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New Strategies for Brain Drug Delivery: A Review

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ABSTRACT

The central nervous system is one of the most delicate microenvironments of the body which is protected by certain barriers like the blood-brain barrier (BBB), blood-cerebrospinal fluid barrier (BCSFB), blood-retinal barrier, blood spinal cord barrier, etc. regulating its homeostasis. Out of which BBB is a highly complex structure that restricts the number of macromolecules from the blood to the brain which is necessary to protect it from injuries and diseases. It also restricts the movement of ions to a limited number of small molecules. The treatment of central nervous system (CNS) disorders always remains challenging for the researchers because of various physiological barriers presence, primarily the blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) which limits the entry of molecules to the brain and hind the efficacy of various drug therapies. Hence, the development of a promising therapy for the treatment of brain disorders is essential where drugs will target the brain, particularly to the diseased cells by avoiding the physiological barriers. In this review, it has been discussed the role of various physiological barriers including the BBB and blood-cerebrospinal fluid barrier (BCSFB) on drug therapy. Further, different novel and current strategies for drugs targeting the brain including, polymeric nanoparticles, lipidic nanoparticles, inorganic nanoparticles, liposomes, nanogels, nanoemulsions, dendrimers, quantum dots, viral vectors, exosomes, etc. along with the intranasal drug delivery to the brain have been discussed in the review. It has also been discussed in the review that drugs which successfully cross the BBB formulated by the novel and current methods.

1.1 INTRODUCTION

The brain is one of the most complex and vital organs which covers around 2.0% of the total body weight (1.2–1.4 kg).[1] It is the commanding center of the nervous system (Figure 1) which controls the respective response through motor neurons by receiving the signals from the concerned sensory organs. It also regulates activities like muscular movement, physiological secretion from the glands, hormone secretion, controlling body temperature, breathing, physical growth, etc. Mind senses the environment and the surrounding stimuli for deciding, processing, controlling and integrating all the information's; developing thoughts and plans accordingly and memorizing of events throughout the life.[2] The Brain is protected by various physiological barriers like a blood-brain barrier (BBB) and blood-cerebrospinal fluid barrier (BCSFB) which regulates the entry of antigens like toxins and other harmful stimuli thus maintaining the homeostasis of the brain.[3]

The functions of barriers due to physical changes, environmental factors, toxins, infection, mutation, aging, etc. and any variation in the structure and function of the brain may result in various neurological disorders including brain cancer, Alzheimer's disease, Parkinson's disease, stroke, and multiple sclerosis.[4,5] Pathophysiology involving protein aggregations which lead to neuro-degeneration or dysfunction of the brain.[6]

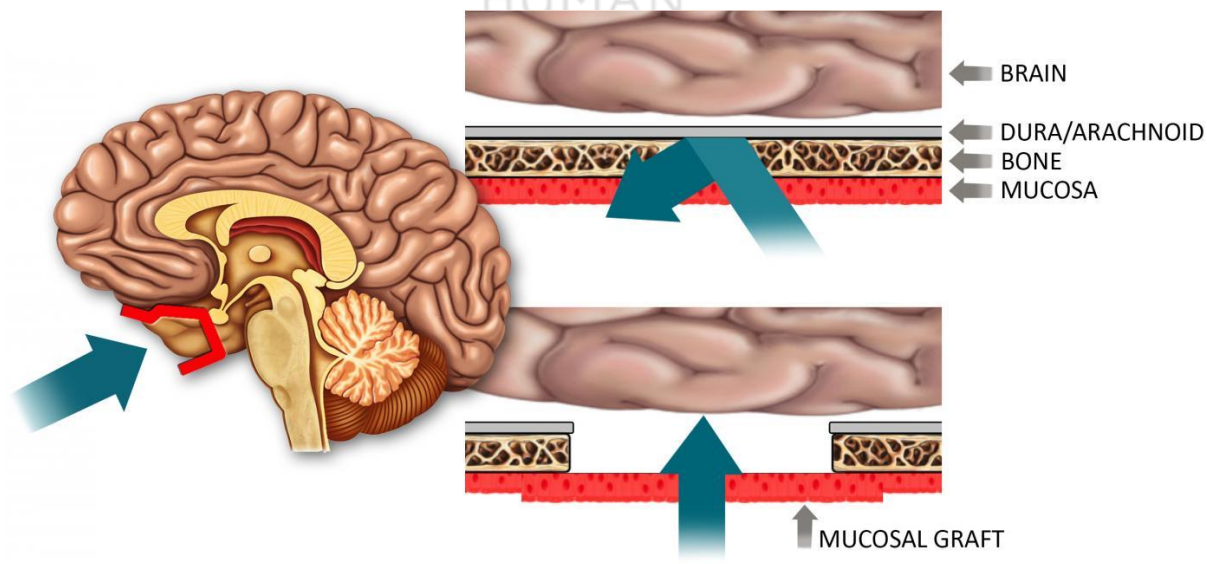

Figure No. 1: Alternate mechanism to bypass the Blood-Brain Barrier

Treatment for brain diseases is presently difficult due to the complexity of the brain, side effects of drugs, and the impermeable blood-brain barrier (BBB) compared to other organs of the body. Further, the drug development for curing diseases of the brain requires a longer period and more complex clinical trials as compared to the formulation of drugs for curing other organs. However, the poorest success rates in drug development for brain diseases have been recorded as compared to other therapeutic areas. Also, to deliver the drugs across the BBB hinders CNS drug development due to the lack of efficient technologies. Investigation of both small molecules and macromolecules are as effective therapeutic agents to treat various brain diseases. Only small molecules that are lipid-soluble and also have a molecular weight < 400 Da can cross the BBB but most of the macromolecules cannot penetrate the brain endothelium.[7,8] Different strategies have been developed for circumventing the BBB, like invasive direct injection or infusion, modification of therapeutic agents, and carrier-mediated transport.[9] Among these strategies, intranasal (IN) delivery is a non-invasive approach for direct drug delivery to the brain via the nose, bypassing theBBB.[10]

1.2 BARRIERS IN TARGETING BRAIN DRUG DELIVERY

The external stimuli, pathogens, toxins, foreign materials, and separated from the peripheral system of the human brain is protected via various physiological barriers. These barriers regulate the passage of essential nutrients and maintain the homeostasis of the brain and also provide entry and exit to the ions, proteins, metabolites etc.[11]. The main physiological barriers of the brain are discussed in detail below.

1.2.1BBB

Paul Ehrlich firstly reported the BBB in the year 1885 while studying brain complexity. The BBB structure is the essential barrier which separates the brain from the systemic circulation.[12] The BBB maintains the homeostasis of the brain and also protects the brain from a noxious mulus, toxins, and infectious particles.[13] The brain contains different types of cells like brain capillary endothelial cells (BCECs), astrocytes, pericytes, and nerve cells. The BCECs is responsible for selective permeability to small lipophilic molecules being the primary component of BBB. These cells with the help of a tight junction held together which prevents the paracellular drug transport across the BBB. The tight junction also causes the high trans-endothelial electrical resistance (TEER) between the brain and blood and therefore, inhibits the passive diffusion of external compounds.[14,15] The pericytes and

astrocytes support the BCECs and help to maintain the structure and functions of BBB.[16] The BBB is a highly selective semi-permeable membrane that allows the entry of only small, low molecular weight, non-polar compounds (<400 Da) to the brain.[17] Although the BBB is furnished with some special transport proteins, receptors or other mechanisms like efflux transporters, ion mediated channel, etc. to provide the passage of many essential components and metabolites to the brain.[18] A better understanding of the physiology of BBB and the nature and function of transport mechanisms help in the development of a promising carrier system for delivering the drug to the brain.

1.2.2 BCSFB

The BCSFB is a barrier between the blood circulation and cerebrospinal fluid (CSF) which restricts the entry of drugs and antigens to the CSF. It comprises of arachnoidal and choroid epithelial cells that separate the sub-arachnoidal CSF and ventricular CSF respectively, from the systemic circulation. The primary component of BCSFB is choroid plexus, which is made of choroidal epithelial cells.[19] The choroid plexus serves as a physical, immunological, and enzymatic barrier that helps in the drug transport, metabolism, and signaling functions. The epithelial cells at the choroid plexus are joints together via gap-junction which limits the permeability of the BSCFB. The gap junctions are less stiff than the tight junctions and hence more permeable for the drug and other substances.[20]

1.3 CURRENT STRATEGIES TO DELIVER DRUGS TO THE BRAIN

1.3.1 Viral vectors:

Simply introducing naked DNA into the body of hosts is inefficient.[21] The viruses have a natural ability to infect cells with nucleic acid and because of this, they have gained much attention as a vector for delivery of genetic material.[22] The ideal vector should have to possess high-transduction efficiency, target area specificity, acceptable safety profile, appropriate level and length of transgene expression, etc.[23] In general, the transfection efficiency of viral vectors is as high as almost 80% [24]. The vectors of Lentivirus, herpes simplex virus, adenovirus and adeno-associated virus (AAV) have achieved gene transduction in the brain.[25, 26]

➢ The vectors of herpes simplex virus type 1 (HSV-1) are enveloped 100 nm particles with a foreign DNA packaging capacity of more than 100 kb. The high packaging capacity and natural neuro-tropism via retrograde axonal transport are the major advantages.

➢ Vectors of Lentivirus are enveloped 100 nm particles with a foreign DNA packaging capacity of 9 kb which while pseudotyped, have high neuronal tropism.

➢ Adenoviral vectors are non-enveloped 100 nm particles with a foreign DNA packaging capacity of 25 kb one of the first viral-based gene therapy vectors, because of high cytotoxicity of these vectors are generally not suited to CNS application.

➢ AAV vectors are non-enveloped 25 nm particles with a foreign DNA packaging capacity of 4.6 kbhence clinically demonstrated to be safe in the CNS, and certain serotypes display strong neural tropism.

Advantages: High gene transfection efficiency

Disadvantages: The limitations of using viral vectors for drug delivery include difficulties in its manufacturing, high production cost, most importantly the safety of viral vectors because of the death of patients in clinical trials hence before their use for clinical applications safety must be confirmed.[26-29]

1.3.2 Exosomes:

These are the small extracellular vesicles discharged by cells. The non-immunogenic nature of exosomes versus other synthetic nanoparticles is the major advantages that lead to prolonged and stable circulation. The components of exosomes isolated from brain ECs act as regulators for exchanging molecules across the BBB and maintaining cell to cell communication in the brain.[30] Exosomes are being utilized to deliver small molecules, proteins, and nucleic acids to cross the BBB.[31]

Advantages: Gene delivery to the brain; potential ability to cross the BBB,

Disadvantages: Exosome donor cells; loading procedure; in-vivo toxicity and pharmacokinetics.[32]

1.3.3 Liposomes:

The small lipophilic vesicles are called Liposomes, primarily consisting of one or more concentric phospholipid bilayer or rarely made with the cholesterol or combination of different natural lipids (phosphatidylcholine, egg yolk phosphatidylcholine, soy lecithin, soybean phosphatidylcholine, etc.) or synthetic lipid (dipalmitoylphosphatidylcholine, etc.) with an aqueous core.[33-35] The basic properties of the liposomes such as fluidity, rigidity, size and surface behavior may vary with the selection of lipid component and method of preparation.[36]

Advantages: Liposome offers site-specific delivery, safeguards the drug from enzymatic degradation, decreases the adverse effect and represents a biodegradable and biocompatible delivery system which increases both the research and commercial interest for novel drug delivery.[37-39]

Disadvantages: The low encapsulation efficiency and poor stability limit its applicability to some extent.[40]

Drugs that cross the blood-brain barrier by incorporating into the liposomes: Many studies have narrated the use of liposomal formulations to deliver anti-cancer drugs, like methotrexate [41], 5-fluorouracil [42], paclitaxel [43], doxorubicin [44,45] and erlotinib. [44]

1.3.4 Nanogels:

The nanogels are primarily the nanosized hydrogel or in other words, defined as chemically or physically crosslinked 3 Dimensional networks of polymers that swell in water or aqueous fluid. [46,47]

Advantages: The higher water content of the hydrogel imparts excellent biocompatibility and facilitates the drug diffusion (both the drug loading and release) from the swollen network of the polymer.[48,49] These properties of nanogel make its candidature a potential carrier for brain drug targeting.

Drugs which cross the blood-brain barrier: The development of doxorubicin-loaded pH-responsive PVA nanogel targets the human glioblastoma or tumor cells. The nano gel comprising of disulfide and surface modified with cyclo RGD peptide. The study reflects the

drug-carrier system was inactive in normal physiological condition and releases the drug to the tumor site due to change in pH; hence found it effective in targeting the drug.[50]

The surface-modified methotrexate loaded nanogel consisting of sodium tripolyphosphate and chitosan and surface modified with polysorbate 80 which impart site specificity for the treatment of brain tumor. Although the study reflects that only in vitro examination was conducted.[51]

1.3.5 Nanoemulsion

The nanoemulsions are referred to as nanosized based on heterogeneous dispersion of water-in-oil or oil-in-water stabilized through a suitable emulsifier.[52] The nanoemulsions are found suitable for the delivery of both hydrophilic and lipophilic drugs. The permeation of nanoemulsion via RMT was facilitated by the surface functionalization with a suitable ligand. The formulation of nanoemulsions with vegetable or animal oils like peanut oil, flaxseed oil, sunflower oil, fish oil, hemp oil, wheat germ oil, egg phosphatidylcholine, etc. makes it highly biocompatible with the biological membranes being the very small size of nanoemulsion<200 nm makes it a promising carrier system for brain targeting of drugs.

Advantages: Biocompatible[53]

Disadvantages: Stability issues limit its application.[46]

Drugs that cross the blood-brain barrier: An encapsulated zolmitriptan drug, an anti-migraine agent to the mucoadhesive nanoemulsion, delivered it via the intranasal route. The researchers assessed the brain targeting efficiency of nanoemulsion and observed the mucoadhesive intranasal nanoemulsion significantly enhances the drug permeability, AUC and bioavailability in the brain.[54]

1.3.6 Dendrimers

Dendrimers are highly branched, monodispersed, symmetric polymeric macromolecules with some reactive groups on the surface. The dendrimer is a 3 Dimensional shaped spheroidal carrier system, composed of repetitively branched molecules.[55, 56] The core is suitable for drug loading while the surface with some reactive ends allows the multi-functionality and closely packed to improve the drug loading ability. The nanosized dendrimers represent an attractive drug carrier system for brain targeting.[57, 58]

Drugs which cross the blood-brain barrier

- Polyamidoamine dendrimers are the most commonly studied dendrimers for brain disease treatment.

- The encapsulation of carbamazepine, an anti-epileptic drug, has been reported for the treatment of Alzheimer's disease.[59]

- Poly(ethylene glycol) conjugated polyamidoamine dendrimers have also been used as vehicles for the delivery of drugs and reducing blood clotting for ischemic stroke therapy.[60]

1.3.7 Quantum dots

Quantum dots are colloidal nanocrystalline semiconductor materials, consists of metalloid crystal core and nonreactive metallic shell which cover the crystalline core.[61,62] The long-term photostability, high brightness, size-tunable narrow emission spectra make it a promising diagnostic tool.[63]

Advantages: It also offers a great surface area and can encapsulate a wide variety of therapeutic and diagnostic agents. Thus, it can also be used as a promising carrier system for brain targeting.[64]

Disadvantages: However, just like inorganic nanoparticles the higher toxicity profile, nonbiodegradability, and poor drug release profile limit its application.[46]

Drugs which cross the blood-brain barrier:

- Tang *et al.* (2017) constructed a novel PEGylated quantum dot nanoprobe conjugated with aptamer 32 for fluorescent imaging of brain tumors. It possesses the ability to specifically binds with the glioma cells and thus could be used as a promising tool for diagnosis, investigation, and surgical intervention of brain tumors. [65]

- Similarly, Yang *et al.* (2017) also used quantum dots as a promising diagnostic tool. They Cd-Se-ZnS quantum dots, incorporated into pH-triggered polymeric micelle and used as fluorescent imaging nanoprobe to distinguish cerebral ischemia affected region in the brain.[66]

1.3.8 Nose-to-brain delivery system

In the past few years, the intranasal route appears as an alternative and effective approach for drug delivery to the brain. It is claimed to deliver the drug directly to the brain without entering into the systemic circulation.[67-68] The nasal cavity is divided into three different regions (Figure 2):

(1) Vestibular region

(2) Respiratory region

(3) Olfactory region.

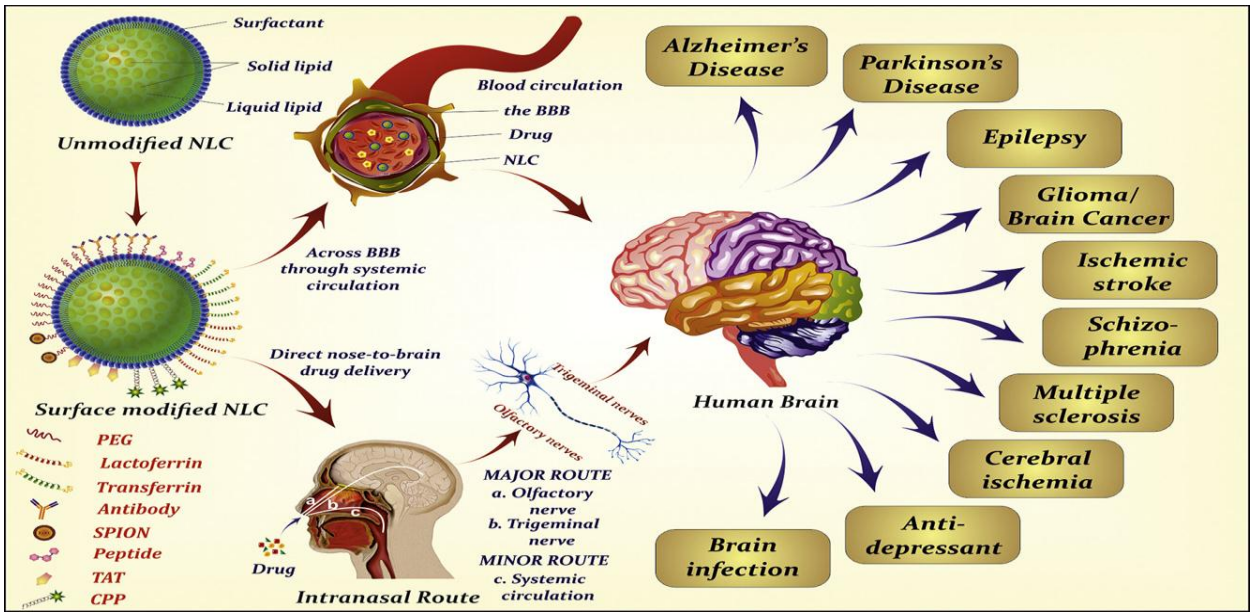

Figure No. 2: Nasal Drug Delivery Strategies

The drug or any dosage form instilled into the nasal cavity can primarily absorb through the respiratory area and enters into the systemic circulation. This region also consists of some trigeminal neurons; hence some of the drugs reached directly to the brain via trigeminal nerves. Also, the drug reached/or instilled in the posterior region, i.e., the olfactory region, enter directly to the brain via olfactory and trigeminal neurons.[67,69] The drug entered into the systemic circulation further needs to cross the BBB while the drug entered through the intra-neural pathway follows cellular transport mechanism. From the olfactory region, the drug primarily enters into the olfactory bulb via trigeminal and olfactory neurons, followed by

absorption into lamina propria and then entered in the CSF. It further, reaches to different brain region from the CSF.[9,70]

Disadvantages: On the other hand, the intranasal route also has some limitations which reduce its efficiency. Firstly, the volume of the nasal cavity is very small which only allows a lower volume of drugs to be instilled. Secondly, the shorter drug retention time again reduces the amount of drug available for absorption into the brain or systemic circulation. Further, mucociliary clearance and enzymatic degradation also reduce bioavailability.[67] Thus, various novel drug delivery strategies are under investigation which coverup such limitations and improves the efficiency of the intranasal route.

Drugs which cross the blood-brain barrier:

Nigam *et al* (2019) utilized PLGA nanoparticle for direct nose-to-brain delivery of lamotrigine. The study shows the intranasal PLGA-nanoparticle significantly improved the pharmacokinetic behavior of the drug and also the brain targeting efficiency. [71]

1.3.9 Nanoparticles:

Nanotechnology has brought new possibilities in the development of various delivery systems such as systemic CNS delivery. Nanotechnology has been applied in the production of materials, devices, and electronic biosensors with sizes ranging from low to high nanometers. Nanotechnology-based products are being extensively used in clinics, drug delivery, and diagnosis.[72] Nanocarriers are colloidal systems in which the drug is either entrapped within the colloidal matrix of the nanoparticle or coated on the particle surface via conjugation or adsorption. Various nanocarriers have been developed and examined for delivery and diagnostic purposes such as polymeric, lipid-based, magnetic, and dendritic nanocarriers.[73] Other types of nanocarriers include micelles, nanogels, nanoemulsions, nanosuspensions, and ceramic as well as metal-based nanocarriers.[74,75]

Advantages:

(1) Drugs are loaded in, adsorbed or chemically coupled onto the NPs surface. In this way, NPs shell could protect therapeutic agents from degradation or deactivation before reaching target sites and allow their sustained release.

(2) Coating the surface of NPs with polyethylene glycol (PEG), or ‘‘PEGylation’’, is a commonly used approach for shielding NPs from aggregation, opsonization, and phagocytosis, prolonging systemic circulation time.[76,78]

(3) NPs functionalized with target moieties are used for targeted delivery, which significantly improves the drug distribution in diseased tissues.[79]

(4) The compositions of stimulus-responsive polymers in NPs facilitate achieving a controlled drug release.[80]

Table No. 1: Drugs Formulated by Various Methods to Target Brain Drug Delivery

Drug	Formulation Type	Route Of Administration	Uses
Venlafaxine	Polymeric Nanoparticles	Nose To Brain	Antidepressant [81]
Estradiol	Polymeric Nanoparticles	Nose To Brain	Alzheimer's Disease [82]
Zonisamide	Microemulsion	Nose To Brain	Epilepsy [83]
Risperidone	Polymeric Nanoparticles	Nose To Brain, Parenteral	Psychiatric [84]
Olanzapine	Nanoemulsion	Nose To Brain	Psychiatric [85]
Doxorubicin	Carbon Based Quantum Dots	----------	Cancer Targeting In Brain 86
Methotrexate	Nanogel	Intranasal,	Brain Disorder [87]
Antisense Oligonucleotide	Nanogel	Intravenous	Brain Tumors, Alzheimer's Disease & Cute Ischemic Stroke 88
Carbamazepine	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Neurodegenerative Diseases [89]
Curcumin	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Glioma [90]
Docetaxel	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Glioblastoma [91]
Doxorubicin	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Brain Tumors [92]
Estramustine & Podophyllotoxin	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Glioma [93]
Haloperidol	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Psychiatric [94]

Minocycline	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Stroke [95]
Paclitaxel	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Brain Tumors [96]
Risperidone	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Psychiatric [97]
Tamoxifen And Doxorubicin	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Glioma [98]
Venlafaxine	Dendrimers	Intravenous, Oral, Transdermal, And Ocular Delivery Systems	Psychiatric [99]
Cytarabine	Multivesicular Liposomes	Intravenous	Lymphomatous Malignant Meningitis [100]
Paclitaxel	SLN	Intravenous	Glioblastoma [100]
Amphotericin B	Liposomes	Intravenous	Cryptococcal Meningitis [100]
Daunorubicin	Liposomes	Intravenous	Pediatric Brain Tumors[100]

CONCLUSION

From the present review, it is been suggested that some methods are now available for brain drug delivery. By these options of drug delivery, it becomes possible for the treatment of many untreated ailments that were posing a problem in the past. Moreover, the availability of such a large number of options has given the physician and pharmaceutical companies an added advantage. This has also reduced the economic overburden to the patients which was earlier prevailing due to very limited options to treat brain-related disorders.

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