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Review Article

Unveiling Psychosis; Clinical Presentation, Therapeutic Modalities, and Key Signaling Pathways

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ABSTRACT

Individual well-being is greatly influenced by their mental health, affecting their willingness to contribute to society. Mental illnesses might trigger complications that worsen physical health and cause disabilities that may finally lead to death. In the general population, psychosis is a complicated multivariate neurological condition that is most prevalent in childhood, adolescence, and early adulthood. Recent research has highlighted the significance of psychosis across various healthcare disciplines, including its economic costs and service utilization. Schizophrenia, the predominant type of psychosis, impacts approximately 1% of the global population. Nonetheless, psychotic disorders impose a substantial burden on public health. Psychosis encompasses several forms, including numerous neurochemical and molecular pathways. Although schizophrenia lacks specific biological markers, several hypotheses, such as neurodevelopmental and neurochemical theories, have been proposed to elucidate its neuropathology. Such hypotheses may limit the diversity and effectiveness of available drugs for managing psychosis. The primary goals of the management of psychosis include alleviating acute symptoms, enhancing quality of life, and decreasing recurrence rates. This review provides important insights by highlighting key characteristics of psychosis, such as its underlying mechanisms, therapeutic options, and prominent symptoms.

Keywords: *Psychosis; Schizophrenia; Mental illnesses; pathways; treatment; diagnosis.*

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1. Introduction

Psychosis is a chronic neurological disorder associated with psychological symptoms. Such symptoms may result in a disconnection from reality. Thus, it is a disabling disorder affecting patients' quality of life. This appears *via* interfering with their social and mental activities. According to the latest statistics, it affects nearly 1.5% to 3.5% of the population worldwide. In addition, other people may experience at least one psychotic episode during their lives **[1]**. Therefore, psychosis may be considered a mental disorder with disturbance in daily functioning, as well as an inability to communicate with the external world environment **[2]**. Neuropathological evidence indicated the presence of synaptic and dendritic impairments in various brain regions, like the prefrontal cortex, hippocampus, and striatum, among individuals with schizophrenia **[2]**.

1.1. Epidemiology

The disease typically begins after adolescence, generally between the ages of 20 and 35, with a greater occurrence of psychotic symptoms in males. Females may experience a second peak in onset between the ages of 40 and 60. Psychosis affects approximately 0.30% to 0.66% of the population over their lifetime **[3]**, and individuals affected typically have a lifespan that is 12 to 15 years shorter than average, a gap that continues to widen **[4]**. The prevalence of a first psychotic episode is approximately 86 for every 100,000 person-years among people aged 15 to 29, compared to 46 for every 100,000 person-years among people aged 30 to 59. Although the incidence is lower in the older age group, the population at risk in the 30 to 59 age range is twice as large as that in the 15 to 29 age range **[5]**.

2. Methods

2.1. Literature search strategy

A literature search was carried out utilizing electronic databases, including PMC, Google Scholar, and PubMed. The following keywords were used: (“psychosis” OR “psychotic disorders”) AND (“symptoms” OR “clinical features”), (“treatment” OR “management”) AND (“neurobiology” OR “pathophysiology”) AND (“neurotransmitters” OR “brain imaging”). On the basis of titles and abstracts, search results were filtered for relevancy. Comprehensive reviews, meta-analyses, clinical trials, observational studies, and peer-reviewed journal publications were the main focus of the inclusion criteria. Exclusion criteria involved studies that were not in English, had no direct connection to psychosis, or lacked pertinent reviews or source data were disqualified.

3. Main text

3.1. Signs and symptoms

Schizophrenia presents three primary categories of symptoms: positive symptoms like hallucinations (visual, auditory, and olfactory), delusions, illusions, disorganized speech, and catatonic behavior; negative symptoms such as apathy, social isolation, reduced emotional expression, lack of motivation, and inability to experience pleasure (anhedonia); and cognitive symptoms characterized by deficits in learning and memory **[6]**.

Negative symptoms mainly affect goal-directed activity maintenance and decrease emotional feelings and expression. They are termed “Negative” because they occur when the normal function is “absent” **[7]**. They include lack of speech (or speech poverty) and motivation, decreased ability to enjoy things (anhedonia), and social withdrawal. When present, negative symptoms may remain as residual symptoms even after positive symptoms improve **[7]**. By contrast, they may be present for weeks prior to positive symptoms and are called "Prodromal" symptoms.

Positive Symptoms are termed “positive” owing to the presence of more matter than normal. They include hallucinations, thought disorders, perceptual experience, and catatonic behavior. Hallucinations may affect any sense, including auditory, visual, and olfactory. Delusions are false, fixed beliefs regarding the external world that are mainly self-centered **[8]**.

Cognitive symptoms are a group of symptoms affecting the learning and memory capabilities of schizophrenic patients. This occurs due to the inclusion of the hippocampus brain area in schizophrenia pathogenesis **[9]**.

3.2. Different types of psychosis

3.2.1. Schizophrenia

It describes a form of psychosis where

psychotic symptoms persist for approximately six months. However, the duration and severity of symptoms differ between individuals. Disorganized thoughts and behaviors, as well as delusions and hallucinations, are among the main symptoms recognized in schizophrenia **[1]**.

3.2.2. Schizophreniform disorder

This kind of psychosis closely resembles the previous one. The only difference is that these symptoms persist for fewer than 6 months. This condition either resolves entirely or progresses to schizophrenia **[10]**.

3.2.3. Schizoaffective disorder

In this disorder, a person can have both mood disorder symptoms and schizophrenia, either at the same time or alternately **[10]**.

3.2.4. Delusional disorder

Intensely strong and untrue beliefs are expressed. Typically, hallucinations are absent in this form of psychosis. Psychosocial functioning does not commonly vary significantly, nor are there any unusual behaviors **[10]**.

3.2.5. Brief psychotic disorder

This disorder's psychotic symptoms appear suddenly in response to a highly stressful life event. Symptoms can be intense but transient, typically lasting no longer than a month. The patient may or may not recognize his/her behavior **[11]**.

3.2.6. Organic psychosis

Physical ailments, neurological damage or epilepsy, brain tumors, trauma, and infections can cause this form of psychosis **[12]**. To determine or verify the type of psychosis, a comprehensive medical examination should be performed. Brain scanners and electroencephalograms are two of the tests that are used.

3.2.7. Postpartum psychosis

This can occur within six months of giving birth. It is usually associated with severe mood changes. Symptoms include hallucinations (especially auditory hallucinations), delusions, confusion, paranoia, mania, depressive mood, irritability, and insomnia. Early detection of postpartum psychosis symptoms is crucial for promptly initiating treatment and providing the security of the newborn baby **[13]**.

3.2.8. Substance-induced psychosis

Both using and withdrawing from substances like alcohol and drugs such as cocaine, marijuana, LSD, or amphetamines can cause psychotic symptoms. Typically, once the effects of the substances wear off, the symptoms of psychosis generally subside **[14]**.

3.2.9. Psychotic depression

It is a depressive disorder marked by delusional thinking and sensorial-perceptual hallucinations. The delusions typically reflect the patient's depressed mood. The most prominent type of hallucination is auditory hallucination, the content of which is closely connected to the mental state it arises **[15]**.

3.3. Factors affecting psychosis

3.3.1. Genetic Factors

Several studies support the idea of the relationship between psychosis and hereditary genes. Idiopathic psychotic disorder can be inherited through generations. It is believed that psychotic patients' siblings can acquire psychotic symptoms 10-15 times more frequently than the normal population. There are two hypotheses proposed regarding psychosis: the common disease–common allele hypothesis and the common disease–rare allele hypothesis **[16]**.

The common disease–common allele hypothesis postulates that dominant genes with low penetrance may synergistically *via* epistasis, resulting in enhanced potential of psychotic

mood disorder, and schizophrenia **[16]**. The second hypothesis was reported to be associated with recessive genes and de novo mutations that may occur in a small population; otherwise, it is highly profound.

3.3.2. Neurodevelopmental Factors

Exposure to prenatal factors like maternal infections, drug poisoning, and dietary deficiencies, as well as birth complications and postnatal injuries, increases the likelihood of developing psychotic disorders later in life **[17]**. Despite their small effect sizes, these environmental factors are believed to interact with genetic factors to enhance vulnerability to psychotic disorders, cause independent effects, or generate phenocopies of psychotic disorders **[18]**.

3.4. Pathophysiology

Psychosis as a neuropsychiatric disorder is mainly related to neurodevelopmental pathogenesis; however, neurodegeneration pathways may also be implicated. The neurodevelopmental and neurodegenerative hypotheses may be interconnected **[19]**. For instance, as neurotrophic factors are important in both neural survival and central nervous system (CNS) development, reduced neurotrophic factor signaling may result in both altered neural death and CNS development. So, in psychosis, rather than being mutually exclusive, the hypothesis regarding neurodegeneration and altered CNS development may potentially be complementary **(Fig. 1) [19]**.

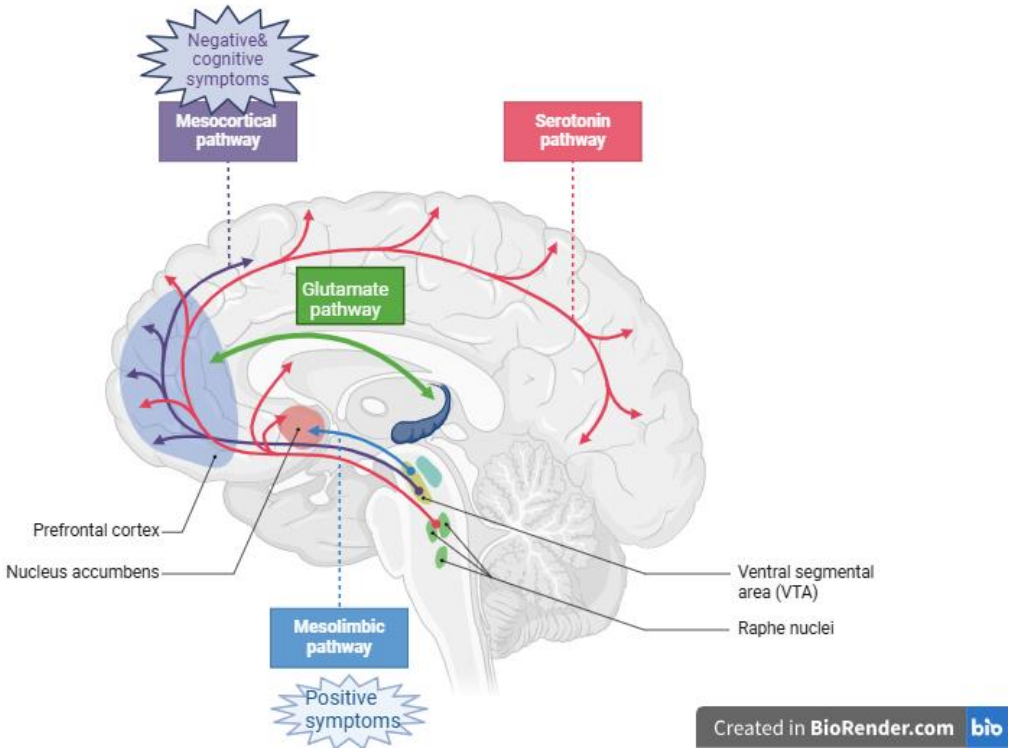

Fig. 1. Pathophysiology of psychosis and the associated symptoms.

3.4.1. Neurotransmitters' imbalance

Brain levels of neurotransmitters have been proven to perform a pivotal function in schizophrenia pathogenesis, leading to the three main symptom classes defined in schizophrenia **[20]**. Previous studies have demonstrated abnormalities in glutamate (Glu), gamma-aminobutyric acid (GABA), serotonin (5-HT), dopamine (DA), and acetylcholine (Ach) levels in the hippocampus, midbrain, corpus striatum, and prefrontal cortex, resulting in the onset of psychotic manifestations **[21]**.

Various forms of induced psychosis have been researched to gain insights into neurotransmitter mechanisms. As an example, both synthetic and natural cannabinoid products containing specific cannabis receptor subtype agonists, specifically those activating cannabinoid-1 receptors, can provoke or heighten the vulnerability to psychosis. Cannabinoid receptors influence molecular processes that regulate dopamine and glutamate transmission at neural synaptic sites **[22, 23]**.

3.4.1.1. Glutamatergic excitotoxicity

Several studies have found downregulated glutamatergic receptors (N-methyl-D-aspartate receptors (NMDAR)) expression in postmortem brains of people with schizophrenia. Excitotoxic injuries in the prefrontal cortex of neonatal rats have been shown to result in an enhanced dopamine-mediated response in the nucleus accumbens during adulthood **[24]**. This reaction resembles the one postulated to take place during the emergence of schizophrenia. In addition, glutamatergic neurons in the medial prefrontal cortex extend to the nucleus accumbens, where they attenuate their impact on glutamate receptors (GluRs) to affect dopamine discharge in this limbic part of the brain **[25]**. Therefore, reduced prefrontal cortical projections to the nucleus accumbens, likely due to cell death, may disinhibit glutamatergic regulation and boost dopamine release in this nucleus. Thus, schizophrenia is always associated with prefrontal cortical glutamate excitotoxicity together with NMDA receptor dysfunction **[26]**.

3.4.1.2. GABAergic dysfunction

Through N-methyl D-aspartate receptors (NMDAR), glutamatergic neurons in the prefrontal cortex activate GABAergic interneurons **[27]**. In the frontal cortex, these GABAergic interneurons suppress pyramidal neurons **[28]**. Several researchers have demonstrated that reduction of cortical inhibitory tone takes place due to NMDAR blockade, thus raising the firing rate of glutamatergic neurons, resulting in excitotoxic death through non-NMDAR at postsynaptic (GABAergic) neurons **[27]**.

3.4.1.3. Dopaminergic overstimulation

Neuroimaging studies supplied greater evidence that higher levels of D2 receptor binding and dopamine neurotransmitter discharge have been observed in the brains of schizophrenic models **[29]**. Dopamine transporter (DAT) reuptake and monoamine oxidase (MAO) metabolism can eliminate the excessive release of dopamine by the disinhibited dopaminergic terminal in the prefrontal cortex in schizophrenia patients; consequently, the substantial increase in dopamine available at cortical synapses is expected to manifest as both tonic and phasic events **[30]**. Thus, activation of this dopamine receptor signalling pathway may also contribute to dendritic structure loss and increased apoptotic susceptibility in cortical neurons along the course of the disease **[31]**.

3.4.1.4. Cholinergic dysfunction

Cognitive abnormalities, such as decreased working memory and attention, are features of schizophrenia. The fact that abnormal ACh signaling could potentially exacerbate

perturbations

has been a central focus of current hypotheses regarding the pathophysiology of schizophrenia **[32]**. Cholinergic activity has been connected to controlling brain circuits involved in attention, short-term memory, and perception, cognitive functions that are impaired in individuals with schizophrenia **[32]**.

Moreover, reduced expression of cholinergic receptors has been reported in the prefrontal cortex and hippocampus of post-mortem brains of schizophrenic individuals **[33]**. ACh activates both mAChRs and nAChRs, which raises the excitability of many different types of neurons at the cellular level, involving pyramidal cells and dendrite-targeting GABAergic interneurons. According to the most recent research, cholinergic modulation in the cortex is thought to increase neurons' sensitivity to extrinsic stimuli and therefore, assist them in focusing attention on sensory information **[32]**.

3.4.2. Mitochondrial dysfunction and oxidative stress

Several reports have shown that oxidative stress may contribute to the pathogenesis of schizophrenia **[34]**. Degraded total glutathione amounts have been observed in the hippocampi and prefrontal cortices of schizophrenic rats. Both raised lipid peroxidation levels and reactive oxygen species (ROS) were found in the striata and prefrontal cortices of rats. Such effects may reflect enhanced oxidative stress and reduced antioxidant defense **[35]**. Oxidative stress was found to induce apoptosis in the brains of schizophrenic patients, leading to mitochondrial dysfunction and programmed cell death **[36]**.

However, oxidative stress has been linked to learning impairments, suggesting that it may play a role in the cognitive deficits observed among schizophrenia patients. This could involve a decline in glutamatergic neurotransmission due to the oxidation of regions that are sensitive to redox changes in the NMDAR, restricting this receptor's activation **[37]**.

3.4.3. Apoptotic signaling

According to research, structural brain alterations such as progressive ventricular volume changes, a decrease in whole brain volume, deficiencies in the temporal lobe, reductions in prefrontal cortical grey matter, and hippocampal volume are always linked to schizophrenia **[38]**. These findings imply that neurodegeneration could take place during the development of schizophrenia **[39]**. Multiple studies have highlighted the involvement of apoptosis in schizophrenia through both intrinsic (mitochondrial-mediated) and extrinsic (death receptor-mediated) pathways **[40]**.

The intrinsic process depends on controlling the stimulation of "caspase" proteins, which are cysteine-dependent aspartate-directed proteases**.** Caspases known as initiator caspases (caspase-8, -9, and -10) facilitate the cleavage and activation of downstream caspases (caspase-3, -6, and -7), with caspase-3 being the effector caspase most frequently linked to apoptosis in the CNS **[41]**. Effector caspases undergo cleavage to become active caspase-3, which then cleaves various distinct structural and functional proteins, such as Bcl-2, Bax, and cytochrome-c **[42]**.

The mitochondrial pathway regulates caspase activity by releasing cytochrome c from mitochondria. Cytochrome c then binds with caspase-9 to make an apoptosome, which triggers procaspase-3 into active caspase-3. This enzyme initiates the breakdown of cellular structure **[43]**. The common downstream effector caspase-3 can then be activated by these initiator caspases. Moreover, caspase-8 can upstreamly activate the mitochondrial pathway by facilitating the release of cytochrome c, which is initiated by Bax by cleaving the Bid protein to generate tBid **[44]**.

The death receptor pathway, commonly referred to as the extrinsic pathway, begins with the binding of certain receptor ligands (such as TNF-α and FasL) to their respective tumor necrosis factor (TNF) receptors. This binding activates caspase-8 and caspase-10 **[45]**. The common downstream effector caspase-3 can then be activated by these initiator caspases. Moreover, caspase-8 can upstreamly activate the mitochondrial pathway by facilitating the release of cytochrome c, which is initiated by Bax by cleaving the Bid protein to generate tBid **[46]**.

In brief, there is evidence that mitochondrial dysfunction is associated with schizophrenia and could potentially heighten the vulnerability to excitotoxic damage. However, it has been shown that GABAergic neurotransmission is reduced in this condition and may be a factor in excitotoxic damage by disinhibiting pyramidal neurons. Alternatively, NMDAR antagonism causes neurodegeneration. Moreover, reduced glutamatergic function may also result in diminished antiapoptotic signaling regulated by Akt, as Akt activity is influenced by glutamatergic receptors **[47]**.

3.5. Pathways implicated in psychosis

3.5.1. GSK-3β/Akt pathway

Glycogen Synthase Kinase-3 (GSK-3) is a type of serine/threonine kinase that participates in the control of cell metabolism, neurogenesis, and neuronal polarization in the central nervous system **[48]**. Furthermore, GSK-3β may promote neurodegeneration through the activation of pro-apoptotic mitochondrial disturbances (the intrinsic apoptotic pathway **[49]**. Unlike many protein kinases, GSK-3β is mainly suppressed by phosphorylation of the serine 9 residue, a process facilitated by protein kinase B (Akt) **[50]**. Therefore, phosphorylation of the serine 9 residue renders GSK-3 non-functional and hence decreases GSK-3β activity.

Protein kinase Akt phosphorylates substrates on particular serine and threonine residues and is engaged in many cellular processes, such as cell stress, metabolism, apoptosis, and regulation of the cell cycle. Akt has a crucial function in controlling the survival and size of neuronal cells. It is believed that it may have an impact on brain processes like working memory, fear conditioning, and long-term potentiation since it modulates synaptic plasticity **[51]**.

The Akt/GSK-3β pathway is a crucial signaling pathway involved in neuronal survival and development **[52]**. Akt is attracted to the surface of neuronal cells by adhering to lipids produced by phosphatidylinositol 3-kinase (PI3K). Upon activation of plasma membrane tyrosine kinases, PI3K produces phosphatidylinositol 3,4,5-trisphosphate (PIP3) that acts as the signaling lipid at the cell surface **[53]**. Subsequently, Akt undergoes activation *via* phosphorylation by intracellular kinases such as PDK1 (3-phosphoinositide-dependent protein kinase 1) and rictor-mTORC2 (mammalian target of rapamycin complex 2) **[51]**.

Moreover, Dopamine could influence Akt-mediated antiapoptotic signaling since D2 receptor stimulation causes this protein's phosphorylation to decrease, whilst D2 receptor inhibition causes it to increase **[54]**. In addition, subcortical dopaminergic overstimulation of D2 receptors declines Akt activation, reducing its antiapoptotic properties **[55]**. Activation of dopamine D2 class receptors (D2–4 receptors) modulates Akt activity. When dopamine binds to the dopamine D2 receptor, it triggers the recruitment of β-arrestin 2 (also known as arrestin 3), a scaffolding protein. This recruitment promotes receptor desensitization and further internalization **[56]**. Within this complex, Akt and the phosphatase PP2A are also recruited. PP2A dephosphorylates and thereby deactivates Akt, leading to enhanced GSK-3

activity. Therefore, dopamine D2 receptor stimulation hinders Akt activity *via* an arrestin-mediated pathway that is independent of G protein signaling **[57]**.

3.5.2. Wnt/β-catenin pathway

Canonical Wnt signaling is a signaling pathway crucial for regulating neurogenesis. This pathway is activated when the Wnt ligand binds to the Frizzled cell-surface receptor, triggering the activation of intracellular Dishevelled proteins. This activation subsequently modulates the levels of beta-catenin within the cell **[58]**.

After the Wnt ligand binds to the Frizzled family receptor, the APC/AXIN/CKI/GSK-3β destruction complex is inhibited. This inhibition stabilizes beta-catenin, allowing it to accumulate and translocate into the nucleus. Inside the nucleus, beta-catenin interacts with T-cell-specific transcription factor/lymphoid enhancer-binding factor (TCF/LEF) family transcription factors, thereby regulating the expression of target genes involved in neuronal development. Without Wnt ligand binding, cytoplasmic beta-catenin is phosphorylated by the APC/AXIN/CKI/GSK-3beta complex. Phosphorylated beta-catenin is subsequently ubiquitinated and degraded by proteosomes [59]**.** This detailed regulation suggests that the Wnt signaling pathway could have a significant function in the pathogenesis of schizophrenia **[58]**.

In brief, in the absence of Wnt ligand binding, a complex forms inside the cell involving glycogen synthase kinase-3 β (GSK-3β), Axin, adenomatous polyposis coli (APC), and casein kinase 1α (CK1α). This complex phosphorylates β-catenin, marking it for degradation by the proteasome, which minimizes the amount of β-catenin in the cytoplasm[60]. On the other hand, when Wnt ligands bind to their receptor complex composed of a Frizzled family member and low-density lipoprotein 5/6 (Lrp5/6), APC and Disheveled (Dvl) are recruited to the cell membrane. This recruitment causes the destruction complex to dissociate, leading to decreased phosphorylation of β-catenin. Consequently, β-catenin accumulates and stabilizes in the cytoplasm, allowing it to enter the nucleus. Inside the nucleus, β-catenin binds to co-factors to activate T-cell factor/lymphoid enhancing factor (TCF/LEF)-mediated gene transcription. This regulatory mechanism underscores the leading role of the Wnt signaling pathway in influencing cellular processes, including those potentially relevant to conditions like schizophrenia **[61]**.

3.5.3. TLR4/NLRP3 pathway

Psychotic disorders, like schizophrenia, can be induced by multiple risk factors, including variations in genes and alterations in gut permeability, which may increase the translocation of gram-negative bacteria coupled with a deficiency in innate immune response **[62]**. First-episode schizophrenia is frequently associated with moderate cytokine storm, stimulation of M1 macrophage, T helper (Th)-1 and Th-2 phenotypes, which indicates a viral or bacterial infection **[63]**.

The innate immune system recognizes foreign molecules and then activates downstream signaling processes in which Receptors and sensors on the cell surface or intracellular vesicles, such as Toll-like receptors (TLRs), and in the cytosol, such as retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) and nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), trigger the proper immune response **[64]**. Toll-like receptors (TLRs) consist of a family of TLRs (TLR1-TLR13) that distinguish various types of molecules, including glycans, nucleic acids, proteins, lipids, and lipoproteins **[65]**.

The NLR family pyrin domain containing 3 (NLRP3) could recognize different exogenous and endogenous stimuli and assemble the NLRP3 inflammasome, a multiprotein complex that includes inflammatory caspases, a sensor protein, and occasionally an adapter protein. upon inflammasome activation, canonical caspase-1 (cas1), noncanonical caspase-11 (or the human equivalents of caspase-4 and caspase-5), or caspase-8 triggers the production of IL-1β and IL-18 causes apoptosis and pyroptotic cell death **[66]**.

TLRs and NLRs crosstalk was found to play a vital role during CNS infection, injury, and neurodegeneration **[67]**. This positive correlation between the TLR genes and the components involved in the inflammasome pathway illustrates that NLRP3 acts in a synergistic way with TLR2/TLR4 and TLR3 to regulate inflammatory reactions to bacterial and viral infections, respectively **[68]**. The stimulation of TLRs results in the NLRP3 and Cas1 activation and this results in the stimulation of IL-1β and IL-18. The collaborative function of these molecules may result in pyroptosis, which contributes to schizophrenia pathogenesis **[69]**. Stimulation of TLRs and inflammasomes in the brain triggers microglial induction and enhances neuroinflammation present in the pathophysiology of schizophrenia **[70]**.

Patients with schizophrenia exhibit abnormal expression of TLR molecules and core components of the inflammasome in both peripheral blood and postmortem brain samples. This includes the altered activity of innate immune cells and enhanced gene expression of CASP1, NLRP3, PYCARD, and IL1β. These findings support the presence of peripheral inflammation and neuroinflammation energized by TLR and inflammasome pathways, which contribute to cell death and neurodegeneration **[71]**.

3.6. Diagnosis of psychosis

Diagnosis mainly depends on the patient's family history, behavior, and mental examinations. Diagnostic tests such as neuroimaging and electroencephalographic (EEG) are only reserved for patients with an initial psychotic episode or with symptoms and neurodegenerative disorder comorbidity.

3.6.1. Neuroimaging

Neuroimaging could not be used solely for diagnosis owing to its low sensitivity to differentiate between psychosis and other mental illnesses. Psychotic neuroimaging is performed mainly using Positron-Emission Tomography (PET) and Magnetic Resonance Imaging (MRI). Patients with bipolar disorder with psychosis, schizoaffective disorder, or schizophrenia benefit from them. Neuroimaging may show reduced cortical thickness or focal decline in the temporal, frontal, and parietal lobes **[72]**. PET neuroimaging revealed enhanced synaptic dopamine in the ventral striatum but reduced amounts in the prefrontal cortex **[73]**. In addition, MRI shows augmented glutamate amounts in the prefrontal and temporal brain sites **[74]**.

3.6.2. Neurophysiological Test

When psychotic symptoms first appear in patients with a seizure disorder, a causative medical issue, neurodegenerative disease, or substance abuse, an EG assessment may be performed. Specialized brain potentials, elicited potentials, such as those resulting from a range of motor, sensory, and cognitive events ("event-related potentials"), have been discovered to be aberrant in individuals suffering from psychotic disorders. These tests identify variations between groups of individuals who are affected and those who are not, and they also shed light on the aberrant physiology of these disorders. However, they lack the sensitivity and specificity required by clinical usage **[75]**.

3.6.3. Serologic Tests

Serologic testing for syphilis is suggested when assessing a first episode of psychosis. However, the possibility of tertiary syphilis damaging the brain, sometimes known as "general paresis of the insane," is rare in developed nations. Furthermore, immunological problems should be considered when the sudden onset of psychotic symptoms occurs at an age beyond the normal range for idiopathic psychotic disorders, or when it is coupled with a systemic viral infection. Detecting IgG antibodies against the NR1 subunit of NMDA receptors in cerebrospinal fluid or blood is frequently necessary for the diagnosis of these conditions **[76]**.

3.7. Treatment options

3.7.1. Non-pharmacologic therapy

3.7.1.1. Psychosocial Approaches

Cognitive and behavioral rehabilitation have been used to treat idiopathic psychotic disorders, most notably schizophrenia **[77]**. One of the most extensively researched approaches is social skills training, where individuals learn appropriate behaviors and communication techniques, as well as essential life skills that could have been affected by psychotic disorders once acute symptoms have subsided. Family psychoeducation is a strong empirical method that involves educating family members to assist in the patient's recovery process **(Fig. 2) [78]**.

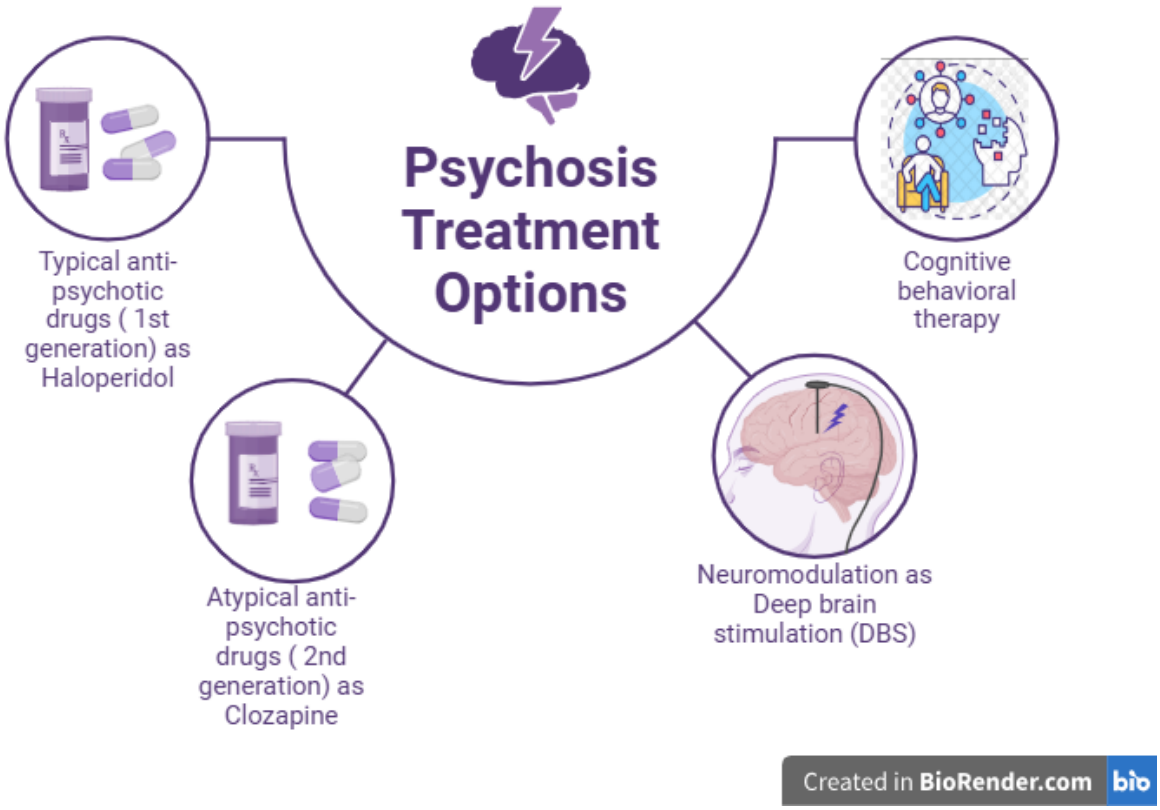

Fig. 2. Treatment options for psychosis.

Cognitive behavioral therapy (CBT), which was initially established to treat mood and anxiety disorders, may also be beneficial for psychotic symptoms. Cognitive restructuring

(i.e., encouraging patients to modify their beliefs about their hallucinations and delusions), behavioral exposure to stimulating psychotic symptoms to promote reality testing, self-monitoring, and graded coping skills are specific CBT approaches used in the management of patients with schizophrenia. CBT can also assist patients with schizophrenia in decreasing the distress resulting from hallucinations or delusional beliefs **[76]**.

3.7.1.2. Neuromodulation

Electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), transcranial direct-current stimulation (tDCS), and deep-brain stimulation (DBS) are all brain-stimulation techniques that have been utilized to treat psychotic symptoms in specific disorders **[79]**. ECT is an effective technique for mood disorders and catatonia with psychotic symptoms. It is used in patients with schizophrenia or schizoaffective disorders when antipsychotic medications are ineffective **[80]**. Controlling psychotic auditory or verbal hallucinations is one promising application of neuromodulation. TMS was applied to the left temporal lobe part that overlies the auditory cortex in the initial studies **[81]**.

Recently, tDCS applied over the auditory cortex part has resulted in a decrease in hallucinations as well as permanent negative symptoms of schizophrenia as apathy and social withdrawal **[82]**. When all other treatments have failed, DBS, the most invasive of the neuromodulation techniques, has been utilized for the treatment of psychotic states. The procedure involves the surgical implantation of an electrode into specific regions of the brain, which is then used to deliver high-frequency electrical pulses for therapeutic purposes. Currently, the FDA has approved DBS for the management of Parkinson's disease and refractory obsessive-compulsive disorder **[83]**.

3.7.2. Pharmacologic therapy

Several treatment options for schizophrenia have been introduced, including first-generation dopamine antagonists (i.e., haloperidol) with inadequate ability to manage extrapyramidal side effects in addition to negative and cognitive problems. Second-generation selective dopamine antagonists (i.e., clozapine) have also been used more effectively for negative and cognitive symptoms with fewer extrapyramidal side effects **[84]**. However, they may cause weight gain, glucose and lipid metabolism disturbances, and metabolic abnormalities **[85]**.

The main classes evolved for schizophrenia treatment may be classified according to Mailman and Murthy (2010) as follows: First generation (dopamine antagonists) as chlorpromazine, pimozide, haloperidol, and fluphenazine. Second generation (dopamine-serotonin antagonists) such as risperidone, paliperidone, clozapine, olanzapine, ziprasidone, quetiapine, and asenapine. Third generation (partial dopamine-selective antagonists) including aripiprazole, brexpiprazole, and cariprazine **[86]**.

While the first generation is primarily dopamine D2 antagonists, the second and third generations act at other receptor sites such as dopamine D1, D2, D3, and D4, adrenergic alpha1 and alpha2, serotonin 5HT2A and 5HT2C, muscarinic, and histamine receptors. Third-generation drugs are regarded as functionally selective/partial D2 agonists (“dopamine stabilizers”) with potential actions on 5-HT1A and 5-HT2A sites **[87]**.

A chief problem with the potent D2 antagonists, i.e., first-generation medications (haloperidol and fluphenazine), is that their effectiveness in addressing the negative and cognitive aspects of the disease is limited, and they pose a risk of causing extrapyramidal

symptoms. Likewise, medications targeting other receptor sites, such as dopamine D1, D2, D3, and D4 receptors, alpha1 and alpha2 adrenergic receptors, 5HT2A and 5HT2C receptors, histamine receptors, and muscarinic receptors, are related to concerns about gaining weight and the risk of metabolic syndrome **[88]**.

3.7.1. First-generation antipsychotics

3.7.1.1. Haloperidol

Being first generation (typical) antipsychotic, haloperidol is not selective for the D2 receptor. It also inhibits noradrenergic, cholinergic, and histaminergic transmission. The inhibition of these receptors is linked to a variety of adverse drug reactions **[89]**. It induces its effect on positive symptoms of psychosis, such as delusions and hallucinations **[90, 91]**.

Haloperidol exerts its anti-psychotic action by inhibiting dopamine D2 receptors in the brain. The maximum effect of the drug is attained when it blocks 72% of dopamine receptors. Additionally, Haloperidol is available in different forms, with the oral route being the most common one. It is offered in tablet and oral concentrate forms for oral administration, as well as in a nasal spray formulation. Haloperidol lactate is present in the form of a short-acting solution for intramuscular and intravenous use **[92]**. Haloperidol decanoate is provided as a long-acting intramuscular preparation**.** Here, both oral and intramuscular formulations are suitable. For moderate symptoms, the suggested dosage lies between 0.5 to 2 mg orally 2 to 3 times daily. In resistant cases, doses of up to 30 mg per day may be essential. An intramuscular injection every 4 to 8 hours at a dose of 2 to 5 mg can be used to rapidly alleviate and control acute agitation. The highest intramuscular dosage is 20 mg per day **[92]**.

Haloperidol use in pregnant women has not been a focus of any well-controlled research. However, there are numerous case reports of malformations of limbs in newborns whose mothers used haloperidol, but causal connections and relationships were not sufficiently proven in these cases. Because these observations do not eliminate the possibility of fetal anomalies associated with haloperidol, this medication ought to be used only when its benefits exceed any possible risks to the fetus **[93]**.

Haloperidol and other typical antipsychotic drugs inhibit the dopamine pathway in the brain, which explains why they are associated with extrapyramidal symptoms **[94]**. These symptoms include acute dystonia, which can occur within hours to days of starting treatment and can show up as oculogyric crises, rigidity, or muscular spasms. Akathisia, another extrapyramidal symptom, typically develops within days to months of haloperidol use and is attributed to intense restlessness **[92]**. Lastly, neuroleptic malignant syndrome is a rare but serious condition that can occur after administration of haloperidol. It occurs as high-grade fever and muscle rigidity. Finally, tardive dyskinesia, which develops after years of haloperidol administration, presents as chorea, especially orofacial region **[92]**.

3.7.2. Second generation

3.7.2.1. Clozapine

The atypical antipsychotics, especially clozapine, are the most widely prescribed class of drugs used to treat schizophrenia. However, they may alter other receptor sites, resulting in weight gain and metabolic abnormalities, including hyperglycemia, hyperlipidemia, and agranulocytosis. The risk of agranulocytosis has restricted clozapine use **[95]**. Clozapine, on the other hand, has been linked to critical side effects such as seizures (in about 4% of patients), myocarditis (in 1%), and agranulocytosis (in 0.8%), and is thus reserved primarily for the

management of refractory psychotic symptoms or resistant schizophrenia **[95]**.

Some of the mechanisms believed to contribute to these side effects include increased appetite and overeating, potentially influenced by antagonism of histamine H1 and serotonin 5HT2C receptors in the hypothalamus. Additionally, changes in hypothalamic fatty acid metabolism and neuropeptide expression are thought to play a role **[96]**. Others have suggested that antipsychotics induce hepatic glucose production by suppressing insulin secretion from β-cells and reducing hepatic insulin sensitivity **[97]**. Moreover, clozapine has been found to stimulate lipogenesis in cultured cells by activating sterol regulatory element-binding proteins (SREBPs) and their downstream target genes related to fatty acid and cholesterol synthesis **[98]**.

Furthermore, administration of acute clozapine into rats appears to initially cause in vivo activation of SREBP target genes in the liver, resulting in a substantial hepatic buildup of triacylglycerols, phospholipids, and cholesterol as well as several subsequent lipogenic, lipid oxidation, and lipolytic transcriptional responses. Several clinical studies have demonstrated that clozapine treatment is linked with a significant increase in triacylglycerol serum concentrations **[99]**.

3.7.3. Benzodiazepines

Benzodiazepines are a class of psychoactive drugs that are known for their sedative effects and have also been used extensively to achieve rapid tranquillization for the management of agitation **[100]**.

Its mechanism of action is intrinsically linked to its capacity to augment the binding affinity of gamma-aminobutyric acid (GABA) for its GABA-A receptors, which act as ligand-gated chloride channels. Benzodiazepines, such as lorazepam, are the preferred medications for calming extremely agitated individuals **[101]**. Lorazepam especially has a more consistent onset and duration of effect. The IM route typically gets utilized in situations requiring rapid tranquillization. A standard dosage is 2-4 mg, with an onset of action lasting approximately 15 minutes and a total duration of 8-12 h **[102]**.

3.7.4. Drug-Resistant Schizophrenia

Treatment-resistant schizophrenia (TRS), also known as drug-resistant schizophrenia, is characterized by a poor response to at least two separate antipsychotic trials conducted at appropriate dosages and times. Specialized methods are needed to manage TRS, such as the following **[103]**:

- Clozapine Therapy (Gold Standard for TRS)[104]
- Long-acting injectable Antipsychotics (LAIs) such as Risperidone, Aripiprazole, and Olanzapine LAI.
- Combination Therapy (Antipsychotics + Adjunctive Medications such as mood stabilizers (lithium, and valproate), antidepressants, or NMDA modulators (glycine, and D-serine)).
- Moreover, several studies have examined the use of adjunct benzodiazepines in treatment-resistant schizophrenia. Benzodiazepines may be useful in the treatment of anxiety and irritability of this disorder; however, concomitant therapy of clozapine with a benzodiazepine should be closely monitored [105].
- Non-pharmacologic therapies could be considered.

3.7.4. Drugs in Clinical Trials

There is a constant argument regarding

whether drugs designed to target a single molecular target (referred to as "magic bullets") or those targeting multiple molecular targets (referred to as "magic shotguns") will result in the development of more recent and powerful remedies for schizophrenia **[106]**.

While all presently available antipsychotic drugs act on dopamine D2 receptors, there is increasing interest in clinical trials exploring agents that directly or indirectly affect the glutamate system, particularly for their potential to enhance cognitive and negative symptoms in schizophrenia. These agents, including glycine agonists, glycine transporter 1 inhibitors, and metabotropic glutamate receptor agonists, are at various stages of development. These agents have been investigated for use alone or in combination with antipsychotics. Recent clinical trials showed the following findings:

a) Bitopertin, a non-competitive GlyT1 inhibitor that promotes NMDA receptor function, did not demonstrate efficacy in improving negative symptoms when used alongside antipsychotics **[107]**.

b) Acetylcholinesterase inhibitors (e.g., galanthamine), partial muscarinic agonists (e.g., xanomeline), and nicotinic receptor agonists have been studied to enhance cognition and sensory gating in schizophrenia **[108]**.

c) Vabicaserin (SCA-136): an agonist of the 5-HT2C receptor, has shown potential therapeutic benefits in various psychiatric disorders established on preclinical animal models[109].

d) Ondansetron, a 5-HT3 receptor antagonist approved for treating nausea and vomiting due to chemotherapy, is currently undergoing Phase III trials to assess its efficacy combined with antipsychotics across major symptom domains **[110]**.

4. Schizophrenia in Pregnancy and Lactation

The management of schizophrenia in the context of gestation requires a meticulous balance between the well-being of the mother and the safety of the fetus. Treatment with antipsychotic medications during pregnancy should only be reserved for severe psychological conditions that are otherwise unmanageable **[111]**. The prescribed doses should be divided into many doses throughout the day and adjusted based on plasma levels and changes in drug metabolism during pregnancy. Adequate medical examinations and follow-ups must be performed regularly. Atypical (second-generation) antipsychotics are typically recommended owing to their superior safety profiles and decreased likelihood of extrapyramidal adverse effects **[112]**. Considering clozapine can cause seizures and agranulocytosis, it should only be used when needed **[113]**. Valproate and carbamazepine are examples of mood stabilizers that should be avoided in pregnant woman in light of their teratogenic risks (e.g., neural tube abnormalities) **[114]**. Decisions regarding breastfeeding must consider the advantages linked to maternal-infant attachment and the possible risks of pharmacological exposure *via* breast milk. Notably, olanzapine and quetiapine are frequently preferred as they have lower concentrations in breast milk. Risperidone and aripiprazole can be used but necessitate close infant monitoring **[105]**.

Conclusion

Psychosis is a complex condition that has captured the interest of researchers, clinicians, and members of the general public for decades. This review has thoroughly investigated the multifaceted features of psychosis, clarifying its molecular basis, therapeutic choices, and clinical manifestations. A wide range of symptoms that profoundly affect cognitive and emotional functioning can be suggestive of psychosis.

These include paranoia, weakened insight, and auditory hallucinations. To differentiate psychosis from other psychiatric and medical illnesses, a differential diagnosis is necessary. This process calls for a comprehensive clinical evaluation and frequent, long-term observation. Exploring multiple crucial pathways is essential to comprehend the physiological basis of psychosis and its treatment options. Neurotransmitter system dysregulation, specifically involving glutamate and dopamine, structural and functional brain abnormalities, and the involvement of neuroimmune interactions and inflammatory processes in psychosis can affect the beginning and course of the illness.

Future Implications

Future research should focus on clarifying the exact mechanisms underlying psychosis to enhance the precision of diagnosis and effectiveness of treatment. Finding early signs and creating targeted treatments have been rendered possible by advancements in neuroimaging, genetics, and biomarker research. Furthermore, studies investigating the integration of personalized medicine approaches in the management of psychosis and optimizing treatment regimens to achieve an optimal balance between efficacy and tolerability are needed.

Declarations

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Not applicable

Consent to publish

Not applicable

Availability of data and materials

Data will be made available on reasonable request.

Competing interests

The authors declare that no competing interests exist.

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Author's Contribution

A.H.A.: Literature review, Supervision, Data collection, Writing, First draft. N.S., N.M., N.A.A., N.A., N.M., N.T., N.S., M.S., N.E.: Data collection, Literature review, Investigation, Writing, First draft. M.Y.G.: Conceptualization, Literature review, Writing - Review & Editing, Supervision. All authors approved the final version of the manuscript.

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