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NOVEL THERAPEUTIC AGENT TRANSFER SYSTEM FOR TREATING NEUROPSYCHOLOGICAL DISORDER

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ABSTRACT
The demand for development of therapeutic techniques for the curement of ND disorders increased in recent years due to an ageing population that is still growing. Neuronal death is commonly linked with ND, defined by progressive loss of neuronal structure or activity. Despite the testing of various medications, there is presently no one curementthat can stop the progression of these conditions or cure them. BBB, BCFB, and P-glycoproteins are some of the key potential causes of therapy failure in ND illnesses. By employing nanotechnology and creating nanomaterial that improves transfer of active therapeutic agent entities, current breakthroughs in nanotechnology offer chances to get over the constraints outlined. The local distribution of pharmaceuticals, binding sites-mediated transcytosis, and other disruptions are some of fundamental and emerging ways to overcome therapeutic agent transfer interfaces. The use of NPs recently explored to increase effectiveness of medicine transfer. Nano engineered particles can penetrate BBB and exhibit reduced invasiveness. As an illustration, consider the inorganic, magnetic, polymeric, and carbon NPs that have been designed to increase the effectiveness of medication administration. There are still various problems that need to be resolved despite the large number of articles that have been published in this field in order to successfully treat ND illnesses. Here, they are discussed.

Keywords: Neuropsychological, Nanoparticles; Alzheimer's, Parkinson's, Blood Brain Interfaces, Neurodengerative, stem cells.

1. INTRODUCTION

The brain is the most sensitive component of CNS, connecting sensory indevelopment from all organs, taking learning and memory into account, and allowing for restores to regulate active activity(1). As global population ages, neurological disorders are now responsible for 6.3% of the total conditions burden. These disorders consequently result in serious health problems that render patients disabled, necessitating additional medical care and prolonged care. Despite fact that there is a relatively high blood flow, transfer of therapeutic moiety through CNS is significant challenge. The CNS has developed a number of interfaces to protect it. Two physiological interfaces separate brain from its blood supply (2,3). The strongest interface is BBB, which prevents noxious and harmful entities from entering blood flow and control transfer of nutrients to brain for general activity. The BBB is diffusion interface that is semi-permeable and is made up of astrocytes, endothelial cells, tight junctions, pericytes from neurons, and basal membrane (4,5). Both blood-to-brain and blood-to-blood directions are utilized by these transfer tools. The blood to brain transport system, however, is highly crucial for therapeutic agenttransfer than other transport systems (6–8). A systemically regulated therapeutic agent is encountered by BCSFB before it enters CNS, which is next interface after BBB. This is situated at the choroid plexus, which also secretes new CSF and control the flow of solutes from blood to CSF. The choroidal epithelium is a multiactivityal organ that also performs neuroimmune and neuroinflammatory retorts, therapeutic agent and toxin metabolism, and neuroendocrine signalling, metabolism, and transport (9,10) (**Fig 1**). The blood vessel walls are where the BBB is located. (A) The BBB's structure can be seen in cross section of cerebral capillary, which is made up of network of pericytes, neurons, astrocytes, and endothelial cells. (B) Various therapeutic agenttransfer methods across the BBB. Water-soluble entity enter the BBB (I), lipid-soluble entity spread across the endothelial cells (II), small entity and peptides are transported via transport machinery (III), cationic therapeutic moiety are improved by adsorptive-mediated transcytosis (IV), and larger entity are brought in via binding sites-mediated transcytosis (V). Despite advancements in conditions pathology, the number of medications for neurological disorders is still quite small. In treating ND disorders, therapeutic agent librateto the brain in particular continued to be a significant issue. Nanotechnology has the potential to be very beneficial in overcoming these constraints (11,12). Nanotechnology can be distinguished from other traditional technologies by its extremely small size and high surface area. Nearly all macromolecular therapeutic moiety currently on the market and more than 98% of small therapeutic agent entity have failed to cross BBB, and therapeutic agent entities have poor biopharmaceutical and pharmacokinetic abilities (7). The distribution of therapeutic agent entity therefore urgently in needs have appropriate therapeutic agent transfer systems that

don't harm healthy organs and tissues. Although NPs given systemically are highly chemically stable, they have disadvantages related to their preparation, particularly large-scale industrial formulation and quality regulate. Further study is required on safety of injection and impact of NPs on CNS after they pass through BBB (7,13,14). Modern treatments for ND conditions like implant therapy and utilization of biomaterials like hydrogels that are loaded with anticancer therapeutic moiety (15,16).

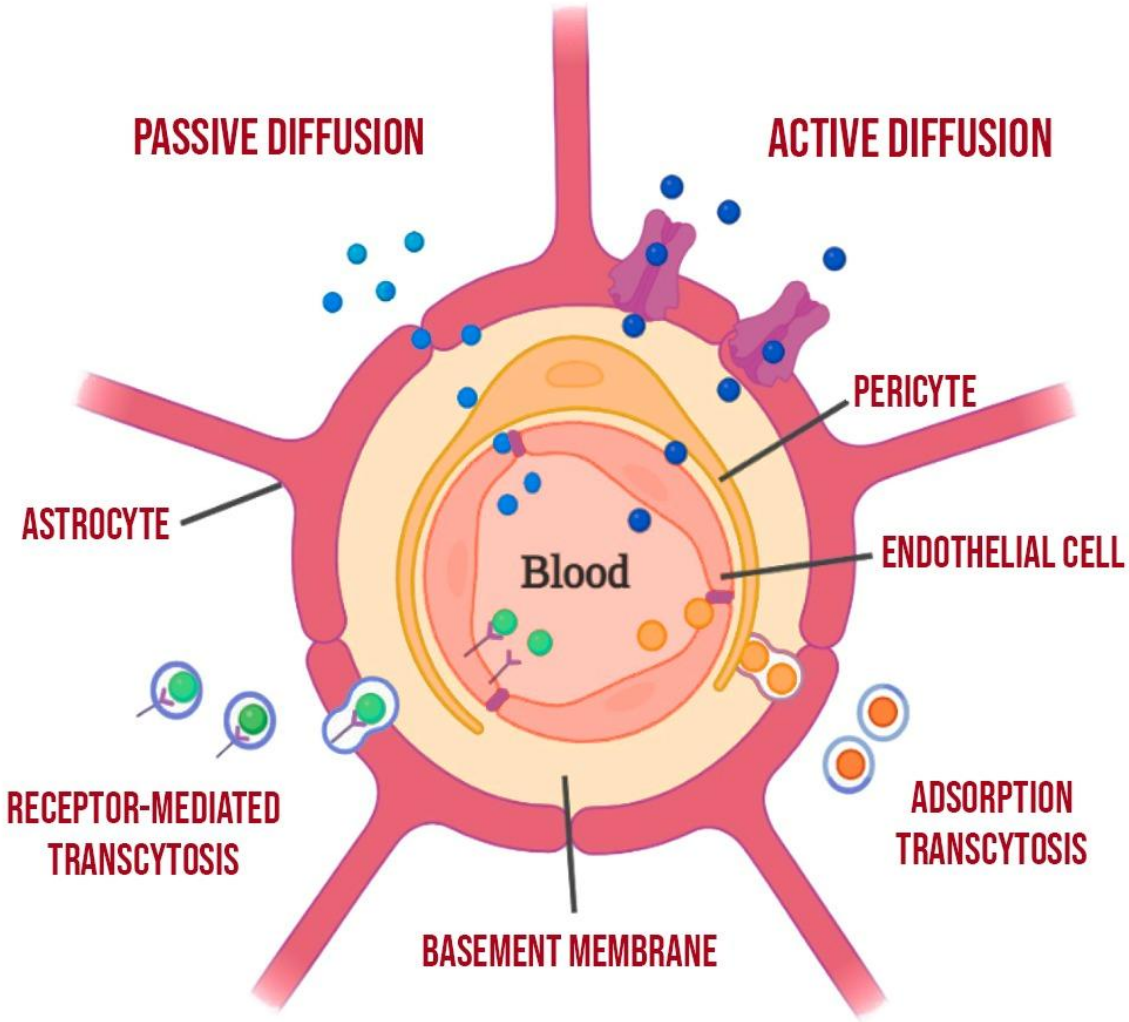

Fig 1:- Illustrating active and passive transport.

2. Neurodegenerative disorders

When brain nerve cells stop working properly or die prematurely, various ND disorders develop (17–19) (**Fig. 2**). The growth of ND disorders has been attributed to a variety of variables, making them complex conditions. Researchers have created multiaim-directed ligands to address other pathways implicated in such conditions due to their intricacy and rapid progression (20). One important contributing component to the pathophysiology of ND disorders is genetics. Additionally, pathophysiology of ND conditions and cautilizing neuronal damage appear to be heavily influenced by the clustering of amyloid fibrils, chronic inflammation, oxidative stress, cellular senescence and genome instability, proteostasis dysregulation, high metal clustering in the brain, and problems in mitochondrial activity (20,21). Although there are pharmaceutical treatments for ND illnesses that can minimize its significant negative effects, there is presently no one curementthat can completely reverse the conditions or stop it from progressing (22–24). The most typical signs and traits of these illnesses will be covered in this article.

Fig 2:- Various Neurodegenerative disorder.

2.1. Alzheimer's conditions

Alzheimer's conditions is linked to severe cognitive impairment (25,26). The early beginning of AD 15 is significantly influenced by amyloid plaques, which are extracellular deposits of the Aβ peptide, and intracellular hyperphosphorylated neurofibrillary tangles. Numerous indications also pointed to the glutamatergic system's activation as being crucial to AD pathogenesis (25,27,28). Starting with limited forgetfulness and issues with memory imprinting, the symptoms progress to short-term and then long-term memory issues (22,29). Plaques and tangles eventually cover the entire brain region, and the sufferer inevitably depends on others. Current therapies for AD patients call for long-term infusion of potent anti-A antibodies that may cross the BBB and flush out brain A plaques. The fundamental issue with treating AD is that a considerable amount of anti-A antibodies stay in the blood flow because only up to 0.1% of peripherally injected anti-Aβ antibodies can arrive brain (30). Overall, the AD curement process is quite complicated and calls for additional work and highly focutilized study (31).

2.2. Parkinson's conditions

With highly than 6.3 million sufferers globally, Parkinson's conditions today ranks second (32). The loss of dopamine-releasing neurons in brain causes progressive degradation of motor activities, though presence of nonmotor symptoms corroborates loss of neurons in nondopaminergic areas (33). Since the conditions 's primary causes are substantial motor deficits, the identification of this condition is frequently delayed, which makes management highly challenging. hGDNF one of the therapeutic options for Parkinson's conditions , has been reported to show promise. Utilizing a system adapted from mammalian cells, it has been shown to be quick and easy to manufacture a significant amount of pure hGDNF (34).

2.3. Huntington's conditions

HD is occurring due to Huntingtin gene's aberrant CAG nucleotide repetition. In brain, highly specifically in striatum (35), the enlarged CAG repeat of HTT gene causes abnormal development of polyQ and the aggregation of mutant HTT protein. In brain cells, HD is linked to protein aggregations such as mutant HTT, polyQ-expanded ataxins, and -synuclein, just as other NDconditions (36,37).

A variety of amyloid deposits can be recognized by conformation-dependent, oligomer-specific antibodies despite the fact that amyloid proteins have various amino acid sequences. Specifically binding to the oligomer region was an amyloid oligomer-specific scFv antibody coupled to PEGylated superparamagnetic iron oxide NPs. It demonstrates potential for early HD diagnosis and suggests a viable method for bridging the BBB (38). There is currently no known medical curementthat can stop HD (38,39) from progressing, though.

2.4. Acute Muscular Dystrophy (ALS)

The motor neuron conditions , also called as ALS is characterized by progressive muscular paralysis cauterized by deterioration of motor neurons in main motor cortex, brain stem, and spinal cord. The body location of onset, the relative mix of UMN and LMN involvement, the rate of progression, and cognitive impairment all play a role in highly varied phenotypic manifestation of ALS. The early symptoms of ALS, such as muscle twitching, cramping, stiffness, weakness, involuntary jerking motions, tremors, an inefficiency to regulate one's bowels or bladder, or an inefficiency to move or fully open one's eyes, may seem so slight that they are typically ignored. Electromyography is most significant technical test to support diagnosis of ALS up to this point, which is still a clinical diagnosis. While imaging and laboratory tests, such as MRI, do not always provide diagnostically useful information, they are important to rule out alternative conditions that might be highly curable (40).

2.5. Prion Conditions

There have been reports of prions, also called TSEs in both people and animals. Prion illnesses are a class of disorders that rapidly advance and are distinguished by a specific range of clinical abnormalities. The number of illnesses in s and animals classified as TSEs has recently increased. They all exhibit comparable symptoms, such as the formulation of varied amyloid plaques and spongiform degeneration of the brain (PrPSc). In actuality, PrPSc is an isoform of naturally occurring prion protein, which can manifest as amyloid deposits (41).

3. Interface for therapeutic agent transfer

Various interfaces, such as the BBB, BCB, and Blood-Tumor Interface, prevent therapeutic moiety from arriveing CNS through CVS. The specifics of these interfaces are examined in the current study (42).

3.1. Blood-Brain Interface

Astrocytes and pericytes are two of major components of the BBB, which is made up of brain capillary endothelial cells (43). Proteins, enzymes, and nutrients can pass across the permeable BBB, but water-soluble compounds cannot. As a result, it limits the use of medications and other therapeutic and diagnostic moiety while treating ND illnesses (44). The aq. paracellular diffusional pathway between cells is sealed by cerebral endothelial cells' development of tight junctions at their borders. The endothelium is partially surrounded by pericytes, which are dispersed unevenly outside of the cerebral capillaries. The extracellular matrix of glial end foot is various from that of cerebral endothelial cells and pericytes, which collectively participate to and surround local basement membrane BL1 (BL2) (**Fig. 3**). A complex network surrounded by the capillaries is created by astrocytes walking on it, and this close cell union is crucial to regulatinginterface qualities. Vasoactive peptide administration control BBB permeability. The endothelial cell membranes of endothelial cells may operate as passive or active carriers, or motion of solutes over BBB may be passive with highly lipid-soluble entity.

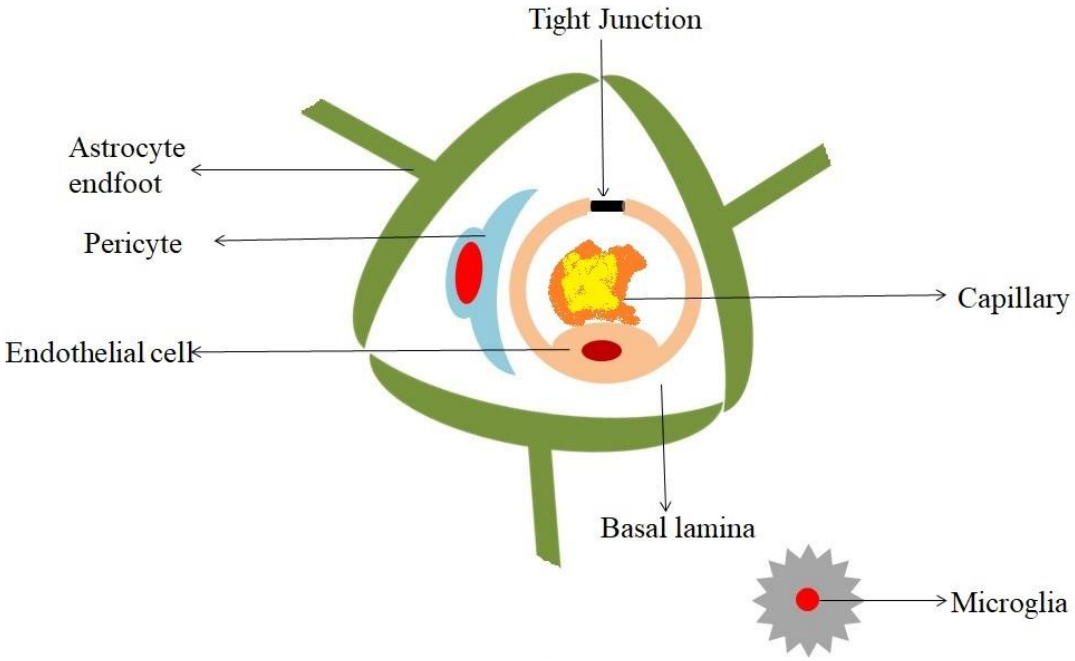

Fig 3:- Various elements blood-brain interface(45).

3.2. Blood-cerebrospinal fluid interface

Before entering CNS, BCB experiences a therapeutic entity that is systemically operated. The interstitial fluid of brain parenchyma and CSF can exchange entity, and CSF can precisely regulate the entry of blood-borne entity into CSF. This is found in highly vascularized stroma with connective tissue and choroidal epithelial cells that makes up the choroid's plexus epithelium (**Fig. 4**). The lateral, third, and fourth ventricles of brain are where CP is located. Additionally, CP establishes a connection between peripheral blood and cerebrospinal fluid (CSF), which accounts for up to 50% of all CSF. In addition to possibly being a component of the circadian regulation system, the CP's main activity is to create BCSF and the CSF interface. The choroid plexus operates as physical, immunological, and enzymatic interface that aids in therapeutic agent transport, metabolism, and signalling processes while also preventing transit into the CSF (46,47). The choroid plexus strictlycontrol molecular concentration in CSF, and various transfer and secretion channels active in choroid plexus epithelial cells make them desirable to regulate the molecular and cellular composition of brain fluid and CSF, as well as between the blood and CSF at the interfaces, when combined with the arachnoid membrane (48,49). As a result, the CSF actively removes therapeutic organic acids (29, 30).

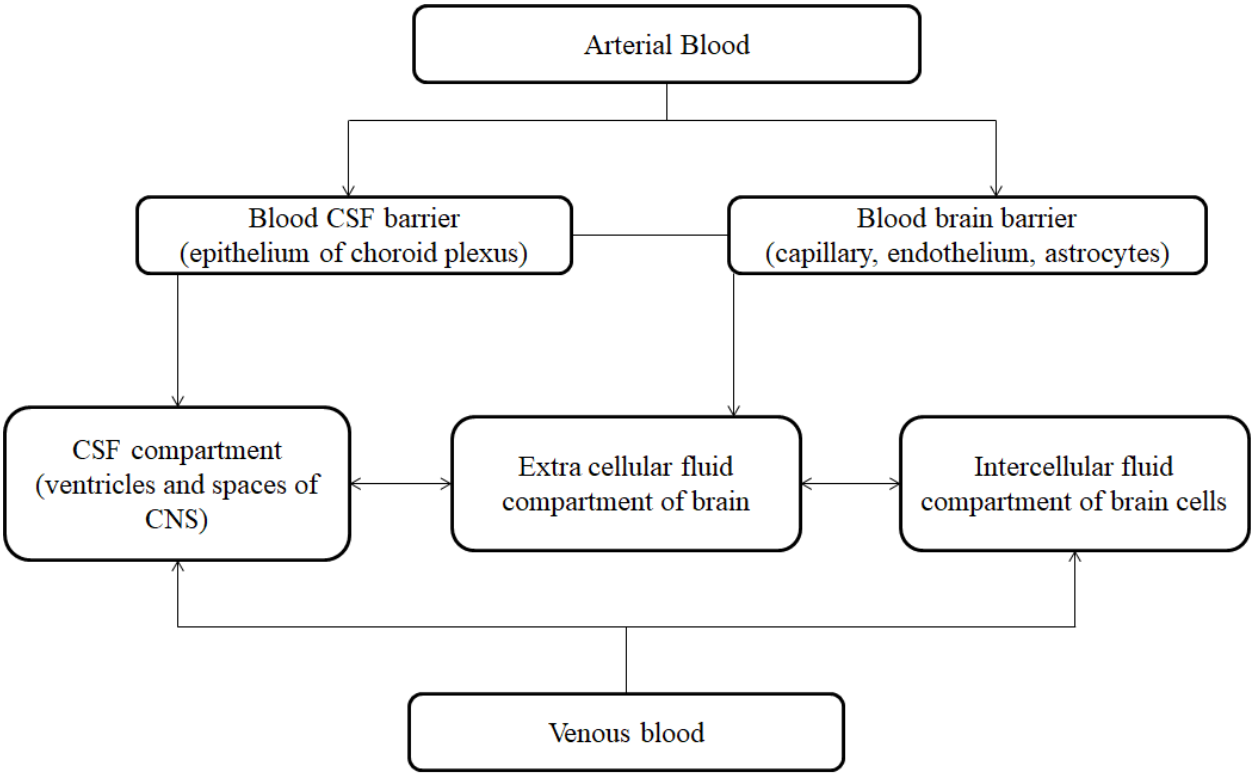

Fig.4:-Presentation of the BBB,CSF, and cerebral CSF in a diagram(45).

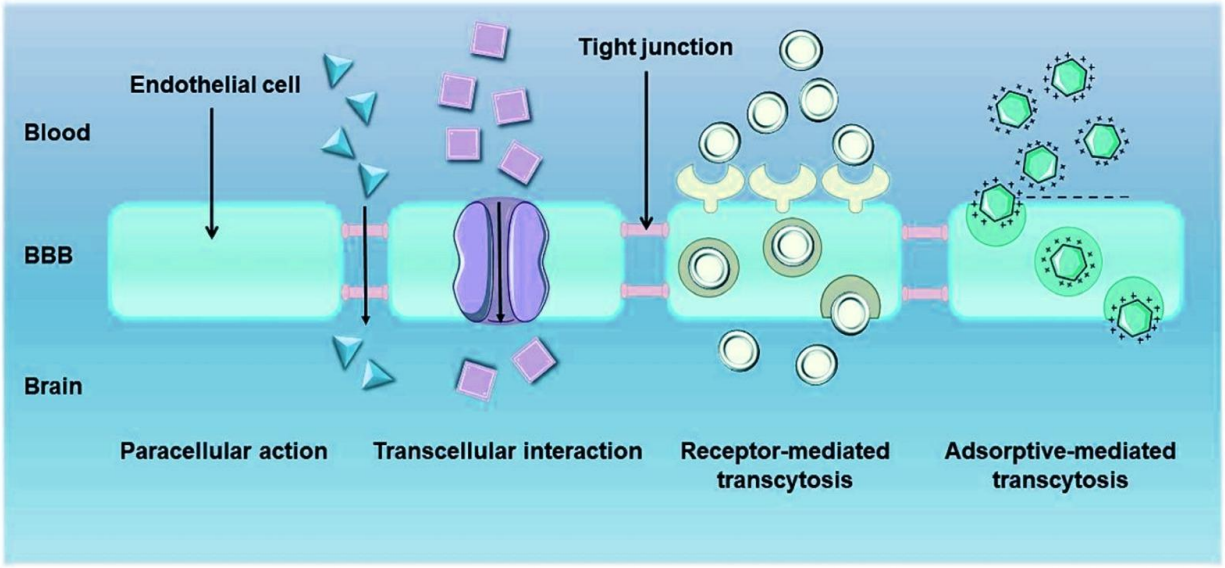

Fig.5:- Penetration of drug through BBB interface.

3.3. Blood-tumor interface

When there are CNS malignancies, intracranial therapeutic agent administration becomes highly challenging. BBB exhibits clinical results in the CNS tumours' microvasculature. In CNS cancers, the physiological interfaces prevent medication transport through the circulatory system. Inhibiting efflux therapeutic agent transporters, opening TJs with mannitol hyperosmotic solution, and binding sites-mediated therapeutic agent transfer systems are some methods that may be utilized to help therapeutic moiety pass through it (50,51). In contrast, show a schematic picture of the blood–brain interface (**52**) (**Fig.5**).

The three primary interfaces in the CNS are BBB, the choroid plexus interface, and meningeal or arachnoid interface.

The arachnoid and choroid plexus interfaces divide blood from CSF, and blood-brain interface separates blood from ISF.

The mural, glial cells, and basement membrane that make up the blood brain interface have a complicated architecture that works together to regulate blood brain interface's integrity and regulate its permeability.

Table 1:- Various methods to deliver the therapeutic agent to the brain (45).

S.no.	1.	2.	3.	4.	5.	6.	7.
Approach	BBB disruption	Biotechnology based transfer	Chemistry based transfer	Intracerebral transfer	Intrathecal transfer	Intranasal transfer	Noninvasive transfer
Advantages	Clinically applicable Enhanced stability of cargoes; Non-immunologic.	Effective pathway for the neuro-pharmaceuticals to the brain tumors and PD.	Re composition of the therapeutic agent results in the generation of a pro-therapeutic agent.	Sustained release. Favorable results are obtained with high level of therapeutic agent concentration.	Cost effective with the least side effects.	Rapid absorption and onset of action; enhanced bioavailability.	Helpful in the passage of BBTB
Disadvantages	Nonselective; neurotoxic.	Grafts do not survive for long time.	Adverse pharmacokinetics and the increased molecular weight of the therapeutic agent.	Slow motion of Compounds. Therapeutic agent dosage Restricted by implant size.	Highly invasive, poor patient consent.	Decay of therapeutic agents via mucosal enzymes appropriate only for strong therapeutic agents.	widespread therapeutic agent distribution Poor transfer of the therapeutic agents.

4. THERAPEUTIC AGENT ADMINISTRATION APPROACHES IN BRAIN

Various therapeutic agent transfer approaches have been studied, described in **Table 1**, for efficient therapeutic agent transfer without any restrictions (52). Up until now, these methods have included various invasive, non-invasive, and other techniques.

4.1. Invasive Method

Only a few peptides, low molecular weight entity, and lipid-soluble nutrients can significantly cross the interface when utilizing the invasive method, either through active diffusion or specific transport mechanisms. Direct invasive transfers of medication into brain via a craniotomy and intrathecal administration are implied. Both of them have a wide range of small and big molecule transfer. Through this intranasal pathway, a number of entities, including pathogens, toxic moiety , and viruses, among others, can be delivered to the CNS. The main drawbacks are physiological stress and the unintended liberate of anticancer moiety into healthy brain tissues (3,53).

4.2. Transfer Intracerebrally

Direct injection into specific area is facilitated through stereotactic coordinates and/or the continuous intraventricular infusion of therapeutic moiety into brain tissue. This technique enables a precise and concentrated release of therapeutic moiety to specific regions of the brain, leading to highly focused and effective outcomes. Positive results have been observed in clinical trials for Parkinson's condition utilizing this approach. This approach had positive outcomes in Parkinson's condition clinical trials. Due to the nearly arranged cells in the grey and white matter microenvironments, compounds in the brain move slowly. As a result, a greater dose is necessary to achieve the proper therapeutic agent concentration (54).

The intended implanted devices are based on polymeric matrixes with therapeutic moiety encapsulated inside that are biodegradable and biocompatible. At the intended transfer site, where the reservoir is to be implanted, the skull is opened. The therapeutic agent's physicochemical behavior has a significant impact on how well it penetrates the body, and in most cases, only a little amount of the molecule is given. For instance, treating quadriplegic patients with a nerve growth factor implant after inserting it into the brain produced better results (55).

4.3. Interruption Of BBB

The biochemical disruption of the blood-brain barrier (BBB) is employed to enhance the therapeutic impact of medications, facilitating their specific delivery to the brain. This method involves the direct administration of medication compounds to the central nervous system (CNS) utilizing energy or specific entities. One notable advantage of this approach is its capability to target specific brain regions. Two methods are employed to induce BBB disruption: 1. To enhance the delivery of chemotherapy medications to brain tumors, various chemical compounds with higher osmotic pressure, such as mannitol hyperosmotic solution, are commonly used. Unlike ultrasound and electromagnetic radiation, this approach induces the shrinkage of endothelial cells and the expansion of tight junctions. Clinical utilization s often involve the use of ultrasonic waves within recommended frequencies of 0.2 to 1.5 MHz. 2. Microbubbles are intravenously injected to disrupt the BBB, typically lasting from a few hours to around a day. This method is distinct from ultrasound and electromagnetic radiation and is particularly effective in clinical utilization s.(56)

4.4. Transfer Intrathecally

Here, the neuro-therapeutic moiety are intrathecally given straight into the brain's cisterna magna. In cases of spinal disorders and diffuse meningeal conditions, this is the best pathway for therapeutic agenttransfer. The key benefit of this strategy is that it does not necessitate the extensive use of therapeutic medications because it enables the transport of a bigger number of enzymes to the brain. Additionally, this approach avoids the issue of systemic exposure and toxicity while regulateling the issues with medications' short half-lives in the blood. The main drawback of this approach, however, is the potential of therapeutic agent diffusion along the distal region of the spinal canal (57).

4.5. Non-Invasive Strategy

The wide therapeutic agent distribution throughout the brain blood vascular network is made possible by a number of non-invasive brain therapeutic agent transfer techniques. With the BBTB becoming highly permeable thanks to this procedure, medications can pass through with highly efficiency. Claudins, occludin, and junctional adhesion entity are the main proteins in tight junctions (TJs) in the BBB (JAMs). Microbubbles and ultrasound irradiation, which temporarily opens the BBB without having a deleterious effect on healthy brain tissue, can be utilized to reduce the expression of these TJ proteins. These methods frequently rely on therapeutic agent modifications, such as carrier-mediated therapeutic agent transfer, binding sites-mediated therapeutic agent transfer, chemical therapeutic agenttransfer, protherapeutic moiety , and lipophilic analogues. The development of new therapeutic agent-aiming strategies, however, has been hampered by the difficulty of systemic transfer of medications to the brain in a non-invasive manner (3,11).

4.6. A chemistry-based strategy

This strategy takes into account the appropriate chemicals for therapeutic agent material distribution via BBB. In this method, the medication can be lapidated in two various ways. First, the polar activityal groups on the therapeutic agent's water-soluble entity can be hidden by conjugating them with entity that is lipid-soluble.

Second, a lipid-soluble therapeutic agent carrier can be conjugated to a water-soluble medication. Although Various strategies for delivering neurotherapeutics have been created, these methods have been the subject of intense study for the past 20 years. Cationic proteins and chimeric peptides are two examples (57).

4.7. Utilizing Biotechnology

The field of biotechnology has garnered a lot of interest from scientists in a variety of various disciplines. This method, which is frequently utilized in recombinant DNA and polymerase chain reaction protein engineering, entails implanting embryonic neural grafts into the defective area of the brain. The biotechnology offers an efficient pathway for the transfer of therapeutic moiety to brain tumours and neuro-pharmaceuticals to the brain. Parkinson's conditions can also be effectively treated utilizing this strategy. However, without neovascular innervation, these grafts do not survive for a longer period of time (55).

4.8. Transfer Via Inhalation

For systemic pharmacological action, the intranasal pathway has been utilized to deliver therapeutic moiety directly into the blood flow through the nasal mucosa. This eats the trigeminal nerves that connect the nasal mucosa and trigeminal nerves in the brain, takes a little dose, is self-administered, and does not use sterile procedures. Bypassing GI breakdown and protein binding in the circulation, this enables rapid absorption and the commencement of action, the absence of hepatic, simple administration, and all of the above. This increases therapeutic agent absorption and decreases systemic adverse effects. The transfer of cytokines, neurotrophins, neuropeptides, genes, and chemotherapeutics are a few examples of intranasal administration. The obvious negatives of this method include the mucosal enzymes that break down medications, the fact that it is not administered by a medical practitioner, the brief hold time in the nasal cavity, and the limitations imposed by the nasal anatomy. These consequently follow brief therapeutic agent doses that arrive the CNS(58,59) (**Fig.6**).

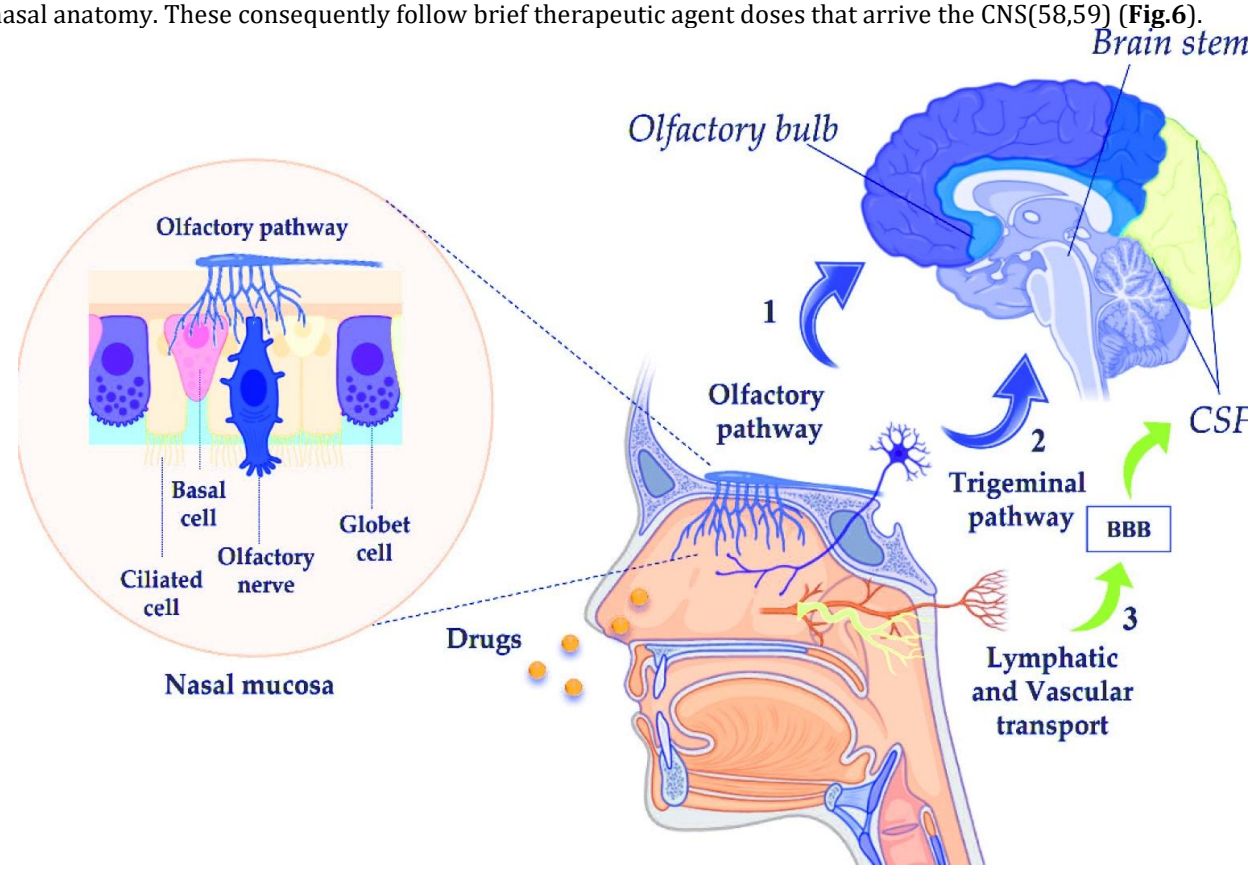

Fig.6:- Drug delivery through nasal route.

5. Nanotechnology Tools For ND Conditions

Materials with at least one dimension less than 100 nm are known as NPss. They can be categorized into zero-dimensional materials, which include NPss and quantum dots, one-dimensional materials, which include nanofibers, nanotubes, and nanowires, and two-dimensional materials, which include graphene based on their structure.

Nanomaterials have many uses in the biomedical industry today, including medication transfer, biosensors, bioimaging, and highly. 6, 58–6. Engineered nanomaterials created as treatments for NDconditions are referred to as neuronanomedicine (60). In order to create nanoscale devices that can interact with biological systems on a molecular level, nanotechnology creates tailored nanomaterials 62. These nanotechnology-based devices can

interact, react, and trigger aim cells and tissues to produce the desired physiological retort while minimising negative side effects. Some NPss are made to aim particular cell domains and increase BBB penetration. The location of intracellular or extracellular entities, such as amyloid beta plaques in Alzheimer's conditions , is the focus of their work.

Adsorptive and binding sites/transporter-mediated transcytosis would be utilized to help NPs penetrate the BBB after surface alteration to create highly positive particles. Transport of lipoproteins (LPs) to the brain is facilitated by recognition of apolipoprotein E (Apo E) by certain binding sitess found on BBB. When NPs are activityalized with LPs, for as by conjugating Apo E to albumin-NPs or liposomes, they can be transported and identified by certain binding sitess on BBB (61) (**Fig.7**).

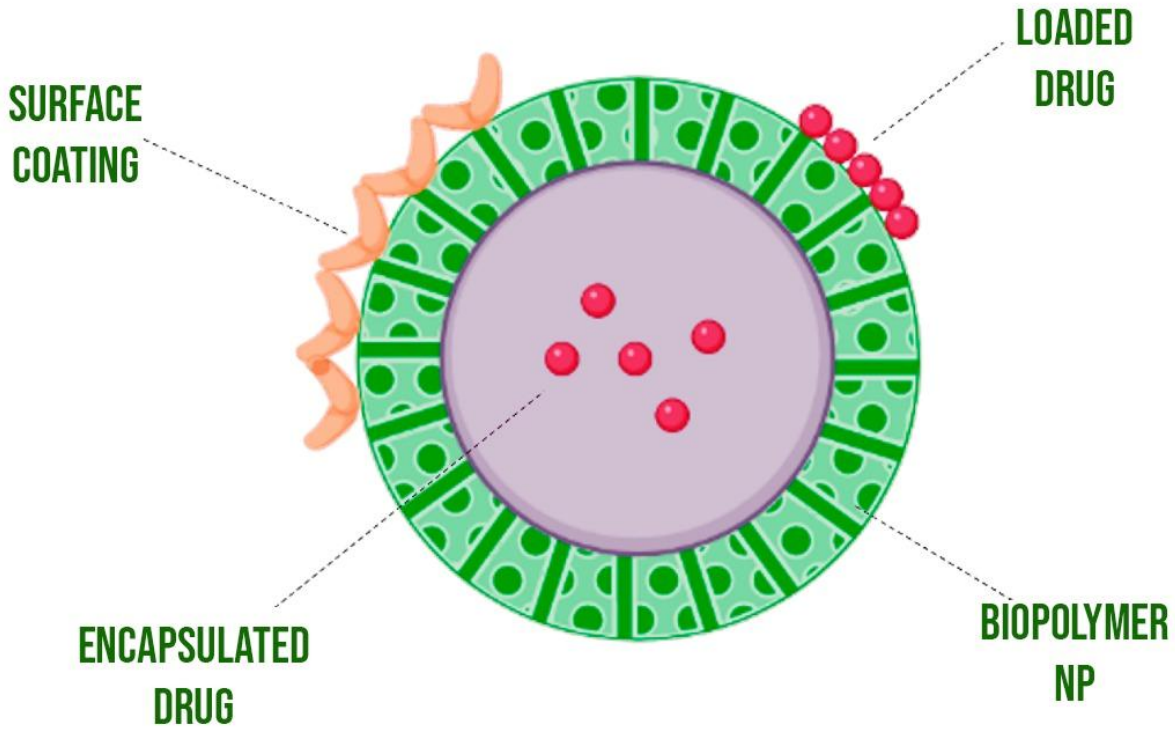

Fig.7:- Illustration of drug loading, encapsulating and surface coating.

The ability to modify complex biological systems with highly selection and specificity is provided by nanotechnology. It is still a critical requirement for nanomedicine to develop nanocarriers that can regulate stability in the blood flow, shield the medication from metabolism, and encourage long-lasting therapeutic agent release, however this is now thought to be insufficient. Pharmaceutical nanotechnologists are currently faced with difficulties in colloidal chemistry and, most importantly, in the characterization of the engineered nanocarriers from a technological and physiological point of view. This presents a challenge for active aiming of specific pathological cells (55). Nanoengineered entities, such as nanotherapeutic moiety , can penetrate the BBB and exhibit lower invasiveness. The most studyed NPs for non-invasive brain medication administration include liposomes, polymeric NPs, and solid-lipid NPs (SLN), which have unique abilities like biocompatibility, stability, low antigenicity, and high biodegradability. They have become one of the best smart platforms for carefully discharging their cargo at the intended locations. Therefore, therapeutic agenttransfer systems may be the most significant utilization of NPss in the biomedical field . Here, we'll go over a few ways that these nanomaterials can be utilized to deliver therapeutic moiety to treat NDconditions:

5.1. Inorganic NPss

5.1.1. Gold NPss—Due to their multiactivityal abilities in treatments, imaging, and surface modification, gold NPss (AuNPs) have been widely exploited as nanomaterials for theranostic utilization s (61). It has been demonstrated that synthetic AuNPs combined with exosome-derived membranes have special characteristics for aimed transport to the brain. Additionally, aimed-exosome coated AuNPs were able to aggregate in the mouse brain following intravenous administration, according to the bioluminescence imaging. A highly innovative and successful method for providing excellent brain aiming may involve surface modification of synthetic AuNPs with the brain-aimed exosome.

Amyloid conditions such as Alzheimer's and Parkinson's conditions are associated with the development of harmful intermediates during the self-assembly process in amyloidosis disorders. This process is linked to the misfolding of typically soluble peptides and proteins, resulting in the creation of amyloid fibrils. As a result,

therapeutic strategies for Alzheimer's conditions often focus on inhibiting, delaying, or dissociating A oligomers and fibrils. While nanoparticles (NPs), specifically AuNPs (gold nanoparticles), have demonstrated significant effects on the A fibrillation process in this context, their impact on memory and cognitive function has not been thoroughly investigated in vivo.

The protein -lactalbumin was selected as a suitable sample for researching amyloid development arising from the creation of a molten globule state. This choice aims to assess the influence of AuNPs on amyloid formation.

5.1.2. Silver NPss: Following in vivo implantation, silver nanoparticles (SNPs) traverse from the bloodstream to the brain. In an in vitro model employing rat brain micro-vessel vascular endothelial cells (BMVECs), the distribution of SNPs crossing the blood-brain barrier (BBB) was examined. Results demonstrated that, after 4 hours of cultivation in a medium containing 100 g/mL of either SNPs or silver microparticles (SMPs), SNPs were capable of crossing the BBB and accumulating within BMVECs, whereas SMPs did not exhibit a similar ability. Transcytosis of capillary endothelial cells may be the primary mechanism by which SNPs are transported across the BBB. Similar findings on SNPs' ability to cross the BBB showed that only SNPs, when subcutaneously injected into rats' brains at a dose of 62.8 mg/kg each of SNPs and SMPs, could cross the BBB and enter the brain as a particle. When SNPs are injected into the brain, they can attach to neurons, build up there, and cause toxicity consequences that impair neuron activity. The librateof SNPs from the membranes of brain cells can impact nearby neurons, cause neural cell death, and ultimately cause pathogenic changes in neural cells. Specific vascular endothelial cell transcytosis and BBB disruption by weakening of the tight connections or by dissolving the membrane of the endothelial cells are the proposed mechanisms of admission of SNPs into the brain through rupture of BBB. By building up in the brain over time, they can cause further neuronal degeneration and necrosis. Particularly for solid core NPs that would not disintegrate, the risk of some NPss being retained in the brain over an extended period of time can be very concerning. Newly developed nanoplatforms are built to have certain nano-abilities that can be utilized to regulate cell metabolism and cell-cell communication. However, the immune system's oxidative alteration of these new components may have unanticipated consequences and detrimental impacts on cell processes. Although timely and efficient degradation of these therapeutic agent carriers is a crucial component of their design, it must be optimised based on nano-carrier degradation versus therapeutic agent-payload degradation (62). It's crucial to take into account some of these NPss' side effects, or the reason behind any potential harm they may cause to metabolic pathways. According to reports, amyloid precursor protein (APP) gene expression was enhanced in brain cells after curementwith AgNPs. Neprilysin, a significant A-degrading enzyme in the brain, and low-density lipoprotein binding sites, which enhances A uptake and degradation in the brain, are two additional factors that inhibit the progression of Alzheimer's conditions . These factors were both decreased in neural cells, as well as their protein levels. As a result, it is important to pay attention to the location of AgNPs in the environment.

5.2. Magnetic Nanomaterials

Magnetic NPss from a variety of disciplines, one of the main areas of interest for studyers. Magnetic NPss (MNPs) have gained highly and highly attention in the biomedical community. MNPs have special qualities that can be utilized for cell sorting and medication aiming, such as how they respond to magnetic fields. Numerous studies have been conducted on the relationship between astrocytes and iron oxide NPss (IONPs) (63).

The idea behind magnetic aiming is to provide therapeutic agent-attached magnetic NPss, direct them to a aim area under a confined magnetic field gradient, keep them there until the therapy is finished, and then remove them. In order to obtain high local concentration and prevent toxicity and other negative effects brought on by high therapeutic agent doses in other areas of the organism, magnetic therapeutic agent carriers have the capacity to carry a large dose of the therapeutic agent.

5.3. Polymeric Nanomaterials

Polymeric NPss are particles made of polymers that typically range in size from 1 to 1000 nm (64). Due to its low toxicity, customizable breakdown rates, high therapeutic agent loading capacity, ability to cross the blood brain interface, and ability to aim the CNS 82, degradable NPss in particular have emerged as the primary kind of NDtherapeutic agent carriers.

The widespread utilization of biodegradable polymer-based nanoparticles (NPs) enhances the therapeutic benefits of various water-soluble/insoluble medications and bioactive entities, including improvements in solubility, bioavailability, and retention time. The key considerations for the successful utilization of these polymeric systems in medicine and pharmaceuticals revolve around their biodegradability, biocompatibility, non-toxicity, non-immunogenicity, and non-carcinogenicity. In the field of medicine and pharmaceuticals, polylactic acid (PLA), polyglycolic acid (PGA), and poly lactic-glycolic acid (PLGA) are frequently employed for their advantageous properties.

5.4. Carbon Nanomaterials

Carbon-based nanomaterials with hydrophobic surfaces, such as zero-dimensional fullerene (C60), one-dimensional carbon nanotubes, and two-dimensional graphene, have attracted significant attention in

nanomedicine. Their distinctive combinations of chemical and physical properties make them particularly intriguing in the realm of nanomaterials. (65). We'll talk about a few of these nanomaterials' utilization s here.

5.4.1. Graphene — Due to its beneficial features, graphene and graphene oxide (GO) have lately gained popularity as innovative and competitive therapeutic agenttransfer methods that have the potential to be utilized in systemic, aimed, and local therapeutic agenttransfersystems. For graphene-based materials to have the desired abilities, chemical alterations or activityalization are usually necessary. Graphene-based materials typically aggregate in aq. medium containing proteins, salts, or other ions. Studyers can alter the fundamental electrical and optical characteristics of graphene by activityalization. Additionally, these alterations enable the conjugation of genes, medicines, contrast moiety , antibodies, peptides, ligands, and graphene NPs's surface(66).

The layer-by-layer deposition of graphene-heparin/poly-L-lysine polyelectrolytes onto 2D surfaces and 3D electrospun nanofibers was employed for their construction. Both 2D and 3D graphene-based polyelectrolyte multilayers were found to regulate neuron cell adhesion and neurite development in cell culture studies, with no observable cell death. This electroactive scaffold modification through LbL deposition holds potential for creating useful and biocompatible polymer scaffolds, particularly in utilization s such as electrical entrainment or biosensing, contributing to neuronal regeneration.

5.4.2. Fullerenes-Fullerenes provide their protective role primarily in two ways: radical sponge and hydrophobic surface. A "radical sponge" that can trap multiple radicals in a single molecule sphere is an example of the unique structure of fullerene and results in an efficient antioxidant activity against cytotoxicity brought on by intracellular oxidative stress (67). In neuroblastoma cell Parkinson's conditions model cautilized by 1-methyl-4-phenylpyridinium (MPP1), the protective benefits of the polyhydroxylated fullerene derivative $C_{60}(OH)_{24}$ were investigated. According to the findings, polyhydroxylated fullerene derivative $C_{60}(OH)_{24}$ is a powerful antioxidant with strong mitochondrial protective antioxidant with direct radical scavenging activity and indirect antioxidant inducing activity. It is a potential agent for preventing mitochondrial dysactivity and oxidative damage in an MPP1-cell.

5.4.3. Carbon nanotubes- are carbon allotropes having a cylindrical nanostructure. The fullerene family, which includes nanotubes, has members with long hollow structures built of sheets one atom thick. They contain one or highly layers of single-wall and multiwall CNTs (68), respectively, of carbon. These carbon-based NPs are useful in basic medical procedures. The CNTs exhibit unique mechanical, chemical, and electrical characteristics (69). CNTs have both their pure and modified (by various polymers) forms assessed. Nanotube-neural hybrid networks can facilitate synapse formation, network connectivity, and neuronal activity. Due to the outstanding physical characteristics of these nanomaterials and their recently discovered capacity to interface with neuronal circuits, synapses, and membranes, CNT-based technologies are likely to be particularly helpful in the future for promoting activity recovery of neurons after brain damage (45).

6. Extracellular Vesicles Mesenchymal Stem Cells

It was thought that utilizing stem cells may be an effective technique for treating neurodegenerative conditions s. Adult tissues can be used to produce stem cells, which are unvariousiated totipotent or multipotent cells (70). In vitro, osteoblasts, adipocytes, and chondrocytes may be formed from mesenchymal stem cells (MSCs) (71). MSCs have been thought to have the ability to heal wounded, harmed, or sick tissues because of their ability to transvariousiate in vitro into epithelial cells and lineages descended from the neuroectoderm (72). Additionally, MSCs have the crucial capacity to control the immune response of a variety of immune cells both in vitro and in vivo (73–76). MSCs must have simple access to the target organ in order to be used for tissue repair. Numerous studies have shown that they may migrate from the circulation into inflammatory tissues and home in on the injured brain, where they have a neuroprotective impact.

Several preclinical investigations have shown the effectiveness of MSCs in treating neurological disorders. Although MSCs have therapeutic effects, only a limited proportion of variousiated, identifiable MSCs engraft in central nervous system (CNS) tissues following transplantation. These characteristics imply that MSCs' capability for transvariousiation may not be as important to tissue healing as their ability to alter the tissue microenvironment via secretion of soluble molecules (77–81).

6.1. Utilization of EV MSC

As was previously mentioned, preclinical evidence for EVs-based therapeutics are quite positive. Despite the fact that there aren't many accessible clinical data yet, MSC-EV treatments have proven to be significantly safer and more adaptable than cell therapy (82,83). Exosome-related research have been filed on https://beta.clinicaltrials.gov (accessed on January 25, 2023). The bulk of these research use EVs from patient bodily fluids for diagnostic and prognostic purposes and are observational in nature. In other disorders, encouraging outcomes have been verified (84). Ischemic stroke and its recurrence were studied by stereotaxic injection of MSC-EVs overexpressing miR-124 in the clinical experiment NCT03384433. There are now just two studies filed that include MSC-EVs and chronic neurodegenerative conditions s: Alzheimer's conditions (NCT04388982) and depression, anxiety, and dementias (NCT04202770). In NCT04202770, specific ultrasound was utilized to improve the intravenous transport of EVs from MSCs to the hippocampus for patients with

cognitive impairment, the amygdala for patients with anxiety, and the subgenual target for patients with resistant depression. MSC-EVs are repeatedly administered intranasally (at low, medium, and high dosages, respectively) for 12 weeks to patients with mild to moderate dementia as part of the registered trial NCT04388982 to assess their safety and effectiveness.(81)

Conclusion

Numerous studies have undoubtedly confirmed the crucial part played by BBB in preserving the CNS's normal physiological activity. There are studies that BBB impedes therapeutic agent bioavailability, which is basic fundamental and important problem in curement of ND illnesses, though. Therefore, design of brain-aimed medication carriers is crucial. The ability to overcome obstacles in pathway of delivering medications to aimed brain cells is represented by the rapid advancements in nanotechnology, which have led to the introduction of numerous unique and promising designed NPss and nanomaterials. There are still a lot of unanswered questions and gaps regarding the use of nanomaterials for biomedical utilization s, despite the fact that there have been many studies devoted to utilization of NPss on therapeutic agent transfer systems as fresh sector. Additional consideration should be given to the following factors: 1) The adverse effects of various NPs on the organs and the cells they aim. Numerous nanomaterials have capacity to enter CNS and cause hazardous effects, as almost all recorded investigations clearly reveal. The coating of NPs with desirable biodegradable polymeric shells, which can increase therapeutic efficiency of transfer systems while lowering their unintended harmful consequences, is one potential option. 2) Improving the structural layout and enhancing the operation of these particles to maximize the amount of medication placed on them. High-therapeutic agent loading nanomedicines are currently plagued by significant issues with excepients evaporation and degradation rates. Some kinds of excipient-free, carrier-free nanomedicines have been created as a remedy. However, the majority of recent investigations on high therapeutic agent-loading nanomedicine has concentrated on design and manufacture rather than in vivo or clinical tests. As a result, it will take lot of time and money to enhance these nanomedicines and obtain FDA approval. 3) Off-aim therapeutic agent interactions with non-specific binding sites, especially for binding sites-mediated transcytosis techniques. Numerous nanomaterials have been shown to be capable of interfering with biological processes all of which are present in the majority of ND illnesses. 4) Investigation of innovative, unstudied NPs and filling in the gaps found in therapeutic agent transfer systems for brain-aiming therapeutic moiety . The effectiveness of therapeutic agent transfer by NPs can be increased by combining nanotechnology with other cutting-edge high-tech approaches. Another useful method to address the issues with therapeutic agent transfer methods is the development of engineered NPs with integrated therapeutic and diagnostic uses. Therefore, keeping up with the most recent formations in this exciting field can give you methodical knowledge to plan future initiatives and improve how NPs are utilized to treat ND illnesses.

List of abbreviations

BBB- Blood Brain Barrier
ND- Neuropsychological Disorder
CNS- Central Nervous System
CSF- Cerebral Spinal Fluid
AD- Alzheimer’s conditions
NPs- Nanoparticles
Aβ- Amyloid Beta
ALS- Acute Muscular Dystrophy
Prpc- Prion Protein
BCB- Blood Cerebral Barrier
ISF- Intestinal Fluid

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