Neuroscience Education Institute

UPDATE ON SCHIZOPHRENIA: NEW TREATMENTS AND NOVEL TARGETS

Learning Objectives

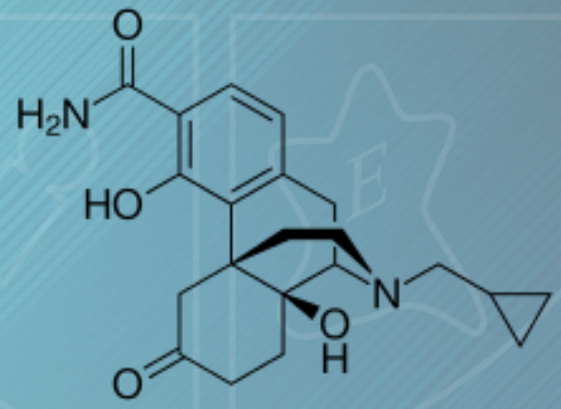
- Review clinical advances in our understanding of schizophrenia
- Update knowledge on novel treatments for schizophrenia

Novel Pharmacological Treatment for Ameliorating Adverse Events

Olanzapine/Samidorphan

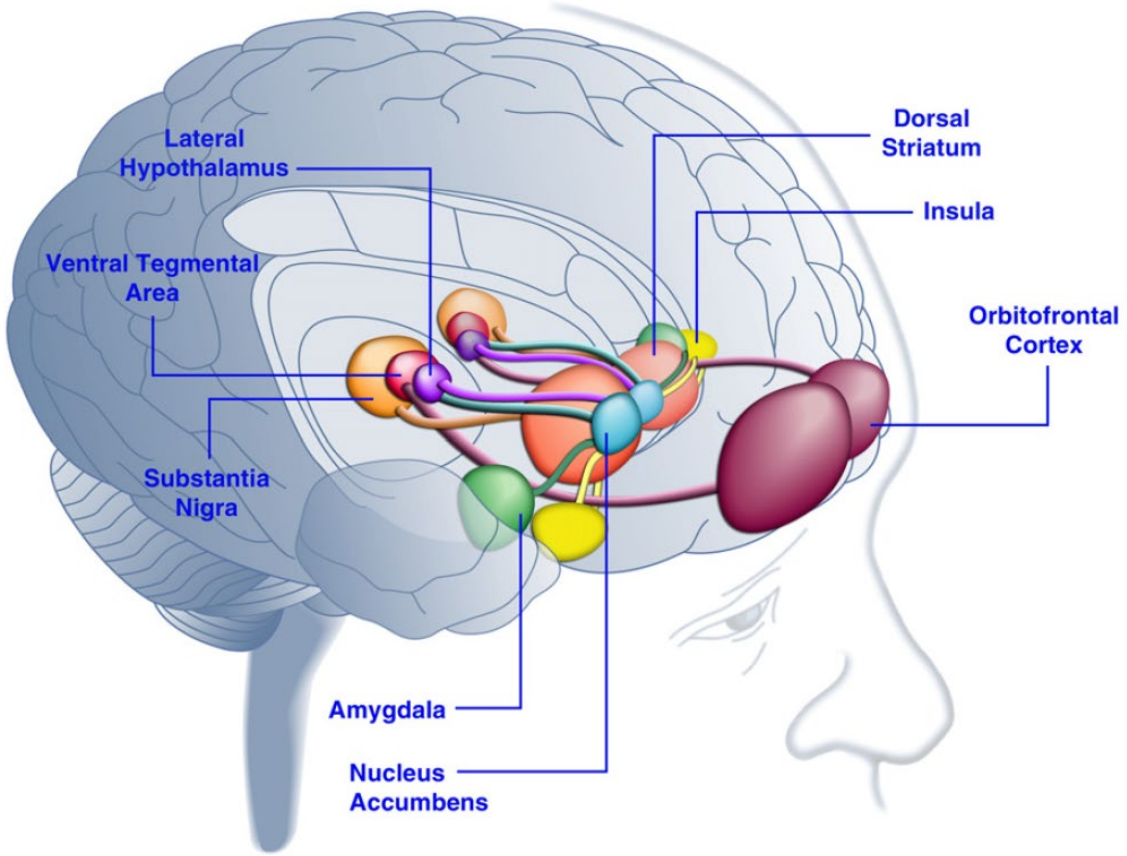
- Samidorphan (SAM) is an opioid antagonist at the μ-opioid receptor, with significant activity at k-opioid receptors
  - By blocking opioid receptors involved in the brain reward pathway, reinforcement is reduced
  - Shows similar efficacy to naltrexone but with reduced side effects
  - Investigated for addiction treatment (e.g., alcohol, cocaine)
- Co-administration of olanzapine and SAM, but not naltrexone, mitigated olanzapine-induced weight gain, suggesting that the added k-opioid receptor properties may be clinically relevant

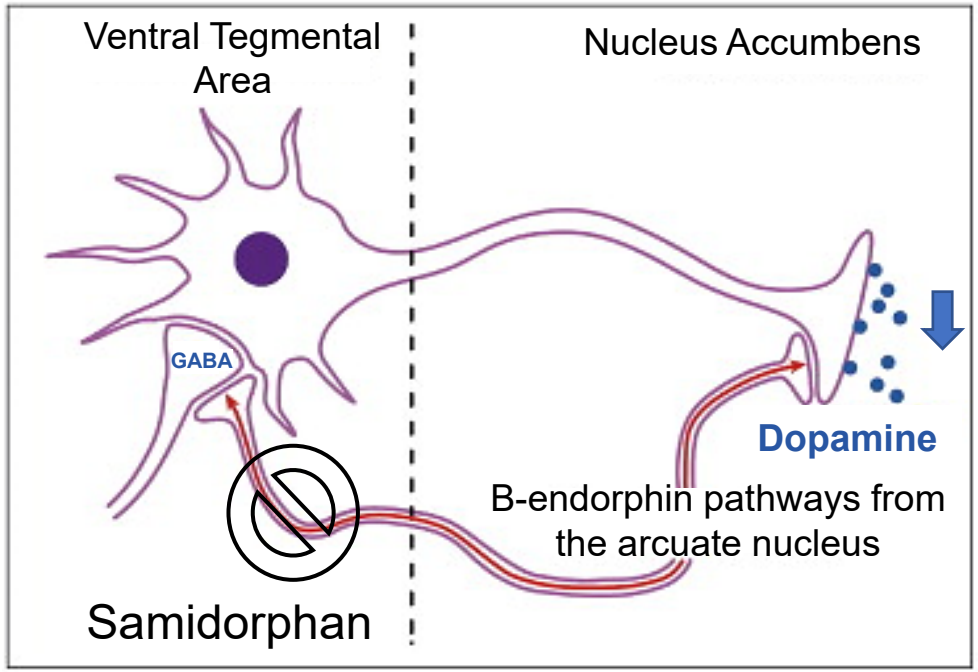
Receptor	Ki (nM)
μ	0.052
k	0.28
δ	2.6



Silverman BL et al. Schizophr Res 2018;195:245-51.

Proposed Mechanism: Brain Reward Pathway





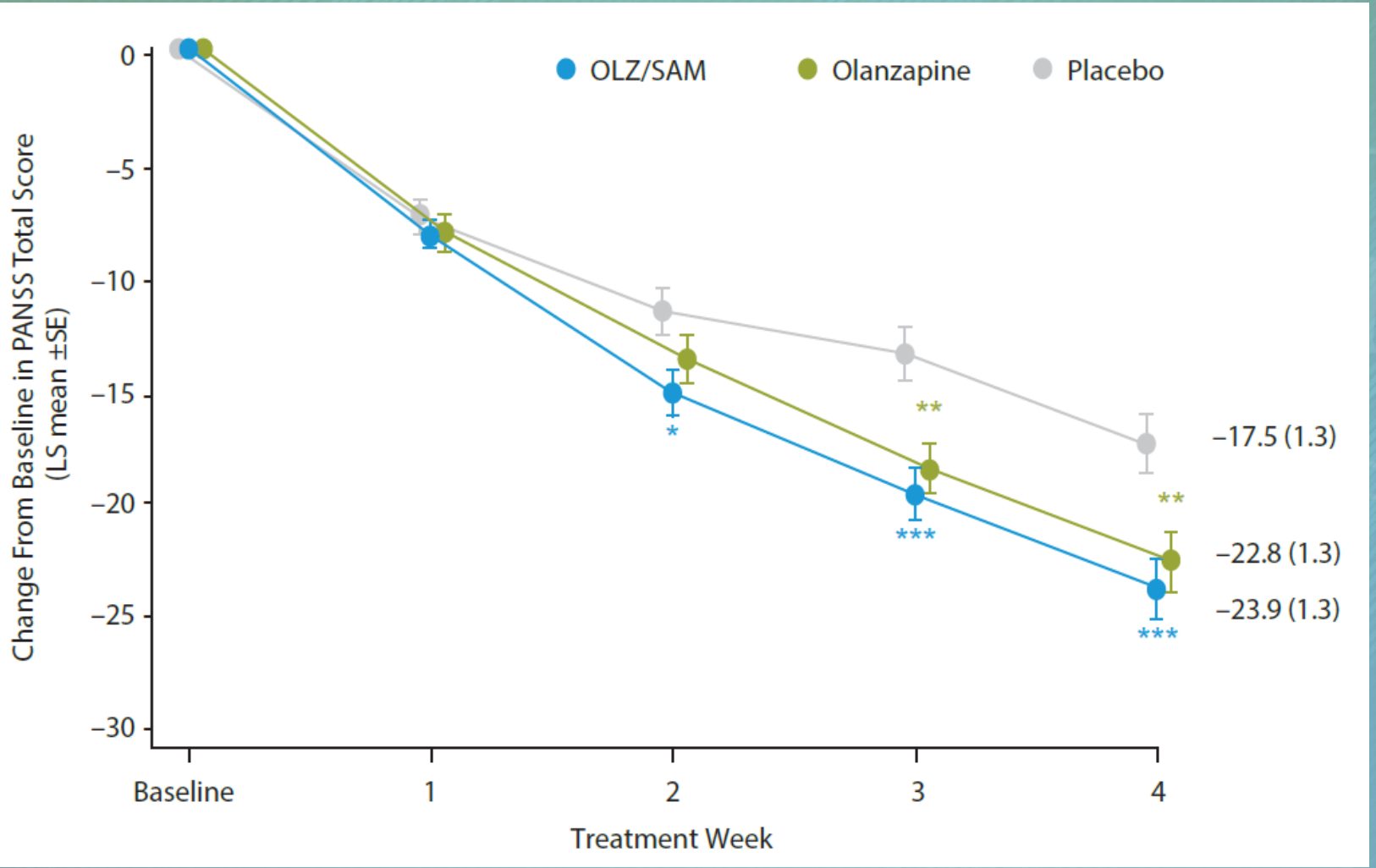
Krogmann A et al. CNS Spectr 2019;24(S1):38-69;
Peckham AM et al. Ment Health Clin 2018;8(4):175-83;
Kenny PJ. Neuron 2011;69(4):664-79.

Olanzapine (OLZ)/Samidorphan (SAM) Study Program

- **ALKS 3831:** flexible dose of olanzapine and a fixed dose of 10 mg SAM
  - The combination has been studied in phase I trials (healthy volunteers) and phase II trials (patients with stable schizophrenia)
  - In the phase II study, co-administration of SAM mitigated OLZ-associated weight gain, and OLZ/SAM combination had similar antipsychotic efficacy to OLZ
- **Phase III (ENLIGHTEN II):** 4-week randomized, double-blind active (OLZ monotherapy), and placebo-controlled study of ALKS 3831 in acute exacerbation of schizophrenia
  - Significant improvement versus placebo in PANSS total scores
  - Superior to placebo in reducing olanzapine-induced weight gain

Silverman BL et al. Schizophr Res 2017;195:245-51; Martin WF et al. Am J Psychiatry 2019;176(6):457-67; Potkin SG et al. J Clin Psychiatry 2020;81(2):19m12769.

Olanzapine/Samidorphan (OLZ/SAM): Phase III (ENLIGHTEN II) Efficacy Results



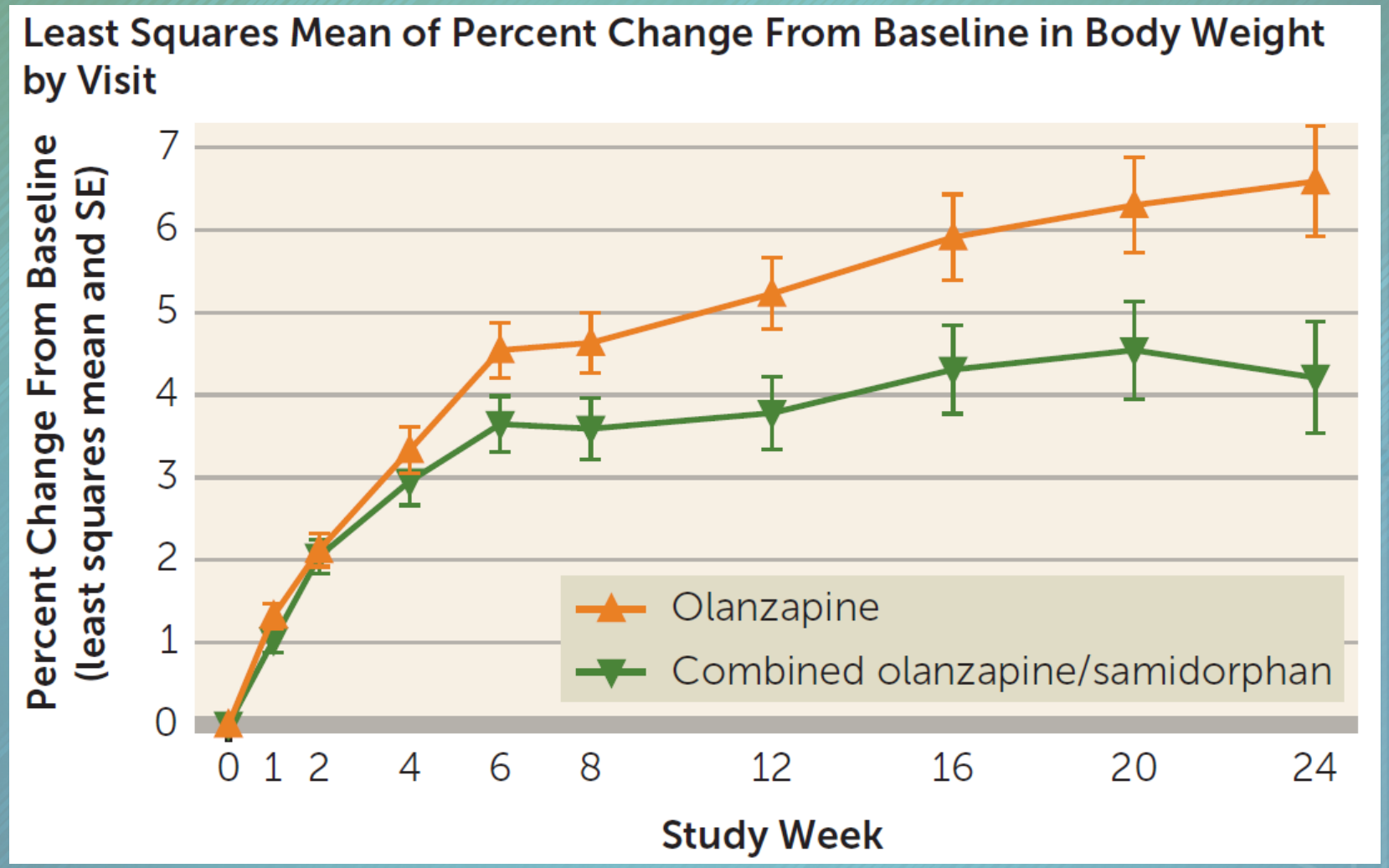
* $p < 0.05$ versus placebo

** $p < 0.01$ versus placebo

*** $p < 0.001$ versus placebo

Potkin SG et al. J Clin Psychiatry 2020;81(2):19m12769.

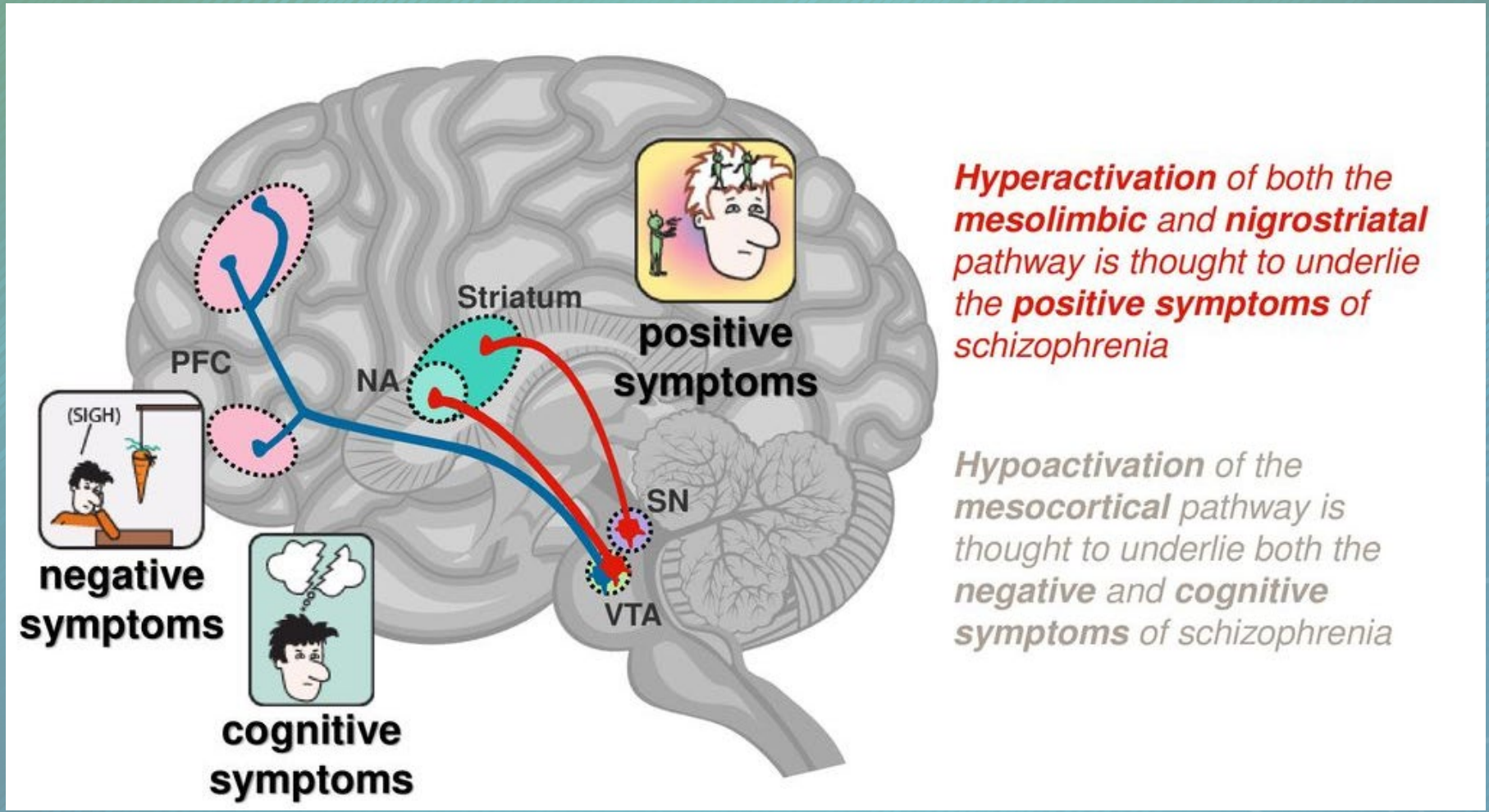
Olanzapine/Samidorphan: Phase III (ENLIGHTEN II) Weight Gain Results



Correll CU et al. Am J Psychiatry 2020;Epub ahead of print.

Advances in the Understanding of Schizophrenia: What's New With Dopamine?

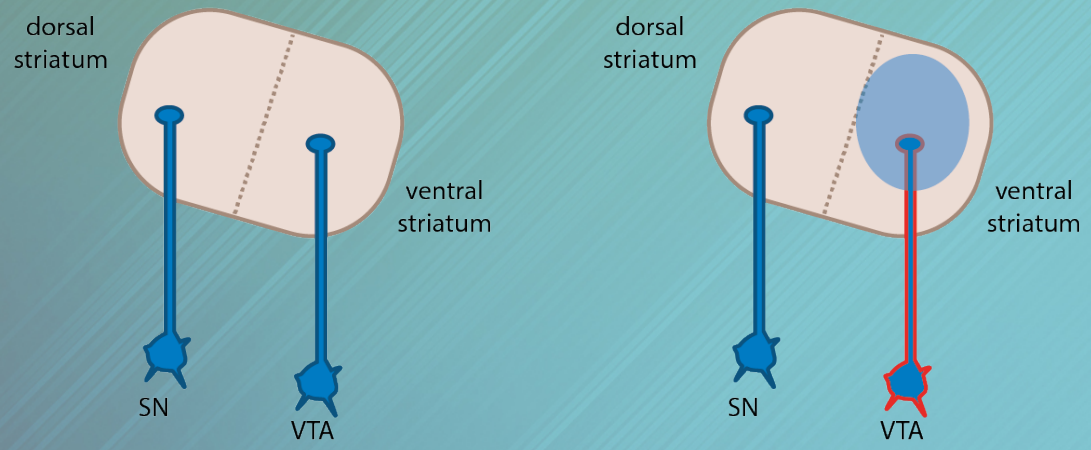
Dopamine Pathways Relevant to Schizophrenia Symptoms



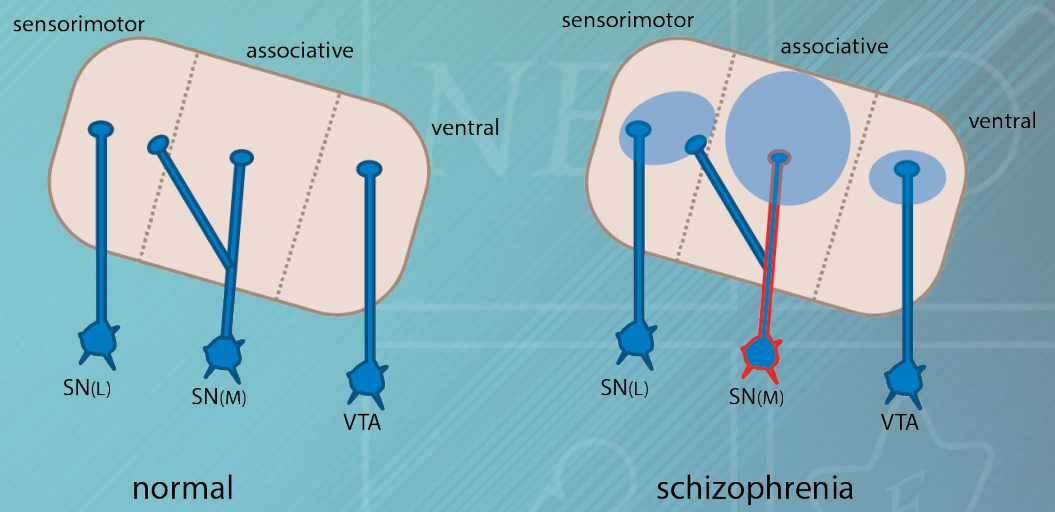
Stahl SM. Stahl's essential psychopharmacology, 4th ed. 2013;
Kegeles LS et al. Arch Gen Psychiatry 2010;67(3):231-9.

New Developments in the Dopamine Hypothesis of Positive Symptoms of Psychosis in Schizophrenia

Classic Mesolimbic Hyperdopaminergia



New Concept: Integrative Hub Mesostriatal Hyperdopaminergia

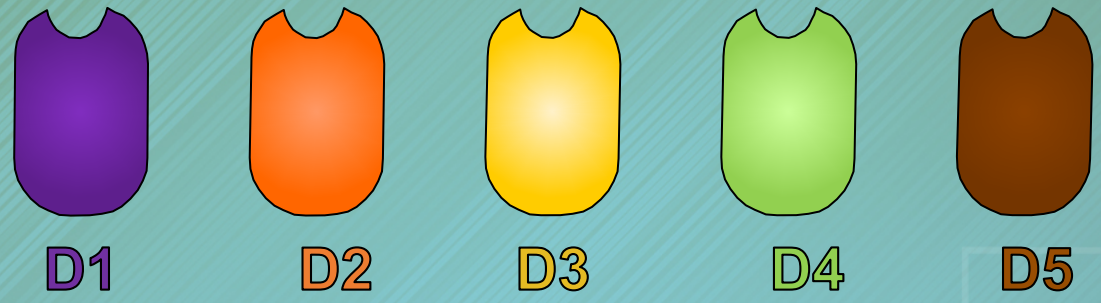


overactivation

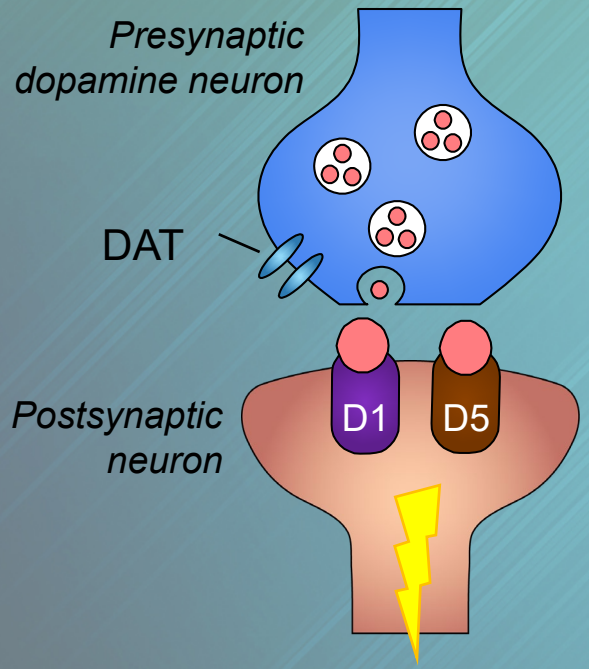
SN(L) substantia nigra lateral
SN(M) substantia nigra medial
VTA ventral tegmental area

Stahl SM. Stahl's essential psychopharmacology. 5th ed. In Preparation.

Postsynaptic Dopamine Receptor Signaling

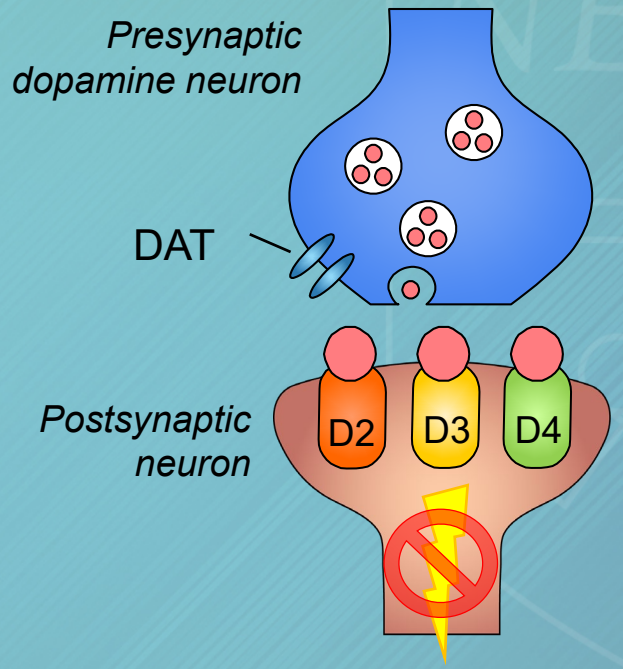


D1-Like Receptors



Believed to **stimulate** neurotransmitter release

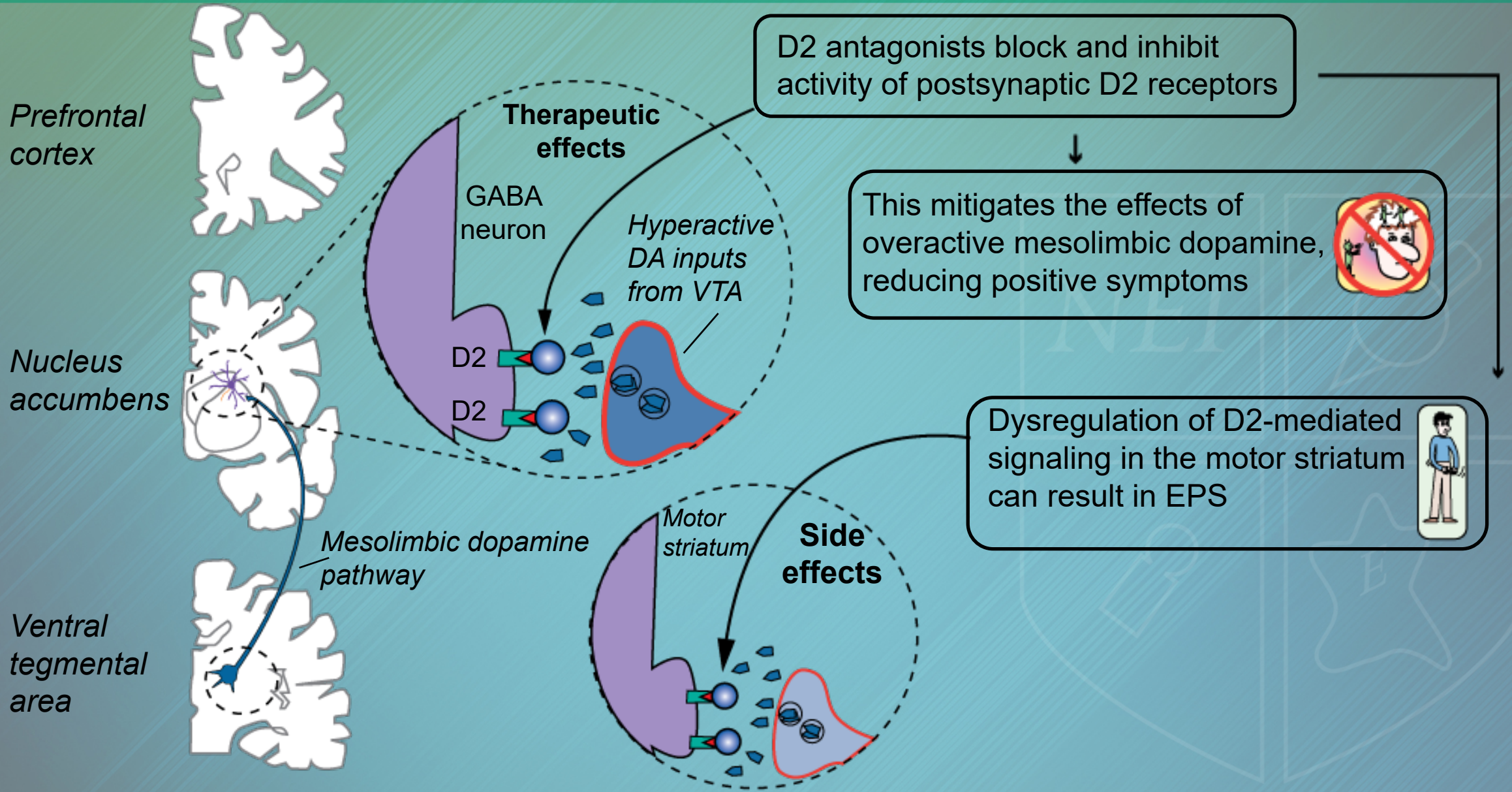
D2-Like Receptors



Believed to **inhibit** neurotransmitter release

Tritsch NX, Sabatini BL. Neuron 2012;76(1):33-50.

Antagonist/Partial Agonist Effects at D2 Dopamine Receptors

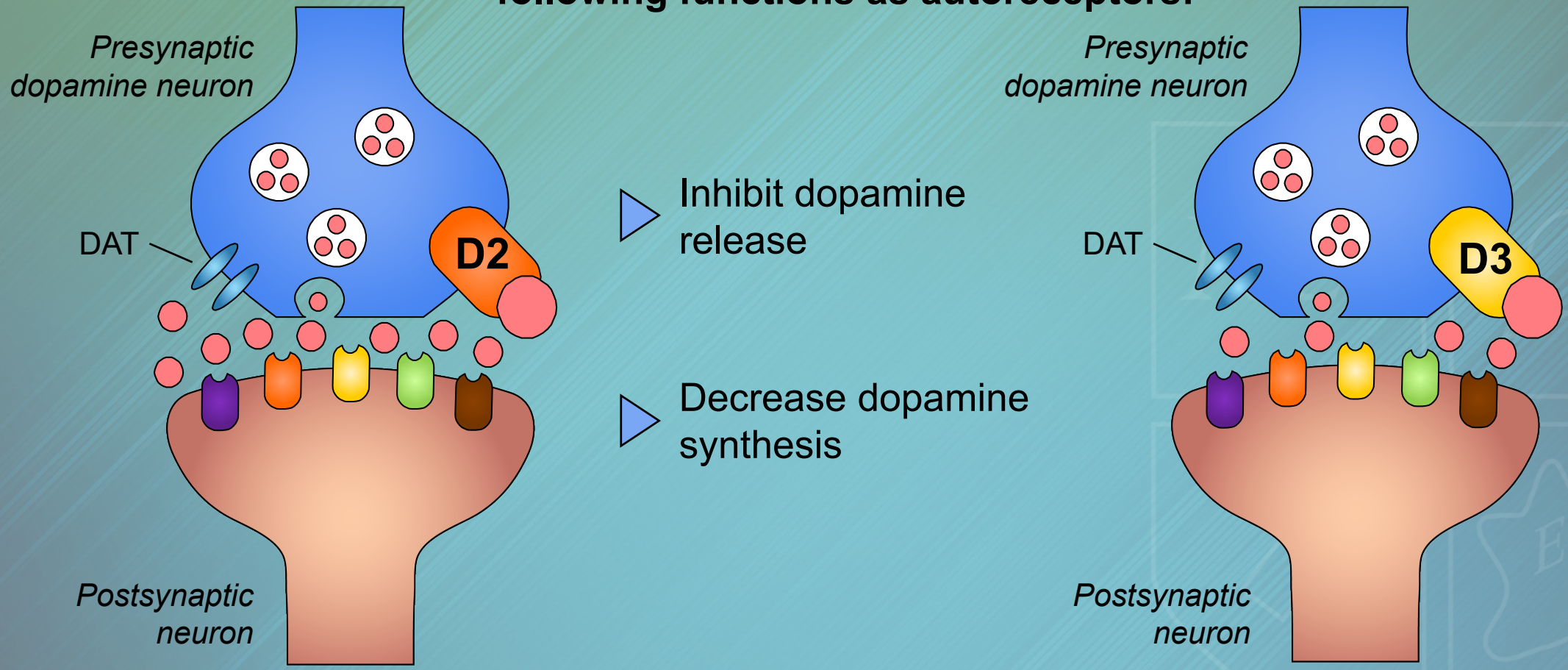


Stahl SM. CNS Spectr 2017;22(5):375-84.

Novel Dopaminergic Treatments: D2 Presynaptic Agonists and D3 Antagonists/Partial Agonists

Presynaptic Striatal Dopamine Receptor Signaling

D2 and D3 receptors are also theorized to sit presynaptically and provide the following functions as autoreceptors:

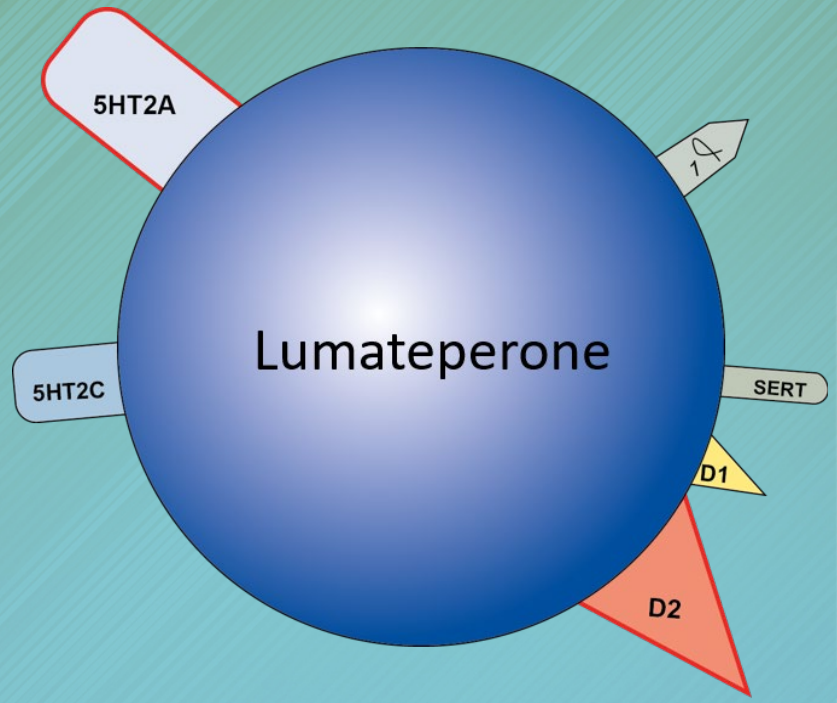


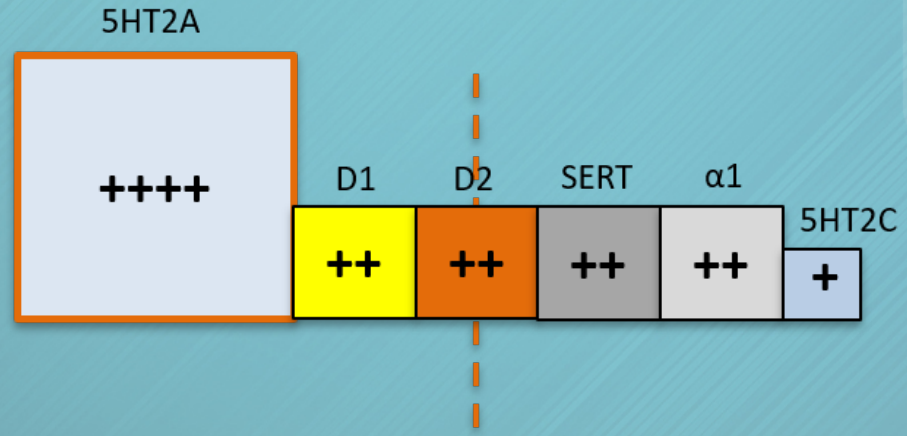
DAT: dopamine transporter

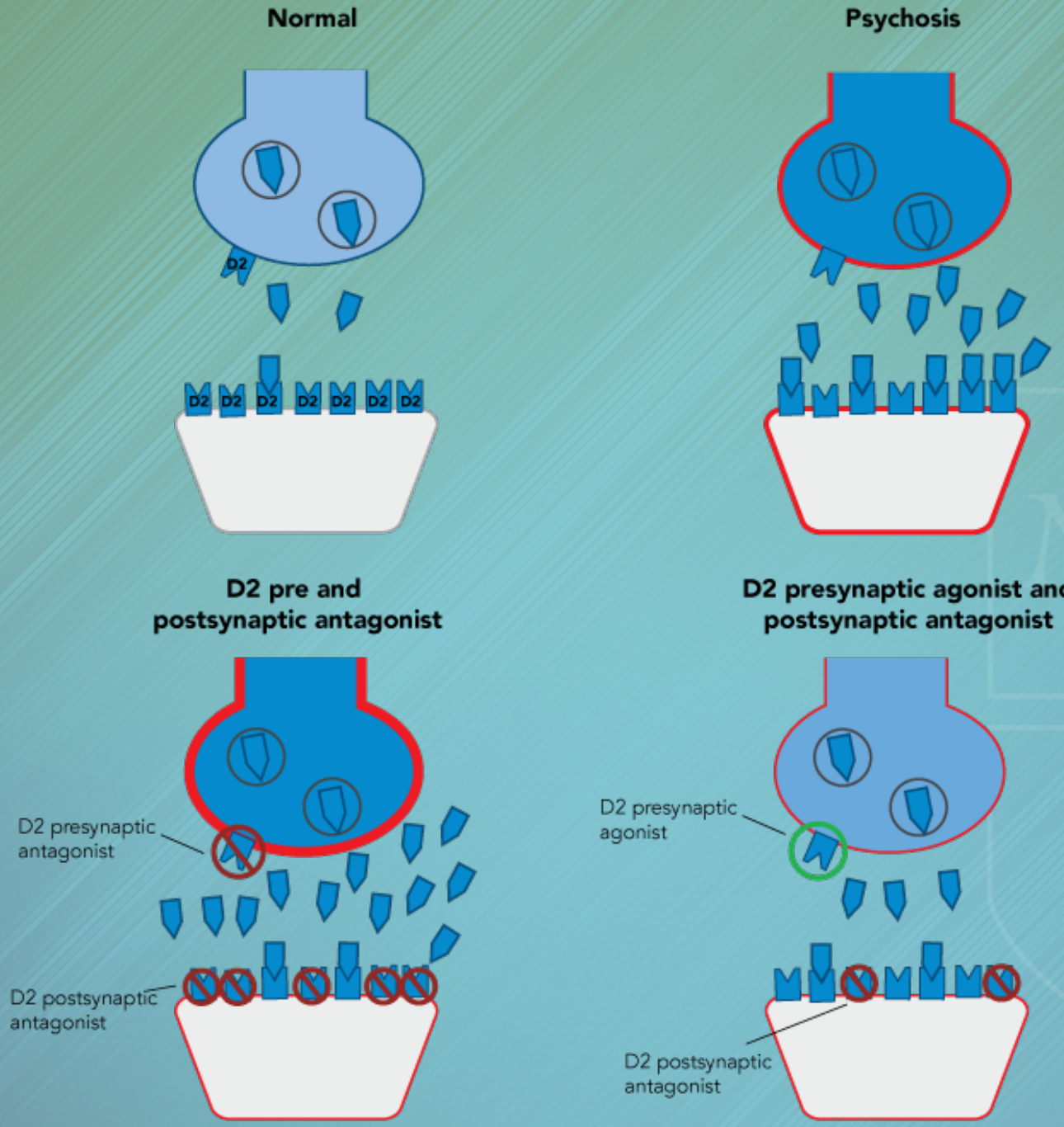
Gobert A et al. J Pharmacol Exp Ther 1995;275(2):899-913;
Dwoskin LP, Zahniser NR. J Pharmacol Exp Ther 1986;239(2):442-53.

Lumateperone

FDA-Approved
December 23, 2019






Normal
Psychosis
D2
D2 D2 D2 D2 D2 D2 D2
D2 pre and postsynaptic antagonist
D2 presynaptic agonist and postsynaptic antagonist
D2 presynaptic antagonist
D2 postsynaptic antagonist
D2 presynaptic agonist
D2 postsynaptic antagonist

D2 Occupancy of Lumateperone and Other Antipsychotics

Drug	Dose Range	Mean D2 Receptor Occupancy in Caudate and Putamen [a]
Lumateperone	60 mg/day	~40%
Clozapine	75-90 mg/day	48-61%
Quetiapine	150-750 mg/day	30-62%
Ziprasidone	40-160 mg/day	56 to >59%
Risperidone	4 mg/day	72-81%
Olanzapine	5-60 mg/day	61-80%
Lurasidone	40-80 mg	>65%
Cariprazine	1.5-3 mg/day	69 to >99%
Aripiprazole	10-30 mg	88-90%

[a] Measured by displacement of [^{11}C]-raclopride

Vanover KE et al. Neuropsychopharmacology 2019;44(3):598-605.

Lumateperone: Placebo-Controlled Clinical Trials

Randomized Controlled Trial	Sample Size	Design	Primary Endpoint Results
005	N=335	60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone, or placebo for 4 weeks	60 mg dose: significant improvement over placebo at Day 28 on PANSS total score; no significant difference in PANSS total score between ITI-007 and risperidone groups
301	N=450	60 mg ITI-007, 40 mg ITI-007, or placebo for 4 weeks	40 + 60 mg dose: significant improvement over placebo at Day 28 on PANSS total score
302	N=696	60 mg ITI-007, 20 mg ITI-007, 4 mg risperidone, or placebo for 6 weeks	Neither dose of ITI-007 separated from placebo at Day 28 on PANSS total score [a]

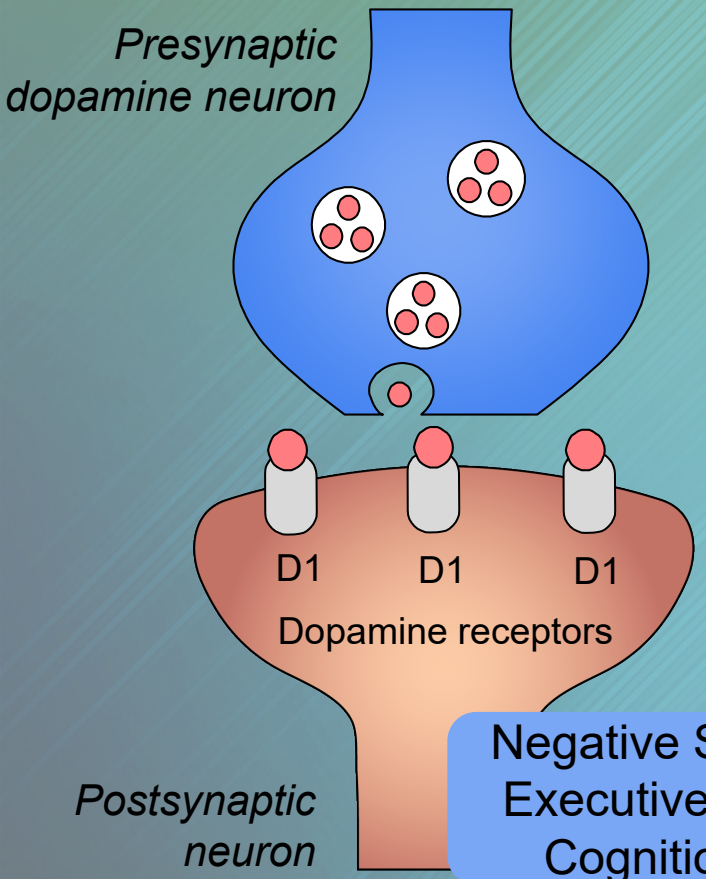
[a] High placebo response in Study 302. ITI-007: lumateperone; PANSS: Positive and Negative Syndrome Scale.

Lumateperone has a favorable safety profile; the most common adverse effects (≥5%) are somnolence, sedation, fatigue, and constipation

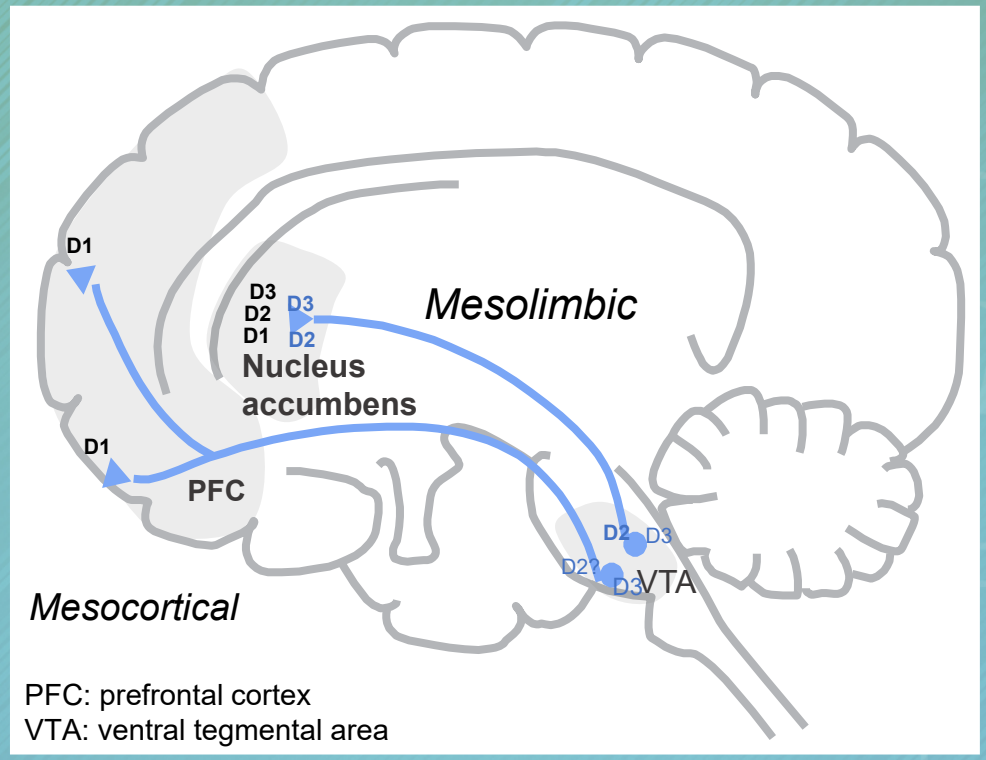
Vanover K et al. CNS Spectr 2019;24(1):190-1;
Lieberman JA et al. Biol Psychiatry 2016;79(12):952-61;
Correll CU et al. JAMA Psychiatry 2020;77(4):349-58.

Different Dopamine Pathways Are Hypothesized to Modulate Different Aspects of Behavior

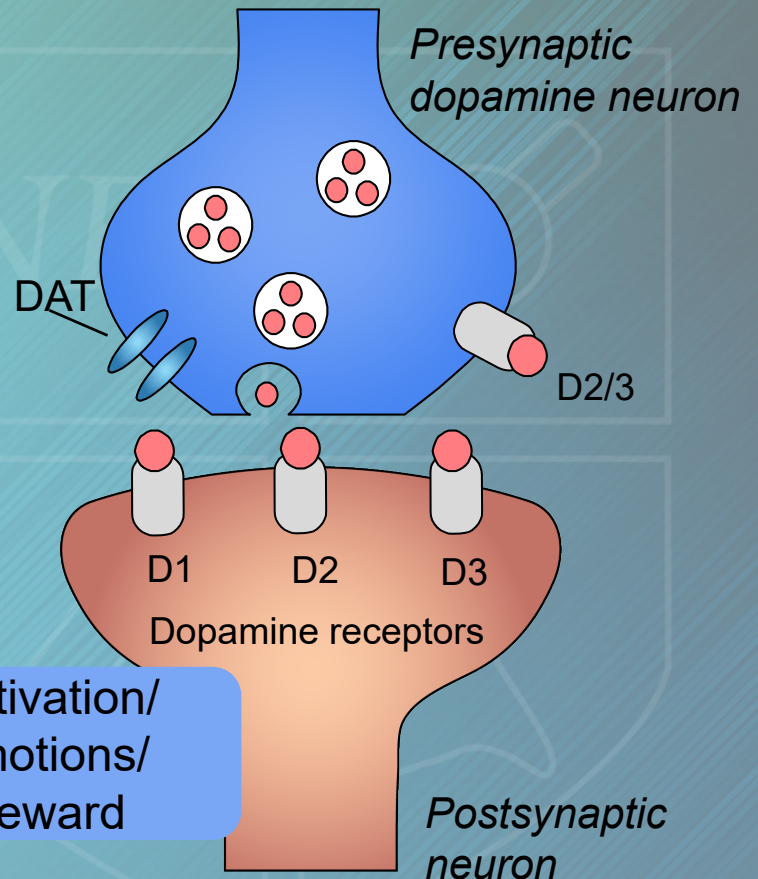
Mesocortical Dopamine



Negative Symptoms/ Executive Function/ Cognition/Mood



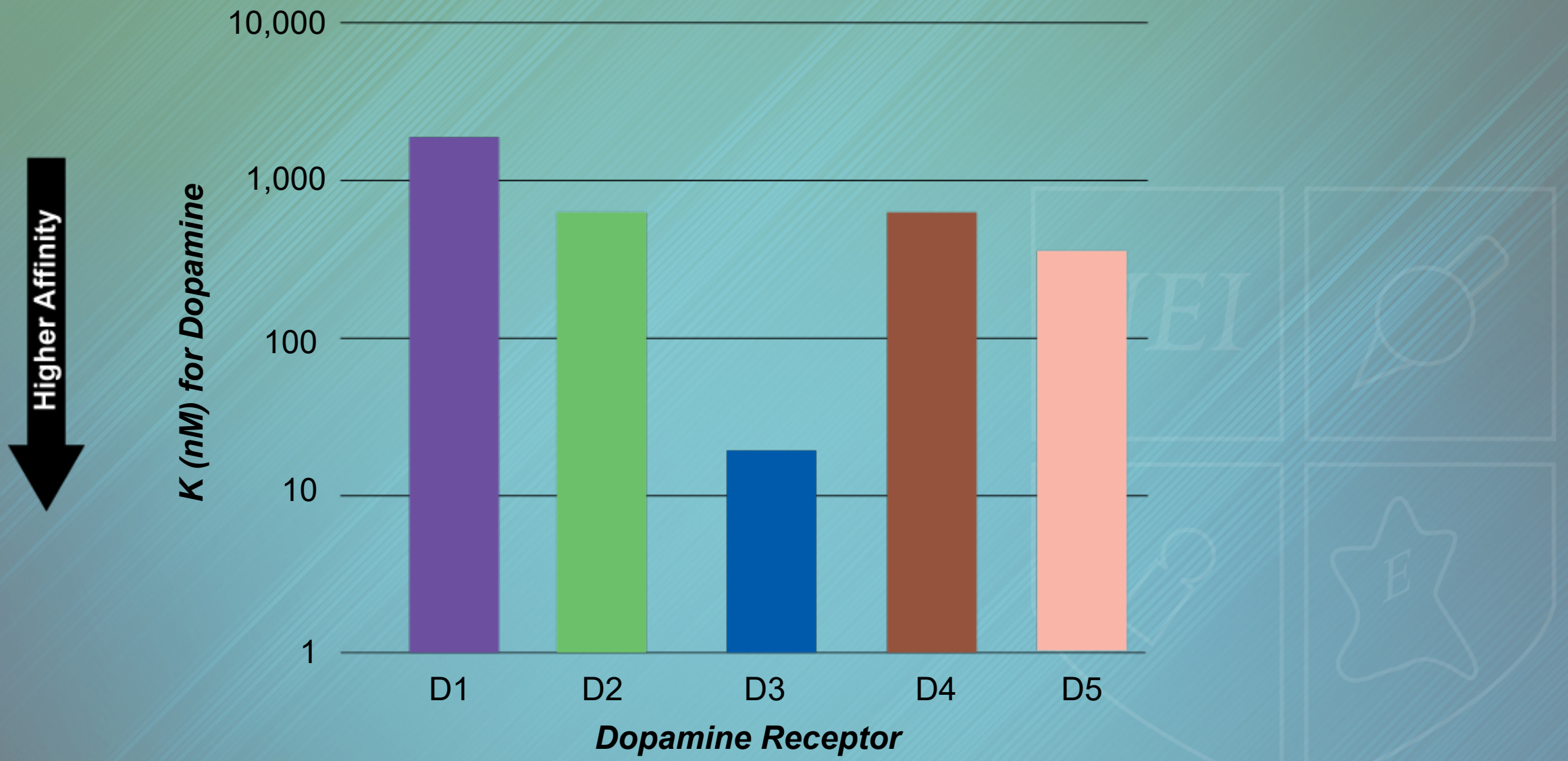
Mesolimbic Dopamine



Motivation/ Emotions/ Reward

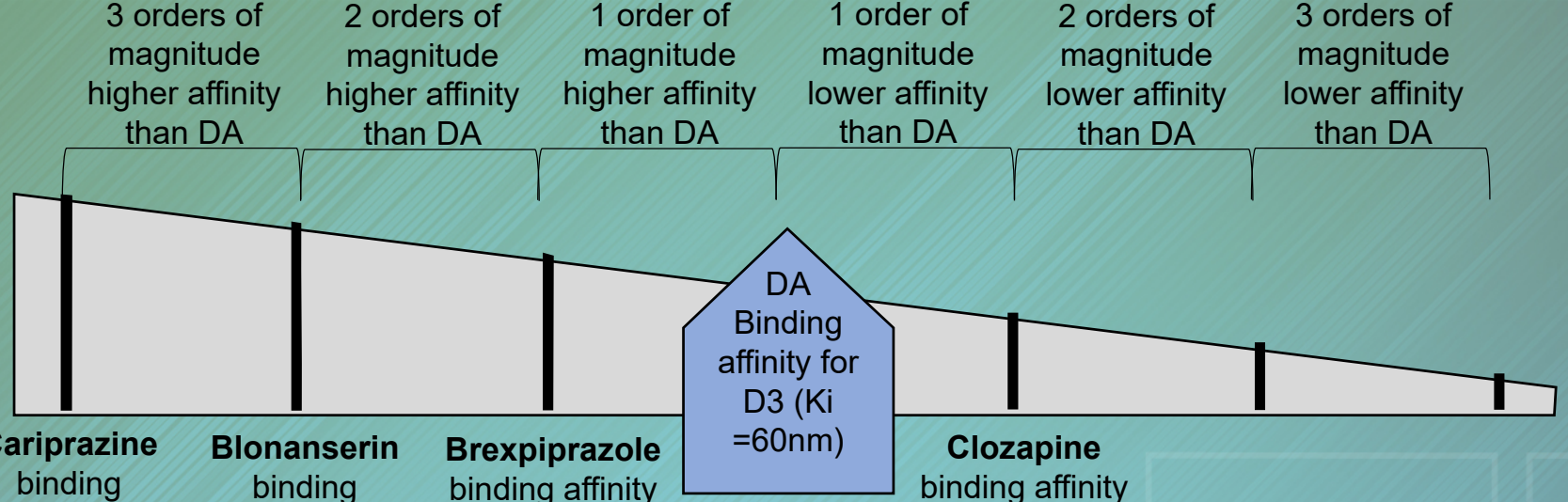
Der-Avakian A, Markou A. Trends Neurosci 2012;35(1):68-77; Carr DB, Sesack SR. J Neurosci 2000;20(10):3864-73; Stahl SM. Stahl's essential psychopharmacology, 4th ed. 2013; Stahl SM. CNS Spectr 2017;22(4):305-11.

Dopamine Receptor Affinities



Stahl SM. CNS Spectr 2017;22(4):305-11.

Antipsychotic D3 Affinities versus Dopamine (DA) D3 affinity



Cariprazine binding affinity for D3 (0.09nM)

Blonanserin binding affinity for D3 (0.49nM)

Brexpiprazole binding affinity for D3 (1.1nM)

Asenapine binding affinity for D3 (1.8nM)

Paliperidone binding affinity for D3 (2.6nM)

Aripiprazole binding affinity for D3 (4.6nM)

Risperidone binding affinity for D3 (7.3nM)

Ziprasidone binding affinity for D3 (7.3nM)

Iloperidone binding affinity for D3 (10.5nM)

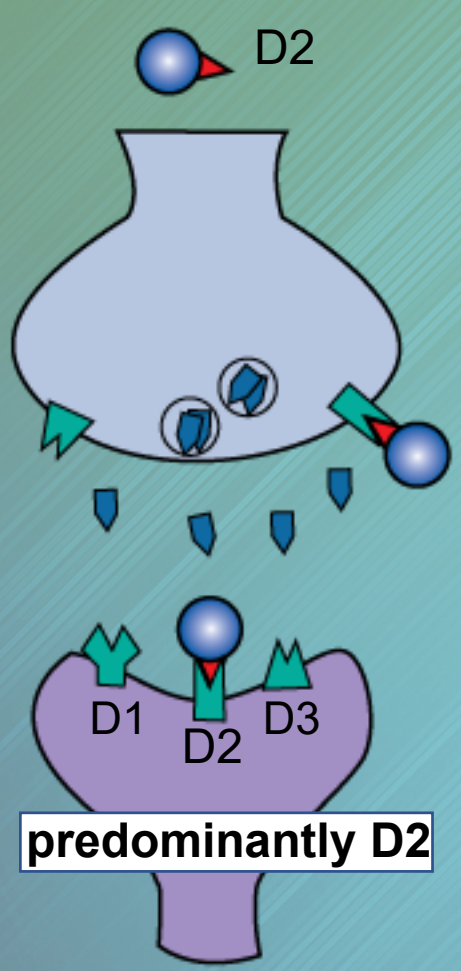
Lurasidone binding affinity for D3 (15.7nM)

Olanzapine binding affinity for D3 (38.1nM)

Clozapine binding affinity for D3 (310nM)

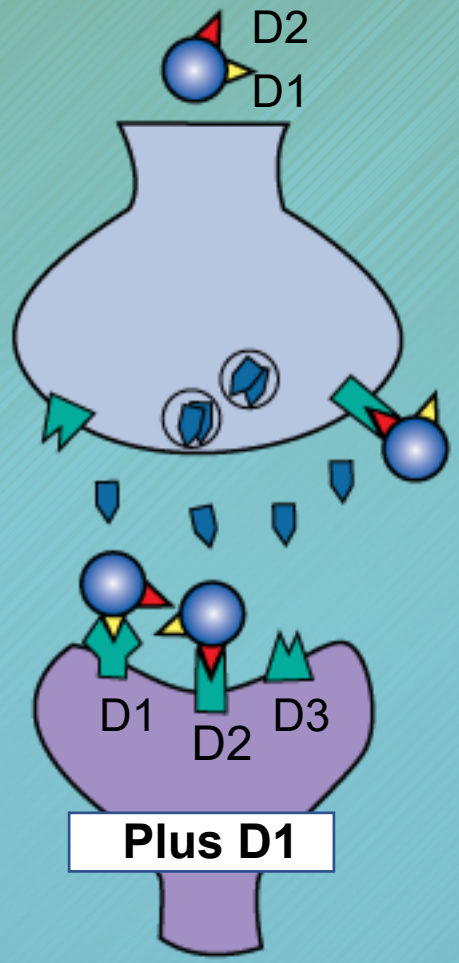
Quetiapine binding affinity for D3 (394nM)

Antipsychotic Binding at Dopamine Receptors



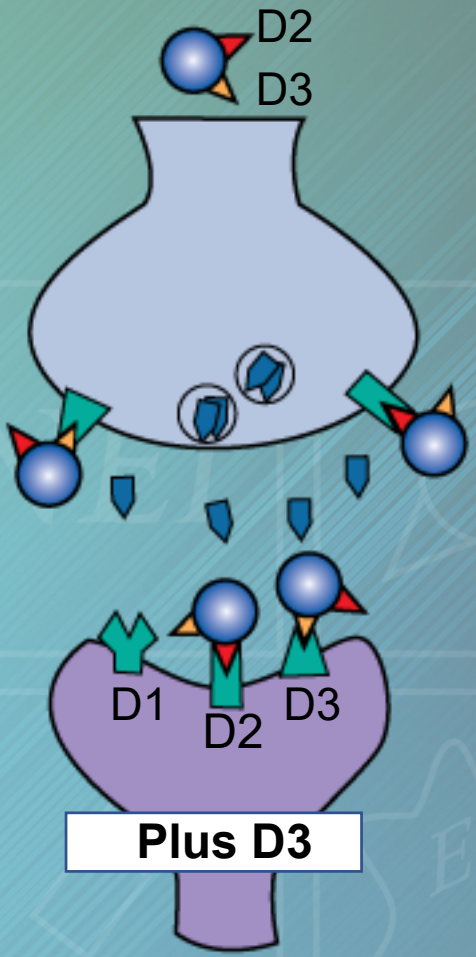
predominantly D2

brexpiprazole
paliperidone
aripiprazole
risperidone
ziprasidone
iloperidone
lurasidone
quetiapine



Plus D1

asenapine
olanzapine
clozapine

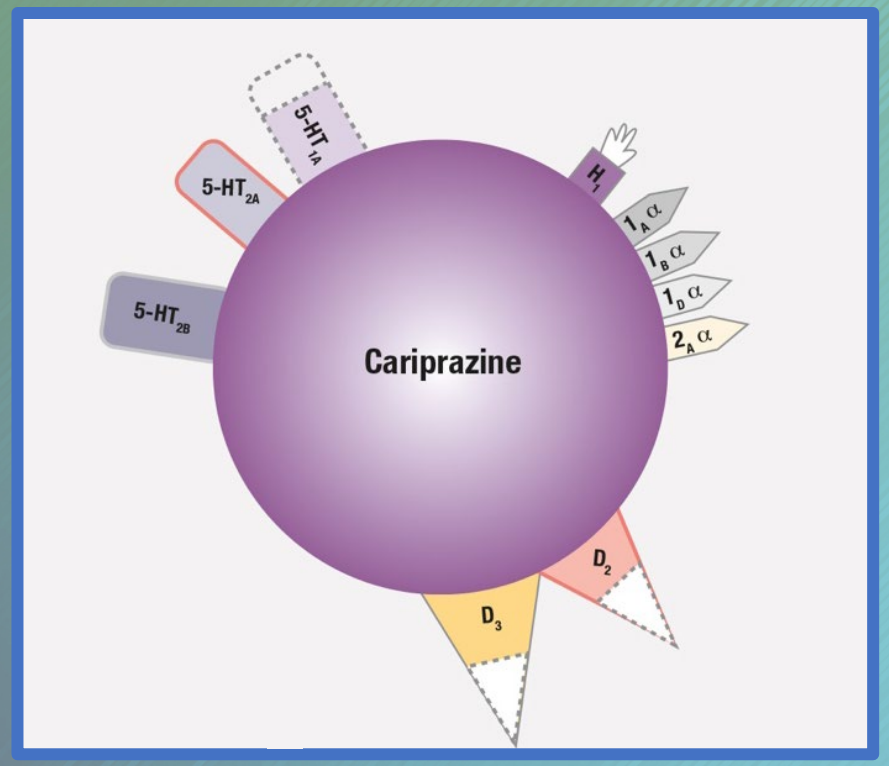


Plus D3

cariprazine
blonanserin

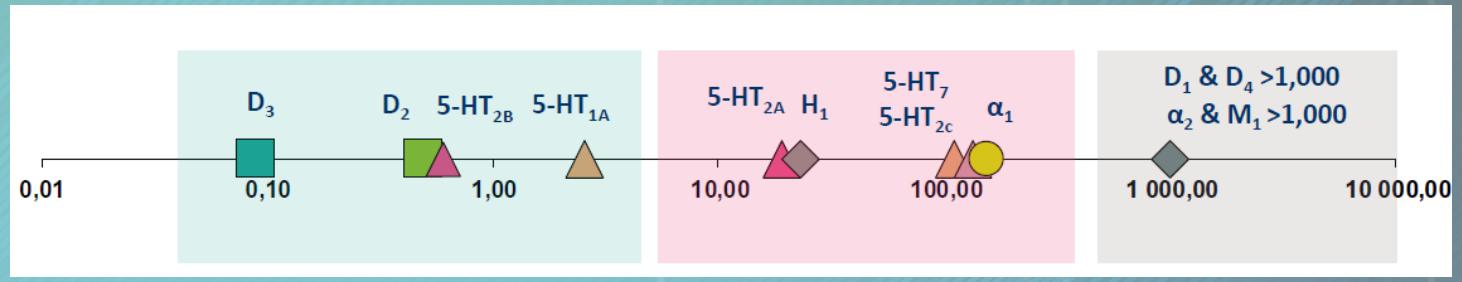
Stahl SM. CNS Spectr 2017;22(5):375-84.

Cariprazine Receptor Profile and Receptor Affinities



Cariprazine is a dopamine D3 and D2 receptor partial agonist with preferential binding to D3 receptors

Cariprazine differs from all available antipsychotics due to its greater affinity for D3 receptors *in vivo*



High affinity
Dopamine D3 partial agonist
Dopamine D2 partial agonist
Serotonin 5HT2B antagonist
Serotonin 5HT1A partial agonist

Moderate affinity
Serotonin 5HT2A antagonist
Histamine H1 antagonist
Serotonin 5HT2C antagonist
Adrenergic α1 antagonist

Low or no affinity
Dopamine D1 & D4 antagonist
Adrenergic α2 antagonist
Muscarinic M1 antagonist

Image adapted from Stahl SM. CNS Spectr 2016;21(2):123-7;
Kiss B et al. J Pharmacol Exp Ther 2010;333(1):328-40.

Efficacy and Safety of F17464, a Preferential D3 Antagonist

PANSS: Positive and Negative Syndrome Scale

Most common adverse events were insomnia, agitation, and increased triglycerides

No weight gain or extrapyramidal disorder except rare akathisia

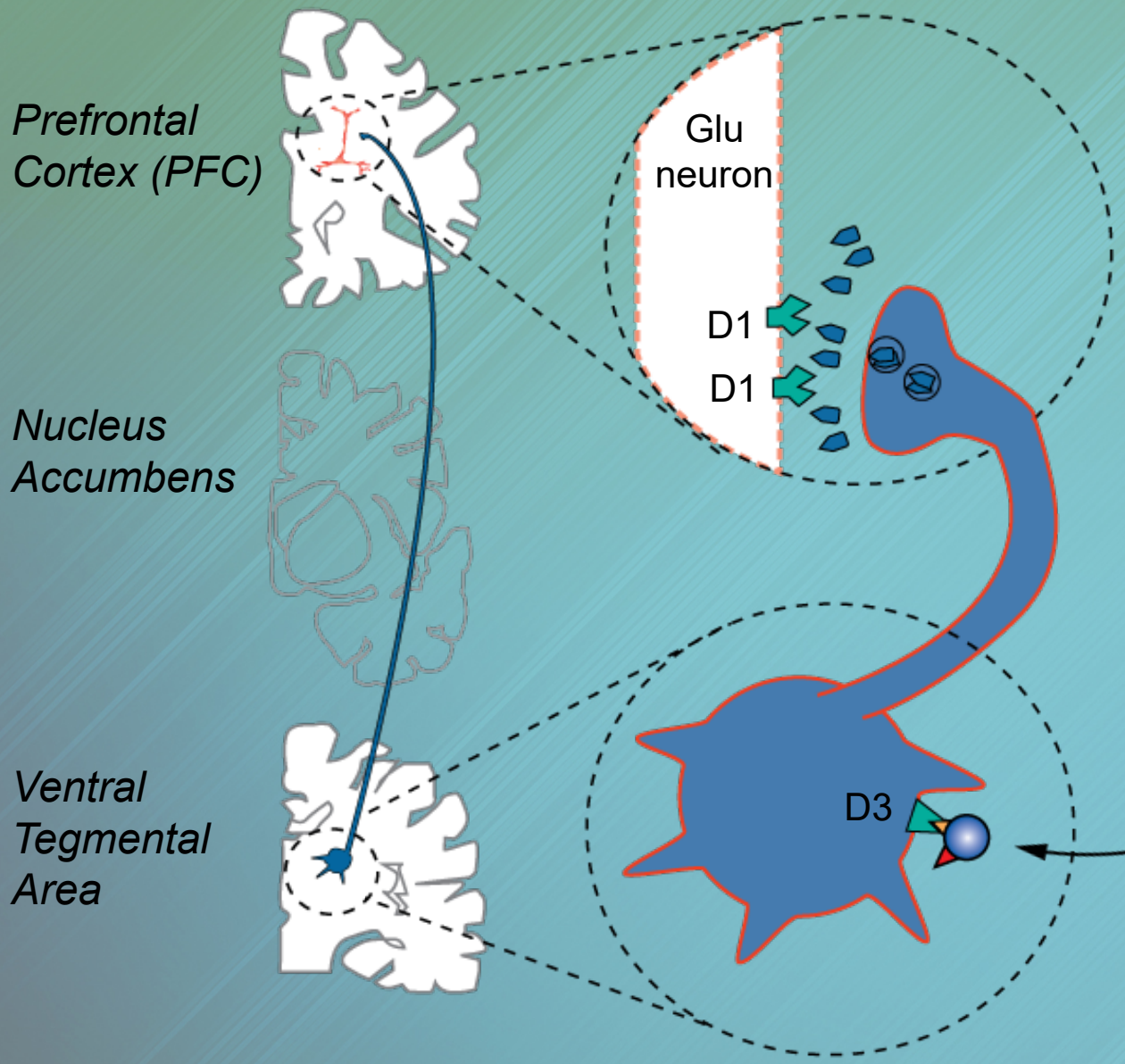
Results from a phase II, randomized, double-blind study examining the efficacy of F17464 (20 mg twice daily) versus placebo treatment for 6 weeks in adult patients with acute exacerbation of schizophrenia.

Bitter I et al. Neuropsychopharmacology 2019;44(11):1917-24.

Conclusions

- Almost all antipsychotics have about the same affinity for D3 receptors as dopamine, resulting in little net D3 blockade in the presence of dopamine and at antipsychotic doses
- However, two antipsychotics have even higher affinity for D3 receptors than dopamine does, and would theoretically result in net blockade of D3 receptors at clinical doses and in the presence of dopamine
  - cariprazine > blonanserin

Antagonist/Partial Agonist Effects at D3 Dopamine Receptors



Increased DA release in the PFC re-regulates aberrant cortical activity and could theoretically improve negative symptoms and cognitive impairment

↑

This results in an increase in DA release in the PFC

↑

D3 antagonists/partial agonists block and inhibit the activity of somatodendritic D3 receptors

Stahl SM. CNS Spectr 2017;22(5):375-84.

SUMMARY:

How could a drug for schizophrenia simultaneously block too much dopamine in the mesolimbic pathway and enhance too little dopamine in the mesocortical pathway?

Simultaneous blockade of D2 and D3 receptors could hypothetically result in net blockade of D2 receptors in mesolimbic pathway and net stimulation of D1 receptors in mesocortical pathway

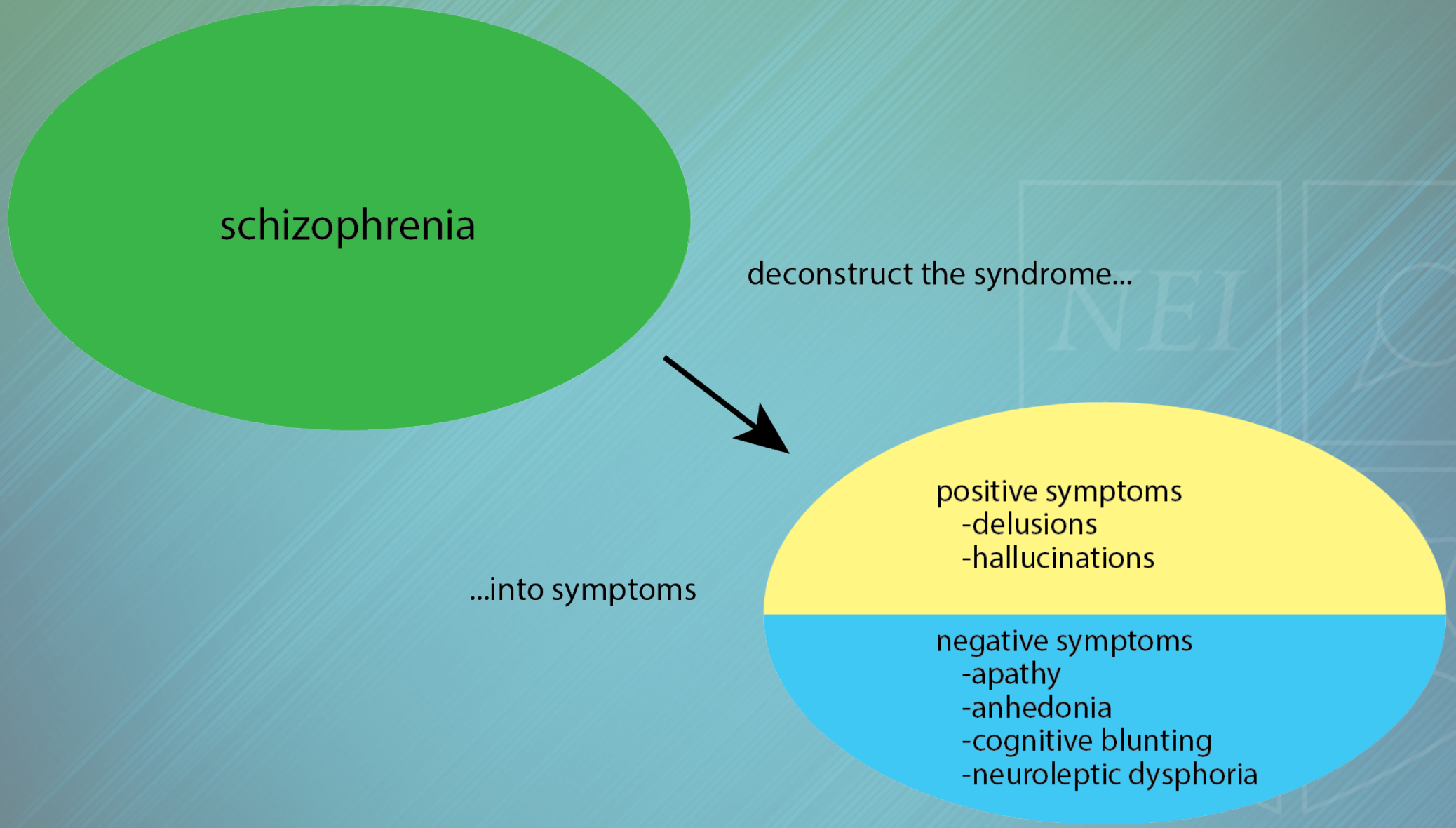
Neurotransmitter Systems Linked to Psychosis

Dopamine Theory
Hyperactive dopamine at D2 receptors in the mesolimbic pathway

Glutamate Theory
N-Methyl-D-Aspertate (NMDA) receptor hypofunction

Serotonin Theory
5HT2A receptor hyperfunction in the cortex

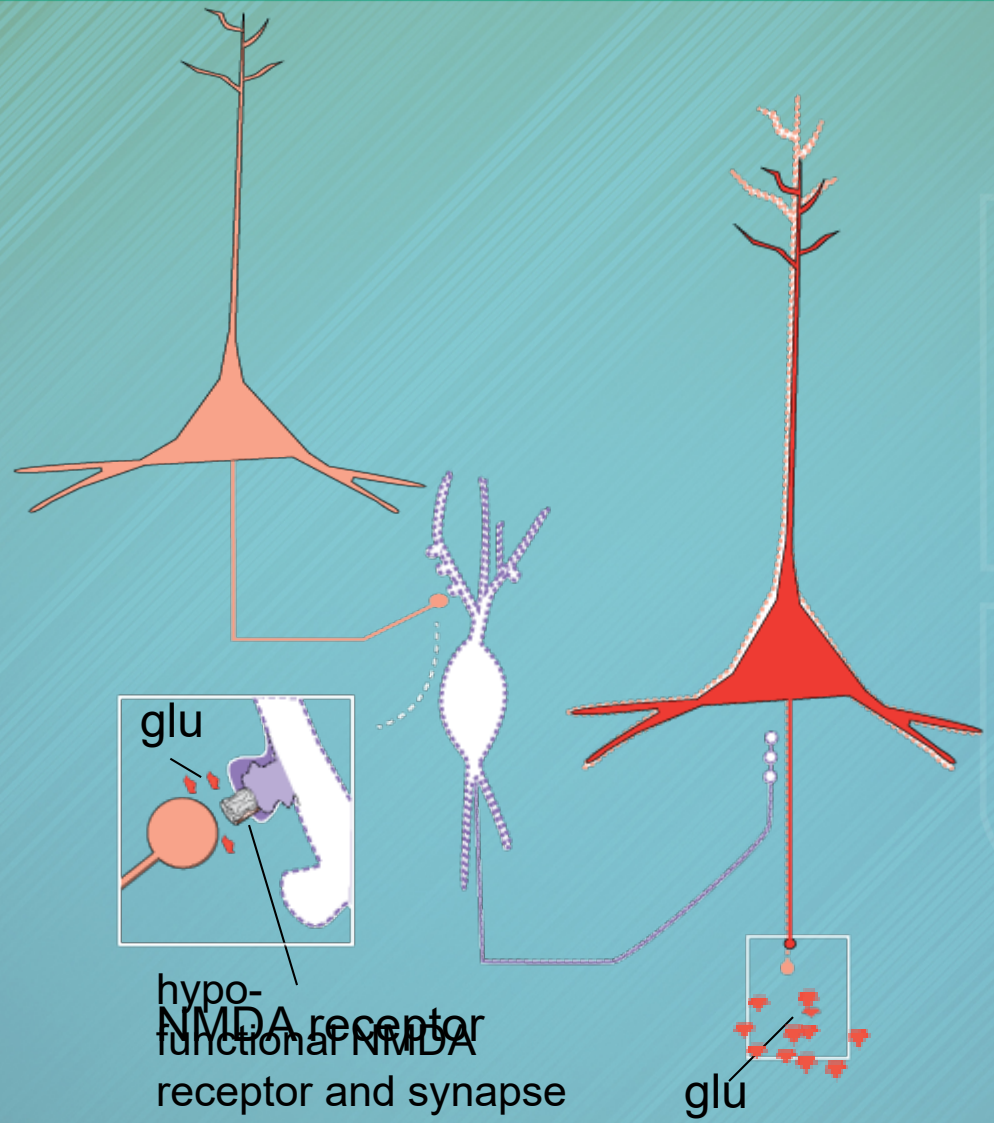
Schizophrenia: The Phenotype



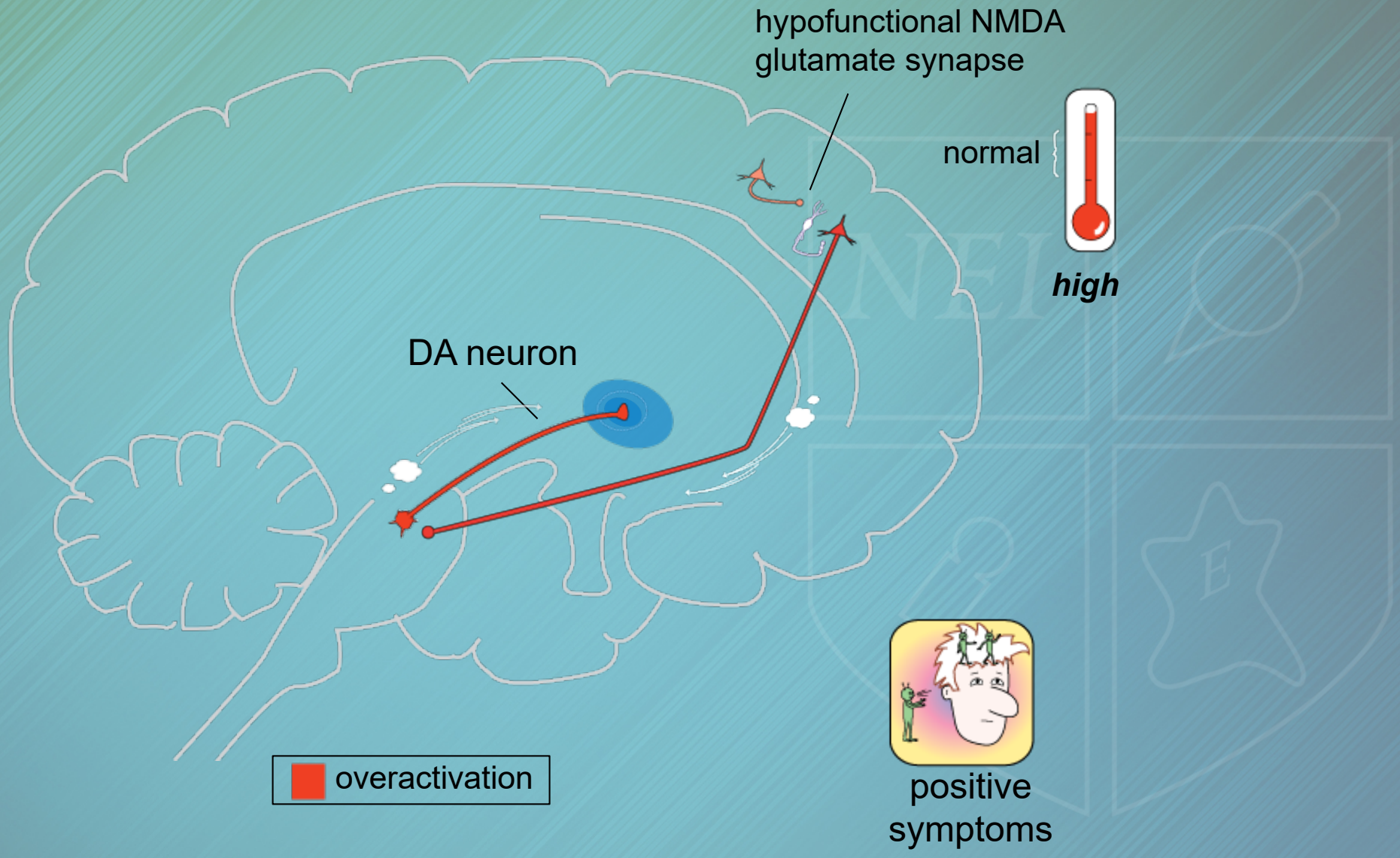
Glutamate and Schizophrenia

- NMDA hypofunction hypothesis of schizophrenia
- Neurodevelopmentally abnormal glutamate synapses
- Hypofunctional NMDA receptors
- Overstimulation of downstream glutamate receptors

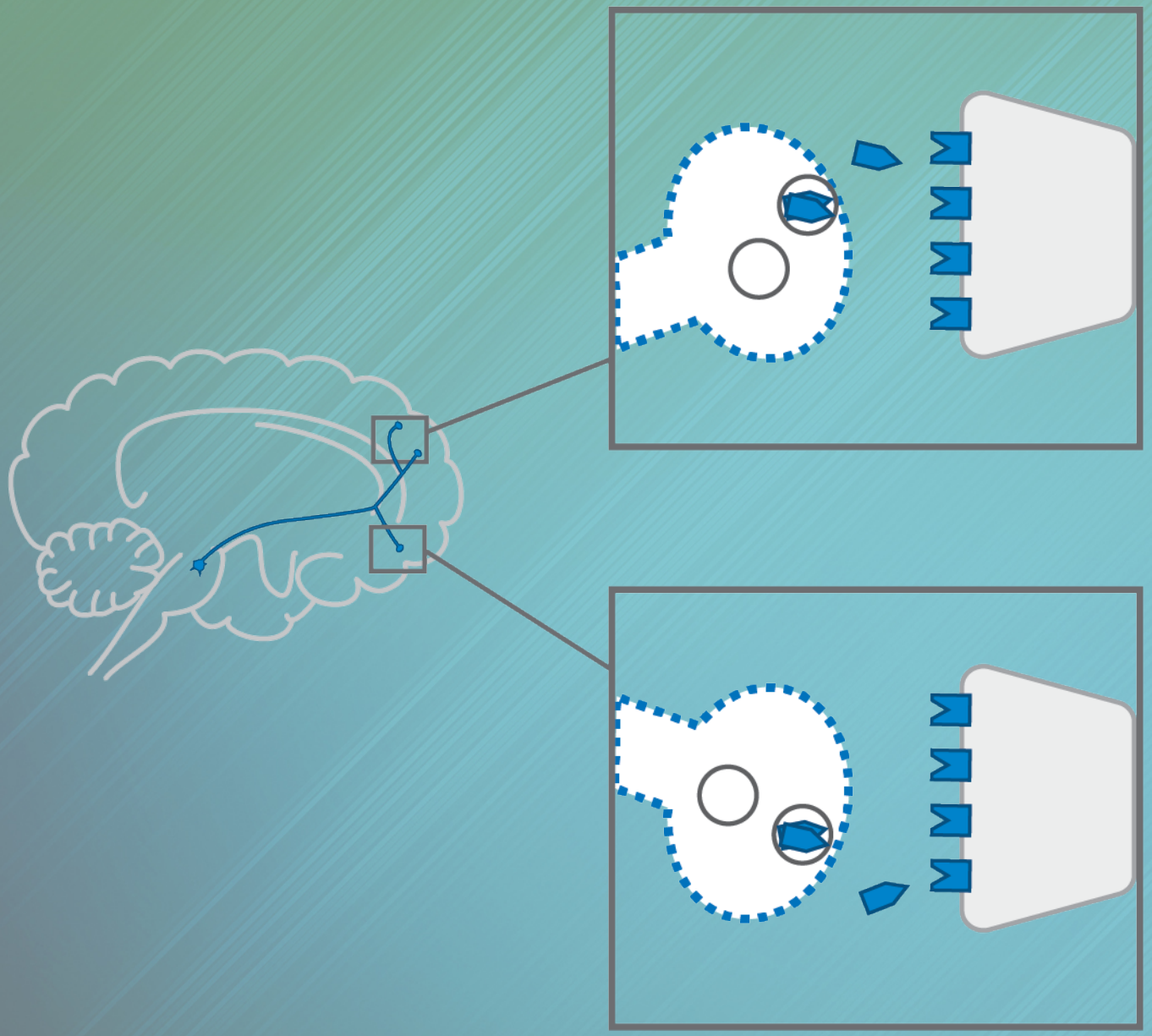
NMDA Hypoactivity Yields Glutamate Hyperactivity Downstream



NMDA Glutamate Hypoactivity Leads to Mesolimbic Dopamine Hyperactivity Downstream in Psychosis



Mesocortical Dopamine: Negative Symptoms

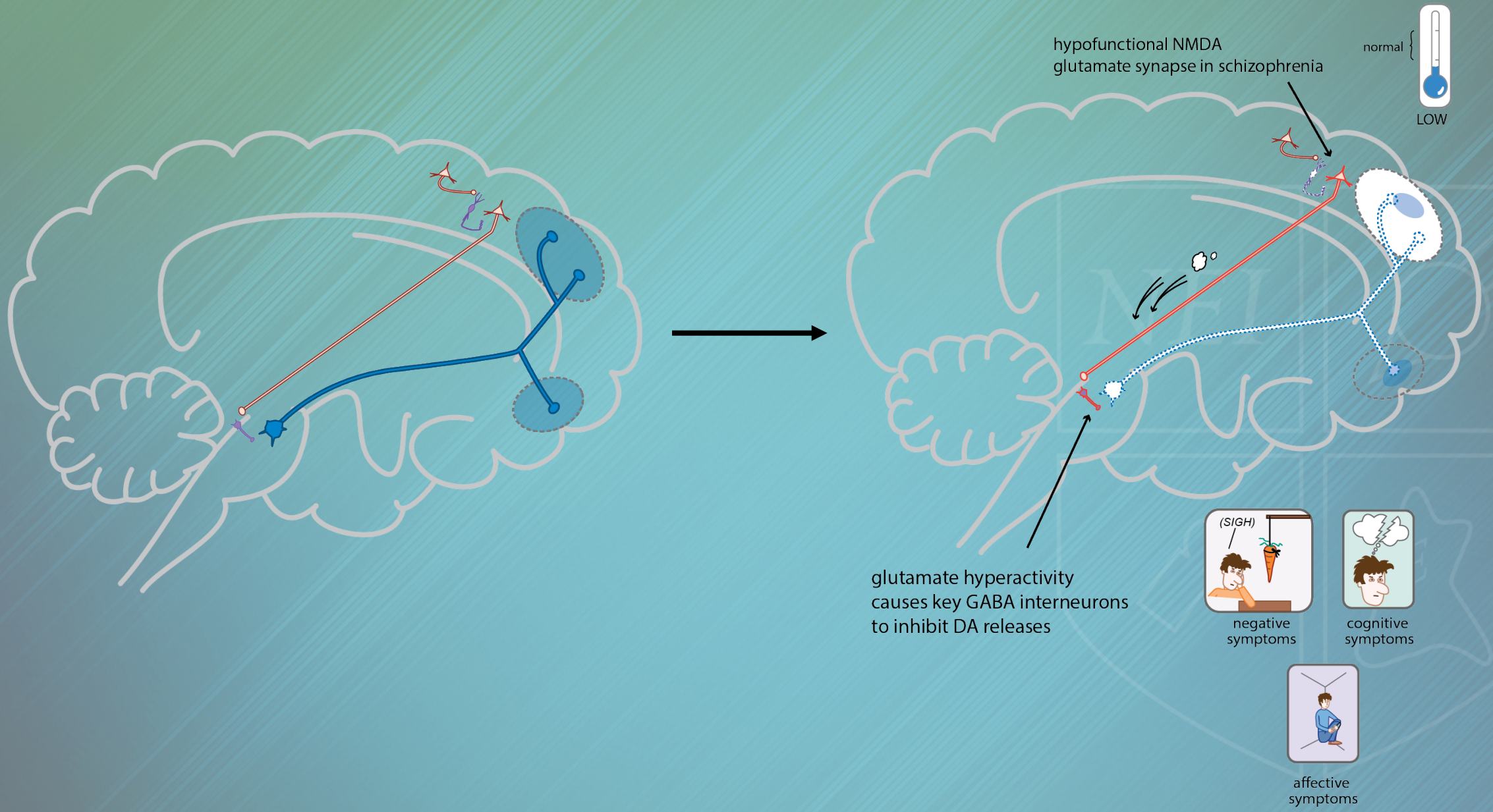


cognitive symptoms

negative symptoms

affective symptoms

NMDA Receptor Hypofunction: Negative Symptoms



Treatment of Negative Symptoms: Glutamatergic Strategies

Topiramate

- Multiple meta-analyses show efficacy

Metabotropic glutamate receptor (mGluR) 2/3 agonists

- Disappointing results

Lamotrigine, memantine, amantadine, NMDA agonists

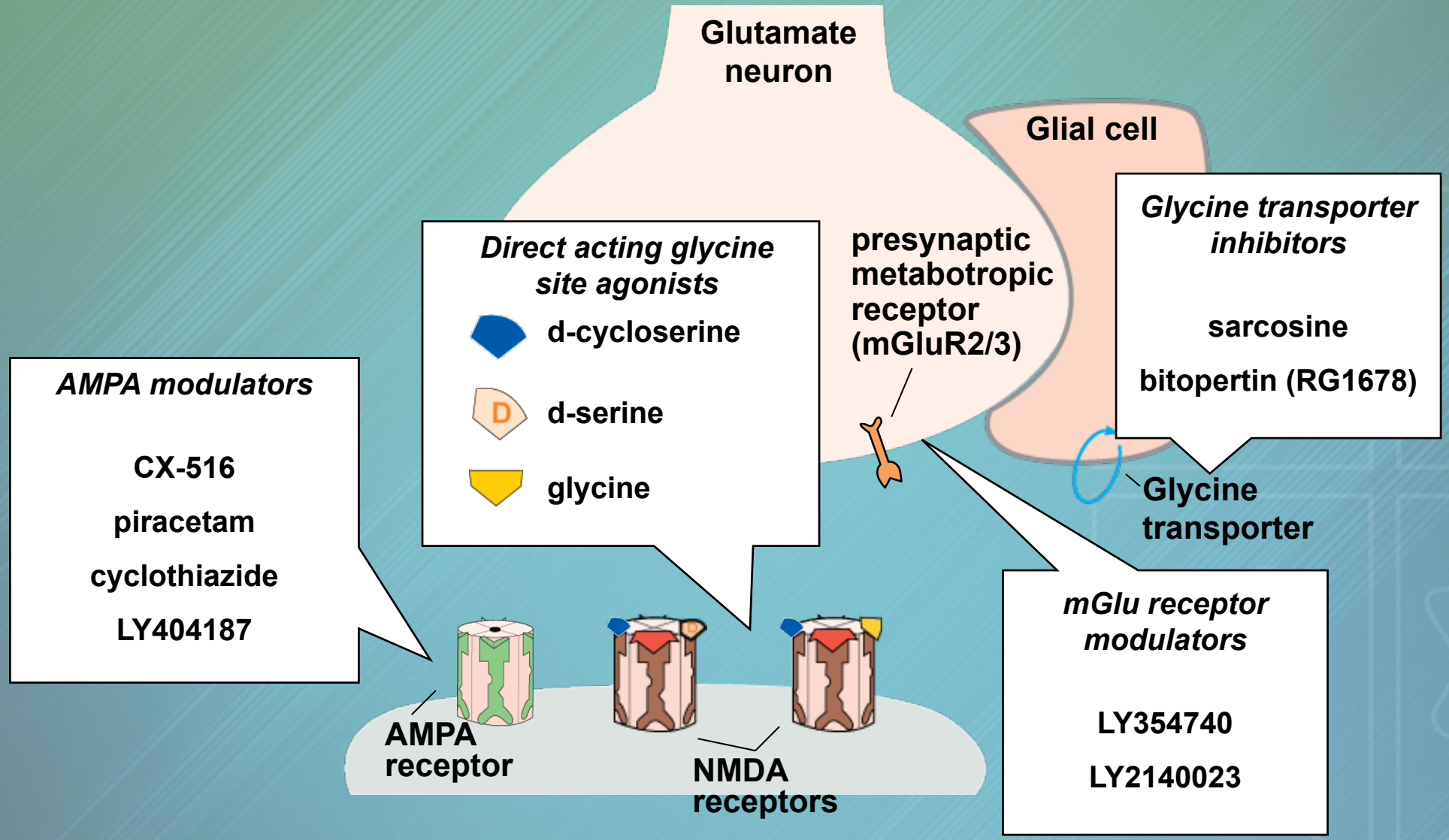
- Inconsistent or disappointing results

mGluR positive allosteric modulators

Efficacious in animal studies; currently phase II

Veerman SRT et al. Drugs 2017;77(13):1423-59.

Novel Treatment Mechanisms: Glutamate

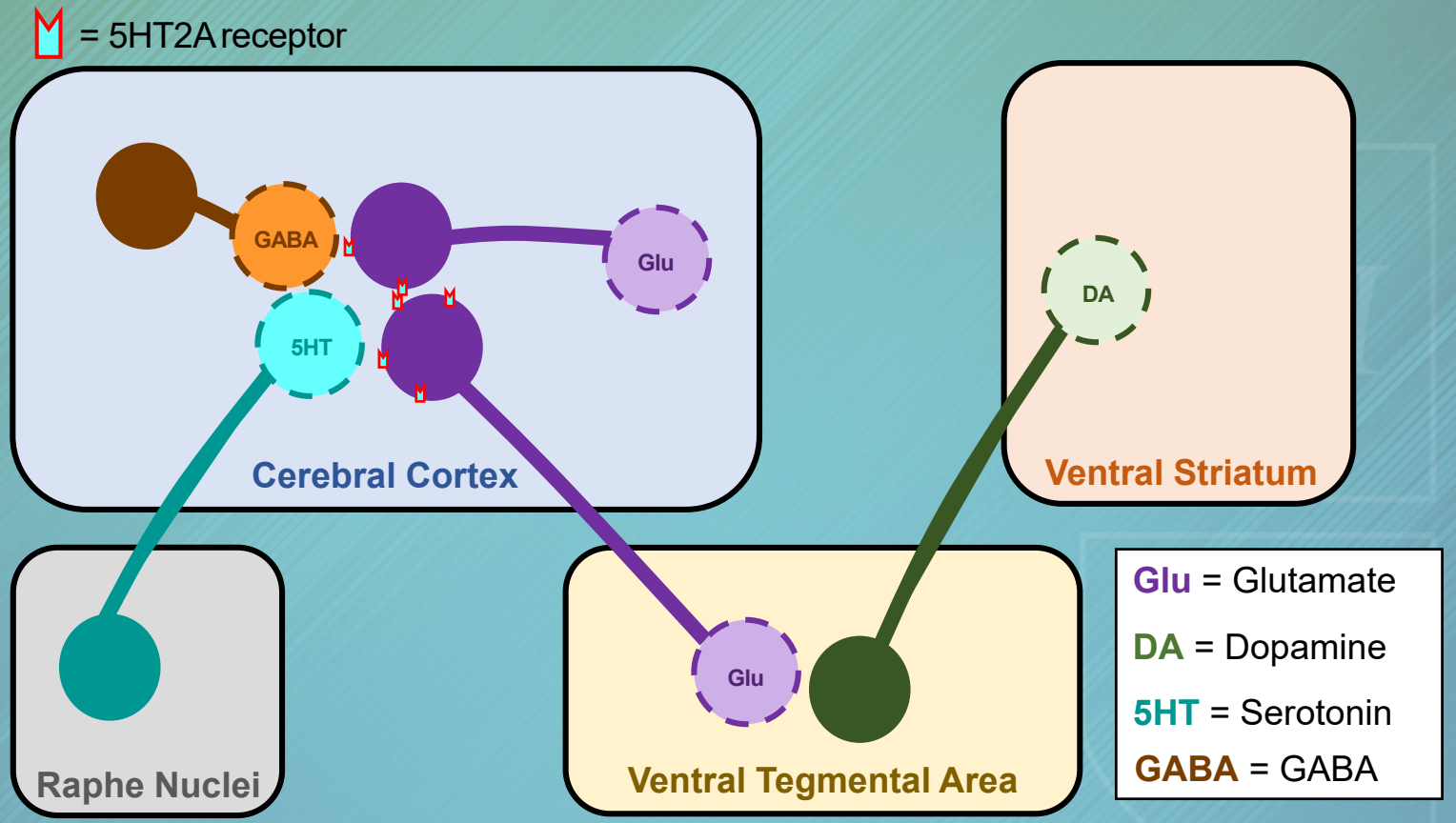


TAK-831—A D-amino Acid Oxidase (DAAO) Inhibitor

- D-serine is an endogenous ligand for the glycine modulatory binding site on the NR1 subunit of NMDA receptors
- Since D-serine is degraded by the flavoenzyme DAAO, DAAO inhibitors may improve NMDA functioning and negative symptoms in schizophrenia
- Phase II testing for the treatment of negative symptoms in schizophrenia is ongoing (NCT03382639)
  - 12-week, placebo-controlled trial of three doses (50, 125, and 500 mg/day)
  - **Primary outcome**: PANSS negative symptoms factor score

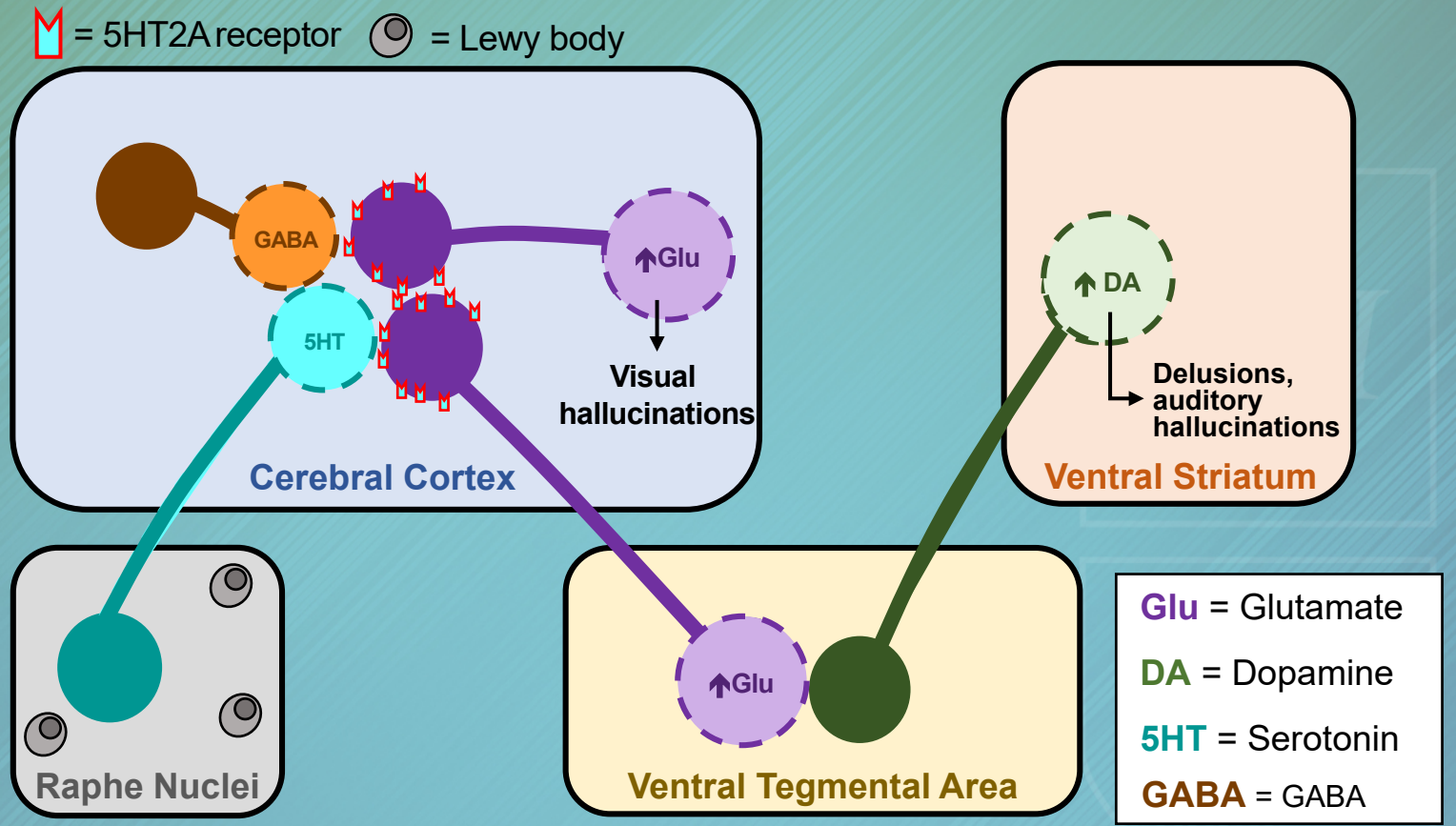
Krogmann A et al. CNS Spectr 2019;24(S1):38-69.

Neural Circuits Implicated in Psychosis



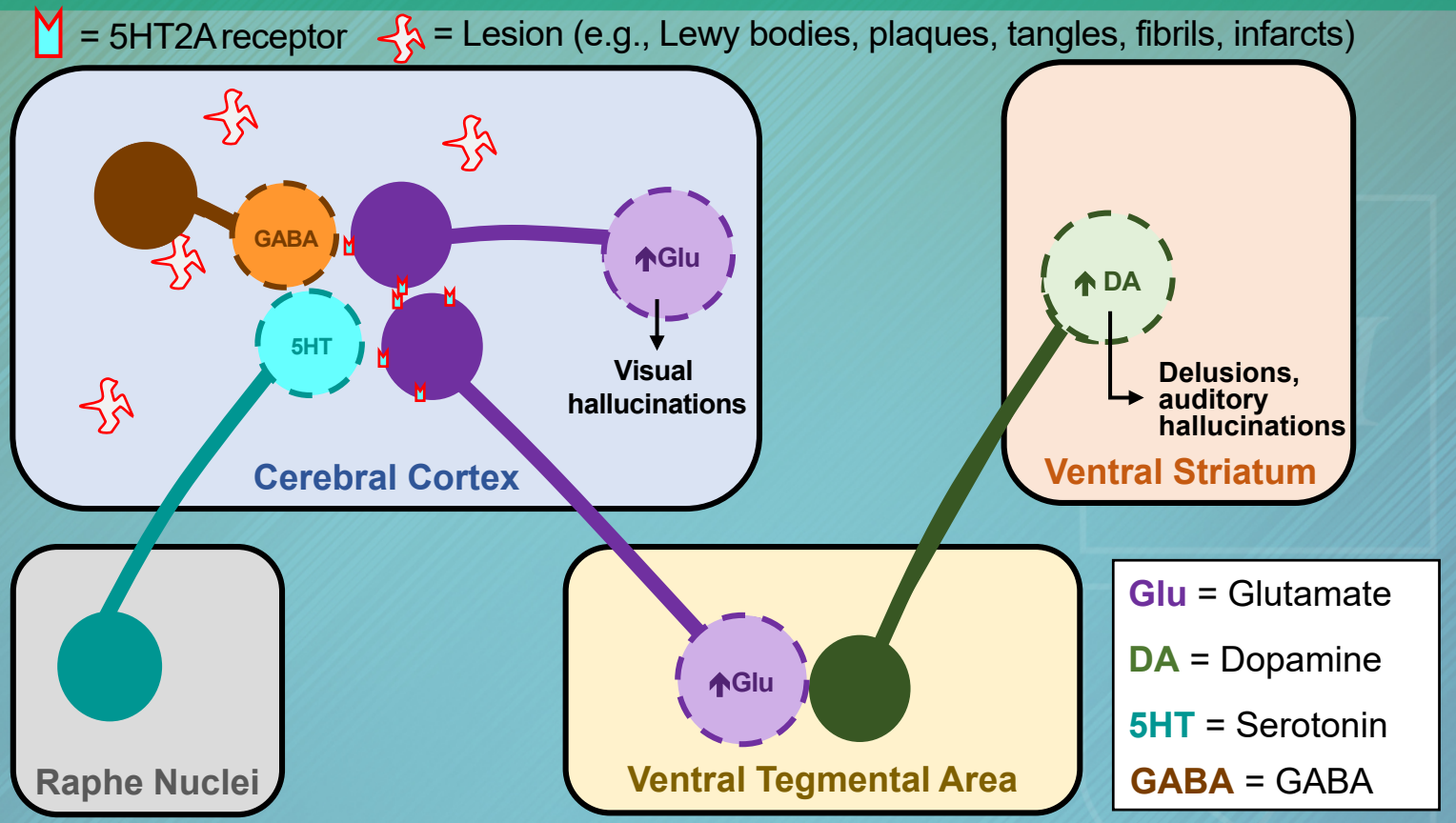
Stahl SM. CNS Spectr 2016;21(5):355-9;
Stahl SM. Stahl's essential psychopharmacology, 4th ed. 2013.

Neural Circuits Implicated in Parkinson's Disease Psychosis



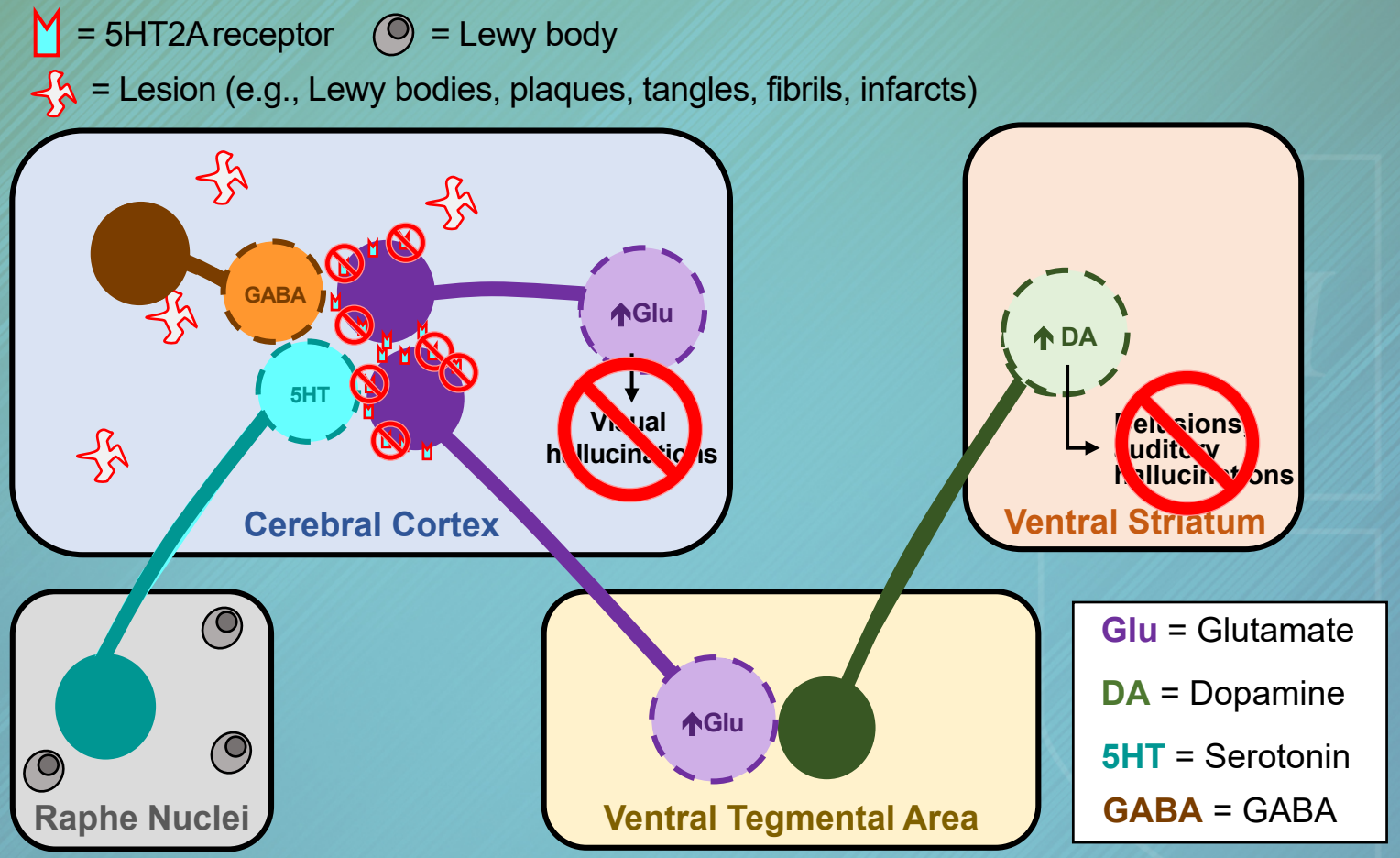
Braak H et al. Neurobiol Aging 2003;24(2):197-211; Stahl SM. CNS Spectr 2016;21(5):355-9; Albin RL et al. J Cereb Blood Flow Metab 2008;28(3):441-4; Kerenyi L et al. Arch Neurol 2003;60(9):1223-29; Balcioglu A et al. 2003;119(4):1045-53; Rozas G et al. Neurosci Lett 1998;245(3):151-4; Prinz A et al. Exp Neurol 2013;248:236-45; Politis M et al. Neurobiol Dis 2010;40(1):216-21; Ballanger B et al. Arch Neurol 2010;67(4):416-21; Huot P et al. Mov Disord 2010;25(10):1399-408.

Neural Circuits Implicated in Dementia-Related Psychosis



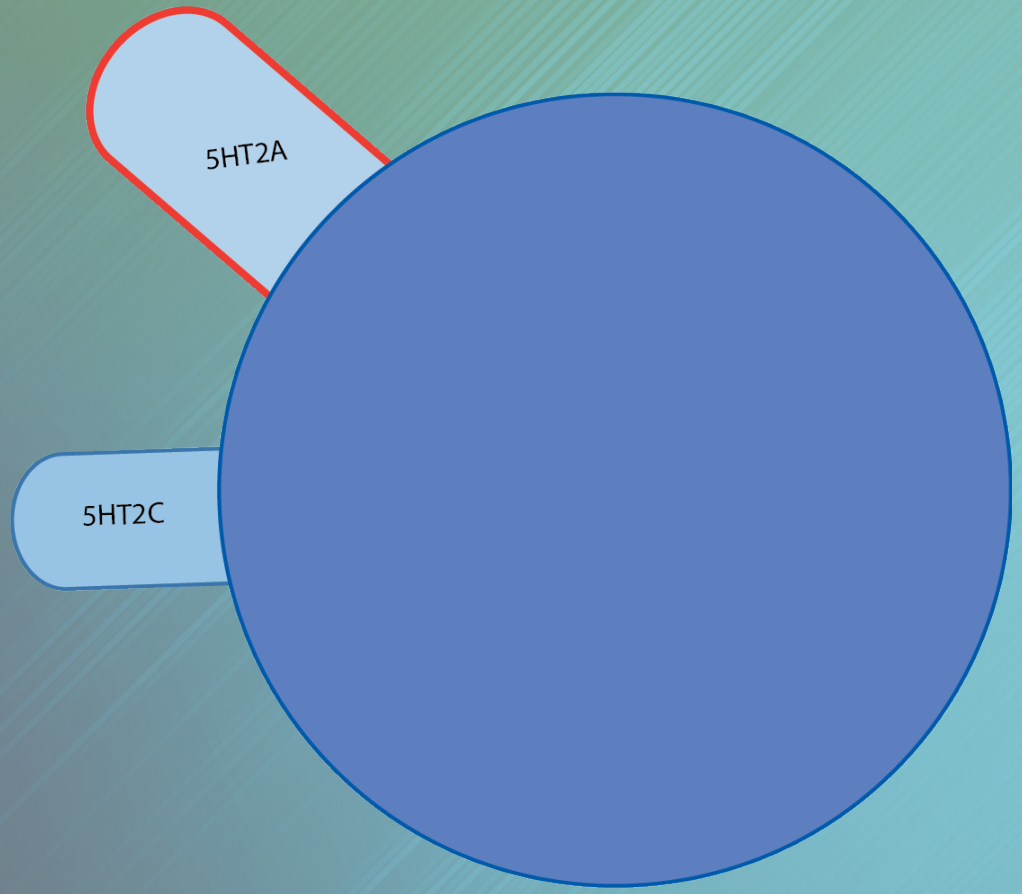
Colom-Cadena M et al. Brain 2017;140(12):3204-14; Hamilton RL. Brain Pathol 2000;10(3):378-84; Hyman BT et al. Alzheimers Dement 2018;8(1):1-13; Rosso SM et al. Brain 2003;126(9):2016-22; Jellinger KA, Stadelmann C. J Alzheimers Dis 2001;3(1):31-40; Roman GC et al. Neurology 1993;43(2):250-60; Stahl SM. Stahl's illustrated Alzheimer's disease and other dementias 2019; Stahl SM. CNS Spectr 2016;21(5):355-9; Stahl SM. Stahl's essential psychopharmacology, 4th ed. 2013; Mega MS et al. J Neurol Neurosurg Psychiatry 2000;69(2):167-71; Nagahama Y et al. Brain 2010;133(Pt 2):557-67; Devenney EM et al. Neuroimage Clin 2016;13:439-45; Ibarretxe-Bilbao N et al. J Neurol Neurosurg Psychiatry 2010;8(6):650-7.

Mechanism of Action of Pimavanserin in Dementia-Related Hallucinations and Delusions



Stahl SM. CNS Spectr 2016;21(5):355-9;
Stahl SM. CNS Spectr 2018;23(5):291-7.

Pimavanserin—A 5HT2A Antagonist

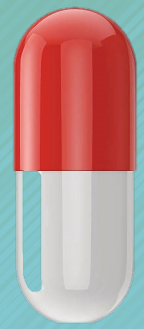


- Potent 5HT2A antagonist with lesser 5HT2C antagonist actions
- Only known drug with proven antipsychotic efficacy that does not have D2 antagonist/partial agonist actions

Stahl SM. Stahl's essential Psychopharmacology, 5th ed. In Preparation.

Case Series: Pimavanserin

Patients who had not responded to clozapine (n=10)



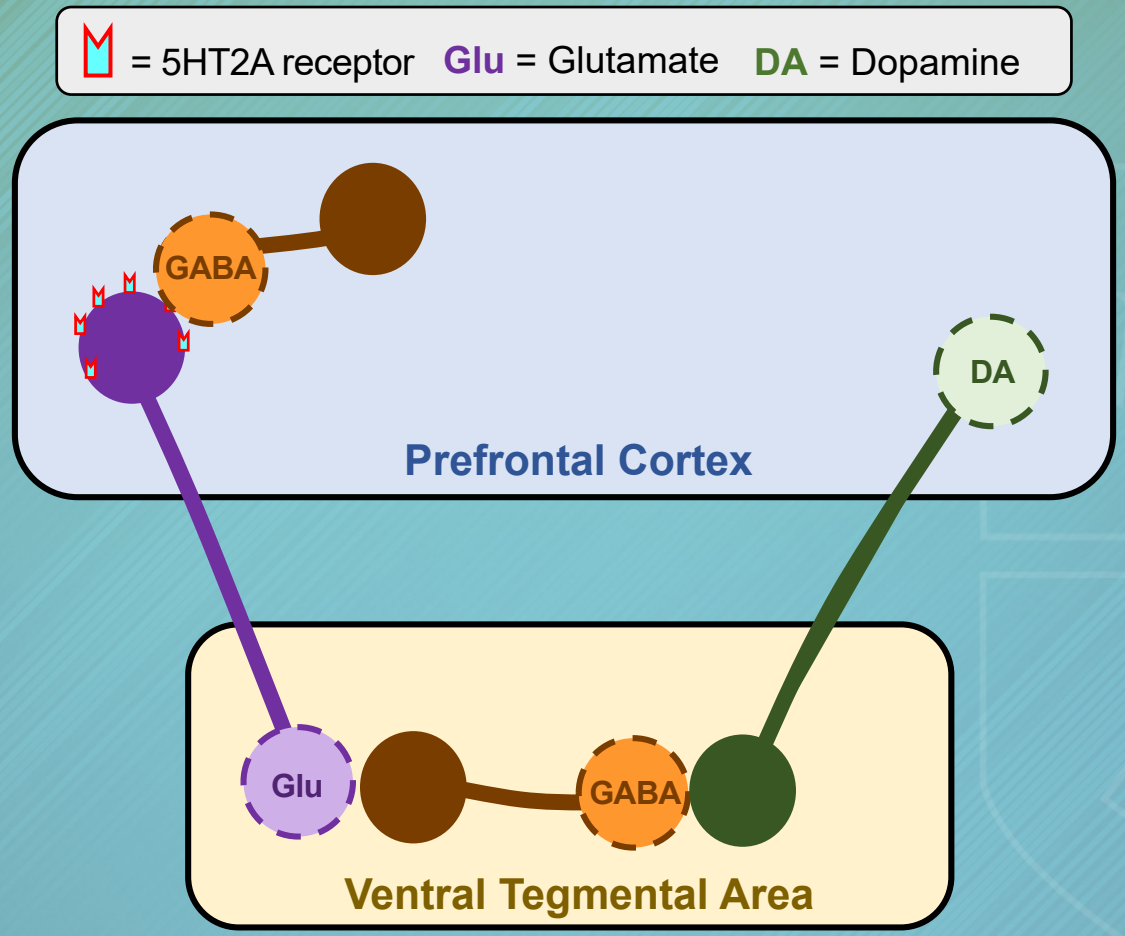
34 mg/day pimavanserin for 4–8 weeks

Patients who had not responded to non-clozapine antipsychotics (n=10)

- All 10 patients with refractory hallucinations/delusions demonstrated marked response to pimavanserin, with continuation of response for several months of follow-up
- Improvements in negative symptoms and social functioning were also observed

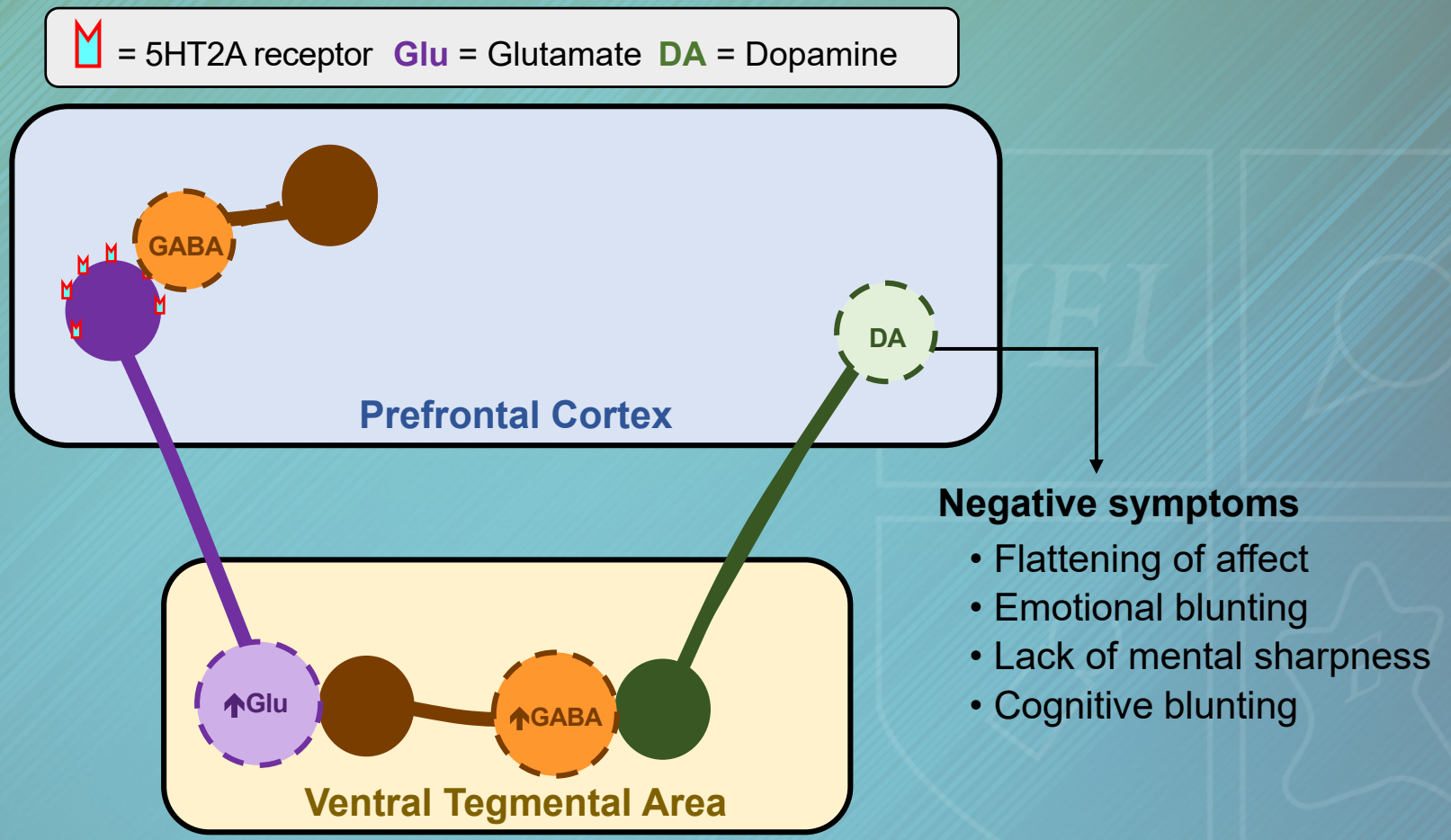
Nasrallah HA et al. Schizophr Res 2019;208:217-20.

Neural Circuits Implicated in Schizophrenia Negative Symptoms



Stahl SM. Stahl's essential Psychopharmacology, 5th ed. In Preparation.

Negative Symptoms of Schizophrenia

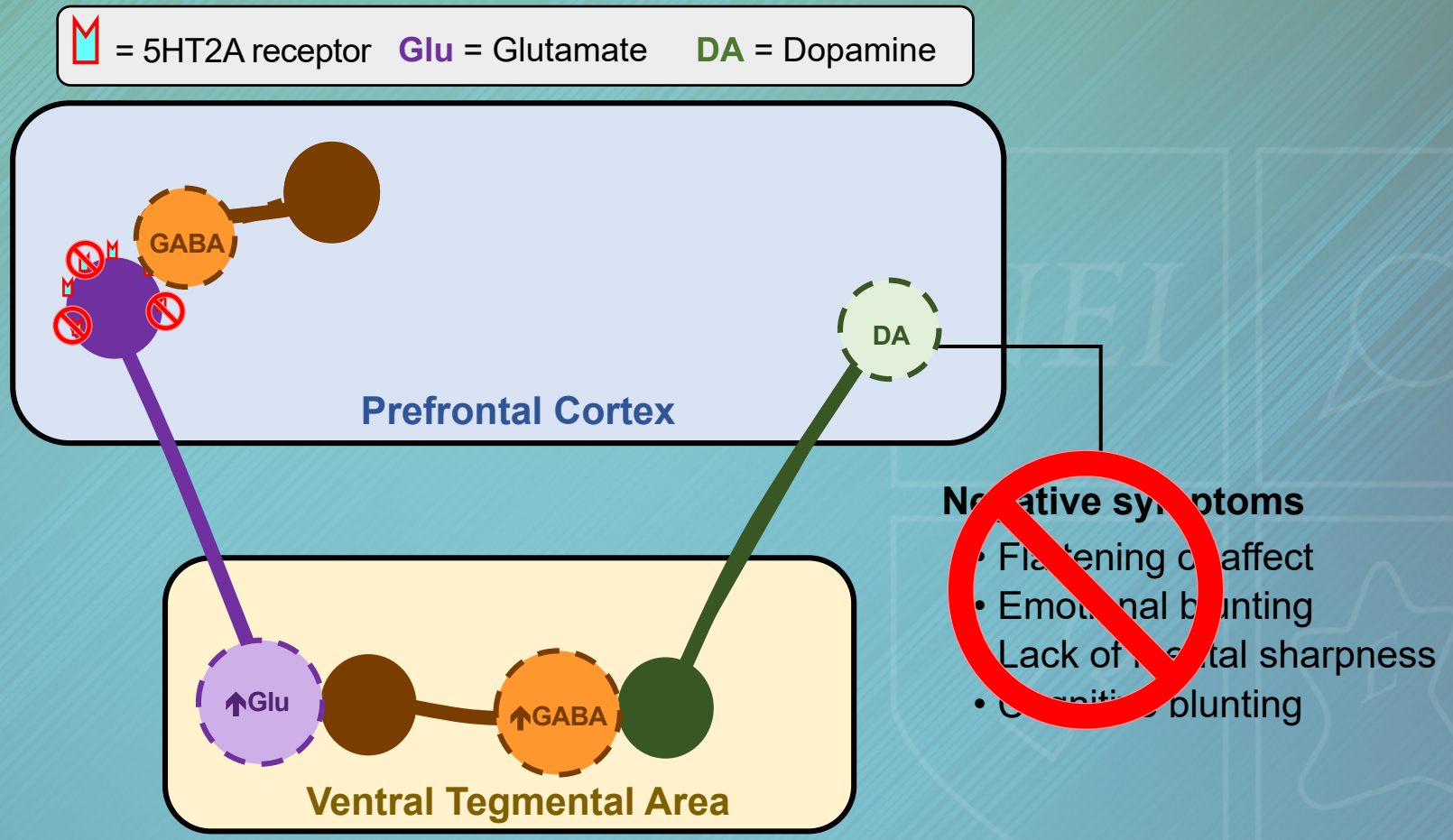


Negative symptoms

- Flattening of affect
- Emotional blunting
- Lack of mental sharpness
- Cognitive blunting

Stahl SM. Stahl's essential Psychopharmacology, 5th ed. In Preparation.

Mechanism of Action of 5HT2A Antagonism on Negative Symptoms of Schizophrenia

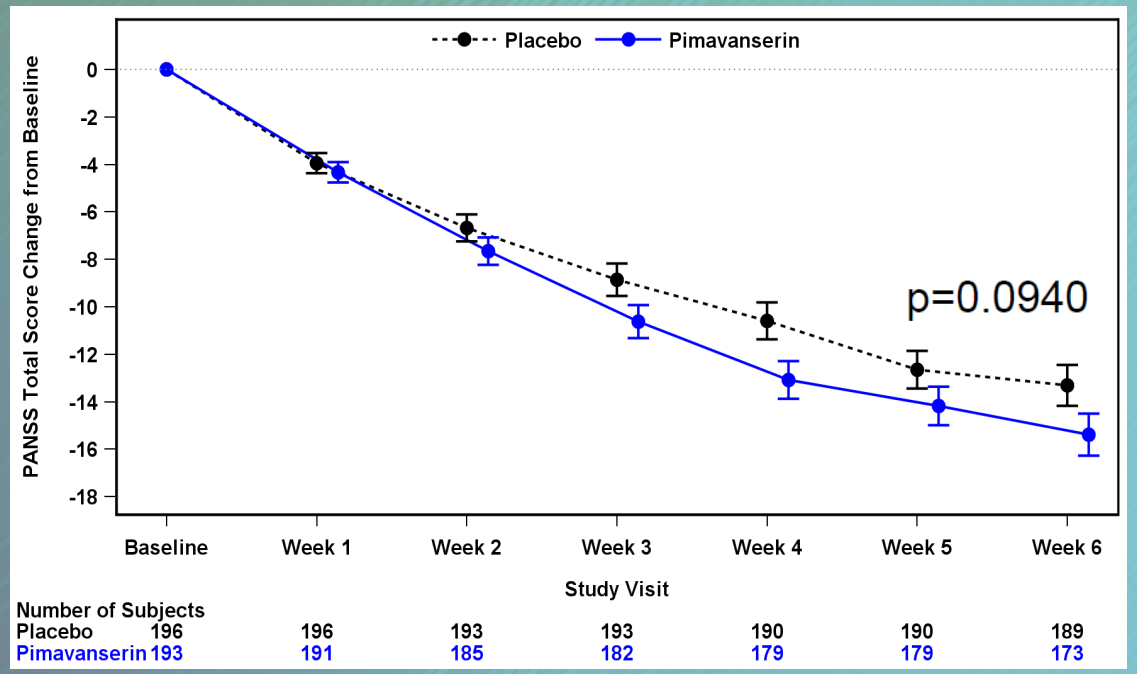


Stahl SM. Stahl's essential Psychopharmacology, 5th ed. In Preparation.

Pimavanserin

- Approved to treat Parkinson's disease psychosis
- Pimavanserin has unique selective 5HT2A/5HT2C antagonist actions

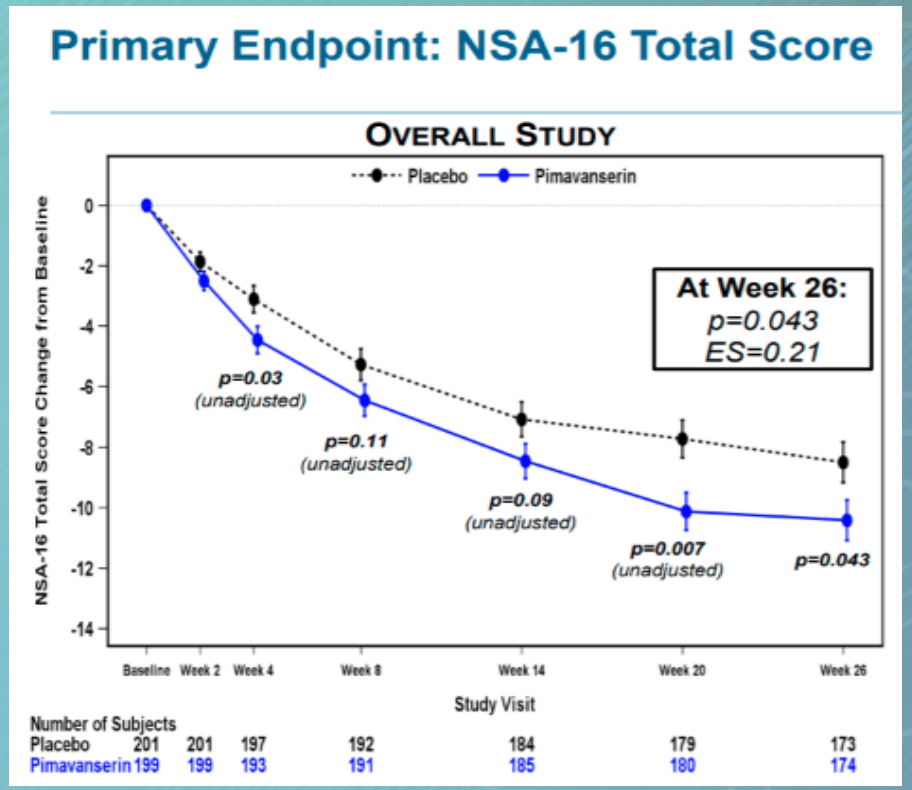
ENHANCE Study: Adjunctive Treatment for Schizophrenia



Results from the PANSS Negative Subscale: (p=0.0474)

Most common adverse events (>5% in either group) placebo vs. pimavanserin were headache (18% vs. 13%), somnolence (7% vs. 13%), and insomnia (7% vs. 10%)

ADVANCE Study: Negative Symptoms in Schizophrenia

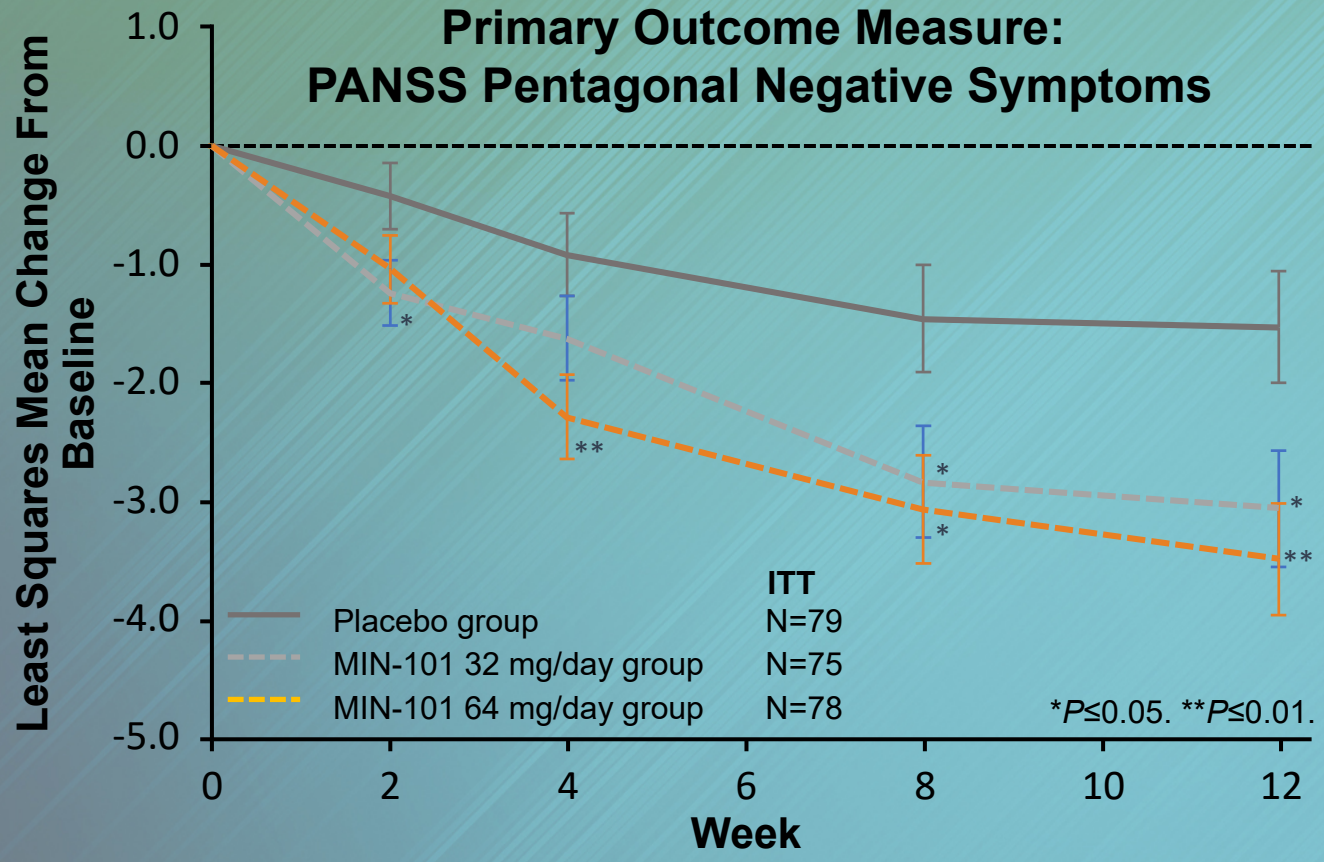


Results for the 34 mg dose

At Week 26:
p=0.0065
(unadjusted)
ES=0.34

Roluperidone (MIN-101)

- Roluperidone has high affinity for both sigma 2 and 5HT2A receptors



Most Common Adverse Events in the MIN-101 Groups

Adverse Event	Placebo (%)	Combined MIN-101 Groups (%)
Any Adverse Event (%)	43.4	57.7 (32 mg), 57.1 (64 mg)
Headache	3.6	7.5
Anxiety	6.0	6.8
Insomnia	9.6	5.6
Schizophrenia Symptoms	10.8	5.6
Asthenia	2.4	5.6
Nausea	3.6	3.7
Somnolence	0.0	3.7

"Roluperidone failed to meet endpoints in a Phase III clinical trial for the treatment of negative symptoms in schizophrenia."

Adapted from Davidson M et al. Am J Psychiatry 2017;174(12):1195-202;
Minerva Neuroscience Press Release June 1, 2020.

Beyond the Three Hypotheses of Psychosis (Dopamine, Glutamate, and Serotonin) to the Novel Pharmacological Treatments in the Cholinergic and Trace Amine Systems

M1/M4 Muscarinic Agonists for Treatment of Schizophrenia

- M2/M3 receptors are the major peripheral subtypes hypothesized to underlie dose-limiting clinical side effects (e.g., gastrointestinal)
- Patients with schizophrenia have lower levels of muscarinic M1 receptors, muscarinic M4 receptors, or both receptors in the cortex, hippocampus, and striatum
- Xanomeline is a muscarinic M1/M4 agonist that improved Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome (PANSS) scores in patients with schizophrenia
  - Gastrointestinal side effects limited further clinical development

Dean B, Scarr E. Psychiatry Res 2020;288:112989;
Shekhar A et al. Am J Psychiatry 2008;165(8):1033-9.

Xanomeline/Trospium (KarXT)

- Trospium is a muscarinic receptor antagonist that has minimal, if any, penetration of the blood brain barrier, blocking unwanted peripheral cholinergic side effects of xanomeline

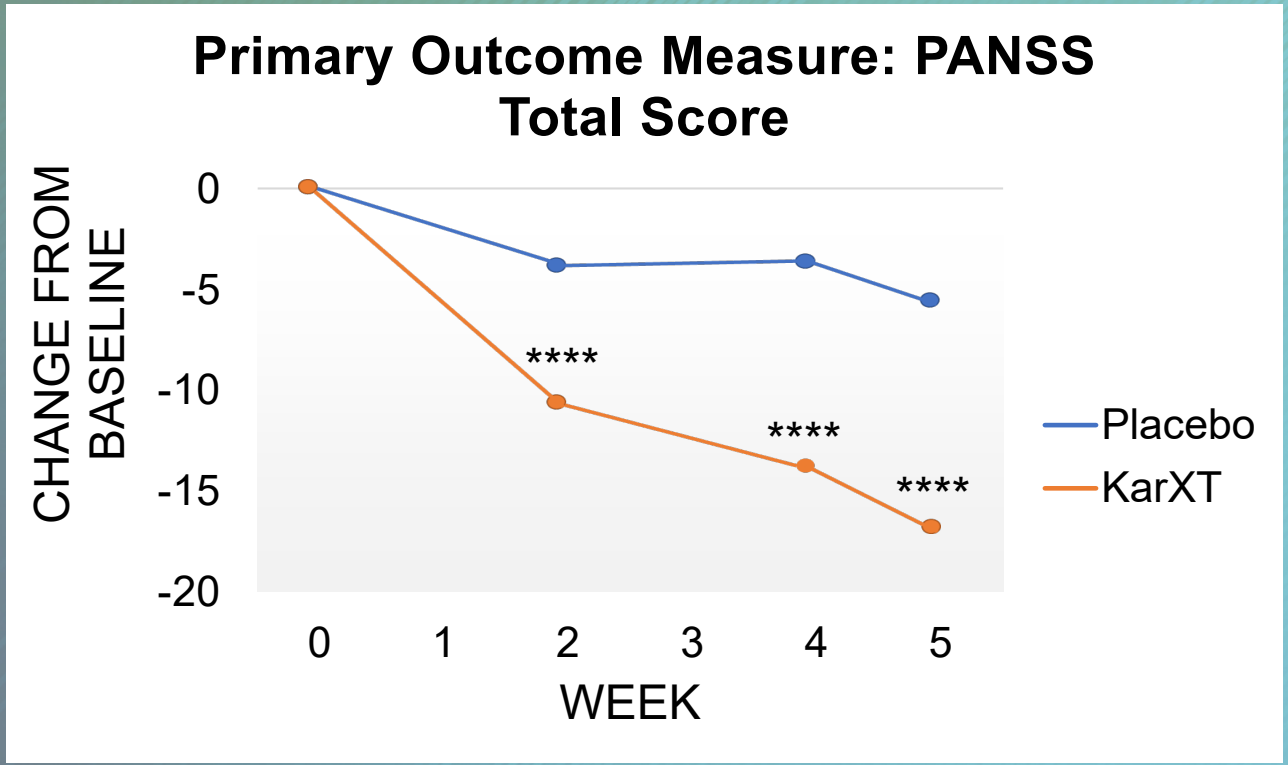
Randomized Controlled Trial	Number of Patients	Design	Results
Phase I study on xanomeline + trospium (KarXT)	n=69	225 mg xanomeline + placebo or 225 mg xanomeline + 40 mg trospium	KarXT co-formulation demonstrated improved tolerability; side effects were mild to moderate
Phase II study on xanomeline + trospium (KarXT)	n=160	120 mg/20 mg xanomeline/trospium with an option to increase dose to 125 mg/30 mg xanomeline/trospium following week 1	Significant and clinically meaningful 11.6 point mean reduction in total PANSS score compared to placebo ($p<0.0001$); demonstrated good overall tolerability

PANSS: Positive and Negative Syndrome Scale.

Brannan S et al. Biol Psychiatry 2020;87(9):S169.

Efficacy and Safety of KarXT

- Results from 5-week, double-blind, placebo-controlled phase II study:



Safety population	Placebo (n=90)	KarXT (n=89)
Any AE (N, %)	39 (43.3%)	48 (53.9%)
AEs ≥ 5%		
Constipation	3 (3.3%)	15 (16.9%)
Nausea	4 (4.4%)	15 (16.9%)
Dry mouth	1 (1.1%)	8 (9.0%)
Dyspepsia	4 (4.4%)	8 (9.0%)
Vomiting	4 (4.4%)	8 (9.0%)
Headache	5 (5.6%)	6 (6.7%)
Somnolence	4 (4.4%)	5 (5.6%)

Adapted from Brannan S. ASCP 2020 [Oral Presentation].

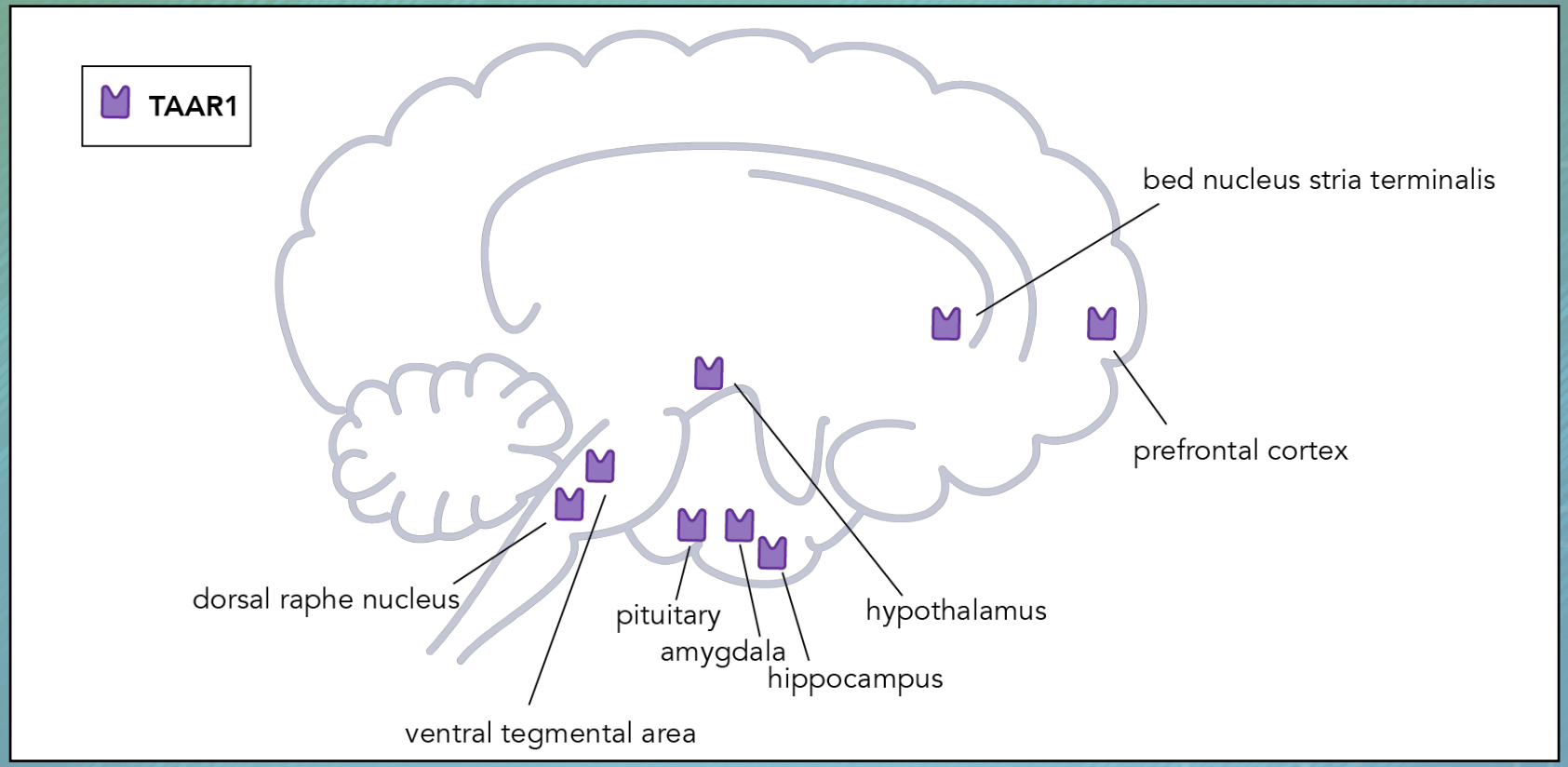
Novel Targets in Schizophrenia

- Trace amine associated receptor type 1 (TAAR1) agonism

What Is a Trace Amine?

- Formed from amino acids when TyrOH or TrypOH omitted
- <50 ng/g (<500 nM) and binds a TAAR (trace amine associated receptor), usually TAAR1
- Not released by depolarization
- Organic cation transporter 2 for transport
- TAAR1 localized in monoamine brainstem centers and in monoamine projection areas

Localization of Trace Amine Associated Receptor Type 1 (TAAR1)

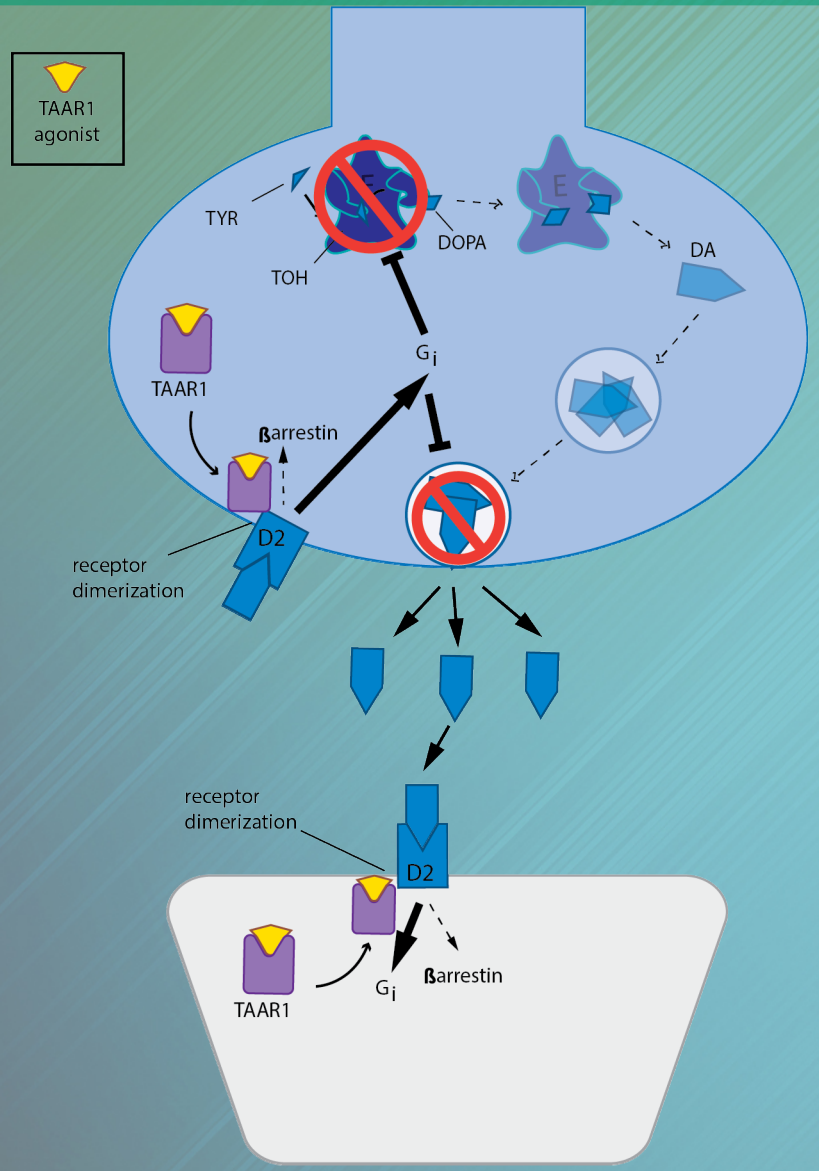


TAAR1 is widely expressed throughout the brain, including in monoamine brainstem centers (dorsal raphe nucleus, ventral tegmental area) and in monoamine projection areas

TAAR1 and Dopamine

- Much is yet to be learned about trace amines and their receptors, but it does appear already that:
  - Trace amines are not classical neurotransmitters
  - TAAR1 agonism may have opposite effects when it is heterodimerized with D2R, and TAAR1 heterodimers may have opposite effects on dopamine presynaptically versus postsynaptically
- Trace amines and TAAR1 are positioned to potentially serve as the “rheostat” of dopamine neurotransmission and TAAR1 agonists may have therapeutic actions in schizophrenia to modulate dysfunctional dopamine neurotransmission
- Trace amine-associated receptor-1 (TAAR1) agonist RO5263397 and SEP-363856 are in clinical development with -856 showing efficacy in a Phase II trial of schizophrenia and now breakthrough status at FDA

Agonism of TAAR1

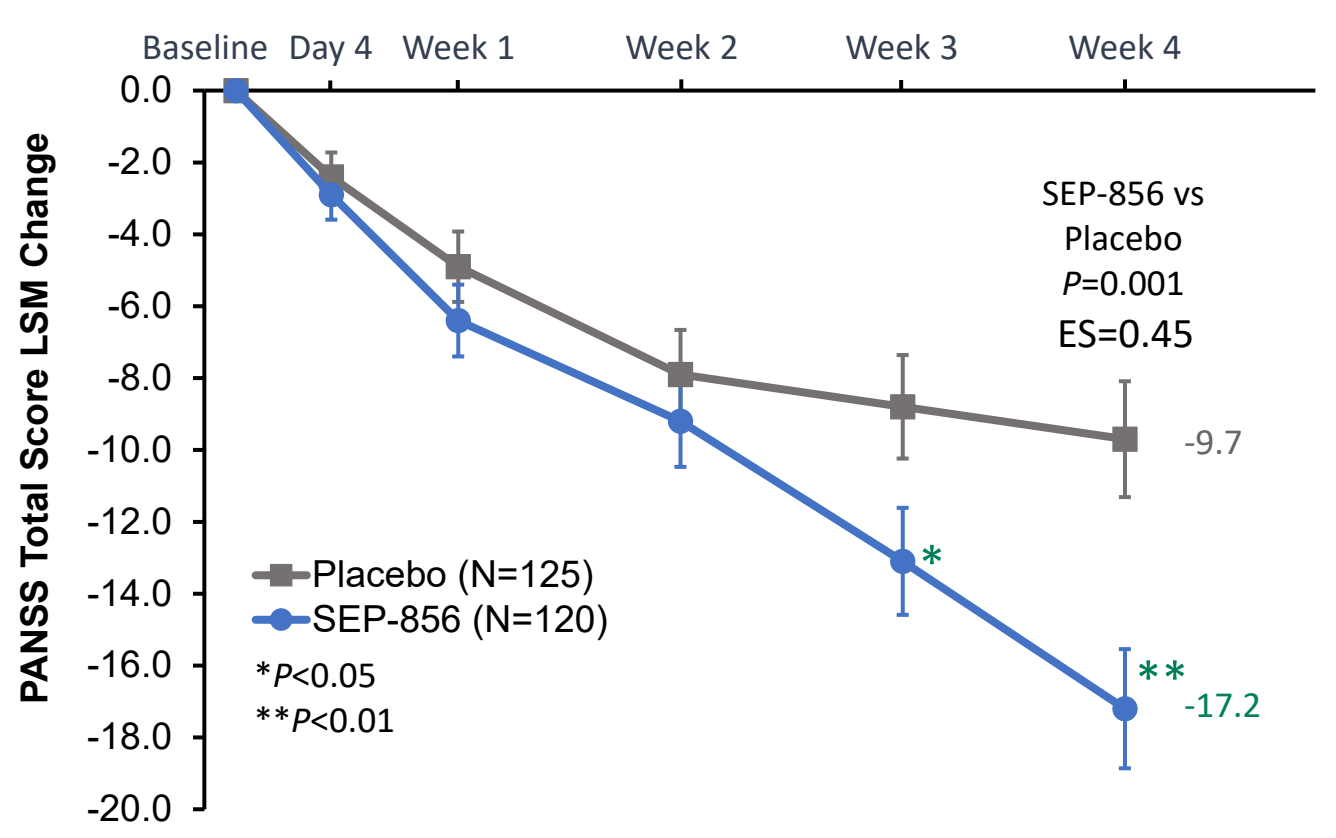


- When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with D2 receptors
- Amplification of the G_i pathway leads to inhibition of the synthesis and release of dopamine, which would be beneficial in cases of psychosis

Stahl SM. Stahl's essential psychopharmacology, 5th ed. In Preparation.

SEP-363856

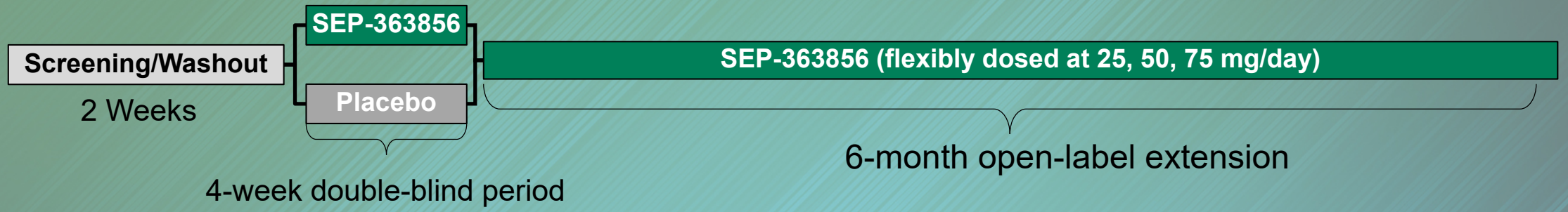
- SEP-856 is a trace amine associated receptor type 1 (TAAR1) agonist with 5HT1A activity
- SEP-856 lacks activity at D2 and 5HT2A receptors
- Results of a 4-week, double-blind, placebo-controlled phase II study of patients with an acute exacerbation of schizophrenia:

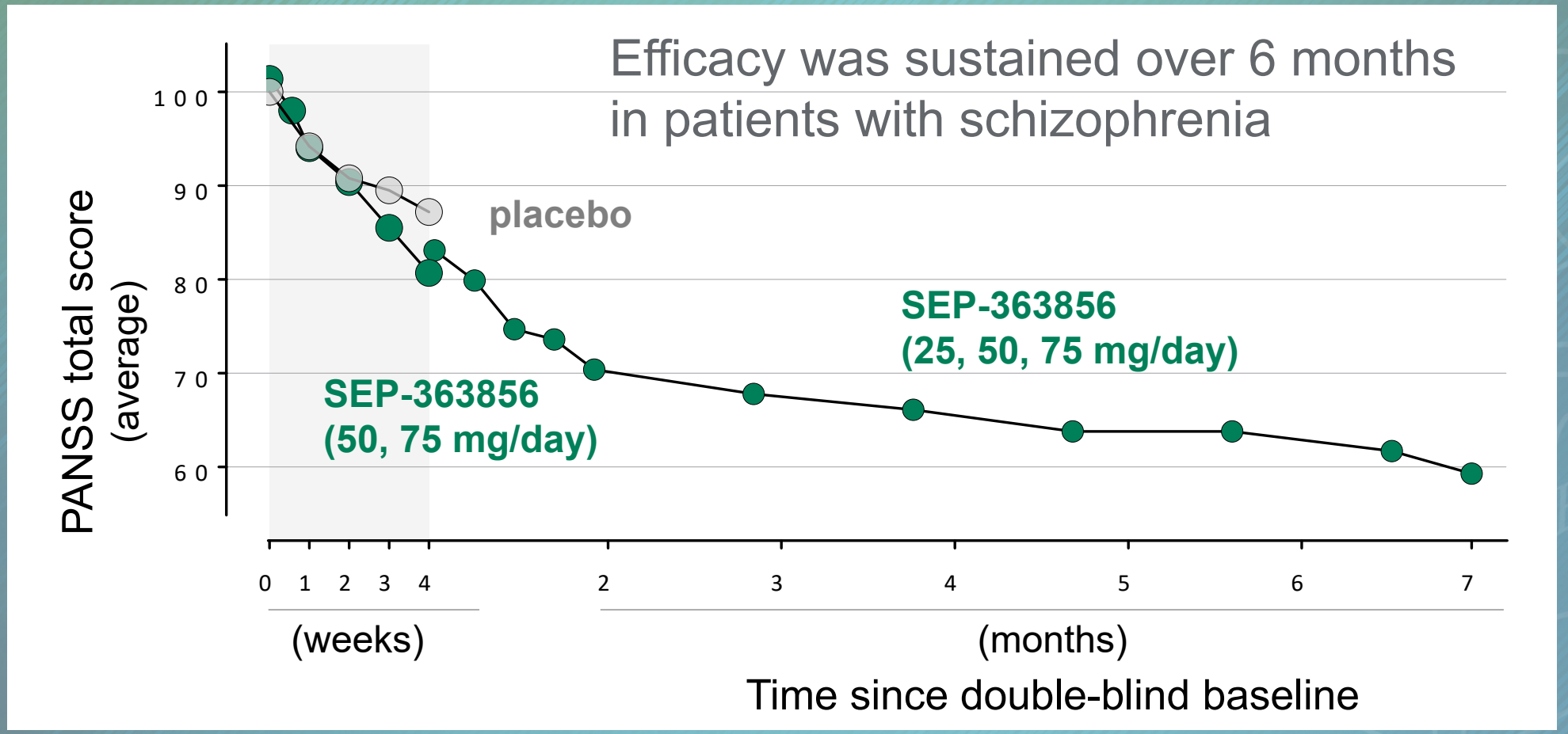


Adverse Events ≥ 2% in Either Treatment Group and Greater Than Placebo		
Preferred Term	**Placebo (N=125), n (%)**	**SEP-856 (N=120), n (%)**
Somnolence	6 (4.8)	8 (6.7)
Agitation	6 (4.8)	6 (5.0)
Nausea	4 (3.2)	6 (5.0)
Diarrhea	1 (0.8)	3 (2.5)
Dyspepsia	0	3 (2.5)

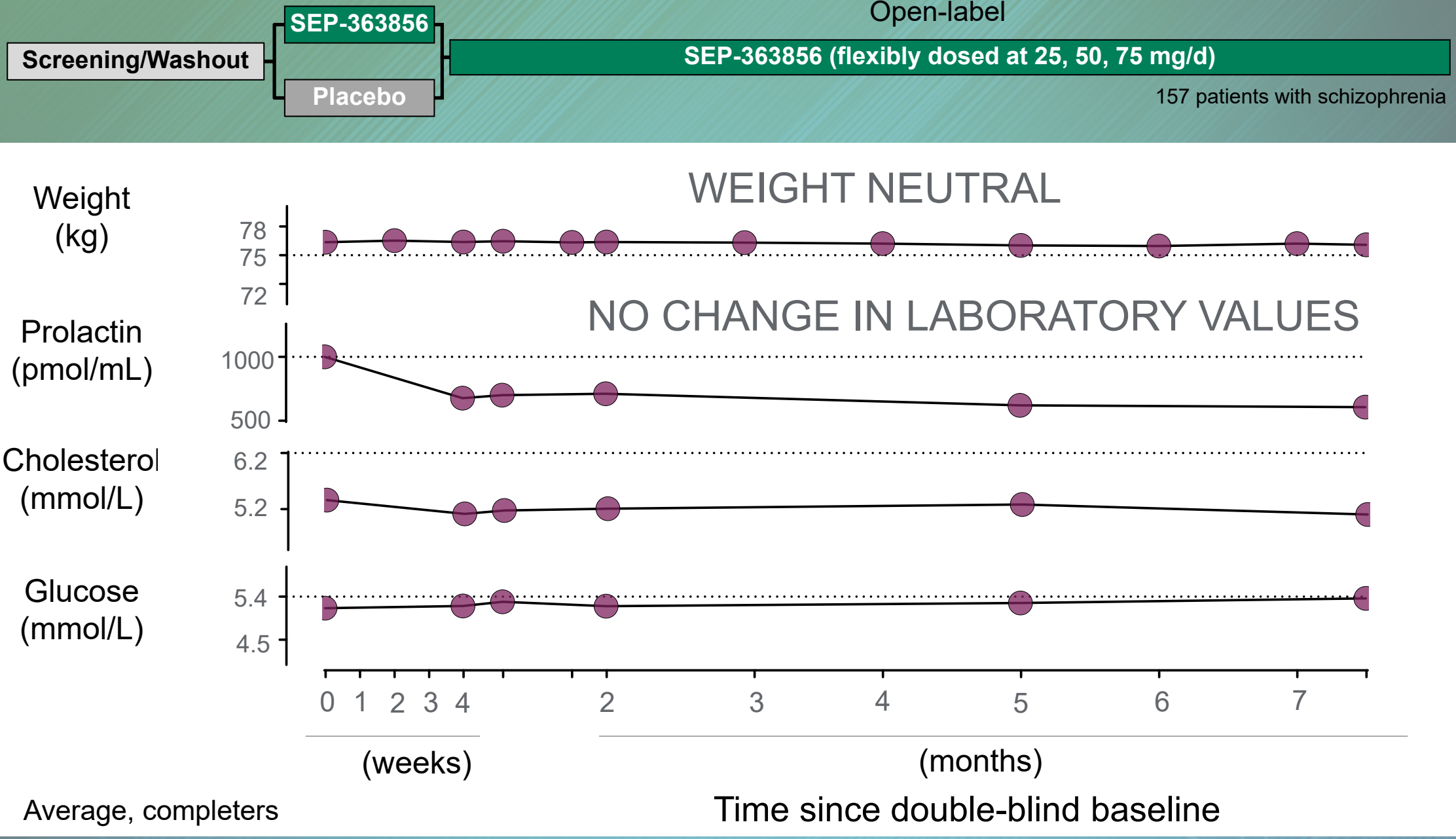
Results from the Brief Negative Symptom Scale: p<0.001, ES=0.48

Adapted from Koblan KS et al. N Engl J Med 2020;382(16):1497-506.

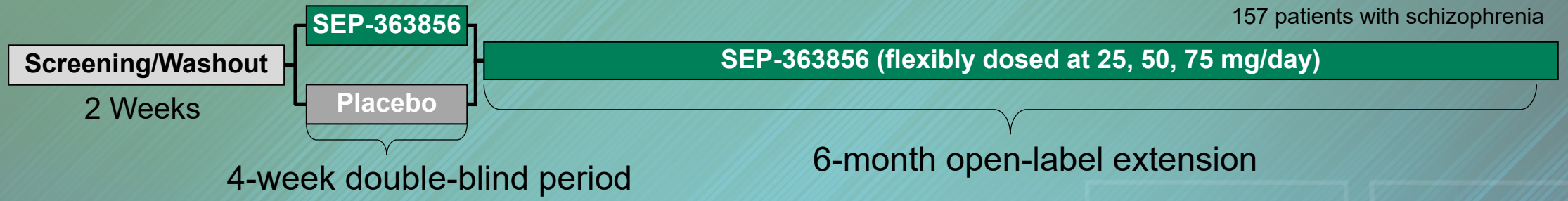




Sunovian Pharmaceuticals Inc.


Screening/Washout
SEP-363856
Placebo
Open-label
SEP-363856 (flexibly dosed at 25, 50, 75 mg/d)
157 patients with schizophrenia
WEIGHT NEUTRAL
NO CHANGE IN LABORATORY VALUES
Weight (kg)
78
75
72
Prolactin (pmol/mL)
1000
500
Cholesterol (mmol/L)
6.2
5.2
Glucose (mmol/L)
5.4
4.5
0 1 2 3 4
2 3 4 5 6 7
(weeks)
(months)
Average, completers
Time since double-blind baseline

Rates of EPS Were Similar to Placebo



Preferred Term	Placebo (N = 125)	SEP-363856 (N = 120)
Subjects with any EPS	**4 (3.2%)**	**4 (3.3%)**
Akathisia	1 (0.8%)	2 (1.7%)
Restlessness	1 (0.8%)	0
Joint stiffness	1 (0.8%)	0
Musculoskeletal stiffness	2 (1.6%)	1 (0.8%)
Nuchal rigidity	1 (0.8%)	0
Postural tremor	0	1 (0.8%)
Tremor	2 (1.6%)	0

Preferred Term	Total (N = 156)
Subjects with any EPS	**5 (3.2%)**
Parkinsonism	2 (1.3%)
Dyskinesia	1 (0.6%)
Tremor	1 (0.6%)
Restlessness	1 (0.6%)

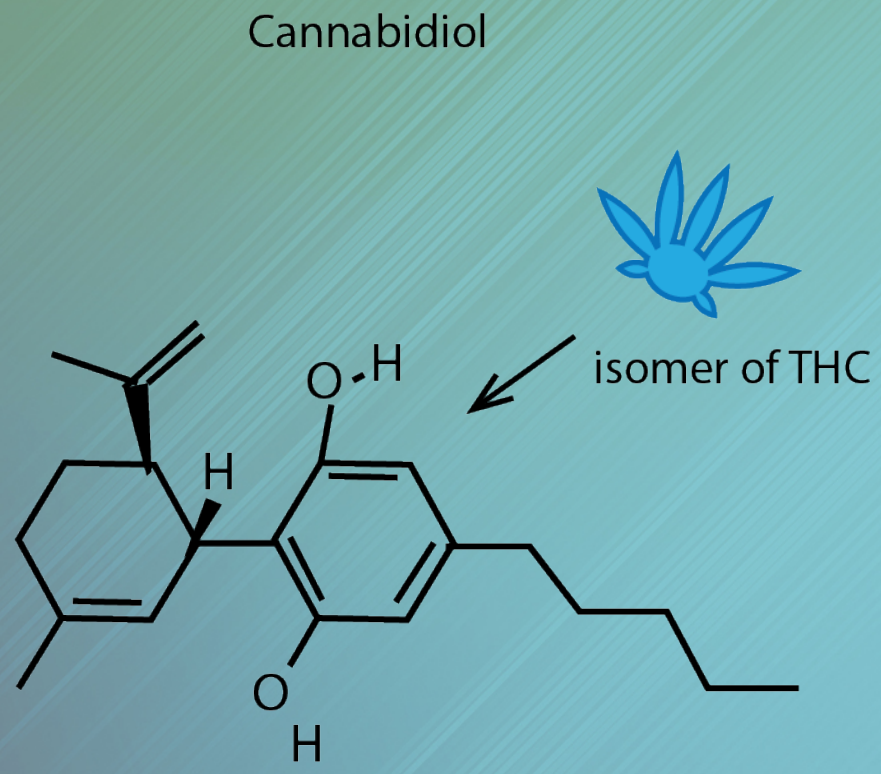
RO5263397: Another TAAR1 Receptor Agonist

- Suppresses dopamine-dependent hyperactivity in mice lacking the dopamine transporter
- Shows pro-cognitive and antidepressant-like properties in rodent and primate models
- Results of phase II clinical trial are pending

Espinoza S et al. Front Pharmacol 2018;9:645;
Revel FG et al. Mol Psychiatry 2013;18(5):543-56.

Still Other Treatment Strategies

Antipsychotic Properties of Cannabidiol (CBD)



- Mechanism of action is not well understood
- Relatively inactive at cannabinoid receptors 1 and 2
- Does not appear to involve direct antagonism of dopamine receptors
- In healthy volunteers, pretreatment with CBD attenuates the experimental induction of psychotic symptoms of delta-9-tetrahydrocannabinol (THC)

Miyamoto S et al., Mol Psychiatry 2012;17(12):1206-27;
Bhattacharyya S et al. Neuropsychopharmacology 2010;35(3):764-74.

Treatment of Negative Symptoms: Other Strategies

Anti-inflammatory agents

- Disappointing results for NSAIDs
- Meta-analysis showed efficacy for minocycline

Hormone treatment

- Preliminary evidence for raloxifene (selective estrogen receptor modulator)

Antioxidant

- Mixed results for N-acetylcysteine (NAC)
- Meta-analysis shows moderate efficacy for Ginkgo biloba

HMG CoA reductase inhibitors

- Small positive trial of adjunct simvastatin

Veerman SRT et al. Drugs 2017;77(13):1423-59;
Tajik-Esmaeeli S et al. Int Clin Psychopharmacol 2017;32(2):87-94.

Summary

- Pharmacological management of schizophrenia can be challenging, especially because of the need for increased efficacy, reduced side effects, and relief from negative and cognitive symptoms
- All approved medications bind D2; there are several in development that focus on mechanisms that extend beyond the dopamine/D2 hypothesis of schizophrenia
- Exciting developments have also been made in behavioral and other non-pharmacological approaches to treat cognitive impairment in schizophrenia

Posttest Question 1

Which dopaminergic pathway is most relevant for the negative symptoms of schizophrenia?

A. Mesolimbic
B. Mesostriatal
C. Mesocortical

Posttest Question 2

All approved medications for schizophrenia bind to which receptor?

A. D1
B. D2
C. 5HT7
D. 5HT1

Posttest Question 3

Which of the following investigational agents being tested for treatment of schizophrenia binds primarily to serotonin 5HT2A receptors?

A. Roluperidone
B. Xanomeline/trospium
C. Cannabidiol