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Emerging Strategies for Targeted Drug Delivery across the Blood–Brain Barrier in Neurological Disorder

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Keywords

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Abstract

The Blood–Brain Barrier is an obstacle in the treatment of neurological disorders since it selectively only allows some substances to pass through. Its poor permeability greatly limits access of certain therapeutic agents in the brain. In order to successfully treat glioblastoma, Parkinson's disease, Alzheimer's disease, and other illnesses of the central nervous system, it will be crucial to overcome the Blood Brain Barrier. Recent developments in targeted drug delivery systems have presented promising potential for this challenge. Emerging strategies include nanotechnology-based systems, receptor-mediated transport, cell-penetrating peptides, focused ultrasound, and advanced carrier designs. Nanotechnology-based systems, including liposomes, polymeric nanoparticles, and SLNs, offer controlled drug release and improved bioavailability, while surface modifications enhance Blood–Brain Barrier penetration through receptor-specific targeting. By conjugating medications to ligands that attach to certain receptors on Blood–Brain Barrier endothelial cells, receptor-mediated transport strategies facilitate active transport across the barrier. Cell-penetrating peptides are short peptides that have been utilised to deliver a variety of medicinal substances because they can pass through cell membranes. When combined with microbubbles, focused ultrasounds can momentarily breach the Blood Brain Barrier, enabling tailored medication administration without the need for invasive procedures. In addition, sophisticated carrier designs like dendrimers and mesoporous silica nanoparticles enhance drug stability and provide prolonged release. These strategies have great promise in improving drug delivery into the brain, treatment efficacy, and minimizing side effects.

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1. Introduction

The blood-brain barrier (BBB) is a specialized endothelial structure crucial for maintaining brain homeostasis. It regulates the selective passage of essential nutrients and signaling molecules into the brain while blocking harmful substances in the bloodstream. This protective function is vital for preserving neuronal function and the brain's delicate microenvironment. However, the BBB also poses a significant obstacle in treating neurological disorders, as many therapeutic agents are unable to penetrate it in adequate concentrations to achieve effective results [1]. For direct brain therapy, novel drug delivery techniques that avoid or make use of the

blood-brain barrier (BBB) are vital. The need for efficient treatment options is underscored by the substantial load that neurological conditions such as multiple sclerosis, Parkinson's disease, Alzheimer's disease, and brain tumours like glioblastoma place on the world's healthcare systems [2]. It is anticipated that the frequency of neurological illnesses would increase as populations age, creating a pressing need for efficient therapies. Drug development for the central nervous system (CNS) has not been particularly successful despite years of study since many intriguing candidates fail clinical trials because they are not well able to penetrate the blood-brain barrier (BBB). Conventional methods frequently depend on systemic drug delivery, which raises the possibility of systemic adverse effects and results in less than ideal brain medication concentrations. Therefore, resolving the BBB delivery issue is essential to developing successful CNS treatments [3].

Our knowledge of the structure and function of the BBB has advanced significantly in recent years, opening the door for the creation of innovative drug delivery systems. Multidisciplinary initiatives involving pharmacology, nanotechnology, bioengineering, and molecular biology are responsible for these developments. Cell-penetrating peptides (CPPs), receptor-mediated transcytosis, nanoparticle-based delivery systems, and ultrasound-mediated techniques are some of the new approaches; each has specific benefits and drawbacks [4]. Novel approaches seek to improve the efficacy, safety, and accuracy of medication delivery to the central nervous system (CNS), which might revolutionise the management of neurological disorders. A flexible and promising method for bridging the blood-brain barrier is the use of nanoparticles (NPs). Nanoparticles may be made to interact with BBB endothelial cells in a particular way by altering their size, shape, surface charge, and functional characteristics. These modifications make it possible to efficiently transfer therapeutic medicines to the brain by using a variety of transport systems, including transcytosis and endocytosis [5]. NPs can enhance the pharmacokinetic characteristics of medicinal drugs and shield them from enzymatic breakdown. The potential of metallic NPs, polymeric NPs, and lipid-based carriers to transport a variety of treatments, such as small molecules, peptides, proteins, and nucleic acids, has been investigated. Surface alterations like ligand attachment or PEGylation improve their capacity to target the brain while reducing off-target effects [6].

One potential method for targeted medication administration across the blood-brain barrier (BBB) is receptor-mediated transcytosis (RMT). This technique takes use of the inherent transport channels of BBB endothelial cells' transferrin, insulin, and lactoferrin receptors, among other receptors. medications may be efficiently and precisely delivered to the central nervous system by binding therapeutic molecules to ligands that bind these receptors. This allows for the selective transport of medications into the brain by endocytosis and subsequent transcytosis [7]. RMT-based delivery systems are especially appealing for treating localised CNS illnesses because of their specificity, which reduces systemic exposure and improves brain targeting. But there is still a risk of receptor saturation and off-target effects, which calls for more optimisation [8]. A supplementary method for navigating the BBB is provided by CPPs. These brief sequences of amino acids possess the special capacity to engage with cell membranes and promote the absorption of a wide variety of cargos, from macromolecules to tiny molecules. CPPs do this by causing temporary lipid bilayer disturbances or initiating endocytosis, which enables their cargo to get beyond the BBB's restrictions [9]. There is a lot of interest in using CPPs for CNS medication delivery because of their adaptability and relative ease of use. But the possibility of cytotoxicity and non-specific interactions emphasises the necessity of thorough testing and design to guarantee their efficacy and safety [10]. A non-invasive way to temporarily increase BBB permeability is using ultrasound-mediated approaches, which have attracted interest. When combined with microbubbles, focused ultrasound (FUS) can cause localised, reversible breakdown of the blood-brain barrier, enabling medications to enter the brain parenchyma [11]. Preclinical and early clinical research has demonstrated the potential of this strategy for delivering gene treatments, antibodies, and chemotherapeutics to CNS targets, such as glioblastoma. FUS is an effective instrument for BBB modulation because of its precise control and compatibility with a variety of treatment modalities. However, maintaining this technique's safety and reproducibility is still crucial for its clinical use [12].

Emerging technologies such as exosome-based delivery, bioengineered peptides, and advanced gene therapy approaches are beginning to reshape the landscape of BBB-targeted drug delivery. For instance, exosomes are naturally occurring vesicles that may be modified to deliver therapeutic drugs

with minimal immunogenicity and great selectivity across the blood-brain barrier. Similarly, CRISPR/Cas9 and other gene-editing tools are being adapted to address genetic underpinnings of neurological disorders, offering a new dimension of precision in CNS therapeutics [13]. Even with the advancements, there are still a number of obstacles to overcome in the creation and application of BBB-targeted medication delivery systems. Ensuring the biocompatibility, stability, and scalability of these technologies is critical for their clinical adoption [14]. Moreover, the heterogeneity of the BBB across individuals and disease states complicates the design of universal delivery platforms. Personalized approaches that account for patient-specific BBB properties and pathological conditions are probably going to be crucial in overcoming these hurdles. Additionally, integrating computational modeling and machine learning into the design and optimization of drug delivery systems can accelerate their development and enhance their performance [15].

The quest to overcome the BBB's formidable barrier represents among the biggest obstacles and possibilities in the development of CNS drugs. Emerging strategies for targeted drug delivery are beginning to unlock new possibilities for treating neurological disorders that were once deemed intractable [16]. By combining innovative technologies with a deeper understanding of BBB biology, researchers are opening the door for safer, more individualized, and more effective treatments for the millions of individuals affected by these debilitating conditions. Continued interdisciplinary collaboration and investment in this field will be essential to translate these promising strategies into tangible clinical benefits [17].

2. The BBB: Structure and Function

By controlling the chemical exchange between the circulation and the brain, the highly specialised blood-brain barrier (BBB) maintains brain homeostasis. It is mostly made up of endothelial cells that line the blood arteries in the brain, which are very different from those in the rest of the body. Tight connections between these cells provide a selective barrier that blocks the majority of chemicals and ions, allowing just particular substances to flow through and protecting the brain's fragile environment [18]. In contrast to other blood arteries, the BBB's endothelial cells have a thicker basement membrane that reinforces the structure and no fenestrations, or holes. Endothelial cells are surrounded by astrocyte end-feet, which are projections from astrocytes, a kind of glial cell, and are essential for maintaining the blood-brain barrier (BBB). By affecting tight junction integrity and offering biochemical support, these end-feet contribute to the stability and functionality of the blood-brain barrier. Furthermore, by controlling blood flow, maintaining vascular stability, and promoting the development of tight junctions, pericytes—which envelop capillaries—help to strengthen the blood-brain barrier and strengthen its protective properties [19]. The combined effect of these components creates a highly regulated environment, where only essential substances like glucose, amino acids, and certain ions can pass through using specific transporters, while harmful substances, including toxins and most pathogens, are largely prevented from entering the brain [20]. The CNS's resident immune cells, known as microglia, are involved in both fighting against possible threats and keeping an eye on the barrier's integrity. The blood-brain barrier's (BBB) selective permeability is crucial for preserving the delicate chemical balance of the brain, shielding neurones from toxins, and guaranteeing healthy central nervous system operation. However, because it reduces the efficiency of many drugs, this same trait presents difficulties in treating neurological illnesses. The complex structure of the blood-brain barrier (BBB), which is made up of endothelial cells, pericytes, astrocytes, and a basement membrane, creates a dynamic yet extremely protective barrier that protects the brain while controlling the flow of chemicals between the blood and neural tissue [21].

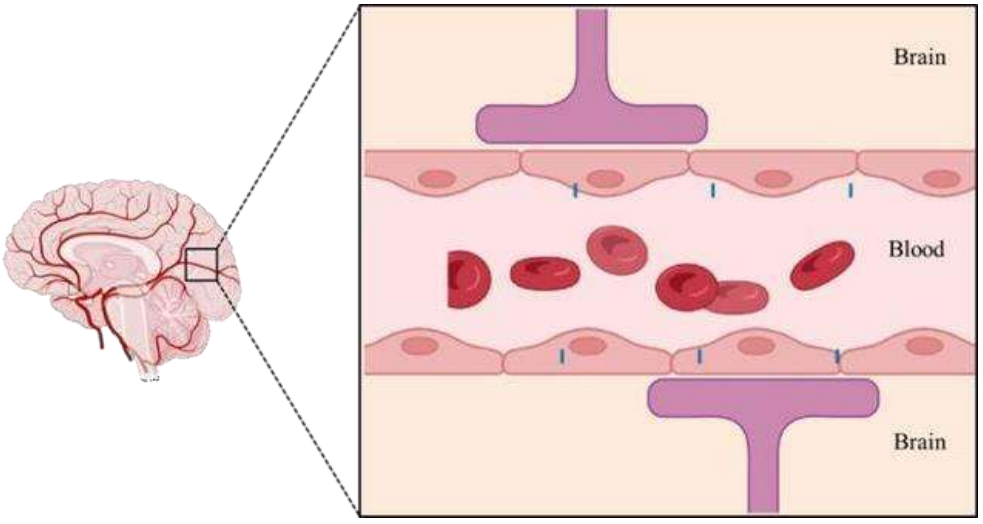

Figure 1: Blood Brain Barrier (Simple Longitudinal Zoom)

Functions

To preserve the brain's microenvironment and guarantee its healthy operation, the BBB performs a number of essential tasks:

1) **Selective Permeability**: Essential chemicals like oxygen, glucose, and amino acids may enter the brain selectively thanks to the blood-brain barrier, while restricting the passage of larger molecules, toxins, and pathogens. This controlled permeability ensures that the brain receives the nutrients it needs without exposure to harmful substances [22].

2) **Protection Against Pathogens and Toxins**: The brain is protected by the blood-brain barrier (BBB), preventing the entry of most pathogens, harmful chemicals, and toxins that might be present in the bloodstream. This helps protect the central nervous system (CNS) from things that might harm it and from infections [23].

3) **Ion and Neurotransmitter Regulation**: The BBB is essential for preserving the ionic equilibrium in the brain and guaranteeing healthy neuronal activation and preventing fluctuations in ion concentrations that could disrupt brain function. Additionally, it regulates the levels of neurotransmitters in the brain, preventing them from entering from the bloodstream, which would interfere with normal brain signaling [24].

4) **Efflux Mechanisms**: The BBB contains active transport mechanisms, including P-glycoprotein is one example of an efflux transporter that actively pumps out potentially hazardous compounds or excess chemicals that have crossed the barrier. This ensures that any harmful substances that may have penetrated the BBB are removed, maintaining the brain's chemical stability [25].

5) **Homeostasis Maintenance**: The blood-brain barrier (BBB) helps maintain the exact biochemical and physiological environment required for neurones to operate properly by controlling the exchange of chemicals between the blood and the brain. This is crucial for processes like synaptic transmission and neuronal plasticity [26].

3. Emerging Strategies for BBB Penetration

Emerging strategies for BBB penetration focus on overcoming its selective permeability to deliver therapeutic agents to the brain. The use of NPs, such as liposomes, polymeric NPs, and solid lipid NPs, is one potential strategy. These NPs may be designed to penetrate the blood-brain barrier by either improving their surface characteristics to better interact with endothelial cells or by taking use of natural transport processes [27]. FUS combined with microbubbles is another innovative technique, which temporarily disrupts the BBB in a targeted manner, allowing drugs to enter the brain while minimizing damage to surrounding tissues. Using certain endothelial cell receptors, receptor-mediated transcytosis transfers therapeutic substances across the blood-brain barrier. Drugs can be transported over the barrier by conjugating them to ligands that bind to these receptors (such as insulin or

transferrin receptors) [28]. Through their interactions with endothelial cell membranes, CPPs—short peptides—can help move medications or therapeutic molecules over the blood-brain barrier. Additionally, gene therapy techniques, including the use of viral vectors or CRISPR-based delivery systems, are being explored to directly target brain cells for the treatment of genetic disorders. These emerging strategies offer new avenues for effective treatment of neurological diseases that were previously challenging due to BBB restrictions [29].

Table 1: Emerging strategies for BBB penetration

S. No.	Strategy	Description	Advantages	Challenges	References
1.	**Nanotechnology-Based Systems**	Use of NPs (liposomes, polymeric NPs, solid lipid NPs) to encapsulate drugs and enhance BBB penetration.	Improved bioavailability, targeted delivery, reduced side effects.	Potential toxicity, optimization of size and surface properties.	[30]
2.	**Receptor-Mediated Transport (RMT)**	Conjugating drugs to ligands (e.g., transferrin, insulin) that bind to specific receptors on BBB endothelial cells, facilitating active transport.	Increased medication efficiency and targeted distribution to particular brain areas.	Ensuring targeting specificity, optimizing ligand-receptor interactions.	[31]
3.	**CPPs**	Short peptides that can cross cell membranes and transport drugs across the BBB, including large molecules.	Makes it possible to transport a variety of cargoes, such as proteins and nucleic acids.	Risk of toxicity, optimizing peptide-drug conjugates for specific targeting.	[32]
4.	**Focused FUS**	Microbubbles and high-frequency ultrasonic waves are used to momentarily breach the blood-brain barrier and permit medication entrance.	Non-invasive, localized, precise drug delivery, real-time monitoring.	Need for careful control to prevent tissue damage, limited scalability.	[33]
5.	**Advanced Carrier Designs**	Creation of specialised carriers for the regulated, prolonged release of medications, such as dendrimers and nanostructured lipid carriers (NLCs).	High drug loading capacity, controlled release profiles, stability.	Complexity of carrier design, ensuring long-term biocompatibility.	[34]

3.1. Nanotechnology-Based Systems

For BBB-targeted delivery, NPs such liposomes, polymeric NPs, and dendrimers have been thoroughly investigated. Receptor-mediated transport is made possible by surface modifications using ligands or antibodies. Therapeutic chemicals can be encapsulated in functionalised nanoparticles (NPs), offering regulated release and defence against

enzymatic breakdown. Systems based on nanotechnology have become a viable way to get beyond the BBB's obstacles in medicine delivery [35]. NPs are able to pass through the complex structure of the blood-brain barrier more easily than larger molecules due to their small size, often falling between 1 and 100 nm. One of the most studied forms of nanotechnology for BBB penetration is liposomes, which are lipid-based nanoparticles that can encapsulate hydrophilic and lipophilic drugs and protect them from degradation in the bloodstream [36]. Targeting ligands, such peptides or antibodies, can be added to the surface of liposomes to improve their capacity to attach to certain receptors on the BBB's endothelial cells. This would enable receptor-mediated transcytosis and enable tailored drug administration [37].

Polymeric nanoparticles (NPs) are another emerging nanomaterial that may be created for controlled medication release, increasing therapeutic efficacy and decreasing negative effects. Additionally, these NPs can be altered to contain surface coatings that interact with endothelial cell tight junctions to improve BBB penetration [38]. Researchers are also looking into the possibility that solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) might cross the blood-brain barrier and provide sustained medication release, extending the duration of therapeutic action. Because of their special qualities, such as their large surface area and capacity to functionalise their surface for drug loading and targeting, carbon-based nanomaterials, such graphene oxide and carbon nanotubes, have potential for BBB penetration. These materials can be utilised to treat neurological problems, cancer, and distribute genes [38].

3.2. Receptor-Mediated Transport (RMT)

RMT targets receptors like transferrin, insulin, or low-density lipoprotein receptors in order to take advantage of the BBB's inherent transport pathways. Effective BBB crossing is possible with drug conjugates or nanocarriers functionalised with ligands for these receptors. RMT is a potentially effective method of getting medicinal substances into the brain by getting beyond the Blood–Brain Barrier (BBB) [31]. This method entails taking use of certain receptors on the BBB's endothelial cells to make it easier for medications or NPs to get over the barrier. RMT depends on the normal cellular processes that enable the receptor-ligand interactions that carry certain substances into the brain, including as hormones, nutrients, and peptides [39].

Finding and focussing on receptors that are highly expressed on the BBB endothelium is essential to RMT. For instance, transferrin receptors are involved in iron transport, and insulin receptors regulate glucose uptake. By conjugating therapeutic agents or drug-loaded NPs to ligands that bind to these receptors, it is possible to deliver medications to the brain in a specific way [40]. Once the ligand binds to the receptor on the endothelial cell surface, the complex is internalized via endocytosis and transported across the cell in vesicles, ultimately releasing the drug into the brain parenchyma. RMT offers several advantages, such as increased specificity, reduced side effects, and the potential for delivering larger molecules (e.g., proteins, peptides, or gene therapy vectors) that otherwise cannot cross the BBB [41]. Various strategies, including nanoparticle-based drug delivery, have been developed to exploit this mechanism. However, challenges remain in optimizing the targeting efficiency, minimizing potential immune responses, and ensuring that the drug reaches its intended site of action within the brain. Nonetheless, RMT is an exciting approach for drug delivery to treat neurological disorders [42].

3.3. Cell-Penetrating Peptides

TAT and penetratin are examples of CPPs that help therapeutic drugs move across cellular membranes, including the blood-brain barrier. These peptides can be conjugated to drugs or nanocarriers to improve brain targeting. Short peptides called CPPs, which usually include 5–30 amino acids, have the unusual capacity to pass across cell membranes, including the blood-brain barrier, without the aid of energy-dependent procedures like endocytosis [43]. Basic amino acids like arginine and lysine, which are frequently abundant in CPPs, interact with negatively charged lipid membranes to make it easier for the proteins to enter cells. Because of this feature, CPPs are a desirable medication delivery method, especially when it comes to brain targeting [44]. Upon conjugation, CPPs help therapeutic agents—such as drugs, proteins, or nucleic acids—cross the blood-brain barrier and enter the brain. In the central nervous system (CNS), CPPs have been shown to increase the bioavailability of drugs. They can transport a wide range of cargos, from small molecules to larger therapeutic proteins. The capacity of several well-known CPPs to penetrate cellular barriers, such Penetratin from Drosophila and TAT (Transactivator of Transcription) from HIV, has been well investigated [45].

CPPs can cross the BBB through direct translocation across the endothelial cell membranes or by using endocytosis, a process where the cell engulfs the peptide-drug complex in vesicles. Once inside the cell, the cargo is released into the brain, often with the help of endosomal escape mechanisms. Despite their potential, challenges remain, including the optimization of CPPs for selective brain targeting, reducing toxicity, and ensuring controlled release of the therapeutic cargo. Nonetheless, CPPs represent a promising strategy for drug delivery in neurological disorders [46].

3.4. Focused Ultrasound

The BBB is temporarily broken when FUS and microbubbles are combined, allowing drug molecules to flow through. Because of its accuracy and capacity to target certain brain areas, this non-invasive technique is becoming more and more popular. FUS is a non-invasive technique that is increasingly being researched as a means of opening the Blood–Brain Barrier (BBB) both temporarily and permanently to facilitate medication entry into the brain [47]. By applying high-frequency sound waves to a particular area of the brain, FUS creates mechanical pressures that have the potential to damage the BBB's endothelial cell connections. Larger molecules like therapeutic medications, nanoparticles, and gene therapy agents can pass through the barrier and enter the brain tissue as a result of this disturbance [48].

Microbubbles, which are tiny spheres packed with gas that are injected into the circulation, are frequently utilised in conjunction with FUS. When exposed to ultrasound waves, these microbubbles oscillate and cause localized mechanical stress on the BBB, temporarily creating microscopic pores that permit the passage of therapeutic agents. Because the ultrasonic waves may be carefully focused on the region of concern, this approach is extremely targeted and reduces the possibility of damaging nearby tissues [49]. The non-invasive aspect of FUS, which does not need surgery or catheter-based procedures, is one of its primary benefits. Additionally, it enables exact control over the position and degree of BBB opening through real-time monitoring and management. FUS has shown promise in preclinical and early clinical trials for the treatment of brain tumours, Parkinson's disease, and Alzheimer's disease. FUS has the potential to enhance drug delivery to the brain, however problems with process optimisation, safety, and lowering the risk of tissue damage still exist [50].

3.5. Advanced Carrier Designs

Hybrid carriers combining liposomes, micelles, and exosomes are being developed to enhance BBB penetration. These carriers leverage the advantages of multiple systems for improved stability, biocompatibility, and targeting efficiency. One new tactic to enhance the passage of medicinal drugs over the Blood–Brain Barrier (BBB) is the use of advanced carrier designs [51]. These carriers, which are frequently created at the nanoscale, are made especially to improve the delivery of medications, proteins, and gene therapy vectors to the brain. Lipid-based carriers, such liposomes and SLNs, are a common method because they can encapsulate both hydrophilic and hydrophobic medications, preventing degradation and enabling targeted distribution. Receptor-mediated transcytosis is made possible by surface modification of these carriers with targeted ligands, such as peptides or antibodies, which improves their capacity to bind with certain BBB endothelium receptors [52].

Polymeric nanoparticles (NPs) are another potential carrier design that can encapsulate a variety of therapeutic substances and provide regulated degradation rates and remarkable diversity in drug release patterns. To improve their BBB penetration, polymeric carriers can be functionalised with targeted moieties [53]. Because of their large surface area, which enables the attachment of several therapeutic agents or targeting ligands, dendrimers—highly branched, tree-like molecules—are being investigated for their potential to carry medications across the blood-brain barrier effectively [54]. Nanostructured lipid carriers (NLCs) and mesoporous silica nanoparticles (MSNs) are also being researched for improved medication delivery. These carriers are perfect for long-term treatments because of their substantial payload capacity, improved stability, and controlled release. These cutting-edge carriers' design also attempts to enhance the drug's pharmacokinetic characteristics and lessen toxicity. When combined, these cutting-edge carrier systems provide a potential way to improve medication transport to the brain and provide treatments for a range of illnesses affecting the central nervous system [55].

4. Applications in Neurological Disorders

4.1. Alzheimer’s Disease

Alzheimer's disease (AD) is a progressive neurological illness characterised by cognitive impairment, memory loss, and aberrant conduct. One of the biggest challenges in treating AD is the Blood–Brain Barrier (BBB), which keeps therapeutic medications from getting to the brain [56]. New developments in

medication delivery techniques, however, are raising hopes for getting around this obstacle and enhancing AD therapy alternatives. Systems based on nanotechnology, including SLNs, polymeric NPs, and liposomes, have been investigated for targeted medication administration in AD [57]. Better bioavailability and less systemic adverse effects can be achieved by engineering these carriers to pass through the blood-brain barrier and deliver medications straight to the brain. For instance, anti-amyloid medication distribution to specific brain regions can be improved by nanoparticles coated with antibodies that target amyloid plaques, a defining feature of AD, potentially delaying the course of the illness [58]. Receptor-mediated transport (RMT) is another strategy under investigation for AD therapy. Active drug transport into the brain is possible by conjugating medications to ligands that attach to receptors, such as transferrin or insulin receptors on the BBB endothelial cells. This method can be used to deliver neuroprotective agents, enzyme inhibitors, or areas [63]. Receptor-mediated transport (RMT) is another strategy for PD treatment, where therapeutic agents are conjugated to ligands (e.g., insulin or transferrin) that bind to BBB receptors, enhancing brain penetration. This approach can improve the small molecules that target the underlying pathophysiology of AD, such as beta-amyloid aggregation or tau protein tangles [59]. FUS combined with microbubbles has also shown promise in temporarily opening the BBB in a controlled and localized manner, allowing drugs like anti-inflammatory agents or neuroprotective compounds to enter the brain and target regions involved in AD. These emerging drug delivery techniques hold significant promise in improving the efficacy of AD treatments, potentially delaying disease onset, slowing progression, and providing better outcomes for patients with this debilitating condition [60].

4.2. Parkinson’s Disease

The deterioration of dopamine-producing neurones in the brain's substantia nigra is the main cause of Parkinson's disease (PD), a neurodegenerative condition that impairs motor function. Bradykinesia, stiffness, tremors, and postural instability are the symptoms that arise from this. Despite the availability of symptomatic treatments like levodopa, these therapies often lose effectiveness over time and cannot halt disease progression [61]. The BBB, which restricts the transport of several therapeutic medicines to the brain, is one of the major obstacles in treating Parkinson's disease. New developments in drug delivery methods, however, provide encouraging approaches to enhance the results of PD therapy [62]. For Parkinson's disease, medication delivery methods based on nanotechnology are being thoroughly investigated. Dopamine precursors or neuroprotective drugs can be encapsulated and delivered straight to the brain using polymeric nanoparticles, liposomes, and SLNs. These systems may be altered to include targeted ligands that attach to certain BBB endothelial cell receptors, enabling receptor-mediated transcytosis, which enables medications to flow through the barrier and enter the impacted brain delivery of dopamine agonists or neurotrophic factors that could help protect and regenerate dopaminergic neurons [64]. Microbubbles and FUS have demonstrated the ability to momentarily open the BBB, enabling the direct delivery of drugs or gene therapies targeting PD-related pathways. These therapies could include the delivery of growth factors, neuroprotective agents, or gene-editing tools aimed at restoring dopamine production or repairing damaged neurons. These emerging drug delivery strategies hold great promise in advancing Parkinson’s disease therapies, enhancing patient outcomes and maybe reducing the rate of disease development by breaching the blood-brain barrier [65].

4.3. Glioblastoma

Glioblastoma (GBM) is a highly invasive and aggressive kind of brain cancer that grows quickly, is resistant to therapy, and has a dismal prognosis. A major obstacle in the treatment of GBM is the Blood–Brain Barrier (BBB), which prevents many traditional chemotherapy drugs from reaching the tumour site [66]. New approaches to medicine delivery, however, are giving promise for better cures for this debilitating illness. Because nanotechnology-based devices may transport therapeutic compounds directly to the brain and tumour cells while avoiding the blood-brain barrier, they have drawn a lot of attention in the treatment of GBM [67]. Targeted agents or chemotherapeutic medications, like temozolomide, can be encapsulated in liposomes, polymeric nanoparticles, or dendrimers and delivered to the tumour more effectively. Tumor-targeting ligands, including peptides or antibodies, can be functionalised into these nanoparticles to enable precision delivery to the GBM cells by binding to epidermal growth factor receptors (EGFR) or other tumor-specific indicators [68]. In addition to increasing the drug's effectiveness, this focused strategy lessens systemic adverse effects. Another approach being considered for GBM is RMT. Drugs can enter the brain and tumour site actively by

conjugating them to ligands that target certain BBB or tumour cell receptors, such as transferrin or folate receptors [69]. This approach has the potential to improve the efficacy of GBM therapy by increasing the administration of immunotherapeutics, gene therapies, or chemotherapeutics. Research has looked into using FUS in conjunction with microbubbles as a non-invasive technique to locally and carefully open the BBB temporarily [70]. This method makes it possible to administer medications or other therapeutic substances straight to the tumour location, enabling better targeting of GBM cells. These innovative drug delivery strategies offer the potential for more effective treatments for glioblastoma, overcoming the barriers that have hindered progress in treating this aggressive brain cancer [71].

5. Challenges and Future Perspectives

While emerging drug delivery strategies, including nanotechnology, RMT, FUS, and CPPs, offer promising solutions for overcoming the BBB, several challenges remain in their widespread application for treating neurological disorders [72]. To fully utilise these cutting-edge technology in clinical settings, these issues must be resolved. One of the primary challenges is the heterogeneity of the BBB. The BBB's permeability can vary significantly across different regions of the brain, and it may be altered in certain neurological conditions, such as tumors or neurodegenerative diseases [73]. The creation of universal medication delivery systems that can efficiently target every area of the brain is made more difficult by this variety. Moreover, the BBB can undergo structural changes in response to disease progression, making it even more difficult to design systems that can adapt to these alterations. Another issue is the toxicity and biocompatibility of the materials used in drug delivery systems [74]. Nanoparticles, liposomes, and other carriers, while effective in transporting drugs, may present potential risks such as immune responses, inflammation, or toxicity in healthy tissues. Long-term safety data is often lacking, especially for new materials, and ensuring that these carriers do not cause harm to the brain or other organs is a significant concern [75]. Controlled release of therapeutic agents is another challenge. While nanoparticles and liposomes can encapsulate drugs, ensuring that the drug is released at the right time, in the right amount, and at the target site is not always straightforward. Improper release profiles may lead to premature drug degradation, low bioavailability, or systemic toxicity. Developing advanced carriers that provide precise and sustained release of drugs over time is essential for maximizing therapeutic efficacy while minimizing side effects [76]. Targeting specificity is also a key hurdle. While receptor-mediated delivery and functionalized nanoparticles can enhance targeting, ensuring that drugs are delivered specifically to the desired brain regions, such as those affected by Alzheimer's disease or glioblastoma, remains a complex task. Overcoming off-target effects, where drugs bind to unintended tissues or cells, is crucial for improving the safety and efficacy of therapies [77]. Furthermore, because the BBB may restrict the entry of bigger molecules like proteins or gene therapy vectors, it is still difficult to guarantee that the medication crosses the barrier and reaches therapeutic concentrations in the brain. Clinical translation of these innovative drug delivery systems is another barrier. Most of the promising technologies are still in preclinical or early-phase clinical trials, and translating these findings into large-scale, FDA-approved treatments is a time-consuming and costly process [78]. Regulatory approval processes for new drug delivery systems are often complex, as these technologies may not fit within traditional drug development frameworks. Standardization of manufacturing processes and rigorous clinical testing are necessary to ensure the safety, quality, and efficacy of these new therapies [79]. Looking ahead, future perspectives for BBB drug delivery systems include personalized medicine, where drug delivery methods can be tailored to individual patients based on their specific disease characteristics, genetic makeup, and BBB permeability [80]. Advances in real-time imaging and monitoring will enable clinicians to assess drug delivery in real-time, providing a better understanding of how these therapies are working in vivo and allowing for more precise adjustments during treatment. Furthermore, combination therapies that use multiple drug delivery systems in tandem, such as combining FUS with nanoparticles or CPPs, could provide more effective treatment strategies for complex neurological disorders [81].

Conclusion

Since the BBB effectively restricts the delivery of therapeutic drugs to the brain, breaking through it continues to be one of the most difficult difficulties in the treatment of neurological illnesses. However, new approaches to drug delivery, such as systems based on nanotechnology, RMT, FUS, and CPPs, have showed great promise in overcoming this obstacle. These cutting-edge methods provide fresh ways to transport medications to the brain more efficiently, enhancing the effectiveness of treatment for diseases including glioblastoma, Parkinson's disease, and Alzheimer's,

which have traditionally been difficult to treat due to BBB limitations. Despite the promising potential of these technologies, several challenges persist, including issues of toxicity, targeting specificity, controlled release, and the heterogeneous nature of the BBB. Resolving the difficulty of accurately identifying the parts of the brain impacted by neurological disorders and guaranteeing the safety and biocompatibility of these systems continue to be crucial factors. Furthermore, in order to address the needs of patients and healthcare systems, clinical translation of these technologies from the lab to actual therapies necessitates thorough study, stringent regulatory approval, and careful optimisation. Future developments in combination medicines, real-time imaging, and personalised medicine might improve the accuracy and effectiveness of medication delivery to the brain. The integration of these technologies could revolutionize the way neurological diseases are treated, leading to better outcomes, reduced side effects, and more effective long-term management. With continued innovation and collaborative efforts in research, these innovative medication delivery techniques might revolutionise the field of neurology, offering hope for patients with currently unmet therapeutic needs.

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Author Contributions

S. A. conceptualized the study, supervised the research, and prepared the manuscript draft. **S. A. A.** contributed to data analysis and reviewed the manuscript critically for intellectual content. **M. K.** and **I. J.** assisted in the experimental design and data collection. **J. H.** provided technical support and helped with the literature review.

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Conflicts of Interest

No conflicts of interest are disclosed by the authors.

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