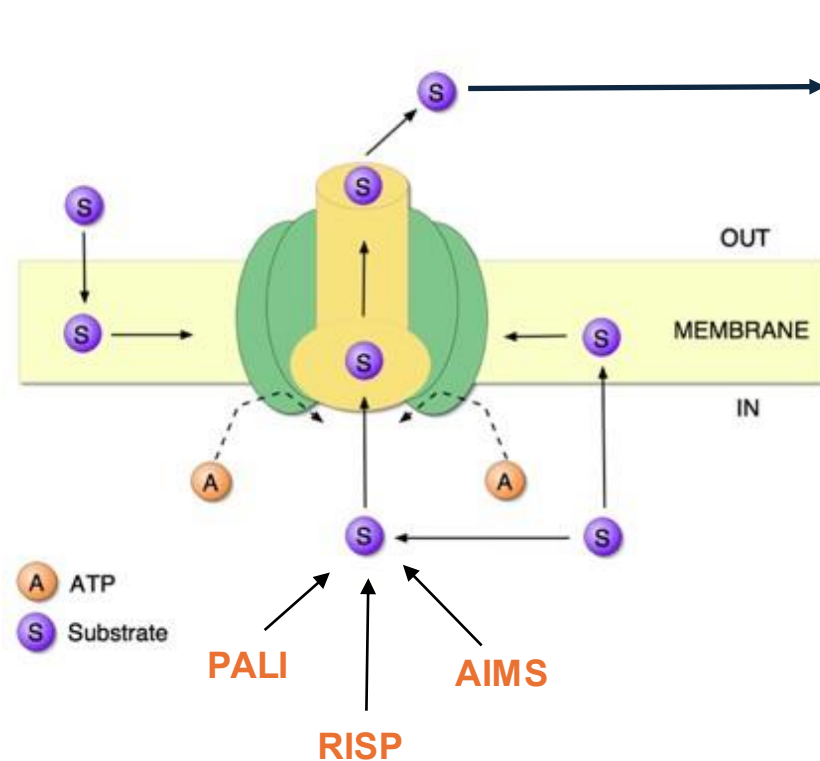
## Hyperprolactinemia

|                |              |
|----------------|--------------|
| Amisulpiride   | Lumateprone  |
| Aripiprazole   | Lurasidone   |
| Asenapine      | Olanzapine   |
| Brexipiprazole | Paliperidone |
| Cariprazine    | Quetiapine   |
| Clozapine      | Risperidone  |
| Iloperidone    | Ziprasidone  |
| KarXT          |              |

**Amisulpiride**  
**Paliperidone**  
**Risperidone**

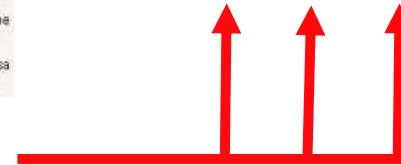
# *P-Glycoprotein Transporter*

- Found in endothelial cells in blood brain barrier
- Facilitates efflux of drugs from CNS to Periphery



**Block D<sub>2</sub>Rs  
In Pituitary Gland**

**Prolactin**



***RISP, PALI and AIMS have high affinity for  
P-Glycoprotein Efflux Transporter***

# *Glimpse into the Future*

## **Muscarinic Drugs**

### **M1/M4 Receptors**

**ML-007C-MA**

### **M4 Receptors**

**Emraclidine**

**NBI1117568**

**NTX-253**

## **DA/5-HT Drugs**

**LB-102 (N-methyl amsulpride)**

**Brilaroxazine**

***Thank you!***