Neuroscience Education Institute

TARGET ACQUIRED? NEW RECEPTOR SCIENCE IN THE TREATMENT OF SCHIZOPHRENIA

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Learning Objectives

- Describe the limitations associated with first- and second-generation antipsychotic medications
- Identify the clinical data on novel and emerging pharmacological agents for the treatment of schizophrenia
- Prescribe novel pharmacotherapies to address unmet needs in schizophrenia, including residual symptoms, functional impairment, and medication side effects

THE SHIFT…FROM OLD TO NEW WAYS OF THINKING ABOUT THE NEUROCIRCUITRY OF SCHIZOPHRENIA

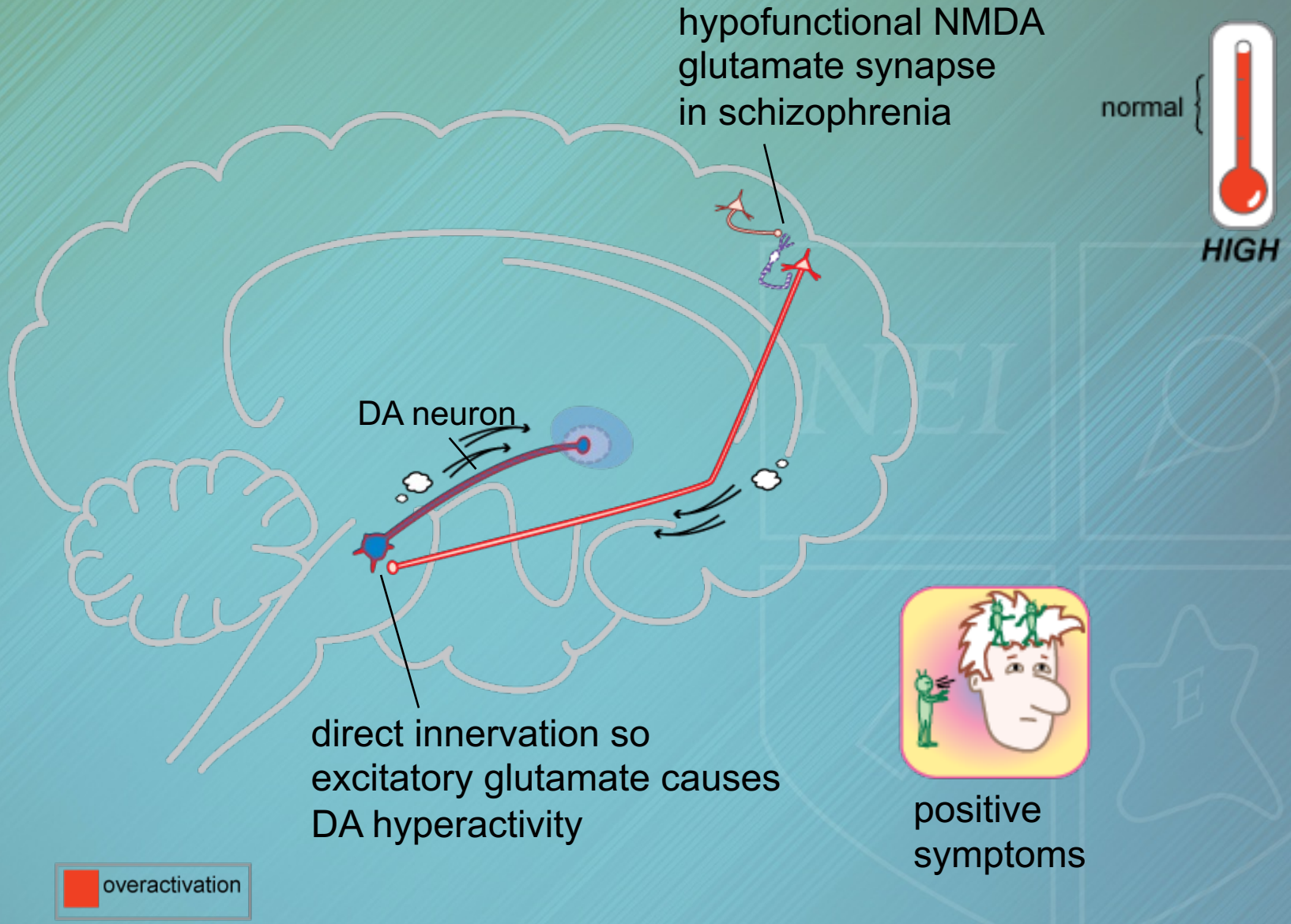
Dopamine, Psychosis, and Schizophrenia

- The dopamine hypothesis of schizophrenia remains as the major theory for symptoms in schizophrenia

- Hyperactive mesolimbic dopamine pathway leads to positive symptoms of psychosis

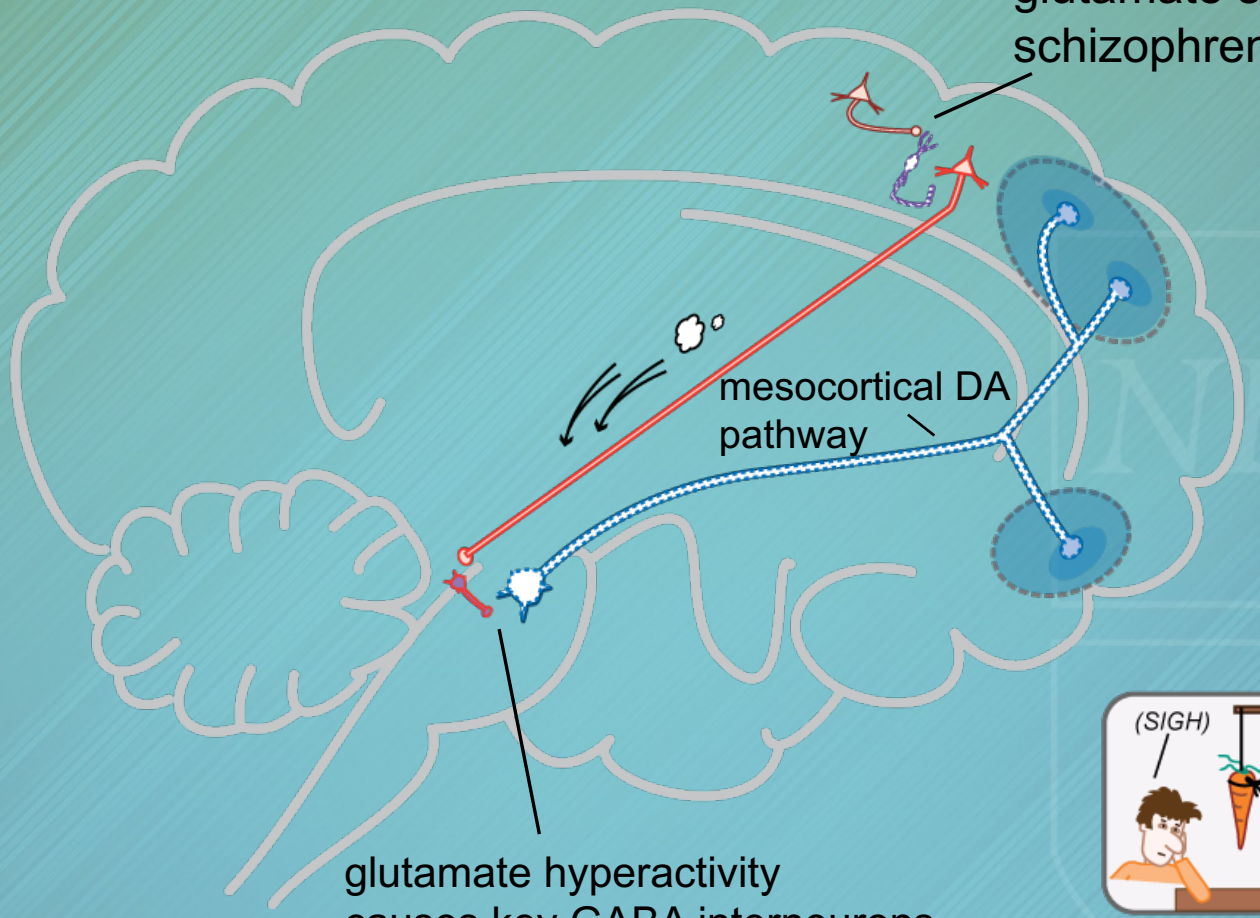
- Hypoactive mesocortical dopamine pathway leads to negative symptoms of psychosis, cognitive impairment, affective symptoms

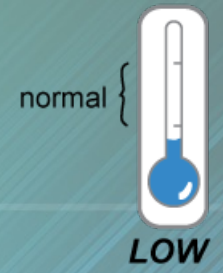
Psychosis in Schizophrenia

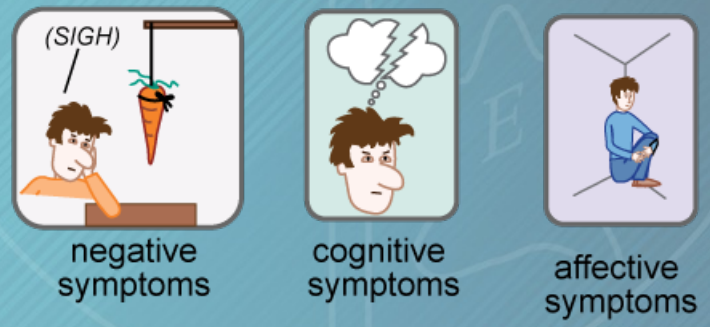


Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Negative and Cognitive Symptoms in Schizophrenia







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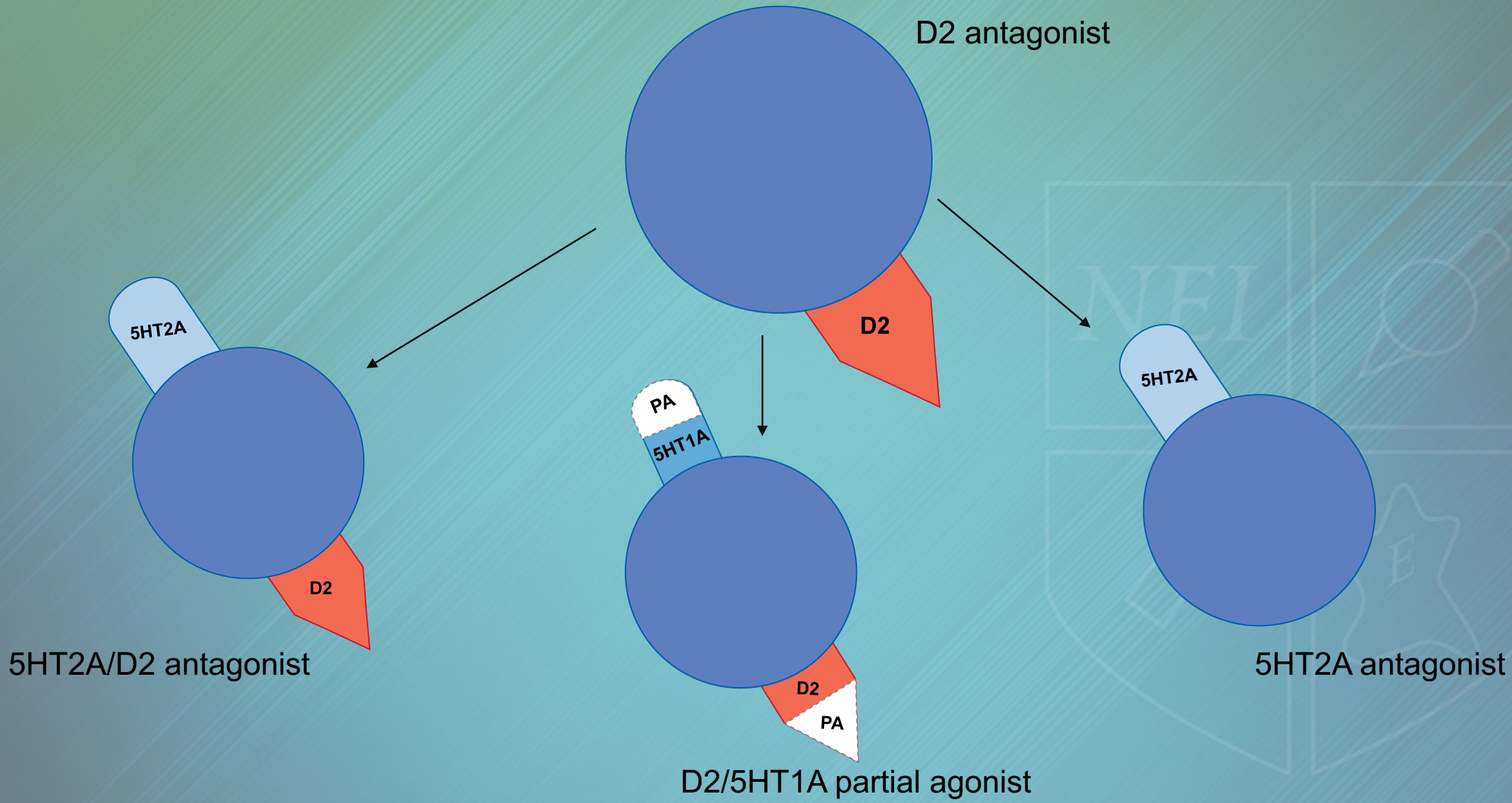
First-Generation Antipsychotics

- The first and most widely hypothesized mechanism of therapeutic action for psychosis has been dopamine 2 antagonism
- D2 antagonism is efficacious at treating positive symptoms of psychosis, but can cause secondary negative symptoms, increase prolactin, and cause motor side effects
- Administration of additional drugs may help with these side effects, but could cause additional problems (e.g., anticholinergics may cause sedation and cognitive difficulties).

Therapeutic Mechanisms of Drugs for Psychosis



Second-Generation “Antipsychotics”

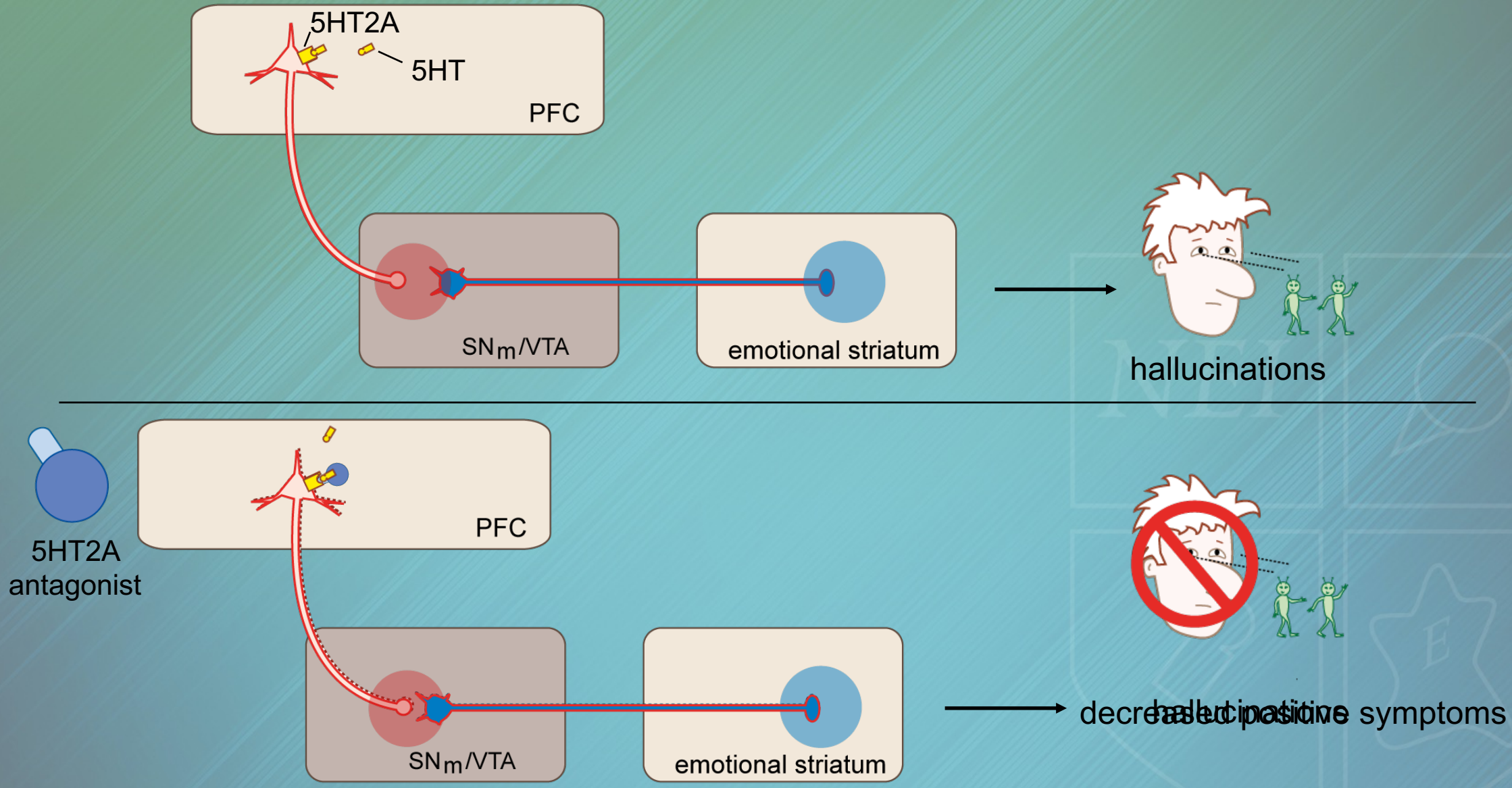
- An attempt to improve the efficacy and the tolerability of the first-generation antipsychotics

- By combining D2 antagonism with 5HT2A antagonism this class of drugs effectively improved:

  -Negative symptoms of psychosis in schizophrenia

  -Motor side effects

  -Hyperprolactinemia



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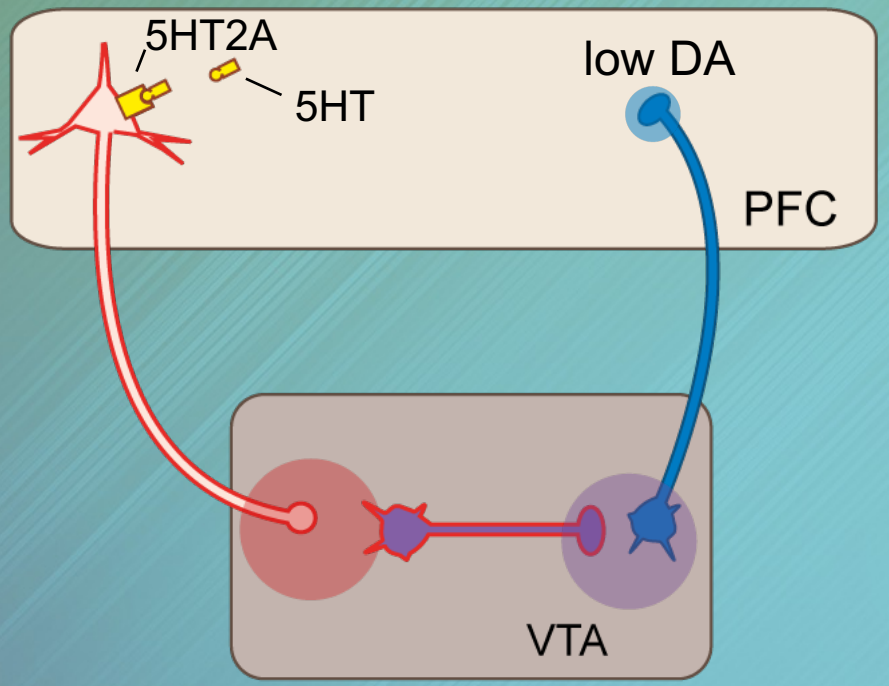
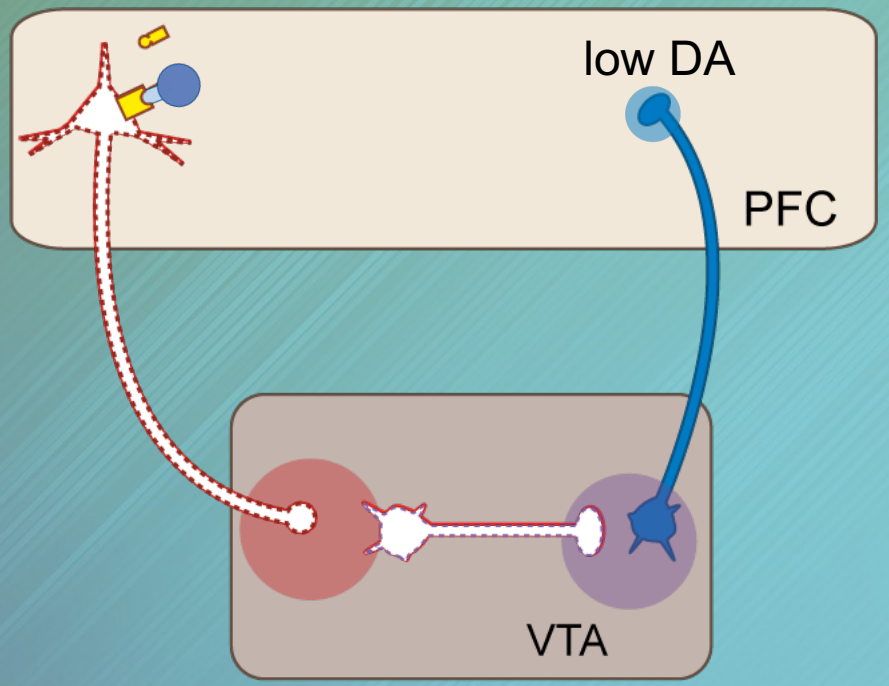


emotional blunting,
flattening of affect

lack of mental sharpness

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

5HT2A
antagonist



reduced emotional blunting,
flattening of affect

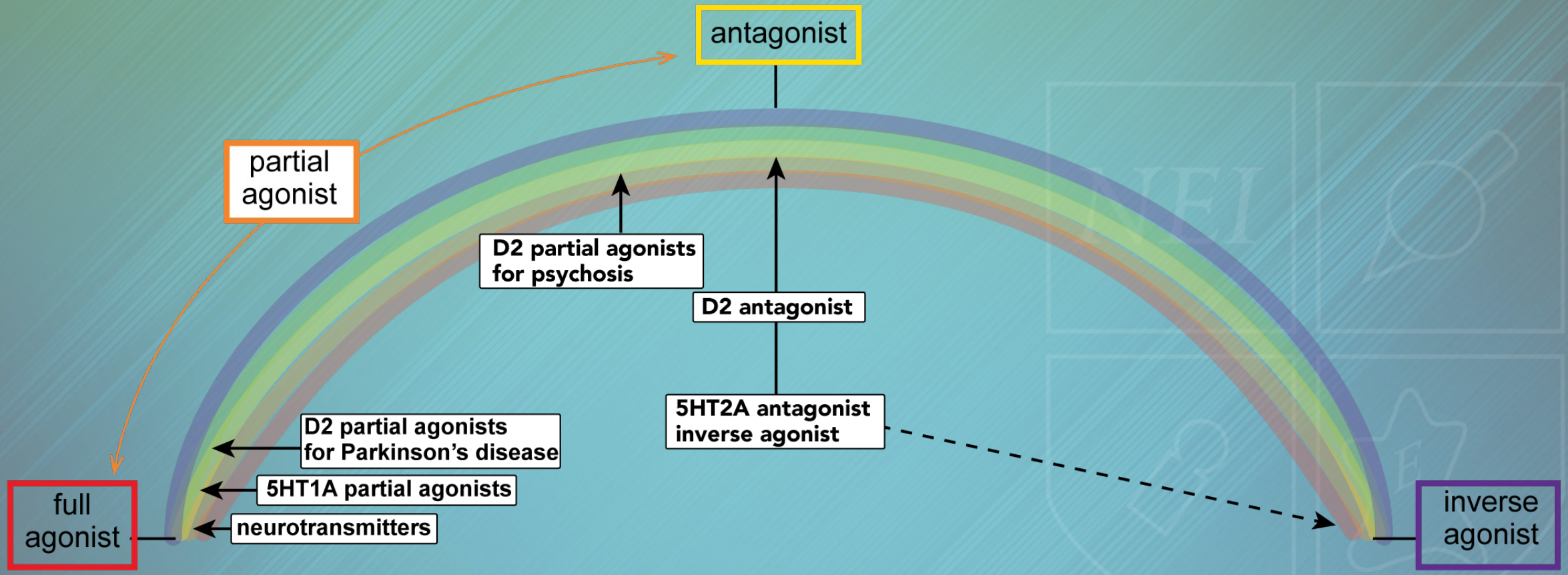
reduced lack of mental sharpness

Stahl SM. Stahl's essential psychopharmacology, 5th ed; 2021.

Newer Drugs for Psychosis

- Newer drugs for psychosis have 5HT2A antagonism (with or without D2 antagonism), 5HT1A partial agonism, and/or D2 partial agonism
- 5HT2A antagonists may have efficacy for psychosis and also reduce side effects associated with D2 antagonism
- D2 partial agonists may also have efficacy for psychosis with reduced side effects by allowing intermediate output from the D2 receptor
- D2 partial agonists used for psychosis lie close to the antagonist end of the spectrum
- 5HT1A partial agonists have similar effects to those of 5HT2A antagonists

Where on the Agonist Spectrum Do Drugs for Psychosis Lie?



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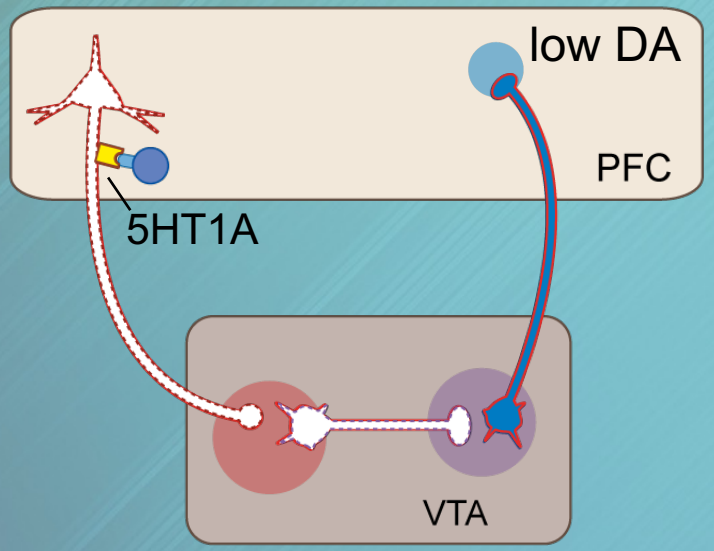
5HT1A Partial Agonism

5HT1A Partial Agonism and Negative/Cognitive Symptoms

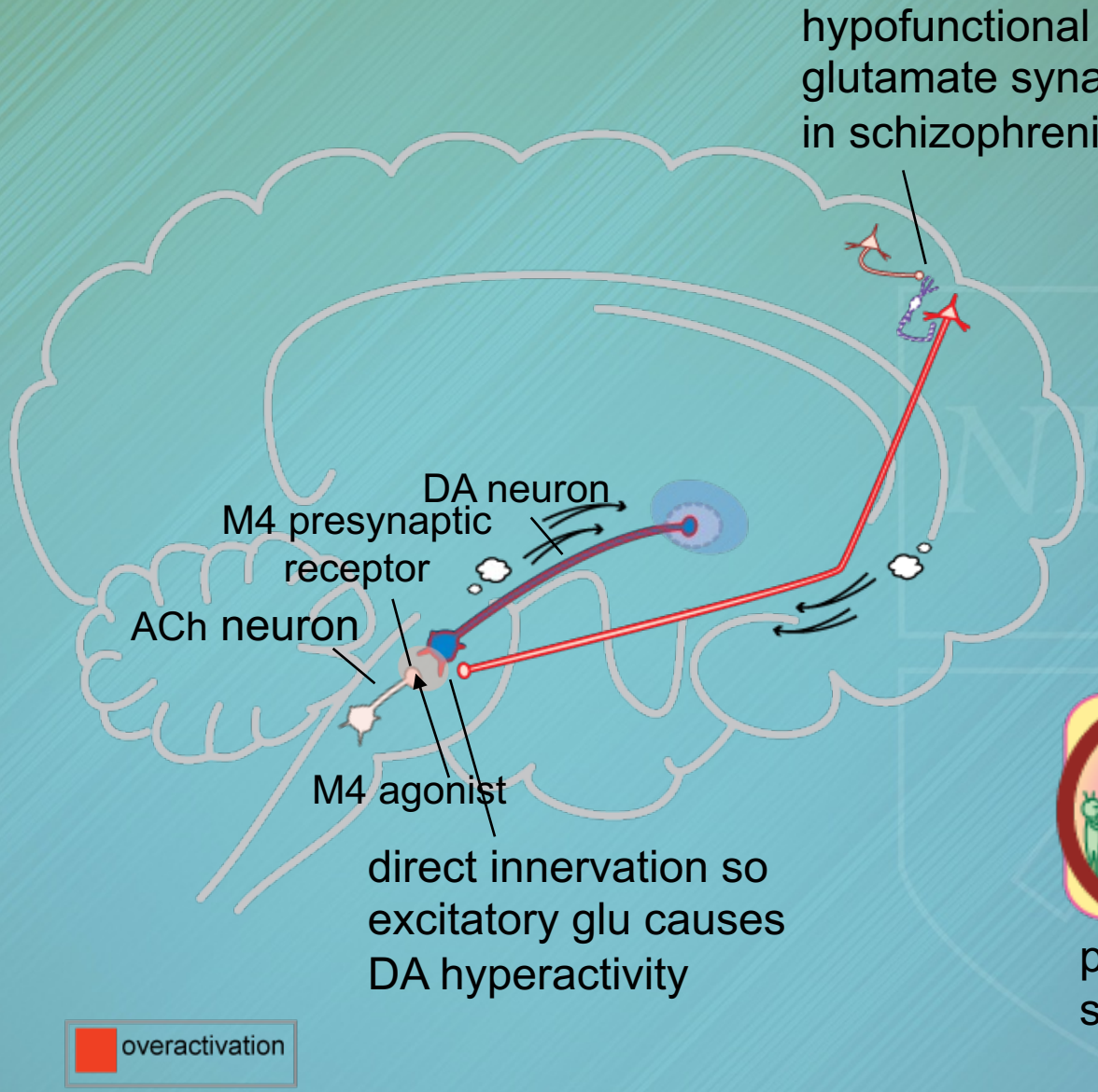


Procholinergic Treatment of Schizophrenia

Role of Procholinergic Treatment for Positive Symptoms

- Procholinergic treatment of positive symptoms
  - M4 agonist at presynaptic side of ACh receptors in the hindbrain, shuts off activation of mesolimbic dopaminergic (DA) neurons

Psychosis in Schizophrenia

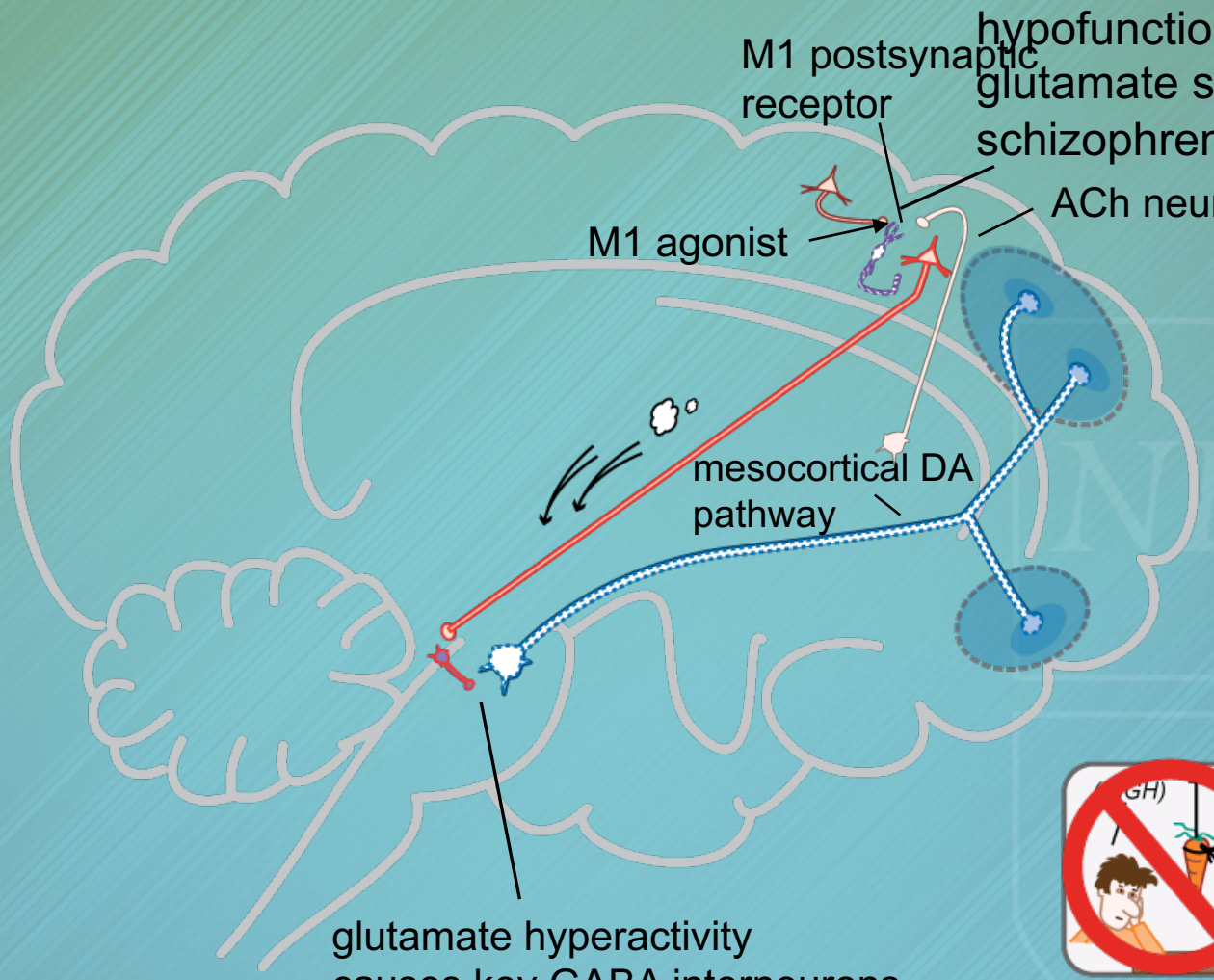


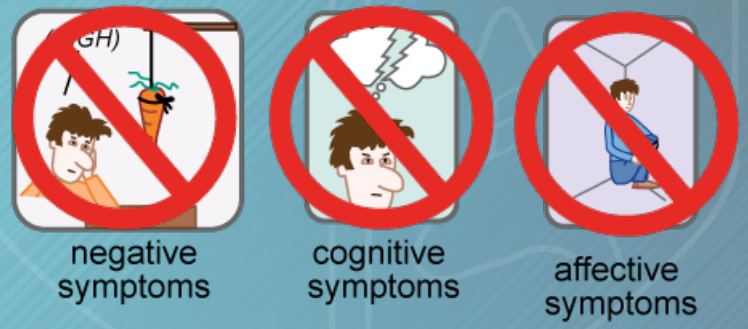
positive
symptoms

Role of Procholinergic Treatment for Negative Symptoms

- Procholinergic treatment of negative symptoms
  - M1 agonist binds postsynaptic M1 receptor on hypofunctional GABA interneurons in frontal cortex, activating them!
  - Through a series of steps, this takes excessive glutamate's foot off the brakes and increases dopamine release in the mesocortical pathway

Negative and Cognitive Symptoms in Schizophrenia





Understanding How Agonists/Modulators Work

- Orthosteric agonists versus allosteric modulators

- Orthosteric agonists bind to the same receptor site as the endogenous agonist (i.e., acetylcholine)
  - Kar XT (xanomeline-trospium) is an orthosteric agonist that binds to M1 and M4 receptors in the same place acetylcholine binds

- Allosteric modulators bind to a different receptor site than the endogenous agonist
  - Allosteric binding changes the overall receptor's response to stimulation
  - In other words, allosteric binding modulates/changes the way the receptor works when something binds its orthosteric site

Understanding How Agonists/Modulators Work Part 2

- There are 3 types of allosteric modulators: positive, negative, and neutral
- Positive allosteric modulators (PAMs) increase the response of the receptor by increasing the probability that an agonist will bind to a receptor (i.e., affinity), increasing its ability to activate the receptor (i.e., efficacy), or both
  - Examples include alcohol (ethanol), benzos, Ambien, etc.—all of which are $GABA_A$ PAMs
- Negative AMs decrease the agonist affinity and/or efficacy
- Neutral AMs don't affect agonist activity but can stop other modulators from binding to an allosteric site
- Some modulators also work as allosteric agonists (just to make things more confusing)

Agonists/Modulators vs Antagonists (Current "Antipsychotics")

- Nearly all current antipsychotic drugs are antagonists of dopamine and serotonin receptors
  - Most reduce excessive neurotransmission/hyperactivity by "blocking" a large amount of postsynaptic receptors to keep them from being stimulated
- Presynaptic agonists/modulators are believed to shut off neurotransmission, having a downstream effect of preventing hyperactivity/stimulation (i.e., similar net-effect of a postsynaptic antagonist)
- Unlike antagonists, agonists do not need to occupy the majority of binding sites to have an effect
- Antagonists shut down all signal transduction but that does not mean that agonists do the opposite (i.e., agonists don't always enhance all signal transduction)
- Some agonists do not appear to be "functional," i.e., they do not trigger signal transduction
  - e.g., the apparent situation with serotonin receptor binding by xanomeline

Pulling It All Together: Agonists/Modulators vs Antagonists

- Both orthosteric and allosteric receptor sites can be linked to second messenger systems (i.e., G-protein coupled receptor, or “GPCR”)
- Binding or modulating them can activate signal transduction pathways and exert downstream effects on one or more neurotransmitter systems (or circuits) without all of the pharmacologic effects of potent antagonists
- Cholinergic neurons in the brain can play a role in regulating dopamine neurotransmission in areas relevant to psychosis
- Multiple cholinergic agonists (M1/M4) and PAMs are being developed to treat psychotic disorders

Overview: M1 and M4 Antipsychotic Action

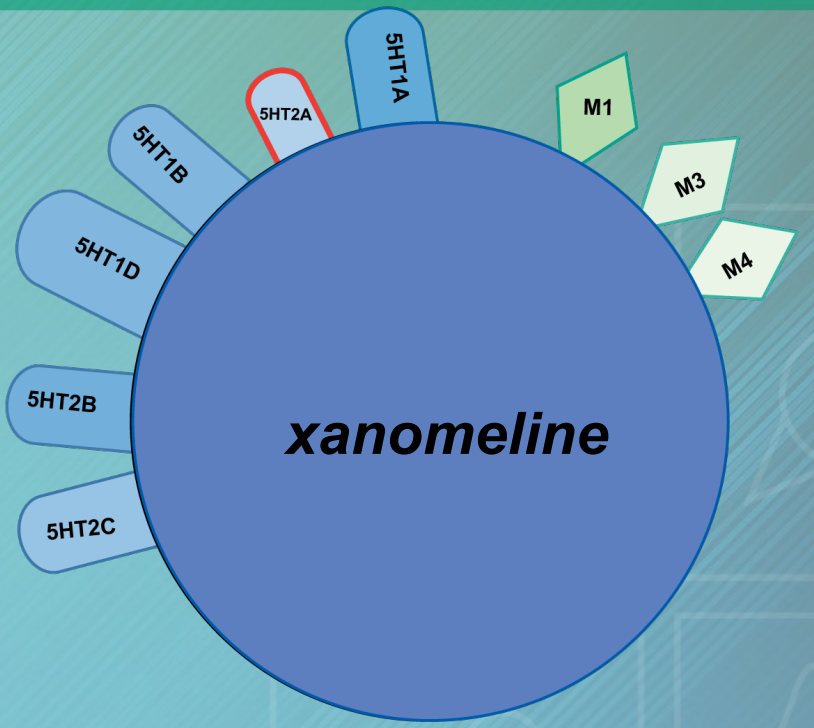
- The dopamine hypothesis of schizophrenia remains as the major theory for symptoms in schizophrenia
- M4 agonist binding on presynaptic side of Ach receptors (in the hindbrain) shuts off activation of mesolimbic DA neurons, reducing positive symptoms
- M4-mediated inhibition of Ach interneuron activity also decreases local ACh tone, decreasing dopamine hyperactivity and positive symptoms
- M1 agonist binds postsynaptic M1 receptor on hypofunctional GABA interneurons (in frontal cortex) activating them! This takes glutamate's foot off the brakes and increases DA release in the mesocortical pathway, reducing negative symptoms

Agents in Development

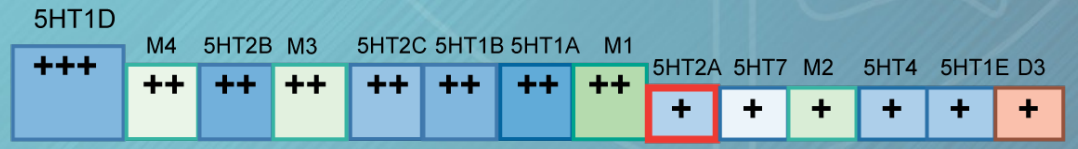
- Karuna's KarXT M1/M4 Agonist (M2/M3 peripheral antagonist)
- Cerevel's Emraclidine is a selective M4 PAM
- Neurocrine Biosciences anticipates initiating a Phase 2 study with the selective M4 agonist HTL-0016878 in schizophrenia in 2022 and Phase 1 studies for a dual M1/M4 and selective M1 agonist in 2023
- ACP-319 is a highly selective M1 PAM and may represent a novel approach for improving cognitive function and other neuropsychiatric symptoms in patients suffering from CNS disorders

Xanomeline

- M4/M1 central agonist
- Decreases DA firing in the VTA, resulting in reduced positive symptoms
- Increases extracellular levels of DA in the PFC, improving cognitive, negative, and affective symptoms



DA=dopamine; PFC=prefrontal cortex



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Trace Amine-Associated Receptor 1 (TAAR1) Agonists

What Is a Trace Amine?

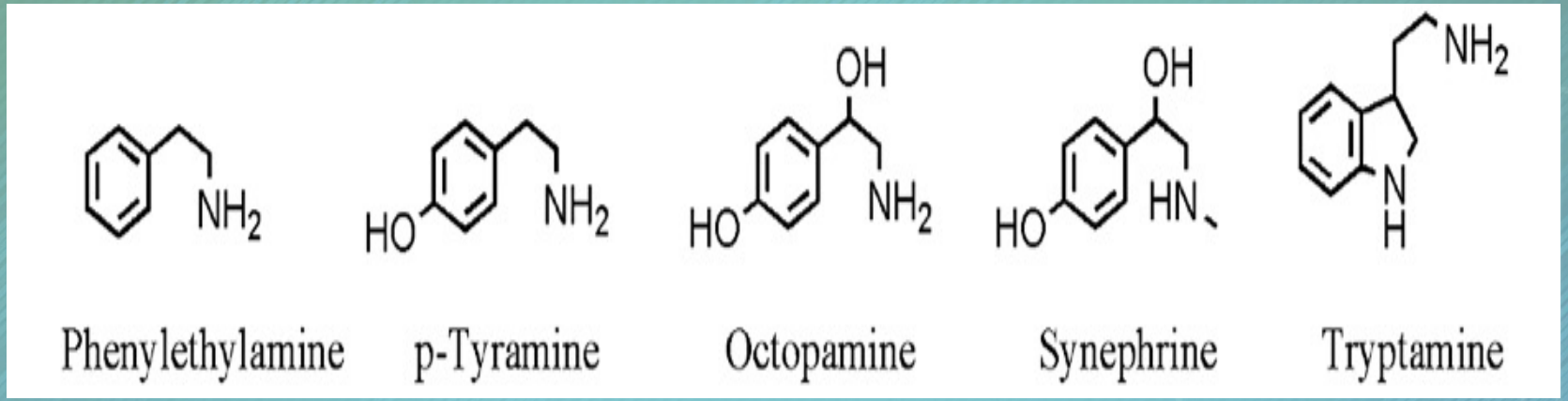
- Amines formed in trace concentrations from the amino acid tyrosine when tyrosine hydroxylase omitted

- or

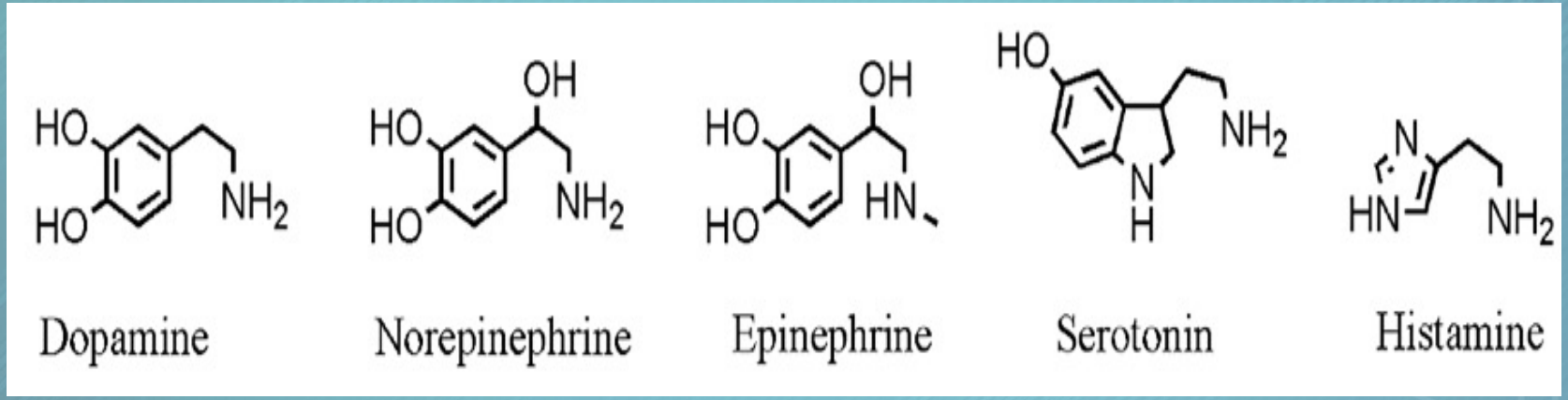
- Amines formed in trace concentrations from the amino acid tryptophan when tryptophan hydroxylase omitted

Trace Amines and Monoamines

Trace Amines



Monoamines

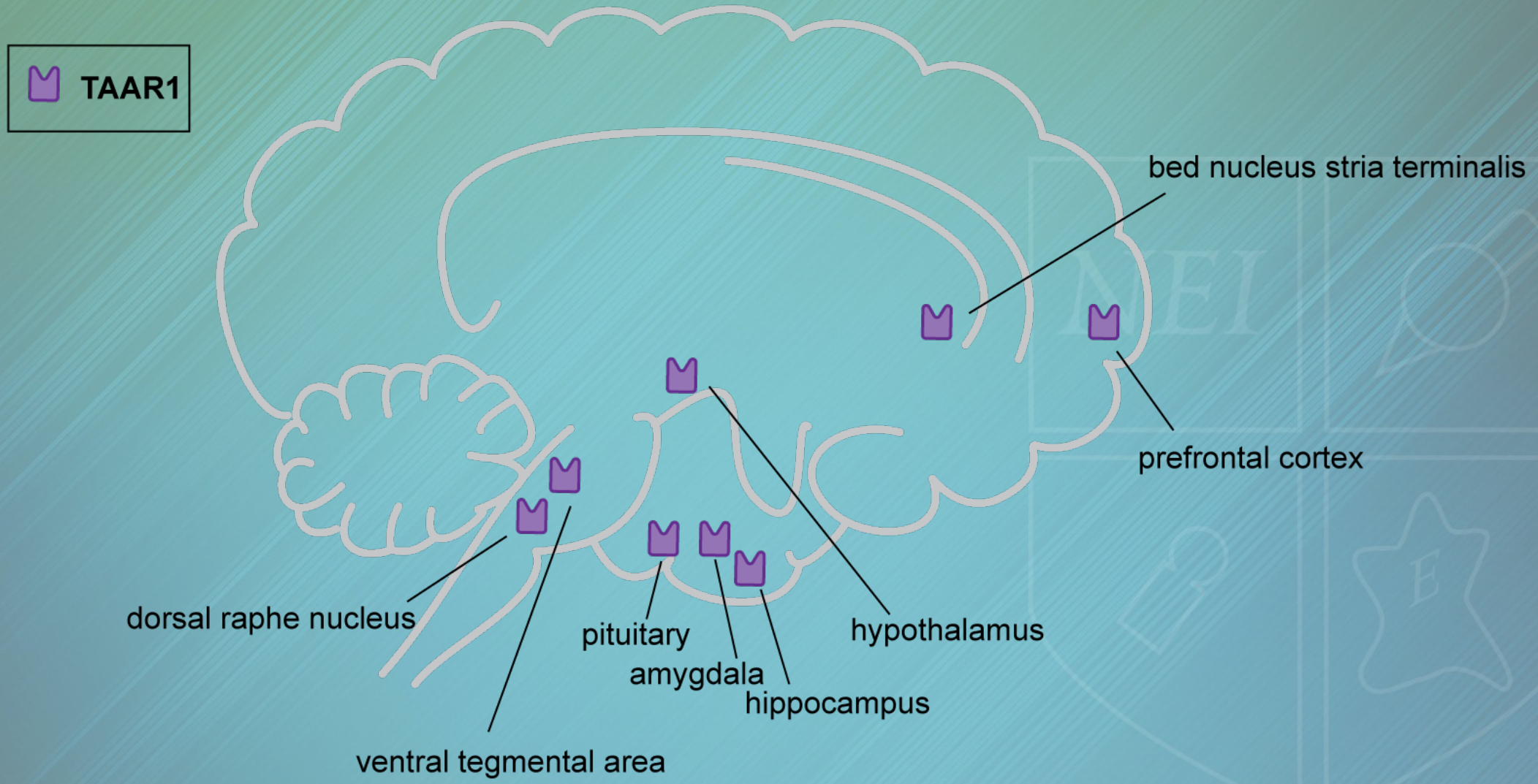


Trace Amines and Their Receptors

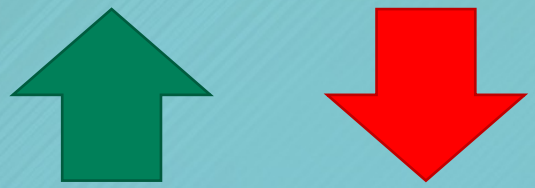
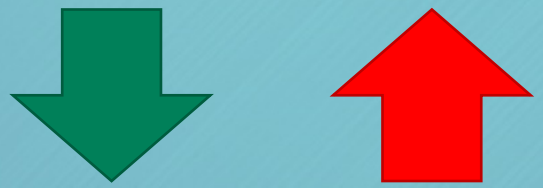
- Five principal trace amines in humans
  - β-Phenylethylamine (PEA)
  - p-Tyramine
  - Tryptamine
  - p-Octopamine
  - p-Synephrine

- Six human trace amine-associated receptors (TAARs)
  - **TAAR1 (main TAAR in humans)**
  - TAAR2
  - TAAR5
  - TAAR6
  - TAAR8
  - TAAR9

TAAR1 Distribution



TAAR1 Effect on Neurotransmitters: Dopamine

- TAAR1 is expressed in the ventral tegmental area (VTA) and to a lesser extent the substantia nigra
- TAAR1 agonism is a novel way to prevent hyperactivity of the dopaminergic system:
  - TAAR1 activity,  DA neurotransmission
  - TAAR1 activity,  DA neurotransmission

TAAR1 Effect on Neurotransmitters: Serotonin

- TAAR1 is expressed within the dorsal raphe nucleus (DRN)
- TAAR1 agonists decrease firing frequency of 5-HT neurons in the DRN of mice
- TAAR1 likely functions endogenously to maintain a balance in serotonergic activity
- TAAR1 may heterodimerize with 5HT1B receptors
  - *Heterodimerization i*s a concept where two different receptors join together molecularly

TAAR1 Effect on Neurotransmitters: Glutamate

- TAAR1 can regulate Glu neurotransmission in the prefrontal cortex

- TAAR1 appears to prevent hypoglutamatergic states, thereby causing an increase in activity in the prefrontal cortex

TAAR1 and Dopamine Systems

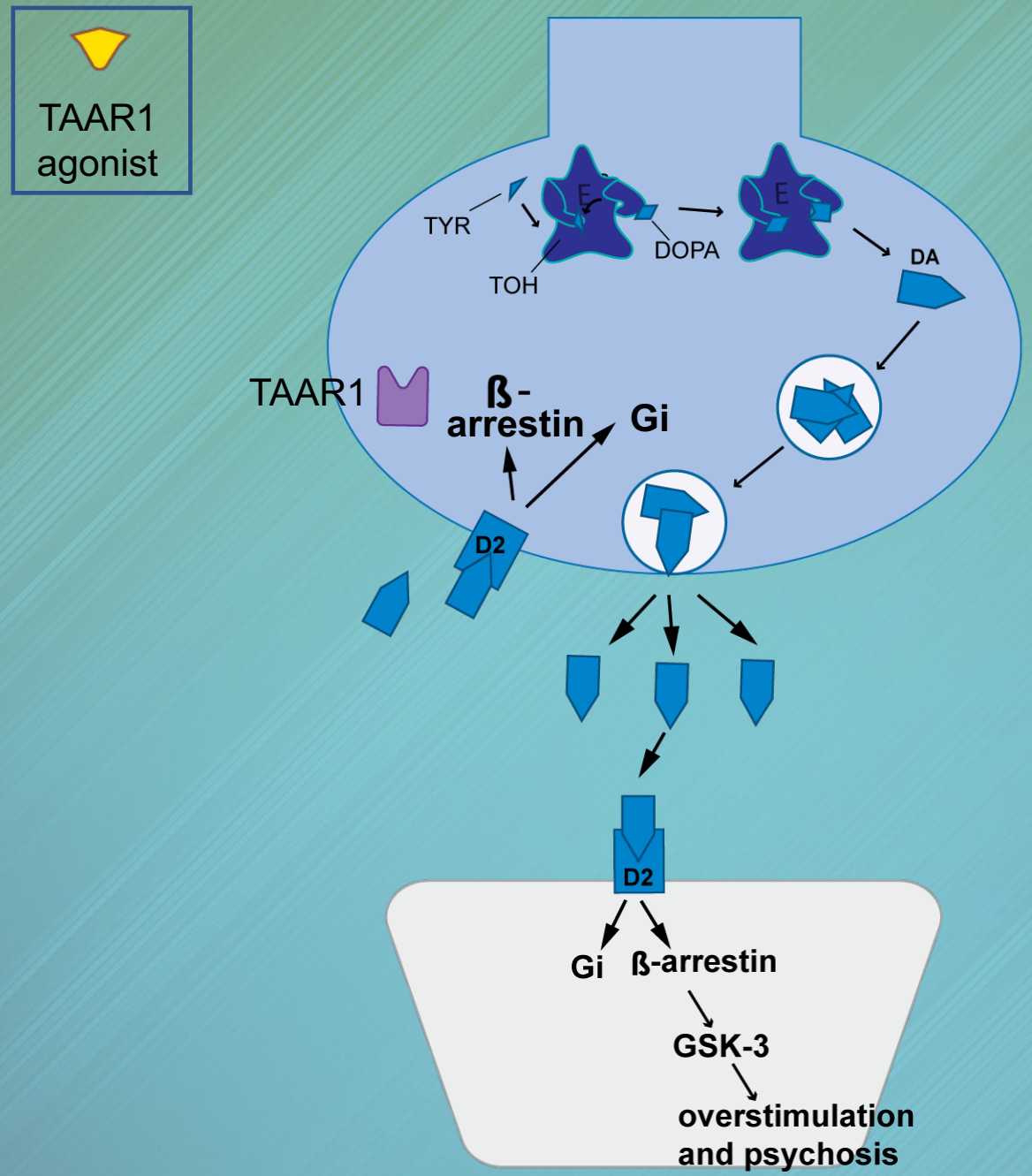
- Beta phenethylamine (PEA) and tyramine (Tyr) are synthesized in dopamine terminals
- Not stored within synaptic vesicles and readily diffuse across plasma membranes
- Reuptake into presynaptic terminals via OCT2 (postsynaptic?)
- TAAR1 predominantly intracellular, both pre- and postsynaptic
- Suggestion that TAAR1 tonically acts to prevent dopaminergic hyperactivity and that TAAR1 agonists are a novel way to prevent overactivity by D2 receptors
  - (TAAR1 also acts to prevent hypoglutamatergic states)

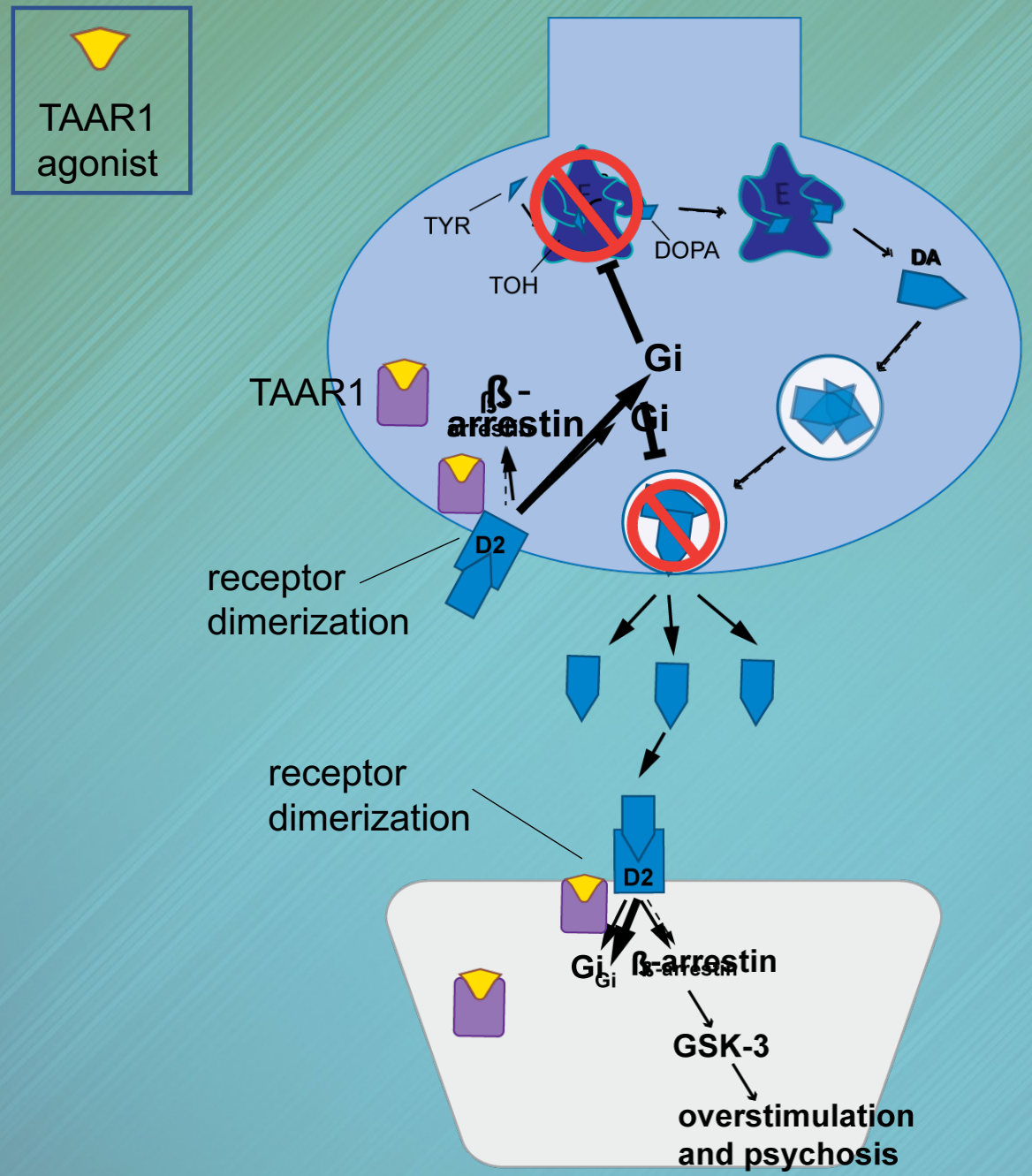
“Neural Mechanisms That We Don’t Know”

- TAAR1 may translocate to cell surface after *“heterodimerization”* with D2R by *“biasing”* signal transduction to the Gi signal transduction cascade to inhibit dopamine synthesis rather than to the beta arrestin 2 pathway

- Evidence that TAAR1 reduces both presynaptic and postsynaptic D2 function

- TAAR1 heterodimers with D2 receptors to positively modulate presynaptic D2 autoreceptors (i.e., make them stop dopamine synthesis and release) while negatively regulating postsynaptic D2 receptors via the inhibitory Gi pathway


TAAR1
agonist
TYR
TOH
DOPA
DA
TAAR1
ß-
arrestin
Gi
D2
D2
Gi
ß-arrestin
GSK-3
overstimulation
and psychosis


TAAR1 agonist
TYR
TOH
DOPA
DA
Gi
TAAR1
ß-arrestin
Gi
D2
receptor dimerization
receptor dimerization
D2
Gi
ß-arrestin
GSK-3
overstimulation and psychosis

TAAR1 Agonists in Clinical Development

- **RO6889450** (Ralmitaront, Roche)— TAAR1 partial agonist
  - Currently in Phase 2 trials for the treatment of patients with schizophrenia or schizoaffective disorder
    - Two active Phase 2 studies (recruiting)
    - Acute exacerbation
    - Negative symptoms
- **SEP-363856** (Ulotaront, Sunovion/Otsuka)—TAAR1 agonist with 5-HT_{1A} agonist activity
  - Phase 2 studies complete
    - Safe and effective in a 4-week study in patients with an acute exacerbation of schizophrenia
    - Demonstrated continued effectiveness in a 26-week open-label extension study with no new safety concerns
  - Currently in Phase 3 development for the treatment of schizophrenia

TAAR1 Partial Agonist in Development—Roche RO6889450 (Ralmitaront)

- Currently in Phase 2 trials for the treatment of patients with an acute exacerbation of schizophrenia or schizoaffective disorder
  - One study terminated: preliminary analysis showed that the primary endpoint was negative
  - Second study (12-week) currently recruiting

Effects of RO6889450 (Ralmitaront) in Participants With Schizophrenia or Schizoaffective Disorder and Negative Symptoms

NCT03669640- Phase 2, Two Experimental Arms
Currently recruiting patients aged 18–55 years

A

- Ralmitaront monotherapy vs. placebo
- 12 weeks

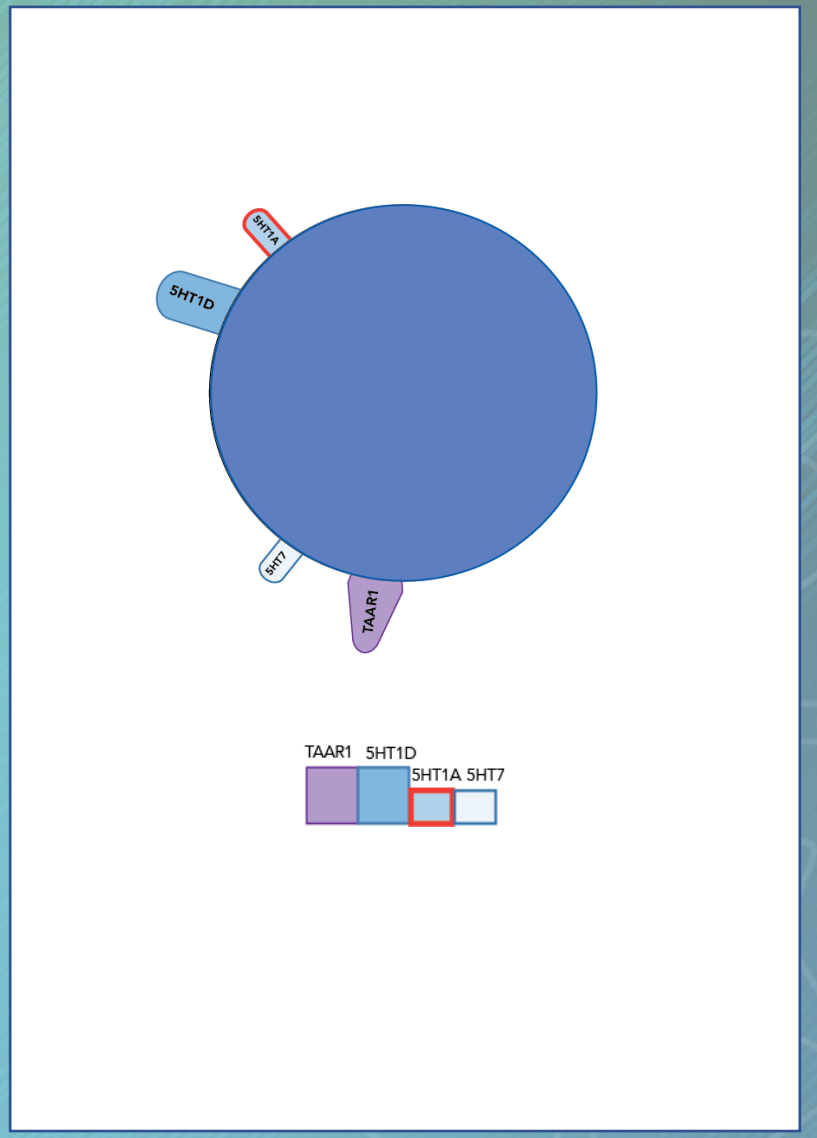
B

- Add-on Therapy
- Ralmitaront (low or high dose) + current antipsychotic therapy vs. placebo
- 12 weeks

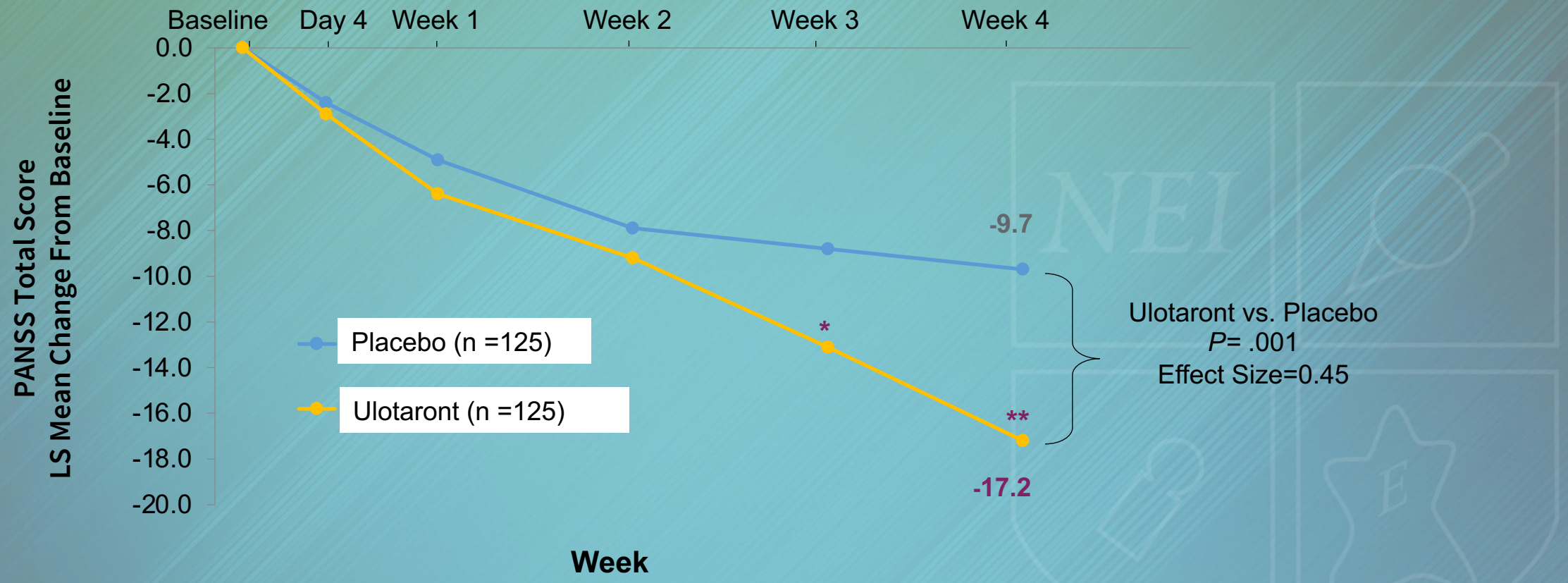
Primary Outcome Measures: Brief Negative Symptoms Scale (BNSS) Avolition/Apathy Subscore at Week 12
Estimated enrollment: 247 participants
Estimated completion date: December 24, 2022

TAAR1 Agonist in Development: Ulotaront

- TAAR1 agonist with 5-HT1A agonist activity
- Lacks activity at D_2 and 5-HT_{2a} receptors
- Phase 2 study demonstrated efficacy for positive and negative symptoms and safety in a 4-week study in patients with an acute exacerbation of schizophrenia
- Phase 2 study demonstrated continued effectiveness in a 26-week open-label extension study with no new safety concerns
- Currently in Phase 3 development for the treatment of adults and adolescents (ages 13–17) with schizophrenia



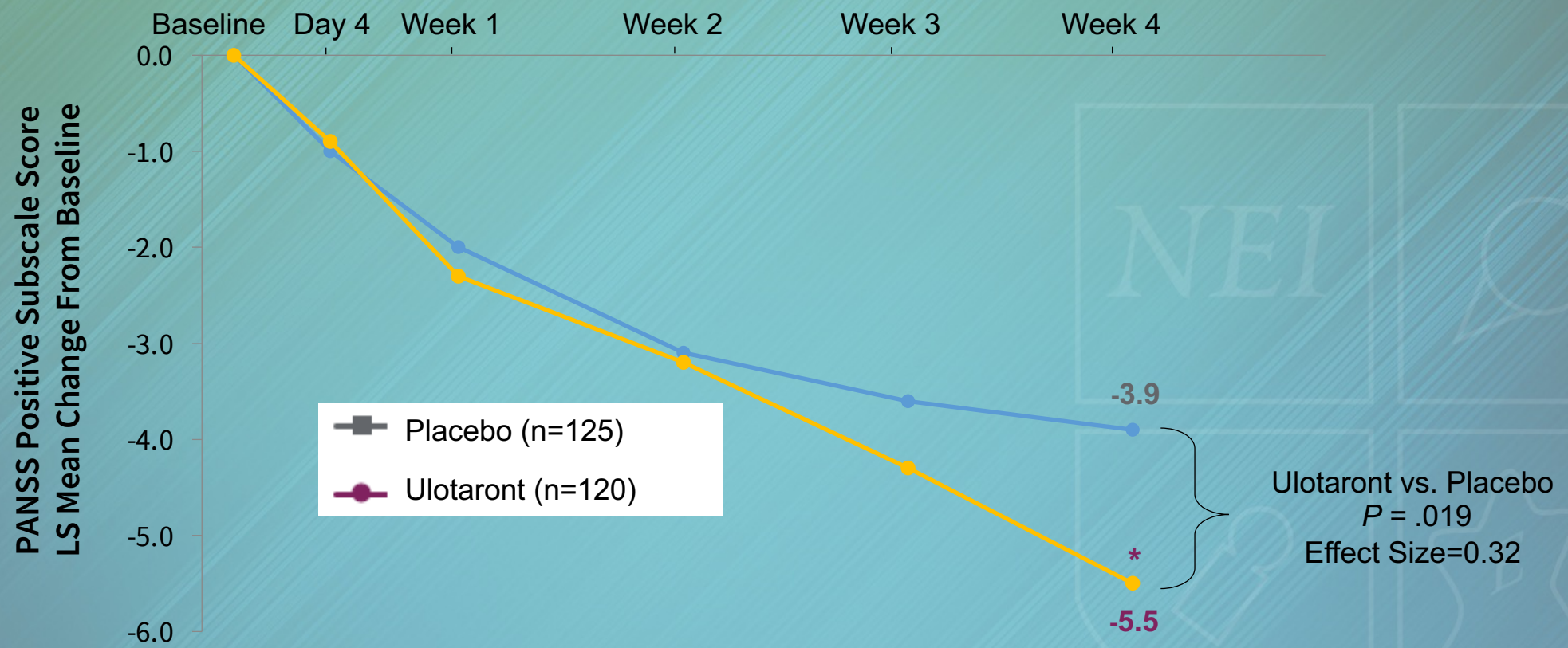
Ulotaront Phase II Trial in Schizophrenia: PANSS Total Score



*P < .05; **P < .01.
LS, least squares.

Koblan KS et al. N Engl J Med 2020;382(16):1497-506; Data on file, Sunovion Pharmaceuticals Inc.

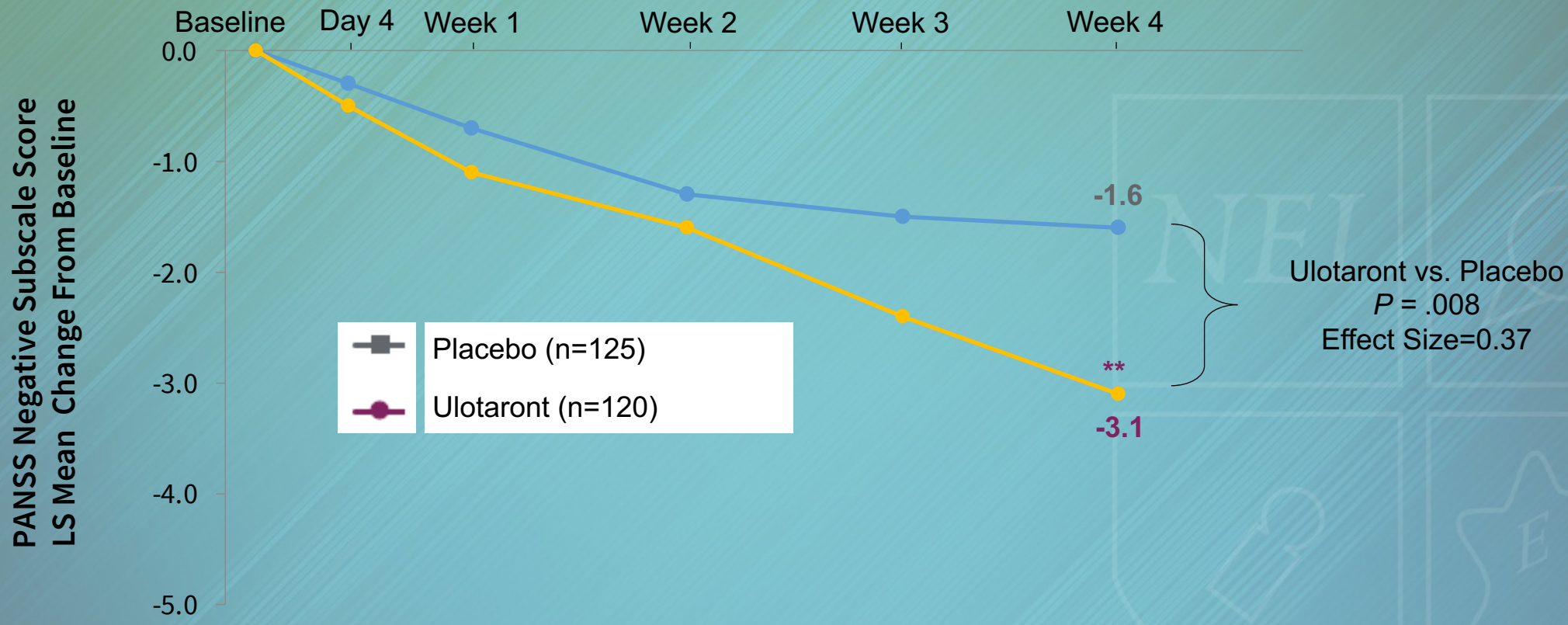
Ulotaront Phase II Trial in Schizophrenia: PANSS Positive Symptom Subscale Score



*$P < .05$.

Koblan KS et al. N Engl J Med 2020;382(16):1497-506; Data on file, Sunovion Pharmaceuticals Inc.

Ulotaront Phase II Trial in Schizophrenia: PANSS Negative Symptom Subscale Score



**$P < .01$.

Koblan KS et al. N Engl J Med 2020;382(16):1497-506; Data on file, Sunovion Pharmaceuticals Inc.

Ulotaront Phase II Trial in Schizophrenia: Open-Label Extension (OLE) Adverse Events

- Overall, 56% of patients treated with ulotaront in the 26-week OLE study experienced an AE; only headache, schizophrenia (worsening or exacerbation of schizophrenia), insomnia, and anxiety occurred at an incidence greater than 5%
- Rate of serious AEs in patients treated with ulotaront was low (5.1%), with the only severe AE observed in more than 1 patient being schizophrenia
- Overall incidence of EPS-related adverse effects (parkinsonism, dyskinesia, tremor, and restlessness) was low (3.2%)
- Over the 26 weeks, rate of AEs leading to discontinuation was 11.5% in patients treated with ulotaront
- Study completion rates were 66.9%

	Ulotaront (n =156)
Patients with any AEs, n (%) [a]	88 (56.5)
Headache	18 (11.5)
Schizophrenia	19 (12.2)
Insomnia	13 (8.3)
Anxiety	8 (5.1)
Somnolence	7 (4.5)
Irritability	5 (3.2)
Nausea	6 (3.8)
Nasopharyngitis	7 (4.5)
Influenza	5 (3.2)
Weight decreased	5 (3.2)
Blood prolactin increased	4 (2.6)
Serious AE, n (%)	15 (9.6)
AEs leading to discontinuation, n (%)	18 (11.5)

[a] Indicates any event with a reported frequency >2.

Data on file, Sunovion Pharmaceuticals Inc.

Ulotaront Phase II Trial in Schizophrenia: OLE Weight, Metabolics, & Sleep

- Overall, the metabolic profile of ulotaront following up to 26 weeks of treatment was similar to OL baseline and not clinically notable
- Effect of ulotaront on prolactin levels was negligible at week 26

Measurement	Ulotaront (n=156) Change From OL Baseline
Weight/BMI, mean (SD) change at week 26	
Weight, kg	–0.3 (3.20)
BMI, kg/m^2	–0.1 (1.03)
Laboratory values (fasting), median change at week 26	
Total cholesterol, mmol/L	2.00
HDL cholesterol, mmol/L	2.00
LDL cholesterol, mmol/L	–1.00
Triglycerides, mmol/L	0.00
Glucose, mmol/L	2.00
HbA1c (%)	0.00
Prolactin, male/female	
pmol/L	–1.26/–2.10
PSQI global score, mean (SD) change at week 26	–2.0 (2.97)

Data on file, Sunovion Pharmaceuticals Inc.

Summary

- Understanding the underlying neurocircuitry of positive and negative symptoms of schizophrenia is essential for appropriate treatment decisions and medication selection
- First-generation “antipsychotics,” while effective at reducing psychotic symptoms, can result in worsened negative symptoms and side effects
- Second-generation “antipsychotics” were developed in an effort to reduce many of these side effects
- Novel agents in development, such as M1/M4 agonists and TAAR1 agonists, and have demonstrated efficacy in treating both positive and negative symptoms
- These novel agents may be able to address unmet needs in schizophrenia, including residual symptoms, functional impairment, and medication side effects

Posttest Question 1

Which of the following mechanisms underly negative and cognitive symptoms in schizophrenia?

1. Hypofunctional NMDA glutamate synapses in the prefrontal cortex
2. Overactivation of the mesolimbic pathway, resulting in agitation, aggression, and impulsivity
3. Glutamate hyperactivity, which causes key GABA interneurons to inhibit dopamine release in the mesocortical pathway
4. 1 and 2
5. 1 and 3

Posttest Question 2

Which of the following is the correct mechanism for procholinergic treatment of positive symptoms in schizophrenia?

1. M4 agonist binds to postsynaptic M4 receptor on hypofunctional GABA interneurons in the frontal cortex, activating them and resulting in enhanced dopamine in the mesocortical pathway
2. M4 agonist at the presynaptic side of Ach receptors in the hindbrain inhibits activation of mesolimbic dopaminergic neurons by inhibiting the release of ACH
3. M4 agonist at the presynaptic side of Ach receptors in the hindbrain increases activation of mesocortical dopaminergic neurons
4. M1 agonist binds to the postsynaptic M1 receptor on hypofunctional GABA interneurons in the frontal cortex, activating them and resulting in enhanced dopamine in the mesocortical pathway
5. None of the above

Posttest Question 3

Results from early studies of TAAR1 agonists in schizophrenia show

1. Promising signs of efficacy for total, positive, and negative symptoms
2. Some motor side effects greater than placebo
3. Some weight gain and dyslipidemia greater than baseline in 6-month study
4. Some wearing off of efficacy in long-term extensions
5. All of the above