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A Review on Neurodegenerative Disorders : Current Therapeutic Approaches and the Potential Role of Nanotherapeutics

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Abstract: *Neurodegenerative disorders are primarily characterized by neuron loss. The most common neurodegenerative disorders include Alzheimer's and Parkinson's disease. Although there are several medicines currently approved for managing neurodegenerative disorders, a large majority of them only help with associated symptoms. This lack of pathogenesis-targeting therapies is primarily due to the restrictive effects of the blood–brain barrier (BBB), which keeps close to 99% of all "foreign substances" out of the brain. Since their discovery, nanoparticles have been successfully used for targeted delivery into many organs, including the brain. This review briefly describes the patho-physiology of Alzheimer's, Parkinson's disease, and amyotrophic lateral sclerosis, and their current management approaches. We then highlight the major challenges of brain-drug delivery, followed by the role of nano-therapeutics for the diagnosis and treatment of various neurological disorders.*

Keywords: nanoparticle; neurodegenerative disorder; neurogenesis; Alzheimer's disease; Parkinson's disease; blood–brain barrier; amyotrophic lateral sclerosis

I. INTRODUCTION

Neurodegeneration has been identified as the pivotal pathophysiological change in most brain-related disorders [1]. Regardless of the incessant efforts by modern science to create a medical or surgical solution, the outcome has not been favorable. Neurodegenerative disorders (NDs) such as Alzheimer's and dementia continue to be a clinical concern in most older people [2]. The highly effective blood–brain barrier (BBB) continues to be a real barrier towards the successful management of NDs. Despite the several successes that have been demonstrated with surgeries and highly evasive techniques, their clinical acceptance is limited due to varying concerns about their long-term benefit, owing to the potential damage to the brain barrier. As a suitable alternative for halting or reversing neurodegeneration, nanotherapeutics with the potential to cross the BBB (without damage to the barrier) have been proposed and demonstrated in many cases [3]. Nanotherapeutic use is gaining traction due to the several benefits compared to conventional dosage forms [4].Despite this great progress,there is a need to refine nanotherapeutics to ensure optimum outcomes. In this review, we initially describe the pathophysiology of major NDs and their current management strategies. We also discuss the role of BBB and other challenges for brain-targeted drug delivery. Further, we look at the potential role of nanotherapeutics in the fight against neurodegeneration. Finally, we discuss breakthroughs and current findings in nanotherapeutics to manage NDs and provide perspectives for future application.

2. Neurodegenerative Disorders; (NDs):

Neurons are central to the proper functioning of the human brain since they play a critical role in communication [5]. Most neurons originate in the brain; however, neurons are present everywhere in the body [6]. During childhood, neural stem cells produce the majority of neurons, the number of which is significantly reduced in adulthood [7]. Although neurons are not immortal, the progressive loss of neurons, neuron structure, and/or their functions, known as neurodegeneration, is central to the pathophysiology of several brain disorders [8] and is also a major health concern. Neurodegeneration is associated with dysfunction of the synapse, neural network, and the deposition of physiochemically

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altered variants of proteins in the brain (Figure 1) [9]. Diseases with neurodegeneration as their hallmark feature are collectively termed NDs. The most common NDs include Alzheimer's disease, Parkinson's disease, prion disease, Amyotrophic lateral sclerosis, motor neuron disease, Huntington's disease, spinal muscular atrophy, andspinocerebellar ataxia [10].

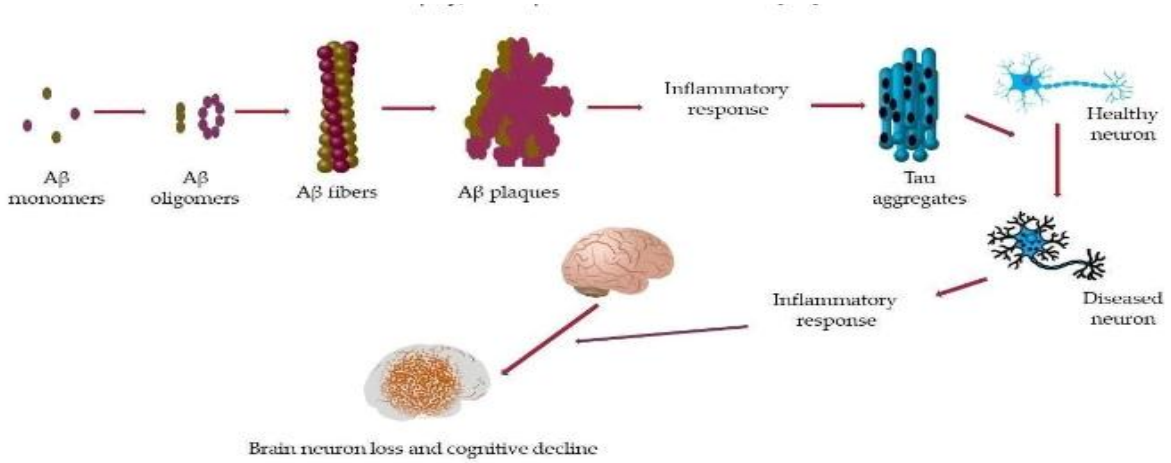

Figure 1. Path to cognitive decline in neurodegeneration. Amyloid-beta (Aβ) monomers clump together to form oligomers of variant structures. Subsequently, the oligomers aggregate to form Aβ fibers, which misarrange to form Aβ plaques. Plaque formation induces an inflammatory response which includes the formation of tau aggregates leading to the conversion of healthy neurons to diseased neurons. The presence of more diseased neurons triggers another inflammatory response leading to more neuron loss and a subsequent loss in brain function as well as cognitive decline.

Neurodegenerative disorders affect millions of people worldwide. Although age is the single most contributing risk factor to the development of all NDs, recent findings reveal that a combination of an individual's genetic makeup and environmental factors can equally contribute to increasing the risk for NDs. Further, despite the expression of specific genes (within an individual) accountable for NDs [11], Thus, NDs can be very serious or even, in certain instances, life threatening; however, it solely depends on the type and stage of the disease. Since the brain controls several aspects of the body's function, neurodegenerative diseases consequently affect multiple facets of human functioning and limit the ability to perform both basic (e.g., speech, movement, stability, and balance) and complicated tasks (e.g., bladder and bowel functions, and cognitive abilities). Most NDs progress without remission, whilst in some cases, treatments target the improvement of symptoms, relief ofpain if present and/or the restoration of balance and mobility. In the following sections we will briefly discuss some common NDs.

2.1. Alzheimer's Disease (AD):

Alzheimer's disease is progressive brain disorder that destroys memory, thinking skills ,and ability to cut out daily tasks. It is most common disease cause by loss of brain cells . Its symptoms likes changes in confusion ,changes in behavior and personality difficulty with language etc,.

2.2 Parkinson's disease [PD]:

Parkinson disease is a progressive neurological disorder that leads to tremors, muscle stiffness, an unsteady walk, and balance and coordination difficulties. Both genetic and non-genetic stimuli cause PD. Age is considered the primary risk factor for PD other risk factors is excessive caffeine intake, smoking, and exposure to environmental toxins etc,. [36].

2.3. Amyotrophic Lateral Sclerosis (ALS):

ALS, more commonly referred to as motor neuron disease or Lou Gehrig's disease, is a progressive disease of the nerve cells and spinal cord, resulting in muscle weakness and paralysis [12]. In ALS, motor neurons gradually deteriorate before they die . When motor neurons are damaged or dead, signals that should be sent to the brain are no longer delivered.

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Although over 30 different genes have been associated with ALS, mutations in four main genes (C9orf72, TARDBP, SOD1, and FUS) account for greater than 70% of ALS cases [13]. These four genes encode for proteins involved in major motor function aspects such as DNA repair, homeostasis, mitochondrial function, and glial cell function. A combination of these impaired functions is believed to contribute to the degeneration of motor neurons observed in ALS. Accumulation of intra neuronal protein aggregates is the pathological hallmark of ALS. The most abundant protein observed in most ALS patients is the TAR DNA binding protein; however, other proteins such as superoxide dismutase-1 and neuro filament can also form aggregates [14].

NeurodegenerativeDisordersAmyotrophic Lateral Sclerosis (ALS) :

3. Current Therapeutic Approaches to Treat ND :

Management of neurodegenerative disorders is often disease-specific. Several approaches to management are currently accepted, which either target the disease pathogenesis or attempt to improve the symptoms experienced. In this review, we consider the therapeutic approaches currently in practice to treat major NDs (Table 1)

Neurological Disorder	Drugs Class	Mechanism	Drugs
1)Alzheimer disease	1) 1Amyloid directed antibody 2) Cholinesterase Inhibitros 3) Glutamate regulators	1) Acts by targeted and removing amyloid-beta plaques. 2) Prevent the knowing of acetycholine 3) Antagonize N-methyl-D-aspartate (NMDA) receptor to improve singnal- to-noise ratio of glutamatergic transmission	1) Aducanumab 2) Donepezil, rivastigmine, galantamine 3) Memantine
2)**Parkinson disease**	1)Dopamine supplement 2)Decarboxylase inhibitors	1) Replenish the decreased dopamine levels 2) prevent peripheral breakdown of levodopa	1)Levodopa 2)Caebidopa
3) Amytrophic lateral sclerosis	1)Glutamate-receptor antagonist 2)Free-radical scavanger	I1) inhibitrs glutamate receptors 2)Scavanges free radicals	1)Riluzole 2)Edaravone

Table 1. Current therapeutic approaches for the management of neurodegenerative disorders.

3.1.1. Antibody Targeting Amyloid-Beta (A) Plaques

Aducanumab(Aduhelm)is the first disease-modifying drug approved forAD patients, and was approved in June 2021. It is administered as an intravenous (IV) infusion over approximately one hour every four weeks. Aducanumab is an IgG1 monoclonal antibody specific to extracellular A plaques in the brain, which binds and helps in clearing the plaques [15]. Although conditionally approved, clinical data on aducanumab show a reduction in the A plaques' load, but with no relationship to improved cognitive function in patients. More clinical data will still be collected to provide conclusive evidence of whether the drug helps in cognitive functions. However, the approval of aducanumab has also created a wave of excitement in AD patients and advocacy groups. Besides being the first therapy to target altering the pathology of the disease, they believe it will create avenues for similar therapies in the near future. Multiple clinical trials have been performed using different bioactive molecules (i.e., secretase inhibitors and therapeutic antibodies), but most of them have terminated so Int. J. Mol. Sci. 2022, 23, 1851 5 of 18 far. Some A targeting antibodies—AAB-003, MEDI1814, RO7126209, and SAR228810— have completed clinical trial phase I. While aducanumab has completed clinical trial phase III, it is also specific towards A aggregation. Similarly, tau or TREM 2 specific antibodies, i.e., BIIB076,

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bepranemab, JNJ-63733657, have completed clinical trial phase I, while gosuranemab is in clinical trial phase 2 [16]. Thus, additional antibody-based targeting medicine may obtain FDA approval for AD treatment shortly.

3.1.2. Cholinesterase Inhibitors :

Tacrine was the first choline esterase inhibitor approved back in 1993 by the FDA, but was discontinued later because of its associated hepatotoxicity. Donepezil is used for mild-to-moderate AD and is administered as oral tablets of 5 or 10 mg/day. More recently, higher doses of donepezil (23 mg/day), alone or combined with memantine, were approved for moderate-to-severe patients. Another acetylcholinesterase inhibitor used for mild-to-moderate AD is rivastigmine. Unlike other cholinesterase inhibitors, rivastigmine is available as a transdermal patch and inhibits both acetylcholinesterase and butyrylcholinesterase enzymes. Galantamine, the next class of cholinesterase inhibitors, was approved for mild-to-moderate AD at a dose range of 16–24 mg/day. Besides its inhibitory effect on cholinesterase activity, it also produces allosteric modulation of nicotinic cholinergic receptors [17]. Although numerous drugs have been developed for AD, cholinesterase inhibitors remain the only option available to patients. The recently approved drug aducanumab is contentious in its efficacy and exorbitant in pricing. However, cholinesterase inhibitors show limited efficacy. They achieve amodest improvemen in patients'cognitive ability, and they are labeled as symptomatic treatment options rather than altering the pathology [18]. Moreover, questions exist on whether current medications can effectively cross the BBB at significant doses to elicit the desired pharmacological effects.

3.1.3. Glutamate Regulators(GR):

Glutamate is the major excitatory neurotransmitter in the brain. Through excessive activation in postsynaptic neurons such as NMDA receptors, glutamates confer neuronal damage, leading to neurodegeneration. However, complete inhibition of NMDA receptors has resulted in severe side effects. Consequently, memantine, an uncompetitive NMDA recep tor antagonist, was developed, which provides pathological benefits with NMDA receptor activation and also protects patients from inhibitory effects due to overactivation [19]. Memantine was approved in 2003 for moderate-to-severe AD patients at a dose of 5–20 mg/day. Monotherapy of memantine benefitted AD patients with improved cognition over a placebo. In combination with acetylcholinesterase inhibitors, clinical trials showed improved efficacy for one year over monotherapy [20]. However, this class of drugs also fails to address the pathology of AD, and is mainly used to alleviate symptoms.

3.2. Therapeutic Approaches For PD

PD is the second most common ND, there is a lack of effective therapy that especially alters the pathophysiology of the disease. Instead, some options address the motor-related symptoms and non-motor-related symptoms separately for symptomatic relief in patients. The principal approach in managing PD is to replenish the decreased dopamine levels in the substantia nigra region of the brain. Numerous approaches have been put in place that aim to replenish dopamine levels. The most common therapy is a combination of levodopa and carbidopa. Levodopa is an immediate precursor of dopamine that helps restore motor functions resulting from the loss of dopamine. Carbidopa is combined with levodopa to inhibit the peripheral breakdown of levodopa before it reaches the brain. Additionally, entacapone and tolcapone are also used to prevent methylation of levodopa through catechol-O-methyl transferase (COMT), thereby preventing levodopa loss through methylation. Dopaminergic agonists such as apomorphine hydrochloride, pergolide, pramipexole dihydrochloride, ropinirole hydrochloride, and rotigotine, which produce an identical effect to dopamine, are also available for the treatment of PD. Monoamine oxidase inhibitors are the next class of drugs available. They inhibit the oxidative deamination of dopamine in the brain and prevent dopamine loss. Selegiline and rasagiline are the two examples of monoamine oxidase inhibitors [21].

3.3. Therapeutic Approaches for ALS

ALS is a motor neuron disease that manifests the symptoms of frontotemporal de mentia, behavioral changes, and cognitive decline with the progression of the disease. ALS patients succumb to respiratory failure and death within three to five years of the appearance of symptoms [22]. There are two approved medications for ALS patients, i.e., riluzole and

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edaravone. Riluzole, a glutamate-receptor antagonist, was approved back in 1995 as an oral tablet with a dose of 100 mg/day. Clinical trials have shown that riluzole use prolongs the life of ALS patients by 3 to 4 months compared to a placebo group. Edaravone, a free-radical scavenger, was recently approved in 2017 as an intravenous infusion with a dose of 60 mg/day, and it helps to delay the progression of the disease [23]. Besides these medications, patients are treated symptomatically for the improvement in their quality of life.

4. Challenges of Brain-Drug Delivery:

Current therapy for the management of NDs has aided in controlling the progression of the disease rather than eliminate the root causes. The problem of neurodegeneration lies behind the BBB, and that is where most of these formulations fail. The inability to transport sufficient doses to the brain limits the successful intervention of NDs. The advanced nature of the BBB, coupled with the poor permeative potency of most,if not all drugs, accounts for the lack of suitable treatment options for NDs.

4.1. Blood–Brain Barrier (BBB)

The BBB has been described diffusion barrier that prevent substances in the blood from entering the brain, allowing the maintenance of homeostasis and the brain's normal functioning[24]..Different cells in the brain (brain microvascular endothelial cells, tight junctions, neurons, astrocytes, and basal membranes) fuse to build a physically tight brain capillary in the BBB [25].The absence of fenestrations within the brain capillary endothelial cells limits the diffusion of small molecules and proteins[26] .The endothelial cells are further linked to a continuous barrier through inter-endothelial junctions, restricting the transport of water- soluble substances .Furthermore, the endothelial cells are surrounded by the basal lamina, astrocytes, and pericytes, limiting access to drug molecules from the blood to the brain[27].The strength of this barrier is complimented by efflux trans porters located in the brain capillary, and these transporters return substances that enter the brain back into the bloodstream.

4.2. Pharmacokinetic Principles and Their Effects on Brain-Drug Delivery :

The efficacy of systematically administered drugs is mostly determined by their pharmacokinetic characteristics [28]. From the point of administration to the target site (in this case, the brain) is a harrowing journey that, in most cases, does not favor the therapeutic molecules. The first point of attention is the presence of various plasma proteins that are embedded within. Some drugs are highly bound to these proteins, thereby limiting the amount of the drug available in circulation, ultimately reducing the free drug available for transportation to the brain[29].

5. Nanoparticles and Their Use in ND :

Limitations caused by the BBB and the disadvantages of the current therapies, as mentioned above, have led to the unmet need for new therapeutic approaches for the treatment of NDs [30].Out of the approaches employed, nanotechnology has emerged as a safe and promising platform for targeted drug/gene delivery to the CNS . This technology employs materials in nano scale, usually ranging from 1–1000 nm, and can interact with biological systems at the molecular level [31]. A variety of materials such as natural polymers (proteins and polysaccharides), synthetic polymers (PLGA and PCL), and inorganic materials (gold, silver, and cerium) have been employed to formulate nanoparticles. Nano carriers have proven to be highly suitable drug/gene carriers to the brain [32].The characteristics of nanocarriers that make them a promising platform for managing and treating NDs include high drug loading capacity, low systemic toxicity, improved drugpermeabilization, and good physical and chemical stability[33].

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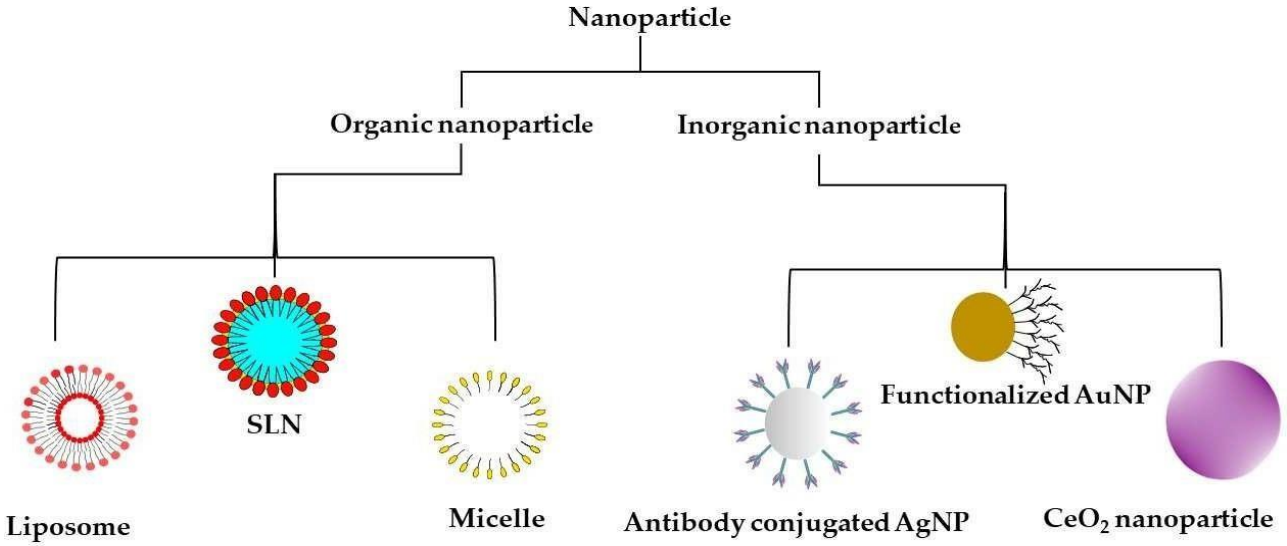

Figure 2. Types of nanoparticles mostcommonly used forthe management of neurodegenerative disorders. SLN—solid lipid nanoparticle; AuNP—gold nanoparticle, AgNP—silver nanoparticle, CeO2NP—cerium oxide nanoparticle.

5.1 Inorganic Nanopartical

Metal nanoparticles have gained much interest due to their ability to easily cross the BBB and accumulate in the brain [34]. Their various properties, such as size, surface modifications, and stability, can be easily modulated for efficient brain targeting [35]. For instance, metal nanoparticles are often functionalized with various brain-targeted ligands, such as antibodies, proteins, and small molecules (e.g., mannose) for enhanced drug delivery to the CNS. These nanoparticles are also widely known for their the agnostic and imaging applications [36]. Among various metallic nanoparticles, gold, silver, and cerium nanoparticles have been the most exploited for CNS delivery [34] and will be discussed here. Gold nanoparticles (AuNPs) have been extensively used in CNS imaging and targeting [38]. Their core has plasmonic properties (i.e., the ability to interact with electromagnetic radiation due to the presence of free electrons), making them ideal for imaging applications using micro-CT scanning or X-rays. The AuNPs are superior in absorbing and reducing the X-rays better than the conventional contrast agents, which allows for higher contrast and precise visualization of the nanoparticles [37]. In a recent study, rhodamine B isothiocyanate (RITC) and poly-L-lysine (PLL) were complexed with 40 nm AuNPs. These modifications increased nanoparticle uptake in human mesenchymal stem cells (hMSC). This gold-labeled hMSC was directly injected into rat brains and could be visualized 30 min post-injection using the micro-CT [39]. In combination with cell tracking and visualization, AuNPs have shown great potential in targeting and degrading β-amyloid aggregates under in vitro conditions [40]. Apolipoprotein E3 (ApoE3) conjugated with the core of the AuNPs, promoted their interaction with the amyloid aggregates and increased penetration in the brain. Curcumin was used as a probe to track these AuNPs. Upon binding of amyloid aggregates and ApoE3-AuNPs, the surface plasmon resonance (SPR) of the AuNPs was used to dissociate the amyloid aggregates by 60% [41]. In another study, AuNPs were surface-modified with brain-targeted exosomes for more effective and enhanced brain delivery [42].

5.2 Organic Nanoparticle

Naturally occurring molecules, such as lipids and other organic molecules, can be exploited as tools for delivering nanomedicine due to their superior biocompatibility compared to inorganic materials. Moreover, a lipid nanocarrier is more effective in protecting the therapeutic moiety from degradation, reducing toxicity and increasing biocompatibility, than the free-drug administration[43]. Among the different lipid carriers, liposomes have been the most extensively explored for brain-targeted delivery. Liposomes dual functionalized with mApoE and phosphatidic acid were developed to enhance delivery across the BBB and target Aβ aggregates with high affinity [44]. This liposomal formulation could disaggregate Aβ fibrils in vitro. The negatively charged phosphatidic acid interacts with the positively charged amino

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acid residues on the Aβ, while the mApoE interacts with the negatively charged regions of the same. In a recent study, our lab has developed surface-modified liposomes for brain-targeted delivery of ApoE2-encoding plasmid DNA [45]. The targeting ligand used was mannose along with a CPP (penetratin and rabies virus glycoprotein peptide, RVG) to enhance brain targeting and cellular internalization, respectively. Similarly, liposomes modified with RV Gand transferrin displayed superior uptake in brain endothelial cells, astrocytes, and neurons as compared to plain liposomes [47]. In a separate study by Rodriguez et al. [46], surface functionalization of liposomes with transferrin and a CPP was sufficient to improve the brain permeability of liposomes in mice after a single intravenous administration. In all of these studies, drug accumulation in the brain was attributed the surface functionalization

6. Nanomedicines under Clinical Trial :

There is an utmost need to develop novel treatment strategies against neurodegenerative disorders, that pause neurodegeneration rather than provide symptomatic relief. Several studies on nanoparticles, show promise of an effective drug delivery approach, which can be a ray of hope against neurodegenerative disorders. A recent search in ongoing clinical trials revealed less than 10 nanoparticle-based formulations under different phases of clinical trials against NDs (Table 2). Only one clinical trial of lipid nanoparticle-based formulation for transthyretin-mediated amyloidosis has been completed and approved for sale in public. While a (CRISPR)/Cas9 gene-based study is in the clinical trial phase I, lipid nanoparticles are being used as a drug delivery platform for this study. An exciting approach of nanoparticle-mediated delivery of APH-1105 against mild-to-moderate AD is enlisted; this clinical trial will be started in 2023. However, a goldnanoparticle-mediated CNM-Au8 delivery approach is in the clinical trial phase 2. On the other hand, multiple studies of CNM-Au8-gold nanocrystals-based studies are in phase 1 and phase 2 of clinical trials against AL

Table.2.Nanocarrier-mediatedformulationunderclinicaltrialsagainst different neuro degenerativedisorders.

Product (active Moleculars/Class)	Nanopart-	Indications	Clinical Phase, NCT Number
Lipidnanoparticle ALN-TTR02(Patisiran) (DLin-MC3-DMA; PEG2000-C-DMG;DSPC; Andcholesterol)		Transthyretinmediated amyloidosis	Approvedformarketing, NCT02939820
APH-1105 (an α-secretase modulator)	Nanopar-	Mild-to-moderateAD,dementia	Phase2,NCT03806478
Lipidnanoparticle(proprietarylipidnanoparticle (LNP)delivery-systemproprietary			

Short palindromicrepeats(CRISPR)/Cas9gene ionizable lipid, combined with aphospholipid,a pegylatedlipid(molecular weight of polyethyleneglycol, 2000Da),andcholesterol)

CNM-Au8(Nanocrysta llinegold)	Gold nanocrystals	ALS	Phase1, NCT04081714
CNM-Au8(Nanocrysta llinegold)	Gold nanocrystals	ALS	Phase2, NCT04098406
CNM-Au8(Nanocrysta llinegold)	Gold nanocrystals	ALS	Phase2, NCT03843710
CNM-Au8(Nanocrysta llinegold)	Goldnanocrystals	PD	Phase2,NCT03815916

AD—Alzheimer's disease; ALS—amyotrophic lateral sclerosis; DLin-MC3-DMA—dilinoleylmethyl-4-dimethylaminobutyrate; DSPC—distearoylphosphatidylcholine; PEG2000-C-DMG—1,2-dimyristoyl-rac-glycero3-methoxypolyethylene glycol-2000; PD—Parkinson's disease

7. Challenges Future Prospectsand Conclusions

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Neuronaldea the the primary characteristic of ND,i.e.,AD and Parkinson's. There- fore, neurogenesis is the most envisioned treatment strategy for these disorders. However, drug delivery to the brain is still achallenge due to multiple crucial factors, including the BBB, lipophilicity,the molecular weight of the drug, etc. These factors limit therapeutic potency of drugs and make NDs more challenging to treat. Thus, nanoparticle-mediated targeted drug delivery to the brain has been explored in recent years for neurogenesis, and it provides a promising platform for improving treatment strategies. Despite these potential advantages,nanocarrier-mediateddrugdeliveryhassomechallengingaspects, including safety, production, and regulations.

Nanomedicine is a ray of hope for NDs, and it can be an effective tool to overrule the barriers of current and traditional treatment approaches [146]. We highlighted nano-particlebased reports against various NDs, which may open the prospect of nano-medicine. Understandably, the development of curative treatment is not an immediate process, but preliminary research in the field may lead to a steppingstone that can help eradicate NDs. However, to prove the efficacy against NDs, the generation of more in vitro and in vivo data is needed. Furthermore, thorough in vitro and in vivo investigations and their correlation establishment are required to assess the efficacy of nanoparticles. This would help the research fraternity to extend or identify the effective nanoparticles for diagnostic or therapeutic applications.

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II. CONCLUSION

An assessment of the synaptic spread and selective vulnerability hypotheses reveals that the field of neuroscience research is not yet at a point where we can conclusively choose one theory over the other as the definitive mechanism of neurodegeneration. In fact, it is likely that both hypotheses are at play in all of these diseases. This, coupled with advances in techniques like neuroimaging, has led to a very exciting time in neurodegenerative disease research in which one can make one's own assessment of the literature on synaptic transmission and selective vulnerability and then one can carefully choose where to spend one's time and effort in pursuing a meaningful project. While many researchers want at some level to discover the next great advance, we have learned from the work of Dr. Freed that publishing seemingly negative results is quite important (Freed et al., 2001). Therefore, we strongly advocate that scientists vigorously continue their research efforts into both the synaptic spread and selective vulnerability hypotheses. Ultimately, the authors of this review view further research into the synaptic spread and selective vulnerability hypotheses as both being critically important in bringing relief to those millions of people who suffer from neurodegenerative diseases. While conducting and critically evaluating this research is certainly time and energy intensive, this work is ultimately all for them.

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