Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology

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This shows elevated striatal dopamine synthesis and release capacity in dorsal regions of the striatum underlies the positive symptoms of psychosis and suggests reduced [dopamine release](https://www.sciencedirect.com/topics/neuroscience/dopamine-release" \o "Learn more about dopamine release from ScienceDirect's AI-generated Topic Pages) in cortical regions contributes to cognitive and negative symptom

Current drugs act downstream of the major dopamine abnormalities and may worsen cortical dopamine function. GABAergic and glutamatergic regulation of dopamine neurons

New approaches include targeting dopamine synthesis and capacity, autoreceptors, trace-amine receptors and other mechanisms.

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Non-dopmaminergic approaches such as those addressing inflammation may prove to be disease modifying.

Dopamine synthesis in the striatum = postive symptoms,

Reduced dopamine release in cortical regions contributes to cognitive and negative symptoms.

[Schizophrenia](https://www.sciencedirect.com/topics/neuroscience/dementia-praecox) is a common [mental disorder](https://www.sciencedirect.com/topics/neuroscience/psychopathology" \o "Learn more about mental disorder from ScienceDirect's AI-generated Topic Pages) characterised by positive symptoms, such as delusions and hallucinations, negative symptoms such as avolition and social withdrawal, and [cognitive impairments](https://www.sciencedirect.com/topics/neuroscience/cognitive-disorders" \o "Learn more about cognitive impairments from ScienceDirect's AI-generated Topic Pages) ([Revier et al., 2015](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib287)). It typically presents in late adolescence to early adulthood, starting with a prodromal phase of subtle changes in thinking and behaviour ([Howes and Murray, 2014](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib125)).

Treatment resistance (Howes et al, 2017)

[Antipsychotic](https://www.sciencedirect.com/topics/neuroscience/antipsychotic) drugs are effective in treating the acute manifestations of the illness and in reducing the risk of relapse ([Leucht et al., 2017](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib192)),

1. Common effects: monoaminergic dysfunction in scz – core to understanding the mechanism of action of AP
2. Receptor binding profiles of commonly used AP

But – imaging studies show an increase in striatal D2/3 receptors in some patients, but no signif. Increase in AP naïve patients (in mea-analyses., and no clear change in cortical dopamine D2/3.

These drugs vary somewhat in the receptors they bind to (see [Fig. 1](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "fig1)), but all bind to dopamine D2/3 receptors to some degree ([Howes et al., 2009a](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib128)). Drug affinity for receptors can be considered in terms of the inhibition constant, Ki, which reflects the concentration of drug required to bind to 50% of the receptors in a competition binding assay. Thus, the inhibition constant Ki is an indicator of [binding affinity](https://www.sciencedirect.com/topics/neuroscience/binding-affinity): a lower value reflects a higher affinity of a drug for a given receptor ([Yung-Chi and Prusoff, 1973](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib363))

However, all currently licensed antipsychotic drugs show appreciable binding to [dopamine D2 receptors](https://www.sciencedirect.com/topics/neuroscience/dopamine-receptor-d2) at therapeutic doses, and this action is core to their therapeutic action ([Kapur et al., 2000](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib161), [Nordstrom et al., 1993](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib254), [Richtand et al., 2007](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib289), [Seeman et al., 1976](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib303)). In view of this, it is useful to consider their affinities at receptors relative to their affinity for D2 receptors

One implication of this finding is that if an antipsychotic drug shows a similar affinity for another receptor as its affinity for D2 receptors, then it is likely to show appreciable blockade of that receptor at clinical doses as well. Thus, it is useful to consider the affinities of antipsychotic drugs for receptors relative to their affinity for D2 receptors for understanding the potential mode of action and side-effect profiles of different drugs.

Clearly, when compared to the other antipsychotics, [clozapine](https://www.sciencedirect.com/topics/neuroscience/clozapine), [olanzapine](https://www.sciencedirect.com/topics/neuroscience/olanzapine), [quetiapine](https://www.sciencedirect.com/topics/neuroscience/quetiapine) and [risperidone](https://www.sciencedirect.com/topics/neuroscience/risperidone) have much higher affinities for other receptors relative to their dopamine D2 receptor affinities. Such antipsychotics with high affinities for receptors other than dopamine D2 will block a significant number of those receptors at clinically effective doses.

In general, molecular imaging studies have shown that dopamine D2 receptor blockade above 50% occupancy is required for a high likelihood of clinical response whilst occupancy above about 85% increases the risk of extra-pyramidal side-effects (see section on side-effects and [Howes et al. (2009b)](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib129) ([Kapur et al., 2000](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub#bib161), [Nyberg et al., 1995](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib260), [Uchida et al., 2011](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib338)). These findings indicate that there is a [therapeutic window](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/therapeutic-window)of between 60 and 80% D2 receptor occupancy that achieves a balance between a high likelihood of response with a low risk of motor side-effects

The evidence discussed above indicates that current antipsychotics primarily act by blocking [dopamine receptors](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dopamine-receptor), which are largely downstream of the main dopamine abnormalities. Moreover, antipsychotics do not normalise the dopamine abnormalities ([Jauhar et al., 2019](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib147)). Dopamine blockade reduces aberrant dopamine signalling but also interferes with physiological signalling that is essential for adaptive learning, motivated behaviour, motor and other functions, leading to some of the side-effects discussed above and non-adherence. Thus, it would be preferable to target the dopamine abnormality itself to correct dysregulated striatal dopamine synthesis and release whilst permitting normal, physiological [dopaminergic](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dopamine-receptor-stimulating-agent)function in the striatum and cortex

However, it is now thought that multiple [neurotransmitter](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/neurotransmitter) systems underlie the cognitive and negative symptoms of schizophrenia ([Galderisi et al., 2015](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib86), [Howes and Kapur, 2009](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib123))

Another strategy might be to modulate the upstream [glutamate](https://www.sciencedirect.com/topics/neuroscience/glutamic-acid) and GABA systems that regulate dopamine neurons ([Fig. 5](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "fig5))

Moreover, altered cortical function is linked to striatal dopamine abnormalities in schizophrenia and at-risk populations ([Bertolino et al., 2006](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib27), [Fusar-Poli et al., 2011](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib84), [Jauhar et al., 2018](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib146), [Meyer-Lindenberg et al., 2005](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib229)), suggesting cortical dysfunction could be linked to striatal dopamine abnormalities. This is consistent with theories that striatal dopamine dysfunction is the consequence of cortical dysregulation, and highlights that treating the latter might address both cognitive impairments and psychotic symptoms.

Conclusion:

Despite this, studies of the dopamine system in patients with schizophrenia have shown that there is not a major alteration in dopamine D2/3 receptors in schizophrenia. Rather the major alteration is presynaptic, characterised by increased striatal dopamine synthesis and release capacity predominantly in dorsal regions of the striatum linked to psychosis, and potentially reduced [dopamine release](https://www.sciencedirect.com/topics/neuroscience/dopamine-release) in cortical regions underlying [cognitive impairments](https://www.sciencedirect.com/topics/neuroscience/cognitive-disorders). These findings explain why post-synaptic [dopamine receptor](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/dopamine-receptor) blockade works to reduce the positive symptoms of schizophrenia. They also highlight that current drugs acts downstream of the underlying dopamine abnormalities and block physiological signalling that is needed for normal brain function as well as.

Current agents also have many off-target effects on other receptors, such as serotonin, histamine, muscarinic and alpha-adrenergic receptors. Our review highlights that there is a paucity of in vivo studies of these systems in schizophrenia, and a need for in vivo studies in patients free from the confound of [antipsychotic](https://www.sciencedirect.com/topics/neuroscience/antipsychotic) treatment. Notwithstanding this limitation, the neurobiological evidence available to date does not clearly implicate these systems in the [pathophysiology](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/pathophysiology) of psychosis, nor does the in vivo evidence support a major role for these receptors in mediating the antipsychotic effect of current drugs. This reinforces the centrality of dopamine receptor blockade for the action of antipsychotics.

However, our review does highlight how many of the common side-effects of antipsychotics, such as sedation and weight gain, can be understood in terms of these off-target effects. Moreover, it shows that particular side-effects are hard to avoid given the pharmacology of some drugs and the need to block dopamine receptors adequately.

We consider several strategies to do this through reducing dopamine synthesis, targeting [autoregulation](https://www.sciencedirect.com/topics/neuroscience/autoregulation), or modulating the upstream control of dopamine neurons via the [glutamate](https://www.sciencedirect.com/topics/neuroscience/glutamic-acid) or GABAergic systems.

A recent study by [Tiihonen et al. (2019)](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib333) provides real-world evidence for the use of some antipsychotics in combination to reduce the risk of rehospitalisation in patients with [schizophrenia](https://www.sciencedirect.com/topics/neuroscience/dementia-praecox). [Clozapine](https://www.sciencedirect.com/topics/neuroscience/clozapine) in combination with [aripiprazole](https://www.sciencedirect.com/topics/neuroscience/aripiprazole) was found to be associated with the lowest rehospitalisation risk and associated with better outcomes than clozapine [monotherapy](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/monotherapy), which was the most effective monotherapy. This could be due to one of three mechanisms: [polypharmacy](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/polypharmacy) leads to greater dopamine D2 occupancy and blockade which increases efficacy; or a reduction in side effects which increases [tolerability](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/tolerability), for example reduced weight gain when aripiprazole is added to clozapine and reduced prolactin levels when aripiprazole is added to other dopamine [D2 antagonists](https://www.sciencedirect.com/topics/neuroscience/d2-antagonists) ([Galling et al., 2017](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib87)); or finally, the addition of a second agent induces beneficial effects via actions at other receptors. Of course, these mechanisms are not mutually exclusive, and further work is required to identify which underlie the potential real-world benefits of polypharmacy.

All drugs currently licensed to treat [schizophrenia](https://www.sciencedirect.com/topics/neuroscience/dementia-praecox) are dopamine D2/3 blockers, despite past efforts to develop alternative approaches ([Millan et al., 2016](https://www.sciencedirect.com/science/article/pii/S002839081930262X?via%3Dihub" \l "bib230)). Moreover, [molecular imaging](https://www.sciencedirect.com/topics/neuroscience/molecular-imaging) studies have shown that D2/3 receptor blockade is necessary for the therapeutic action of current drugs, although it does not guarantee response.