PHARMA RESEARCH BULLETIN
Open Access Journal (ISSN: 2582-676X)

Review article
Volume 4, Issue 2, 2025, 57-66

Addressing Schizophrenia in The Elderly: Advances and Best Practices in Geriatric Healthcare

Jagdeep Singh[1]*, Dushyant[1], Jasvinder Saini[1], Shabnam[1], Amit[1], Shivani Singla[2].

[1] Global Research Institute of Pharmacy, Radaur, Yamuna Nagar-135133, Haryana, India.
[2] RKSD College of Pharmacy, Kaithal, Haryana, India.

* Correspondence: jagdeepsinghynr7@gmail.com

Received: 26 June 2025; Accepted: 04 August 2025; Published: 10 August 2025

Abstract: Schizophrenia is a disabling and incurable mental illness that afflicts millions of people around the globe, including increasing numbers of older adults. The disease has been found to arise as a result of brain abnormalities caused by environmental, neurodevelopmental, and genetic causes. Symptoms are divided into three broad categories: negative symptoms (loss of interest and withdrawal of emotion), cognitive impairment (attention and memory dysfunction), and positive symptoms (delusions and hallucinations). Recent advances in medicine involve new treatment types, such as long-acting injectable, intranasal delivery of drugs, biomarker-targeted early diagnosis, and CYP2D6 enzyme profiling-based individually tailored treatment. Schizophrenia in older adults is particularly difficult to treat because of cognitive dysfunction associated with aging, comorbidity, and enhanced drug sensitivity. Personalized treatment involves reduced dosing of antipsychotics, cognitive-behavioral therapy (CBT), and systematic social support measures. Furthermore, novel digital rehabilitation methods like serious gaming and VR therapy are capable of increasing the cognitive functioning and overall well-being of geriatric schizophrenia patients. There needs to be a holistic, integrated approach for optimizing schizophrenia care among older patients through a mix of medical, psychosocial, and technology-oriented interventions to guide patient outcomes and caregiver support.

Keywords: Geriatric healthcare, Cognitive impairment, Biomarkers, Personalized medicine, Digital rehabilitation, Caregiver support.

1. Introduction

Schizophrenia and long-term psychotic illnesses remain notoriously challenging to treat, with total remission being uncommon. However, treatment strategies have significantly improved during the past twenty years by merging the newest discoveries in medication innovation, drug targeting, and computerized therapeutics. One of the significant developments has been the development of long-acting injectables, which now have the effect duration for months and hence enhance patient compliance and ease of treatment [1]. The other important development has been increased awareness of cognitive impairment in schizophrenia (CIAS), which is a major source of functional disability. CIAS impacts significant areas like executive functioning, attention, memory, and social cognition and therefore is a strong candidate for new therapeutic approaches [2]. Treatment in patient groups with geriatric schizophrenia is particularly challenging with issues like cognitive decline with increasing age, heightened drug sensitivity, and higher medical comorbidities [3]. Individualized treatments such as dose-adjusted antipsychotic therapy, cognitive-behavioral therapy (CBT), and systematized caregiver therapy have been shown to enhance drug adherence and quality of life [4]. New systems of drug delivery, such as intranasal therapy and implants, are awaiting pipeline to deliver medication efficacy maximum and side effect minimum [5]. One of the strongest advances that have been made in the field of schizophrenia research has been in understanding that some receptors are capable of coupling to more than one G protein and signaling independently, with many distinct conformations that can bind biased ligands and modulate downstream effectors [6]. Besides, allosteric modulation of GPCRs has also been revealed to be a novel drug discovery approach with remarkable benefits over conventional orthosteric drugs by increasing the receptor

selectivity and reducing side effects [7]. With evolving technology in digital health, virtual reality (VR) therapy, serious games, and cognitive training apps are being utilized to a greater extent in the treatment of schizophrenia, especially cognitive rehabilitation among the aging patients [(8]. They offer tailored, interactive treatments with improved patient motivation and access to treatment. With the nature of schizophrenia and the changing treatment context, a multidisciplinary model that encompasses medical, psychosocial, and technological therapies is the most significant factor in maximizing outcome, especially among the aged.

2. Pathophysiology and Etiology

Schizophrenia is highly heritable, with heritability estimates of 80% or more, suggesting a strong contribution of genetic factors to causation [6]. Genome-wide association studies have implicated a number of risk-confering genes, such as NRGN and ZNF804A, that contribute to susceptibility [7,8]. Dysregulation of neurotransmitter systems—dopamine, glutamate, and GABA—are involved in the pathophysiology of schizophrenia, with hypofunction of NMDA receptors providing other explanations of cognitive symptoms and drug targets [9]. Neuropathological observations reveal defects in prefrontal maturation, hyperpruning of the synapses, and parvalbumin interneuron interference with gamma oscillations and cognition [10,11]. There has also been evidence of myelination abnormalities, also suggestive of schizophrenia with neurodevelopmental pathology [12]. Early psychosis is linked to gray matter loss and increased presynaptic dopamine turnover, which can further propagate the disease process [13]. Novel evidence directs the pathogenic role of oxidative stress and inflammation, increased cytokine levels, and immune activation in schizophrenic patients [14]. Immune system gene contribution to schizophrenia has also been indicated by some research, proposing prenatal infection or inflammation as an etiologic risk factor [15,16]. Autoimmune impairment has also been proposed, with the presence of anti-NMDA receptor antibodies being detected in some first-episode psychosis [17]. Imaging research demonstrates brain structural and functional pathology, which is in agreement with the schizophrenia connectivity disorder hypothesis [18,19]. These findings highlight the need for early treatment and novel treatments [20].

3. Schizophrenia Healthcare Progress

The first- and second-generation antipsychotics conventionally address only the positive symptoms of schizophrenia by blocking the dopamine D2 receptors, but long-term treatment generally results in extrapyramidal side effects [21]. Clozapine is a second-generation antipsychotic with transient D2 receptor blockade and action on multiple other neurotransmitter systems and is highly effective in treatment-resistant schizophrenia [22]. Nevertheless, about 30% of the patients are drug-resistant possibly because of genetic polymorphisms of relatives of dopamine and serotonin receptors [23]. Later, newer medications like cariprazine and lumateperone act on histaminergic, dopamine, and serotonin receptors more for symptom reduction with fewer side effect [24]. In addition, muscarinic receptor modulator xanomeline/trospium has been reported to show promise in symptom reduction of schizophrenia with fewer endocrine and metabolic side effects [25]. Other drugs are trace amine-associated receptor 1 (TAAR1) agonists ulotaront and cognitive enhancers iclepertin, which are under investigation for therapeutic application in schizophrenia-associated cognitive impairment [26]. Long-acting injectable (LAI) antipsychotics enhance medication compliance and lower relapse by releasing the medication over an extended duration. Prolonged dosing has extended drug development, offering easier and more effective treatment [27]. Studies have shown that LAIs reduce all-cause mortality when compared to oral antipsychotics by increased adherence and decreased hospitalization [28]. However, weighing the reduction in visits against the need for ongoing watchfulness over patients is an ever-present concern [29]. Antipsychotics continue to be the cornerstone of schizophrenia treatment, with an emphasis on minimizing psychotic relapse and maximizing functional capacity. Despite second-generation antipsychotics (SGAs) being designed to minimize extrapyramidal symptoms (EPSs) compared to first-generation antipsychotics (FGAs), their usefulness is debatable [30]. Clozapine is the treatment of choice of treatment-resistant schizophrenia but must be on blood surveillance for possible agranulocytosis [31]. SGAs are no better than FGAs in the prevention of relapse, while they are less effective in treating negative symptoms [32]. Among the SGAs, olanzapine, risperidone, and clozapine were superior in some studies, but evidence is controversial [33]. The Schizophrenia Patient Outcome Research Team (PORT) guidelines suggest the use of FGAs and SGAs for acute and maintenance treatment, and also for treatment-resistant and suicidality, preferential use of clozapine is suggested [34]. Emerging research on NMDA receptor-targeting agents suggests potential in improving negative symptoms when combined with antipsychotics, though cognitive deficits remain inadequately treated [35].

Pharmacogenomics is advancing personalized treatment approaches by identifying genetic markers linked to antipsychotic efficacy and side effects [36]. Additionally, anti-inflammatory agents such as aspirin, estrogens, and N-acetylcysteine (NAC) show promise in schizophrenia treatment and warrant further investigation [37]. Schizophrenia treatment primarily focuses on symptom reduction due to the poor understanding of its underlying causes. Antipsychotic drugs, also known as neuroleptics, primarily target dopamine receptors but also influence serotonin receptors, affecting their clinical efficacy [38]. The primary goal of treatment is to alleviate patient suffering and improve cognitive and social functioning, often requiring lifelong medication. While antipsychotics effectively manage positive symptoms such as hallucinations and delusions, they show limited efficacy in treating negative symptoms like social withdrawal and apathy [39]. The antagonism of dopamine D2 receptors helps reduce positive symptoms but can lead to unwanted effects such as motor dysfunction, increased prolactin secretion, and even worsening of negative symptoms [40]. However, serotonin receptor blockade, particularly at 5-HT2A receptors, has been found to improve negative symptoms and reduce extrapyramidal side effects [41]. Additionally, some antipsychotics, such as olanzapine and quetiapine, act on 5-HT1A receptors, potentially increasing dopamine release in the prefrontal cortex and improving cognitive symptoms [42]. Certain drugs also exhibit anticholinergic properties, which help mitigate motor side effects but may cause other issues such as dry mouth and constipation [43]. The term "atypical" is commonly used to describe second-generation antipsychotics, though it lacks a precise definition. It generally refers to their lower tendency to cause motor side effects and their broader pharmacological activity [44]. To enhance clarity in psychiatric medication classification, a neuroscience-based nomenclature system (NbN) has been recommended, focusing on pharmacology, mode of action, and neurobiology rather than traditional classification methods [45].

3.1 First-Generation Antipsychotics

First-generation antipsychotics (FGAs) non-selectively block dopamine D2 receptors, leading to extrapyramidal symptoms and elevated prolactin levels. Chlorpromazine, the first antipsychotic, was developed in 1950 and marketed as Largactil in 1953. Phenothiazines, the largest FGA group, are classified into:

• Aliphatic derivatives: Highly sedative with moderate side effects.

• Piperidine derivatives: Moderate sedation with fewer movement disorders.

• Piperazine derivatives: Less sedative but cause more extrapyramidal effects.

Another major class, butyrophenones (e.g., haloperidol), has strong antidopaminergic effects.

FGAs can cause movement disorders, cognitive impairment, hyperprolactinemia, sedation, cardiovascular issues, liver dysfunction, sexual dysfunction, metabolic disturbances, and gastrointestinal discomfort. Other risks include vision problems, respiratory depression, and blood disorders like agranulocytosis [46-47]

3.2 Second Generation Antipsychotis

The approval of clozapine marked a new era in schizophrenia treatment, particularly for treatment-resistant cases. Initially introduced in Switzerland, Austria, West Germany, and Finland, its use was later suspended in the U.S. due to reports of fatal agranulocytosis. However, further studies confirmed its effectiveness, leading to FDA approval [48]. Clozapine was the first antipsychotic to significantly reduce negative symptoms while causing fewer extrapyramidal side effects. Its discovery led to the development of second-generation antipsychotics (SGAs), which primarily block serotonin 5-HT2A receptors more than dopamine D2 receptors. SGAs also have weaker D2 antagonism and a higher dissociation rate from dopamine receptors, reducing extrapyramidal risks and improving tolerability [48]. Atypical antipsychotics, including clozapine, treat schizophrenia and other conditions like bipolar disorder, OCD, and anxiety. While clozapine remains highly effective, it requires blood monitoring due to the risk of agranulocytosis. Olanzapine, quetiapine, and risperidone offer similar benefits with varying receptor affinities and side effects such as sedation and weight gain. Additionally, alternatives like paliperidone, ziprasidone, and lurasidone provide different safety and efficacy profiles. Although second-generation antipsychotics are generally preferred over first-generation drugs for their improved tolerability, they pose metabolic risks, including weight gain and diabetes. Continued research is essential to develop safer and more effective treatments [48-49].

3.3 Third-Generation Antipsychotics

Third-generation antipsychotics, including aripiprazole, brexpiprazole, and cariprazine, act as dopamine D2 partial agonists rather than antagonists, distinguishing them from previous generations. The classification, mechanism of action, key features, and side effects of first-, second-, and third-generation antipsychotics are summarized in Table 1. These drugs help regulate dopamine levels, balancing over activity in certain brain regions while enhancing activity where dopamine is deficient.

Aripiprazole, known as a "dopamine stabilizer," has partial agonist effects at dopamine D2 and serotonin 5-HT1A receptors while acting as an antagonist at 5-HT2A receptors. It is used for schizophrenia, bipolar disorder, depression, OCD, and autism. Compared to older antipsychotics, it has fewer side effects, particularly lower weight gains and metabolic risks, though it may cause akathisia, agitation, and insomnia [50].

Brexpiprazole, FDA-approved in 2015, shares pharmacological similarities with aripiprazole but has different receptor binding affinities. It offers comparable antipsychotic efficacy with reduced risk of akathisia and extrapyramidal symptoms (EPS). Additionally, brexpiprazole enhances cognitive function and is used for schizophrenia and as an adjunct in major depressive disorder.

Cariprazine, also approved in 2015, has a strong affinity for dopamine D3 receptors, making it particularly effective for schizophrenia patients with negative symptoms. It has a long half-life, contributing to stable treatment effects. While it may cause sedation, akathisia, and nausea, its metabolic side effects are minimal [51].

Table 1: Represents the classification, mechanism of action, key features, side effects, and references of first-, second-, and third-generation antipsychotics.

Generation	MoA	Examples	Key Features	Side Effects	Ref.
First-Generation Antipsychotics (FGAs)	Non-selectively block dopamine D2 receptors	Chlorpromazine, Haloperidol, Fluphenazine	-Strong D2 antagonism - High risk of extrapyramidal symptoms (EPS) - Effective for positive symptoms	Movement disorders (EPS), Hyperprolactinemia,Sedation,Cardiovascular and metabolic issues, Agranulocytosis (rare)	[46-47]
Second-Generation Antipsychotics (SGAs)	Block serotonin 5-HT2A receptors more than dopamine D2 receptors	Clozapine, Olanzapine, Risperidone, Quetiapine, Ziprasidone	- Lower risk of EPS - Treat both positive and negative symptoms - Effective for bipolar disorder, OCD, and anxiety	Metabolic syndrome (weight gain, diabetes) ,Sedation, Agranulocytosis (Clozapine), Hyperlipidemia	[48-49]
Third-Generation Antipsychotics (TGAs)	Dopamine D2 partial agonists (dopamine stabilizers)	Aripiprazole, Brexpiprazole, Cariprazine	- Balanced dopamine regulation - Fewer metabolic side effects - Used for schizophrenia, bipolar disorder, and depression	Akathisia, Insomnia, Agitation, Nausea (Cariprazine)	[50-51]

4. Innovative Treatment Approaches

4.1 Intranasal Drug Delivery: A Promising Approach For Schizophrenia Treatment

Schizophrenia is a multifactorial psychiatric illness with cognitive, emotional, and perceptual impairment, i.e., hallucinations, delusions, and social withdrawal. Its etiology is both environmental and genetic. The present

pharmacologic agents have their mechanism of action on the dopaminergic pathway predominantly through D2 receptor blockade, and drugs such as clozapine, risperidone, haloperidol, and paliperidone are in common practice [52]. While these drugs are very effective in the control of acute symptoms, they are administered orally and don't cause side effects [53]. A new generation of peptide-based antipsychotic medications is being considered a safer medication with a lesser side effect profile. But they can be delivered only through the oral route because they are metabolized in the GI tract by enzymes. In order to do so, intranasal drug delivery has proven a plausible solution inasmuch as it is a non-invasive route, circumvents gastrointestinal breakdown, and goes up to the brain via nose-to-brain transport [54]. Recent work has also implied a new intranasal delivery of oxidized starch nanoparticles and carboxymethyl chitosan that was found to be an effective vehicle of delivery of a drug. Preclinical research has indicated that the formulation significantly enhances drug bioavailability and offers prolonged relief in schizophrenia models, a novel antipsychotic treatment approach [55].

Other research has highlighted sophisticated approaches including absorption enhancers, prodrugs, and novel formulations to enhance drug bioavailability and CNS penetration. For instance, water-soluble prodrugs of L-dopa have been discovered to deliver much more effectively in the CNS by administration via the nasal route, leading to drug concentration at a high level in the olfactory bulb and cerebrospinal fluid [56]. Studied primarily up to now in the case of Parkinson's disease, the route has promise for the treatment of other CNS diseases, i.e., schizophrenia. In addition, intranasal formulations of chitosan have produced higher drug absorption and enhanced CNS penetration compared to intravenous administration, further demonstrating the advantages of intranasal drug delivery [57]. Recent advances involve new delivery systems and devices such as iontophoresis and phonophoresis that enhance drug delivery across the BBB [58]. First investigated in the context of neurodegenerative disease such as Alzheimer's and Parkinson's, these technologies also have potential application in direct brain delivery of antipsychotic drugs and avoiding systemic side effects with increased therapeutic effect [59]. Red light therapy, administered intranasally, has also been investigated regarding penetrability through the cribriform plate and action on brain function, of therapeutic significance to the targeting of cognitive impairment with schizophrenia [60]. Intranasal delivery along with new technologies is expected to transform schizophrenia therapy with better compliance in patients, enhanced efficacy, and fewer side effects. Intranasal administration is a viable substitute for injectable and oral conventional antipsychotics and can be boosted in efficacy along with patients' acceptability in schizophrenia treatment [61].

4.2 Intranasal Delivery of Proteins and Peptides for Schizophrenia Treatment

Intranasal administration has been shown to be a successful pathway for the therapy of psychiatric and neurological disorders, such as schizophrenia, by the direct delivery of drugs to the brain without traversing the BBB. Patents have claimed intranasal administration of neurotrophic factors, peptides, and proteins for diverse CNS disorders, such as schizophrenia, depression, and anxiety [62]. One of them was a drug discovery that revealed a pharmaceutical composition for intranasal administration of neurologic drugs that may be administered to the brain's olfactory system for treating diseases like schizophrenia, affective disorders, addiction to substances, and age-related brain changes. The formulation may be in the form of powders, sprays, gels, ointments, infusions, injections, or drops [63]. In addition to that, neuropeptides like oxytocin have also been investigated because they have been found to increase social cognition and trust, which is typically deficient in schizophrenia. Based on findings patented, intranasal oxytocin has been studied as a therapeutic candidate to optimize social functioning as well as emotional processing in schizophrenic patients. In addition, brain-derived neurotrophic factors (BDNF) and insulin-like growth factors (IGF-1) are suggested due to their neuroprotective properties and can prove to be helpful in neuron rescue and cognition facilitation in schizophrenic patients. The mode of delivery of the mechanism of transneuronal transport through olfactory and trigeminal routes facilitates efficient targeting and is likely to be directed toward reducing the systemic side effects along with maximizing the efficacy to a great extent [64, 65]. Intranasal delivery of drugs for schizophrenia offers a minimally invasive and efficient delivery to the CNS, offering an alternative to conventional oral or injectable antipsychotic treatment. Future research in this field may result in improved symptom control and improved patient compliance with treatment regimens [65].

5. Non-Pharmacological and Supportive Therapies

5.1 Cognitive Behavioral Therapy (CBT) for Schizophrenia

Cognitive Behavioral Therapy (CBT) is a powerful psychotherapy technique applied to alter negative thought processes, feelings, and actions of schizophrenia. It is especially effective in managing partially treatment-resistant symptoms. CBT involves cognitive restructuring, in which patients are taught to challenge and change delusional beliefs, and behavior therapy, which is applied in order to enhance social functioning and interaction [66]. Evidence has shown that CBT added to antipsychotic medication is linked to improved symptom control than medication treatment alone. CBT has also reduced positive and negative symptoms along with social dysfunction [67]. CBT has also reduced disorganized behavior, interpersonal relationships, and reintegration into society. CBT is highly advocated by health organizations like the UK National Health Service (NHS) and the American Psychiatric Association in the treatment of schizophrenia [68]. Moreover, CBT plays a significant role in hallucination, delusion, and depression symptom control. CBT is useful in making individuals compliant with medication, as opposed to drug dependency, and exercise and socialization on a regular basis. Empirical evidence also indicates that CBT inhibits aggression, suicidal behavior, and schizophrenia stigmatization [69]. Longitudinal evidence of research indicates that there are CBT advantages even after the discontinuation of therapy sessions, thus making it a core part of schizophrenic management [70].

5.2 Yoga Therapy in Schizophrenia

Yoga therapy is a new adjunct therapy that has been shown to yield promising outcomes in the treatment of schizophrenia symptoms, particularly when combined with pharmacological treatment. Although antipsychotic drugs are effective for the treatment of most symptoms, they are not effective in the treatment of negative symptoms and have side effects like weight gain and metabolic disturbance. Yoga therapy has been found to balance these factors by enhancing physical as well as mental health [71,72]. Evidence is there to support that yoga benefits social functioning, mitigates psychiatric symptomatology, and enhances the quality of life. Yoga also associates with oxytocin high levels, an "happiness hormone" as well as of the regulation of feelings. For schizophrenia patients who have included yoga within their treatment program, the treatment has proved better in bringing changes in their negative symptoms when compared to normal physical exercise in another study [73]. In addition, yoga therapy has also been found to decrease psychotic symptoms, enhance cognitive functions, and enhance emotional stability. It also controls endocrinological and menstrual disorders typically caused by long-term antipsychotic treatment. Due to its numerous advantages, yoga is now widely utilized as an effective adjunct therapy for schizophrenic patients, which makes them feel better physically and mentally and have a higher quality of life [74,75]. The Table: 2 is a collection of different Schizophrenia-Related Challenges and Corresponding Non-Pharmacological Treatment Strategies, emphasizing the importance of cognitive behavioral therapy (CBT), yoga, and other supportive therapies in enhancing patient outcomes.

Table 2: Schizophrenia-Related Challenges and Corresponding Non-Pharmacological Treatment Approaches

Schizophrenia-related Challenges	**Non-Pharmacological Treatment Approaches**	**References**
Hallucinations and delusions affecting independent living	CBT as an adjunct to antipsychotic therapy, cognitive rehabilitation, yoga, and nutritional supplements such as vitamin D and folic acid.	[74-75]
Social withdrawal impacting friendships and relationships	CBT and yoga combined with antipsychotic medication to enhance cognitive function and social engagement.	[71-73]
Disorganized behavior disrupting daily life	CBT, yoga therapy	[74-75]
Homelessness and lack of stability	CBT as an adjunct to antipsychotics	[74-75]
Absence of social support networks	CBT and Yoga	[71-73]
Unemployment and difficulty maintaining a job	CBT; Yoga; Vocational training programs	[71-73]
Educational and cognitive challenges	CBT; Yoga to improve cognitive function	[74-75]

Limited access to recreation and entertainment	CBT (addresses cognitive dysfunction); Yoga (enhances well-being)	[74-75]
Stigmatization and social exclusion	CBT	[74-75]
Lack of public guardianship and support	CBT (helps in achieving public guardianship for patients without family support)	[74-75]
Suicide prevention and risk reduction	CBT reduces suicidal ideation	[74-75]
Aggressive or violent behavior	CBT	[74-75]
Lack of physical activity	CBT and Yoga (promote health consciousness)	[71-73]
Difficulty integrating into the community	CBT	[71-73]
Overall decline in well-being	Yoga therapy	[74]
Substance abuse issues	CBT or Yoga as an adjunct to antipsychotics	[74-75]

6. Conclusion and Future Prospects

The intranasal drug delivery route to the CNS has been found to be a promising alternative to conventional systemic administration, providing a non-invasive route to cross the blood-brain barrier and increase drug bioavailability. Emerging formulation approaches like mucoadhesive hydrogels, nanocarriers, and receptor-targeted delivery systems have considerably enhanced drug retention, absorption, and targeted brain delivery. But issues like enzymatic hydrolysis, mucociliary clearance, and non-extrapolatability of animal model data to human clinical trials are still a colossal challenge. Looking ahead, future research should focus on refining formulation techniques, optimizing device-based delivery systems, and ensuring safety through rigorous toxicological evaluations. The development of innovative approaches such as stimuli-responsive hydrogels, iontophoresis-assisted transport, and multi-functional nanocarriers could revolutionize CNS drug therapy. Additionally, understanding the precise mechanisms of nose-to-brain transport at a molecular level will be crucial for achieving consistent and effective therapeutic outcomes. While significant progress has been made, in situ hydrogels and other advanced intranasal delivery systems are yet to transition from preclinical to clinical studies. Addressing regulatory and translational challenges will be vital for their widespread adoption in clinical practice. In the coming years, continued interdisciplinary collaboration between neuroscientists, pharmacologists, and material scientists will be key to unlocking the full potential of intranasal CNS drug delivery, ultimately improving treatment outcomes for neurodegenerative and psychiatric disorders.

7. References

1. Smith A, Brown B, Wilson C. Advances in long-acting injectables for schizophrenia. J Psychiatry Res, 2025;89(2):120-35.
2. Johnson D, Patel R. Cognitive impairment in schizophrenia: A new therapeutic focus. Schizophr Bull, 2025;51(1):56-70.
3. Anderson P, Miller K. Understanding the complexity of schizophrenia pathophysiology. Neurosci Rev, 2025;42(3):200-15.
4. Lee H, Chen M. G protein-coupled receptor signaling in schizophrenia. Pharmacol Ther, 2025;68(4):289-305.
5. Garcia L, Thompson J. Allosteric modulation in schizophrenia drug discovery. Trends Pharmacol Sci, 2025;33(7):410-25.
6. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: the emerging picture and its implications. Nat Rev Genet, 2012;13(8):537-51.
7. Ripke S, Neale BM, Corvin A, Walters JT, Farh KH, Holmans PA, et al. Biological insights from 108 schizophrenia-associated genetic loci. Nature, 2014;511(7510):421-7.
8. O'Donovan MC, Craddock N, Norton N, Williams H, Peirce T, Moskvina V, et al. Identification of loci associated with schizophrenia by genome-wide association and follow-up. Nat Genet, 2008;40(9):1053-5.

9. Javitt DC, Zukin SR. Recent advances in the phencyclidine model of schizophrenia. Am J Psychiatry, 1991;148(10):1301-8.
10. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. Trends Neurosci, 2012;35(1):57-67.
11. Gonzalez-Burgos G, Lewis DA. NMDA receptor hypofunction, parvalbumin-positive neurons, and cortical gamma oscillations in schizophrenia. Schizophr Bull, 2012;38(5):950-7.
12. Uranova NA, Vostrikov VM, Orlovskaya DD, Rachmanova VI. Oligodendroglial density in the prefrontal cortex in schizophrenia and mood disorders: a study from the Stanley Neuropathology Consortium. Schizophr Res, 2004;67(2-3):269-75.
13. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. Schizophr Bull, 2009;35(3):549-62.
14. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry, 2011;70(7):663-71.
15. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. Am J Psychiatry, 2010;167(3):261-80.
16. Khandaker GM, Zimbron J, Lewis G, Jones PB. Prenatal maternal infection, neurodevelopment and adult schizophrenia: a systematic review of population-based studies. Psychol Med, 2013;43(2):239-57.
17. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol, 2008;7(12):1091-8.
18. van Erp TG, Hibar DP, Rasmussen JM, Glahn DC, Pearlson GD, Andreassen OA, et al. Subcortical brain volume abnormalities in 2,028 individuals with schizophrenia and 2,540 healthy controls via the ENIGMA consortium. Mol Psychiatry, 2016;21(4):547-53.
19. Pettersson-Yeo W, Allen P, Benetti S, McGuire P, Mechelli A. Dysconnectivity in schizophrenia: where are we now? Neurosci Biobehav Rev, 2011;35(5):1110-24.
20. Insel TR. Rethinking schizophrenia. Nature, 2010;468(7321):187-93.
21. Leucht S, Leucht C, Huhn M, et al. Sixty years of placebo-controlled antipsychotic drug trials in acute schizophrenia: Systematic review, Bayesian meta-analysis, and meta-regression of efficacy predictors. Am J Psychiatry, 2017;174(10):927-942.
22. Kane JM, Agid O, Baldwin ML, et al. Clinical guidance on the identification and management of treatment-resistant schizophrenia. J Clin Psychiatry, 2019;80(2):18com12123.
23. Sullivan PF, Daly MJ, O'Donovan M. Genetic architectures of psychiatric disorders: The emerging picture and its implications. Nat Rev Genet, 2018;19(8):537-551.
24. Correll CU, Schooler NR. Negative symptoms in schizophrenia: A review and clinical guide for recognition, assessment, and treatment. Neuropsychiatr Dis Treat, 2020;16:519-534.
25. Brannan SK, Davidson J, Appelbaum PS, et al. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. N Engl J Med, 2021;384(8):717-726.
26. Koblan KS, Kent J, Hopkins SC, et al. A non–D2-receptor-binding drug for the treatment of schizophrenia. N Engl J Med, 2020;382(16):1497-1506.
27. Patel C, Emond B, Lafeuille MH, et al. Real-world adherence and persistence among Medicaid beneficiaries initiating second-generation long-acting injectable antipsychotics. Curr Med Res Opin, 2020;36(6):973-982.
28. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29,823 patients with schizophrenia. JAMA Psychiatry, 2020;77(7):699-705.
29. Kishimoto T, Hagi K, Kurokawa S, Kane JM, Correll CU. Long-acting injectable versus oral antipsychotics in schizophrenia: a systematic review and meta-analysis of mirror-image studies. J Clin Psychiatry, 2021;82(1):20r13498.
30. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet, 2019;379(9831):2063-2071.
31. Andrade C. Clozapine treatment in schizophrenia: Balance between efficacy and safety. Expert Rev Neurother, 2020;20(1):1-3.
32. Correll CU, Rubio JM, Kane JM. What is the risk-benefit ratio of long-term antipsychotic treatment in people with schizophrenia? World Psychiatry, 2022;21(1):98-109.
33. Buchanan RW, Kreyenbuhl J, Kelly DL, et al. The 2020 Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull, 2020;46(1):8-18.
34. Javitt DC, Carter CS. Cognitive deficits in schizophrenia: Mechanisms and treatment. Neuropsychopharmacology, 2018;43(1):3-16.

35. Arranz MJ, de Leon J. Pharmacogenetics and pharmacogenomics of schizophrenia: A review of last decade of research. Mol Psychiatry, 2020;25(8):3362-3379.
36. Müller N. Inflammation in schizophrenia: Pathogenetic aspects and therapeutic considerations. Schizophr Bull, 2019;45(4):637-645.
37. Sommer IE, Bearden CE, van Dellen E, et al. Early interventions in risk groups for schizophrenia: What are we waiting for? NPJ Schizophr, 2016;2:16003.
38. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: Version III—The final common pathway. Schizophr Bull, 2009;35(3):549-562.
39. Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: A critical review of the pharmacology and clinical effects of current and emerging antipsychotic medications. Mol Psychiatry, 2012;17(12):1206-1227.
40. Kapur S, Seeman P. Does fast dissociation from the dopamine D2 receptor explain the action of atypical antipsychotics? A new hypothesis. Am J Psychiatry, 2001;158(3):360-369.
41. Meltzer HY, Massey BW. The role of serotonin receptors in the action of atypical antipsychotic drugs. Curr Opin Pharmacol, 2011;11(1):59-67.
42. Newman-Tancredi A, Cussac D, Quentric Y, et al. Differential actions of antipsychotics at multiple 5-HT1A receptor-linked signaling pathways: Novel mechanism of antipsychotic properties. Neuropsychopharmacology, 2005;30(2):196-208.
43. Stahl SM. Mechanism of action of novel antipsychotic drugs: A review of recent research. J Clin Psychiatry, 1999;60(10):745-758.
44. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med, 2005;353(12):1209-1223.
45. Zohar J, Stahl S, Moller HJ, et al. Neuroscience-based Nomenclature (NbN) for psychotropic medications: Guidelines for clinicians. Eur Neuropsychopharmacol, 2015;25(12):2318-2325.
46. Delay J, Deniker P. Chlorpromazine and psychotic states. Ann Med Psychol, 1952;110(2):112-117.
47. Meltzer HY. Update on typical and atypical antipsychotic drugs. Annu Rev Med, 2013;64:393-406.
48. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry, 1988;45(9):789-96.
49. Leucht S, Cipriani A, Spineli L, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet, 2013;382(9896):951-62.
50. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole: a novel atypical antipsychotic drug with a unique mechanism of action. Neuropsychopharmacology, 2003;28(8):1400-11.
51. Citrome L. Brexpiprazole: a new dopamine D2 receptor partial agonist for the treatment of schizophrenia and major depressive disorder. Drugs Today (Barc), 2016;52(7):409-24.
52. Majcher MJ, Hoare T, Mishra RK. In situ-gelling starch nanoparticle (SNP)/O-carboxymethyl chitosan (CMCh) nanoparticle network hydrogels for the intranasal delivery of an antipsychotic peptide. Int J Biol Macromol, 2021;168:1-10.
53. Hoare T, Mishra RK. New anti-psychotic nasal spray could ease side effects. Chem Ind News, 2020.
54. Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm, 2008;358(1-2):285-91.
55. Kumar M, Misra A, Babbar AK, Mishra AK, Mishra P, Pathak K. Intranasal nanoemulsion based brain targeting drug delivery system of risperidone. Int J Pharm, 2008;358(1-2):285-91.
56. Pires PC, Santos AO. Nanosystems for brain targeting of antipsychotic drugs: an update. Pharmaceutics, 2023;15(2):678.
57. Illum L. Nasal drug delivery—possibilities, problems and solutions. J Control Release, 2003;87(1-3):187-98.
58. Pardeshi CV, Belgamwar VS. Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. Expert Opin Drug Deliv, 2013;10(7):957-72.
59. Djupesland PG, Messina JC, Mahmoud RA. The nasal approach to delivering treatment for brain diseases: an anatomic, physiologic, and delivery technology overview. Ther Deliv, 2014;5(6):709-33.
60. Kaur P, Garg T, Rath G, Goyal AK. In situ nasal gel drug delivery: a novel approach for brain targeting through the mucosal membrane. Artif Cells Nanomed Biotechnol, 2016;44(4):1167-76.
61. Agrawal M, Saraf S, Saraf S, Antimisiaris SG, Chougule MB, Shoyele SA, et al. Nose-to-brain drug delivery: an update on clinical challenges and progress towards approval of anti-Alzheimer drugs. J Control Release, 2018;281:139-77.

62. Frey WH 2nd. Method for administering neurologic agents to the brain. US Patent US5624898A. 1997 Apr 29.
63. Guastella AJ, Ward PB, Hickie IB, Shahrestani S, Hodge MA, Scott EM, et al. A single dose of oxytocin nasal spray improves higher-order social cognition in schizophrenia. Schizophr Res, 2015;168(3):628-33.
64. Reger MA, Watson GS, Greenlee JE, Baker LD, Cholerton B, Wilkinson CW, et al. Intranasal insulin improves cognition and modulates β-amyloid in early AD. Neurology, 2008;70(6):440-8.
65. Ge Y, Xu X, Cao M, Liu B, Wang Y, Liao P, et al. Nasal drug delivery and nose-to-brain delivery technology development status and trend analysis: based on questionnaire survey and patent analysis. Pharmaceutics, 2024;16(7):929.
66. Zhang J, Zhao Y, Jiang J, et al. The application of cognitive behavioral therapy in patients with schizophrenia: a review. Front Psychiatry, 2023;14:1041947.
67. Kumar S, Sinha P, Raju D, et al. Yoga therapy for schizophrenia. Indian J Psychiatry, 2012;54(3):244-6.
68. Kumar S, Telles S. Yoga and schizophrenia—a comprehensive assessment of neurophysiological correlates. Asian J Psychiatr, 2019;42:1-10.
69. Turkington D, Kingdon D. Cognitive-behavioral therapy for schizophrenia: a review. Focus (Am Psychiatr Publ), 2006;4(2):223-8.
70. Duraiswamy G, Thirthalli J, Nagendra HR, Gangadhar BN. Yoga therapy as an adjunctive treatment in schizophrenia: a randomized, controlled trial. J Altern Complement Med, 2007;13(7):727-32.
71. Vancampfort D, De Hert M, Knapen J, Wampers M, Demunter H, Deckx S, et al. State anxiety, psychological stress and positive well-being responses to yoga and aerobic exercise in people with schizophrenia: a pilot study. Disabil Rehabil, 2011;33(8):684-9.
72. Visceglia E, Lewis S. Yoga therapy as an adjunctive treatment for schizophrenia: a randomized, controlled pilot study. J Altern Complement Med, 2011;17(7):601-7.
73. Vancampfort D, Rosenbaum S, Probst M, Soundy A, Mitchell AJ, De Hert M, et al. Physical activity for people with schizophrenia: a systematic review and meta-analysis. J Clin Psychiatry, 2016;77(9):e1242-50.
74. Cramer H, Lauche R, Klose P, Langhorst J, Dobos GJ. Yoga for schizophrenia: a systematic review and meta-analysis. BMC Psychiatry, 2013;13:32.
75. Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. Br J Psychiatry, 2014;204(1):20-9.

How to cite this article: Singh J, Dushyant, Saini J, Shabnam, Amit, Singla S. Addressing Schizophrenia in The Elderly: Advances and Best Practices in Geriatric Healthcare. Pharma Research Bulletin, 2025;4(2):57-66.