THE SEARCH FOR THE PERFECT ANTI-PSYCHOTIC

Continuing Education Seminar for Pharmacists

Jamaica Pegasus Hotel

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APOTEX

Disclaimer:
These slides are adapted from
Dr. Stephen Stahl's Psychopharmacology Series

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APOTEX

Psychopharmacology of Schizophrenia: Objectives

- Review the circuits and receptors that are currently linked to the symptom dimensions of schizophrenia
- Review the widely hypothesized mechanism of therapeutic action of antipsychotics as D_2 antagonists and partial agonists
- Introduce the potential glutamate-linked actions of atypical antipsychotic drugs
- Discuss the multifunctional pharmacologic and clinical properties of serotonin 5-HT_{2A} antagonism and 5-HT_{1A} partial agonism of atypical antipsychotics

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APOTEX

Psychotic and Cognitive Symptoms of Schizophrenia

PATHWAYS, CIRCUITS, AND NEUROTRANSMITTERS

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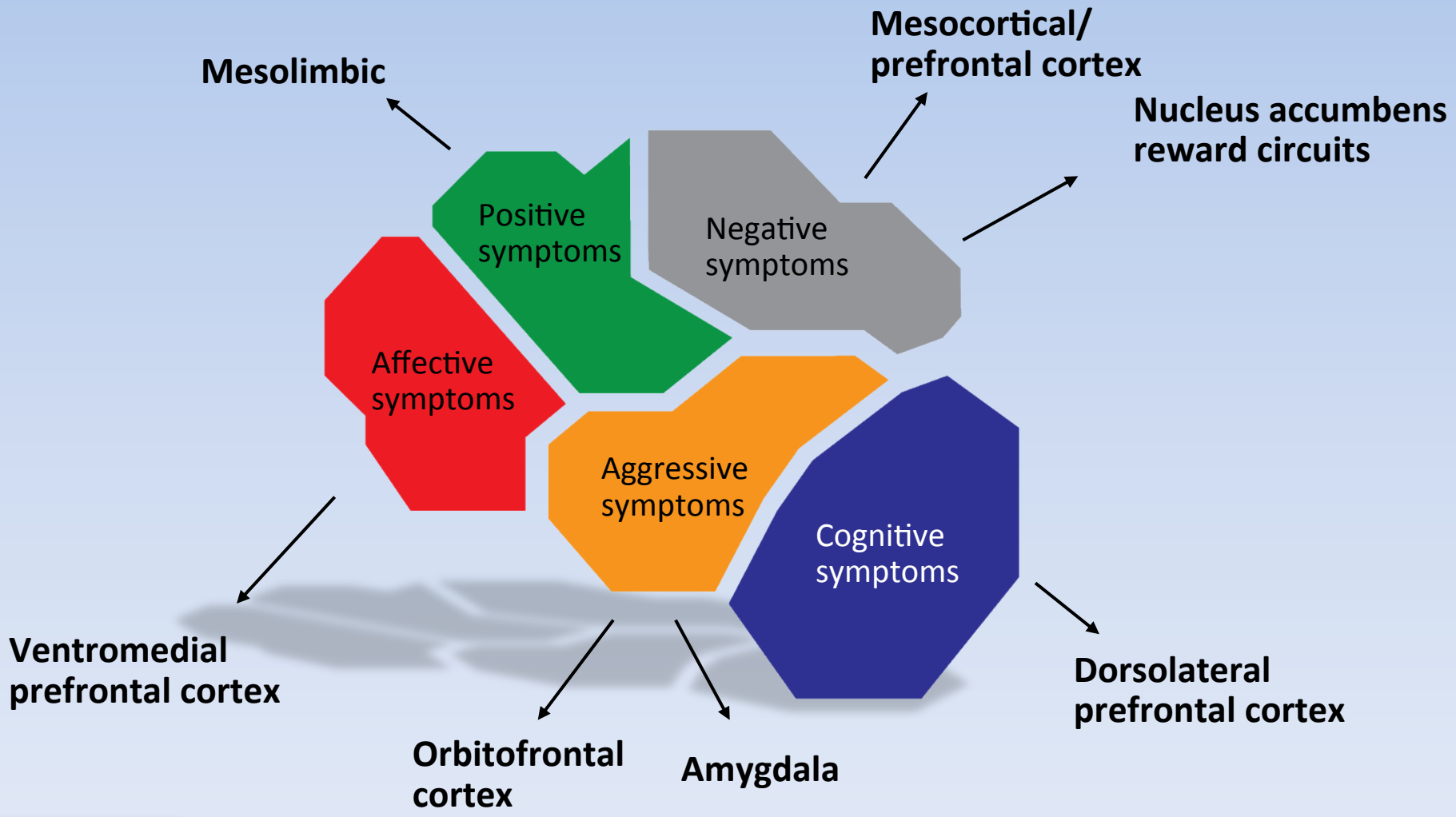
APOTEX

Symptom Dimensions Match Hypothetically Malfunctioning Brain Circuit



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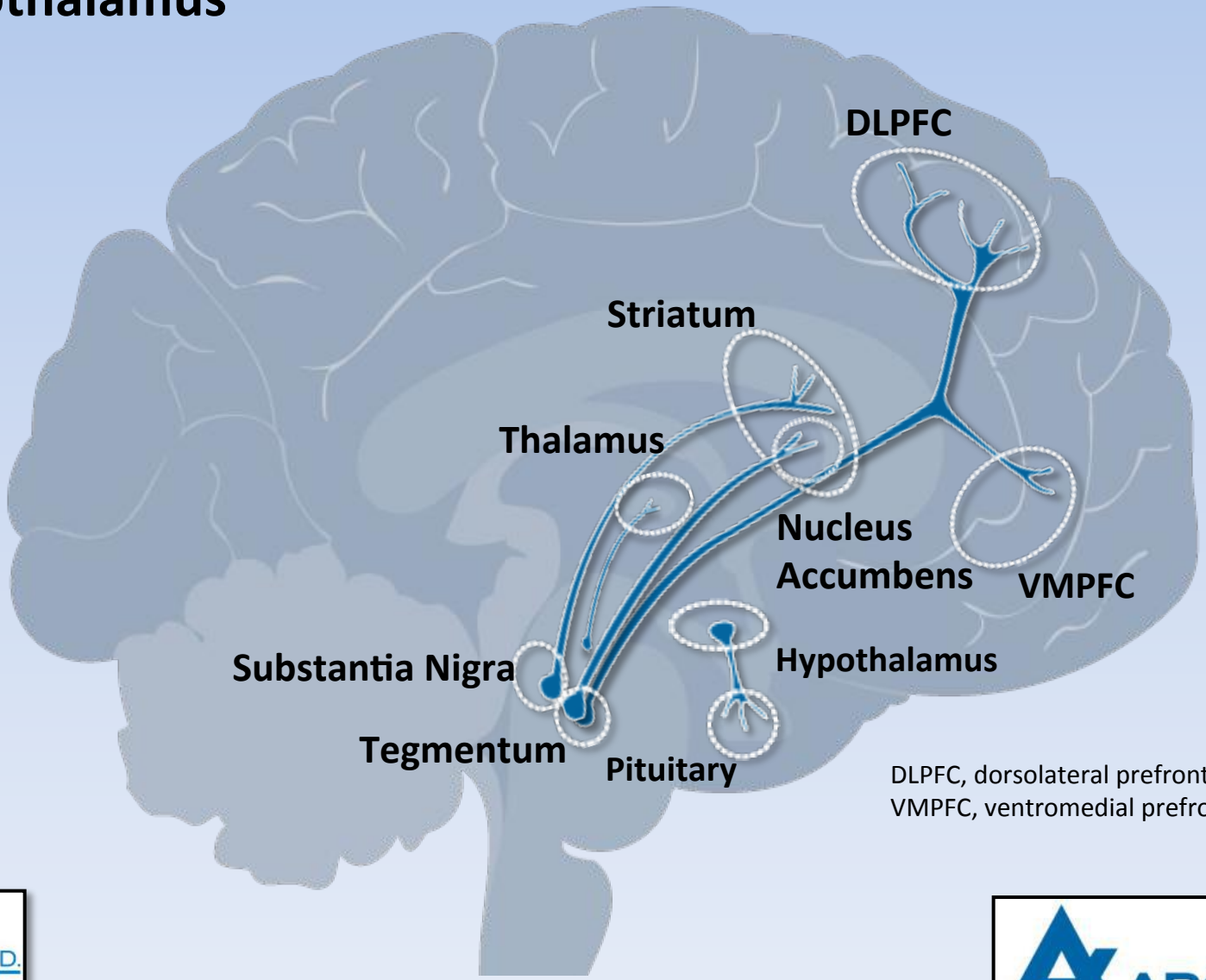
Dopamine Pathways Project from Neurotransmitter Centers to the Striatum, Prefrontal Cortex, Thalamus, and Hypothalamus



DLPFC, dorsolateral prefrontal cortex;
VMPFC, ventromedial prefrontal cortex

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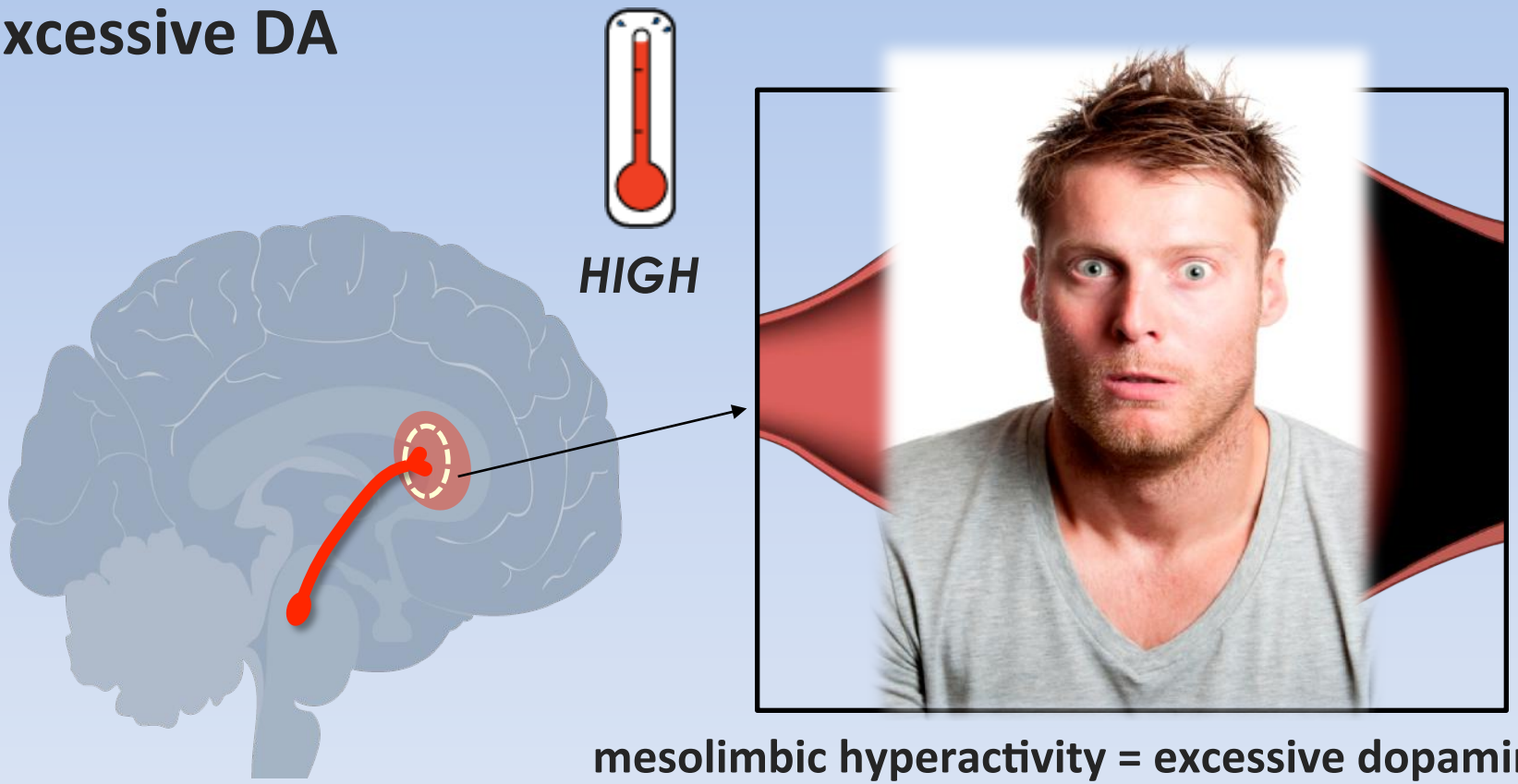
The Mesolimbic Dopamine Hypothesis of Positive Symptoms of Schizophrenia Describes the Effects of Excessive DA



mesolimbic hyperactivity = excessive dopamine

DA, dopamine; D, dopaminergic

Positive Symptoms

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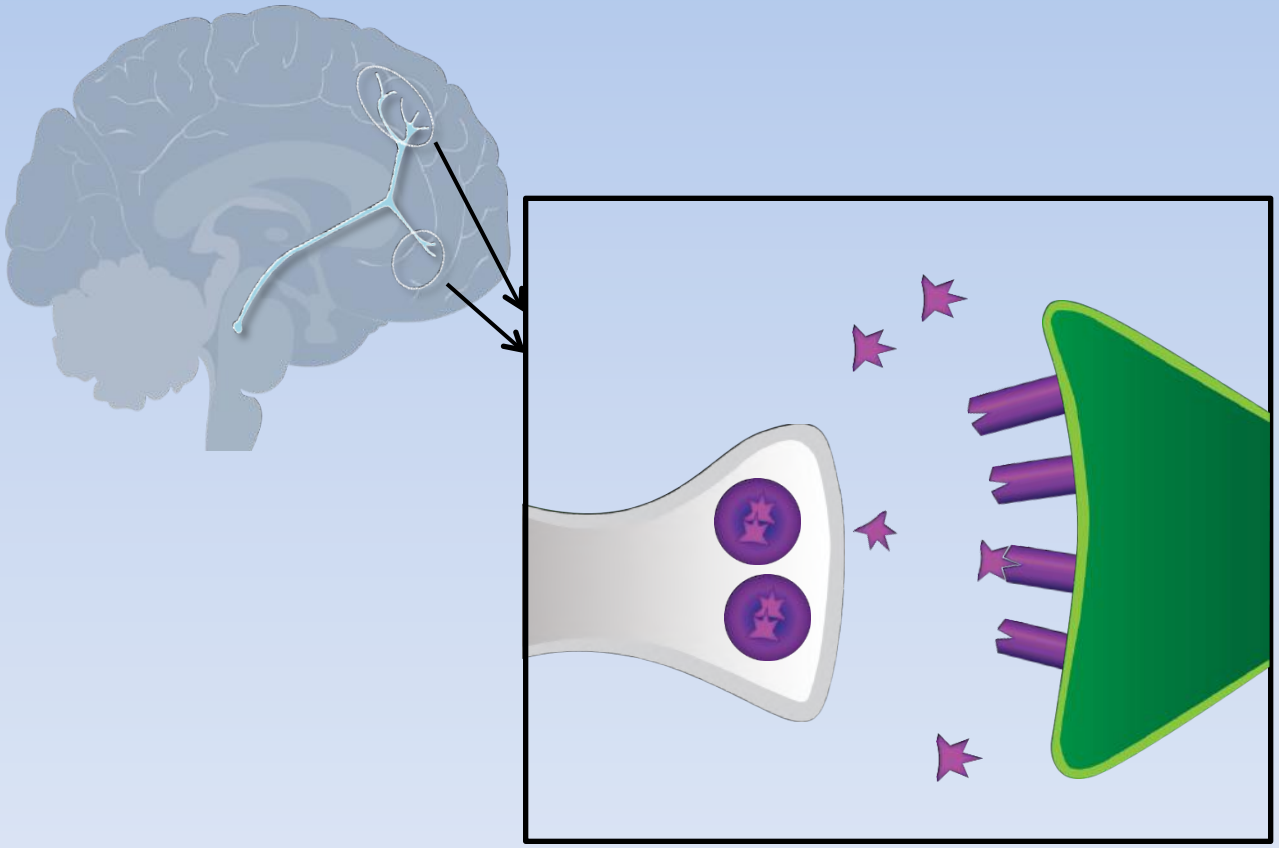
D_2 Hypoactivity Along the Mesocortical Pathway is Also Related to Negative, Cognitive, and Affective Symptoms



Cognitive symptoms

Negative symptoms

Affective symptoms

D, dopaminergic

Mesocortical underactivity = negative, cognitive, and affective symptoms of schizophrenia

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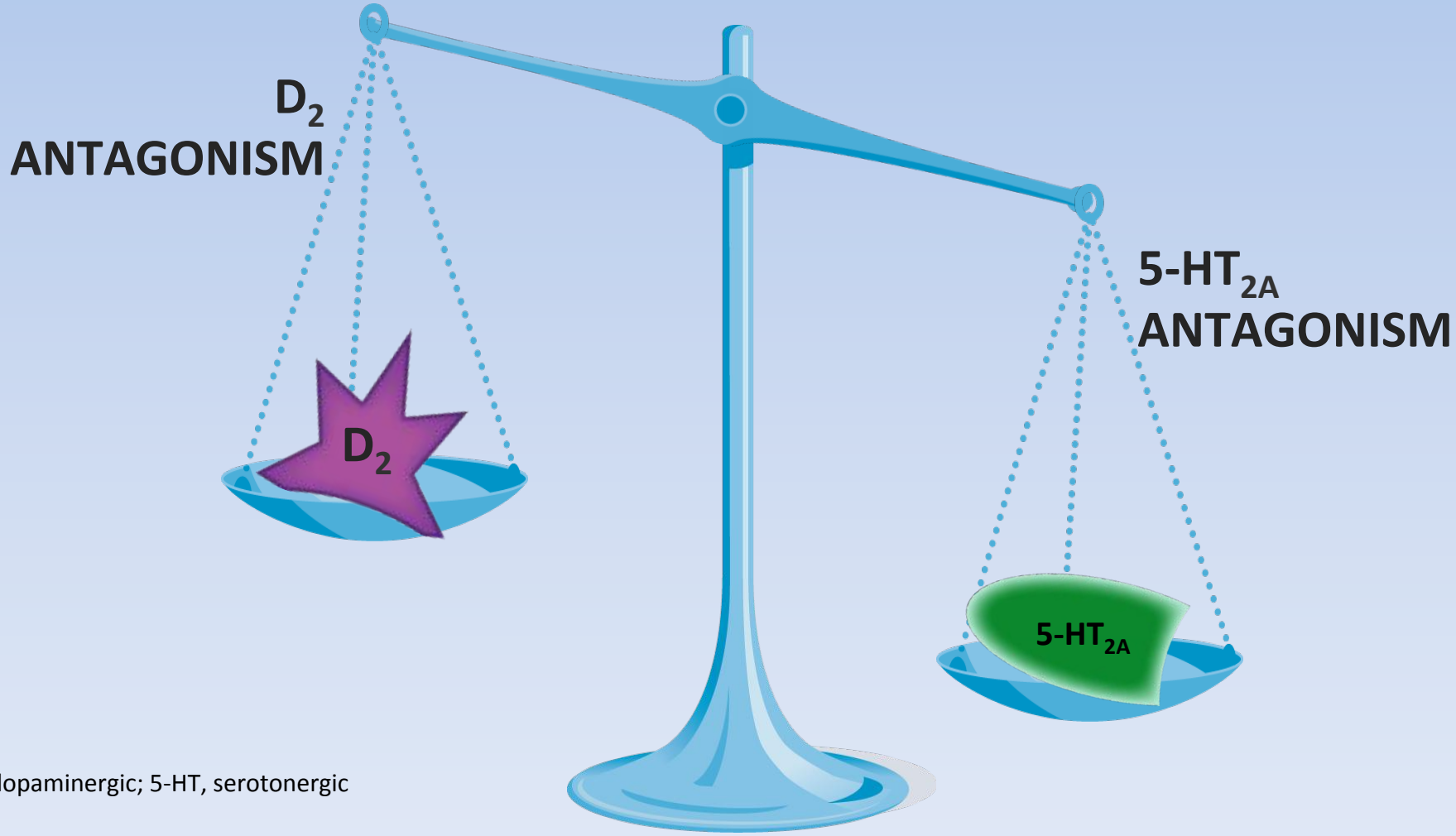
Which Action Predominates?



D, dopaminergic; 5-HT, serotonergic

The answer depends on the region of the brain

Psychotic and Cognitive Symptoms of Schizophrenia

NMDA AND GLUTAMATE

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The NMDA-Glutamate Hypofunction Hypothesis Can Explain Psychotic and Cognitive Symptoms

- Implicates dysfunctional NMDA receptors in the prefrontal cortex, especially for the cognitive dysfunction of schizophrenia
- NMDA antagonists (like ketamine and PCP) exacerbate psychotic symptoms and cognitive impairment in patients with schizophrenia
- NMDA antagonists also induce these symptoms in healthy volunteers
- Atypical antipsychotics share a common property of augmenting NMDA-evoked responses in pyramidal cells of the prefrontal cortex, implying facilitation of NMDA receptor-mediated transmission

NMDA, N-methyl-d-aspartate; PCP, phencyclidine

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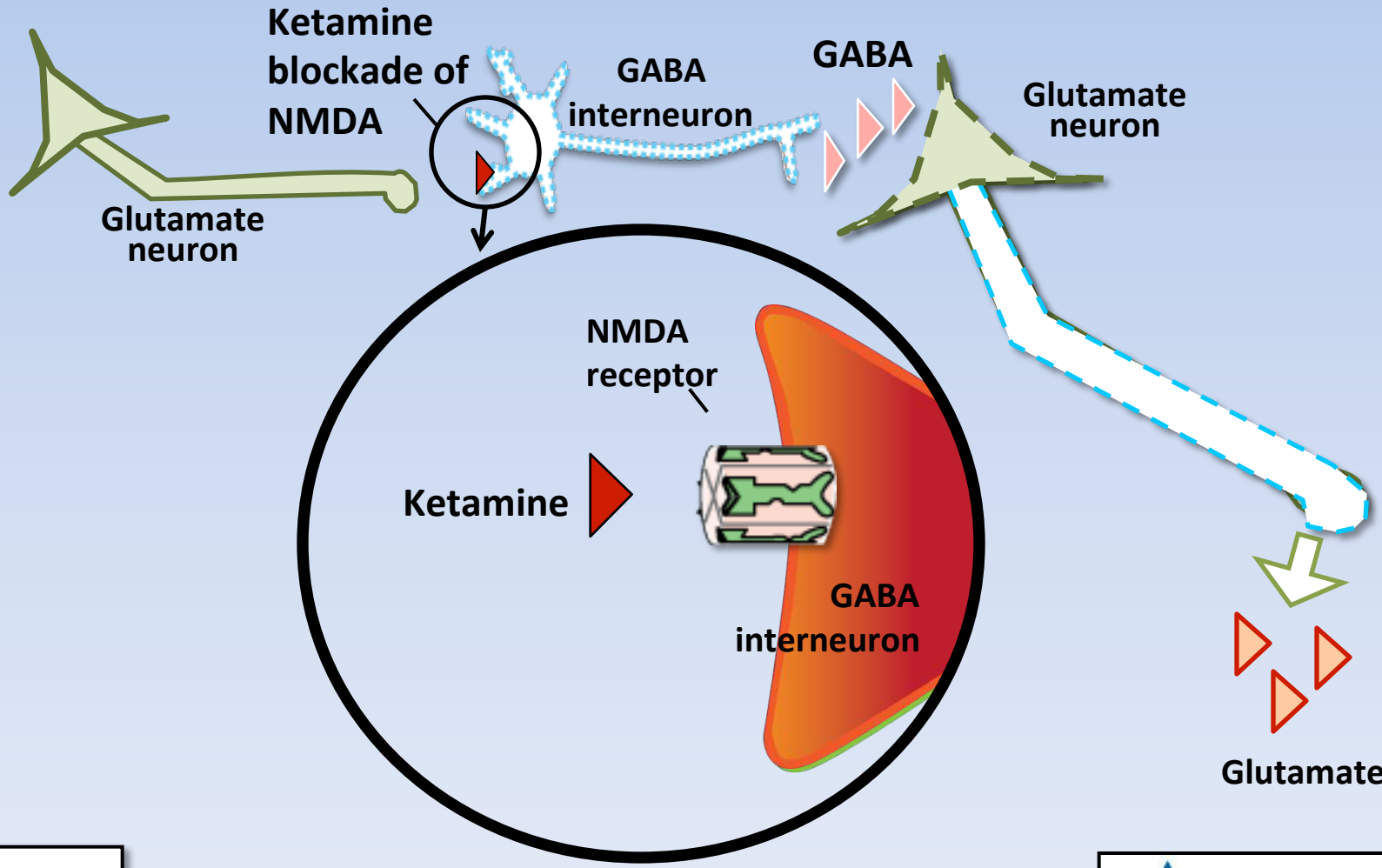
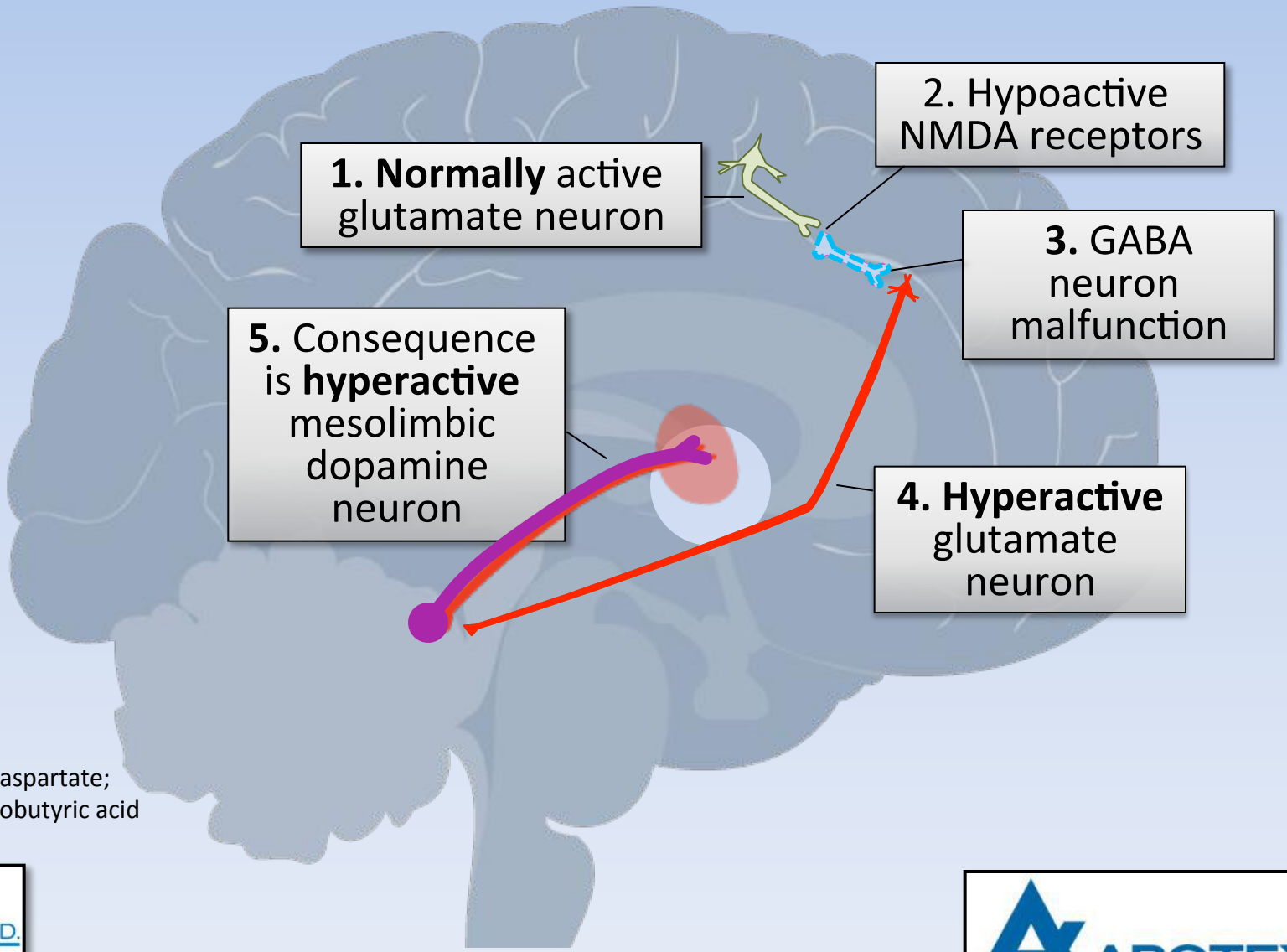
The "PCP-Ketamine Model of Schizophrenia" Suggests Ketamine Blocks NMDA Receptors



PCP, phencyclidine; NMDA, N-methyl-d-aspartate; GABA, gamma aminobutyric acid

Glutamate Dysfunction Can Cause Mesolimbic Hyperactivation



NMDA, N-methyl-d-aspartate;
GABA, gamma aminobutyric acid

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Glutamate, Serotonin, and Antipsychotic Actions

- Hypothetically, overactive glutamate neurons in the prefrontal cortex may accompany psychosis and mania
- These neurons project to the ventral tegmental area and drive DA neurons there into a state of hyperactivity
- Serotonin regulates the cortical glutamate neurons via 5-HT_{2A} receptors
- Blocking 5-HT_{2A} receptors on prefrontal glutamate neurons may reduce overactivity and lead to normalization of DA, and thus a reduction of psychosis and mania

DA, dopamine; 5-HT, serotonergic

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CURRENT TREATMENT OPTIONS: ANTIPSYCHOTIC MEDICATIONS

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Learning Objectives

- Review the **dopamine D_2 and serotonin 5-HT_{2A} antagonist** properties of all atypical antipsychotics
- Demonstrate that all atypical antipsychotics have **numerous additional binding properties**, but no two agents are identical
- Propose that these differences in binding properties comprise the most rational hypothesis to explain differences in efficacy and tolerability of atypical antipsychotics in **individual patients**

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APOTEX

Asenapine – Saphris (US), Sycrest (UK)
Clozapine – Clozaril
Aripiprazole – Abilify
Ziprasidone – Geodon, Zeidox, Zipwell
Iloperidone – Fanapt, Fanapta, Zomaril
Lurasidone - Latuda

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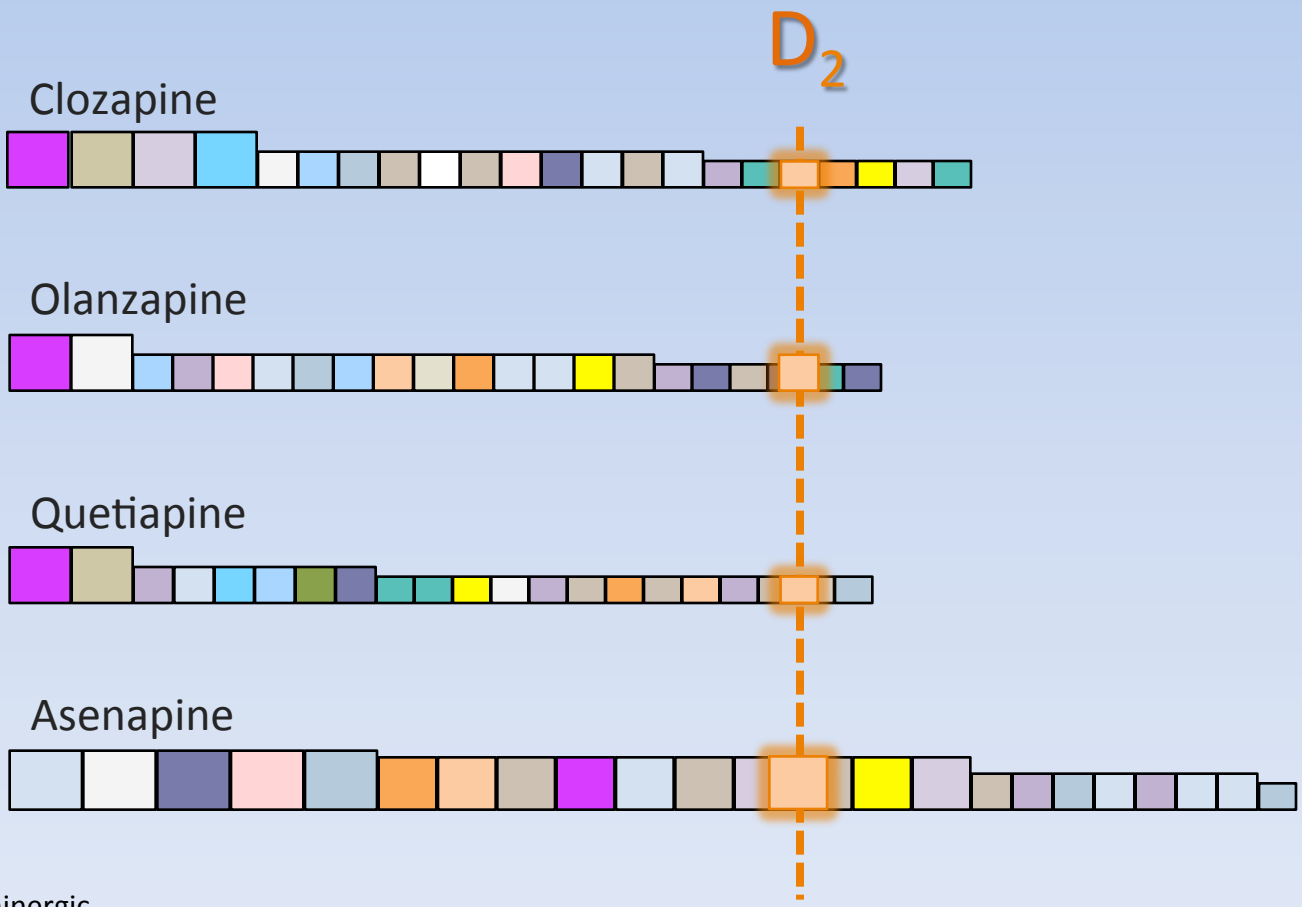
APOTEX

Conventional Antipsychotics have D_2 Antagonist Actions
D_2 Relative Receptor Binding Affinity for the "-pines"



Antipsychotic Actions

D, dopaminergic

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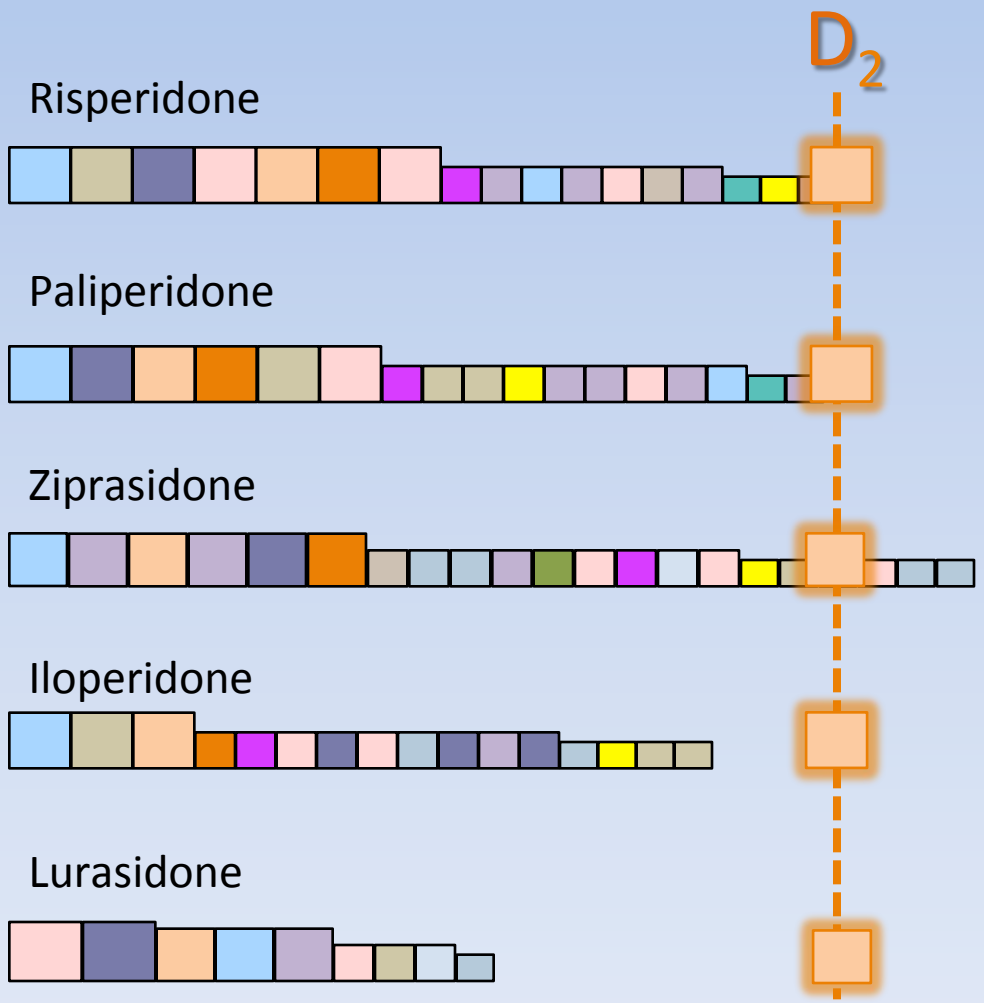
APOTEX

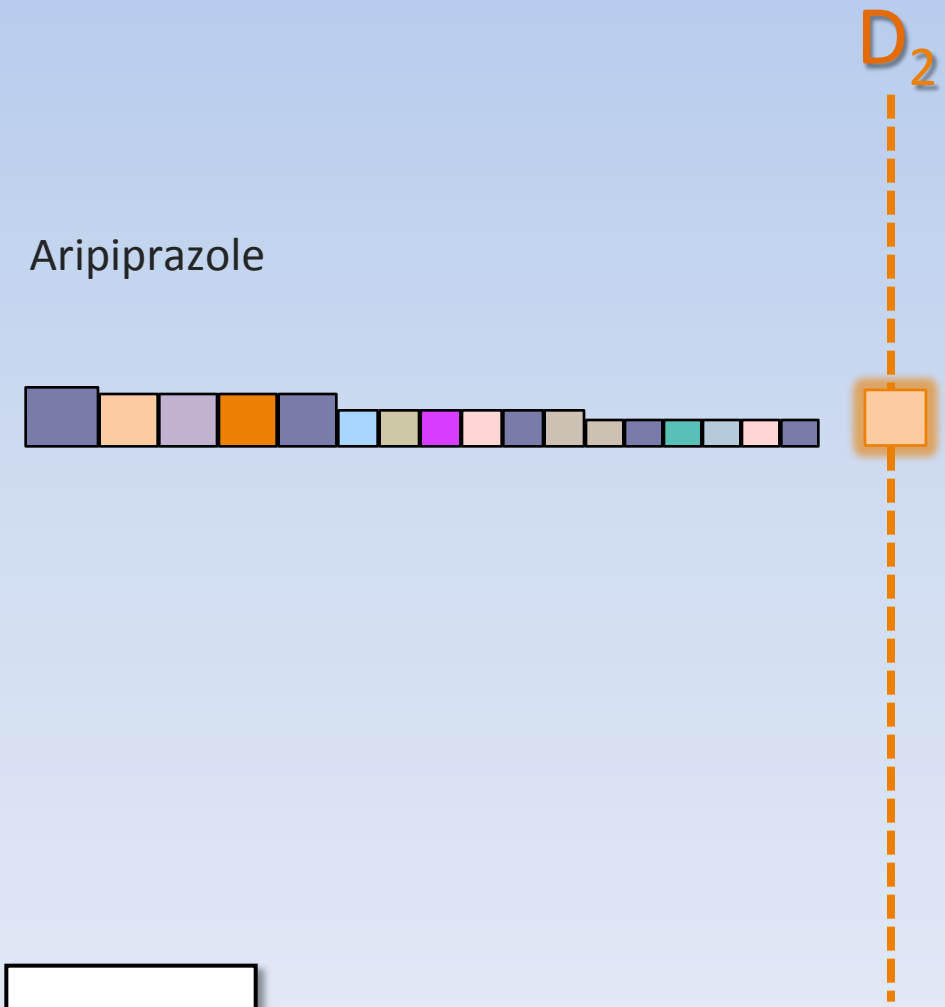
Conventional Antipsychotics have D_2 Antagonist Actions
D_2 Relative Receptor Binding Affinity for the "-dones"



Antipsychotic Actions

D, dopaminergic

D_2 Receptor Binding Affinity: Partial Agonist



Antipsychotic Actions

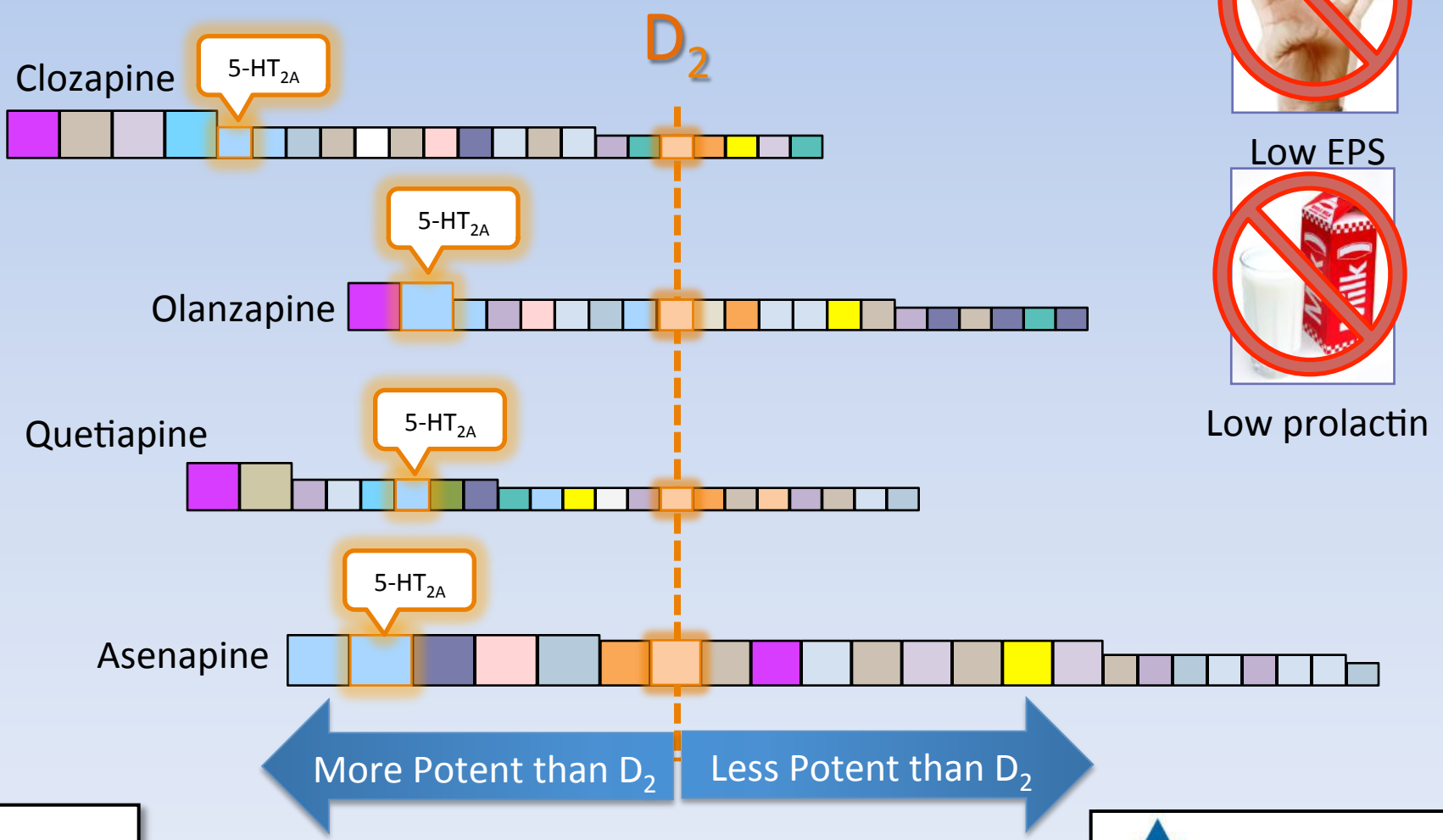
D, dopaminergic

Outline

- Conventional antipsychotic: D_2
- **Atypical antipsychotic: D_2 + 5-HT_{2A}**
- Some mediators of therapeutic actions:
  - 5-$HT_{1A, 2C, 7}$
- Some mediators of side effects:
  - H_1 and M_1

D, dopaminergic; 5-HT, serotonergic; H, histaminergic; M, muscarinic

5-HT_{2A} Relative Receptor Binding Affinity for the "-pines"

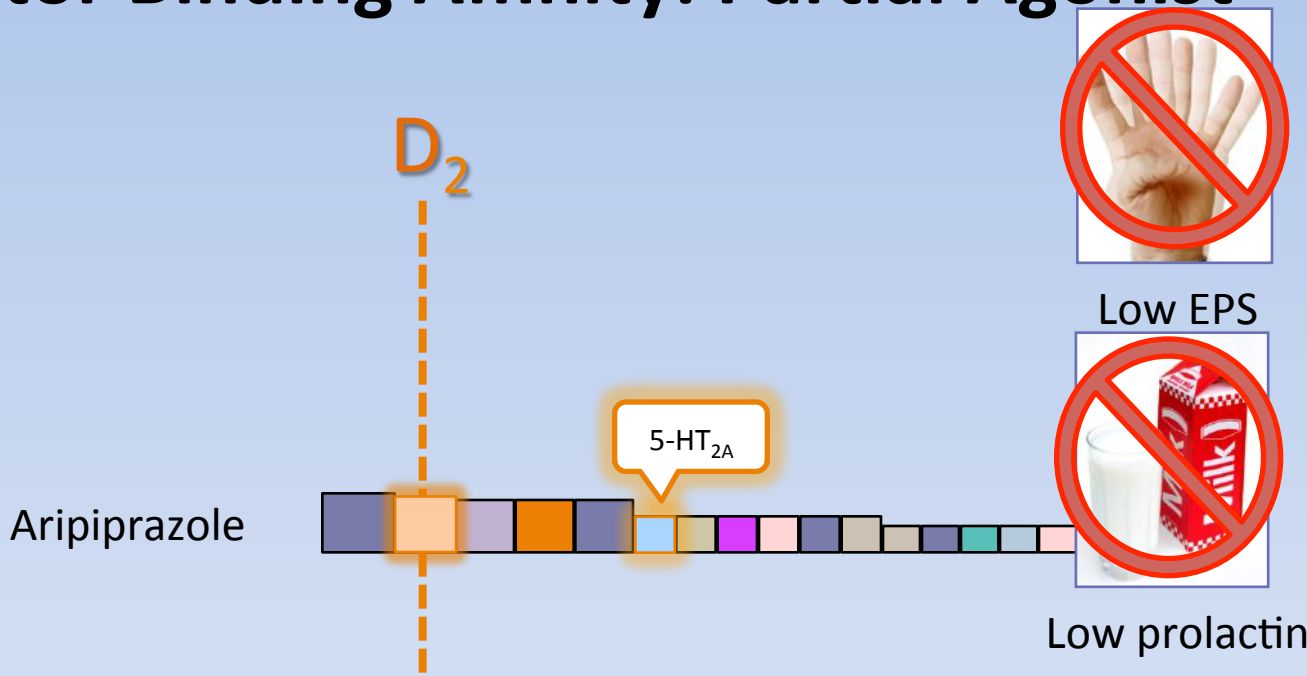


Low EPS

Low prolactin

5-HT, serotonergic; D, dopaminergic; EPS, Extrapyramidal Symptoms

5-HT_{2A} Receptor Binding Affinity: Partial Agonist



5-HT, serotonergic;
D, dopaminergic;
EPS, Extrapyramidal Symptoms

Outline

- Conventional antipsychotic: D_2
- Atypical antipsychotic: D_2 + $5\text{-}HT_{2A}$
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D, dopaminergic; 5-HT, serotonergic; H, histaminergic; M, muscarinic

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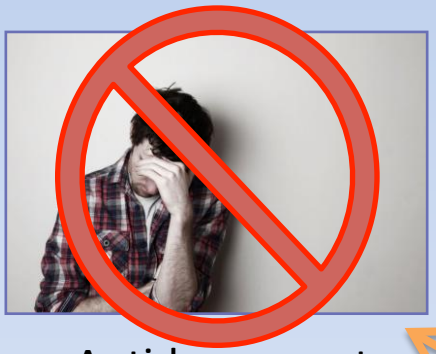
APOTEX

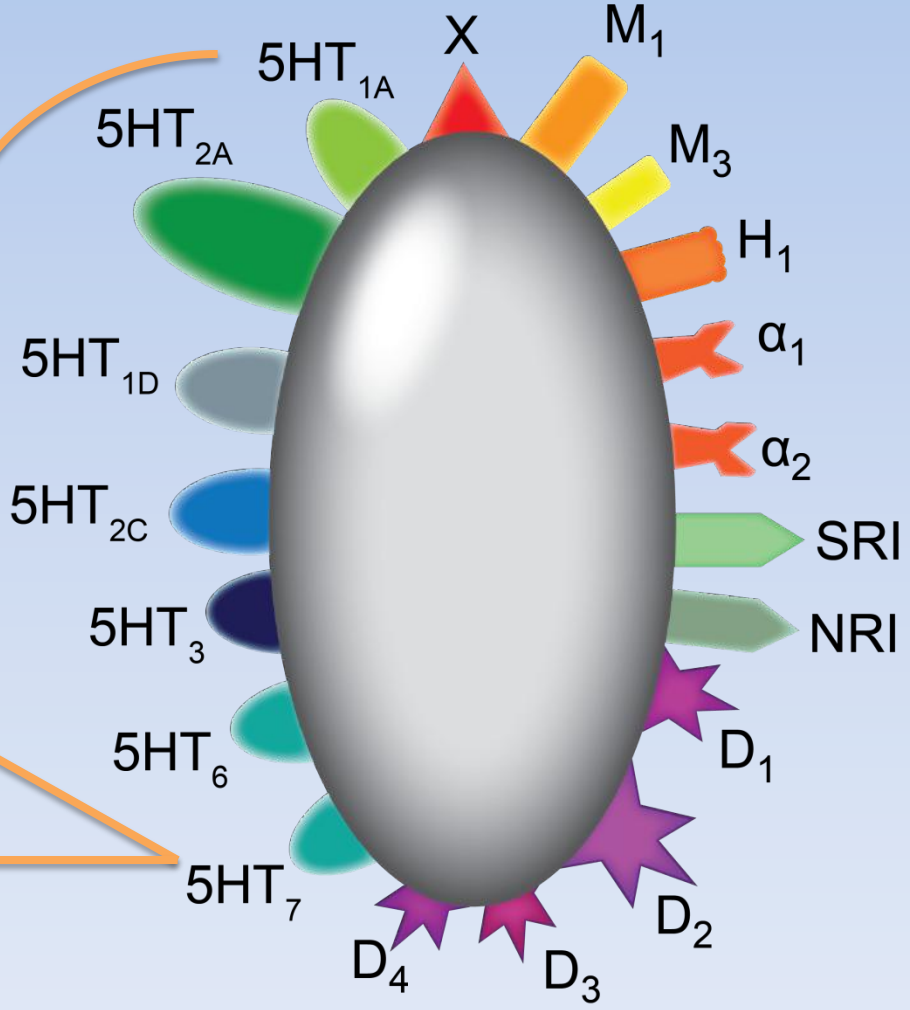
Additional Antipsychotic Binding Properties

Hypothetical Mediators of Therapeutic Actions



Antidepressant

Good Cognition



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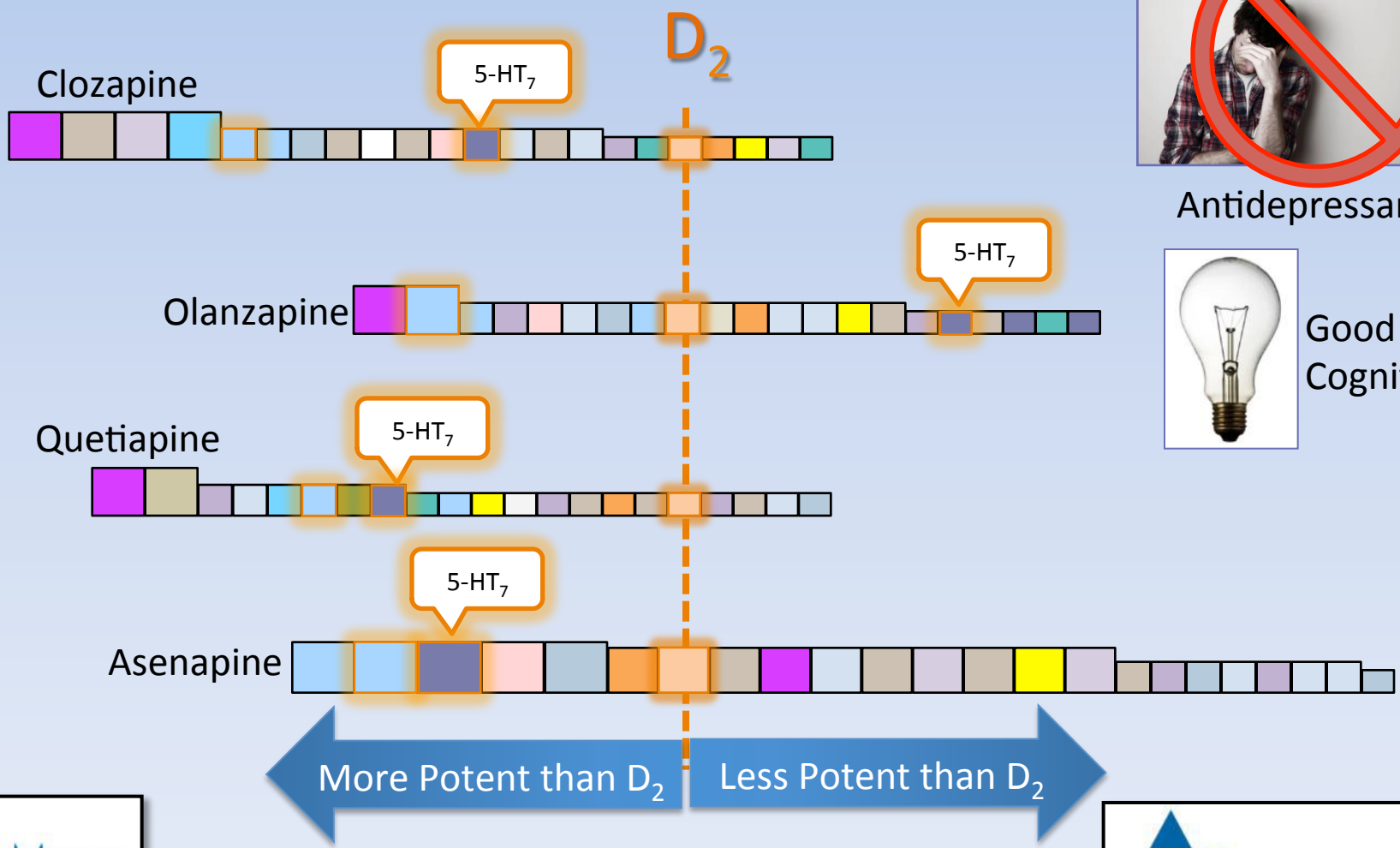
D, dopaminergic; 5-HT, serotonergic; H, histaminergic; M, muscarinic; α, alpha-adrenergic; SRI, serotonin reuptake inhibitors; NRI, noradrenaline reuptake inhibitor

APOTEX

5-HT$_7$ Relative Receptor Binding Affinity for the "-pines"

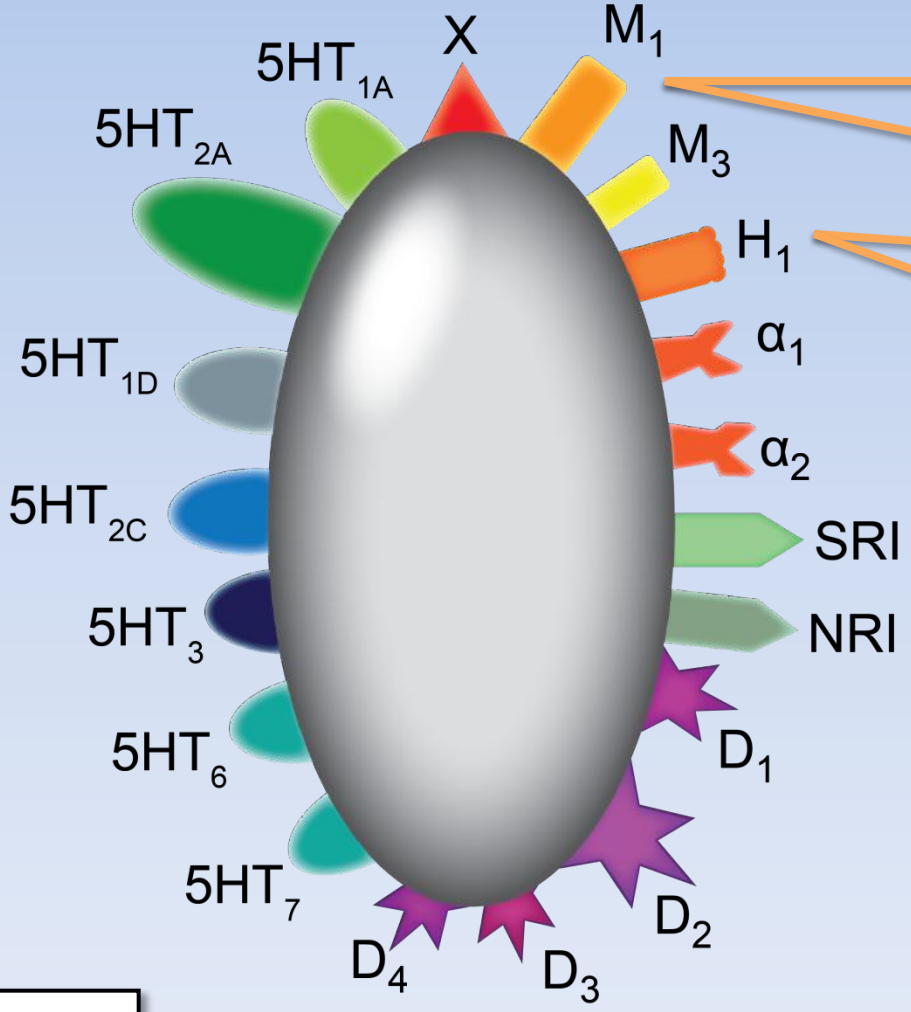
Antidepressant

Good Cognition



5-HT, serotonergic; D, dopaminergic

Additional Antipsychotic Binding Properties Hypothetical Mediators of Side Effects



Dry mouth

Sedation

Weight gain

D, dopaminergic; 5-HT, serotonergic; H, histaminergic; M, muscarinic; α, alpha-adrenergic; SRI, serotonin reuptake inhibitors; NRI, noradrenaline reuptake inhibitor

Summary: Atypical Antipsychotics as a Class

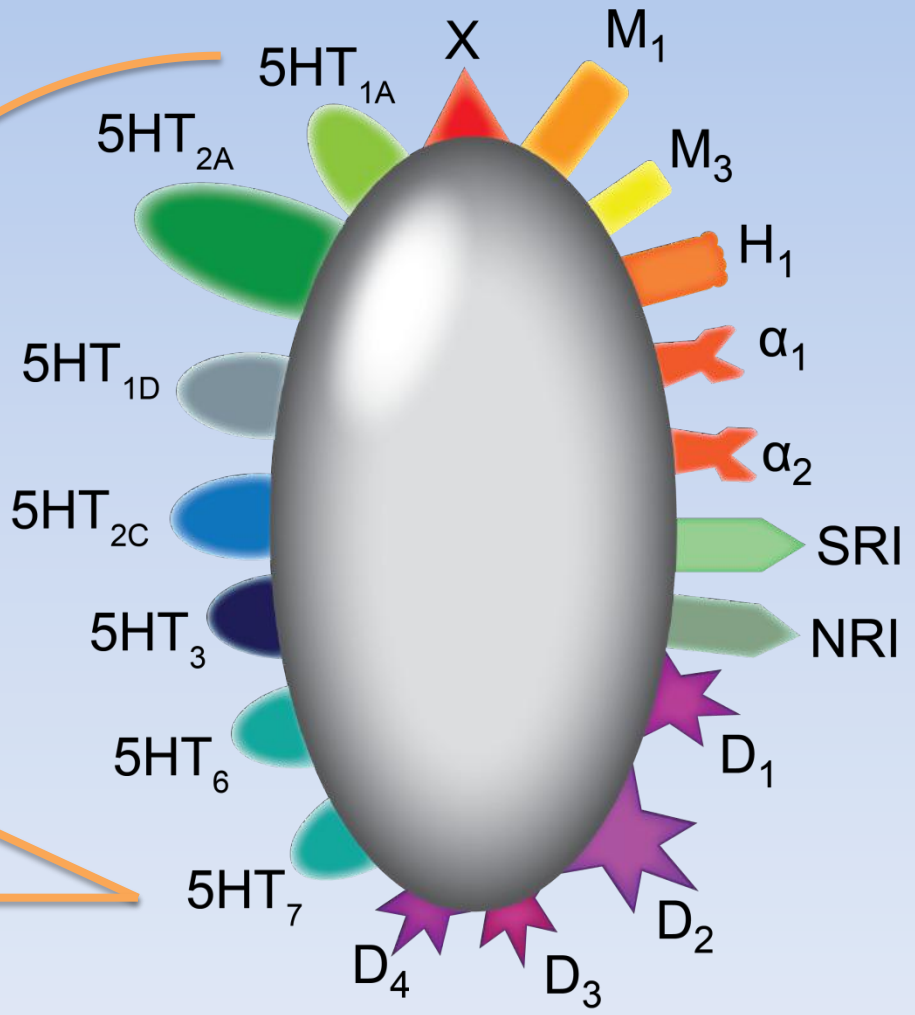
- All atypical antipsychotics have dopamine D_2 and 5-HT_{2A} antagonist properties
- All atypicals have numerous other binding properties and are linked to various clinical effects, but no two agents are identical
- Differences in binding properties are the most rational explanation for differences in efficacy and tolerability in individual patients

D, dopaminergic; 5-HT, serotonergic

Additional Antipsychotic Binding Properties Hypothetical Mediators of Therapeutic Actions

Antidepressant

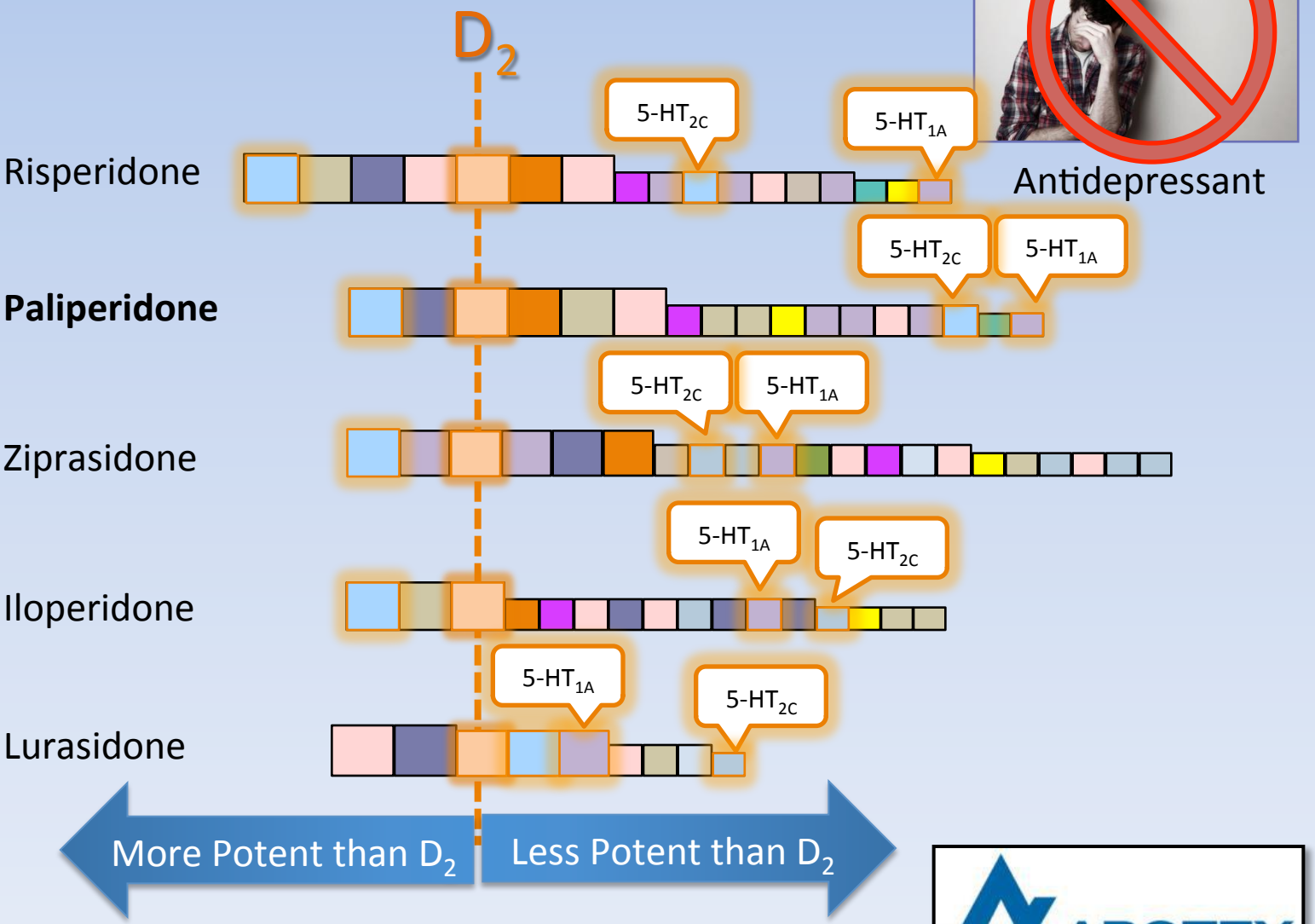
Good Cognition



D, dopaminergic; 5-HT, serotonergic; H, histaminergic; M, muscarinic; α, alpha-adrenergic; SRI, serotonin reuptake inhibitors; NRI, noradrenaline reuptake inhibitor

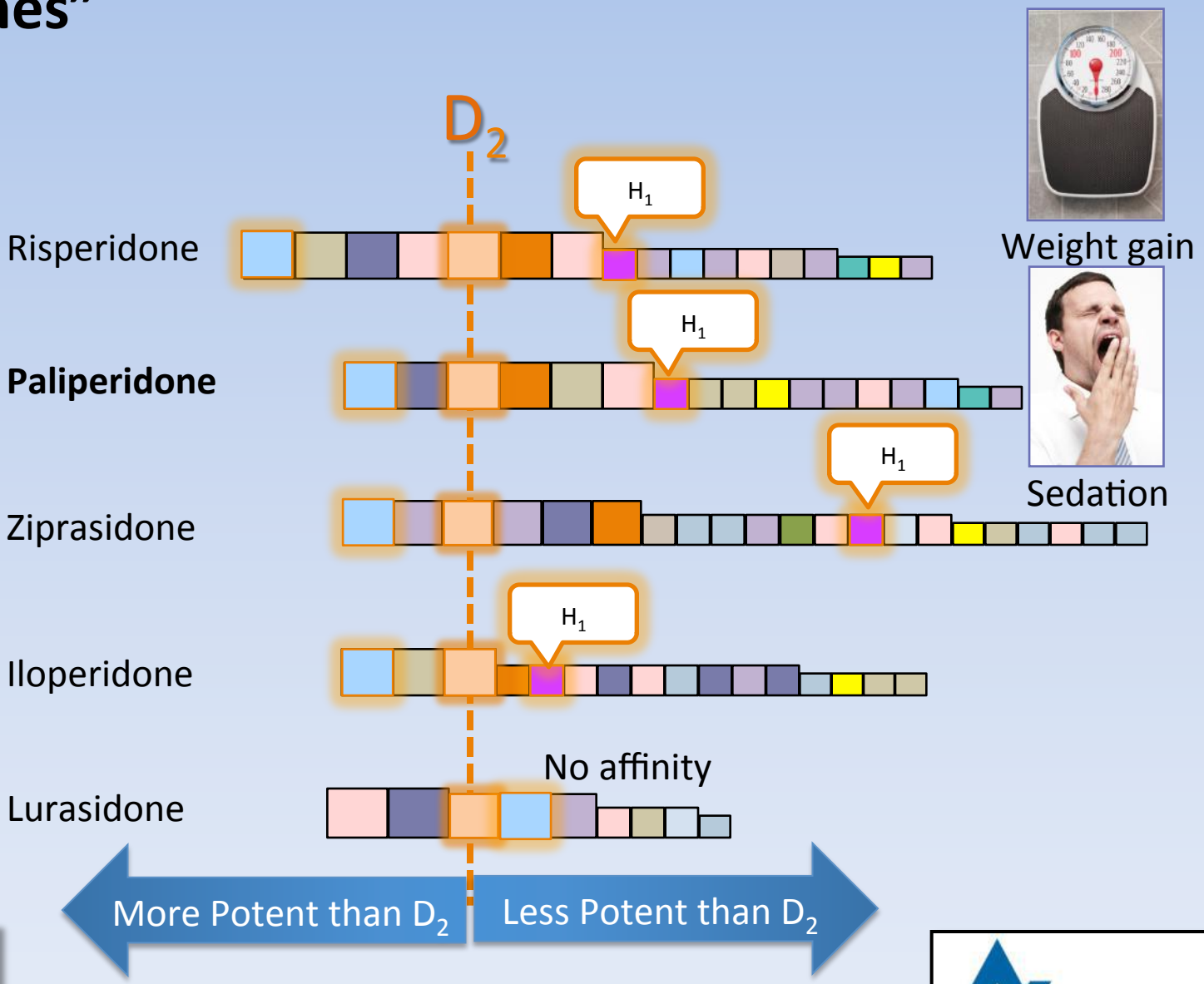
5-$HT_{1A\ and\ 2C}$ Relative Receptor Binding Affinity for the "-dones"

Antidepressant



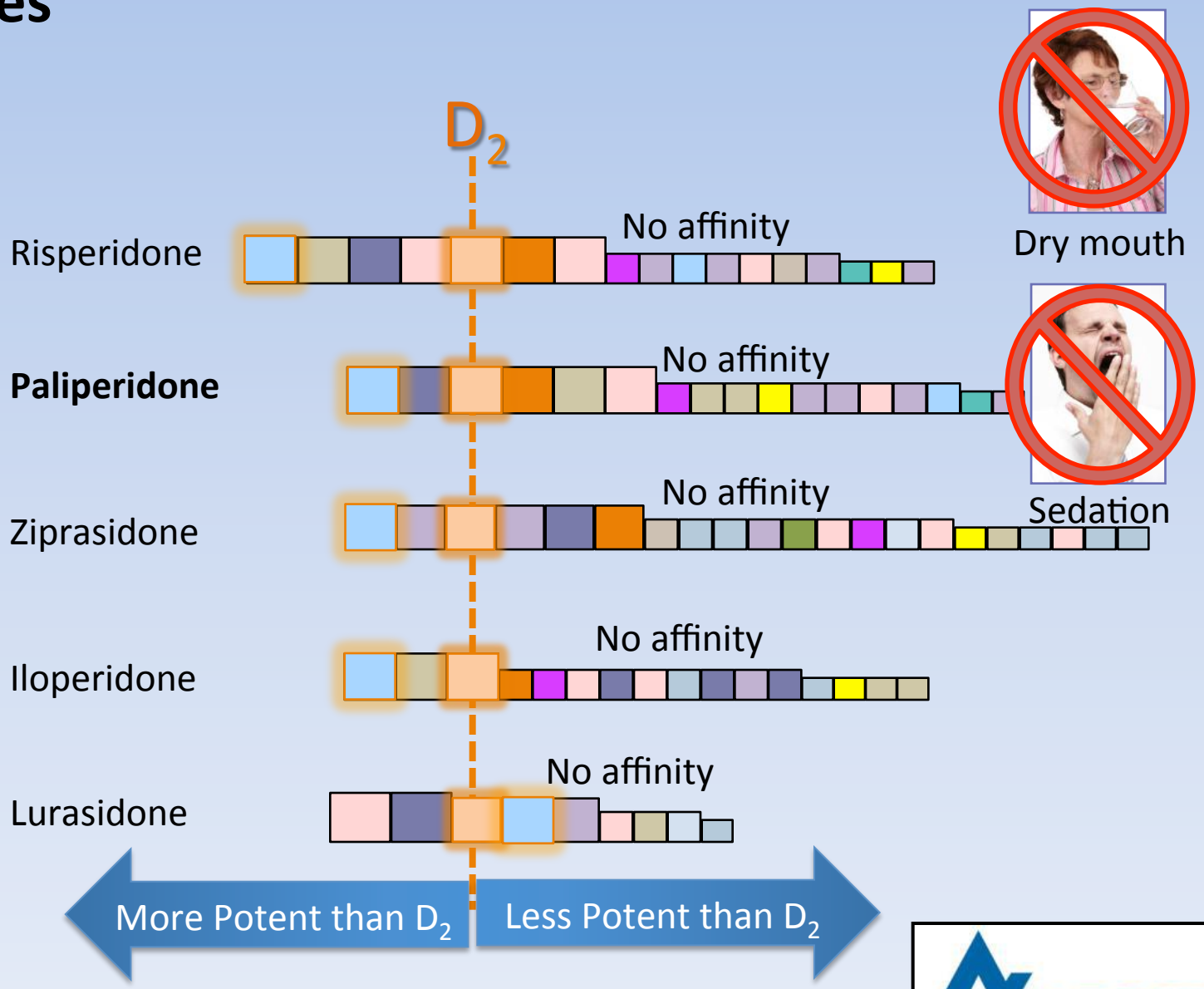
5-HT, serotonergic; D, dopaminergic

H_1 Relative Receptor Binding Affinity for the "-dones"



H, histaminergic; D, dopaminergic

M_1 Relative Receptor Binding Affinity for the "-dones"



M, muscarinic; D, dopaminergic

Thank you!

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APOTEX