Psych Congress Network

# Mastering Schizophrenia Treatment:

## Optimal Use of Oral Antipsychotics Based on Neurobiological and Clinical Evidence

Psych Congress Network

# Neurobiological Insights into the Unmet Needs of Patients with Schizophrenia

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# Learning Objectives

- Assess the burdens of schizophrenia and common challenges and shortcomings in its treatment

- Describe the evolution of neurobiological models of schizophrenia, focusing on the role of presynaptic mechanisms and multiple neurotransmitters in addition to dopamine

# Overview of Schizophrenia

# Clinically Relevant Domains of Schizophrenia

## Physical Morbidity

- Cardiovascular diseases
- Inflammation, oxidative stress

## Reward Dysregulation

- Smoking and substance use disorders
- Aberrant salience and reward anticipation

## Positive Symptoms

- Hallucinations
- Delusions
- Thought disorder
- Hostility
- Excitability


## Negative Symptoms

- Affective flattening
- Alogia
- Anhedonia
- Amotivation
- Asociality

## Motor Symptoms

- Motor delay
- Dyscoordination
- EPS, e.g.,
  - Parkinsonism
  - Dyskinesia

## Affective Symptoms

- Depression
- Anxiety
- Suicidality

## Cognition

- Attention
- Working memory
- Verbal memory
- Visual memory
- Executive functioning
- Processing speed
- Social conditioning

**EPS = extrapyramidal side effects**

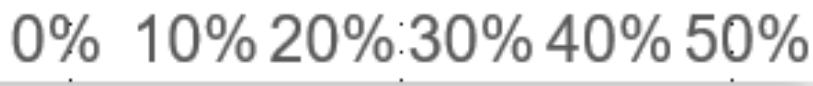
**Carbon M, Correll C. *CNS Spectr*. 2014;19(Suppl 1):38-52.; Millan MJ, et al. *Eur Neuropsychopharmacol*. 2014;24(5):645-692.; Morrens M, et al. *Front Psychiatry*. 2014;5:145.; Millan MJ, et al. *Nat Rev Drug Discov*. 2012;11(2):141–168.; Ventriglio A, et al. *Front Psychiatry*. 2016;7:116.; Pillinger T et al. *Mol Psychiatry*. 2019;24(6):928; Kesby JP, et al. Biol Psychiatry Glob Open Sci. 2021 Dec 11;3(1):33-46.**

# Substance-Induced Psychotic Disorder is a Strong Risk Factor for a Subsequent Diagnosis of Schizophrenia

**25%**

of patients with substance-induced psychosis had a subsequent diagnosis of schizophrenia over a mean follow-up of 4 years

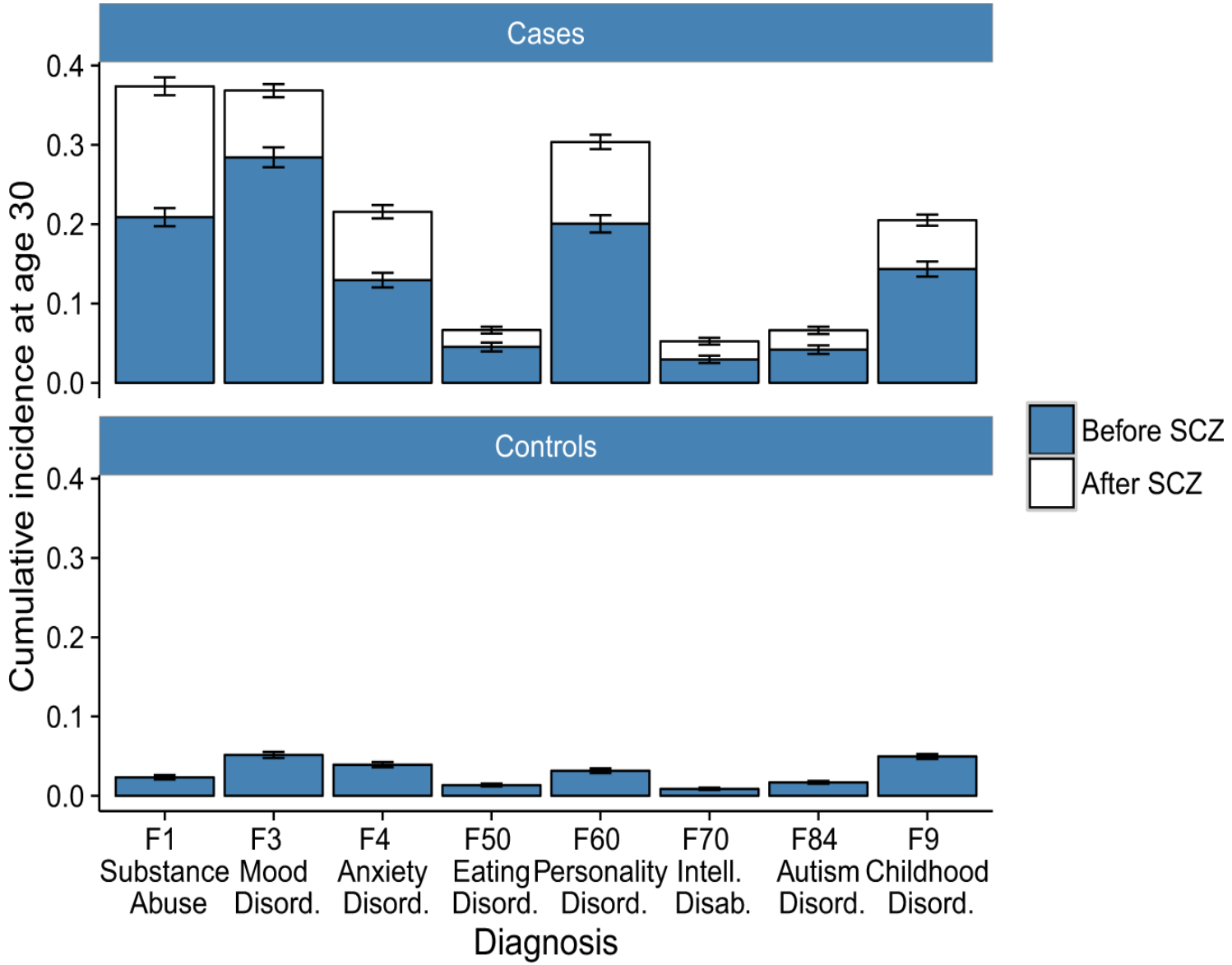
| Substance | # of studies | N | Percent of patients with subsequent diagnosis of schizophrenia |
|---|---|---|---|
| Alcohol | 5 | 19358 | 9% |
| Sedatives | 2 | 223 | 10% |
| Opioids | 3 | 664 | 12% |
| Amphetamines | 5 | 2284 | 22% |
| Hallucinogens | 3 | 208 | 26% |
| Cannabis | 6 | 3040 | 34% |




Murrie et al. Schizophr Bull. 2020;46(3):505-516.

# Frequent Psychiatric Comorbidities Before and After Onset of Schizophrenia -

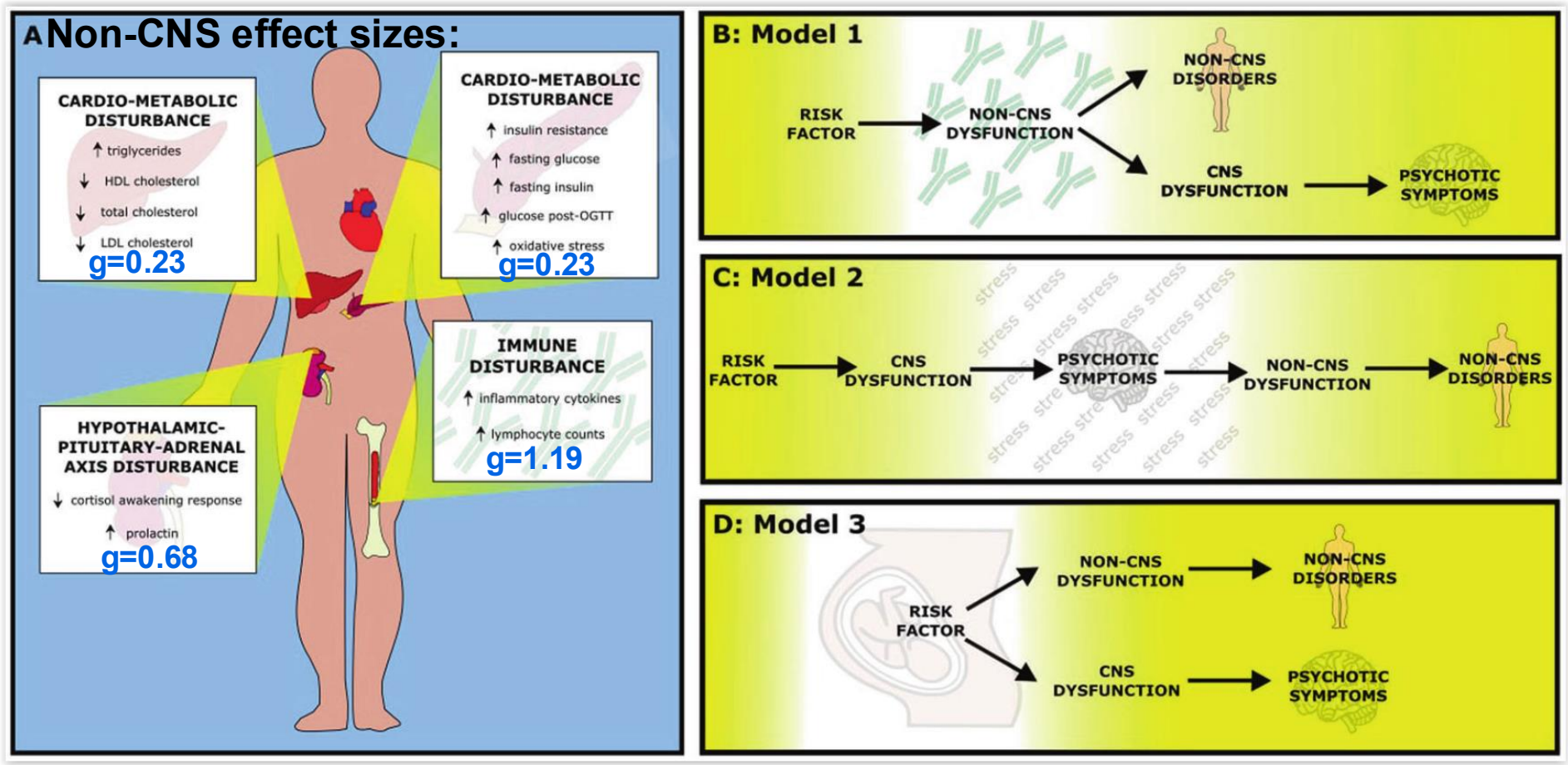
## Results from a Danish Cohort of 5432 Individuals with Schizophrenia and 10,864 Random Population Controls




Krebs MD, et al. Nat Commun. 2021 Nov 16;12(1):6617.

# Case-Control Studies in First Episode SCZ vs Controls: Similar Effect Sizes for CNS and Non-CNS Alterations

**CNS effect sizes: brain structure: g=0.40; neurophysiology: g=0.80; neurochemistry: g=0.43**

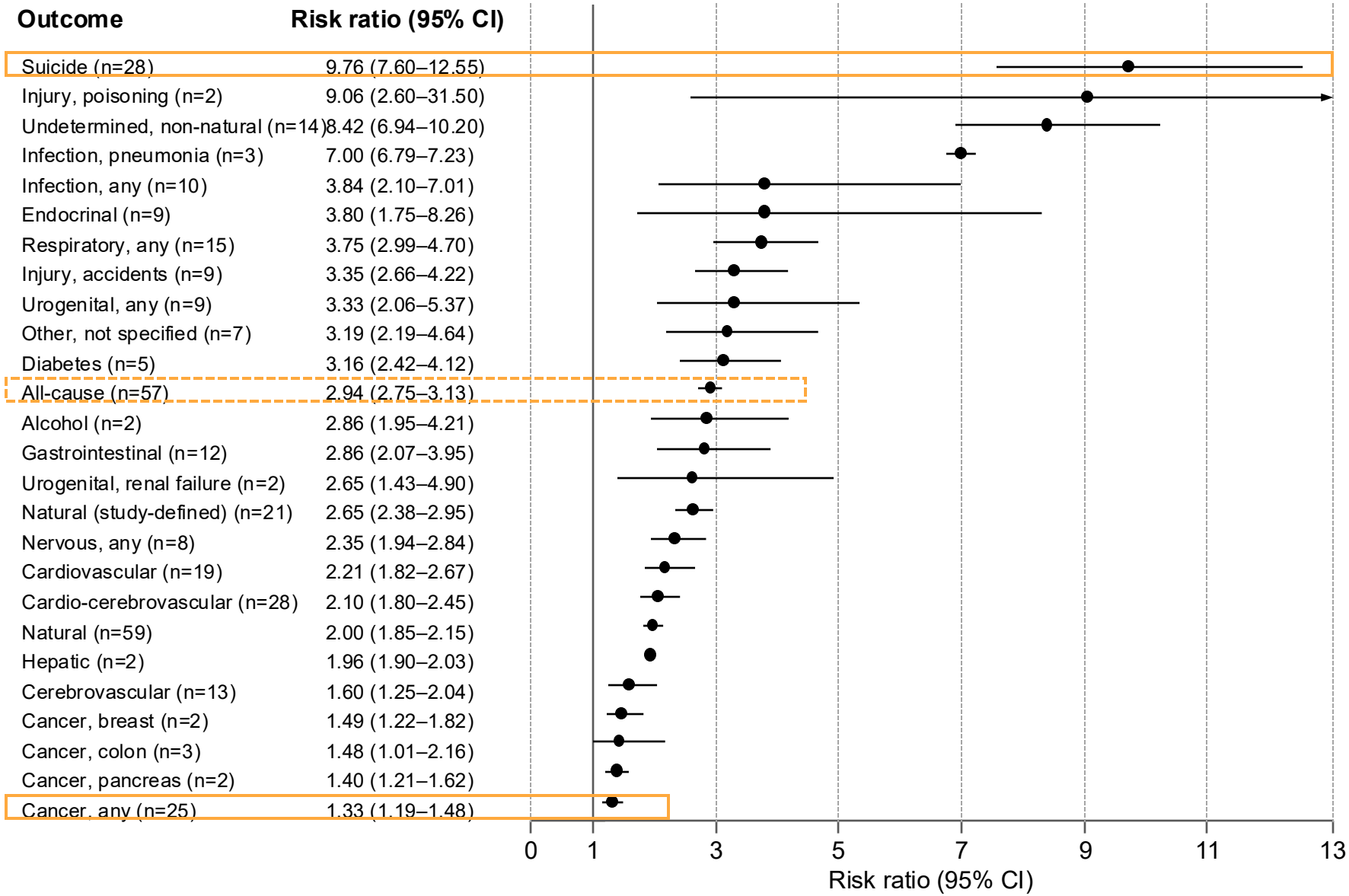



165 case-control studies, n=13,440

**Pillinger T et al. Mol Psychiatry. 2019 Jun;24(6):928.**

# Increased All-Cause and Specific Cause Mortality in Patients with Incident and Prevalent Schizophrenia

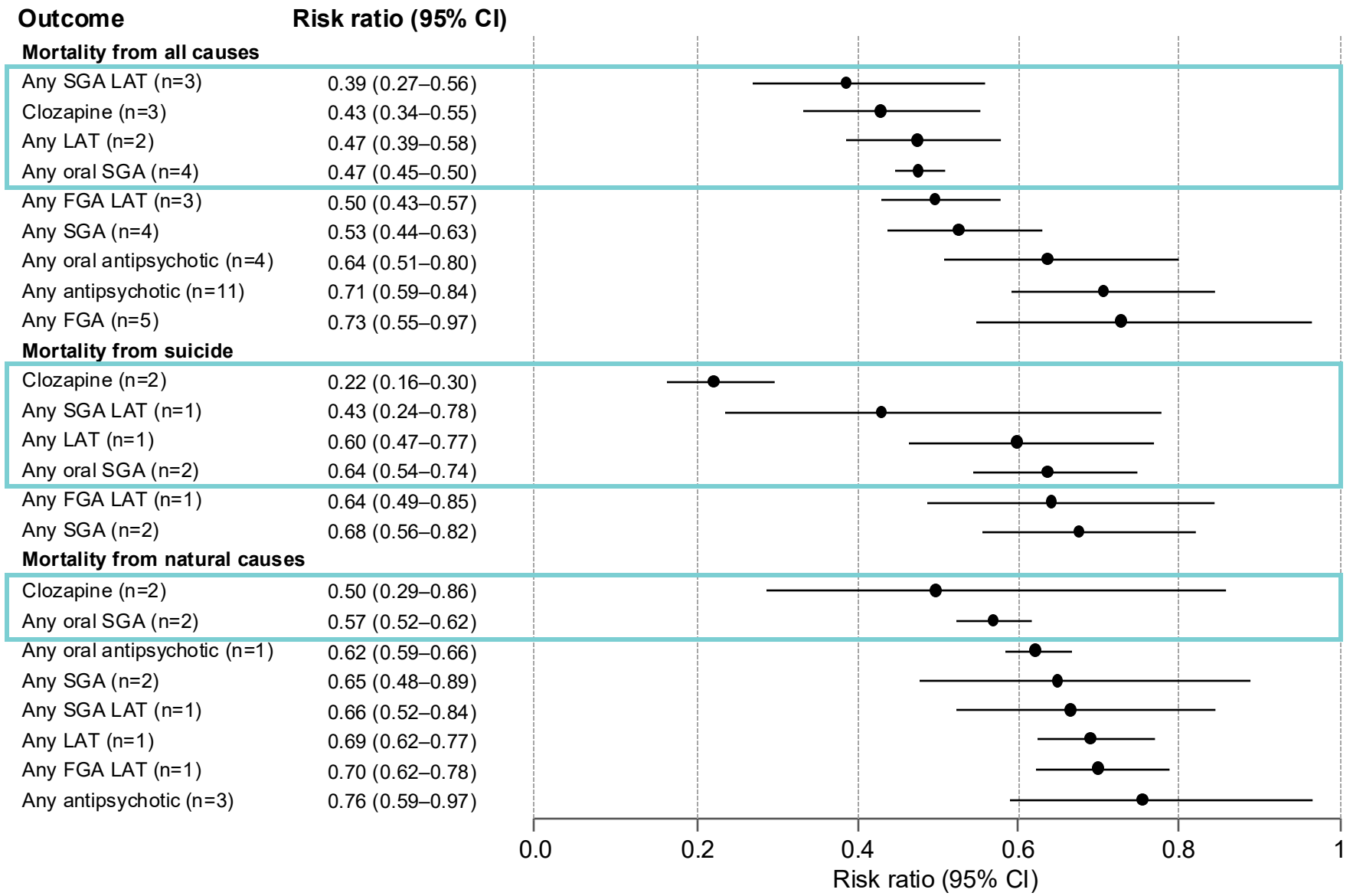
*compared to the general population*




**CI=Confidence Interval.**

**Correll CU, et al. *World Psychiatry* 2022;21:248–271.**

# Reduction in Any-, Suicide- and Natural-Cause Mortality in Patients with Schizophrenia On vs. Off Antipsychotics



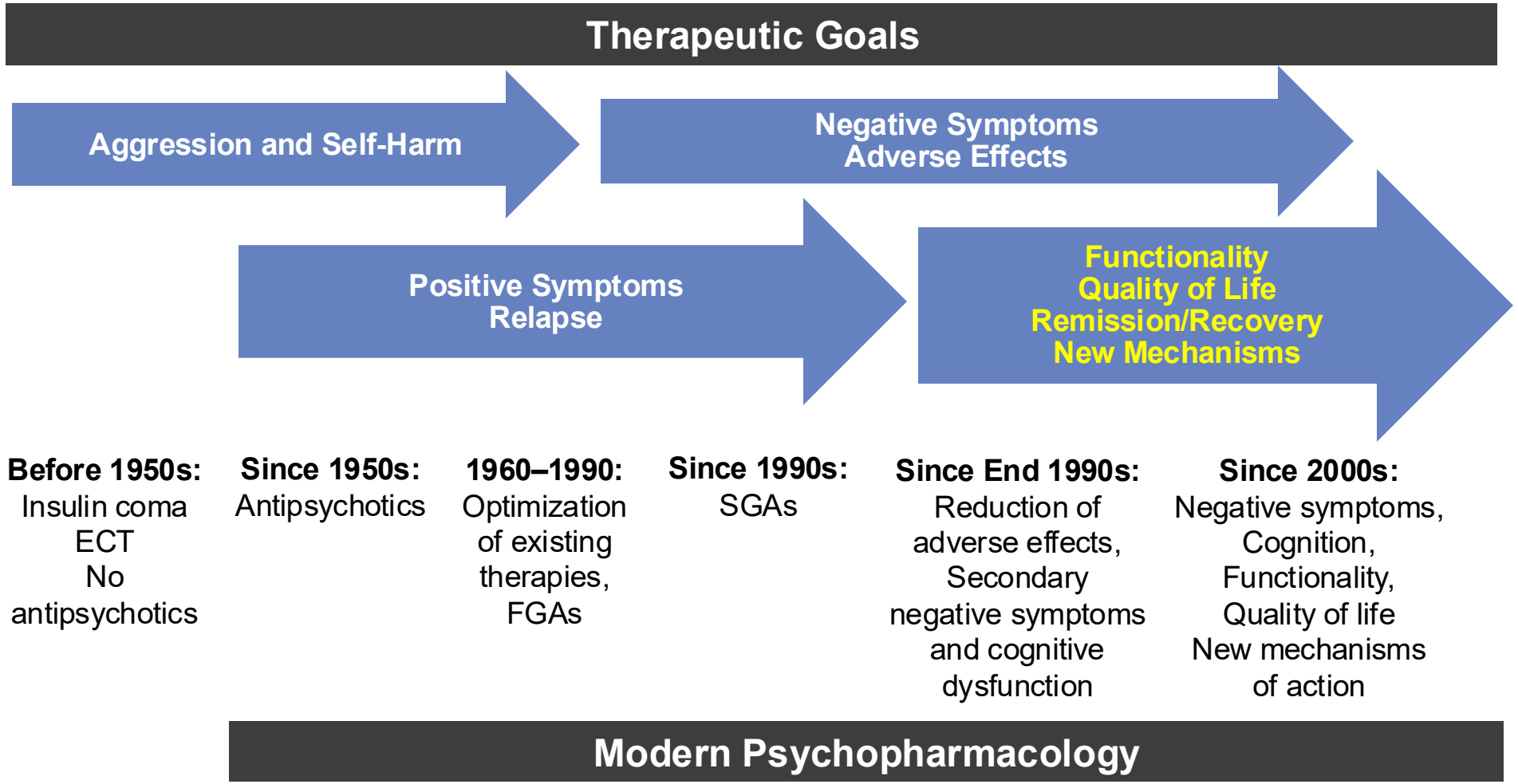

CI=Confidence Interval; FGA=First-generation antipsychotic; LAT=Long-acting therapy; SGA=Second-generation antipsychotic.
Correll CU, et al. *World Psychiatry* 2022;21:248–271.

# Key Learning Points

- Schizophrenia is a multidimensional, complex and severe mental disorder
- Multiple treatment target exists with different and, in parts, opposing neurobiological underpinnings
- Comorbid psychiatric and medical conditions are common
- Mortality risk is significantly increased
- Antipsychotic treatment significantly reduces the mortality risk

# Unmet Needs of Patients with Schizophrenia

# Evolution of Treatment Goals in Schizophrenia: The Recovery Model




**FGA=First-Generation Antipsychotics; SGA=Second Generation Antipsychotics.**
**Adapted from: Correll CU. *Nervenarzt*. 2020;91(1):34-42.**

# One Treatment *Does Not* Fit All: Inadequate Efficacy Across Symptom Domains

- **Positive symptoms**: antipsychotics are generally effective, but a minority remain partial/non-responders; clozapine needed for many treatment-resistant cases.
- **Negative symptoms**: limited pharmacologic options produce meaningful functional gains; treatments show small effect sizes.
- **Cognitive deficits**: minimal improvement with current antipsychotics; cognition strongly predicts long-term outcome but remains largely untreated by standard meds.
- **Functional recovery**: symptom reduction does not automatically translate into employment, relationships, or quality of life.

**Leucht et al. 2013; Huhn et al. 2019; Sabe et al. 2021; Haddad 2018.**

# Time Course of Antipsychotic Adverse Events

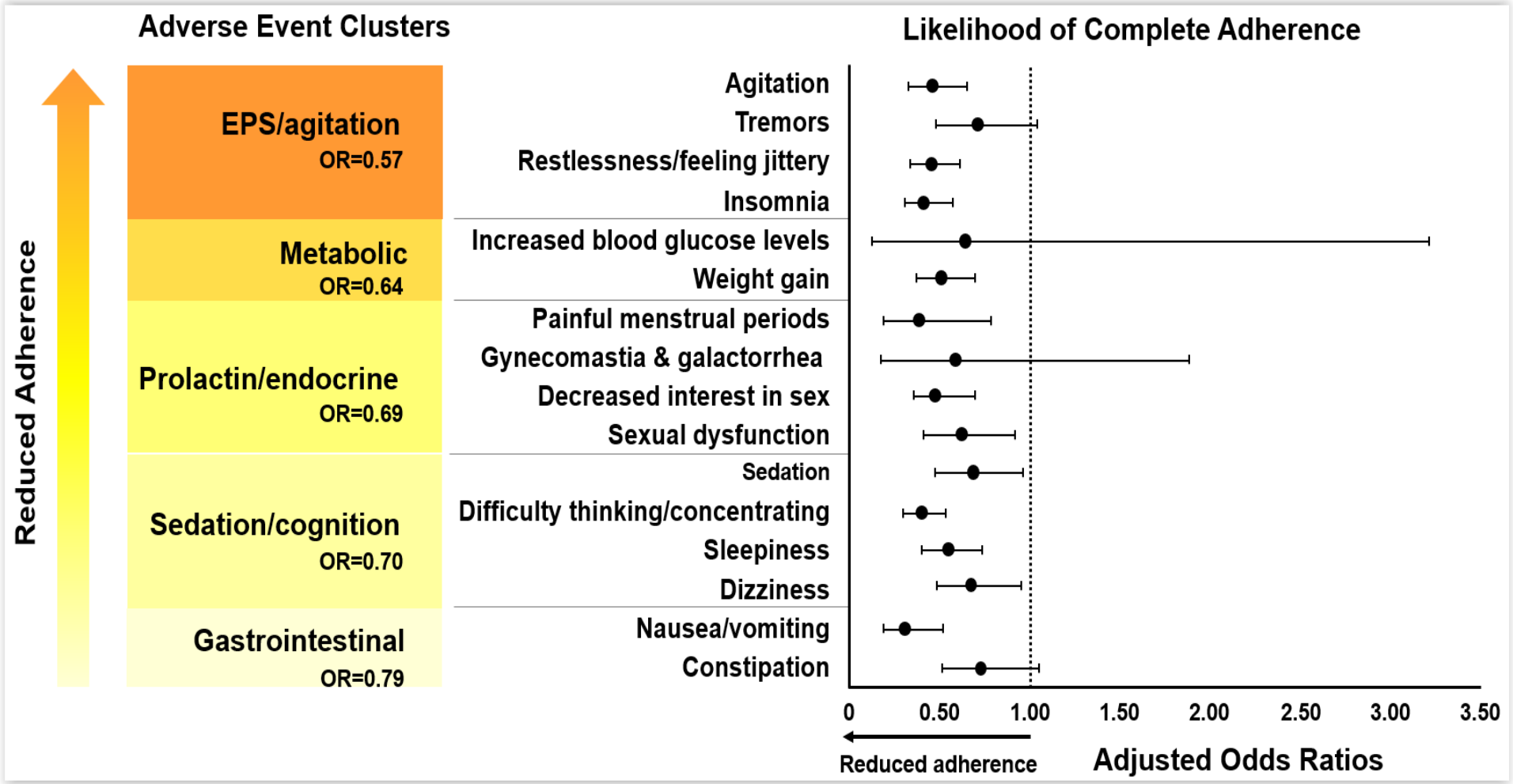
| Receptor | Acute: <1 Week | Consequence | Early: <3 Months | Consequence | Late: ≥3 Months | Consequence |
|---|---|---|---|---|---|---|
| $a_1$ | Hypotension* | Falls<br>Nonadherence | Hypotension* | Falls<br>Nonadherence | Hypotension | Falls<br>Nonadherence |
| $D_2$ | Dystonia*<br>Parkinsonism* | Pain<br>Nonadherence | Parkinsonism*<br>Akathisia* | ↓Cognition<br>Nonadherence | TD | Stigma<br>↓Socialization<br>↓Quality of life |
| | ↑Prolactin (*) | Sexual dysfunction<br>Nonadherence | ↑Prolactin (*) | Sexual dysfunction<br>Hypogonadism<br>Nonadherence | ↑Prolactin (*) | Osteoporosis<br>? CHD<br>? Breast cancer |
| $H_1$ | Sedation* | ↓Cognition<br>↓Functioning<br>Nonadherence | Sedation* | ↓Cognition<br>↓Functioning<br>Nonadherence | Sedation | ↓Cognition<br>↓Functioning<br>Nonadherence |
| | ↑Weight | ↑Lipids / Glucose | ↑Weight | ↑Lipids / Glucose<br>Nonadherence | Diabetes<br>Dyslipidemia<br>CHD | ↓Functioning<br>↓Quality of life<br>Early death |
| $M_{1–4}$ | Blurry vision*<br>Dry mouth* | Discomfort<br>Nonadherence | ↓Cognition<br>Blurry vision*<br>Dry mouth<br>Constipation* | ↓Functioning<br>Discomfort<br>Nonadherence | ↓Cognition<br>Blurry vision*<br>Dry mouth*<br>Constipation | ↓Functioning<br>Discomfort<br>Nonadherence |

**Acute (<1 week)** **Early (<3 months)** **Late**

***Tolerance may develop. CHD = coronary heart disease; TD = tardive dyskinesia.**

**Correll CU. *CNS Spectr*. 2007;12(12 Suppl 21):10-14.**

# Adverse Events Lead to Treatment Nonadherence



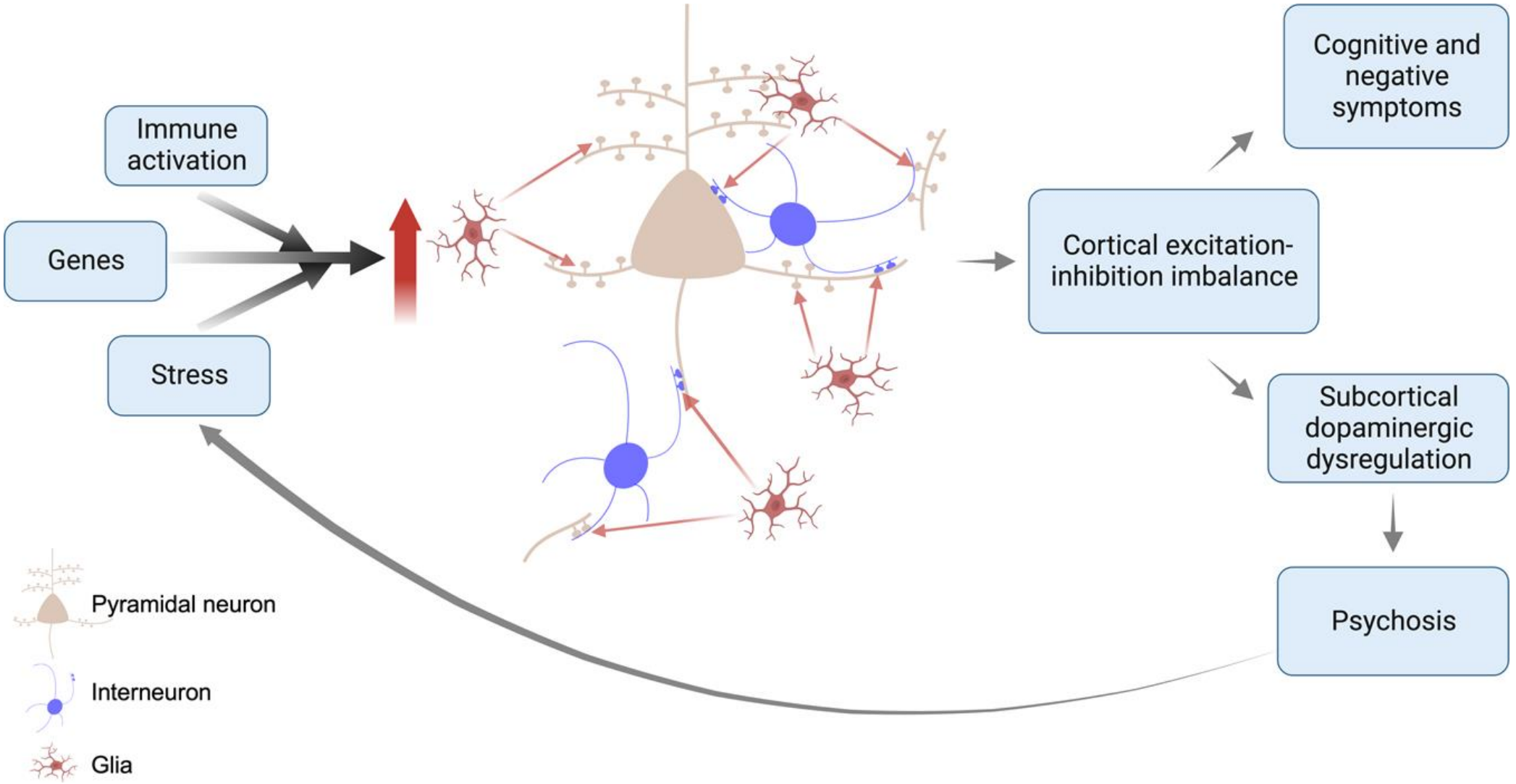

Odds ratios based on multivariable logistic regression with adherence as dependent variable.
Dibonaventura M, et al. BMC Psychiatry. 2012;12:20.

# Key Learning Points

- Short and long-term treatment goals in schizophrenia have evolved over time toward **functional recovery** and **improved quality of life**
- Current treatments have mixed efficacy across clinically relevant domains in schizophrenia
- Adverse events (i.e, weight gain, DIMDs) may lead to treatment nonadherence, highlighting a need for novel treatment targets

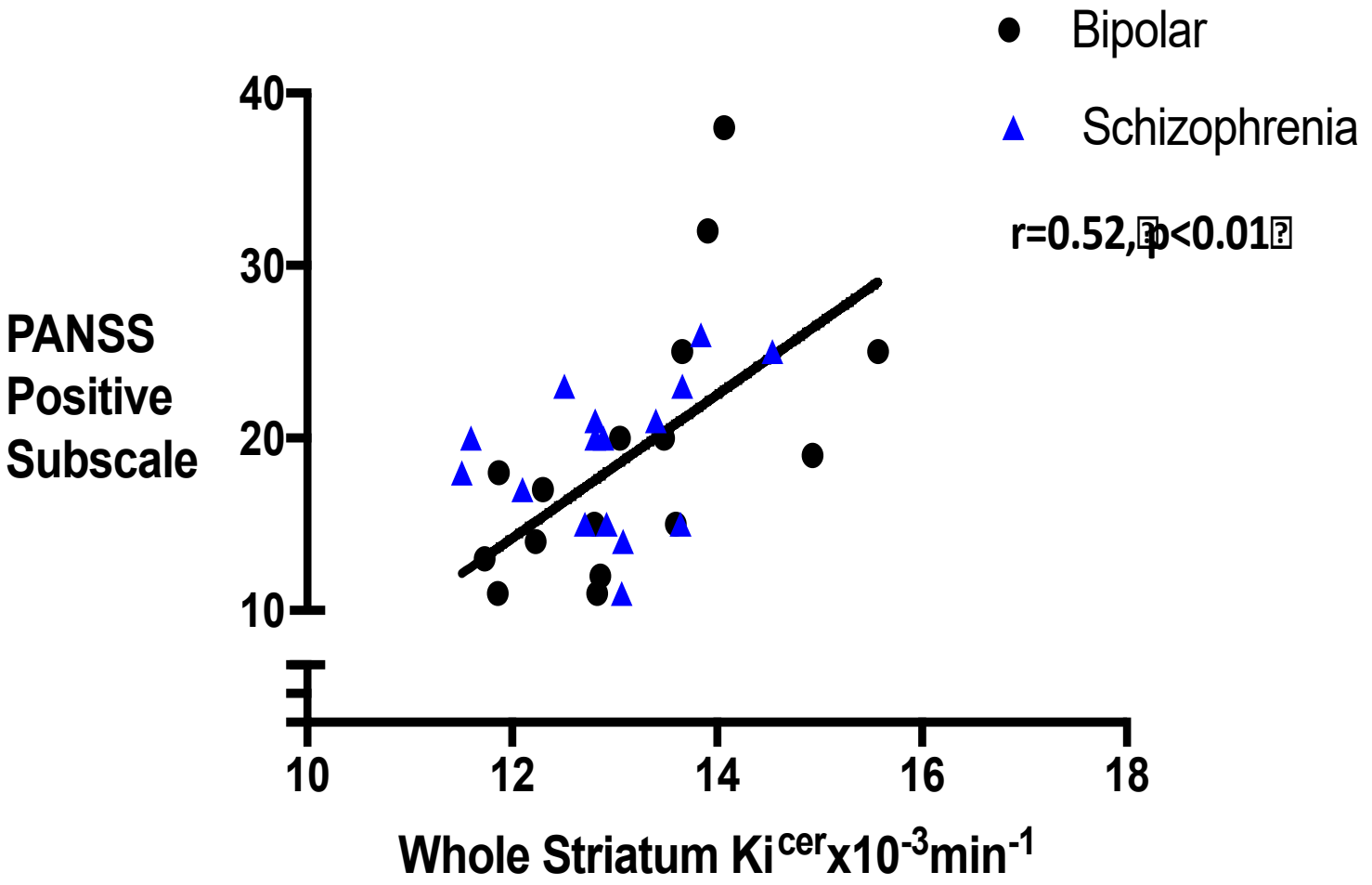
# Evolving Models of Dopaminergic Dysregulation in Schizophrenia

# Evolving Our Understanding of Schizophrenia




Howes OD, Onwordi EC. *Mol Psychiatry.* 2023;28(5):1843-1856.

# Increased Dopamine Synthesis Capacity: Direct Relationship with Psychotic Symptoms

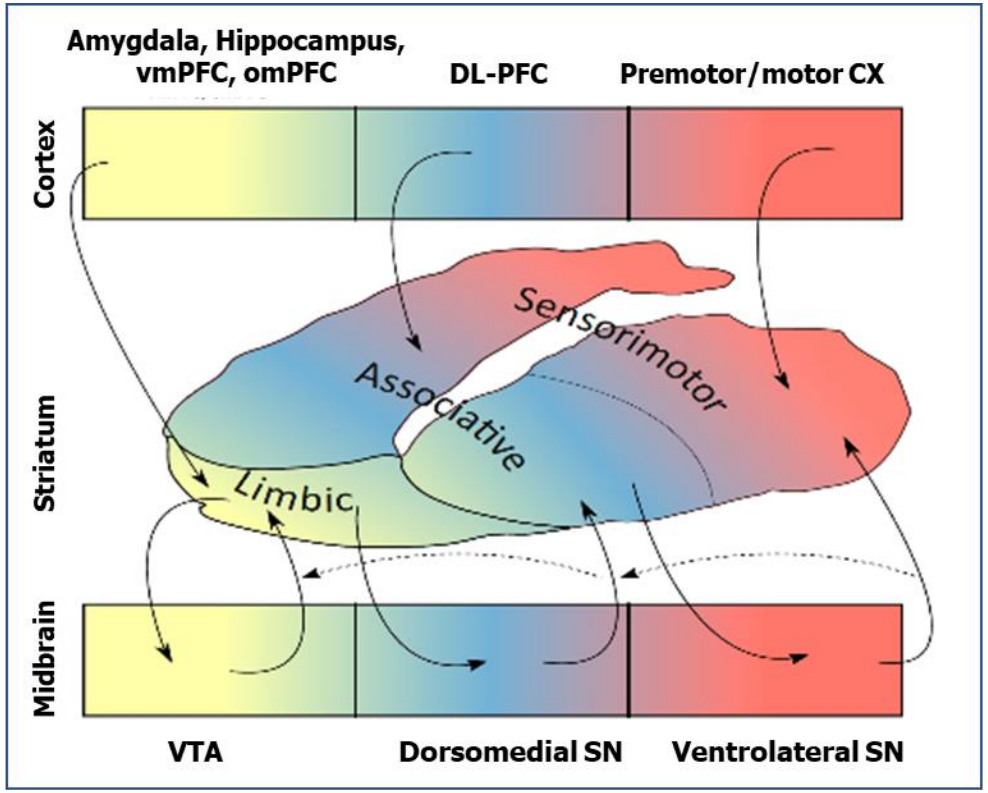



PANSS=Positive and Negative Syndrome Scale.

Jauhar S, Nour MM, Veronese M, et al. JAMA Psychiatry. 2017;74(12):1206-1213.

# Current Concepts About Schizophrenia and Dopamine Dysfunction in Humans

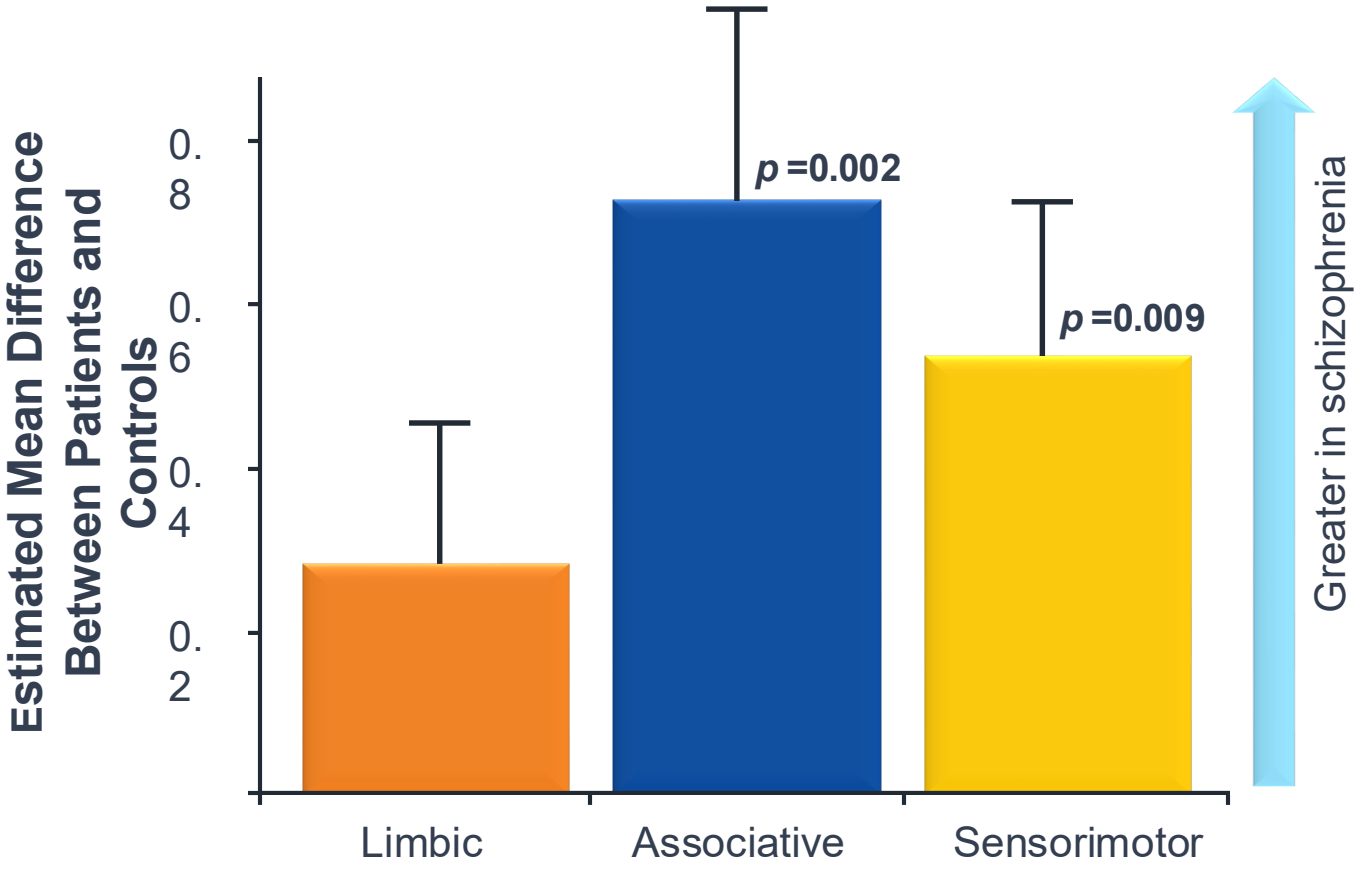
- In humans, recent neuroimaging data suggest that presynaptic dopaminergic overactivity is associated with positive psychosis symptoms as predicted by animal models.
- However, this presynaptic dopamine problem occurs in the associative striatum and adjacent sensorimotor striatum, not in the mesolimbic pathway.
- Descending glutamate pathways from prefrontal cortex (PFC) interact with the VTA. Excessive glutamatergic stimulation increases presynaptic striatal VTA dopamine release resulting in positive symptoms of psychosis.
- Excessive PFC glutamate output can be due to deficient muscarinic $M_1$ signaling, 5-$HT_{2A}$ agonism, and NMDA hypofunction of parvalbumin positive GABAergic PFC interneurons.




**Presynaptic dopamine dysfunction in humans occurs in the associative striatum and is linked to positive symptoms of psychosis.**

**McCutcheon RA, et al. Trends Neurosci. 2019;42(3):205-220.**

# The Primary Dopamine Dysfunction of Schizophrenia is *Not in the Mesolimbic*



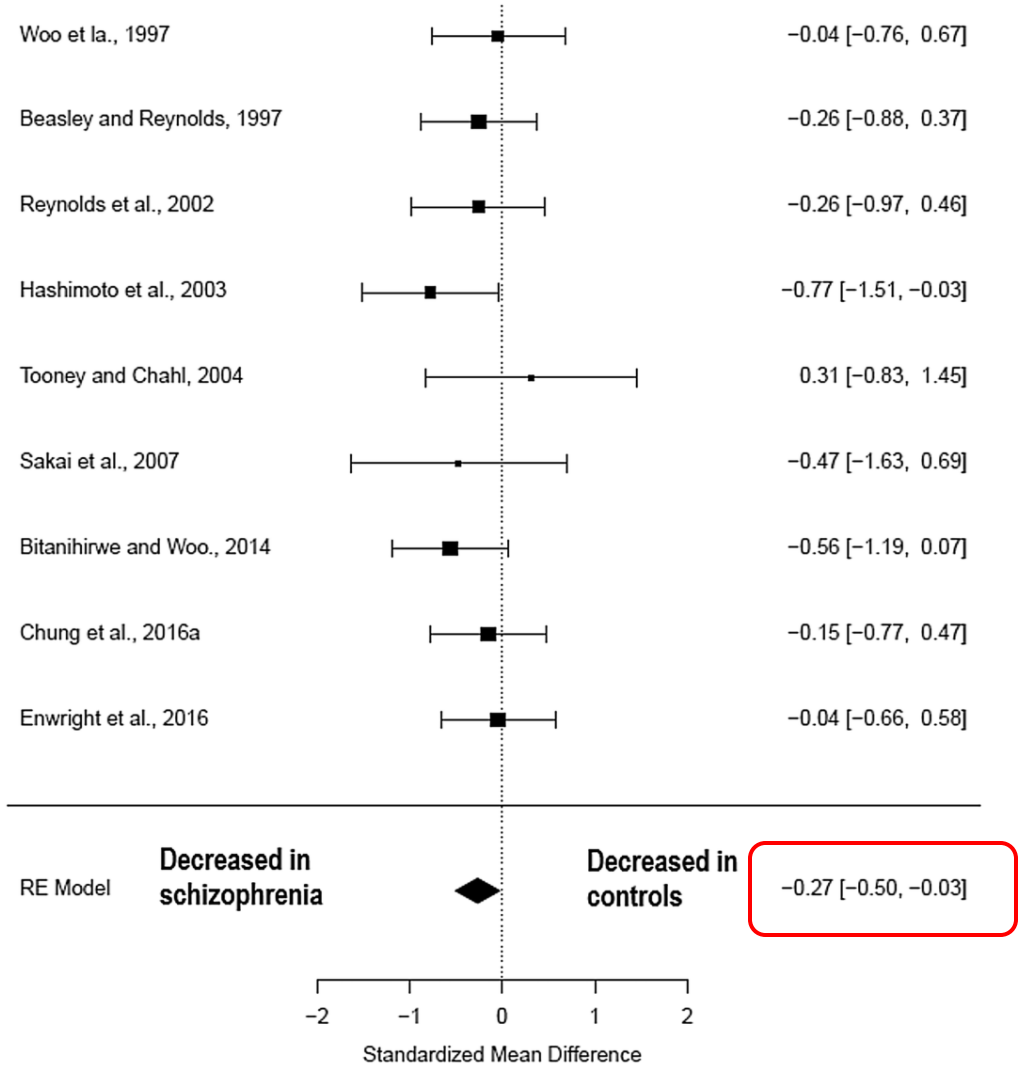

Increased presynaptic dopamine turnover in patients with schizophrenia vs controls is seen in the **associative and sensorimotor striatum**

Improved spatial resolution in imaging studies find that dopaminergic function is significantly elevated in associative and sensorimotor regions but **not** significantly altered in the limbic subdivision

Literature referring to mesolimbic hypotheses of positive symptoms is incorrect and outdated

**McCutcheon RA, et al. Trends Neurosci. 2019;42(3):205-220.**

# Postmortem Evidence: Lower Levels of Markers Expressed in GABA Interneurons in the Frontal Cortex

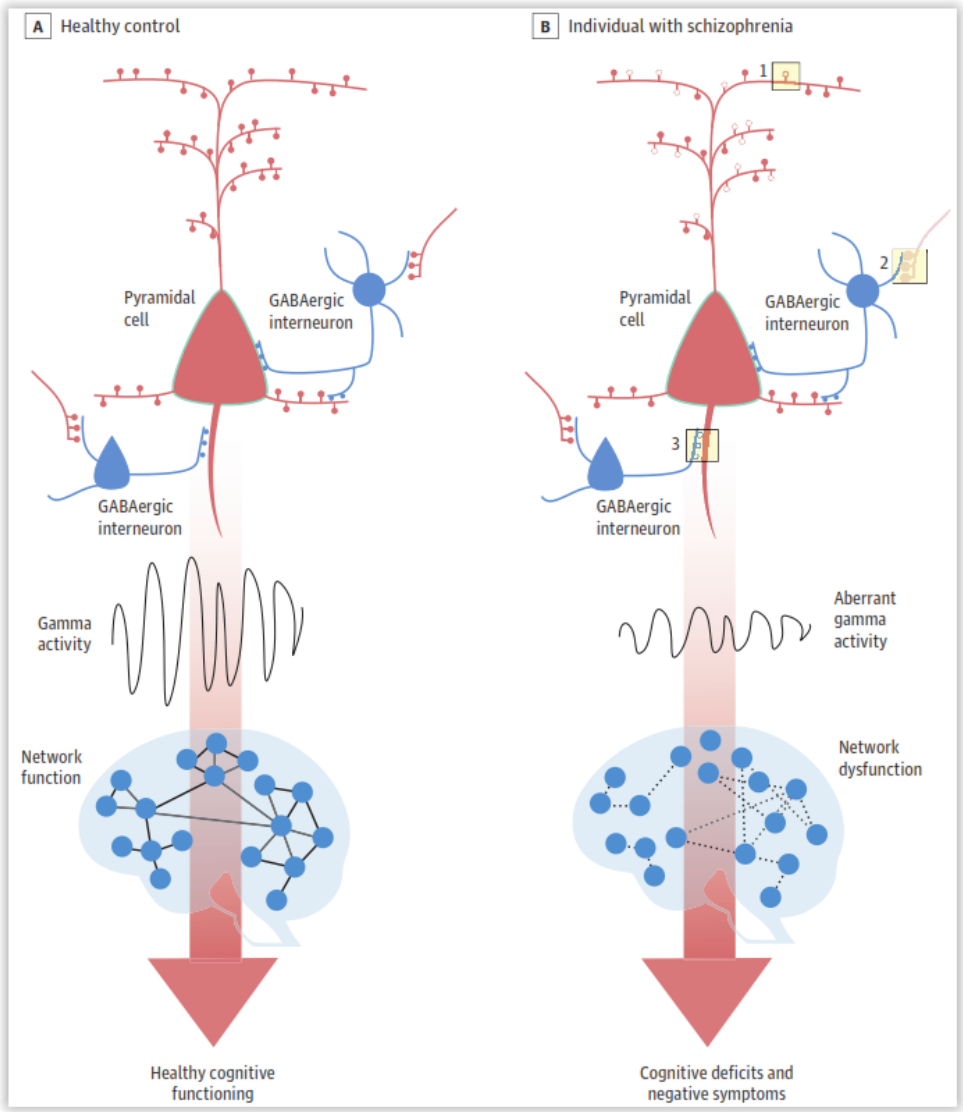


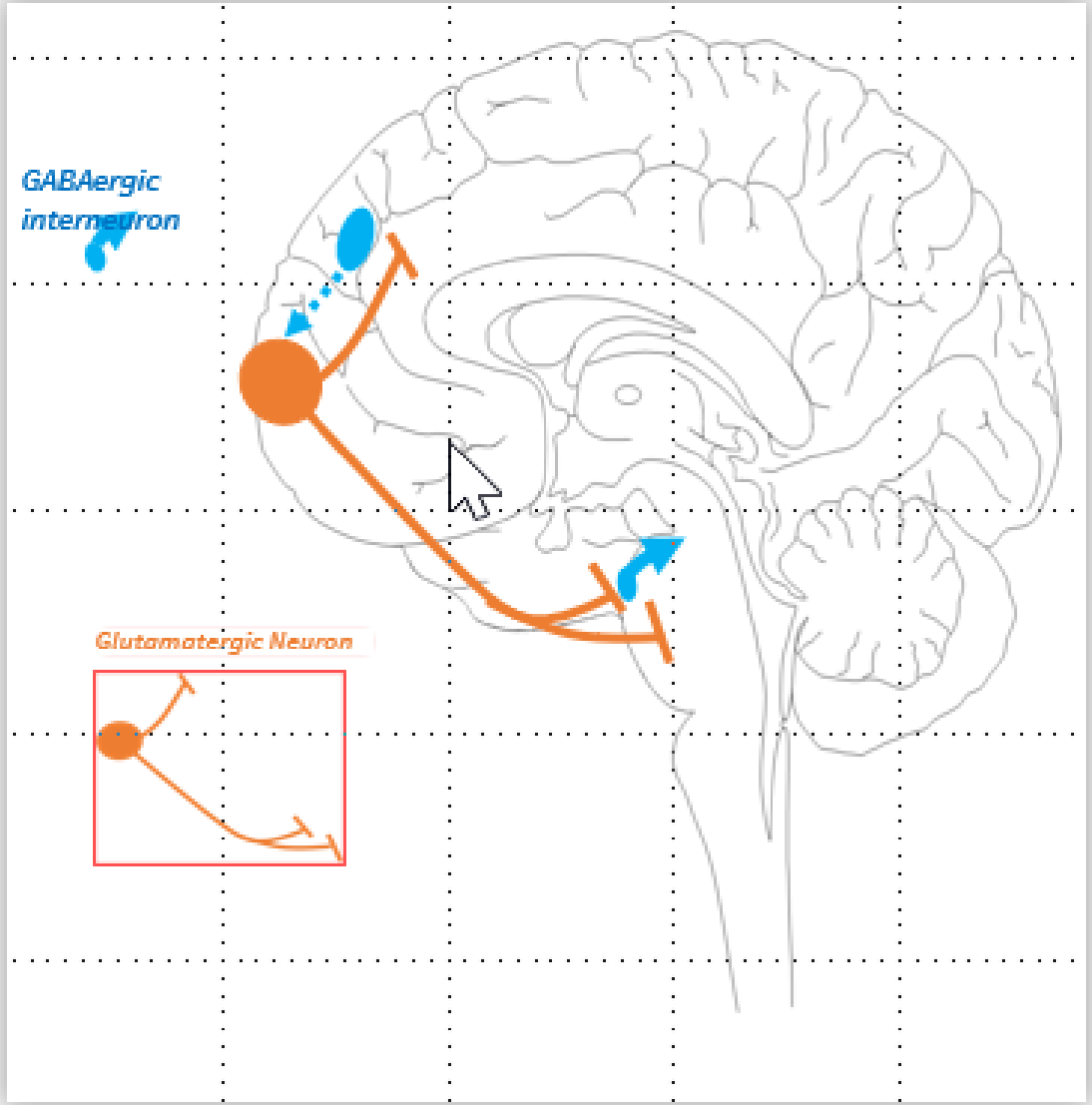

Parvalbumin
GAD67

Lower parvalbumin +ve cell density in patients with schizophrenia

Kaar SJ, et al. *J Neural Transm (Vienna)*. 2019;126(12):1637-1651; Kaar SJ, et al. *Neuropharmacology*. 2020;172:107704.

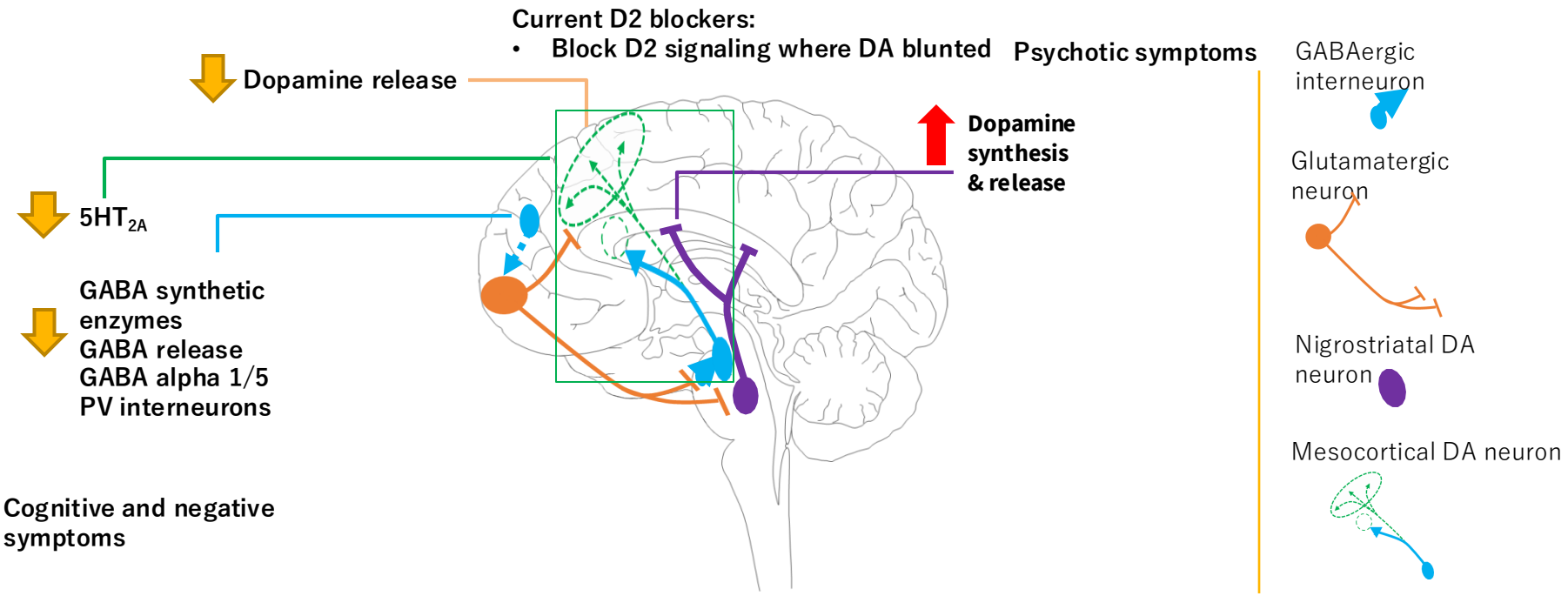
# GABA-Glutamate Circuits Involved in Schizophrenia



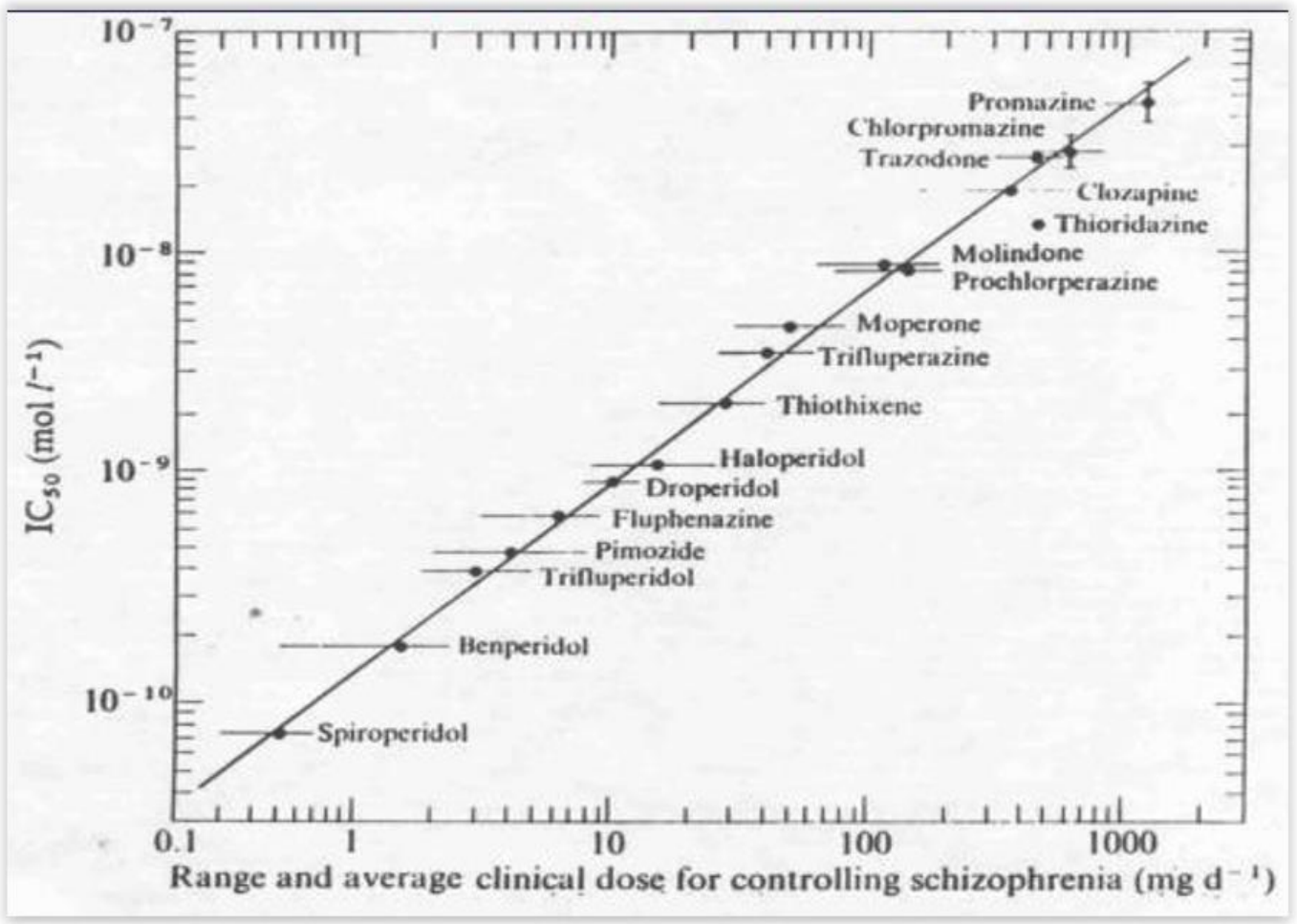

McCutcheon RA, et al. JAMA Psychiatry. 2020;77(2):201-210; Kokkinou M, et al. Mol Psychiatry. 2021;26(6):2562-2576.

# Neurotransmitter Circuits Involved in Schizophrenia




Based on: McCutcheon RA, et al.. World Psychiatry. 2020 Feb;19(1):15-33.

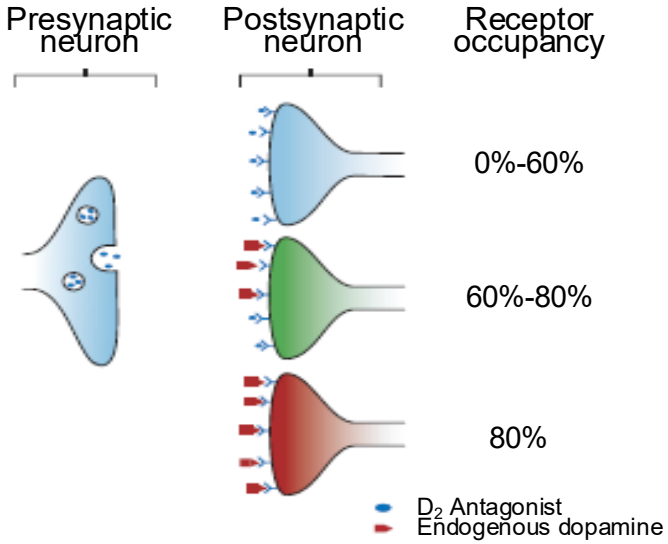
# Inverse Relationship Between D2 Antagonist Potency and Average Daily Dose

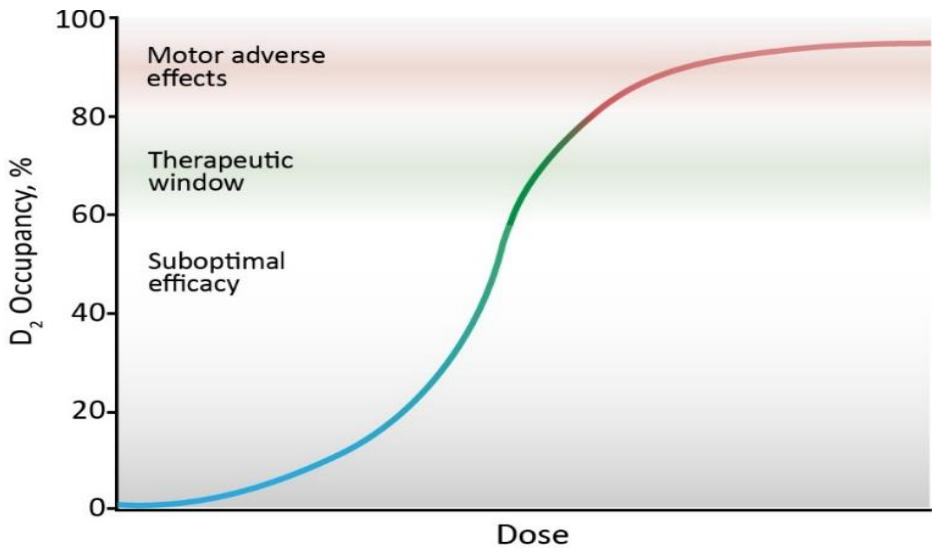



Seeman P, et al. *Nature*. 1976;261(5562):717-9.

# All Current Licensed Treatments for Schizophrenia Are Functional Dopamine D2-Receptor Blockers (median effect size: 0.42)

- PET studies of **$D_2$-antagonist antipsychotics** suggest presence of a therapeutic window
  - Striatal $D_2$-receptor occupancy >60% is generally required for a higher likelihood of improving
  - Occupancy levels >80% are associated with a high likelihood of motor adverse effects
  - High $D_2$ occupancy does not guarantee response
- PET studies of **$D_2$ partial agonist antipsychotics** suggest presence of a therapeutic window
  - Striatal D2-receptor occupancy >90% is generally required for a higher likelihood of improving, as functional agonism needs to be subtracted to get to the net functional antagonism
  - High $D_2$ occupancy does not guarantee response




**Huhn et al. Lancet. 2019 Sep 14;394(10202):939-951; McCutcheon RA, et al. *JAMA Psychiatry*. 2020;77(2):201-210; Grunder G et al. *Arch Gen Psychiatry*. 2003 Oct;60(10):974-7. .**

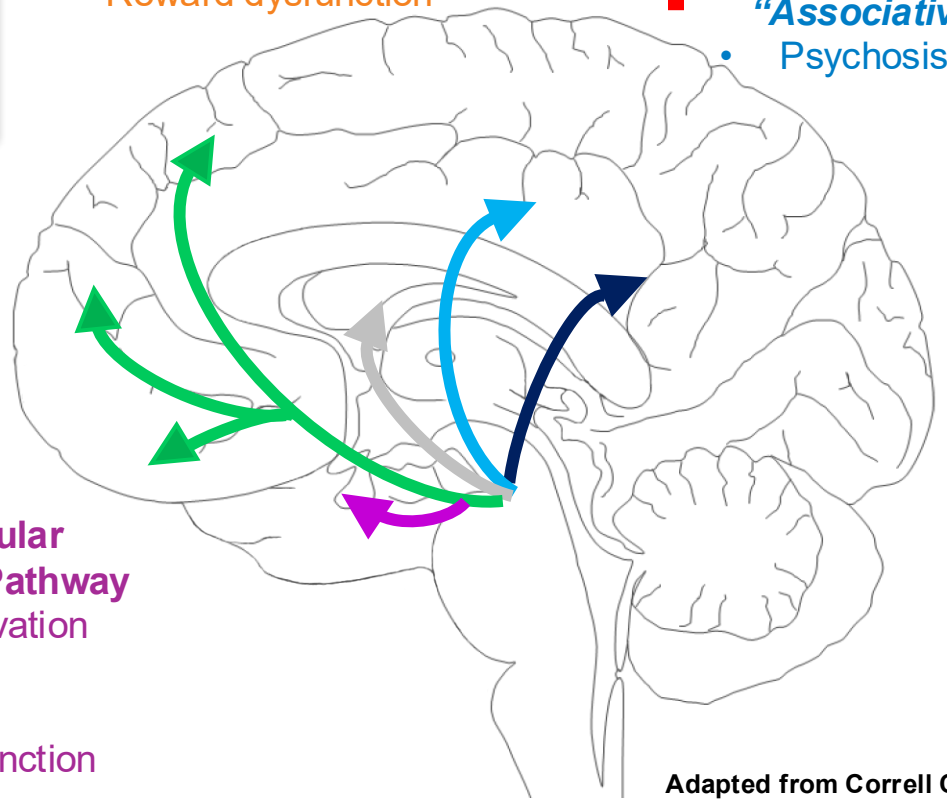
# Disruption of Dopamine Circuits in Schizophrenia

**Overactivity** in the **nigrostriatal pathway** ***"Associative Striatum"*** leads to **positive symptoms**

**Mesolimbic Pathway***
***"Limbic Striatum"***
- Negative symptoms
- Reward dysfunction

**Nigrostriatal Pathway 1**
***"Associative Striatum"***
- Psychosis

**Underactivity** in the **mesolimbic** and **mesocortical** pathways lead to **negative and cognitive symptoms**



**Mesocortical Pathway**
- Learning and memory
- Negative symptoms
- Cognitive symptoms
- Depression

**Nigrostriatal Pathway 2** →/↓
***"Sensorimotor Striatum"***
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

**Tuberoinfundibular Hypothalamic Pathway**
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction

**Adapted from Correll CU, Abi-Dargham A, Howes O. 2022.**

*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is greatest within nigrostriatal pathways, implicating the dorsal striatum. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.

**Correll CU, et al. J Clin Psychiatry. 2022 Feb 15;83(1):SU21204IP1; McCutcheon RA, et al. Trends Neurosci. 2019;42(3):205-220.**

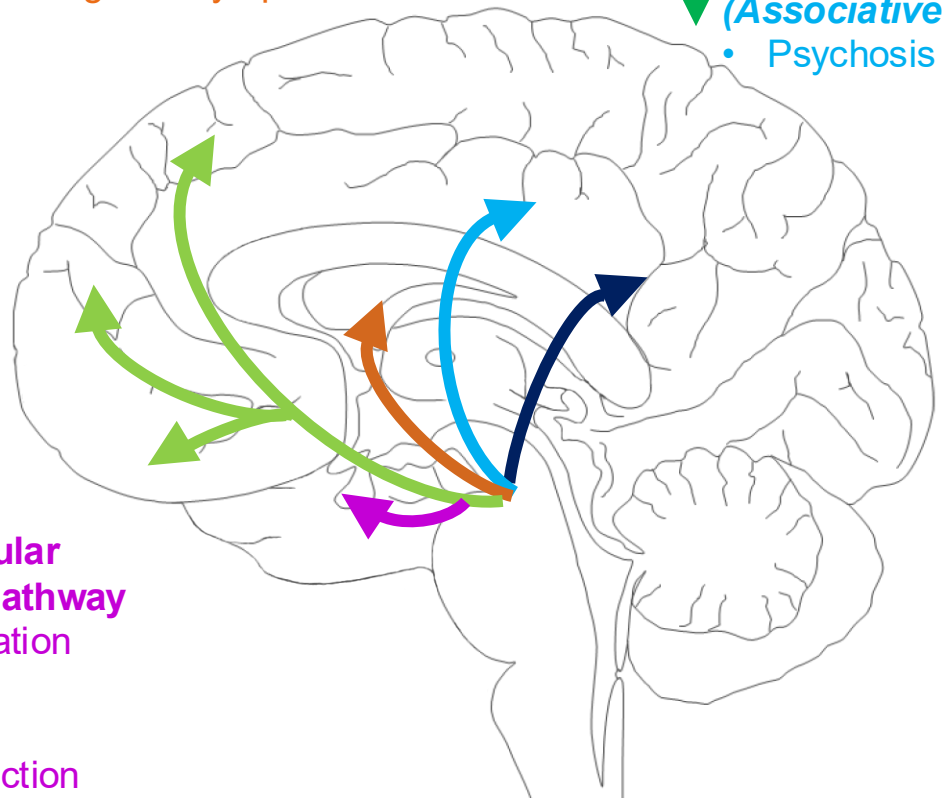
# Effects of D2 Receptor Blockade on Neural Circuits

Underactivity of these circuits is associated with schizophrenia; the goal is to increase the activity

Overactivity of this circuit is associated with schizophrenia; the goal is to reduce the hyperactivity

**Mesolimbic Pathway***
***(Limbic Striatum)***
- Negative symptoms

**Nigrostriatal Pathway**
***(Associative Striatum)***
- Psychosis



**Mesocortical Pathway**
- Negative symptoms
- Cognitive symptoms
- Depression

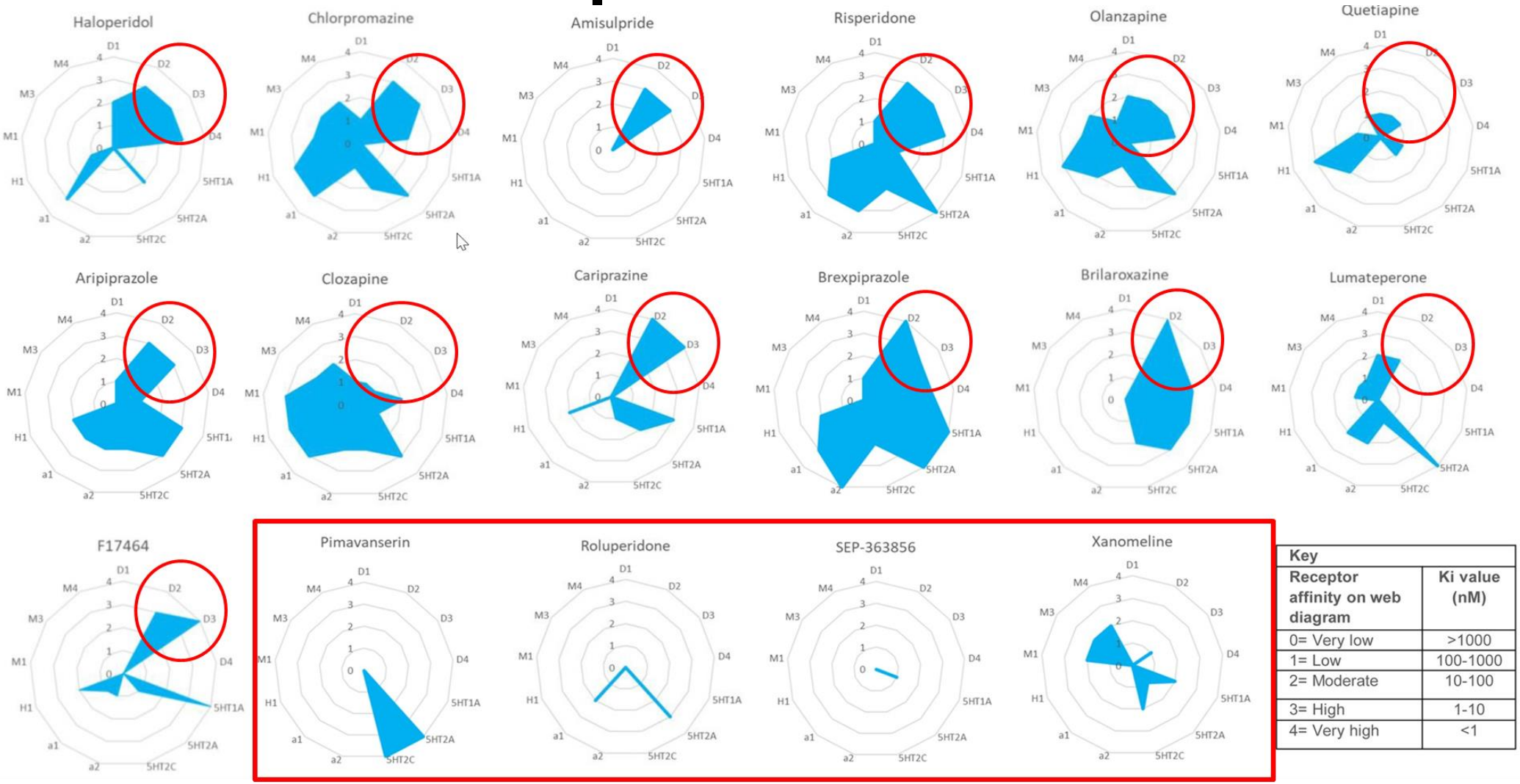
**Nigrostriatal Pathway**
***(Sensorimotor Striatum)***
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

**Tuberoinfundibular Hypothalamic Pathway**
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction

*Advances in neuroimaging techniques found that DA dysfunction in schizophrenia is greatest within nigrostriatal pathways, implicating the dorsal striatum. DA overactivity in the circuit from the dorsomedial substantia nigra to the associative and adjacent sensorimotor striatum is linked to positive symptoms.

**Correll CU, et al. J Clin Psychiatry. 2022 Feb 15;83(1):SU21204IP1; McCutcheon RA, et al. Trends Neurosci. 2019;42(3):205-220.**

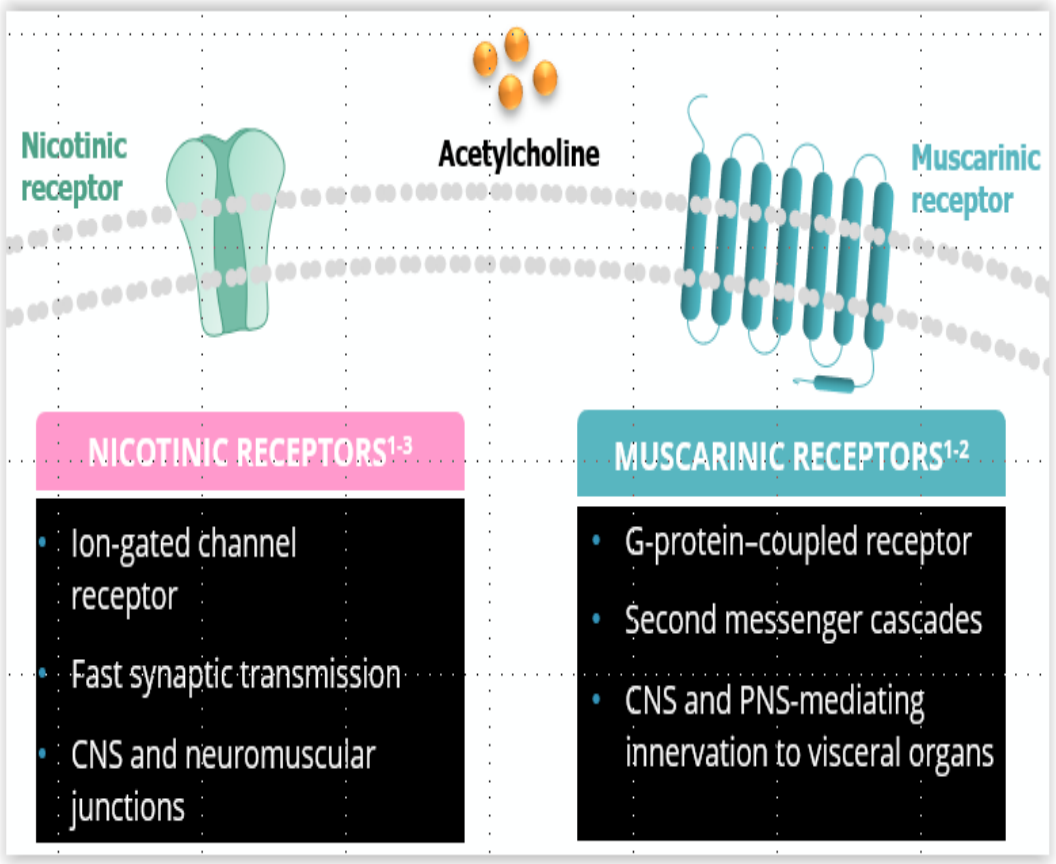
# Pharmacology of Existing and Emerging Schizophrenia Treatments




| Key | |
|---|---|
| Receptor affinity on web diagram | Ki value (nM) |
| 0= Very low | >1000 |
| 1= Low | 100-1000 |
| 2= Moderate | 10-100 |
| 3= High | 1-10 |
| 4= Very high | <1 |

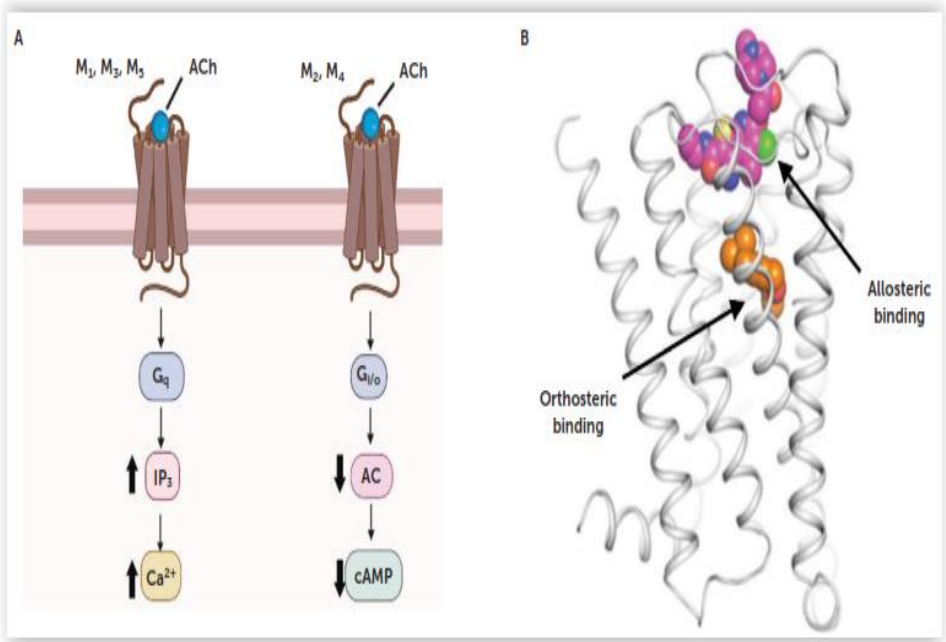
Lobo MC, et al. *Neurosci Biobehav Rev*. 2022;132:324-361; Kaar SJ, et al. *Neuropharmacology*. 2020;172:107704.

# The Nicotinic vs Muscarinic Cholinergic Receptor System




Signaling Selectivity Among Muscarinic Acetylcholine M1-M5 Receptors

**Postsynaptic Receptor** **Presynaptic Autoreceptor**

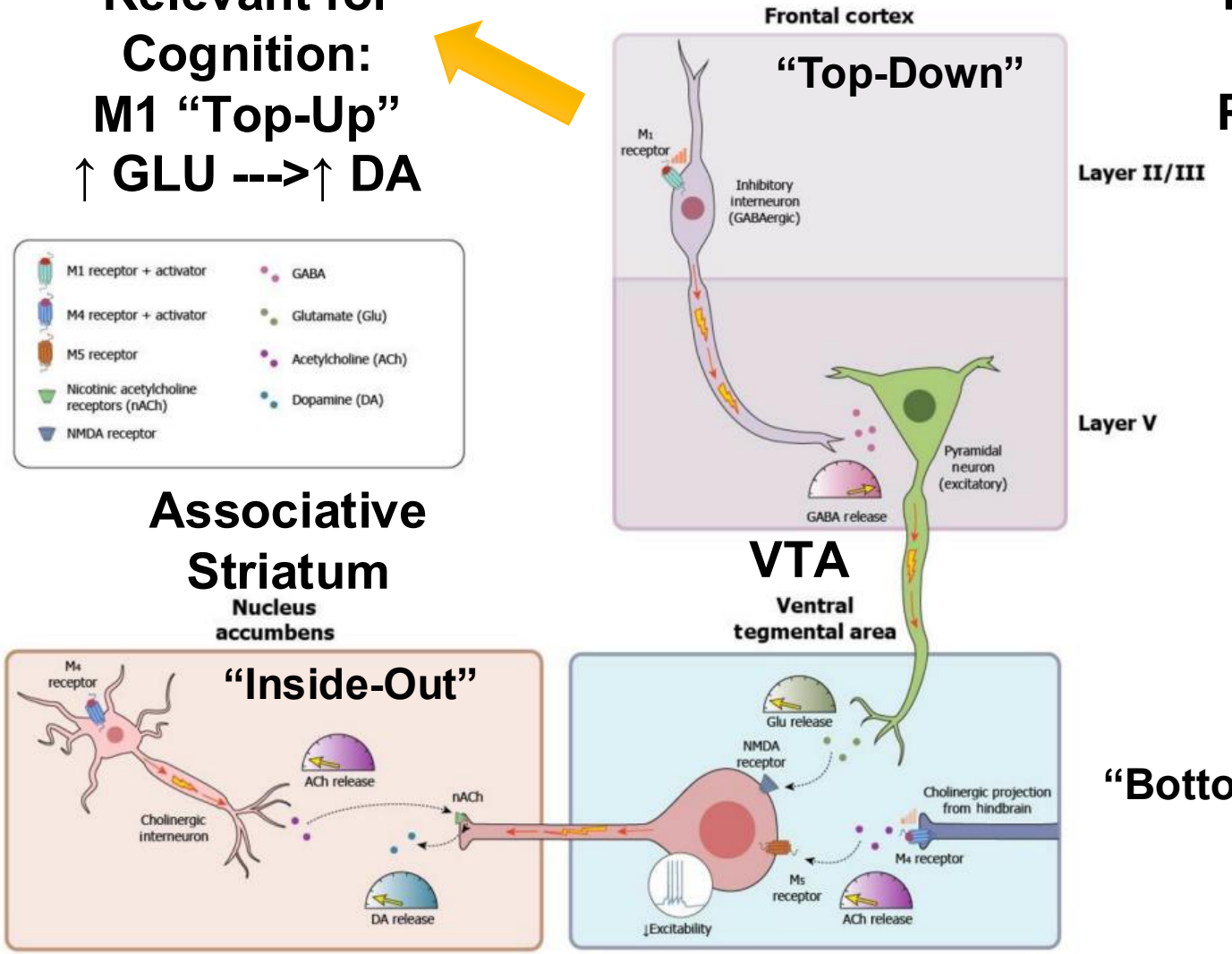



**Stimulatory** **Inhibitory**

**Paul SM, et al. *Am J Psychiatry*. 2022;179(9):611-627; Brown DA. *Brain Neurosci Adv*. 2019;3:1-10; Unwin N. *Q Rev Biophys*. 2013;46(4):283-322.**

## Regulation of Dopamine Circuits Relevant for Cognition: M1 "Top-Up" ↑ GLU --->↑ DA

## Frontal Cortex




## Regulation of Dopamine Circuits Relevant in Psychosis by M1 & M4 Receptors:

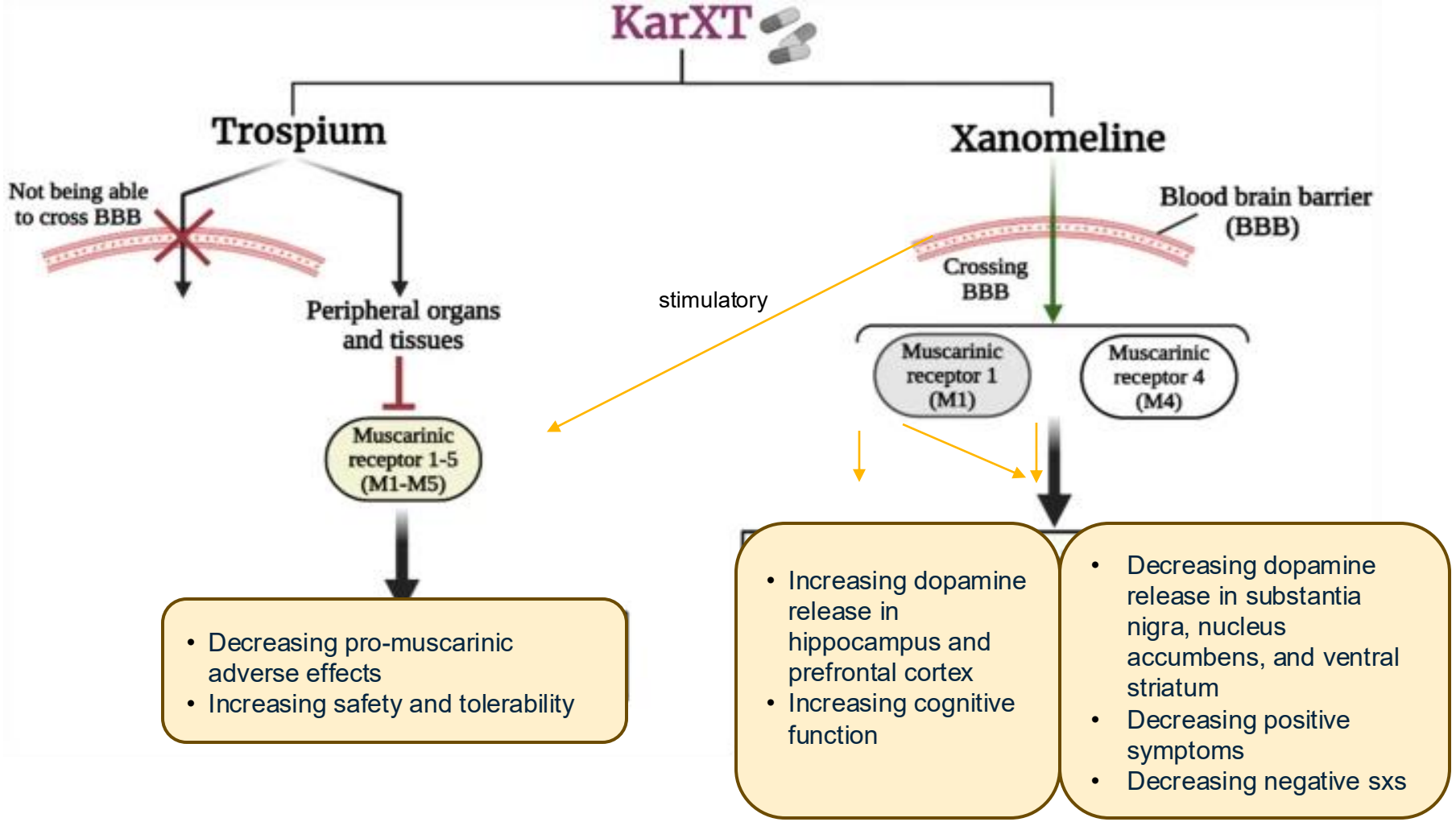
**M1: "Top-Down"**

**M4: "Bottom-Up; and Inside-Out"**

**"Bottom-Up"**

Adapted from: Yohn SE et al. Trends Pharmacol Sci. 2022 Dec;43(12):1098-1112.

# Mechanism of Action: Xanomeline + Trospium Chloride




**Adapted from Azargoonjahromi, A. *Clin Drug Investig. 2024;*44, 471–493.**

# Need for MOAs that Modulate Presynaptic Dopamine Synthesis and Release

- First- and second-generation antipsychotics block post-synaptic dopamine D2 receptors in that part of the striatum that is responsible for positive psychotic symptoms
- Unfortunately, this leads to “collateral damage”
  - Blockade of postsynaptic dopamine D2 receptors in the motor striatum
    - Results in possible drug-induced parkinsonism, acute dystonia, acute akathisia, and eventually, tardive dyskinesia
  - Blockade of dopamine D2 receptors in the hypothalamic-pituitary axis
    - Results in greater prolactin release
- Pre-synaptic decrease in dopaminergic output can avoid the above, if selective
  - Two approaches: modulation of the synthesis of dopamine and/or the release of dopamine

# Key Learning Points: Evolving Models of Dopaminergic Dysregulation in Schizophrenia

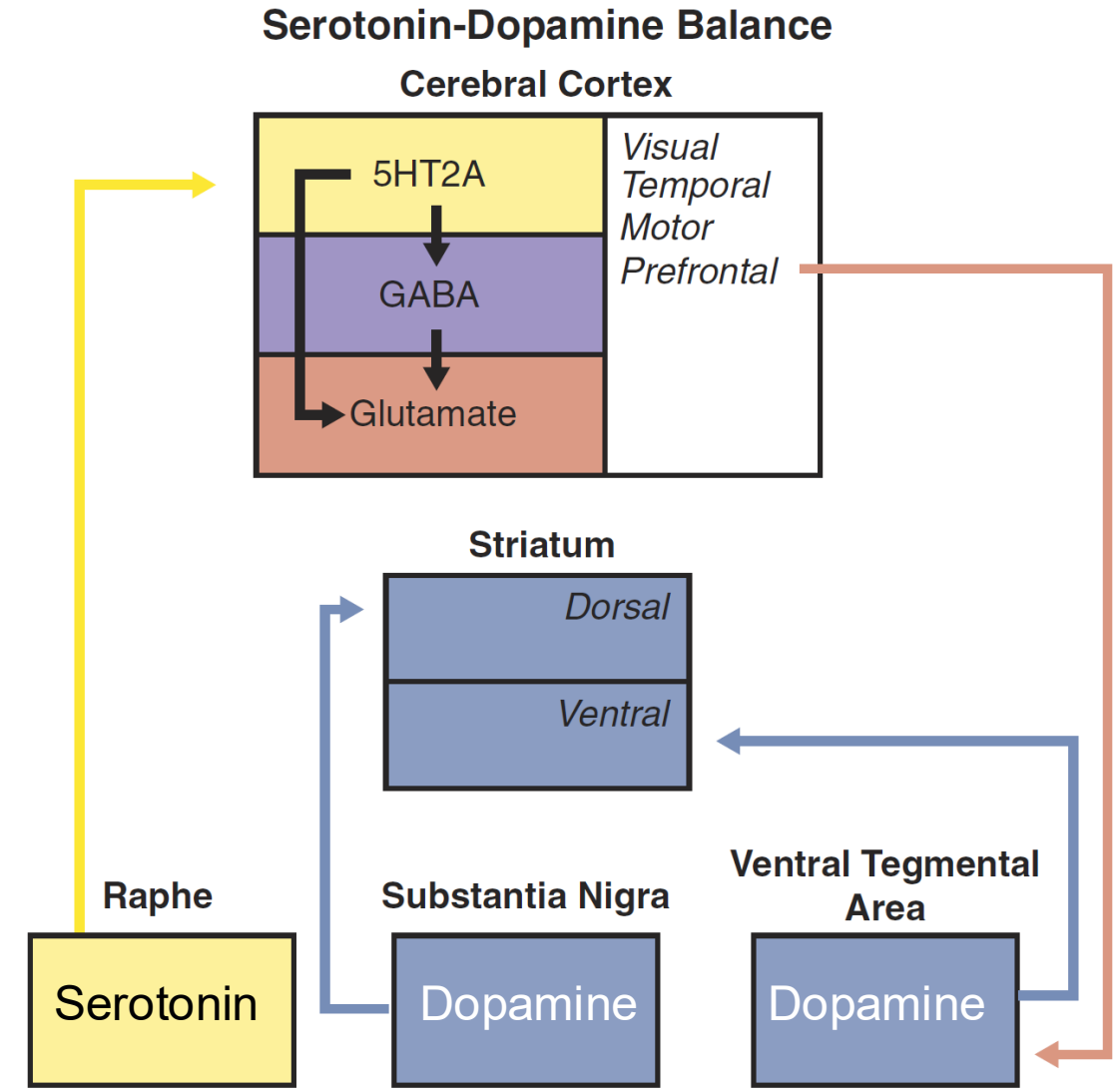
- The old model of the mesolimbic pathway explaining positive symptoms in humans, is obsolete
- The new model, supported by modern imaging techniques has identified a pathway from part of the substantia nigra going to the “associative” striatum as explanatory for positive symptoms in humans
- Pre-synaptic dopamine dysregulation in the associative striatum affects fronto-striatal-thalamic circuits
- Can address this by either decreasing dopamine synthesis/release or by post synaptic dopamine D2 receptor blockade
  - Blocking dopamine receptors in only one location of the brain is not possible, thus resulting in clinically relevant drug-induced motor symptoms and/or hyperprolactinemia in some patients
  - Decreasing dopamine synthesis/release can be more selective

# Understanding Other Neurotransmitters in Relation to Dopamine in Schizophrenia

# All Roads Lead to Dopamine

- Dopamine is the final common pathway but is influenced by
  - GABA
  - Glutamate
  - Serotonin
  - Acetylcholine
  - And all of the above working in tandem

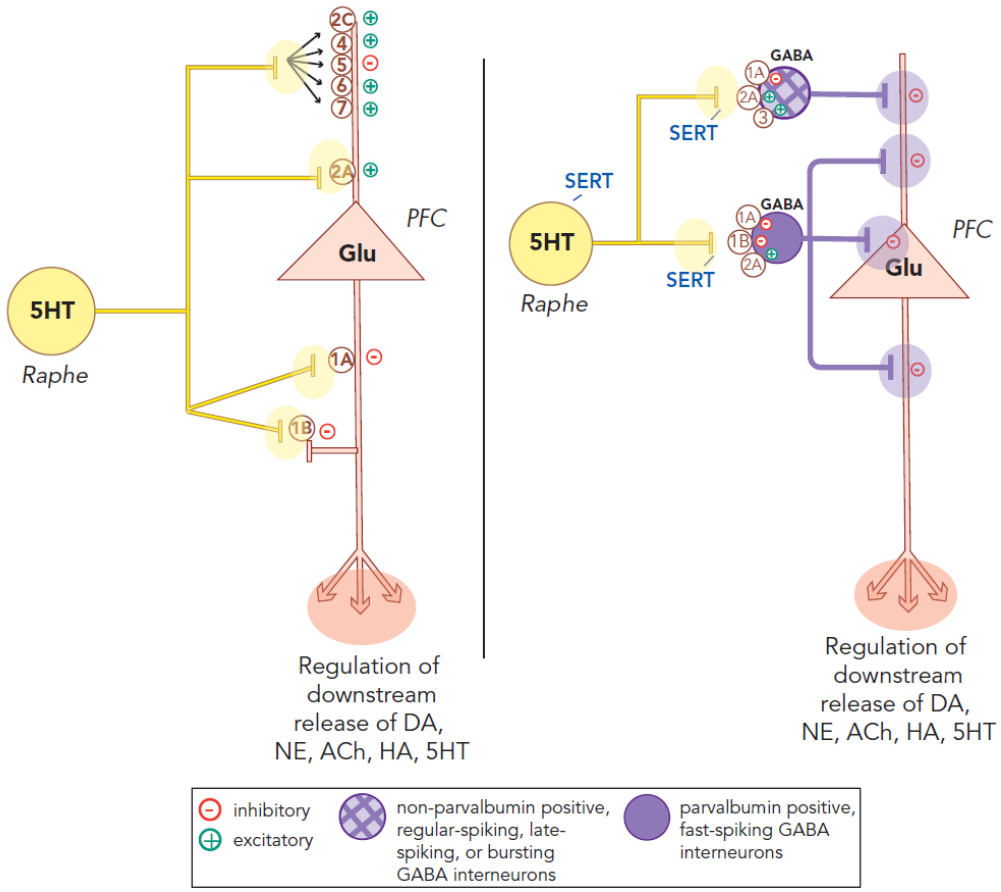
# Serotonin-Dopamine Imbalance Hypothesis




- Normally, **serotonin** and **dopamine** are balanced in neuronal circuits
- Shown here are **5HT2A** receptors regulating GABA and glutamate in the cerebral cortex and dopamine in the downstream ventral tegmental area and the ventral striatum

Stahl SM. CNS Spctr. 2016; 21: 355-359. e

# 5HT Receptors Regulate Glutamate Release Directly and Indirectly Through GABA



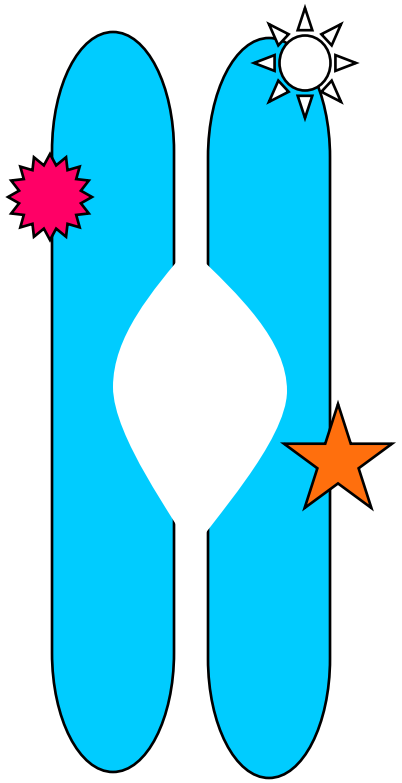

Stahl SM. Stahl's Essential Psychopharmacology, 5th Edition. Cambridge University Press, 2021

# NMDA Hypothesis of Schizophrenia

- In patients with schizophrenia there is insufficient excitation of the GABA interneuron because of *NMDA glutamate receptor hypofunction*
- The NMDA receptor on the GABA interneuron when activated, will excite the GABA interneuron, allowing it to inhibit the glutamatergic neuron next down the chain
- This does not happen in patients with schizophrenia, and the relevant glutamatergic neuron down the chain is *disinhibited* and *too much dopamine* is ultimately released in the circuit responsible for psychosis

**Nakazawa K, et al. Neuropharmacology. 2012;62(3):1574-1583.**

# Regulation of NMDA Receptors



Glutamate binding site

Glycine/D-serine site
[Co-agonist; Required for NMDA receptor activation]

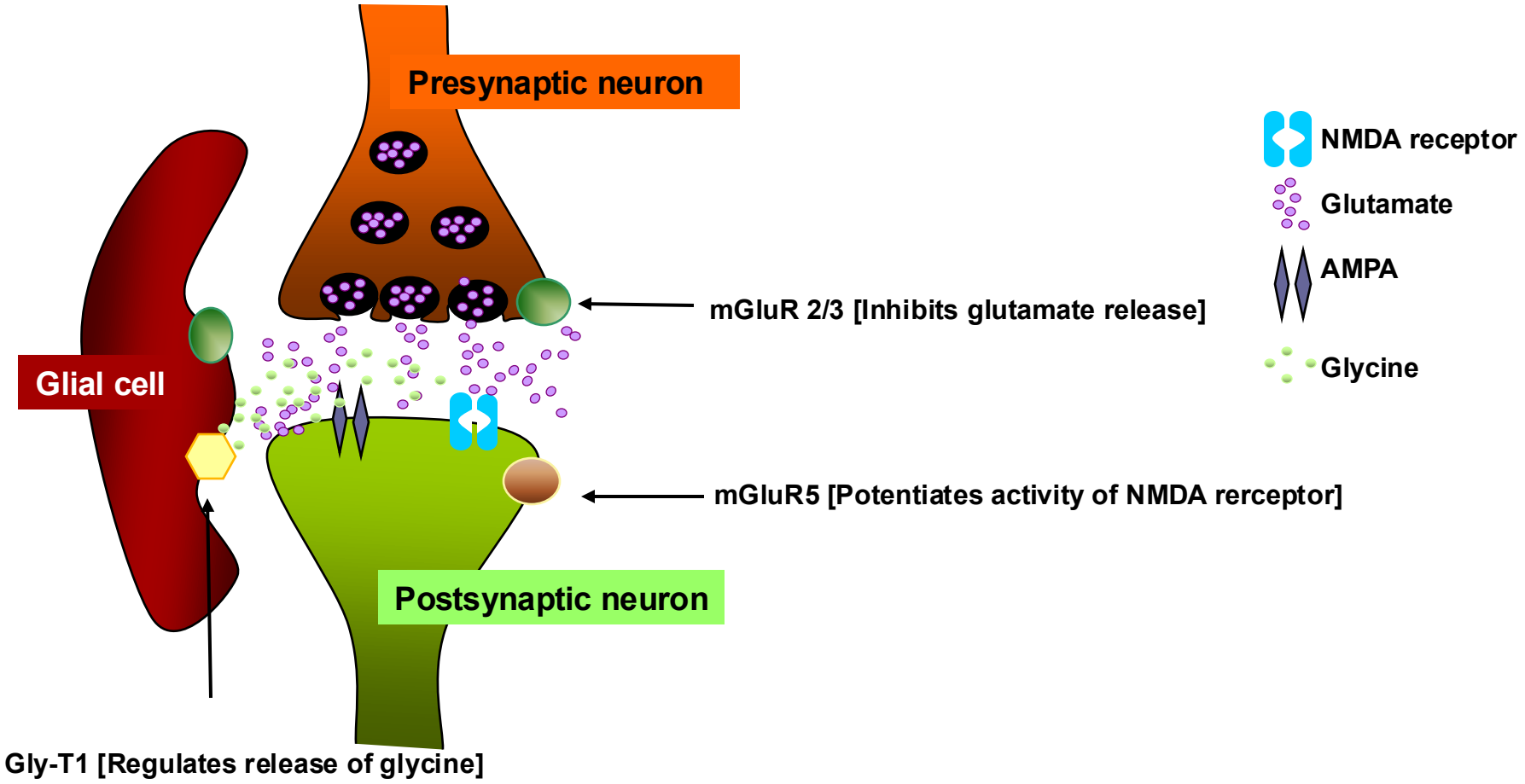
Redox sensitive site
[Modulates NMDA receptor activity]

**NMDA Receptor**

Structurally complex; activation occurs only if simultaneous glutamate and glycine binding and partial depolarization of the membrane potential (co-localized with AMPA receptors)

Stone JM. *Ther Adv Psychopharmacol.* 2011;1(1):5-18.

# Molecular Targets to Increase NMDA Receptor Activity



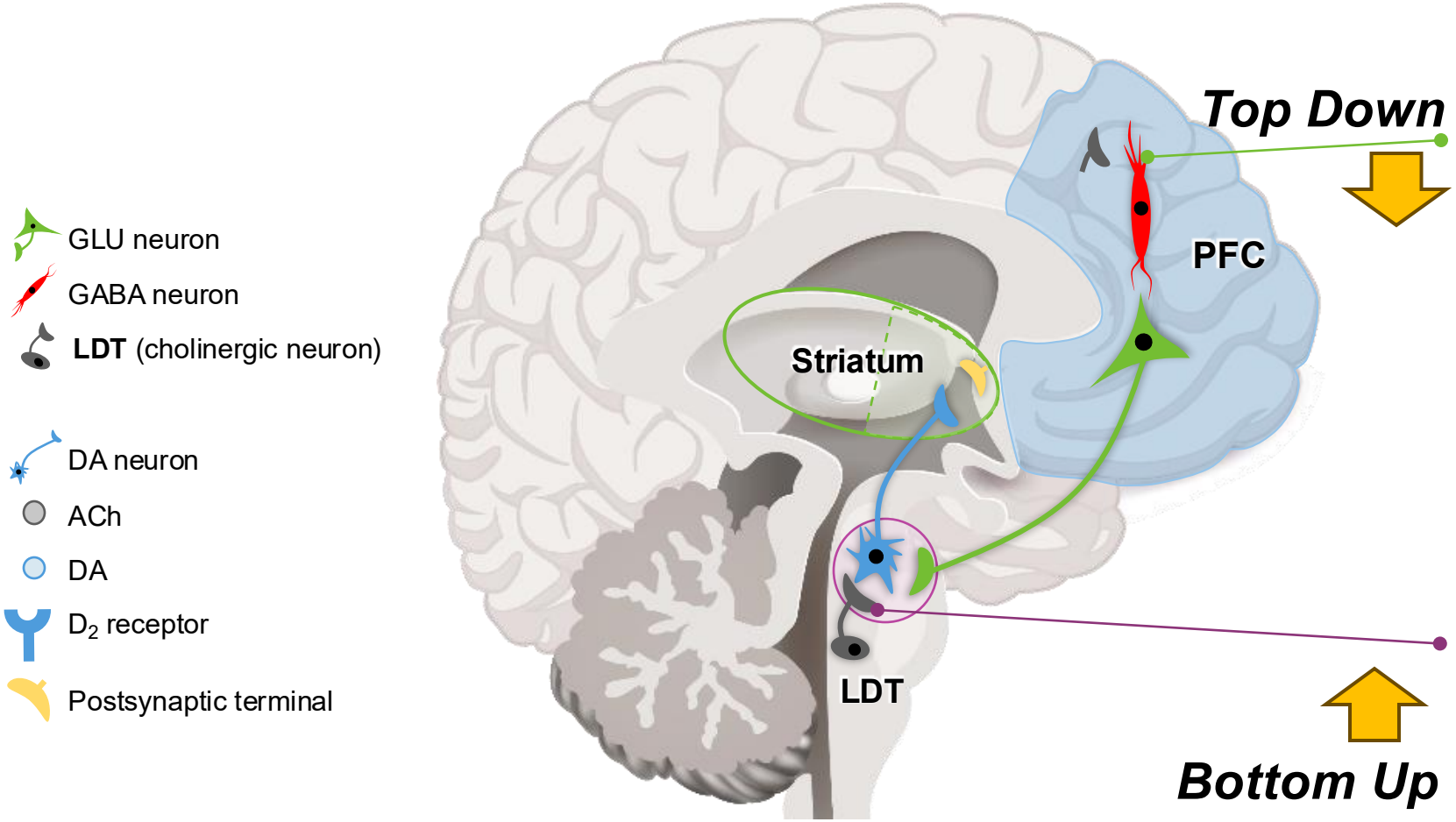

Stone JM. *Ther Adv Psychopharmacol.* 2011;1(1):5-18.

# Muscarinic Cholinergic Hypothesis of Schizophrenia

- Pro-cholinergic drugs were observed to increase “lucid intervals” in patients with psychosis in the 1950s, but were not well tolerated, and further development was abandoned, until now
- We now know that cholinergic systems directly **modulate** striatal **dopaminergic function** in areas associated with positive symptoms of schizophrenia and also regulate descending **glutamate** pathways that interact with striatal dopamine circuits
- Postmortem studies show reductions in M1 and M4 receptor expression in brain regions implicated in schizophrenia. 25% of patients have ≥75% reduction in M1 receptor expression
- M1/M4 receptor knockout models replicate the phenotype of schizophrenia in mice, and muscarinic agonists, especially for M4, improve positive and negative symptoms of schizophrenia in mice and humans

**Pfeiffer CC et alAnn N Y Acad Sci. 1957;66(3):753-764; Kruse AC et al. Nat Rev Drug Discov. 2014;13(7):549-560; Matsumoto I et al. Neurosci Lett. 2005;379(3):164-168; Dean B et al. Psychiatry Res. 2020;288:112989; Paul SM et al. Am J Psychiatry. 2022;179(9):611-627; Brannan SK et al. N Engl J Med. 2021;384:717-726.**

# $M_1$ and $M_4$ Receptor Stimulation Selectively Regulate Presynaptic Dopamine Release in Striatal Areas Associated With Positive Symptoms by via 2 Circuits




- **GABA-ergic interneurons:** Control glutamate pathways which themselves stimulate presynaptic dopamine release
- **The GABA-ergic interneuron expresses stimulatory $M_1$ receptors on the cell body**

- **LDT:** Nucleus of cholinergic neurons that stimulates presynaptic dopamine release.
- **The LDT has inhibitory $M_4$ <u>autoreceptors</u> on axonal terminals**

**ACh = acetylcholine; DA = dopaminergic; GLU = glutamatergic; LDT = laterodorsal tegmental.**

**Paul SM, et al. Am J Psychiatry. 2022;179(9):611-627; Yohn SE, et al. Trends Pharmacol Sci. 2022;43(12):1098-1112; Ballinger EC, et al. Neuron. 2016;91(6):1199-1218.**

# Remember the NMDA Hypofunction Hypothesis?

- In patients with schizophrenia there is insufficient excitation of the GABA interneuron because of NMDA glutamate receptor hypofunction
- The NMDA receptor on the GABA interneuron when activated, will excite the GABA interneuron, allowing it to inhibit the glutamatergic neuron next down the chain
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**Nakazawa K, et al. Neuropharmacology. 2012;62(3):1574-1583.**

# Muscarinic M1 Receptors To The Rescue!

- Muscarinic M1 receptors on the GABA interneuron can also excite the GABA interneuron
- The M1 receptor on the GABA interneuron when activated, will excite the GABA interneuron, allowing it to inhibit the glutamatergic neuron next down the chain
- This can treat patients with schizophrenia because the relevant glutamatergic neuron is *inhibited* and *less dopamine* is ultimately released in the circuit responsible for psychosis

**Nakazawa K, et al. Neuropharmacology. 2012;62(3):1574-1583.**

# Potential Treatment Implications

- Improved symptom coverage through engagement of multiple neurotransmitter systems
- Targeting dopamine modulation via serotonin, glutamate, norepinephrine, or GABA pathways may reduce reliance on direct dopamine blockade
- Potential for enhanced efficacy in complex or treatment-resistant conditions
- May allow for lower doses of dopamine-specific agents, reducing risk of EPS, TD, and hyperprolactinemia
- Safety, tolerability, and optimization considerations
- Understanding MOA interactions aids in selecting complementary agents rather than redundant or conflicting ones
- Personalized treatment selection can leverage multi-MOA agents to target specific symptom clusters

# Key Learning Points

- Targeting serotonergic, glutamatergic and muscarinic brain circuits can regulate dopamine, and potentially treat the symptoms of schizophrenia
- By not blocking post-synaptic dopamine D2 receptors, we can avoid drug-induced movement disorders and hyperprolactinemia