STM JOURNALS

Research & Reviews: A Journal of
Life Sciences

https://journals.stmjournals.com/rrjols/

ISSN: 2249-8656 (Online)
ISSN: 2348-9545 (Print)
Volume 14, Issue 1, 2024
January–April
DOI (Journal): 10.37591/RRJoLS

Research RRJoLS

Application of Drug Delivery Using Nanotechnology to Cure Mental Disorders (Schizophrenia)

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Abstract

Nanotechnology involves the manipulation of the count at an atomic scale to create novel systems, materials, and devices. This groundbreaking era holds substantial potential for scientific development across various domain names, which includes manufacturing, patron items, electricity, substances, and remedies. In current times, the sphere of prescribed drugs has witnessed a brilliant surge in the usage of nanotechnology for the improvement of revolutionary medications. Schizophrenia, a neuropsychiatric disorder affecting the central worried gadget, outcomes in delusions, and social disengagement, in addition to visual and auditory hallucinations. The situation usually arises from imbalances in key neurotransmitters like dopamine and serotonin. Genetic factors, lifestyle changes, and environmental influences also play a role in the improvement of schizophrenia. To manipulate the signs and symptoms, abnormal antipsychotic medications which include NDMA inhibitors and dopamine receptor D1-D2 antagonists are normally prescribed. Olanzapine, haloperidol, and clozapine are the various maximum widely used antipsychotics, being critical in counteracting the effects of different neurotransmitters and addressing symptomatology. However, the complex and multifaceted nature of schizophrenia makes it a tough infection to diagnose and manipulate. Millions of individuals are impacted by neuropsychiatric disorders, which are one of the primary causes of disability. Various medications are used to treat it, but no proven cure has yet been discovered. Drug distribution to target cells in the brain tissues is considerably complicated by the blood-brain barrier. Using nanocontainer systems is one way of addressing issues. Nanotechnology in medicine is ambitious to utilize tiny carriers to enhance the effectiveness of low-weight molecular therapeutics. Our findings suggest that some nanoparticles such as liposomes, PLA, etc. may play a consequential role in the diagnosis and treatment of schizophrenia with resourceful and impactful research further in this vast domain.

Keywords: Nanotechnology, drug delivery, mental disorders, schizophrenia, dopamine, serotonin

INTRODUCTION

Delusions, social disengagement, and auditory and visual hallucinations are hallmarks of schizophrenia, a neuropsychiatric illness that primarily affects the central nervous system. Currently, available therapeutic strategies involve systemic administration of drugs instead of enterally to alter neurotransmitter levels in the brain and to relieve symptoms. The blood-brain barrier (BBB) is the biggest obstacle in CNS drug delivery. These obstacles may be overcome by nanotherapeutic techniques, which would enhance medication delivery, safety, and efficacy. Drugs can be more effectively delivered to the brain to improve the lifestyle quality of patients suffering from schizophrenia. The main barriers to CNS drug delivery are covered in this review, along with the significance of available nanotherapeutic and therapeutic approaches and strategies [1]. Delusions decreased cognitive function, hallucinations, and

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Received Date: March 28, 2024
Accepted Date: April 29, 2024
Published Date: May 02, 2024

Citation: Uday Kapur, Sankalp Tikku, Chakresh Kumar Jain. Application of Drug Delivery Using Nanotechnology to Cure Mental Disorders (Schizophrenia). Research & Reviews: A Journal of Life Sciences. 2024; 14(1): 51–65p.

abnormal speech or behavior are just a few of the many symptoms associated with schizophrenia, which is a chronic and complicated mental health condition. Numerous individuals and their families find the disease a disabling disorder owing to its early onset and chronic course [2]. 24 million people (approx.) That is, 1 in 300 people worldwide suffer from schizophrenia, as per WHO [3]. Positive symptoms of schizophrenia may be linked to elevated dopamine activity in some brain regions. Meanwhile, cognitive and negative symptoms may be affected by decreased dopamine activity in other brain regions. One of the first medications used to treat schizophrenia was reserpine, which is an antihypertensive drug. This medication works by decreasing synaptic dopamine release and helped treat schizophrenia before chlorpromazine's antipsychotic qualities were discovered [4].

SCHIZOPHRENIA

Symptoms and Causes

The levels of dopamine and serotonin, two essential neurotransmitters, are altered in the brain as the disease progresses. A very small percentage of schizophrenia cases are due to hereditary causes, such as deletions of chromosome 22 [5]. Additional factors contributing to illness include changes in lifestyle and the environment. The signs and symptoms of the illness, which include hallucinations, delusions, cognitive impairment, and disordered thinking, are associated with a significant risk of suicidal behavior. The disease typically manifests between the ages of 20 and 35 years, with males receiving a diagnosis more often than females [6].

Risk Factors

Epidemiological studies have explored the role of the environment in the development of schizophrenia by identifying various risk factors. These include obstetric problems, winter or spring birth, behavioral abnormalities, delayed speech, and motor development, exposure to traumatic life events, and drug use in a cohort of 100 patients (45 females and 55 males) [7].

Time, location, and significance of birth seasons. Individuals born at either the end of winter or the start of spring are frequently affected by schizophrenia. Viral infections during pregnancy have the potential to alter the brain and cause schizophrenia. The development of schizophrenia seems to be strongly affected by difficulties during pregnancy and childbirth [8]. It has been reported that flu during pregnancy is a recognized risk factor for cognitive developmental problems in children, including schizophrenia [9]. Drug misuse is one of the most prevalent adverse effects of psychosis. Cocaine, opiates, alcohol, tobacco, cannabis, methamphetamine, phencyclidine, and LSD are examples of these drugs. Many individuals with schizophrenia are dependent on smoking [10].

HISTORY

History of Drug Discovery in Schizophrenia

The first antipsychotic medication for schizophrenia was reserpine, which decreased synaptic dopamine release [11]. Since its introduction in 1952, approximately 50 more antipsychotic medications have been developed, except for aripiprazole, which acts as a dopamine D2 receptor antagonist to produce therapeutic effects [12]. Clozapine is the only drug approved for the treatment of patients resistant to D2 antagonist therapy [13]. However, other new-generation medications have not been able to duplicate the basis for the superiority of clozapine, which is unknown [14].

Syphilitic insanities and brain-behavior connections are thought to explain variations in symptom patterns between individuals. However, research from the early 1970s cast doubt on this idea, showing nearly orthogonal links across symptom complexes and no predictive connections between symptom categories [15]. Additionally, there was a significant temporal relationship between pathologic manifestations within a domain, such as past social functioning projected future functioning and bad symptoms predicted future unfavorable symptoms [16, 17].

The three-part theory of schizophrenia has been reinterpreted with three separate domains: positive psychotic symptoms, negative symptoms, and interpersonal relationship pathology. Clinical evaluations over the past 20 years have not been able to differentiate between basic and secondary ones [18]. The domains of the pathology paradigm identify several features of schizophrenia as pathology targets for further study and therapy development. If successful in assisting the discovery of therapies, further domains will be established.

NANOTECHNOLOGY

Nanotechnology studies materials and technologies with the smallest functional organization of a nanometer or billionth of a meter. It has applications in medicine, including pharmacokinetic studies, fluorescent biological labels, drug delivery, protein identification, tissue engineering, and tumor detection [19, 20].

PATHWAYS

Dopamine Hypothesis

One of the most widely accepted theories among contemporary researchers studying schizophrenia is the dopamine (DA) hypothesis. This idea is related to the main etiology of schizophrenia. Progressive psychotic episodes are caused by dopamine hypoactivity in the frontotemporal region and hyperactivity in the nucleus accumbens [21]. In a rat model, activation of the ventral hippocampus caused an increase in dopamine levels [21]. Current theories on dopamine indicate that schizophrenia symptoms are caused by the hypoactivity of dopamine in the prefrontal and mesolimbic brain regions [22]. Dopamine dysregulation affects the prefrontal cortex and amygdala in patients with schizophrenia, affecting cognitive and emotional processing. Antipsychotics, such as dopamine D2 receptor antagonists, are used to treat psychotic symptoms. Investigating the dopamine hypothesis is crucial for determining whether other neurotransmitters are involved in schizophrenia (Figure 1).

Glutamate Theory

The brain contains glutamate, an excitatory neurotransmitter. NMDARs mediate glutamate neurotransmission that links the limbic system, thalamus, and cortical regions of the brain in schizophrenia. Reduced levels of glutamate in the cerebral fluid of individuals with schizophrenia are associated with this disorder [23]. Patients on ketamine and phencyclidine experience psychotic episodes because they are N-methyl-D-aspartate receptor antagonists. Conversely, those utilizing NMDAR agonists demonstrate a required therapeutic response [24]. Glutamate neurotransmission drugs are crucial in schizophrenia because of their role in negative psychotic symptoms and intellectual impairment. N-methyl-D-aspartate receptor agonists and dopamine antagonists are effective substrates, whereas glycinergic medications such as cycloserine and serine are used as indirect agents [25]. Furthermore, glycine transport inhibitors such as bitopertin have also been well-researched [26]. In preclinical research, these substances have been shown to function as co-agonists at NMDAR sites, increasing the bioavailability of glycine. These drugs reduce the unpleasant symptoms associated with schizophrenia, which has limited advantages (Figure 1).

Serotoninergic Hypothesis

Serotonin, also known as 5-HT, serves as a neurotransmitter that is being studied in connection with the pathogenesis of schizophrenia, together with dopamine. It has been predicted that glutamate neurotransmission is increased in the cerebral cortex and locus coeruleus areas of the brain by phenethylamine (like mescaline) and indoleamine (like LSD) activity mediated via serotonin receptors [27]. Researchers should consider risperidone and clozapine as potentially superior therapeutic targets because of their dopamine-serotonin antagonistic actions. Although serotonin receptors are promising targets for treating schizophrenia, there is still a lack of evidence to support the involvement of serotonin abnormalities in the disease (Figure 1).

Apart from clozapine, all second-generation antipsychotics are ineffective in treating schizophrenia and are mainly useful in managing extrapyramidal side effects. Serotonin reuptake inhibitors, 5-HT2C agonists and antagonists, 5-HT3 and 5-HT6 antagonists, 5-HT1A receptor agonists, and other therapeutic strategies are being researched.[28]. Dopamine antagonists and their medications are being studied in isolation and combination. 5-HT partial agonists and 5-HT2A/D2 antagonists have been commercialized, in addition to further studies. Ondansetron, a 5-HT3 receptor antagonist, has been used because of its potential anti-inflammatory properties, which reduce both the positive and negative symptoms of schizophrenia [29]. In a phase III clinical trial, ondansetron was utilized as an adjuvant drug to assess any potential adverse effects of the illness. Lurasidone, with its 5-HT7 antagonistic activity, was recently released as an antipsychotic medication to help with psychotic mood swings [30].

Cholinergic Hypothesis

Smoking is a poorly recognized cause of schizophrenia and affects most individuals [31]. The severity of illness increases in direct proportion to the smoking rate. According to the patient's statements, smoking helps them cope with bad feelings and counteracts adverse drug effects. These results provide insight into patients' efforts to decrease nicotinic-cholinergic receptor deficiency [32]. Patients with schizophrenia have impaired sensory function [33]. Smoking causes the nicotinic receptor to become desensitized, which attenuates impaired auditory function linked to the α-7 gene of the nicotinic receptor [34]. 28 Consequently, cholinergic drugs such as α-7 nicotinic receptor agonists improve the effectiveness of treatment by reducing the symptoms associated with schizophrenia. A clear focus in schizophrenia is the agonist, which is mediated by nicotinic-cholinergic receptors.

The pathophysiology of schizophrenia involves cholinergic neurotransmission, making it the focus of extensive research. In the early stages of development, several agents, including GTS-21, AQW051, and the α-7 nicotinic receptor agonist EVP-6124, are currently undergoing phase III trials [35]. These medications are intended to treat cognitive impairment linked to schizophrenia; however, the pharmacokinetic profile and unfavorable effects pose a challenge to the development of a successful cholinergic medication (Figure 1).

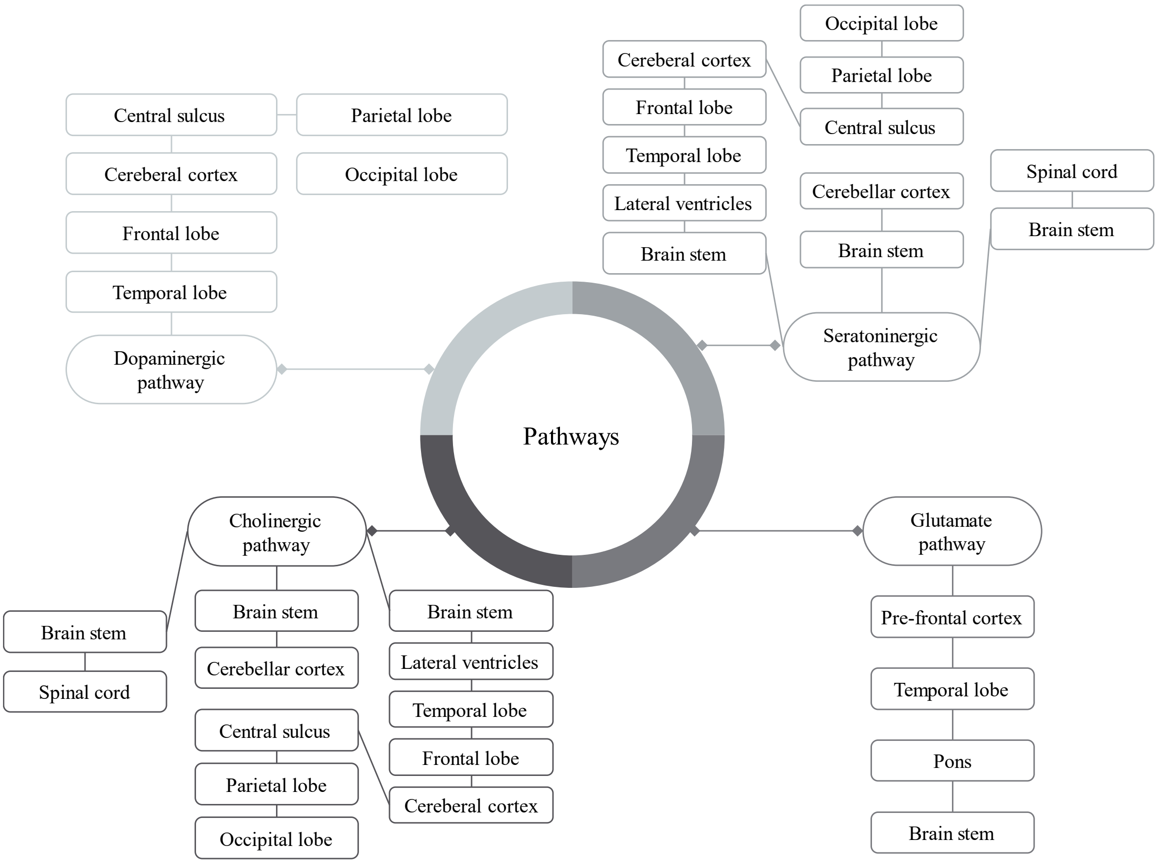

Figure 1. Key pathways involved in schizophrenia.

Inflammation

Other scientific topics related to schizophrenia include inflammation and oxidative stress]. Schizophrenia is associated with altered expression of complementary proteins that are involved in the activation of innate immunity [36]. The synaptic pruning process may be accelerated by these complementary proteins using microglia to disrupt the synapses [37].

Neurotransmitters such as inflammatory cytokines are affected by inflammation, and the pathophysiology of schizophrenia is partially attributed to the concentration of these neurotransmitters in particular brain regions. An illustration of the inflammatory model suggests that a fetus's susceptibility to schizophrenia increases during pregnancy due to increased stimulation of inflammatory markers [38]. Gluten sensitivity is described by another immune model, that is, people with sensitivity to gluten benefit from following a gluten-free diet because it raises transglutaminase antibodies [39].

As anti-inflammatory drugs are involved in the pathogenesis of schizophrenia, they are a better target. Cyclooxygenase enzyme inhibitors such as celecoxib are frequently used as anti-inflammatory agents. Risperidone is added to treat patients with exacerbations of schizophrenia [40].

The outcomes were encouraging, demonstrating a significant improvement in patients receiving celecoxib as opposed to those not receiving celecoxib. According to another study, minocycline, an antibiotic, can improve cognition in patients with schizophrenia by blocking microglial activation and bridging the blood-brain barrier [41]. Furthermore, monoclonal antibodies are being investigated to counteract inflammatory cytokines. Further studies are needed to determine the therapeutic outcome, although their activity is plausible [42].

GABA

The CNS contains the naturally occurring amino acid gamma-aminobutyric acid, which serves as an inhibitory neurotransmitter. Numerous investigations using zoonotic models have demonstrated the role of GABA and dopamine in schizophrenia [43]. The chandelier subtype of parvalbumin-positive GABA neurons is notably affected in schizophrenia [44].

The mRNA of the γ-aminobutyric acid-producing enzyme GAD67 is downregulated in schizophrenia, which results in decreased neuronal density [45]. Moreover, a decrease in GAT-1 mRNA levels in the brain, which reuptake GABA, was found [46]. When GAT-1 expression is decreased, GABA is more easily accessible to the prefrontal cortex. Adding GABA agonists to therapy improves patient outcomes, although the precise role of γ-aminobutyric acid in schizophrenia remains uncertain.

GABA has been cited as a neurotransmitter in the pathogenesis of schizophrenia. γ-Aminobutyric acid receptors have three allosteric sites, one of which mediates the chloride-gated ion channel and is called the benzodiazepine-binding site [46]. Current research has focused on the use of γ-aminobutyric acid-A and γ-aminobutyric acid-B antagonists to treat schizophrenia [47].

BIOMARKERS FOR SCHIZOPHRENIA

Six categories of biomarkers were identified, with positive and contradictory results, after the data on prospective biomarkers for analytical and therapeutic use in schizophrenia were screened and sorted. Biomarkers linked to metabolism, proteins, genetics, and epigenetics make up the other two, while two come from neuroimaging approaches (Figure 1).

Neuroimaging Techniques

Neuroimaging is a novel and exciting technique for studying the morphological characteristics and functional attributes of brain tissues. Part of the brain associated with cognition, as well as hyper- and hypo-activation in schizophrenia, can be identified using neuroimaging techniques [48].

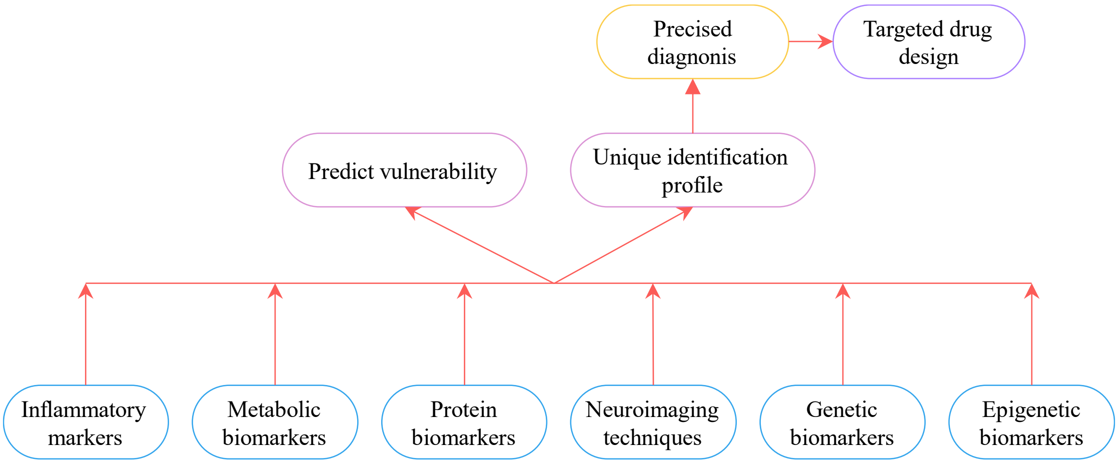

Figure 2. Types of biomarkers for diagnosis and prognosis of schizophrenia.

Genetic Biomarkers

The use of blood cells in microarray research has increased because of their many benefits, including the ability to collect larger sample sizes using a less invasive technique [49]. Genomic technology has advanced our understanding of mental disorders by identifying several genes that affect brain development [50, 51] (Figure 2).

Epigenetic Biomarkers

The very complex molecules known as DNA in the cell nucleus, various histone modifications, DNA modifications, and changes in various non-histone proteins and non-coding RNAs are all involved in epigenetic processes [52]. Non-coding RNA research has exploded, similar to preclinical studies, but very few of these studies have been conducted in humans to identify biomarkers [53] (Figure 2).

Protein Biomarkers

Protein biomarkers hold great promise in their application and influence on the psychopathology of schizophrenia owing to their wide range of uses. Hundreds of proteins may be detected simultaneously with great sensitivity and accuracy using array profiling and multi-analytic approaches. Numerous proteins that are present in different organs, including the blood serum, plasma, cerebrospinal fluid, liver, and fibroblasts, can be used as biomarkers to improve diagnosis [53] (Figure 2).

Inflammatory Biomarkers

High inflammation risk can serve as an early warning indicator, potentially predicting the development of ultra-high risk or complete psychosis in individuals, using blood-based inflammatory biomarkers, such as interleukin-17 and interleukin-1 beta [54] (Figure 2).

DRUG DELIVERY

As we learn more about brain disorders and create treatment plans, one major obstacle still facing us is efficiently getting drugs into the CNS [55]. Because of its function in delivering nutrients and O_2 from the circulation to the brain and protecting the CNS from dangerous substances, the blood-brain barrier is a major barrier that keeps drugs from getting to patients [56–58]. Methods of drug transfer across the blood-brain barrier (BBB) facilitate diffusion, active transport, and passive or transcellular diffusion. The three forms of active transport in the blood-brain barrier are ATP-binding cassette family proteins, carrier proteins, and receptor-mediated transport. BBB permeability is regulated, and medication delivery is enabled by these mechanisms [59, 60]. One of the primary challenges in the contemporary period is the development of drugs that will pass the BBB to treat CNS illnesses. For medicine to effectively elicit a therapeutic response, its concentration needs to grow in the right bodily location and be maintained long enough. The medication concentration in other organs and tissues must be kept low to reduce negative effects. The BBB severely restricts the ability of medications to enter brain tissue. It may be possible to inject medications directly into brain tissue to bypass the BBB. These methods enable differentiation between the delivery of biodegradable chemicals, intranasal administration, and intrathecal or intraventricular injection of medicines for direct transport into the cerebrospinal fluid [61]. Intracellular injection is one method to obtain high drug concentrations in the brain. This technique does not require alterations to the integrity of the BBB and permits the use of low dosages of medication, in contrast to systemic administration. Nevertheless, this is an invasive approach that may result in neurotoxicity and elevated intracranial pressure [62]. Another direct therapeutic agent delivery technique for the treatment of various illnesses and CNS disorders is intranasal administration. This approach is predicated on the relationship between the mucosa lining the olfactory nasal cavity and the cerebrospinal fluid circulation adjacent to the olfactory bulbs [63]. Pharmaceutical delivery via intranasal administration is a noninvasive, secure, and effective therapeutic approach. Loading medications into nanocontainers, which are distinguished by their comparatively small size and capacity to cross the BBB, is a promising strategy for overcoming the BBB. When drugs are delivered using this technique, their bioavailability is greatly increased, and their side effects are decreased.

The mechanisms of NPs transportation through the BBB can be divided into three primary categories [64]:

1. Drug conjugates can permeate into the brain tissue because of the brief opening of the BBB caused by nanoparticles.
2. By adhering to nanocarrier conjugates on capillary endothelium cells, the concentration gradient of the medication is increased, and its passage into the brain is facilitated.
3. The capillary endothelial cells of the brain use the mechanisms of transcytosis, exocytosis, and endocytosis to allow nanocarriers to enter the brain tissue.

Neurons, astrocytes, and microglia in the brain can be targeted for drug delivery using nanoparticles. Neuron-specific delivery is challenging owing to its non-phagocytic nature. Astrocytes, which take up NPs through phagocytosis, are another promising target for nanomedicine, potentially affecting neurotransmitter release and excitability [65].

Specialized neural cells called *oligodendrocytes* are responsible for myelinating axons in the central nervous system. Their surface characteristics can facilitate drug delivery via nanopreparation.

Nanomedicine targets macrophages or microglia through clathrin-mediated endocytosis, with larger surface areas facilitating higher uptake efficiency. Experiments have shown that microglial cells can absorb gold NPs with “urchin-mimicking” geometry more efficiently than spherical and rod-shaped gold NPs [66].

Nanocarriers

- *Polymeric nanoparticles*: Owing to their biocompatibility and low toxicity, PLA and PLGA nanoparticles have become viable alternatives for delivering drugs to the brain. These biodegradable polymer nanoparticles can be used in human medications, biodegradable scaffolds, and implants. FDA-approved PLGA/PLA nanoparticles can arrange therapeutic chemicals into stable structures, increasing the drug concentration in the brain [67]. For example, better curcumin delivery reduces oxidative stress, inflammation, and plaque load more effectively when treating AD.
    - *Dendrimers*: Monodisperse symmetrical macromolecules with inner nuclei surrounded by branched blocks are called dendrimers. Dendrimers are spherical structures composed of an outer layer with functional end groups, a core, and layers of branched repeating blocks emerging from the core. Among all dendrimers, poly(amidoamine) dendrimers are most frequently used in the treatment of brain diseases [68].
    - *Micelles*: In aqueous liquids, amphiphilic block copolymers aggregate to form stable spheroidal nanostructures, known as micelles. These micelles exhibit a hydrophilic surface

    and hydrophobic core. Micelles are potential brain-specific drug delivery systems. The ability of the hydrophobic nuclear region to interact with certain target ligands and the solubility of poorly soluble compounds makes this possible.
- *Lipid-based NPs:*
    - *Liposomes:* The spherical shape and lipid bilayer that characterize liposomes as a family of nanostructures. The ideal size range is 100–200 nm. Doxil, a liposome-based preparation, was the first FDA-approved nano-drug in 1995 [69]. The next 20 years saw the development of all liposome forms, modifications, and construction techniques [70]. Liposomal nanoparticles, for instance, were created using microfluidics. These nanocarriers enable the achievement of a balanced nanocontainer and an increase in the percentage of drug loading [71]. High levels of drug stability, enhanced biodegradability, biocompatibility, and bioavailability are frequently associated with liposomes [72]. They can also alter surfaces to enable active targeting [72]. The structure of the nanoparticles allows for the insertion of auxiliary lipids such as cholesterol or dioleoylphosphatidylethanolamine [73]. For many years, researchers have studied the use of liposomal structures for BBB crossing. The liposomal surface is functionalized by biologically active ligands, such as peptides, antibodies, or small molecules, to target transcytosis via the CNS endothelium.
    - *Solid lipid nanoparticles:* This kind of nanoparticle in contrast to liposomes, solid lipid nanoparticles contain a solid lipid core matrix that surrounds lipophilic molecules instead of a lipid layer. Solid lipid nanoparticles (SLNs) are composed of biocompatible lipids with a hydrophilic-lipophilic balance that is suspended at the nanoscale and stabilized by bioactive chemicals. Examples of these lipids include triglycerides, fatty acids, and waxes. Furthermore, the surfaces of these nanoparticles are altered, which significantly enhances the efficiency of medication administration across the blood-brain barrier [74].
    - *Nanoemulsion:* Stabilized by surfactants, nanoemulsions are heterogeneous dispersions with the composition “oil in water” or “water in oil.” In these nanosystems, the internal phase diameter shrank to the nanometric scale. Owing to their characteristics, nanoemulsions show promise for the transportation of both hydrophilic and hydrophobic medications. Bioactive ligands can also be added to nanoparticle surfaces to alter their properties. Drug delivery through nanoemulsions is accomplished via receptor-mediated endocytosis.
- *Inorganic NPs:* Solid nanoscale objects made of inorganic materials such as metal or metal oxides, silicon dioxide, and carbon nanotubes are known as inorganic nanoparticles. This type of nanoparticle is commonly employed in visualization research such as brain imaging. They are coated with a variety of polymers to facilitate their penetration through the BBB. Polyethylene glycol (PEG) is the most frequently used covering polymer. These surface alterations increase the stability of nanoparticles, increase their solubility in water, and enable the surface modification of particles with vector molecules [75]. This type of PEGylation of nanocontainers prevents nonspecific interactions with opsonin proteins and the ability of RES to capture particles [76] (Figure 3).

Antipsychotic Drugs

Antipsychotics, which reduce patients elevated dopaminergic transmission in the brain, are the primary medications used to treat the illness. Additionally, treatment of bipolar illness has fewer side effects than first-generation pharmaceuticals [77]. Chlorpromazine, the first medication used to treat schizophrenia, was first used in 1952, and in the 1960s, researchers worked on creating long-acting medications comprising an antipsychotic agent and a fat-soluble solution [78]. Despite the introduction of novel antipsychotic drugs that exhibit enhanced effectiveness and notably reduced adverse effects, antipsychotic drug delivery methods continue to rely on conventional drug forms, including tablets, capsules, and solutions, necessitating two or four days of administration. They should lower the frequency of dosages, boost adherence to the treatment plan, and increase medication absorption [79]. Antipsychotics will undoubtedly benefit from new drug delivery methods, such as controlled and steady release systems. Atypical neuroleptics have emerged and proliferated throughout the medical community. Olanzapine is an atypical or second-generation antipsychotic exclusively binds to serotonin

(5-HT(2c)), and central dopamine D2 receptors have been mentioned in several papers on nanocontainers. Liver first-pass metabolism and P-glycoprotein export have low bioavailability and restricted brain permeability [80].

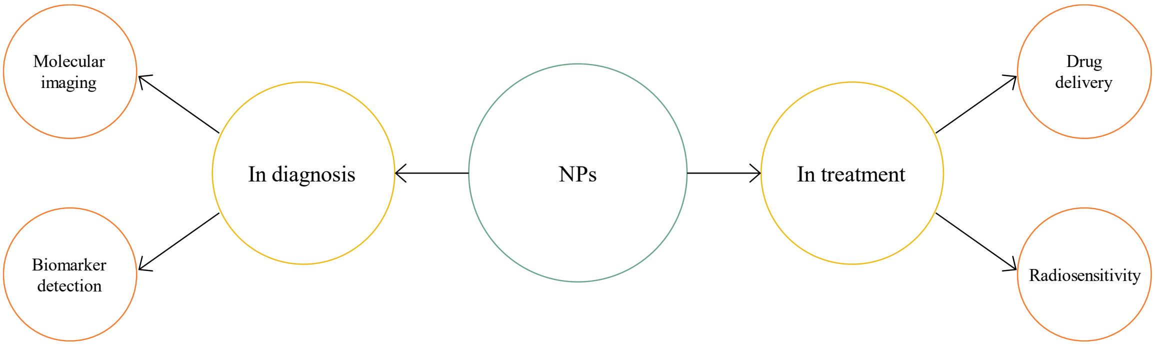

Figure 3. Use of Nanoparticles for diagnosis and prognosis of schizophrenia.

Lurasidone, another unconventional antipsychotic drug, was introduced into the SLNs. Its improved therapeutic impact after oral treatment in rats treated with an MK-801-induced form of schizophrenia has been shown [81].

As a second-generation antipsychotic, aripiprazole is largely insoluble and experiences increased dose-related side effects, as well as extensive hepatic metabolism and P-glycoprotein efflux. Riprazole-infused SLNs increased the bioaccessibility of this neuroleptic [82].

The same type of mucoadhesive device for drug delivery was developed for risperidone, another atypical neuroleptic drug, to treat bipolar disorder and schizophrenia. 90% of the drug was released over eight hours thanks to the use of a mucoadhesive buccal tablet formulation, allowing for the direct systemic administration of risperidone [83].

Due to its 6-hour plasma half-life, quetiapine fumarate, an atypical antipsychotic medication of the second-generation, needs to be administered frequently to maintain an effective therapeutic concentration. During intranasal injection, the bioavailability of the mucoadhesive microemulsion quetiapine increases [84].

Asenapine was first released in 2009. It is a novel atypical antipsychotic that is used to treat bipolar illness and schizophrenia. When taken orally, it has the same drawback of low bioavailability (<2%). The majority of drug metabolism occurs in the liver. The antagonistic action of asenapine on 5-HT2A serotonin receptors and D2 dopamine receptors is assumed to be the cause of its antipsychotic properties. Some researchers have created sublingual, intranasal, and injectable formulations of asenapine to increase its bioavailability [85].

CURRENT CHALLENGES

The BBB is one of the main challenges that medications must overcome to improve the prognosis of schizophrenia. Physiological barriers limit the circulation of drugs, including analgesics, antibiotics, and anticancer drugs. The transmission of drugs to the BBB is hindered by several factors. Thus, medications should be altered in a way that makes it easier for their physicochemical properties to pass through the BBB and have the desired effect. Thus far, a number of studies have demonstrated the significance of understanding in vitro models that traverse the blood-brain barrier. Nevertheless, removing the obstacles that prevent drug transfer over the BBB is the main objective of creating a novel treatment approach for neuropsychiatric disorders [86]. These factors might be the lipophilicity, size, conformation, and plasma-binding properties of the molecules. Furthermore, the bioavailability of the medication in the central nervous system may be poor even when an adequate dosage is administered. The amount of medicine accessible to the central nervous system may be reduced if the drug binds to particular plasma proteins or is inactivated by specific circulating enzymes. This calls for the development of novel therapeutic medicines that can overcome this selection barrier. One treatment strategy that allows for tailored medication distribution with sufficient bioavailability is nanoformulation.

FUTURE PROSPECTS

The treatment of schizophrenia has also been made possible by advances in nanoscience. Examples of nanomedicine techniques include PNPs, nanoemulsions, dendrimers, liposomes, nanocapsules, and nanospheres. These techniques are excellent because they are selective, effective, have low toxicity, and can pass through the blood-brain barrier while simultaneously improving therapeutic efficacy. Biomedical research is being affected by machine learning and artificial intelligence techniques, which also present new opportunities to enhance medication administration. Artificial Intelligence possesses the capability to be an effective instrument for ascertaining the correlations between formulation characteristics and release kinetics, as well as for optimizing drug delivery mechanisms for optimal effectiveness [87]. A cascade model is a type of computer model developed to forecast medication diffusivity from different mucoadhesive formulations [88]. Artificial intelligence is still in its infancy when it comes to practical use, but it has the potential to drastically change how medications are delivered. To fully achieve AI's promise in drug administration, further work is needed to enhance interpretability, offer recommendations for machine learning model selection, and increase the calibration of the data gathered. A fascinating new direction is the combination of soft electronics, sensors, chips, micro- or nano-robots, external or internal power supply, and medication administration. For example, the ingestible wireless transmitter IntelliCap (AAPS) comprises a motor to facilitate medication release, temperature and pH sensors, and a microcontroller to operate the pump [89].

CONCLUSION

Schizophrenia is a severe neurodevelopmental brain condition that is highly heritable and persistent with varied genetic and neurological backgrounds. Getting the medicine beyond the BBB, the physiological barrier, and the method of drug transport are essential for a better therapeutic effect. Fluid biomarkers have a significantly increased potential for diagnosing illnesses. Based on these indicators, it was easy to identify people who were susceptible to schizophrenia. It is critical to discover novel and trustworthy biomarkers that can quickly assess an individual's risk of developing the disease. Addressing treatments requires analysis of other theories. In summary, several solutions are being developed to address the unmet requirements of the schizophrenia sector. It is clear from related news and articles that schizophrenia is no longer a question; rather, it is progressing toward becoming a cure for all issues that would improve people's quality of life.

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