Antipsychotics

INTRODUCTION

OVERVIEW

Antipsychotics are drugs used for the treatment of psychoses, mainly for schizophrenia and bipolar disorder, but also for psychoses associated with other disorders, including neurodegenerative diseases. This article describes first-generation, or typical, and second-generation, or atypical, antipsychotics with D2 antagonism as a common feature and serotonin blocking effect as an additional feature. Some antipsychotics do not fit into these categories. This article describes mechanism of action, indications for use, and adverse effects of various antipsychotic agents.

KEY POINTS

- Antipsychotic agents are dopamine antagonists that were originally designed as an alternative to surgical lobotomy for intractable psychiatric disorders such as schizophrenia.

- Several antipsychotics are approved for schizophrenia as well as bipolar syndrome, whereas others are in use for psychoses associated with other conditions, including neurodegenerative disorders such as Parkinson disease.

- The neurologic adverse effects of antipsychotics include drug-induced
movement disorders such as tardive dyskinesia and neuroleptic malignant syndrome.

- The effective and safe use of antipsychotics requires a personalized approach based on pharmacogenetics, therapeutic drug monitoring, and drug-drug interactions.

**Historical note and terminology**

The term "antipsychotic" is applied to a drug used for the treatment of psychoses, mainly schizophrenia and bipolar disorder. Antipsychotics are sometimes referred to as neuroleptics, which is a broader term that literally refers to drugs "taking hold of the nerve," implying psychotropic as well as adverse effects on the nervous system. Antipsychotics are usually described as typical or first generation and were introduced in the 1950s. The first antipsychotic, chlorpromazine, was originally developed as an anesthetic and was later used on psychiatric patients because of its powerful calming effect, referred to as "pharmacological lobotomy," which was an alternative to the surgical lobotomy that was still performed at that time (17). The first of the atypical or second-generation antipsychotics, clozapine, was introduced in the 1970s. Both types of antipsychotics block dopamine receptors, but atypical antipsychotics block serotonin receptors as well. The division between the 2 types, however, is not accurate. Third-generation antipsychotics are partial D2 agonists. Several new antipsychotic drugs are in development.

The focus of this article is on atypical antipsychotics, which are now used in clinical practice, but the adverse effects of typical antipsychotics will also be considered.

**Pharmacology**

A classification of clinically used antipsychotics is shown in Table 1. Typical antipsychotics are listed according to chemical structure, whereas atypical antipsychotics are classified according to their pharmacodynamic properties and affinity for receptors.
Table 1. Classification of Antipsychotics

<table>
<thead>
<tr>
<th>Category</th>
<th>Examples of drugs</th>
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<tbody>
<tr>
<td><strong>Typical first-generation antipsychotics according to chemical structure</strong></td>
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<tr>
<td>Butyrophenones</td>
<td>benperidol, bromperidol, droperidol, haloperidol</td>
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<tr>
<td>Diphenylbutylpiperidines</td>
<td>fluspirilene, pimozide</td>
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<tr>
<td>Phenothiazenes</td>
<td>chlorpromazine, cyamemazine, fluphenazine, levomepromazine, perazine, perphenazine, pipotiazine, prochlorperazine, promethazine, trifluoperazine</td>
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<tr>
<td>Thioxanthenes</td>
<td>chlorprothixene, clopenthixol, thiothixene</td>
</tr>
<tr>
<td><strong>Atypical second-generation antipsychotics according to affinities for specific receptors</strong></td>
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</tr>
<tr>
<td>5-HT-dopamine antagonists: high selectivity for 5-HT2A and dopamine D2 receptors</td>
<td>brexpiprazole (successor to aripiprazole), iloperidone, lurasidone, <strong>risperidone</strong> and its metabolite paliperidone, ziprasidone</td>
</tr>
<tr>
<td>Multi-action receptor-targeted: D2, D3, and receptors of other systems such as cholinergic, histaminergic (5-HT1A, 5-HT2A, 5-HT1C)</td>
<td>asenapine, cariprazine, clozapine, olanzapine, quetiapine</td>
</tr>
<tr>
<td><strong>Third-generation antipsychotics</strong></td>
<td></td>
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<tr>
<td>Partial dopamine receptor agonists</td>
<td>aripiprazole (currently the only approved drug in this category), brexpiprazole (in clinical trials)</td>
</tr>
<tr>
<td><strong>Designation as typical or atypical uncertain (according to chemical structure)</strong></td>
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The muscarinic receptor agonist xanomeline has antipsychotic properties and is devoid of dopamine receptor-blocking activity but causes cholinergic adverse events. It is combined with trospium, a peripherally restricted muscarinic receptor antagonist that reduces peripheral cholinergic effects of xanomeline.

**Pharmacodynamics.** Decreased dopamine release in the prefrontal cortex, and excess dopamine release in other pathways, are associated with psychotic episodes in schizophrenia and bipolar disorder. Typical antipsychotic drugs such as haloperidol and chlorpromazine block dopamine D2 receptors in the brain so that dopamine released in these pathways has less effect. They are not selective and block dopamine receptors in the mesocortical, tuberoinfundibular, and nigrostriatal pathways, which produces some unwanted side effects.

Typical antipsychotics were usually rated on a spectrum of low potency to high potency, based on the ability of the drug to bind to dopamine receptors and not to the effectiveness of the drug. High-potency antipsychotics such as haloperidol usually require low doses and produce less sedation than low-potency antipsychotics such as chlorpromazine and thioridazine, which require high dosages with greater anticholinergic and antihistaminergic activity that can counteract dopamine-related side effects. Atypical antipsychotic drugs have

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**Benzamides**
- sultopride

**Tricyclics**
- carpipramine, clozapramine, clorotepine, clotiapine, loxapine

**Other drugs with antipsychotic action**

- **5-HT2A receptor antagonists**
  - pimavanserin for psychosis of Parkinson disease

**Antiepileptic drugs**
- *valproic acid* for bipolar disorder

- **Herbal medicines**
  - some Chinese and Ayurvedic herbs

- **Miscellaneous drugs**
  - lithium for bipolar disorder, alternative remedies

- **Muscarinic receptor agonists**
  - xanomeline has antipsychotic properties

The muscarinic receptor agonist xanomeline has antipsychotic properties and is devoid of dopamine receptor-blocking activity but causes cholinergic adverse events. It is combined with trospium, a peripherally restricted muscarinic receptor antagonist that reduces peripheral cholinergic effects of xanomeline.
a similar blocking effect on D2 receptors. However, most of them also act on serotonin receptors, especially 5-HT2A and 5-HT2C receptors. Both clozapine and quetiapine have a duration of binding to D2 receptors that suffices to elicit antipsychotic effects but is not long enough to induce extrapyramidal side effects and prolactin hypersecretion. 5-HT2A antagonism by atypical antipsychotics increases dopaminergic activity in the nigrostriatal pathway, leading to a lowered extrapyramidal side effect liability, which is linked to the strong blockade of D2 receptors. A continuum spectrum of "atypia " has been proposed that begins with risperidone (the least atypical) to clozapine (the most atypical), whereas all the other atypical antipsychotics fall within the extremes of this spectrum (01).

A third-generation antipsychotic, aripiprazole (approved by the U.S. Food and Drug Administration), is the first “dopamine stabilizer” based on D2 partial agonist properties that does not induce D2 supersensitivity, but can reverse this supersensitivity when it has been induced by D2 antagonists (20). Aripiprazole competes with dopamine and causes partial antagonism offering clinical benefit in situations of high extracellular dopamine concentrations, but when extracellular dopamine concentrations are low, the drug can occupy additional receptors and cause partial activation (14). In clinical practice, this impacts the choice of treatment in first episode psychosis as well as in refractory schizophrenia.

Pharmacokinetics of antipsychotics. Common pharmacokinetic characteristics of most antipsychotic drugs include the following:

• Good absorption from the gastrointestinal tract into the blood circulation reaching maximal concentrations within 1 to 6 hours.

• Pharmacokinetics is linear at therapeutic doses so that doubling the daily dose will result in doubling the drug concentration in blood.

• Systemic bioavailability is highly variable ranging from 5% to 100%.

• Blockade of D2 receptors by antipsychotic drugs reduces the binding of radioactive PET ligands, and PET has shown that receptor occupancy correlates better with concentrations of antipsychotic drugs in blood than with daily doses.

• Although ratios of brain to blood concentrations of the different antipsychotic drugs vary considerably, steady state concentrations in blood correlate well with
concentrations.

- Elimination half-life is between 12 to 36 hours, eg, mean value is 14.2 hours for clozapine in steady state conditions. Exceptions include the shorter half-life of ziprasidone (about 2 to 10 hours) and longer elimination half-life of aripiprazole (72 hours).

- Elimination is mainly by hepatic metabolism.

- Differences in blood concentrations of antipsychotic drugs are due to variations in activities of drug-metabolizing enzymes such as cytochrome P450 and UDP-glucuronosyltransferases.

**Therapeutic drug monitoring.** Because of individual variations in relation between dose and plasma concentration, therapeutic drug monitoring is recommended for maintaining the lowest possible dose of an antipsychotic that is effective. Therapeutic drug monitoring considers the interindividual variability of the pharmacokinetics of antipsychotics and, thus, enables personalized pharmacotherapy (11). Therapeutic drug monitoring has been recommended for the following atypical antipsychotics with desirable plasma concentration ranges (22).

- Amisulpride 200–320 ng/ml
- Aripiprazole 150–210 ng/ml
- Clozapine 350–500 ng/ml
- Olanzapine 20–40 ng/ml
- Quetiapine 50–500 ng/ml
- Risperidone and paliperidone 20–60 ng/ml
- Sertindole 50–100 ng/ml
- Ziprasidone 50–130 ng/ml

**Pharmacogenetics of antipsychotics.** Several antipsychotics are metabolized to a significant extent by the polymorphic cytochrome P450 (CYP) 2D6, which shows large interindividual variation in activity. Other CYPs, especially CYP1A2 and CYP3A4, also contribute to the interindividual variability in the kinetics of antipsychotics and the
occurrence of drug interactions. Table 2 shows enzymes that metabolize antipsychotics.

Table 2. Enzymes That Metabolize Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>CYP2D6</th>
<th>CYP2C19</th>
<th>CYP3A4</th>
<th>CYP1A2</th>
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<tr>
<td>Chlorpromazine</td>
<td>+</td>
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<tr>
<td>Clozapine</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Fluphenazine</td>
<td></td>
<td>+</td>
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<tr>
<td>Haloperidol</td>
<td>+</td>
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<td>+</td>
<td></td>
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<tr>
<td>Olanzapine</td>
<td></td>
<td>+</td>
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<tr>
<td>Perphenazine</td>
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<tr>
<td>Risperidone</td>
<td>+</td>
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<td></td>
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<tr>
<td>Sertindole</td>
<td>+</td>
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<tr>
<td>Thioridazine</td>
<td>+</td>
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Pharmacogenetic studies have identified genetic variants that affect response to antipsychotics, their serum levels, and adverse effects such as tardive dyskinesia, particularly associations between dopamine receptor polymorphisms and response. Two genes are associated with tardive dyskinesia as an adverse reaction to antipsychotic treatment in psychiatric patients: (1) dopamine D3 receptor, which involves the pharmacodynamics of antipsychotics, and (2) CYP1A2, which involves the pharmacokinetics of antipsychotics. These 2 polymorphisms have an additive effect for tardive dyskinesia and may be useful for predicting side effects of antipsychotics.

Properly designed studies with large sample sizes are still lacking. Although knowledge of pharmacogenetic status is useful in improving efficacy and safety as well as personalizing antipsychotic therapy, few tests are being used in practice. These are expensive and need improvement by covering more gene variants. Pharmacogenetic studies on the effects of antipsychotics on neurocognitive symptoms of schizophrenia are still in early stages, but findings indicate that these will help to identify factors that influence response to treatment (15).
Clinical trials

**Clinical trial databases.** As of May 2021, 3315 clinical studies involving antipsychotics were listed on ClinicalTrials.gov.

A meta-analysis of randomized controlled clinical trials for the comparison of 15 antipsychotic drugs for the acute treatment of schizophrenia revealed substantial differences in adverse effects, but small differences in efficacy (13). The findings indicate that the classification of antipsychotics into first generation and second generation is less helpful than a classification based on hierarchy in helping clinicians choose an antipsychotic drug best suited for the needs of individual patients.

A systematic review and meta-analysis of randomized trials comparing second-generation antipsychotics head-to-head in schizophrenia and related disorders showed different long-term efficacy and tolerability patterns (12).

- Clozapine, olanzapine, and risperidone were significantly superior to several other second-generation antipsychotics regarding discontinuation, whereas quetiapine was inferior to several others. Regarding intolerability-related discontinuation, risperidone was superior, and clozapine was inferior to several other second-generation antipsychotics.

- Data for other efficacy outcomes were sparse.

- Olanzapine and risperidone were worse than all other second-generation antipsychotics regarding prolactin increase and weight.

- Regarding parkinsonism, olanzapine was superior to risperidone, without significant differences pertaining to akathisia.

- Concerning sedation and somnolence, clozapine and quetiapine were significantly worse than some other second-generation antipsychotics.

A review of randomized clinical trials comparing placebo, haloperidol, risperidone, aripiprazole, quetiapine, olanzapine, and ziprasidone for the treatment of tic disorders
concluded that atypical antipsychotics (risperidone and aripiprazole) are the most robust evidence-based options (23).

In a double-blind, randomized, phase 2 trial on patients with schizophrenia, a xanomeline-trospium combination resulted in a greater decrease in total score on the Positive and Negative Syndrome Scale than placebo but was associated with cholinergic and anticholinergic adverse events (04).

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**Indications**

The following are indications for first-generation antipsychotics approved by the U.S. Food and Drug Administration.

- Chlorpromazine: schizophrenia, bipolar disorder (mania), hyperactivity, severe behavioral problems
- Droperidol: agitation
- Fluphenazine: psychotic disorders
- Haloperidol: schizophrenia, **Tourette syndrome**, hyperactivity, severe childhood behavioral problems
- Loxapine: schizophrenia
- Perphenazine: schizophrenia
- Pimozide: Tourette syndrome
- Prochlorperazine: schizophrenia, generalized nonpsychotic anxiety
- Thiothixene: schizophrenia
The following are indications for second-generation antipsychotics approved by the U.S. Food and Drug Administration.

- Thioridazine: schizophrenia
- Trifluoperazine: schizophrenia, generalized nonpsychotic anxiety

The following are indications for second-generation antipsychotics approved by the U.S. Food and Drug Administration.

- Asenapine: acute schizophrenia, bipolar disorder type 1 (manic/mixed)
- Clozapine: treatment-resistant schizophrenia, reduces the risk of suicidal behavior in younger patients with schizophrenia
- Iloperidone: acute schizophrenia
- Olanzapine: schizophrenia, bipolar disorder (manic/mixed), treatment-resistant depression, agitation associated with schizophrenia and bipolar I mania
- Paliperidone: schizophrenia, schizoaffective disorder
- Quetiapine: schizophrenia, bipolar disorder, adjunctive therapy for major depressive disorder
- Risperidone: schizophrenia, bipolar disorder (manic/mixed), irritability associated with autism
- Ziprasidone: schizophrenia, bipolar disorder, acute agitation in patients with schizophrenia

Indications for aripiprazole, a third-generation antipsychotic approved by the U.S. Food and Drug Administration, are schizophrenia, bipolar disorder (manic/mixed) monotherapy or adjunctive to lithium or valproate, adjunctive treatment of major depressive disorder, irritability associated with autistic disorder, and acute treatment of agitation.

**Off-label uses**
Off-label use of atypical antipsychotics have been reported for attention-deficit hyperactivity disorder, autism, anxiety, dementia, depression, eating disorders, insomnia, obsessive compulsive disorder, and personality disorder. The most prescribed agents for off-label use are risperidone, quetiapine, and olanzapine. A study on older adults living in a community in Canada reported that the prevalence of antipsychotics use was 2.5%, of which 78% was off-label (02).

Antipsychotics are used in the management of agitation and psychoses associated with several neurologic disorders, eg, psychosis of Parkinson disease. Use in psychoses associated with epilepsy is problematic because of the tendency of some atypical antipsychotics, such as clozapine, to induce seizures. However, low doses of antipsychotics do not significantly increase the risk of seizures in epileptic patients who are well-controlled with antiepileptic drugs and can safely be used for postictal and brief interictal psychoses (08).

Antipsychotics have frequently been used for the treatment of agitation and psychosis in Alzheimer disease, although several studies show only modest benefit, which needs to be weighed against their well-established serious side effects, including accelerated cognitive decline (06). There are now several alternative drugs that are safer to use in these patients as well as nonpharmacological approaches that should be considered.

There is a limited and cautious use of antipsychotics in delirium where nonpharmacological interventions have failed. A systematic review of clinical trials that compared an antipsychotic to a nonantipsychotic drug or a typical to an atypical antipsychotic concluded that antipsychotics do not reduce delirium severity, resolve symptoms, or alter mortality (05).

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**Contraindications**

Contraindications are specified for each drug individually.
Goals and duration of treatment

Goals vary according to the disease and antipsychotics used.

**Personalized approach to the use of antipsychotics.** Approximately 30% to 40% of schizophrenic patients do not respond to antipsychotic treatment, and approximately 70% of them develop side effects. This variability in treatment response may have a genetic origin in 2 areas.

1. Genetic mutations in metabolic enzymes can render them inactive and result in the toxic accumulation of drugs or drug metabolites.

2. Genetic variation in drug-targeted neurotransmitter receptors can influence their binding and functional capabilities, affecting the efficacy of treatment.

A model for personalizing antipsychotic dosing has been developed by combining knowledge of pharmacogenetics, therapeutic drug monitoring, and drug-drug interactions, which is applicable to risperidone, 9-hydroxyrisperidone or paliperidone, and clozapine (07).

To compare and rank antipsychotics on the basis of their metabolic side effects, and to investigate the relationship between changes in metabolic parameters with antipsychotic treatment, a study has reviewed over 100 controlled clinical trials involving more than 25,000 patients for treatment-induced changes in body weight, cholesterol, triglyceride, and glucose concentrations (18). Marked differences in metabolic side effects were found between antipsychotics, with worst profiles for olanzapine and clozapine, whereas aripiprazole, brexpiprazole, cariprazine, lurasidone, and ziprasidone had the most benign profiles. Increased baseline weight, male sex, and nonwhite ethnicity are predictors of susceptibility to antipsychotic-induced metabolic change, and improvements in psychopathology are associated with metabolic disturbance. These findings indicate that choice of antipsychotic should be made on an individual basis and consider associated metabolic disturbances.
Dosing

The doses are specified in the individual antipsychotics.

Special considerations

**Pediatric.** Most of the indications for the use of antipsychotics are in adults, and information is available as to those approved for use in children.

**Geriatric.** Antipsychotics should be prescribed with caution in elderly patients with psychoses associated with *cognitive impairment*. A study of Swedish Dementia Registry showed that antipsychotics increased the risk of death in elderly patients with dementia (19). In general, one half to one third the adult dose is recommended in the elderly, who may be more susceptible to parkinsonian and anticholinergic side effects. Persons with dementia who exhibit behavioral and psychological symptoms should not be given antipsychotics before trying other treatments. The risk of hypotension should be considered if phenothiazines are used, and thioridazine may not be considered as a first-choice medicine if other antipsychotics are available. Haloperidol has been widely used in the elderly, but electrocardiogram changes should be monitored because of the risk of cardiovascular disturbances.

**Pregnancy.** Use of antipsychotics during pregnancy should be avoided, particularly during the first trimester. If absolutely indicated, the use of low doses of haloperidol may be considered. Haloperidol is excreted into breast milk.

**Anesthesia.** Schizophrenic patients on antipsychotics are susceptible to the hypotensive action of general anesthesia. In practice, patients with chronic schizophrenia remain on their medications as their discontinuation may precipitate psychotic symptoms such as hallucinations and agitation. Caution is exercised in avoiding the concomitant use of an antipsychotic and anesthetic agent that have potential drug interaction.
Interactions

- Antipsychotics lower the seizure threshold and may, thus, antagonize the action of anticonvulsant drugs.
- Concomitant use of barbiturates with antipsychotics enhances sedative effects.
- **Carbamazepine** reduces haloperidol levels.
- The therapeutic effect of **levodopa** is antagonized by antipsychotics and vice versa.
- Antipsychotic drugs are used for the treatment of behavioral and psychological symptoms of dementia, and extrapyramidal disorders can be potentiated in a synergistic manner by concomitant use of cholinesterase inhibitors, such as **donepezil** for the treatment of Alzheimer disease. However, replacing donepezil by **memantine**, a N-methyl D-antagonist receptor antagonist, reduces antipsychotic-induced extrapyramidal disorders (16).

Adverse effects

Adverse effects should be considered for individual antipsychotics, but they mostly fall into 2 categories: neurologic and anticholinergic. Neurologic adverse effects include parkinsonism (resting tremor, akinesia, rigidity), acute dystonias (slow, prolonged muscular spasms), akathisia (subjective feeling of agitation), neuroleptic malignant syndrome (fever, sweating, confusion, increased blood pressure and pulse, muscular rigidity, high creatine phosphokinase, renal failure), tardive dyskinesia (abnormal involuntary movements of tongue, head, face, mouth), and seizures in approximately 1% of patients. Almost all antipsychotics in use are known to induce seizures in some predisposed patients.
Anticholinergic side effects include peripheral effects (dry mouth, blurred vision, constipation, urinary retention) and central effects (severe agitation, confusion).

Pharmacogenetic studies in psychiatric patients have explored the pathomechanism of antipsychotic-induced extrapyramidal symptoms. One study used bioinformatic tools to identify key transcription factors that regulate each protein-protein interaction network, followed by identification of single nucleotide polymorphisms disrupting the transcription factor binding sites (03). Transcription factors in the genes of each network were selected for genotyping and their associations with extrapyramidal symptoms. The results show the possible role of the disruption of transcription factor binding sites by single nucleotide polymorphisms in the pharmacological response to antipsychotics and extrapyramidal symptoms. These studies may be used for personalized risk assessment of the safety of antipsychotics in the future.

Antipsychotic drugs deregulate mechanisms of temperature regulation and can predispose to heat stroke. Phenothiazines deplete the central stores of dopamine and interfere with the thermoregulatory center of the hypothalamus. Anticholinergic side effects impair the body’s ability to disperse heat by impaired sweating.

The CYP2D6 poor metabolizer phenotype is associated with adverse drug reactions to risperidone and leads to discontinuation of therapy. Susceptible patients can be identified by using an allele-specific PCR test or by the AmpliChip CYP450 microarray system for CYP2D6 alleles.

**Concluding remarks and the future of antipsychotics**

Clozapine is still considered the gold standard in refractory schizophrenia and in psychoses present in Parkinson disease as well as in patients who develop tardive dyskinesia. However, clozapine is associated with adverse effects like agranulocytosis (0.7%) and weight gain, which is an incentive for the pharmaceutical industry to discover new drugs as effective as clozapine, but devoid of its side effects.

D2-like receptor blockade is necessary for the clinical efficacy of antipsychotic drugs, but chronic use further decreases cortical gray matter and hippocampus volume while increasing striatal and ventricular volume in patients with schizophrenia. Antipsychotics targeting D3 are more effective for improving cognition and negative symptoms of schizophrenia. An experimental study in mice provides evidence on the role of D3 receptors in structural changes observed following antipsychotic administration in clinical populations and should
be considered in developing new drugs targeting this receptor (09).

Brain-derived neurotrophic factor plays a role in the modulation of the dopaminergic system, which is involved in the pathophysiology of schizophrenia. There is an association between the $BDNF$ gene Val66Met polymorphism, which has been related to cognition, efficacy, and side effects of antipsychotic drugs (10). These variants could be helpful in the choice of antipsychotics for individual patients as well as targets for developing next-generation antipsychotic drugs.

The study of the metabolome of schizophrenia has uncovered biomarkers for the disease that may change the approach to diagnosis, patient stratification for improved treatment of schizophrenia, and other related idiopathic psychotic disorders (21).

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<tr>
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