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# New Advances in The Treatment of Schizophrenia: A Review

**Galanki Vasantha[1]*, Yellapu Hashika[2], Velampudi Venkata Satya Naga Vyshnavi[3], Bathula Jhansi[4] and Reddi Syamala[5]**

**[1*]Associate Professor, Department of Pharmacology, Vignan Institute of Pharmaceutical Technology, Duvvada, Visakhapatnam-530049.**

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***Corresponding Author Email:** drvasanthaniper@gmail.com

## Abstract

Schizophrenia is a chronic disorder that does not have any cure currently, but the symptoms associated with it can be treated. The pathology of the disease is not completely known, and antipsychotics have certain limitations. In this review, we have concentrated on the pharmacological and non-pharmacological treatment of schizophrenia and new drugs, therapy and treatment options introduced.

**Keywords**

Advance treatment, Schizophrenia, therapy, antipsychotic, Pharmacology, dopamine,

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**INTRODUCTION:**

Schizophrenia is a chronic mental disorder that is characterized by a wide range of symptoms like hallucination, delusion, paranoia, disorganized speech or behavior, and impairment in cognitive ability.[1] schizophrenia affects the person's ability to think, act, and even feel difficulty in doing general activities. [2] For many patients and their families, the disease is a disabling disorder owing to its early start and chronic nature. [1] Disabilities frequently result from both cognitive symptoms such as attention, working memory, or executive function deficits and negative symptoms (characterized by loss or deficits). [3] Furthermore, positive symptoms such as suspicion, delusions, and hallucinations may lead to relapse. [1,3] Since schizophrenia is inherently heterogeneous, there is currently no agreement on the diagnostic standards, etiology, or pathophysiology of the condition. [1,4] Men were shown to experience schizophrenia more frequently and with increased severity than women [5,6]. Alongside the use of antipsychotic drugs, schizophrenia is a chronic condition that can be effectively managed with appropriate care and management techniques.

**EPIDEMIOLOGY:**

In the US population, the prevalence of schizophrenia ranges from 0.6% to 1.9%. [7] In addition, a claims analysis estimated that 5.1 diagnoses of schizophrenia occur annually per 1,000 lives in the United States. [8] Despite the fact that symptoms in males appear earlier than in females, the condition appears to affect both sexes equally in prevalence. [3] In contrast to women, who often first develop symptoms of schizophrenia in their late 20s or early 30s, men tend to develop symptoms in their early 20s. [9]

**SYMPTOMS:**

Positive, negative, and cognitive symptoms of schizophrenia are distinguished from one another. As a clinician works to differentiate schizophrenia from other psychotic diseases such as schizoaffective disorder, a depressive disorder with psychotic elements, and bipolar disorder with psychotic features, each symptom is crucial. [9]

**Positive symptoms** can simply be categorized as "psychotic behaviors not found in healthy persons" and are the easiest to recognize.[10] These symptoms might range in severity from mild hallucinations and delusions to aberrant motor behavior. [9]

**Negative symptoms** are more challenging to diagnose, but since they affect the patient's emotions and behavior, they are also more likely to cause serious complications. [9,10] Reduced emotional expression and avolition are the most typical unfavorable symptoms (decreased initiation of goal-directed behavior). Alogia and anhedonia may also be experienced by patients. Negative symptoms can either be secondary to a concurrent psychotic diagnosis, medicine, or environmental condition, or they can be primary to a diagnosis of schizophrenia. [9,11]

**cognitive symptoms:** The most recent classification for schizophrenia is cognitive symptoms. Since these symptoms are non-specific, someone else must have noticed them if they are severe enough. Disorganized speech, thought, and/or attention are cognitive symptoms that eventually affect a person's capacity to communicate. [9,11]

**Catatonic Symptoms:** Symptoms of Catatonia In addition to aberrant motor behavior, catatonia is a syndrome that also includes diminished affect and volition. Up to 40 symptoms have been listed as catatonic, yet clinical classifications vary. Automatic obedience, negativism, unwillingness to eat, disengagement, and ambition are all indications of volition.[12]

**ETIOLOGY:**

The main risk factor for schizophrenia, which is a complex condition, is a favorable family history.[13]

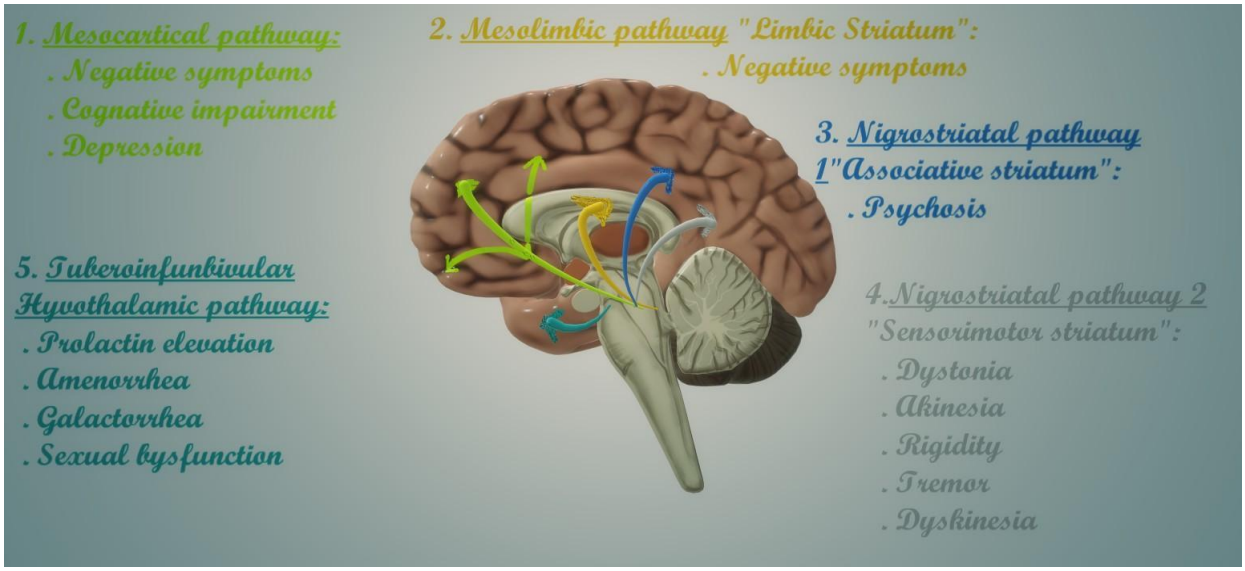
- Dopaminergic Hypothesis
- Glutamatergic Hypothesis
- Serotonergic Hypothesis of Schizophrenia
- Other Aminergic GPCRs in Schizophrenia
- GABAergic Hypothesis of Schizophrenia
- Nicotinic Receptors in Schizophrenia
- The Endocannabinoid System in Schizophrenia

Role of Inflammation and Oxidative Stress in the Patho-mechanism of Schizophrenia [14]

It has been determined that a disruption of dopaminergic signaling is the root cause of these symptoms.[15]

**THE DOPAMINE HYPOTHESIS FOR SCHIZOPHRENIA:**

According to the dopaminergic theory, schizophrenia is caused by changes in dopamine neurotransmission in the mesolimbic system, which are responsible for the positive symptoms, and mesocortical route, which are responsible for the negative symptoms. The glutamatergic hypothesis, which takes into account modifications in prefrontal neuronal connections involving glutamatergic neurotransmission at NMDA receptors, is a supporting theory [16].




**EXISTING TREATMENT:**

**Nonpharmacological therapy:**

Targeting symptoms, avoiding depressive episodes, and enhancing adaptive functioning have all been targets in treating schizophrenia so that the patient can regain social integration.[3] To ensure long-term outcomes, both nonpharmacological and pharmacological treatments must be used even though patients rarely regain their baseline level of adaptive functioning. [3] The backbone of treating schizophrenia is pharmacotherapy, yet persistent symptoms might well remain.

Non-pharmacological treatments, such as psychotherapy, are essential for this reason. [17]

Non - pharmacological therapy can assist patients adhere to their medication schedules by filling the

gaps left by pharmacological treatments. [18] Depending on the report, schizophrenia nonadherence rates range from 37% to 74%. [19] For a wide range of reasons, individuals suffering from mental illnesses tend to be less motivated.

They may have grandiose symptoms or paranoia and they also experience negative consequences that prevent them from taking more medication, completely deny a medical condition, or interpret their need for medication as not necessary. [3]

**Yoga therapy:**

The symptoms of schizophrenia can be treated with yoga therapy, commonly in combination with pharmaceutical drugs. Pharmacological treatment alone may not produce all of the desired results in reducing negative symptoms of schizophrenia [20]. Yoga, especially when combined with antipsychotic drugs, is much more efficient in treating both positive and negative symptoms than drugs alone. Similarly, pharmacological therapy for schizophrenia commonly results in obesity [20]. Antipsychotic medication treatment has been proven to cause weight gain; however, yoga therapy has been found to reduce potential obesity.

**Cognitive therapy:**

Cognitive behaviour therapy (CBT) is a treatment method that assists in reducing negative thinking, emotion, and behavioural patterns. Practical self-help techniques are applied in CBT, and it's been proven that these techniques decrease positive symptoms of schizophrenia. Cognitive behavioural therapy (CBT) combines cognitive therapy and behavioural psychotherapy. The patient may often have healthy thoughts and behaviours due to the combination of these two treatments together. [21].

**Psychotherapy:**

Psychotherapeutic approaches may be divided into three categories: individual, group, and cognitive behavioural[3] The domain of psychotherapy is a discipline that is constantly developing.

Metacognitive therapy, narrative therapy, and mindfulness therapy are characteristics of emerging psychotherapies. Evidence-based psychotherapy for schizophrenia: 2011 update, Dickerson FB, Lehman AF. 2011;199(8):520-526 in J Nerv Ment Dis. [PubMed] using Google Scholar Nonpharmacological therapies are to be used in conjunction with prescription drugs, not as a replacement for them. Nonpharmacological therapies are to be used in conjunction with medications, not as a substitute for them. [3]

**Pharmacological therapy:**

The pathomechanism of schizophrenia is not known exactly, and the severe limitations of today's modern antipsychotics. Well first of all, only about half of patients benefited from these treatments. Second, they only address the core symptoms of illness, positive symptoms including hallucinations and mood disorders which have treated the negative and cognitive symptoms such as flat affect and social withdrawal. Thirdly, they possess severe neurological and metabolic negative impacts that might include agranulocytosis or sexual dysfunction (clozapine).[22]

It is commonly accepted that antipsychotics' capabilities to treat the symptoms of schizophrenia are mediated by interactions with numerous neurotransmitter receptors. Traditional molecular targets for antipsychotic drugs have included a variety of G protein-coupled receptors (GPCRs), mainly dopamine, serotonin, and adrenaline receptors.[22]

For pathophysiology, increased presynaptic dopamine synthesis is essential [23]. First generation antipsychotics, such as aripiprazole,

brexpiprazole, and cariprazine, belong to this category. Second generation antipsychotics, which include multi-target antagonists with higher antagonism at serotonin 5-HT2A receptor than at dopamine D2 receptor, belong to this category. Aripiprazole is a partial agonist of the dopamine D2 receptor in the G-pathway, but according to the signalling readout, it can also produce partial agonist, antagonist, or agonist activity at the dopamine D2 receptor [24]. It specifically inhibits or partially stimulates the -arrestin-2 signalling pathway [24]

**First Generation Antipsychotics:[14]**

Chlorpromazine
Fluphenazine
Thioridazine
Haloperidol
Thioridazine
Flupenthixol
Thiothixene
Perphenazine

**Second Generation Antipsychotics:[14]**

Aripiprazole
Asenapine
Clozapine
Iloperidone
Lurasidone
Olanzapine
Paliperidone
Quetiapine
Risperidone
Ziprasidone

**Third-Generation Antipsychotics:[25]**
Bifeprunox
Aplindore
OPC-4392
Amisulpride
Preclamol
OSU 6162

**Risks of Extrapyramidal Symptoms and Weight Gain with Typical and Atypical Antipsychotic agents: [18,26,27,28]**

| Drug | Weight Gain | Extrapyramidal Symptoms |
|---|---|---|
| **Typical Antipsychotics (First-Generation Antipsychotics)** | | |
| Chlorpromazine (Thorazine) | ++ | +++ |
| Fluphenazine (Prolixin) | + | ++++ |
| Haloperidol (Haldol) | + | ++++ |
| Perphenazine (Trilafon) | + | ++++ |
| Thioridazine (Mellaril) | + | +++ |
| Thiothixene (Navane) | + | ++++ |
| **Atypical Antipsychotics (Second-Generation Antipsychotics)** | | |
| Aripiprazole (Abilify) | + | + |
| Asenapine (Saphris) | + | ++ |
| Clozapine (Clozaril) | ++++ | + |
| Iloperidone (Fanapt) | ++ | ± |
| Lurasidone (Latuda) | ± | + |
| Olanzapine (Zyprexa) | ++++ | ++ |
| Paliperidone (Invega) | ++ | ++ |
| Quetiapine (Seroquel) | ++ | + |
| Risperidone (Risperdal) | ++ | ++ |
| Ziprasidone (Geodon) | + | ++ |

± = negligible risk; + = low risk; ++ = moderate risk; +++ = moderately high risk; ++++ = high risk

**TREATMENT RESISTANCE THERAPY.**

After so many FGA trials, 10%–30percent of respondents of schizophrenia patients experience little symptomatic improvement, whereas an additional 30%–60% of individuals with schizophrenia experience partial or inadequate improvement or unacceptable side effects after antipsychotic therapy.[11] When it comes to treating schizophrenia that seems to be resistant to treatment, clozapine is the most effective antipsychotic. In comparison to the combined use of chlorpromazine and benztropine, which has a 4% efficacy rate, this drug has a 30% efficacy rate in treating schizophrenia episodes in patients who seem to be resistant to therapy. [29] Moreover, it has been shown that clozapine increases serum sodium levels in patients with polydipsia and hypernatremia.[30]

**Augmentation and Combination Therapy.**

Both augmentation therapy (with ECT or a mood stabilizer) and combination therapy (with antipsychotics) may be considered for patients who fail to show an adequate response to clozapine. The following guidelines should be adhered to by clinicians when administering augmentation therapy: [31] Only patients who haven't responded adequately to earlier treatments should receive this treatment. When given alone, augmentation drugs rarely alleviate the signs of schizophrenia. Patients who respond to augmentation therapy tend to experience quick improvement. The agent should be discontinued if an augmentation strategy does not improve the patient's symptoms.

**Janus-Kinase Inhibitors (JAKinibs): A Promising Treatment for Inflammatory Schizophrenia.**

We have seen that a broad range of irregular cytokines were correlated to schizophrenia. These cytokines bind to receptors which trigger the JAK/STAT signaling pathway, which would be involved in gliogenesis, synaptic plasticity, microglia activation, and neurogenesis, all of which are linked to the pathophysiology of schizophrenia [32][33]. Moreover, depressive symptoms are prevalent in schizophrenia, it has been shown that JAK/STAT-dependent mechanisms mediate the antidepressant effects of existing therapies [34]. Jakinibs, which

seem to be JAK small-molecule inhibitors, have been shown to be safe and efficient therapy for rheumatoid arthritis, psoriasis, and inflammatory bowel disease [35] these may also be effective treatments for schizophrenia and should be studied.

**New Drugs:**

**LYBALVI**; Recently, LYBALVI, a drug which combines olanzapine and samidorphan, was approved for the treatment of individuals with BD-I or schizophrenia. We have analysed the economical impact of adding LYBALVI to the formulary from Commercial, Medicaid, and Medicare perspective in the United States (US) [36]

**KARXT;**

Through its activity at M4 and M1, respectively, KarXT, an emerging muscarinic agonist, may carry the potential as a therapeutic treatment for psychosis and cognitive impairment.[37]

**SCHIZOPHRENIA 2020: TRENDS IN THERAPY**

Over the decades, the notions of schizophrenia have evolved, and currently the biopsychosocial model have shaped treatment modalities for schizophrenia, leading to three pillars of schizophrenia therapy: Antipsychotic drugs used in biological therapy modalities block brain dopamine receptors without altering the effects of other brain neurotransmitter systems.

Psychotherapeutic approaches increasingly informed by research on specific psychological aspects of the pathophysiology of schizophrenia as mentioned before (like aberrant salience and jumping to conclusions38 and cognitive training techniques to overcome cognitive impairments, for example of working memory functions) (like aberrant salience and jumping to conclusions38 and cognitive training techniques to overcome cognitive impairments, for example of working memory functions).

Treatments which concentrate on childhood trauma associated with occupational rehabilitation (like supported employment programs).[38]

**BRILAROXAZINE;**

Atypical antipsychotic brilaroxazine (RP5063, also known as RP5000) is being researched and developed by Reviva Pharmaceuticals. It is hypothesized to be a modulator of the dopamine-serotonin system just because it possesses a great affinity for several serotonin and dopamine system receptors. It exhibits structural similarities with aripiprazole, cariprazine, and brexpiprazole in particular. According to research, it has a moderate affinity for the serotonin transporter and high concentrations for the 5-HT1A/2A/2B/2C/6/7 and D2/3/4 receptors.[39]

**ARISTADA;**

Atypical antipsychotic aripiprazole lauroxil is available as a white to off-white sterile extended-release suspension for intramuscular injection. The basic mechanisms of action of aripiprazole lauroxil are transmitted by the parent drug, aripiprazole, and, to a lesser extent, by its major metabolite, dehydroaripiprazole, which also contributes for 30% to 40% of the exposure to aripiprazole in plasma. Following a single IM injection, aripiprazole enters the bloodstream within five to six days and continues to be released for an additional 36 days.[40]

**LUMATEPERONE.**

A revolutionary investigational drug called lumateperone is currently being developed for the treatment of several neuropsychiatric and neurodegenerative conditions, including schizophrenia. Due to its unique receptor affinity profile and synergistic modulation of serotonergic, glutamatergic, and dopaminergic pathways, it is effective against a variety of schizophrenia-related symptoms.[41]

**SAPHRIS;**

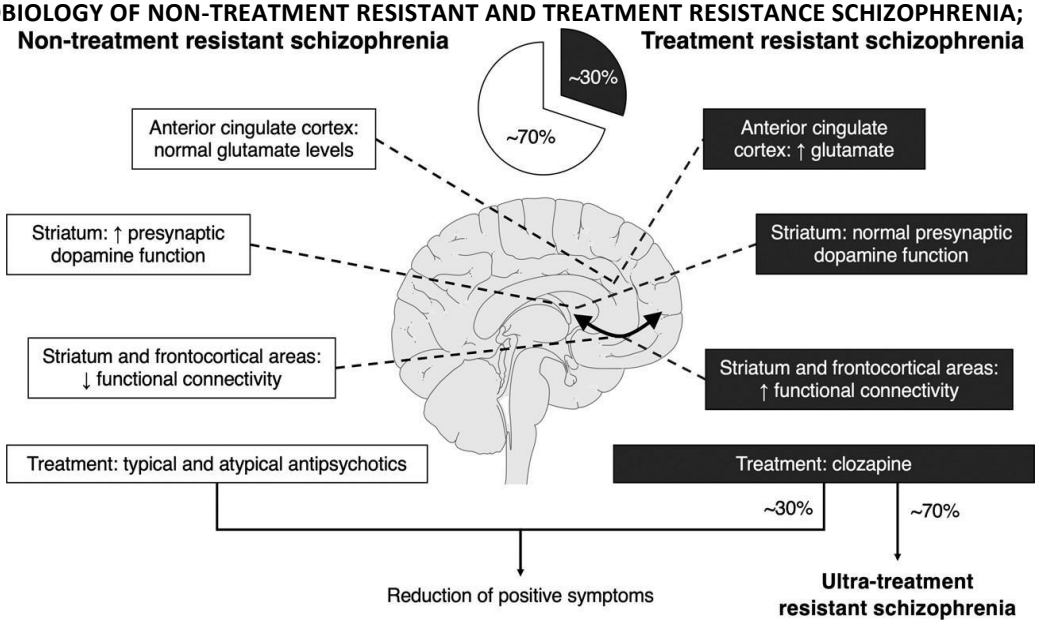
An even more modern atypical antipsychotic is asenapine (Saphris). Introductions include the treatment of schizophrenia, acute mania, and mixed episodes associated with bipolar disorder, type I in adults. 5 mg sublingually twice daily should be begun in schizophrenic patients. For adequate symptom control, the dose may be increased to a maximum of 10 mg twice daily.[42]

**NOVEL PHARMACOLOGICAL AGENTS:**

Targeting brain dopamine D2 receptors is the backbone of antipsychotic therapy today, but types of drugs are now being developed that impact on glutamate receptors, glycine transporters, or the alpha-7-nicotinic acetylcholine receptor.[43] But none of these reducing techniques have, to date, generated soil clinical advances. New therapeutic targets will be "negative" symptoms like avolition and anhedonia, as well as cognitive symptoms like working memory impairments, in contrast to hallucinations and delusions, against which the current antipsychotic medications show sufficient activity. Minimizing the side effects of the present antipsychotic drugs, which may lead to dyskinesias, cardiac arrhythmias, or the metabolic syndrome, all of which frequently inhibit the clinical acceptance of these medications, is another major element. Pharma companies are decreasing their involvement in the research of antipsychotic drugs as developing [44] To mitigate this drawback, it may be necessary to alter the laws that govern market returns. Clearly, another approach would be to persuade

pharmaceutical companies of the etiopathogenesis of schizophrenia. Developing biomarkers for schizophrenia patient segmentation, developing predictive models, an enhancing information sharing, and collaboration are potential extra factors.[45] To figure out the direction of medication development for the treatment of schizophrenia, such measures are considered necessary.

**NEUROBIOLOGY OF NON-TREATMENT RESISTANT AND TREATMENT RESISTANCE SCHIZOPHRENIA;**




**CONCLUSION:**

The approaches now used to define treatment resistance in schizophrenia vary widely. In the past three decades, pharmaceutical and psychosocial treatments for schizophrenia have advanced quickly and differently in different nations, having a substantial impact on patients' symptom management and relapse prevention. The adoption of psychosocial therapies as standard practice within mental health services has been sluggish and uneven due to insufficient consistency in execution and restricted access to various models of successful treatments. The majority of currently employed psychosocial interventions cannot show broad-based or long-term (i.e., >18 months) effects on patients' psychosocial and functional outcomes, as well as quality of life, despite the fact that pharmacological treatment has indicated various kinds and levels of adverse effects.

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