

# Risperidone: The second Generation Antipsychotic Clinical Implication in Schizophrenia Management

S.SHAHNAS<sup>1\*</sup>, ZAINABATH AAMIRA<sup>2</sup>

<sup>1</sup> Lecturer Department of Pharmacology, Malik Deenar Collage of Pharmacy Seethangoli Kasaragod -671321 Kerala India

<sup>2</sup> Student Malik Deenar Collage of Pharmacy Seethangoli Kasaragod

Correspondence To Author: S.Shahnas, Lecturer Department of Pharmacology, Malik Deenar Collage Of Pharmacy Seethangoli Kasaragod – 671321 Kerala India

Correspondence To Author: Shahnas. S

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## ABSTRACT

In the therapeutic treatment of schizophrenia, a chronic illness marked by dopaminergic and serotonergic dysfunction, risperidone, a second-generation antipsychotic, is essential. Risperidone alleviates positive, negative, and cognitive symptoms by blocking serotonin 5-HT<sub>2</sub> and dopamine D<sub>2</sub> receptors. Its effectiveness in first-episode and maintenance therapy is currently supported by research; long-acting injectable versions improve adherence, and the ideal dosage is usually between 3 and 6 mg/day. Weight gain, metabolic syndrome, hyperprolactinemia, extrapyramidal symptoms, and medication interactions with CYP2D6 substrates are among the toxicities. Prolactin levels, metabolic monitoring, and PANSS scales are screening techniques. Risperidone is still a front-line medication despite its side effects; in order to maximize results and reduce side effects, future prospects will concentrate on customized dose, LAI advancements, and biomarker-driven therapy.

## KEYWORDS

Schizophrenia, Risperidone, Future perspective, DSM-5-TR, D<sub>2</sub> antagonist

## I. INTRODUCTION

### Schizophrenia

Schizophrenia is a chronic brain disorder that affects how a person thinks, feels, and behaves, often causing difficulty in distinguishing reality from imagination. It is marked by symptoms such as delusions, hallucinations, disorganized speech or behaviour, and emotional withdrawal, and requires lifelong treatment

### Significance of Selection of Schizophrenia

Studying schizophrenia is important for understanding brain function, improving treatment

outcomes, and promoting early diagnosis and rehabilitation. It significantly impacts multiple domains of human functioning, contributing to disability, hospitalizations, and reduced quality of life

### Current Status of Schizophrenia

Schizophrenia affects around 1% of people worldwide and typically begins in late adolescence or early adulthood. Schizophrenia remains a major contributor to global disability and is ranked among the leading causes of disability worldwide. Between 1990 and 2021, the prevalence of schizophrenia increased from 13.62 million to 23.18 million cases. Incidence rose from 883,000 to 1.223 million cases.

### Pathophysiology of Schizophrenia

Thus far, the pathophysiology of dopaminergic and serotonergic system is best understood. Overactivity of mesolimbic and mesocortical dopaminergic pathway to the temporolimbic region and frontal cortex are believed to explain the positive symptoms of schizophrenia, whereas the relative lack of dopaminergic function in the prefrontal cortex has been suggested to explain the negative symptoms of schizophrenia. Much of this action of antipsychotic drug and their relative efficacy for specific symptoms dopamine blockade is associated with efficacy for positive symptoms. Serotonergic blockade enhance dopaminergic activity in the prefrontal cortex to decrease negative symptoms.

### Etiology

**Heredity:** The incidence of schizophrenia is about 1% in the general population. **Personality:** Many schizophrenic patients show schizoid personality trait. **Family background:** These include faulty parental attitudes, irrational and incoherent family atmosphere, defects in family communication, broken homes and the like. **Social factors:** Schizophrenia is more common in the lower socioeconomic groups. Urbanisation and

industrialization are other significant contributory factors. **Biochemical:** Dopamine hypothesis—It is hypothesized that schizophrenia is the result of dopaminergic hyperactivity. **Stress:** physical stress like infection, injury psychological stress. Life events too are important factors.

#### Types of Schizophrenia

Paranoid type – Characterized by the presence of delusions and auditory hallucinations, while cognitive functions remain relatively intact. Disorganized (hebephrenic) type – Defined by disorganized speech, thoughts, and behaviour, accompanied by flat or inappropriate emotional responses. Catatonic type – Noted for motor disturbances, which can include stupor or rigidity. Undifferentiated type – Exhibits a combination of symptoms that do not align clearly with other classifications.

#### Clinical Features

Thought disturbance: One of the main signs of schizophrenia is thought disorder. Delusions are widespread. Schizophrenia is characterized by such fundamental delusions. Affect disturbances: Schizophrenia can cause any kind of affective alteration. Perception disturbances include auditory hallucinations that take place in a clear, conscious environment. Motor disturbances: The patient lacks motivation, initiative, and vitality. Sometimes there may be a total blockage of motor action (catatonic stupor). Cognitive abnormalities: Schizophrenia impairs alertness, focus, and attention. The immediate memory is negatively impacted by this. Eye signs: There may be more frequent blinks

#### Diagnosis

##### 1. Framework for Diagnosis

DSM-5-TR Standards

The American Psychiatric Association (DSM-5-TR, 2022) states that schizophrenia is identified when: Typical Symptoms: Delusions, hallucinations, incoherent speech, grossly disorganized or catatonic behaviour, and negative symptoms (e.g., avolition, alogia, flat affect) are all present for at least one month. Duration: At least one month of active-phase symptoms and ongoing disruption for at least six months.

##### 2. Clinical Evaluation in Inpatient Environments

Thorough Psychiatric Interview: The current illness's history (onset, progression, causes), prior mental health history. History of substance abuse

Psychosis runs in the family. Functioning in social and professional contexts

Mental Status Examination (MSE): Behaviour and appearance. Speech (incoherent, unorganized, under pressure). Affect and mood. Thought process and content (paranoia, illusions). perception (delusions). Thinking. Perception and

3. Differential diagnosis, which is crucial for inpatients

Bipolar disorder is one of the mood disorders with psychotic features. psychosis and major depressive disorder. Cannabis, amphetamines, and alcohol withdrawal are examples of substance-induced psychosis. Neurological and medical causes include brain tumours, epilepsy, and thyroid disorders.

4. Medical and Laboratory Workup: Electrolytes, thyroid profile, vitamin B12 levels, liver and kidney function tests, complete blood count, and urine toxicology screening

#### Drugs used in the treatment of schizophrenia

Medications for schizophrenia

Traditional antipsychotics: haloperidol, thioridazine, trifluoperazine, and chlorpromazine

Atypical antipsychotics: Aripiprazole, Quetiapine, Olanzapine, Clozapine, and Risperidone

Depot preparations: injectable haloperidol decanoate and fluphenazine decanoate

#### Mechanism of Action of Risperidone

It acts as an antagonist at multiple receptors:

Dopamine D2 receptors improve positive symptoms (delusions, hallucinations) by lowering hyperdopaminergic activity in the mesolimbic pathway. Serotonin 5-HT<sub>2A</sub> receptors → increase dopamine release in the prefrontal brain, which lessens extrapyramidal side effects (EPS) and improves negative symptoms (flat affect, social withdrawal).

#### Pharmacological response

Extrapyramidal symptoms (EPS) can be caused by D<sub>2</sub> blockage in the nigrostriatal pathway in the central nervous system (CNS), but this is less common than with standard antipsychotics. Hyperprolactinemia: When tuberoinfundibular D<sub>2</sub> receptors are blocked, prolactin levels rise, which may have an impact on mood or hormones.

Effects on the Heart and Vascular System: Orthostatic hypotension and associated cardiovascular alterations (such as temporary changes in postural blood pressure) are caused by  $\alpha$ -adrenergic inhibition.

**Renal Response and the Kidneys:** Rats' renal damage: Risperidone administration raised oxidative stress and indicators of renal dysfunction (such as creatinine and BUN), indicating tubular injury in animal models. **Smooth Muscle Vascular smooth muscle:** Risperidone prevents human umbilical artery smooth muscle from contracting in response to serotonin and histamine, which causes vasorelaxation or vascular tone modulation. Constipation, nausea, and vomiting are common clinical side effects of the gastrointestinal tract (GIT).

### Side effects of risperidone

Akathisia, dystonia, and parkinsonism are examples of extrapyramidal symptoms (EPS). Amenorrhea, galactorrhoea, infertility, diminished libido, erectile dysfunction, and sexual dysfunction are all consequences of hyperprolactinemia. Additional cardiovascular and neuropsychiatric effects include dizziness, orthostatic hypotension, sedation, and cognitive decline. Galactorrhea, gynecomastia, amenorrhea, sexual dysfunction, and decreased libido are examples of endocrine effects. **Somnolence and CNS Effects:** Among the most commonly reported are somnolence and sedation. Additional effects on the central nervous system include headaches, restlessness, and dizziness.

### Pharmacokinetics of Risperidone

Oral absorption is quick and peaks in one to two hours. 70% oral bioavailability. Food doesn't make a big difference. frequently administered orally; depot intravenous injection is available. **Distribution:**  $V_d \sim 1-2 \text{ L/kg} \rightarrow$  broad tissue distribution. Extremely protein-bound (~77% metabolite, ~90% risperidone). **Metabolism:** Completely converted to the active metabolite 9-hydroxyrisperidone (paliperidone) in the liver by CYP2D6. Half-life and conversion are impacted by genetic variations. Linear kinetics is the elimination method. Risperidone alone has a half-life of around three hours, while the active moiety has a half-life of about twenty hours. The half-life of poor metabolizers is longer (~19–20 hours).

### Interaction

High-risk major interactions: CNS depressants, such as alcohol, opioids, and benzodiazepines like lorazepam, increase the risk of sedation, respiratory depression, and reduced psychomotor performance.

Other antipsychotics, such as haloperidol and aripiprazole, may raise the risk of metabolic side effects, neuroleptic malignant syndrome, or extrapyramidal symptoms (EPS).

**Moderate Relationships:** Mood stabilizers, such as lithium and valproate, may change metabolism or intensify CNS effects. Amphetamines and methylphenidate are examples of stimulants that can raise cardiovascular strain or reverse the effects of antipsychotics.

**Minor Interactions:** Diphenhydramine and other antihistamines cause mild additive sedation. **Caffeine:** Usually not clinically significant, but may slightly change metabolism.

**Disease Interactions:** Reduced seizure threshold may result from seizure disorders. **Parkinson's disease:** Dopamine antagonism can exacerbate motor symptoms.

**Food and Alcohol Interactions:** **Alcohol:** Strong additive CNS depression (sedation, decreased judgment).

### Toxicity of Risperidone

#### Acute Poisoning

- CNS depression: sleepiness, sedation, disorientation, and, in rare cases, coma.
- Extrapyramidal symptoms include stiffness, tremor, and dystonia.
- Seizures are uncommon.
- Rare but potentially fatal is Neuroleptic Malignant Syndrome.
- Toxic dose: typically several times higher than the therapeutic range; unless paired with other medications, overdoses are frequently not deadly.
- Treatment options include supportive care (ABC), early use of activated charcoal, IV fluids for hypotension, benzodiazepines for agitation or convulsions, ECG monitoring, and anticholinergics for EPS.

#### Chronic Toxicity (Long-Term Negative Consequences)

- Acute dystonia, parkinsonism, akathisia, and tardive dyskinesia are examples of extrapyramidal symptoms.
- Hyperprolactinemia: a prevalent condition that causes amenorrhea, gynecomastia, galactorrhoea, sexual dysfunction, and decreased bone density. Compared to many other antipsychotics, risperidone increases prolactin levels.
- Metabolic side effects: weight gain, dyslipidaemia, hyperglycaemia, and metabolic syndrome (significant but less severe than olanzapine).

- Rare yet dangerous is Neuroleptic Malignant Syndrome.
- Additional toxicities include drowsiness and an elevated risk of falls, particularly in older people.

### Dosage

#### Phase Average Dosage Range Important Notes

Initial dosage: 2 mg daily to reduce adverse effects, start low. utilized during the first one to two days.

Increase by 1-2 mg daily during the titration phase make moderate adjustments over a few days. Keep an eye on tolerance and effectiveness.

4-6 mg daily is the target maintenance. Range that has fewer negative effects and is most effective for controlling symptoms.

High dosage: 8-10 mg daily Although it is associated with greater extrapyramidal symptoms (EPS), it is occasionally used in resistant patients.

Extremely low doses (less than 2 mg daily) are typically useless for treating schizophrenia.

### Screening methods

In order to determine and assess substances (such novel chemical compounds, plant extracts, or biologics) for their possible pharmacological activity, therapeutic effects, or toxicity, screening methods are systematic experimental processes.

### Types

Experiments conducted outside of a living organism are known as in vitro procedures (e.g., cell cultures, separated tissues).

Experiments on living animals are known as in vivo approaches.

### In Vivo Screening Methods for Risperidone

#### Hyperlocomotion Caused by Amphetamine

- The basic idea is that amphetamine causes an increase in dopamine release, which leads to hyperactivity (positive symptoms of schizophrenia).

- Method: Risperidone lowers hyperactivity in a dose-dependent manner; locomotor activity is monitored in an actophotometer or open field before and after amphetamine.

- Interpretation: Risperidone  $\div$  movement; amphetamine  $\div$  movement.
- Stereotyping Induced by Apomorphine
- Concept: The dopamine agonist apomorphine causes stereotyped behaviours such licking, chewing, and sniffing.
- Method: Apomorphine is injected into the animals; risperidone is administered both before and after; behaviours are rated.

- Interpretation: Risperidone lowers stereotypy scores, while apomorphine increases them.

CAR stands for Conditioned Avoidance Response.

- The basic idea is that antipsychotics maintain the escape reaction while suppressing avoidance behaviour to prevent shock.

- Method: Animals are trained to avoid shock following a warning signal; risperidone lessens avoidance reactions while maintaining escape.

- Interpretation: Selective avoidance suppression is a sign of effective antipsychotics.

#### The Catalepsy Test

- The basic idea is to measure extrapyramidal side effects by blocking dopamine in the nigrostriatal pathway.

- Method: The animal's forepaws are set on a bar, and the amount of time it remains motionless is noted.

- Interpretation: Extended immobility increases the risk of catalepsy (EPS liability).

#### PCP-Induced Social Disengagement

- Concept: PCP inhibits NMDA receptors, which causes cognitive impairments and social disengagement (models negative symptoms).

- Method: PCP is administered to the animals, followed by risperidone, and the duration of social engagement is recorded.

- Interpretation: PCP reduces social engagement; risperidone increases it.

### In Vitro Screening Methods for Risperidone

#### Assays for Receptor Binding

- Goal: Evaluate affinity for neurotransmitter receptors associated with schizophrenia.

- Technique: Radioligand binding using human receptors that have been cloned (D2, 5-HT2A,  $\alpha$ 1-adrenergic).

- Results: A dual mechanism of action is supported by a high affinity for 5-HT2A and a moderate affinity for D2

#### Assays Based on Functional Cells

- Goal: Assess antagonist action at serotonin and dopamine receptors.

- Technique: HEK293/CHO cells transfected with receptor genes; tests include recruitment of  $\beta$ -arrestin, calcium mobilization, and cAMP inhibition.

- Results: Antipsychotic efficacy is correlated with a potent antagonist that reduces dopamine-mediated signalling.

#### Studies on Drug Release and Formulation

- Goal: Describe formulations with controlled release. • Method: Release kinetics are measured using dissolution tests in biologically simulated fluids.

- Results: In line with long-acting injectable objectives, risperidone ISM® exhibits rapid initial release followed by continuous release over weeks.

#### Assays for Cytotoxicity and Safety

- Goal: Evaluate formulations' biocompatibility.
- Procedure: MTT tests using glial and neuronal cell lines.

- Results: Low cytotoxicity at therapeutic concentrations, indicating safety for additional in vivo testing.

#### Drug-induced schizophrenia

Short-term hallucinations, delusions, or disordered thinking brought on by intoxication or withdrawal are known as drug-induced psychosis; these symptoms usually go away as the substance is cleared.

Drug-induced schizophrenia: Similar to primary schizophrenia but brought on by substance exposure in susceptible people, persistent psychotic symptoms that persist after more than a month of abstinence.

High-potency THC cannabis, hallucinogens (LSD, psilocybin, PCP), amphetamines/methamphetamines, cocaine, synthetic cannabinoids, cathinones, and dissociative (like ketamine) are examples of common drugs.

Risk factors include pre-existing mental health vulnerabilities, heavy or extended exposure, early initiation of usage, and family history.

Positive symptoms include hallucinations and delusions; negative symptoms include social disengagement and decreased affect; and cognitive symptoms include poor memory and attention problems.

DSM 5 criteria for diagnosis: onset associated with drug use or withdrawal, persistence after abstinence, impairment, and not explained by underlying schizophrenia.

Treatment options include long-term psychosocial rehabilitation, supportive care, antipsychotics, benzodiazepines for agitation, and family support.

#### Future perspectives

Long-acting injectables: By providing quick therapeutic levels with sustained release over weeks, formulations like Risperidone ISM® and microspheres seek to enhance adherence and lower relapse.

Neuroimaging-guided treatment: To track structural and functional changes in the brain, advanced MRI techniques (diffusion kurtosis, diffusion spectrum imaging, covariance networks) are being investigated. These techniques may be used to predict treatment response and guide dosage.

Personalized medicine: Individualized treatment that maximizes effectiveness and minimizes side effects may be made possible by genetic and biomarker analysis (dopamine receptor polymorphisms, metabolic signatures, cognitive indicators).

Combination therapies: To more effectively treat persistent negative and cognitive symptoms, integration with cognitive training and psychosocial interventions is being researched.

Digital health integration: Long-acting formulations could be used with smart injectors and smartphone apps to improve adherence tracking and give physicians real-time feedback.

The outcome

## II. RESULT AND DISCUSSION

Risperidone effectively reduces both positive and negative symptoms of schizophrenia, according to clinical research. Compared to first-generation antipsychotics, its dual mechanism of dopamine D2 and serotonin 5-HT<sub>2</sub> antagonism—offers balanced efficacy with less extrapyramidal adverse effects. Oral dosages between 3 and 6 mg per day are ideal, and long-acting injectables increase adherence. Symptom scores have significantly improved, according to clinical monitoring.

The use of risperidone in the treatment of schizophrenia demonstrates the trend toward second-generation antipsychotics that target both quality of life and symptom control. Although it works well, its toxicity profile—weight gain, metabolic syndrome, and hyperprolactinemia—makes routine screening with prolactin levels and metabolic panels necessary. Careful dose modifications are necessary due to drug interactions caused by CYP2D6 metabolism. Risperidone is still a mainstay treatment despite these difficulties, particularly with long-acting versions that increase compliance. Precision psychiatry is emphasized in future perspectives.

## III. CONCLUSION

By combining great efficacy in lowering both positive and negative symptoms with enhanced tolerability when compared to first-generation drugs, risperidone is a prime example of how antipsychotic medication has evolved. Its availability in long-acting injectable formulations improves adherence and long-term results, but its metabolic and endocrine side effects require careful management. Risperidone continues to be a mainstay of second-generation antipsychotics, balancing symptom management with quality of life and highlighting the significance of precision medicine in the treatment of schizophrenia as psychiatry moves toward tailored treatment approaches.

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With reference to the authorship and publication, the authors affirm that they have no financial or non-financial conflicts of interest, of this piece. The idea, authorship, and choice to submit this paper for publication were not influenced by any pharmaceutical firm or outside organization.

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