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# Perspectives In Schizophrenia:

# Proposed Disease Pathophysiology and Potential Treatment Implications

Otsuka America Pharmaceutical, Inc.



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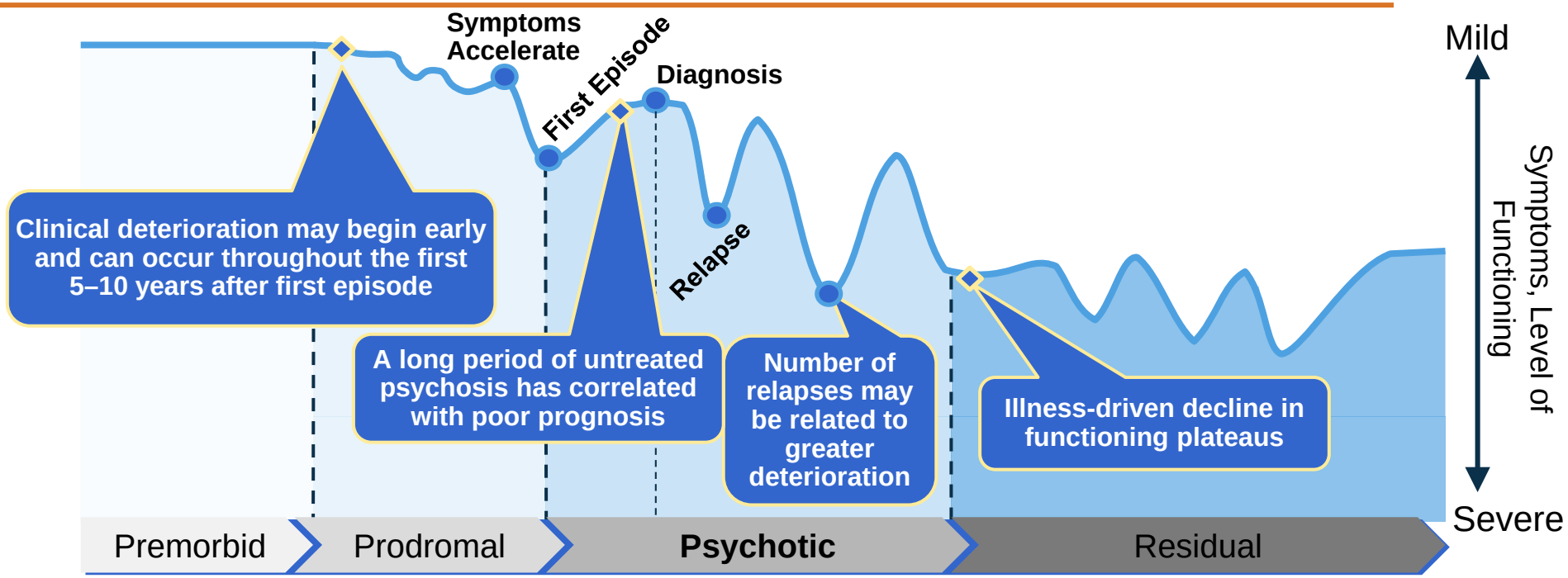
MRC2.CORP.D.00088

# The Theoretical Course of Schizophrenic Progression May Lead to Functional Decline[1-4]




## Childhood

- Functional impairment occurs and is difficult to distinguish from other causes
- Events may trigger disease development

## Adolescence to early adulthood

*Approximately 2-5 y*

- Negative symptoms usually develop first, followed by slight positive symptoms

## Critical years

*Approximately 5 y*

- Majority of clinical deterioration occurs
- High risk of relapse

## Remainder of life

- Disease severity and level of functioning vary; risk of relapse


1. Lieberman JA, et al. *CNS Spectr*. 2007;12(10)(suppl 18):1-16;
2. Emsley R, et al. *BMC Psychiatry*. 2013;13:50;
3. McGlashan TH. *Schizophr Bull*. 1988;14(4):515-542;
4. Lehman AF. *Am J Psychiatry*. 2004;161(suppl 2):1-56.

# Dopamine

- Original neurotransmitter implicated in schizophrenia[1]

## Proposed Actions:

- Utilized in multiple neural circuits in the brain related to reward, cognition, and executive functioning[2,3]
- Related to positive and negative symptoms of schizophrenia and major side-effects of treatment[4,5]
- Effects in schizophrenia mediated largely via $D_2$ receptor type

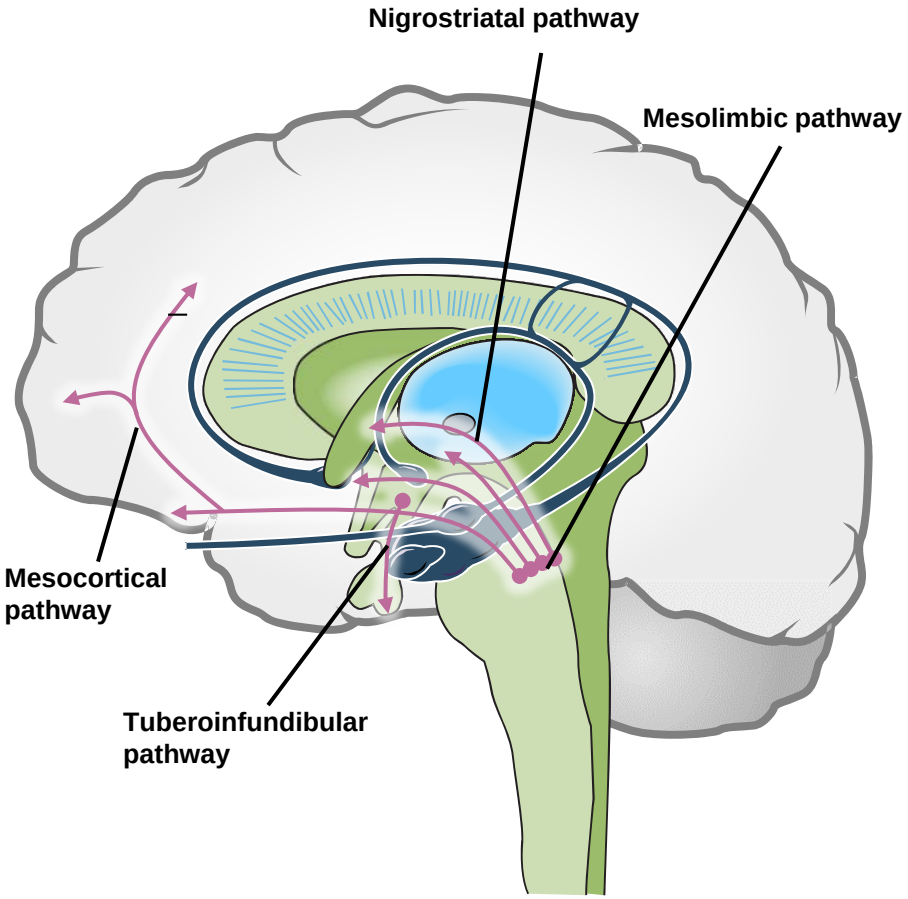



Image: Stahl SM.[5]


1. Brisch et al. *Front Psychiatry*. 2014;5:47;
2. Kandel ER et al (eds). *Principles of Neural Science*. 4th Edition. McGraw-Hill, 2000;
3. Purves D et al (eds). *Neuroscience*. 2nd Edition. Sinauer Associates, 2001;
4. Lieberman JA. *CNS Drugs*. 2004;18(4):251-267;
5. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013.

# Serotonin (5HT)

- Major origin in raphe nuclei with projections to cortex, midbrain, and spinal cord[1,2]

## Proposed Actions:

- Implicated in multiple functions like mood regulation, feeding, sleep, sexual behavior[3]
- Altering 5HT system can affect positive or negative symptoms and cognition in schizophrenia[4]:
  - Modulates DA release through $5HT_{2A}$ and $5HT_{1A}$ receptors[4]

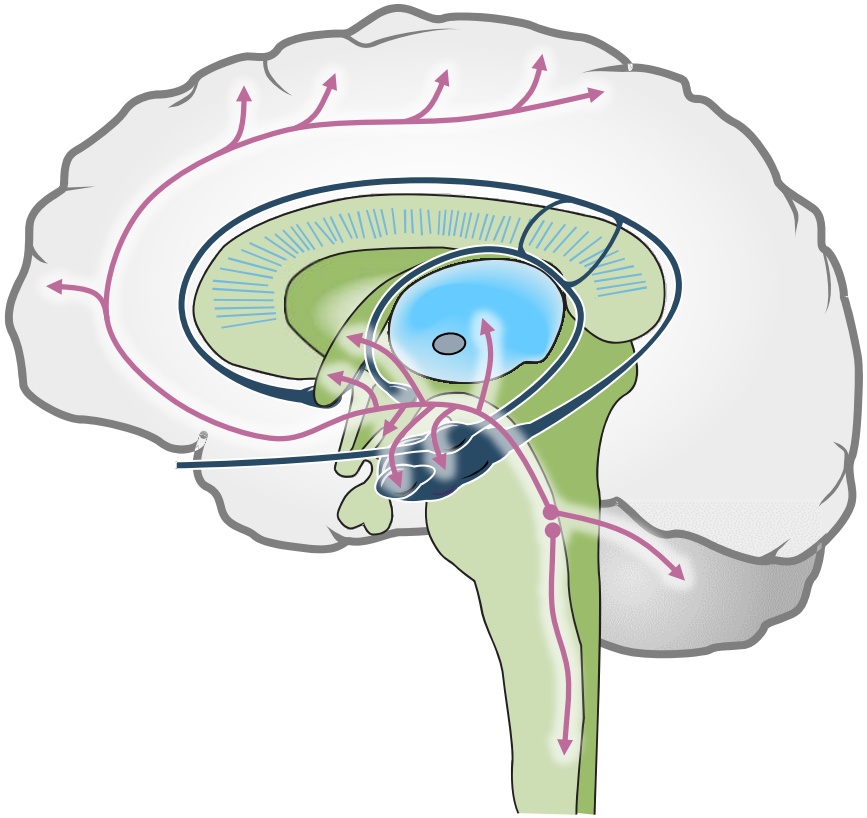


Image: Purves D et al.[3]


1. Aghajanian GK, Sanders-Bush, E. Serotonin. In *Neuropsychopharmacology* - 5th Generation of Progress. Lippincott, Williams, & Wilkins, 2002;
2. Purves D et al (eds). *Neuroscience*. 2nd Edition. Sinauer Associates, 2001;
3. Maejima T et al. *Front Integr Neurosci*. 2013;7:40;
4. Roth & Meltzer. 2000. www.acnp.org/g4/GN401000117. Accessed July 20, 2015.

# Norepinephrine (NE)

- Ascending projections from locus coeruleus to cortex, midbrain, and cerebellum[1]

## Proposed Actions:

- Involved in sleep, wakefulness, attention, and feeding behavior[1]
- NE system manipulations can affect schizophrenia:
  - α1 receptor suppression may reduce positive symptoms[2]; $\alpha_2$ suppression may improve dopaminergic signaling[3]
  - Enhances antipsychotic effects of DA antagonists[3]

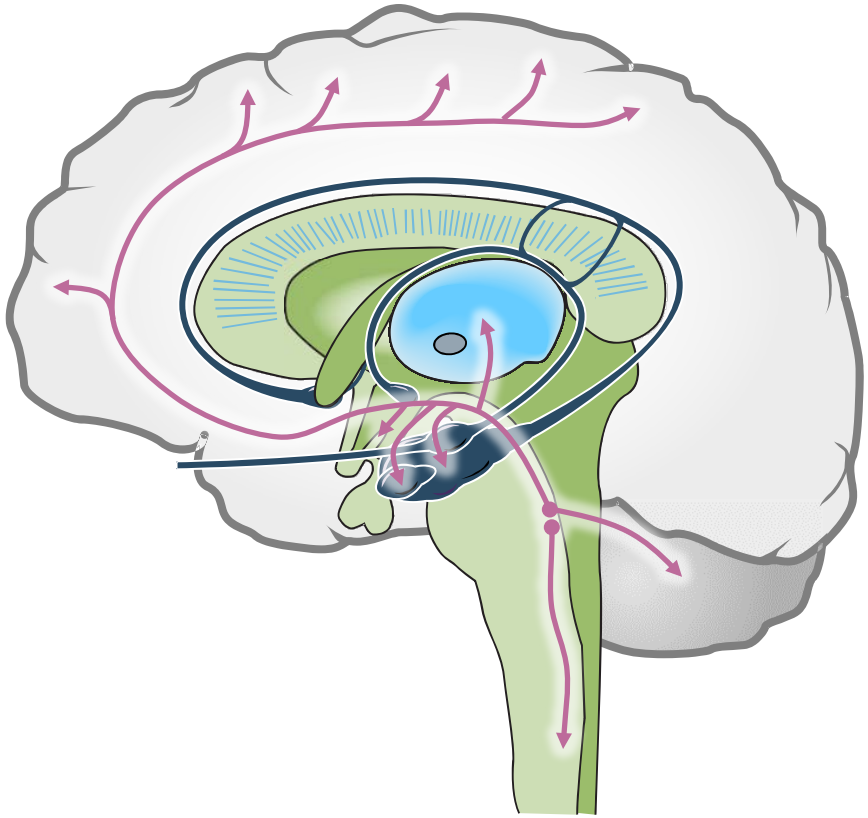


Image: Purves D et al.[1]

DA, dopamine.


1. Purves D et al (eds). *Neuroscience*. 2nd Edition. Sinauer Associates, 2001;
2. Svensson TH. Prog Neuropsychopharmacol Biol Psychiatry. 2003 Oct;27(7):1145-158;
3. Hensler et al. *Adv Pharmacol*. 2013;68:167-197.

# Glutamate (Glu)

- Major excitatory neurotransmitter of the brain[1]
  - Used by ≥ 40% of synapses; found in all cortical efferent neurons[1]

## Proposed Actions:

- Involved in memory, learning, and neuronal development[1,2]
- Strong evidence for reduced glutamate signaling in schizophrenia especially at the NMDA receptor[1]
- Signaling components altered in individuals with schizophrenia[3]
- Genes associated with increased schizophrenia risk are involved in glutamate signaling[4]

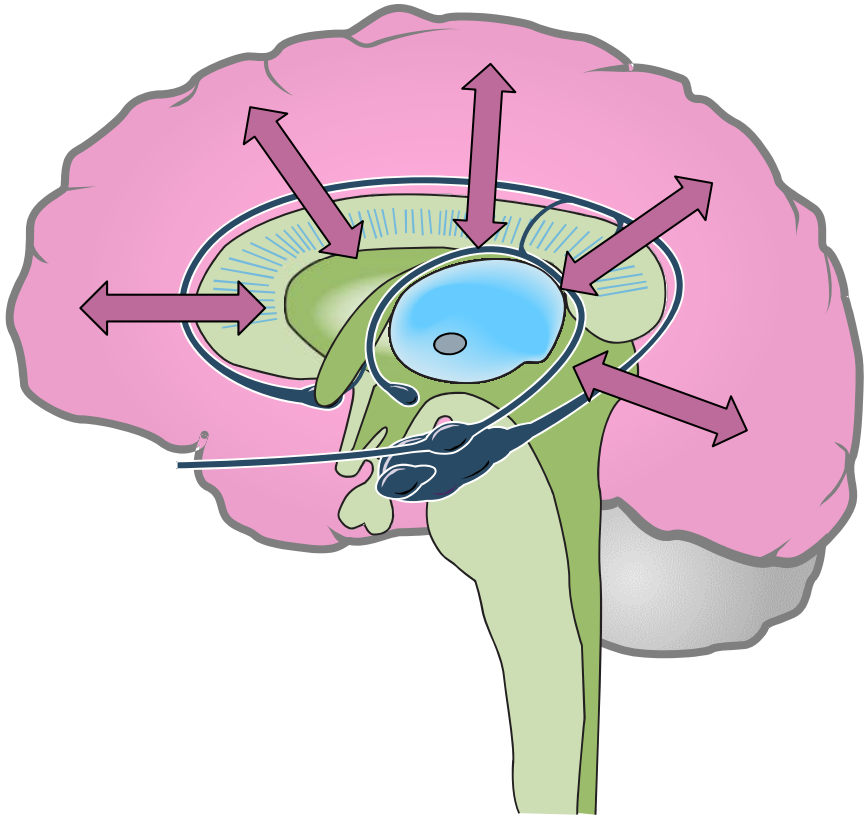


Image: Benarroch EE. *Neurology*. 2008;70(12):964-968.


1. Nasrallah HA, Smeltzer DJ. *Contemporary Diagnosis and Management of Schizophrenia*. 2nd Edition. Newtown, PA: Handbooks in Health Care Company; 2011;
2. Wijetunge LS et al. *J Neurosci*. 2008;28(49):13028-13037;
3. Clinton SM et al. Neuropsychopharmacology. 2004 Jul;29(7):1353-1362;
4. Lisman JE et al. *Trends Neurosci*. 2008;31(5):234-242.

# Current Standard of Care for Schizophrenia Characterized by Impact and Limitations of Treatment[1-4]

| Antipsychotic Classification | Functional Impact | Treatment Limitations |
|---|---|---|
| First-Generation (Typical)<br>• Dopamine $D_2$-receptor antagonism | • Decrease frequency and severity of psychotic episodes<br>• Improve functional capacity | • Adverse events (EPS symptoms)<br>• Suboptimal outcomes |
| Second-Generation (Atypical)<br>• Dopamine $D_2$-receptor antagonism/partial agonism<br>• Serotonin $5HT_{2A}$ antagonism and $5HT_{1A}$ partial agonism | All the efficacy goals of first-generations antipsychotics plus:<br>• Potentially reduced risk of EPS symptom profile<br>• Potential for modest improvement in relapse prevention[2,3] and/or treatment adherence[4] | • No clear superiority over first-generation medication in improving positive, cognitive, and social outcomes<br>• Adverse events (metabolic, weight gain, sedation, agranulocytosis) |

EPS, extrapyramidal symptoms.


1. Haller CS et al. *F1000 Prime Reports*. 2014:57(6):1-11;
2. Leucht S et al. *Am J Psychiatry*. 2003;160:1209-1222;
3. Csernansky JG and Schuchart EK. *CNS Drugs*. 2002;16(7):473-484;
4. Lehman AF. *Am J Psychiatry*. 2010;161(suppl 2):1-56.

# Side Effects Associated With Antipsychotics Can Vary With Treatment Duration and Pharmacologic Profile

| Neuro-transmitter/ Receptor | Acute (≤ 1 week) | | Early (< 3 months) | | Late (≥ 3 months) | |
|---|---|---|---|---|---|---|
| | Adverse Effect | Functional Consequence | Adverse Effect | Functional Consequence | Adverse Effect | Functional Consequence |
| Norepi-nephrine/ $\alpha_1$ | Hypotension* | Falls | Hypotension* | Falls | Hypotension | Falls |
| Dopamine/ $D_2$ | Dystonia*<br>Parkinsonism* | Pain | Parkinsonism*<br>Akathisia* | ↓Cognition | TD | Stigma<br>↓Socializing<br>↓QoL |
| | ↑Prolactin* | Sexual dysfunction | ↑Prolactin* | Sexual dysfunction,<br>Hypo-gonadism | ↑Prolactin | Osteoporosis<br>CHD?<br>Breast Cancer? |
| Histamine/ $H_1$ | Sedation* | ↓Cognition<br>↓Functioning | Sedation* | ↓Cognition<br>↓Functioning | Sedation | ↓Cognition<br>↓Functioning |
| | Weight | ↑Lipids<br>↑Glucose | ↑Weight | ↑Lipids<br>↑Glucose | Diabetes<br>Dyslipidemia<br>CHD | ↓Functioning<br>↓QoL |
| Acetyl-choline/ $M_{1-4}$ | Blurry vision*<br>Dry mouth* | Discomfort | ↓Cognition<br>↓Blurry vision*<br>Dry mouth*<br>Constipation* | ↓Functioning<br>Discomfort | ↓Cognition<br>↓Blurry vision*<br>Dry mouth*<br>Constipation* | ↓Functioning<br>Discomfort |

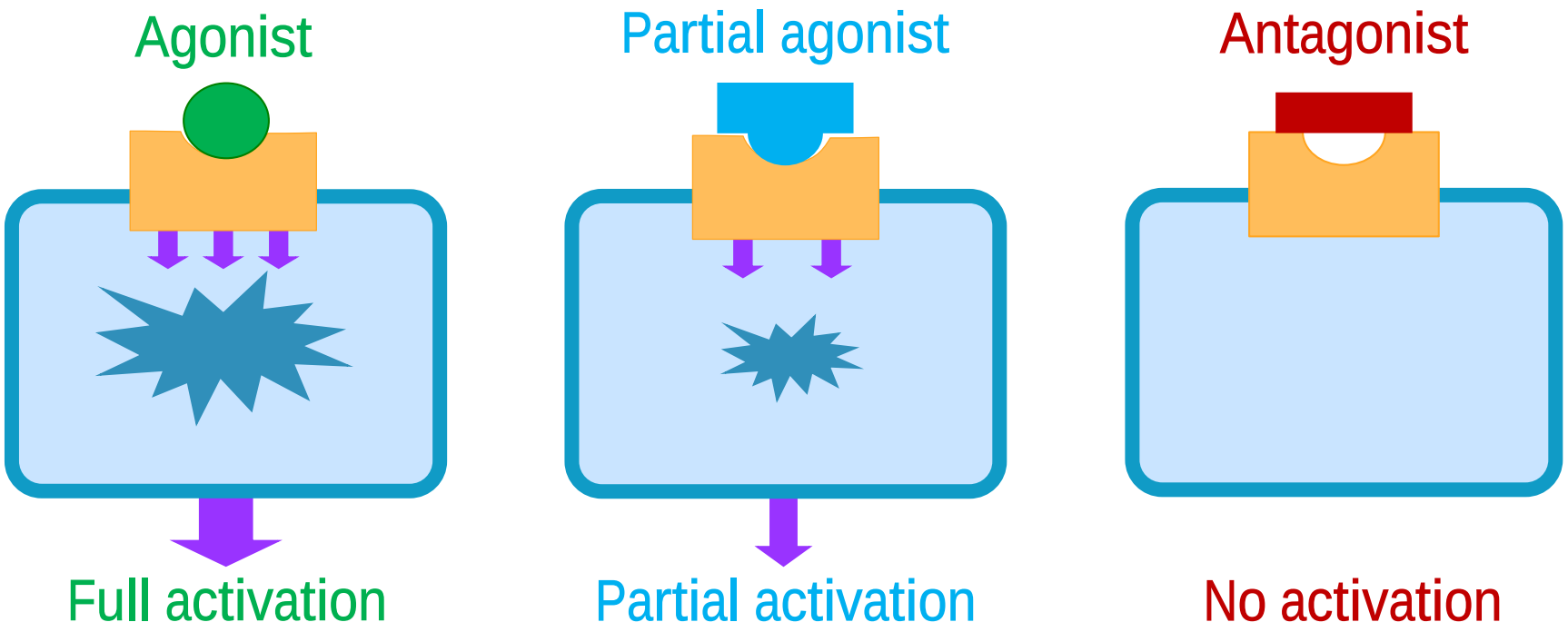
*Tolerance may develop; CHD, coronary heart disease; H1, histamine receptor type 1; M1-4, muscarinic receptor types 1-4,QoL, quality of life; TD, tardive dyskinesia.

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

# Concepts of Receptor Pharmacology

**Intrinsic activity of drug at a receptor**

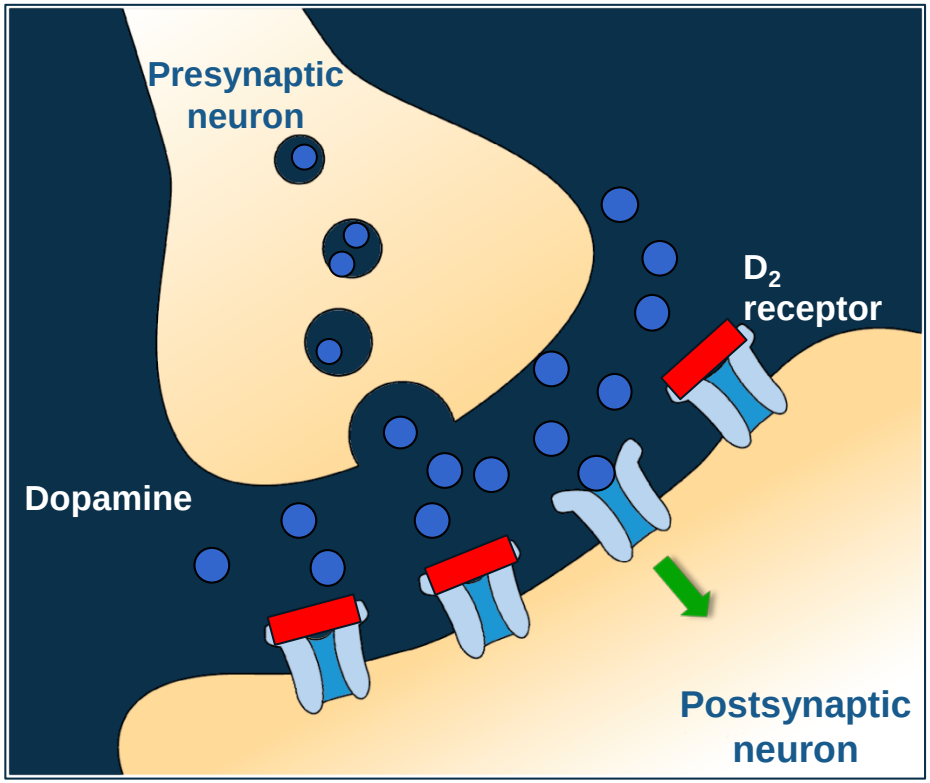
- The physiologic effect a ligand elicits once bound to its receptor
- Ligand can partially or fully stimulate (agonism) or inhibit (antagonism) receptor activity




1. Goodman and Gilman's *The Pharmacological Basis of Therapeutics.* 10th edition; Hardman JG, Limbird LE (eds); New York, NY: McGraw-Hill; 2001 pp36-40.

# Proposed Dopamine Antagonism in the *Mesolimbic* Pathway Improves Positive Symptoms

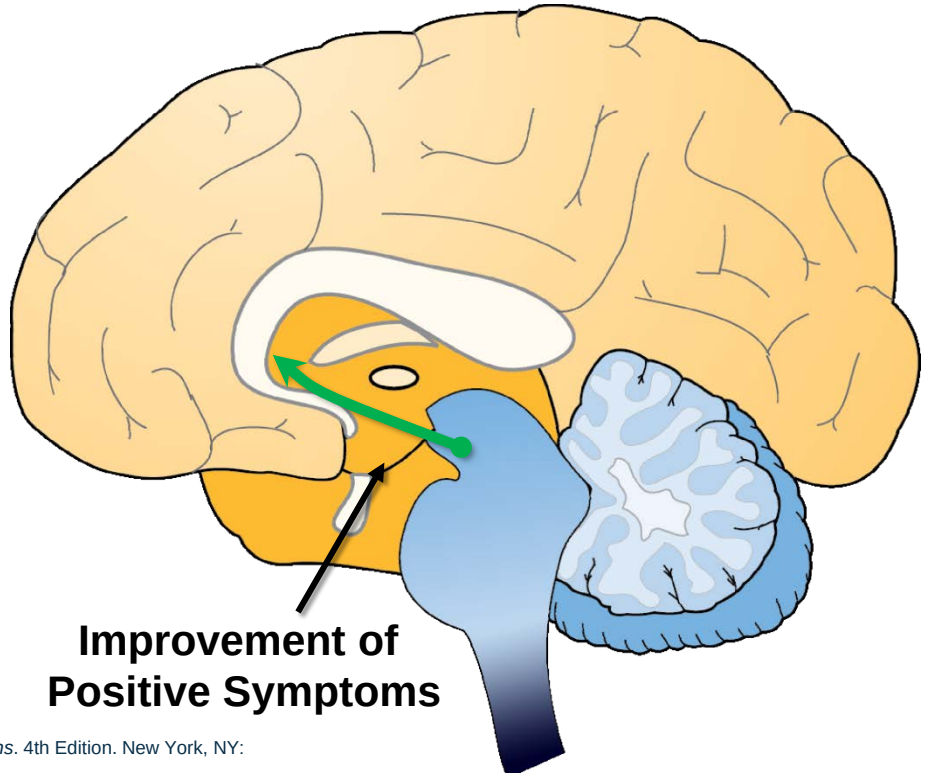
## Mesolimbic Pathway[1,2]




*The mechanism of action of antipsychotics in the treatment of schizophrenia is unknown.*

= $D_2$ antagonist

## Mesolimbic Hyperdopaminergic Pathway

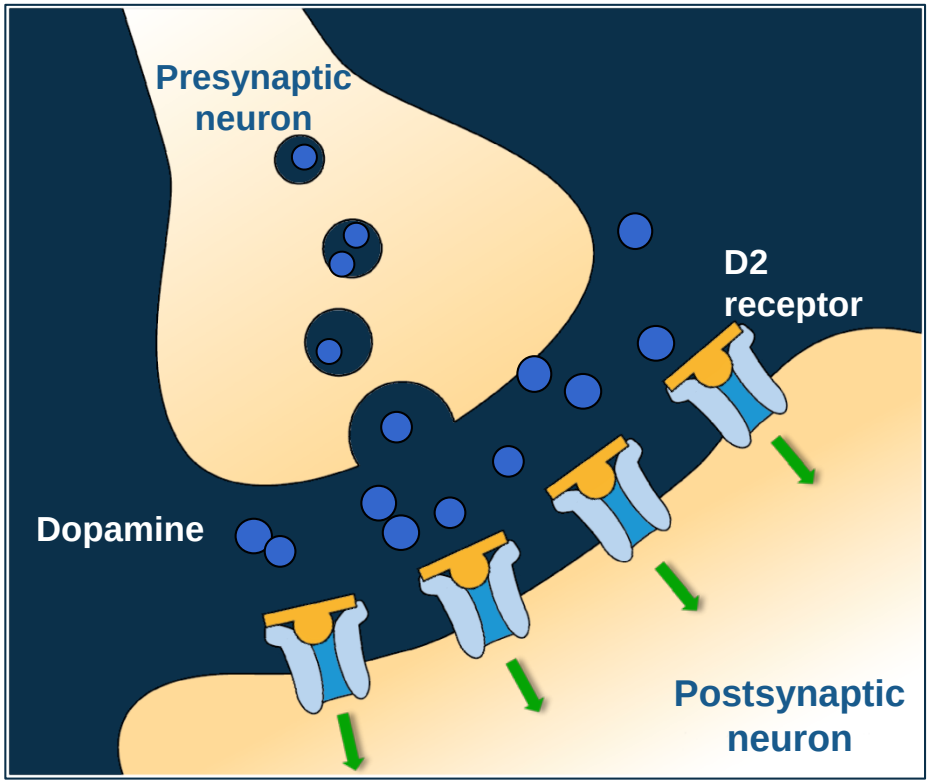


**Improvement of Positive Symptoms**


1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013;
2. Lieberman JA. *CNS Drugs*. 2004;18(4):251-267.

# $D_2$ Partial Agonist May Improve Positive and Negative Symptoms

**Mesolimbic Pathway[1,2]**




*The mechanism of action of antipsychotics in the treatment of schizophrenia is unknown.*

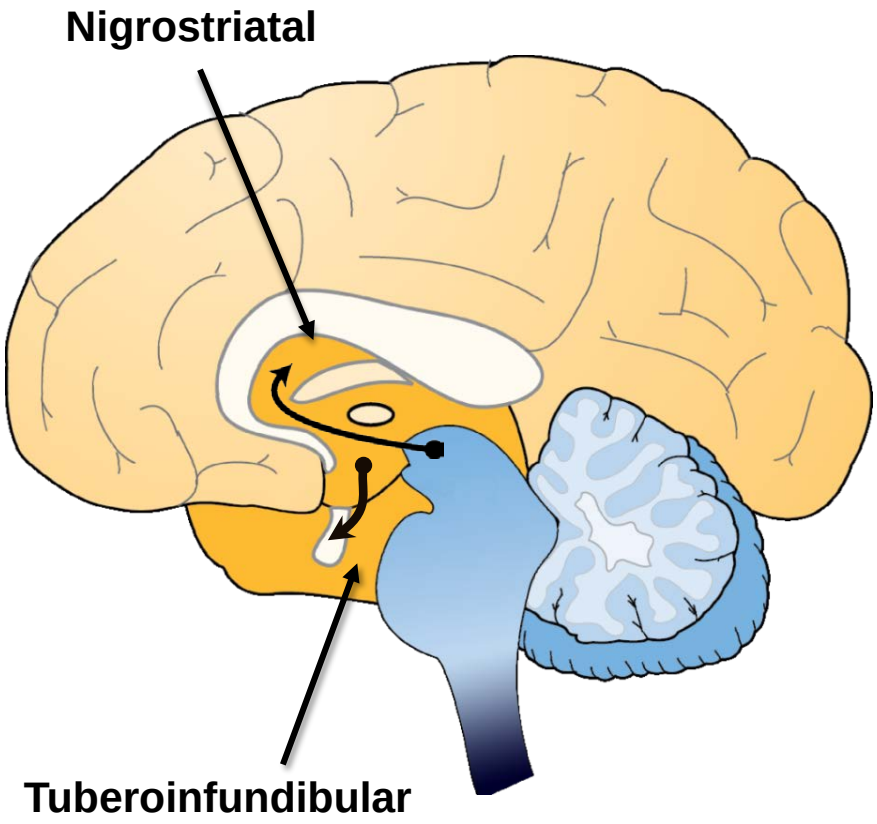
**= $D_2$ Partial Agonist**

- Binds to postsynaptic $D_2$ receptors[2]
- Associated with improvements in psychotic and negative symptoms of schizophrenia[2]


1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013;
2. Lieberman JA. *CNS Drugs*. 2004;18(4):251-267.

# Effects of Antipsychotics in the Nigrostriatal and Tuberoinfundibular Pathways

- Nigrostriatal pathway[1]:
  - Dopamine inactivation may cause EPS[2]
- Tuberoinfundibular pathway[1]:
  - Dopamine inactivation may result in hyperprolactinemia[2]




*The mechanism of action of antipsychotics in the treatment of schizophrenia is unknown.*

EPS, extrapyramidal symptoms.

1. Stahl SM. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th Edition. New York, NY: Cambridge University Press; 2013;
2. Lieberman JA. *CNS Drugs*. 2004;18(4):251-267.

# Alternative Hypotheses

| Hypothesis | Details/Evidence |
|---|---|
| **Neuroinflammation** | • Neuroinflammation, microglial activation, cytokine production, and other immune processes observed in disease[1,2] |
| **Plasticity / Connectivity Changes** | • Possible structural changes at the cellular level and/or functional changes through changes at the synaptic level[3] |
| **Genetics** | • Family, twin, and adoption studies suggest hereditary component<br>• Multiple genes implicated[4] |


1. Girgis et al. *Biol Psychiatry*. 2014;75(4):292-299;
2. Monji A. *Prog Neuropsychopharmacol Biol Psychiatry*. 2013;42:115-121;
3. Stephan KE et al. *Biol Psychiatry*. 2006;59(10):929-939;
4. Sun et al. *PLoS One*. 2010;5(6):e11351.

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