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Antipsychotic Therapy: Pharmacology, Efficacy and Safety

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ABSTRACT:

Conventional and Atypical Antipsychotic Drugs For more than fifty years, conventional (first-generation) antipsychotic drugs have been widely used to manage a variety of serious psychiatric illnesses. In recent years, these medications have been increasingly replaced by newer or second-generation (atypical) antipsychotics, the development of newer agents was strongly influenced by landmark study published in 1998, including aripiprazole, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. therapeutic efficacy, safety profile, adverse effects, and cost of both conventional and atypical antipsychotic drugs. Since the differences in effectiveness and tolerability between many of these medications are relatively small, and some newer agents are associated with important long-term metabolic risks, both first- and second-generation antipsychotics continue to have an important place in clinical practice. Therefore, treatment decisions should be based on each patient's clinical condition, potential benefits, possible risks, and treatment costs.

Keywords: Antipsychotic drugs, schizophrenia, chlorpromazine, brexpiprazole, dopamine, serotonin, D₂ receptor, adverse effects.

1. Introduction:

Psychotic disorders are psychiatric conditions associated with disturbances in perception, thought processes, beliefs and behaviour. Common manifestations include hallucinations, delusions, disorganized thinking and behavioural disturbances.

Schizophrenia is one of the major disorders requiring antipsychotic pharmacotherapy. Treatment is directed toward reducing psychotic symptoms, preventing recurrence and supporting functional recovery. [1]

The introduction of chlorpromazine in the 1950s represented an important development in psychiatric pharmacotherapy. Since then, several antipsychotic medicines have been developed with different receptor-binding characteristics, pharmacokinetic properties and adverse-effect profiles. The development of newer medicines has attempted to maintain antipsychotic efficacy while improving tolerability and addressing limitations associated with conventional dopamine blockade. [2]

2. Classification of Antipsychotic Drugs:

Antipsychotic medicines can broadly be divided into:

First-generation antipsychotics (FGAs): chlorpromazine, haloperidol, fluphenazine and related agents.

Second-generation antipsychotics (SGAs): Clozapine, Risperidone, Olanzapine, Ziprasidone and Quetiapine.

Dopamine partial agonists: aripiprazole, brexpiprazole and cariprazine.

FGAs are predominantly associated with dopamine D₂ receptor antagonism, where as many SGAs combine dopamine and serotonin receptor effects. Partial dopamine agonists produce receptor modulation rather than complete blockade. [3]

3. Therapeutic Role:

The principal purpose of antipsychotic treatment is to reduce psychotic manifestations such as hallucinations, delusions, agitation and disorganized behaviour. Continued treatment may also help decrease the risk of relapse in suitable patients.

Selection of a particular medicine depends on the indication, previous response, adverse-effect susceptibility, drug interactions, monitoring requirements, availability and individual treatment requirements. Therefore, antipsychotic therapy should be individualized rather than based only on drug classification. [4]

4. Mechanism of Action:

Dopamine D₂ receptor modulation is a major pharmacological mechanism underlying the action of many antipsychotics. Conventional agents primarily block postsynaptic D₂ receptors, thereby reducing excessive dopaminergic signalling associated with psychotic symptoms.

However, substantial dopamine blockade can also interfere with physiological dopamine transmission in motor pathways and may produce extrapyramidal adverse effects. Thus, the same receptor system responsible for therapeutic activity can also contribute to unwanted effects. [5]

Many atypical antipsychotics additionally influence serotonin receptors, especially 5-HT_{2A} receptors. Serotonin–dopamine interactions can modify dopaminergic transmission in different brain pathways and contribute to differences in clinical and adverse-effect profiles.

Other receptors are also relevant. H₁ receptor antagonism may contribute to sedation, M₁ receptor blockade can produce anticholinergic effects, and α_1 -adrenergic blockade may contribute to postural hypotension. [6]

4.1 Dopamine Pathways and Clinical Effects:

The mesolimbic pathways dopaminergic system has an important role in cognitive and negative symptoms. Reduction of excessive dopamine activity in this pathway is therefore an important therapeutic objective.

The nigrostriatal pathway participates in motor control. Excessive D₂ receptor blockade in this pathway can result in dystonia, akathisia, parkinsonism, rigidity, tremor and bradykinesia. Long-term exposure may also contribute to tardive dyskinesia.

Conventional dopamine blockade may not adequately improve persistent negative and cognitive manifestations.

The tuberoinfundibular pathway regulates prolactin secretion. Dopamine blockade in this pathway may increase prolactin concentrations and produce endocrine effects. [7]

4.2 Serotonin and Other Receptor Systems:

Serotonin receptor interactions contribute to the pharmacological differences between antipsychotic medicines. 5-HT_{2A} antagonism is particularly important among many second-generation drugs, while selected newer medicines also show activity at 5-HT_{1A} receptors.

Interactions with histamine, muscarinic and adrenergic receptors further influence sedation, autonomic effects, metabolic effects and tolerability. [6]

5. First-Generation Antipsychotics:

First-generation antipsychotics, also known as typical or conventional antipsychotics, were developed before the atypical agents. Their principal pharmacological characteristic is dopamine receptor antagonism, particularly D₂ receptor blockade.

They remain useful for controlling several positive psychotic symptoms, but their use requires awareness of extrapyramidal, autonomic and other adverse effects. [3]

5.1 Chlorpromazine:

Chlorpromazine is a phenothiazine first-generation antipsychotic and is generally regarded as a low-potency conventional antipsychotic. Its principal antipsychotic action is related to dopamine receptor antagonism.

In addition to dopamine receptors, chlorpromazine interacts with histamine H₁, muscarinic M₁ and α_1 -adrenergic receptors. These additional receptor actions help explain effects such as sedation, anticholinergic symptoms and postural hypotension. Because chlorpromazine has a relatively broad receptor profile, its therapeutic effects and adverse effects should both be considered when evaluating treatment. [8]

6. Second-Generation Antipsychotics:

Second-generation or atypical antipsychotics generally possess both dopamine and serotonin receptor activity. Examples include clozapine, risperidone, olanzapine, quetiapine and ziprasidone.

Their receptor-binding profiles differ considerably, and these differences can influence therapeutic response, metabolic effects, movement-related adverse effects and monitoring requirements. [3]

7. Brexpiprazole as a Newer Antipsychotic:

Brexpiprazole is a newer antipsychotic belonging to the serotonin–dopamine activity modulator group. Its major pharmacological actions include partial agonism at dopamine D₂ receptors and serotonin 5-HT_{1A} receptors, together with antagonism at 5-HT_{2A} receptors. Unlike conventional D₂ antagonists, partial agonism allows brexpiprazole to modulate dopamine signalling rather than completely blocking receptor activity. This

pharmacological property contributes to its distinct clinical profile. [9] Brexpiprazole also interacts with additional receptor systems, including D₃, α -adrenergic, 5-HT_{2B}, 5-HT₇ and H₁ receptors. Its relatively long elimination half-life supports once-daily oral administration in routine treatment. [10]

7.1 Pharmacological Significance of Partial Dopamine Agonism:

Partial dopamine agonism can be understood as a balancing mechanism. When dopamine activity is excessive, the drug can reduce functional dopaminergic signalling; when dopamine activity is relatively low, partial agonist activity can maintain some receptor stimulation.

This differs from complete D₂ receptor blockade associated with many conventional antipsychotics. However, partial agonism does not eliminate the possibility of adverse effects, and clinical monitoring remains necessary. [9]

8. Adverse Effects and Safety:

Antipsychotic-associated adverse effects may involve neurological, metabolic, endocrine, cardiovascular and autonomic systems. Their occurrence varies according to the individual medicine, dose and patient characteristics.

Important neurological reactions include dystonia, akathisia, parkinsonism and tardive dyskinesia. Metabolic concerns may include weight gain, impaired glucose regulation and lipid abnormalities, particularly with some second-generation agents. [11] Sedation, orthostatic hypotension and anticholinergic effects can also influence daily functioning and treatment acceptability. Therefore, monitoring should be selected according to the known safety profile of the individual drug.

Clozapine has a specific role in treatment-resistant schizophrenia but requires specialized monitoring because of potentially serious adverse reactions. [12]

9. Adherence and Long-Acting Injectable Therapy:

Regular medication use is important during long-term antipsychotic treatment. Missed oral doses may result in inadequate drug exposure and can contribute to symptom recurrence.

Long-acting injectable formulations can provide an alternative for selected patients who have difficulty maintaining consistent oral treatment. Decisions regarding such formulations should take into account previous tolerability, clinical requirements,

practical factors and patient preference. [13]

10. Limitations of Current Therapy:

Although antipsychotic medicines have substantially improved the treatment of psychotic disorders, limitations remain. Their effects are generally more established for positive symptoms than for persistent negative symptoms and cognitive impairment.

Some patients continue to experience symptoms despite treatment, while adverse effects can limit dose optimization or long-term continuation. These limitations have encouraged research into mechanisms beyond conventional D₂ receptor blockade. [14]

10.1 Individualized Treatment Considerations:

There is no single antipsychotic regimen that is appropriate for every patient. Treatment selection should consider diagnosis, treatment objectives, previous medication exposure, previous response, adverse-effect risk, drug interactions, monitoring requirements and practical accessibility.

Patient preference and the feasibility of oral or long-acting treatment may also influence treatment acceptability. [4]

11. Conclusion:

Antipsychotic drugs remain important medicines for the management of schizophrenia and other psychotic disorders. Their pharmacological development has progressed from conventional dopamine receptor antagonists to agents that combine dopamine and serotonin modulation and, in some cases, partial dopamine agonism.

Chlorpromazine illustrates the traditional first-generation approach, primarily involving dopamine receptor antagonism, while brexpiprazole demonstrates the newer concept of partial dopamine agonism with serotonin receptor activity. Differences in receptor profiles contribute to differences in therapeutic effects and adverse reactions.

Successful antipsychotic therapy requires appropriate selection, monitoring of safety and therapeutic response, attention to adherence and consideration of individual patient requirements.

References

1. World Health Organization. Schizophrenia. Geneva: WHO; 2025.
2. Leucht S, et al. Antipsychotic drugs: a concise review of history, classification, indications, mechanism, efficacy, side effects, dosing and clinical application. *American Journal of Psychiatry*. 2024;181(10):865–878.
3. Meyer JM. How antipsychotics work in schizophrenia: a primer on mechanisms. *CNS Spectrums*. 2024;30(1):e6.
4. World Health Organization. Antipsychotic medicines for psychotic disorders: mhGAP evidence-based recommendations. Updated 2023.
5. Stahl SM. Mechanism of action of antipsychotic drugs and dopamine receptor modulation. *CNS pharmacology literature*.
6. Meyer JM. Receptor mechanisms and pharmacological actions of antipsychotic medications. *CNS Spectrums*. 2024;30(1):e6.
7. Stahl SM. *Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. Cambridge University Press.
8. National Library of Medicine. Chlorpromazine: Drug information and pharmacological profile.
9. Maeda K, et al. Brexpiprazole pharmacology and dopamine–serotonin receptor activity. *Neuropsychopharmacology literature*.
10. Rexulti (brexpiprazole) prescribing information. Pharmacology, dosing and pharmacokinetic information.
11. Lally J, et al. An umbrella review of adverse effects associated with antipsychotic medications. *Schizophrenia*. 2023.
12. World Health Organization. Antipsychotic medicines for psychotic disorders: treatment considerations and monitoring. Updated 2023.
13. World Health Organization. Role of depot antipsychotic medicine in individuals requiring long-term antipsychotic treatment for psychotic disorders. Updated 2023.
14. Meyer JM. Current limitations and mechanisms of antipsychotic treatment in schizophrenia. *CNS Spectrums*. 2024;30(1):e6.
15. World Health Organization. Duration of antipsychotic treatment in individuals with a first psychotic episode. Updated 2023.