

Review Article

Dopamine Modulation by Antipsychotic in Schizophrenia

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Abstract

Schizophrenia is a complex psychiatric disorder characterized by positive, negative, and cognitive symptoms. The dopamine hypothesis of schizophrenia posits that hyperactivity of dopamine pathways, particularly in the mesolimbic pathway, contributes to the positive symptoms of the illness. Antipsychotic medications, the primary pharmacological treatment for schizophrenia, exert their therapeutic effects largely through modulation of dopamine neurotransmission. This document explores the mechanisms by which antipsychotic drugs affect dopamine pathways. Both first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) primarily act as dopamine receptor antagonists, blocking dopamine receptors, particularly the D2 receptor subtype. However, SGAs exhibit a more complex pharmacological profile, often including serotonin receptor antagonism (e.g., 5-HT_{2A}) in addition to dopamine receptor blockade. This serotonin antagonism is thought to contribute to the improved side effect profile and efficacy against negative symptoms observed with some SGAs. The document further examines the regional specificity of antipsychotic effects on dopamine release and metabolism, considering the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways. Understanding these mechanisms is crucial for optimizing antipsychotic treatment strategies, minimizing adverse effects such as extrapyramidal symptoms (EPS) and hyperprolactinemia, and developing novel therapeutic interventions targeting dopamine and other neurotransmitter systems in schizophrenia.

Keywords

Antipsychotic, Schizophrenia, Dopamine, First Generation Antipsychotic Drugs, Second Generation Antipsychotic Drugs

1. Introduction

The hypothesis that dopamine and dopaminergic mechanisms are central to schizophrenia, and particularly psychosis, has been one of the most enduring ideas about the illness. Despite a relatively inauspicious start—dopamine was initially thought to be a precursor molecule of little functional significance—the idea has evolved and accommodated new evidence to provide an increasingly sophisticated account of the involvement of dopamine in schizophrenia.

2. About Schizophrenia

Schizophrenia is a severe mental disorder, with a prevalence rate of 1 in 300 people (0.32%) worldwide and with approximately 24 million people suffering from this disorder. Schizophrenia is associated with high levels of personal and social burden [1, 2, 24]. Patients suffering from schizophrenia are at higher risk—compared to the general population—of developing physical comorbidities, including cardiovascular diseases, diabetes, obesity, and cancer, with a significant reduction in life expectancy by 15–20 years [3, 35, 34]. Furthermore, patients with schizophrenia often suffer from

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Received: 24 April 2025; Accepted: 2 July 2025; Published: 17 December 2025



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comorbid mental disorders, including anxiety disorders, with a prevalence rate of 45% [4]; personality disorders, with a prevalence rate of 25% [5, 26]; or substance use disorders, in up to 70% of patients with schizophrenia [6, 25]. Low levels of long-term functional recovery have been reported by patients with schizophrenia, with frequent relapses and voluntary/involuntary hospitalizations. In fact, the disorder often presents a recurrent course, with relapses and requiring a long-term pharmacological treatment [7, 8]. Schizophrenia has been conceptualized as a heterogeneous disorder with a complex etiopathogenesis, caused by the interplay between genetic, environmental, and psychosocial factors [9, 10]. Thus, multilevel, integrated, and personalized treatment is essential for people suffering from schizophrenia [7, 11, 12]. The treatment choice should be made on the basis of several salient clinical domains, such as positive and negative symptom dimensions [13-15], other psychopathological components, type of onset and course, neurocognition and social cognition, neurodevelopmental indicators, social functioning, quality of life and unmet needs, clinical staging, antecedent and concomitant psychiatric conditions, physical comorbidities, family history, history of obstetric complications, early and recent environmental exposures, protective factors and resilience, and internalized stigma [16, 17].

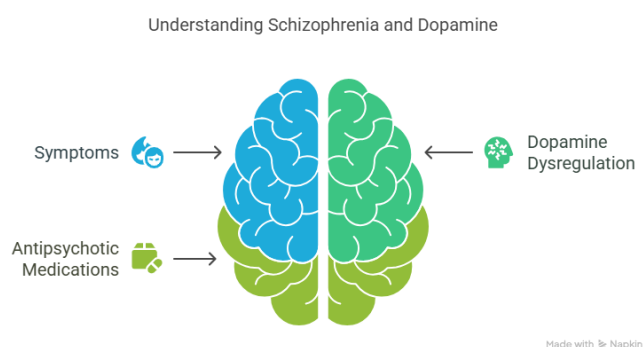


Figure 1. Neural circuitry involved in dopamine regulation and its relevance to schizophrenia.

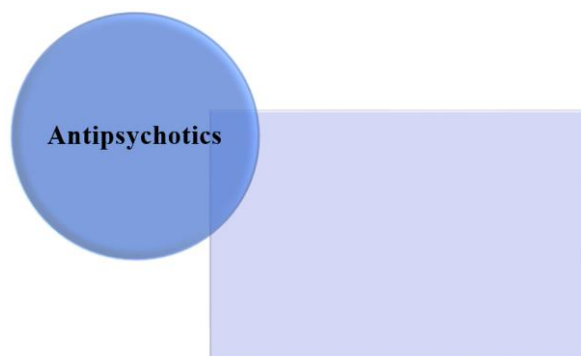


Figure 2. Relationship between dopamine dysregulation, clinical symptoms, and antipsychotic medication effects in schizophrenia.

3. First-Generation Antipsychotics

All dopamine receptor antagonists are available and can be administered in oral form. Except for thioridazine, pimozide, and molindone, all other first-generation antipsychotics can also be given parenterally. Haloperidol and fluphenazine can be delivered in long-acting depot parenteral form [27, 28].

First-generation antipsychotics (FGAs) are associated with significant extrapyramidal side effects. Anticholinergic adverse effects like dry mouth, constipation, and urinary retention are common with low-potency dopamine receptor antagonists like chlorpromazine and thioridazine. The action of H1 histamine blocking by first-generation antipsychotics causes sedation [29]. Chlorpromazine is the most sedating, while fluphenazine, haloperidol, and pimozide are less sedating. First-generation antipsychotics can also lower the seizure threshold, and chlorpromazine and thioridazine are more epileptogenic than others. Haloperidol can cause abnormal heart rhythm, ventricular arrhythmia, torsade de pointes, and even sudden death if injected intravenously [30]. Other FGAs can cause prolongation of QTc interval, prolonged atrial and ventricular contraction, and other cardiac conduction abnormalities. Thioridazine has an FDA-backed warning for sudden cardiac death. Low-potency FGAs, like chlorpromazine or thioridazine, commonly cause orthostatic hypotension. This adverse effect caused by alpha-adrenergic block usually occurs when starting treatment, and patients often develop a tolerance. It is important to avoid treating hypotension with epinephrine. Leukopenia, thrombocytopenia, and blood dyscrasia are rare side effects of treatment with FGAs. Increased serum prolactin concentrations along with galactorrhoea, breast enlargement, amenorrhea, impotence in men, and anorgasmia in women are known adverse effects due to the action of the dopamine receptor block in the tuberoinfundibular tract. Allergic dermatitis and photosensitivity can occur with chlorpromazine. Chlorpromazine is also associated with blue-grey skin discoloration and benign pigmentation of the lens and cornea. Thioridazine can cause retinal pigmentation, which can continue even after discontinuing the drug [6-8, 31].

Clozapine was the first antipsychotic that proved to be efficacious in treatment-refractory schizophrenia [3, 32], but it was also the first antipsychotic devoid of EPS. However, the ability of clozapine to cause agranulocytosis as a serious adverse effect led to voluntary withdrawal of the drug by the manufacturer, with subsequent reintroduction in 1989, followed by strict regulation regarding indications and white blood cells count follow up [4, 33]. The efficacy of clozapine and its inability to produce EPS were motives for the development of similar antipsychotics, but with the safer profile. Second generation antipsychotics such as olanzapine, risperidone, quetiapine, and more recently ziprasidone and aripiprazole soon became the mainstay of the treatment of schizophrenia, despite their higher costs and inconsistency of the data showing their superior efficacy versus FGAs [18].

Clozapine, as the first SGA, actually discredited the theory that EPS are an unavoidable accompaniment of antipsychotic efficacy. Previously, EPS were considered as an essential component of antipsychotic “neuroleptic” effect. The association of antidopaminergic (D2) potency, antipsychotic effect, and EPS (due to loss of dopamine in the extrapyramidal part of the central nervous system) was the foundation for the dopamine hypothesis of schizophrenia.

4. Second-Generation Antipsychotics

These can be administered orally or parenterally. Risperidone, olanzapine, aripiprazole, and paliperidone are extended-release or long-acting injectable forms. Clozapine, asenapine, and olanzapine are available in the sublingual formulation [19, 35].

Neuroleptic malignant syndrome is a rare but fatal adverse effect that can occur at any time during treatment with FGAs. The onset of symptoms is over 24 to 72 hours with increased temperature, severe muscular rigidity, confusion, agitation, elevation in white blood cell count, elevated creatinine phosphokinase concentrations, elevated liver enzymes, myoglobinuria, and acute renal failure. The antipsychotic should be immediately discontinued, and dantrolene 0.8 to 2.5 mg/kg every 6 hours up to 10 mg per day is the drug of choice. [20] Adequate hydration and cooling should be closely monitored, as well as vital signs and serum electrolytes. Though the risk of neuroleptic malignant syndrome is higher with first-generation antipsychotics, second-generation antipsychotics also cause this adverse effect.

Second-generation antipsychotics have a decreased risk of extrapyramidal side effects as compared to first-generation antipsychotics. Second-generation antipsychotics are associated with significant weight gain and the development of metabolic syndrome. The FDA recommends monitoring

personal and family history of diabetes mellitus, dyslipidaemia, weight and height, waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile for all patients. Risperidone is associated with dizziness, anxiety, sedation, and extrapyramidal side effects. [21] Paliperidone can cause temperature sensitivity to hot or cold temperatures and QTc prolongation. Olanzapine is most frequently associated with weight gain, increased appetite, and somnolence. Quetiapine is the least likely to cause extrapyramidal side effects. The most common side effects of quetiapine are somnolence, orthostatic hypotension, and dizziness. [22] Ziprasidone has almost no weight gain but can cause prolongation of QTc. Aripiprazole is the most common side effect of agitation, headache, and akathisia-like restlessness.

Asenapine can cause an increase in serum prolactin concentrations, weight gain, and prolongation of QTc. Clozapine can cause hypersalivation [23], tachycardia, hypotension, and anticholinergic side effects. Clozapine is unusual in that it suppresses dyskinesia. Clozapine can cause clinically important agranulocytosis and leukopenia and, therefore, requires monitoring of white blood cells and absolute neutrophil count. The FDA guidelines indicate monitoring absolute neutrophil count weekly for the first 6 months and, if normal, can be monitored every 2 weeks after that. Treatment with clozapine should be discontinued if absolute neutrophil count drops below 1000 cells per cubic millimetre or below 500 cells per cubic millimetre in those with benign ethnic neutropenia. Clozapine can also cause the rare side effects of cardiomyopathy and myocarditis. FDA boxed warning: Observational studies suggest that similar to second-generation antipsychotics, treatment with first-generation antipsychotics may increase mortality risk in elderly patients with dementia-related psychosis. Larger doses of antipsychotics increase the risk of adverse drug effects.

Table 1. Comparison between first-generation (typical) and second-generation (atypical) antipsychotics based on mechanism of action, examples, extrapyramidal symptoms, and metabolic effects.

Feature	First Antipsychotics Generation	Second Generation Antipsychotics
Mechanism	Strong D2 blockage	D2 +5-HT _{2A} antagonism
EPS Risk	High	Low
Metabolic Effects	Low	High
Sedation	High in low-potency types	Moderate to High
Prolactin	Common	Less common (risperidone)
Example	Haloperidol, Chlorpromazine	Risperidone, Clozapine, Olanzapine

5. Dopamine Hypothesis of Schizophrenia

The ability of a substance to induce EPS experimentally was considered as proof of its antipsychotic potential. However, dopamine hypothesis of schizophrenia became obsolete with the introduction of clozapine and other SGAs. All antipsychotic agents have some degree of antagonistic affinity for dopaminergic D2 receptors. It was shown that first-generation antipsychotics, though known to block other receptors, not only exert their antipsychotic, but also their extrapyramidal effects, primarily by binding to D2 receptors in the central nervous system. First-generation antipsychotics produce their therapeutic (antipsychotic) effect at 60–80% of D2 occupancy, while the 75–80% of D2 receptor occupancy leads to the acute EPS. Therefore, the overlap between desired and adverse D2 receptor occupancy is mostly unavoidable with FGAs. On the other hand, the therapeutic effects of SGAs are attributable also to some degree to D2 antagonism, but more to blockade of certain serotonin (mostly 5HT_{2A}) receptors. Surprisingly, clozapine, as the most effective antipsychotic so far, has the lowest D2 affinity (Table 1). It was also suggested and shown in animal models that SGAs actually bind to and dissociate from D2 receptors in an atypical manner (Kapur, 2001). Loose binding to and fast dissociation of SGAs from D2 receptors may be the cause of their lower EPS propensity. The affinity of antipsychotic drugs for D2 receptors. While the

antipsychotic effect of FGAs correlates with D2 affinity, that is not the case with SGAs [2].

6. Implications of the Dopamine Hypothesis of Schizophrenia

The hypothesis that the final common pathway is presynaptic dopamine dysregulation has some important clinical implications. Firstly, it implies that current antipsychotic drugs are not treating the primary abnormality and are acting downstream. While antipsychotic drugs block the effect of inappropriate dopamine release, they may paradoxically worsen the primary abnormality by blocking presynaptic D2 auto receptors, resulting in a compensatory increase in dopamine synthesis. There is some evidence from healthy volunteers that acute antipsychotic treatment does increase presynaptic dopamine synthesis capacity, and while successful subacute treatment can reduce this, it is nevertheless elevated in patients who have received antipsychotic treatment for many years [17]. This may explain why patients relapse rapidly on stopping their medication, and if the drugs may even worsen the primary abnormality, it also accounts for more severe relapse after discontinuing treatment. This suggests that drug development needs to focus on modulating presynaptic striatal dopamine function, either directly or through upstream effects.

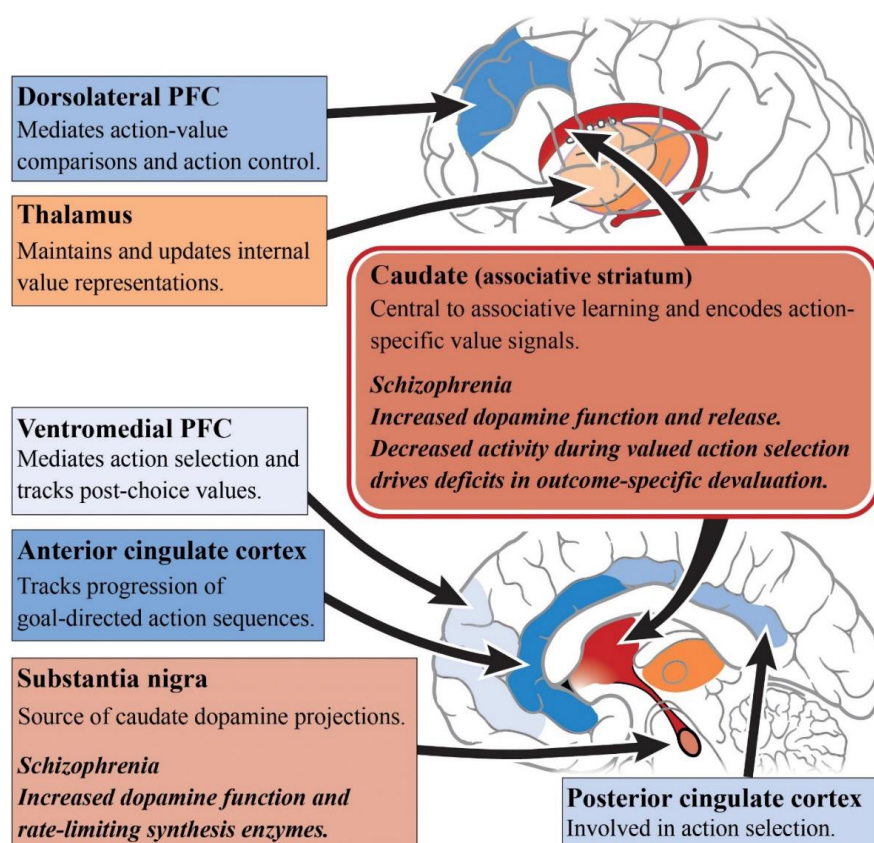


Figure 3. Classification of antipsychotic medications showing major categories and overlapping pharmacological properties.

Author Contributions

Verma Muskan is the sole author. The author read and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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