

## Review

# Lipid and Polymeric Nanoparticles in Neurodegenerative Diseases: Progress and Challenges in Alzheimer's, Parkinson's, and Huntington's Diseases

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## Abstract

Neurodegenerative diseases (NDs) such as Alzheimer's, Parkinson's, and Huntington's disease are progressive and currently incurable conditions characterized by the deterioration of neuronal structure and function. Its incidence is increasing, primarily driven by global aging, and it represents a significant public health concern. Traditional therapies offer only symptomatic relief and are unable to halt or reverse the underlying neurodegenerative processes. One of the key challenges in developing effective treatments is the presence of biological barriers, such as the blood–brain barrier (BBB), which limits drug delivery to the central nervous system (CNS), namely the brain. Nanotechnology has emerged as a promising tool to overcome these obstacles. Nanoparticles (NPs), due to their small size, biocompatibility, and versatility, can be engineered to cross the BBB, protect therapeutic agents from degradation, and deliver them precisely to target sites in the brain. This work explores the current advances in lipid and polymeric-based nanoparticle (LNPs and PNPs, respectively) drug delivery systems (DDS) and their application in pre-clinical studies for the treatment of the NDs previously mentioned. The presented studies suggest that this strategy holds great potential, offering new perspectives and emerging strategies to improve therapeutic outcomes for NDs, and promote neuroprotection of the brain.

**Keywords:** neurodegenerative diseases; nanoparticles; treatment; blood–brain barrier

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## 1. Introduction

NDs have emerged as a critical area of focus in contemporary research, with substantial efforts directed towards exploring therapeutic approaches to prevent or reduce neurodegeneration. According to the World Health Organization (WHO), neurological disorders represent one of the most significant health challenges of the twenty-first century, currently affecting more than one in three individuals globally. Recent findings from the WHO's Global Status Report on Neurology indicate that these conditions now impact over 40% of the world's population, exceeding 3 billion people, and account for more than 11 million deaths annually [1].

While the spectrum of neurological conditions is broad, this paper focuses specifically on three prominent NDs: Alzheimer's Disease (AD), Parkinson's Disease (PD), and Huntington's Disease (HD). These conditions represent a substantial portion of the global neurological burden due to their progressive nature and the intensive care required for affected individuals.

AD is widely recognized as the most prevalent ND and the leading cause of dementia. AD affects approximately 7% of individuals aged 65–69, with exponential growing prevalence of 50–60% among those over 85 years old [2], roughly doubling every five years after age 65 [3].

PD is the second most common ND, surpassed only by AD [4]. According to the Parkinson's Foundation Prevalence Project, it is estimated to affect over 10 million people worldwide [5]. It has a low incidence in individuals under 40 years old, but the risk of developing the disease rises steadily with age. It is estimated that around 3% of people over 80 are affected. Several studies also indicate that men tend to develop PD about two years earlier than women, on average, and that men are twice as likely to be diagnosed with the condition [4].

HD is another common ND that affects between 5 and 15 people per hundred thousand worldwide [5].

In NDs, neurons and their connecting axons gradually degenerate, leading to neuronal dysfunction and, eventually, neuronal death. This neurological dysfunction and cell death result from critical physiological processes, including oxidative stress, proteotoxic stress, neuroinflammation, and apoptosis [5]. During the degenerative phase, these processes induce symptoms such as loss of coordination, memory deficits, and a total inability to carry out routine tasks essential to a healthy life. Aging is regarded as the main risk factor for these diseases, as most NDs emerge later in life. Furthermore, oxidative stress can exacerbate and accelerate this aging-related decline [5].

Given that ND treatment protocols currently only address symptoms, researchers are developing new approaches. From these, a plethora of studies use nanotechnology for the diagnosis and treatment of NDs, as it has been shown to prevent nerve cell apoptosis, reduce inflammation, and improve brain drug delivery. Among nanotechnology-based tools, NPs stand out due to their ability to be functionalized with targeting ligands, enhancing their efficiency in delivering therapeutic agents directly to affected areas of the brain and maximizing treatment outcomes [6].

One major concern is delivering drugs to the nervous system, as natural barriers such as the BBB and the blood–cerebrospinal fluid barrier (BCSFB) make this particularly difficult. Nanotechnology-based DDSs present a novel approach to overcoming these barriers, allowing for direct delivery of therapeutic agents to the CNS and facilitating the treatment of various neurological disorders [5].

This work explores the review of these rising NDs (AD, PD and HD), their pathology and current therapies available. Current advances in DDSs, such as LNPs and PNPs, are also explored. Finally, the therapeutic potential, advantages, limitations, and translational challenges of these nanocarrier systems are discussed, highlighting previous studies as examples. This review focuses on LNPs and PNPs, as they represent the most extensively investigated and clinically relevant nanocarrier platforms for the treatment of NDs. While many reviews have addressed individual NDs or specific nanocarrier systems, this review brings together the available evidence on both LNPs and PNPs across AD, PD and HD. This integrated comparative approach highlights common therapeutic strategies, disease-specific challenges, and the principal translational barriers that remain for their successful clinical application.

## 2. Review Methodology

A literature search was conducted in PubMed and Clinicaltrials.gov. The final search was performed on 8 June 2026. Preclinical studies were identified through a literature search in PubMed using combinations of disease-specific terms (e.g., “Alzheimer’s disease”, “Parkinson’s disease”, and “Huntington’s disease”) with terms related to NPs and nanomedicine (“lipid-based nanoparticles”, “polymer-based nanoparticles”). Studies were selected based on their relevance to the objectives of this narrative review. The selection aimed to include representative examples of different NP platforms and encapsulated therapeutic compounds investigated for NDs. Preference was given to studies providing detailed NP characterization and comprehensive evaluation of therapeutic outcomes in established in vitro and/or in vivo models.

Clinical studies were identified through searches of ClinicalTrials.gov using the disease names (Alzheimer’s disease, Parkinson’s disease, and Huntington’s disease) combined with the keyword “nanoparticles”. All relevant registered clinical studies available at the time of the search were screened for eligibility.

Studies published in English between 1997 and 2026 were considered. The search period was defined to include the earliest relevant publications in the field as well as the most current evidence. Original research articles, clinical trials, observational studies, and systematic reviews relevant to the topic were included. Conference abstracts, editorials, letters, duplicate publications, and studies unrelated to the review objective were excluded.

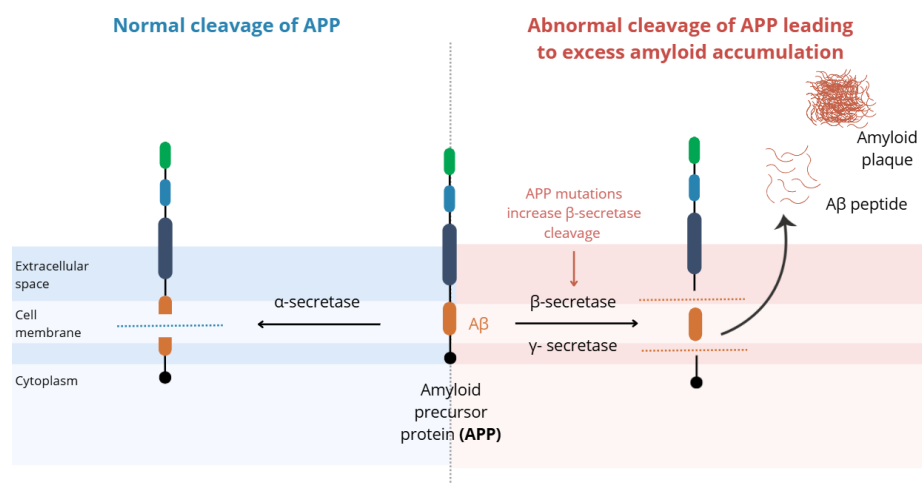
Records retrieved from the databases were imported into Mendeley Version 2.129.0, where duplicates were identified and removed. Retrieved records were first screened based on title and abstract to assess their relevance to the scope of the review. Full-text articles or study records meeting the predefined eligibility criteria were then evaluated for inclusion. Studies not related to NDs of interest or not involving NP-based therapeutic approaches were excluded. The final selection was made to ensure coverage of representative preclinical and clinical evidence on LNPs and PNPs. Figures 1–7 were created using Canva (<https://www.canva.com/>).

## 3. Neurodegenerative Diseases

### 3.1. Alzheimer’s Disease (AD)

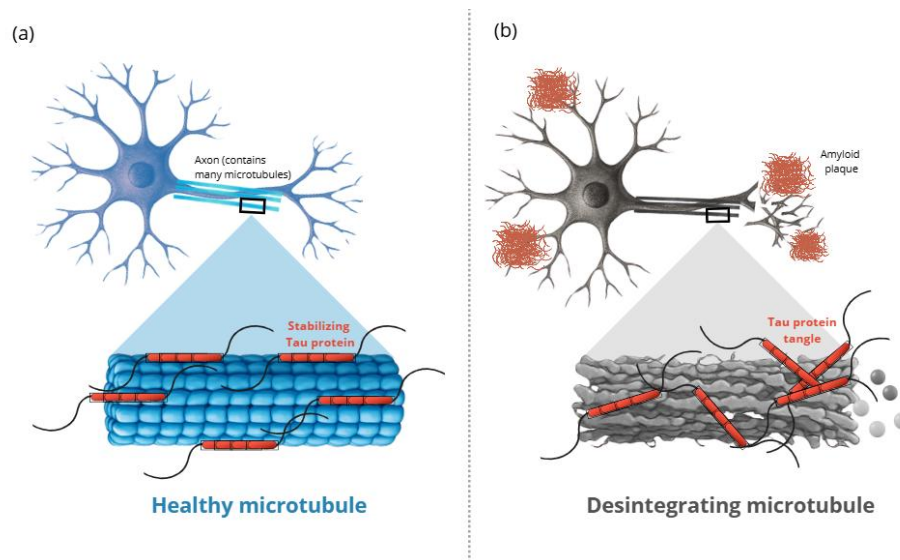
AD’s progress is irreversible and is also described by cognitive and behavioral impairments [5]. This pathology arises from both structural and functional damage to the CNS, which results from ongoing neurodegeneration and the abnormal build-up of proteins in brain tissue. The condition is characterized by two pathological features: amyloid plaques and neurofibrillary tangles (NFTs) [7].

Amyloid plaques are formed by the abnormal extracellular accumulation of amyloid-beta ( $A\beta$ ) peptides. These peptides are produced through the amyloidogenic pathway, where the amyloid precursor protein (APP) is sequentially cleaved by  $\beta$ - and  $\gamma$ -secretases [7,8]. The aggregation of  $A\beta$  peptides outside neurons leads to the formation of plaques (Figure 1), which disrupt hippocampal circuitry, an area crucial for memory, and thereby impair the consolidation of short-term memories into long-term storage [9]. Also,  $A\beta$  plaque deposition is associated with inflammatory and network-level responses that interact bidirectionally with Tau pathology, contributing to NFT formation in a non-linear and heterogeneous disease process [9,10].



**Figure 1.** Amyloidogenic pathway. Under normal conditions, APP is cleaved by  $\alpha$ -secretase generating sAPP $\alpha$ . The physiological functions of sAPP $\alpha$  are poorly understood, but its actions have been generally considered beneficial to neurons [11]. In AD, APP is sequentially cleaved by  $\beta$ - and  $\gamma$ -secretases, leading to the aggregation of A $\beta$  peptides outside neurons and the formation of plaques.

NFTs are the intracellular accumulation of Tau protein aggregates, which are formed because of Tau hyperphosphorylation, leading to neuronal dysfunction. Under healthy conditions, Tau is mainly found in neurons where it plays key roles in supporting microtubules, promoting axon growth, and shaping dendritic structures. However, in pathological conditions such as AD, Tau becomes hyperphosphorylated, detaches from the microtubules, and forms intracellular neurofibrillary aggregates (Figure 2), inducing neurodegeneration [12].

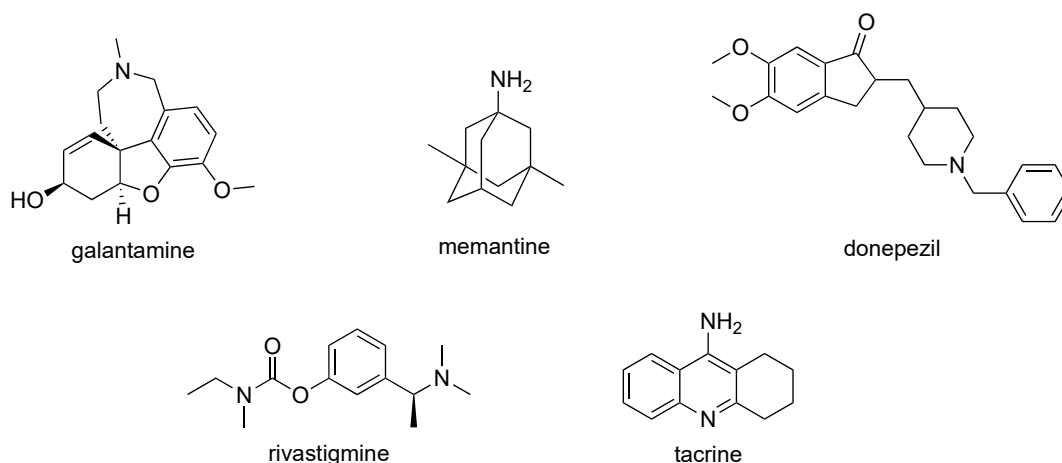


**Figure 2.** AD's histopathology. (a) Under healthy conditions, Tau protein is associated with microtubules, where it plays a critical role in their stabilization, axonal growth, and other essential neuronal functions. There is also no formation of A $\beta$  plaques. (b) Under pathological conditions, A $\beta$  plaques form, triggering an inflammatory response that leads to the development of NFTs when Tau becomes abnormally hyperphosphorylated, dissociates from microtubules, and aggregates into intracellular NFTs.

Moreover, neuronal and synaptic loss often occurs alongside tangle formation. Therefore, the symptoms and severity of AD are more closely linked to the presence of

NFTs, while A $\beta$  pathology reaches a plateau early in the symptomatic phase of the disease [3].

Currently, most of the available treatments for AD only provide symptom relief. Both EMA and FDA agencies have approved a group of five drugs (Figure 3) for managing this condition: memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, and four acetylcholinesterase (AChE) inhibitors, donepezil, rivastigmine, galantamine, and tacrine [5,13].



**Figure 3.** Approved drugs for AD. Most of these compounds share structural features such as rigid scaffolds, often involving aromatic rings, and the presence of primary and tertiary amines, which contribute to their pharmacological profiles.

AChE inhibitors are drugs that block the enzyme AChE, which normally breaks down acetylcholine, a key neurotransmitter in the brain. By inhibiting this enzyme, acetylcholine levels in the brain increase, therefore temporarily enhancing communications between neurons and improving or stabilizing memory and cognitive functions. Galantamine, which is also a nicotinic receptor agonist, not only prevents the breakdown of acetylcholine but also directly stimulates nicotinic receptors [14]. These receptors play a key role in cognitive processes, and by activating them, galantamine helps to boost cholinergic activity further and may enhance the release of other important neurotransmitters, providing additional cognitive support [7]. Tacrine was the first AChE inhibitor approved by the FDA for the treatment of AD and demonstrated efficacy in improving cognition and functional outcomes in patients with mild to moderate AD [15–17]. However, its clinical use was severely limited by significant hepatotoxicity, with more than 25% of patients developing clinically relevant elevations in liver enzymes, requiring regular liver function monitoring throughout treatment [15]. Owing to its unfavorable safety profile and the availability of safer AChE inhibitors, tacrine was withdrawn from clinical use in 2013 and is no longer used in contemporary clinical practice [16,17].

On the other hand, NMDA receptor antagonists, such as memantine, modulate glutamate activity, another crucial neurotransmitter involved in learning and memory. In AD, excessive glutamate stimulation can cause neuronal damage via excitotoxicity. Memantine helps to block this overactivation, protecting neurons and supporting brain function, especially in the moderate to severe stages of the disease [7].

As mentioned before, the available pharmacological treatments for AD were predominantly focused on symptomatic relief and did not substantially modify the underlying disease progression. Recently, the anti-amyloid monoclonal antibodies lecanemab and donanemab have emerged as the first disease-modifying therapies approved for patients with early AD [18,19]. These antibodies reduce amyloid burden

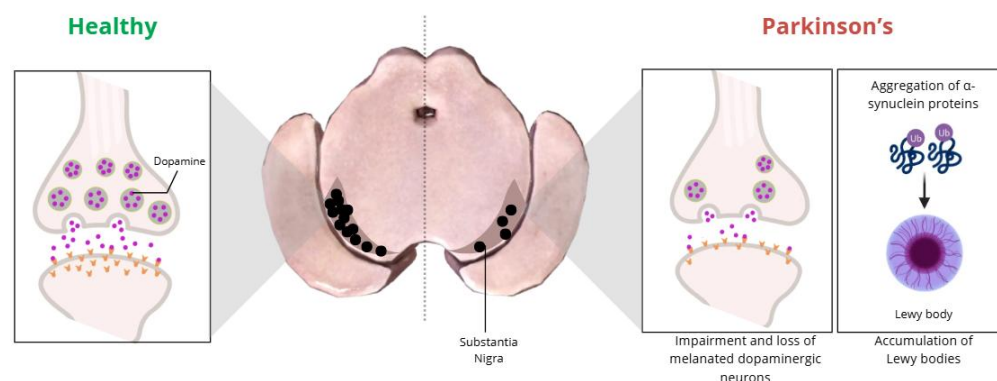
(donanemab primarily target insoluble A $\beta$  plaques, whereas lecanemab is designed to bind the soluble forms of A $\beta$ ) [18] and have demonstrated a statistically significant slowing of cognitive decline in clinical trials [19]. In April 2025, lecanemab became the first anti-A $\beta$  therapy to receive marketing authorization from the European Commission, and in September 2025, donanemab was approved [18]. However, their use is restricted to patients with mild cognitive impairment or mild dementia due to AD with confirmed amyloid pathology and without relevant exclusion criteria [18]. Furthermore, treatment is associated with amyloid-related imaging abnormalities (ARIA), the main treatment-related adverse event detected by magnetic resonance imaging (MRI). ARIA comprises two main forms: ARIA-E, characterized by vasogenic edema or sulcal effusion resulting from fluid extravasation, and ARIA-H, which refers to cerebral microhemorrhages, macrohemorrhages, or superficial siderosis caused by hemosiderin deposition [20]. Consequently, routine MRI monitoring is required throughout treatment. Although these therapies have demonstrated statistically significant slowing of cognitive decline in clinical trials, the magnitude of the clinical benefit remains modest [19].

### 3.2. Parkinson's Disease (PD)

PD is a multifactorial disorder resulting from the interaction of genetic and environmental factors [9]. Genetic studies have shown that mutations in the Synuclein Alpha gene (*SNCA*), which encodes  $\alpha$ -synuclein, can cause inherited forms of PD. In addition to these rare pathogenic mutations, gene multiplications and common genetic risk variants also contribute to PD's susceptibility, whereas most PD cases are sporadic and result from a complex interplay between genetic and environmental factors. This discovery, alongside the increased risk observed in individuals with a family history, confirms the possible genetic contribution to PD's pathogenesis [21]. Age is recognized as the primary risk factor for PD. Additionally, exposure to environmental toxins has been identified as an important contributor to PD's development [9].

Often classified under the broader category of Parkinsonism, PD is a progressive ND primarily affecting motor control. The pathological hallmark of PD is depigmentation of the substantia nigra and locus coeruleus (located in the midbrain and pons, respectively [21]) with neuronal loss in the pars compacta of the substantia nigra [4], which arises from the degeneration of dopaminergic neurons containing neuromelanin [9]. This extensive neuronal loss impairs the nigrostriatal pathway, leading to a reduction in dopamine levels within the striatum and, consequently, the development of the characteristic motor symptoms of PD [9].

Neuronal degeneration in additional regions, such as the nucleus basalis of Meynert, raphe nuclei, locus coeruleus, pedunculopontine nucleus, dorsal motor nucleus of the vagus nerve, hypothalamus, and olfactory bulb, contributes to the manifestation of PD's non-motor symptoms [9]. In neurons affected by PD, one key molecular feature is the misfolding and aggregation of the  $\alpha$ -synuclein protein. In a misfolded state, this protein becomes insoluble and aggregates to form intracellular inclusions into intracellular inclusions, forming Lewy bodies (Figure 4) within the neuronal soma and Lewy neurites within neuronal processes [21]. The  $\alpha$ -synuclein present in Lewy bodies is predominantly phosphorylated and may spread to other regions of the CNS [9,22]. The association between Lewy pathology and the pathogenesis of the disease is yet poorly understood [21].



**Figure 4.** PD's histopathology. Under healthy conditions, the substantia nigra contains dopaminergic neurons that produce and release dopamine, a neurotransmitter essential for regulating voluntary movement. In PD, there is a loss of dopaminergic neurons in the substantia nigra, leading to dysfunction of the nigrostriatal pathway, resulting in reduced dopamine levels. In affected neurons, misfolding and aggregation of the  $\alpha$ -synuclein protein occur. In a misfolded state,  $\alpha$ -synuclein becomes insoluble and aggregates to form Lewy bodies.

As previously mentioned, due to the areas affected in PD, it manifests with a variety of both motor and non-motor symptoms. The classic findings of PD are motor symptoms. They include (the famous) resting tremor, bradykinesia, which refers to slowing of movement and the simplification of complex motor tasks, akinesia, when spontaneous movement is decreased, postural instability, muscular rigidity, and postural and gait impairment [4]. Besides motor symptoms, PD is associated with a wide spectrum of non-motor symptoms, which have become increasingly recognized over time and can be equally disabling as motor deficits. These include cognitive impairment, mood disorders such as depression and anxiety, autonomic dysfunction, and sleep disturbances. Notably, anosmia (loss of smell) affects up to 90% of individuals with PD and may precede the onset of motor symptoms by several years. Cognitive decline can progress over time and may eventually lead to PD's dementia, which affects approximately 30% to 40% of patients worldwide [4].

Evidence indicates that physiotherapy, surgical interventions, and pharmacological treatments can enhance the quality of life in patients with PD. The primary pharmacological approaches for alleviating motor symptoms include dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, and levodopa, which is typically administered in combination with a dopa decarboxylase inhibitor [5]. Among the various treatment options for PD, Table 1 summarizes the drugs currently used and their respective mechanisms of action [23].

**Table 1.** Treatment options for PD and the mechanisms of action.

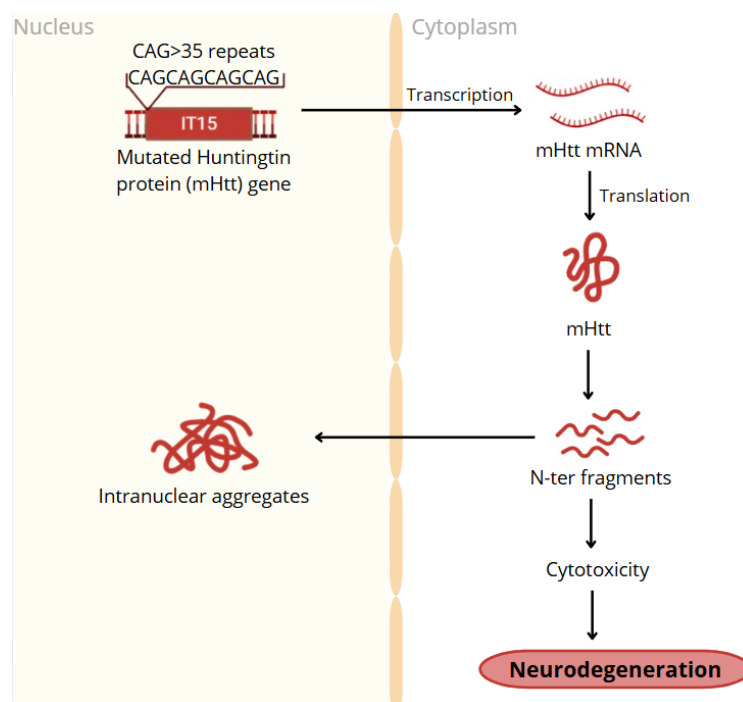
| Drug/Class                    | Examples                                         | Mechanism of Action                                                             |
|-------------------------------|--------------------------------------------------|---------------------------------------------------------------------------------|
| Levodopa (L-DOPA)             | L-DOPA                                           | Precursor converted to dopamine in the brain                                    |
| DOPA Decarboxylase Inhibitors | Carbidopa, Benserazide                           | Prevent peripheral conversion of L-DOPA to dopamine (increase CNS availability) |
| Dopamine Agonists             | Apomorphine, Rotigotine, Pramipexole, Ropinirole | Directly stimulate dopamine receptors                                           |

|                          |                                                         |                                                                               |
|--------------------------|---------------------------------------------------------|-------------------------------------------------------------------------------|
| MAO-B Inhibitors         | Rasagiline, Selegiline                                  | Inhibit MAO-B → reduce dopamine breakdown                                     |
| COMT Inhibitors          | Entacapone, Tolcapone                                   | Inhibit catechol-O-methyltransferase → prolong L-DOPA effect                  |
| NMDA receptor antagonist | Amantadine                                              | Increases dopamine release and blocks reuptake and antagonizes NMDA receptors |
| Anticholinergics         | Bentropine, Orphenadrine, Procyclidine, Trihexyphenidyl | Reduce acetylcholine activity → restore dopamine/ACh balance in the striatum  |

### 3.3. Huntington's Disease (HD)

HD is a hereditary ND transmitted in an autosomal dominant pattern, resulting from the expansion of a cytosine–adenine–guanine (CAG) trinucleotide repeat within the coding region of the huntingtin (HTT) gene, located on the short arm of chromosome four. This gene encodes the HTT protein, which is expressed in numerous tissues across the body, including extensively throughout the CNS. Although the precise physiological role of HTT is not fully understood, it is believed to contribute to vital cellular processes such as protein transport, vesicular trafficking, and selective autophagy. Normally, the CAG trinucleotide counts ranges between six and twenty-six repeats. When the number of repeats exceeds this range, the sequence becomes genetically unstable, particularly during paternal transmission, potentially increasing further in subsequent generations. Repeat lengths between twenty-seven and thirty-five are considered intermediate and are rarely associated with clinical symptoms. The pathological threshold for disease onset is generally accepted to be thirty-six or more repeats, though complete penetrance is typically observed only when forty or more repeats are present. There is a well-established association between longer CAG repeat tracts and earlier disease onset, accelerated progression, and greater clinical severity [24].

In addition to the CAG trinucleotide repeat expansion itself, other factors, such as additional genetic variants or environmentally influenced molecular changes, may also influence the onset and progression of HD. As the number of CAG repeats increases, the resulting elongated polyglutamine (PolyQ) tract in the N-terminal region of the HTT protein promotes misfolding and facilitates the formation of insoluble protein aggregates [24]. This aberrant HTT protein then fragments, causing neuronal malfunction and cytotoxicity in affected neurons, which are commonly detected post-mortem and accumulate in both the nuclear compartment, forming neuronal intranuclear inclusions, and the cytoplasm of affected neurons (Figure 5). The progressive accumulation of these aggregates impairs neuronal function, triggers apoptotic pathways, and ultimately leads to significant atrophy in specific brain regions, most notably the striatum and cortex [24].



**Figure 5.** HD's histopathology. HD results from the expansion (36 or more repeats) of a CAG trinucleotide repeat within the coding region of the HTT gene. This gene encodes the HTT protein, specifically the mHTT protein. As the number of CAG repeats increases, the resulting elongated PolyQ tract in the N-terminal region of the HTT protein promotes misfolding and facilitates the formation of insoluble protein aggregates. This aberrant HTT protein then fragments, leading to neuronal dysfunction and cytotoxicity in affected neurons.

HD is a progressive disease, which usually arises between 30 and 50 years old, typically beginning with subtle symptoms, often going unrecognized for years before a formal diagnosis is made. In the early stages, patients may present with mild involuntary movements, slight impairments in executive functioning, and depressed mood. Despite these initial manifestations, individuals usually maintain independence during this phase. As the disease advances, however, functional decline becomes more evident. Patients may struggle with problem-solving, coordination, and maintaining employment or driving. Falls become more frequent, and increasing assistance is required for daily activities. In the later stages of the disease, patients may lose the ability to speak, walk, or eat independently, often becoming bedridden and dependent on feeding tubes. At this point, dementia is typically severe, impacting all cognitive domains. Death usually occurs around 18 years after symptom onset, with aspiration pneumonia being the most common cause due to impaired swallowing [24].

The symptoms of HD are classically divided into three major domains: motor, cognitive and psychiatric [24]. Among motor symptoms, chorea is the main feature. The patient exhibits abnormal movements [5] including brief, involuntary movements predominantly affecting the trunk, face, and limbs. It progressively disrupts voluntary movements such as walking, speaking, and swallowing. Other motor abnormalities include bradykinesia, dystonia, hyperreflexia, and slowed eye saccades [24]. Cognitive symptoms primarily involve a progressive decline in executive functions, including difficulties with attention, concentration, decision-making, and multitasking. Memory loss, poor insight, and depression are also frequently reported. Psychiatric symptoms in HD are diverse and may even precede motor manifestations. Patients are often initially misdiagnosed with primary psychiatric disorders. Common psychiatric features include irritability, impulsivity, anxiety, obsessive–compulsive behaviors, mania, and psychosis, such as hallucinations or

delusions. Depression is particularly prevalent and is linked to a significantly elevated suicide rate of approximately 7%, far higher than the 2.7% of the general population [25]. Although the exact mechanisms behind the cognitive and psychiatric symptoms are not fully understood, striatal dopaminergic dysregulation is believed to contribute significantly to their development [24].

Despite an extensive understanding of the molecular and genetic mechanisms underlying HD, existing therapeutic approaches are limited to symptomatic relief and do not address the root pathology of this currently incurable disorder [5]. Present treatment strategies focus on managing motor, cognitive, and psychiatric symptoms to enhance the quality of life for affected individuals [24].

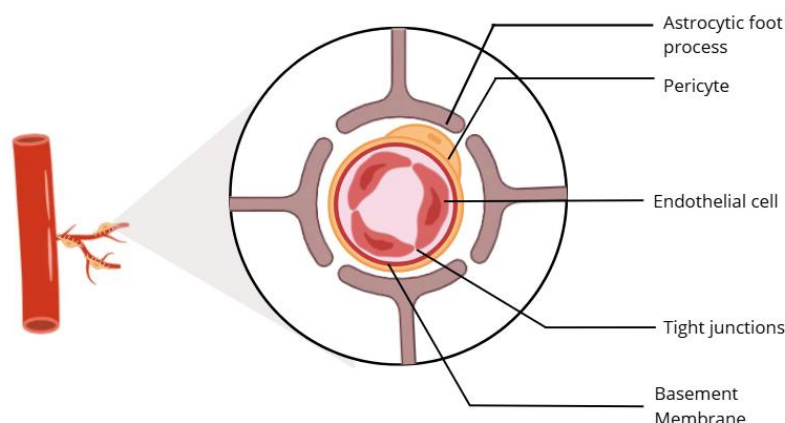
A variety of neuroleptic agents are commonly employed to control chorea associated with HD [26,27]. In cases where patients experience seizures, standard anticonvulsants like valproic acid may be prescribed. Some individuals with HD may also develop Parkinsonian symptoms, which are commonly managed with L-DOPA to help alleviate motor issues. Currently, no medication exists that can directly target or correct the effects of the mutant huntingtin protein (mHTT). Among available treatments, tetrabenazine and its deuterated analogue, deutetabenazine, are considered the most effective in addressing chorea, with neuroleptics and benzodiazepines also offering therapeutic benefits [5,28]. Tetrabenazine is also commonly used for the treatment of chorea [24]. Other drugs used in therapeutics are antipsychotics, such as risperidone and haloperidol, antidepressants, and/or benzodiazepines.

### 3.4. Therapeutic Brain Delivery Obstacles: The BBB

As previously mentioned, current approaches to NDs are limited to symptom relief only. The development of effective treatments for NDs remains a major challenge due to the unique and restrictive environment of the brain, characterized by specialized barriers and a tightly regulated milieu essential for neuronal function [2]. This difficulty is further confirmed by the innate physicochemical properties of many drugs, which hinder their ability to cross both the BBB and the BCSFB. It is predicted that, due to delivery difficulties, roughly 98% of micro drug molecules and 100% of proteins and nucleic acid treatment plans will be rejected from the brain [5].

The BBB is a highly specialized and selective interface that separates circulating blood from the brain's extracellular fluid. Its primary role is to protect the brain from potentially harmful substances, including toxins and/or pathogens, while tightly regulating the transport of essential nutrients and molecules [2]. Structurally (Figure 6), the BBB consists of endothelial cells connected by tight junctions, surrounded by pericytes, astrocytes, neurons, and microglia, which together contribute to its integrity and function [7]. The brain capillaries, which are made by brain microvessel endothelial cells, are responsible for these constraints of the BBB [5]. Due to the presence of tight junctions and high electrical resistance, only small, non-polar molecules can passively diffuse across the BBB. In contrast, larger or polar molecules, such as drugs, amino acids, and glucose, require specific transport mechanisms [7].

Active mechanisms like P-glycoprotein (P-gp) and other multidrug resistance-associated proteins play a critical role in limiting foreign substances from entering the brain [5]. Although the BBB is crucial for brain protection, it poses a significant obstacle to the delivery of therapeutics targeting NDs or other brain-located pathologies. Many promising drug candidates, including small molecules, monoclonal antibodies, peptides, and nucleic acids, fail to reach the brain in effective concentrations due to limitations in absorption, distribution, metabolism, and excretion [2].



**Figure 6.** BBB's structure. The BBB is primarily composed of a polarized layer of microvascular endothelial cells, closely connected by tight junctions. These cells are supported by astrocytes and pericytes.

To successfully cross the BBB, therapeutic molecules must meet specific criteria: they should have fewer than ten hydrogen-bond donors or acceptors, a molecular weight below 500 Daltons, minimal resemblance to BBB-associated enzymes or efflux systems, and low binding affinity to plasma proteins [5].

Moreover, the integrity of the BBB gradually deteriorates with aging, and this decline is commonly observed in most NDs. Several studies have shown that these disorders actively impair the structure and function of the BBB, further contributing to its dysfunction and increased permeability. This disruption not only compromises brain homeostasis but also exacerbates disease progression, making the development of effective brain-targeted treatments even more challenging [2]. There is also evidence that the BBB selectivity might be found compromised by the presence of an illness, tumor and/or disorder, leading to a more leaky BBB and, therefore, a more severe state [29,30]. Additionally, in many NDs, the precise mechanisms and origins of pathology remain unclear, complicating understanding of whether BBB impairment is a driving factor, a consequence, or part of a bidirectional process within the disease. Increased permeability has been associated with the accumulation of blood-derived proteins in the brains of post-mortem AD patients, along with a reported decrease in tight junction proteins, further indicating BBB breakdown [30]. Supporting this, Wisniewski et al. (1997) [31] observed abnormal deposition of albumin and immunoglobulins in brain regions with significant amyloid plaque load, suggesting that the BBB was sufficiently compromised to allow the passage of these typically restricted serum proteins. In parallel, Ryu and McLarnon (2009) [32] reported elevated levels of fibrinogen in affected areas, a finding indicative of vascular damage and inflammatory activation. These histological findings further reinforce the notion of BBB disruption as a contributing factor in AD pathophysiology [33].

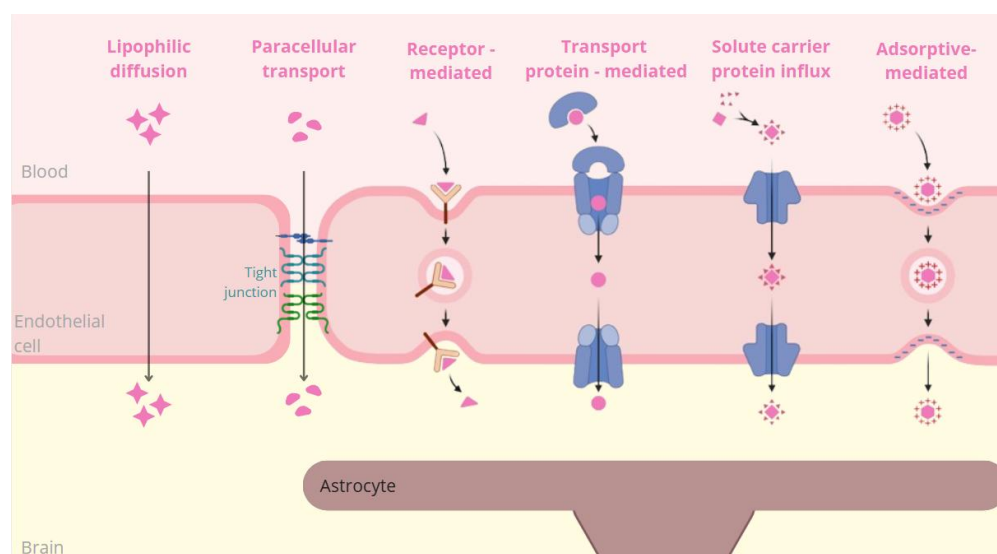
Furthermore, the biological interface that separates the cerebrospinal fluid (CSF) from the bloodstream, the BCSFB, is located at the choroid plexus and serves a protective role like the BBB by blocking toxins from entering the CNS. While choroid plexus epithelial cells are tightly connected to form a mechanical barrier, the capillaries supplying the plexus lack tight junctions, allowing small molecules and nutrients to pass through. However, epithelial tight junctions prevent these substances from entering the CSF. Although the BCSFB has a larger surface area than the BBB, it is considered a secondary

barrier to drug distribution since its exposure to blood is approximately a thousand times smaller in relation to the BBB [5].

With this, it is important to develop a solution to bypass the BBB and/or BCSFB to address and overcome this obstacle in ND therapies. By doing so, many promising drugs that were or are still being discovered can become lead compounds without physicochemical limitations and therefore help address such conditions.

### 3.5. BBB Transport Mechanisms

Transport across the BBB is regulated by a range of distinct transport mechanisms (Figure 7). Transport across the BBB is mediated by several specialized mechanisms, each fulfilling a distinct role. Passive diffusion occurs via paracellular pathways, allowing the limited passage of small, water-soluble molecules between endothelial cells, or via transcellular routes, enabling lipophilic and low-molecular-weight substances to diffuse directly across cell membranes. Efflux transporters, particularly those belonging to the ATP-binding cassette transporters, actively remove potentially harmful compounds from the brain into the bloodstream, thereby contributing to neuroprotection. In contrast, carrier-mediated transport delivers essential nutrients, such as glucose and amino acids, via specific membrane proteins. Larger biomolecules are transported via receptor-mediated transcytosis, which relies on selective ligand–receptor interactions, while adsorptive-mediated transcytosis facilitates the uptake of positively charged molecules through electrostatic interactions with the endothelial surface. Additionally, cell-mediated transcytosis involves the migration of immune cells across the BBB, enabling the transport of substances into the CNS [34].



**Figure 7.** BBB transport mechanisms. The main transport mechanisms across the BBB include lipophilic diffusion (via transcellular routes), paracellular transport, receptor-mediated transcytosis, transporter-mediated processes, solute carrier influx, and adsorptive-mediated transcytosis [35].

## 4. Nanoparticles (NPs)

Efficient drug delivery to the brain remains difficult because of the presence of natural barriers, namely the BBB and BCSFB, described earlier [5]. While surgical and invasive techniques have shown some success in treating NDs, their clinical use remains limited due to concerns about potential long-term damage to the BBB [9]. As a safer alternative, nanotechnology-based DDSs have emerged as a promising approach to bypass the BBB without harming it, enabling effective treatment for NDs [5].

This innovative approach draws upon the principles of nanomedicine, an interdisciplinary field combining nanotechnology and medicine, which uses NPs, at the nanoscale, to deliver therapeutic agents, phytoconstituents, and biomolecules directly to specific anatomical targets, such as the brain [5].

Inspired by Paul Ehrlich's "Magic Bullet", concept introduced in the early 20th century [36,37], the strategy of DDS allows drugs to selectively reach disease sites while minimizing exposure to healthy tissues, thereby increasing bioavailability and reducing side effects [2].

Drugs, transported in conventional dosage forms, often spread systemically after administration, unintentionally affecting healthy organs. In contrast, nanotechnology-based systems enable controlled and targeted drug release, often at a slower rate, which enhances therapeutic effectiveness and further limits adverse effects [6]. This targeted and sustained delivery not only overcomes physiological and cellular barriers, such as the BBB, but also addresses other pharmacological challenges, including low solubility and a short circulation half-life. As a result, NPs are being extensively researched as a viable tool for the diagnosis and treatment of various NDs [2].

NPs are small particles (1–1000 nm) [6], which exhibit diverse chemical properties and a high degree of modifiability, enabling fine-tuning and enhancement of critical functional characteristics. They can encapsulate hydrophilic and hydrophobic molecules with a wide variety of chemical structures and physicochemical properties, serving as efficient delivery systems that protect bioactive compounds during transport [38]. NPs can enhance solubility [39], biodistribution, pharmacokinetics, and stability, and mitigate the potential toxicity of therapeutic agents. Importantly, they have demonstrated the ability to transport molecules into tissues that are typically difficult to access, including the brain. Furthermore, NPs enable controlled drug release kinetics, which are particularly valuable for maintaining sustained therapeutic effects over extended periods [9]. The preparation of NPs with dimensions below 100 nm increases their surface area, thereby enhancing their reactivity with both organic and inorganic molecules [6]. NPs can be broadly categorized into organic and inorganic types. Organic NPs, such as LNPs and PNPs, are especially notable for their superior biocompatibility, biodegradability, and ability to penetrate biological membranes [40,41].

#### 4.1. Lipid-Based NPs (LNPs)

LNPs have emerged as a prominent technology for the targeted and controlled delivery of therapeutic agents to the brain. Their prominence as drug nanocarriers is primarily attributed to their intrinsic safety profile, biocompatibility, and biodegradability [5]. Moreover, a lipid nanocarrier is more effective in protecting the therapeutic moiety from degradation and reducing toxicity than free drug administration [9]. The lipid composition of LNPs is analogous to that of the BBB, thereby enhancing their capacity for transcellular transport across this physiological barrier. Typically, LNPs are composed of phospholipids, fatty acids, monoglycerides, triglycerides, fatty alcohols, and waxes. Among the various subclasses, liposomes and solid lipid nanoparticles (SLNs) represent the most extensively investigated and applied forms, particularly in the treatment of CNS disorders. These nanocarriers have attracted considerable attention due to their potential efficacy in managing NDs. Variations among different types of LNPs are primarily observed in their lipid layer architecture, morphology, drug encapsulation efficiency, mean particle size, and surface electrokinetic properties. A significant advantage of LNPs lies in their dual capacity to encapsulate both hydrophilic and lipophilic drug molecules, thereby offering enhanced formulation versatility. Nonetheless, several limitations continue to hinder their large-scale production and clinical translation. These include limited physico-

chemical stability, complex and resource-intensive manufacturing procedures, unpredictable polymorphic transitions, and premature drug leakage during storage [5,34].

Various types of LNPs have been explored for the treatment of NDs, including liposomes, SLNs and nanostructured lipid carriers (NLCs). Liposomes are composed by amphiphilic phospholipids that spontaneously form spherical lipid structures when exposed to aqueous environments, driven by the thermodynamic favorability of burying their hydrophobic acyl chains away from water. Structurally, liposomes are typically composed of one or more phospholipid bilayers surrounding an internal aqueous compartment. This architecture allows them to encapsulate hydrophobic drugs within their lipid membranes and hydrophilic bioactive compounds within their aqueous core. However, due to the relatively limited internal volume available for hydration, the encapsulation efficiency for hydrophilic substances tends to be lower compared to hydrophobic ones [7]. SLNs which consist of a solid lipid core stabilized by surfactants, remain solid at both room and body temperatures. This structure provides enhanced physicochemical stability and controlled drug release, although their drug loading capacity, particularly for hydrophilic compounds, is relatively limited [42,43]. NLCs, which are considered the second generation of LNPs, share several physicochemical properties with SLNs but differ in their composition. Unlike SLN, the lipid matrix of NLC consists of a blend of solid and liquid lipids [44], which enables the incorporation of a larger number of molecules and provides greater stability during storage when compared to SLN [45]. Moreover, NLCs exhibit high encapsulation efficiency, minimize drug expulsion during storage, and can retain drug compounds at higher concentrations in aqueous media [46]. These systems are stabilized in aqueous dispersions using surfactants or surfactant mixtures, and their composition helps prevent lipid recrystallization over time, further enhancing their drug loading capacity, particularly for lipophilic compounds [44]. Extracellular vesicles (EVs), unlike the previous synthetic nanocarriers, are naturally derived vesicles secreted by cells that inherently reflect the molecular composition and biological function of their cell of origin. Although EVs are not classified as conventional LNPs, they are discussed in this section due to their functional similarities with lipid-based nanocarriers and their relevance in drug delivery applications for NDs. A key distinctive feature of EVs is their intrinsic role in intercellular communication, enabling them to transfer biologically active cargo and modulate recipient cell behavior. Additionally, EVs exhibit a unique innate tropism toward specific tissues, particularly injured or pathological sites, which is not typically observed in conventional NPs without surface modification. They also possess a naturally occurring ability to cross the BBB bidirectionally, a mechanism that remains not fully understood but is closely linked to their biological origin. These properties distinguish EVs from other nanocarriers, although challenges such as heterogeneity, limited control over cargo loading, and difficulties in standardization and large-scale production persist [34].

#### 4.2. Polymer-Based NPs (PNPs)

PNPs are among the most promising approaches in nanomedicine. These nanoscale carriers are colloidal systems constructed from biocompatible, biodegradable polymers with low aqueous solubility, in which therapeutic agents can be dissolved, entrapped, encapsulated, covalently bound, or adsorbed onto the polymeric matrix. Biodegradable PNPs have demonstrated the ability to enhance the pharmacological profiles of therapeutic compounds, thereby improving efficacy, reducing toxicity, and increasing patient tolerability. In addition, they offer numerous advantages, including protection against premature drug degradation and unfavorable interactions with the biological environment, enhanced absorption in target tissues, and improved cellular penetration. Collectively, these unique attributes have driven the development and regulatory approval of several PNP-based drug formulations, with numerous others currently under evaluation in clinical tri-

als [2]. Poly(lactic-co-glycolic) acid (PLGA) represents one of the most extensively employed polymers in the design of PNPs, particularly for applications in brain-targeted delivery and controlled release of therapeutic agents [9].

Examples of PNPs include PLGA NPs and polymersomes (PMs), which are self-assembled vesicles formed from amphiphilic block copolymers that can encapsulate both hydrophilic and hydrophobic therapeutic agents. Compared with liposomes, they possess thicker and more robust membranes, providing enhanced mechanical stability, greater drug retention, and highly tunable physicochemical properties [47,48]. Commonly used copolymers include Poly(ethylene glycol)-poly(lactic acid) (PEG-PLA) or Poly(ethylene glycol)-poly( $\epsilon$ -caprolactone) (PEG-PCL). Only a brief overview of the main classes of NPs will be provided, as their structural and formulation aspects have been comprehensively covered in previous reviews. The present work will primarily address their applications in the treatment of NDs.

#### 4.3. LNPs vs. PNPs

Based on the information presented in the previous sections, LNPs and PNPs exhibit distinct yet complementary properties that influence their performance in brain drug delivery. Owing to their lipid composition, which closely resembles that of biological membranes, LNPs may facilitate interactions with the BBB and have demonstrated promising potential for brain drug delivery. However, BBB penetration is also influenced by several physicochemical properties, including particle size, surface charge, and surface functionalization. In contrast, PNPs typically require surface functionalization to achieve comparable transport efficiency across this barrier. Regarding drug loading, LNPs offer formulation versatility by accommodating both hydrophilic and lipophilic compounds. However, PNPs offer greater structural tunability, which may enable higher loading capacity and more controlled, sustained drug release depending on the carrier design and the physicochemical properties of the therapeutic payload. In terms of stability, PNPs are generally more robust, offering enhanced protection against premature degradation and environmental interactions, whereas LNPs may be more limited by physicochemical instability and potential drug leakage during storage. Finally, with respect to scalability, LNPs benefit from more established manufacturing processes, though challenges such as polymorphic transitions and formulation complexity remain, whereas PNPs often involve more intricate synthesis and scale-up procedures. Collectively, these differences highlight that LNPs may be particularly advantageous for efficient BBB penetration, whereas PNPs may be better suited for achieving controlled drug delivery and enhanced formulation stability.

#### 4.4. Nanotoxicology

The toxicity and biocompatibility of NPs are critical considerations for brain drug delivery. Organic NPs are often regarded as safer alternatives due to their composition from naturally occurring elements, such as carbon and hydrogen. However, they are not devoid of risk. Physicochemical properties, including particle size, morphology, solubility, and aggregation behavior, play a pivotal role in determining their toxicity profile. Notably, these NPs may accumulate in organs such as the liver, spleen, kidneys, and brain, potentially leading to systemic and neurotoxic effects. Within the CNS, their interactions with neurons, astrocytes, and microglia can induce inflammatory responses and cytotoxicity [49].

Although LNPs are generally considered biocompatible, their degradation products, such as free fatty acids and phospholipids, may trigger oxidative stress, inflammation, and neuronal damage. Furthermore, the selection of surfactants and lipid constituents significantly influences their biodegradation kinetics and overall safety profile. PNPs intro-

duce additional complexities. For instance, those derived from PLGA can produce acidic degradation byproducts, which may exacerbate pre-existing neuro-inflammatory conditions. Moreover, concerns regarding their long-term safety persist, particularly in relation to their stability and potential for accumulation within biological systems [49].

#### 4.5. Immunogenicity and Off-Target Effects of NPs

NPs can induce immune-related adverse effects and nonspecific biological interactions according to their physicochemical properties, such as particle size, shape, surface charge, hydrophobicity, and chemical composition. After administration, NPs rapidly interact with blood proteins, forming a protein corona that may modify their biological identity, cellular internalization, and biodistribution. These processes can stimulate both innate and adaptive immune responses, promoting complement activation, inflammatory cytokine production, macrophage uptake, and hypersensitivity reactions. Moreover, the unintended accumulation of NPs in organs, including the liver, spleen, and lymphatic tissues, may lead to off-target toxicity and reduced therapeutic performance. To overcome these limitations, several surface-engineering approaches, such as PEGylation and biomimetic functionalization, have been developed to decrease immune recognition and prolong systemic circulation. Nevertheless, repeated exposure may still trigger immune responses, including the production of anti-PEG antibodies and accelerated NP clearance. Therefore, understanding and controlling NP immunogenicity and off-target effects remain critical for improving the safety and clinical applicability of nanomedicine platforms [50].

### 5. Current Nanoparticles Strategies for ND Treatment

NPs have emerged as promising tools in the search for effective therapies against NDs, owing to their capacity for targeted delivery, ability to cross the BBB, and potential to modulate pathological processes at the molecular level. Several studies have explored NP systems, such as LNPs and PNPs, to evaluate their therapeutic efficacy in ND models.

#### 5.1. AD Studies

Preclinical studies have paired modern LNPs with AD animal models, with promising outcomes. Almuhayawi et al. [51] developed pomegranate extract-loaded SLNs and tested them in an aluminum chloride-induced rat model of AD [5,51]. Pomegranate exhibits antioxidant and antiproliferative effects, largely due to its rich content of phytochemicals such as tannins, alkaloids, and natural pigments, which have shown strong potential in preventing oxidative stress and inhibiting abnormal cell growth [51,52]. The nanoformulation markedly enhanced cognitive performance, antioxidant activity, and histological integrity compared to the free extract. These findings indicate that SLN encapsulation significantly improves the neuroprotective and therapeutic potential of pomegranate extract against AD-related oxidative stress [51].

In addition to pomegranate, other natural compounds with potent antioxidant and neuroprotective properties have also been investigated in the context of AD. Curcumin is the major polyphenolic compound of *Curcuma longa*, an herbaceous tuberous plant endemic to South Asia [53,54]. Curcumin is a versatile compound with a multitude of properties, including potent antioxidant, anti-inflammatory, and neuroprotective effects, which are particularly relevant in the context of AD. In addition to its well-established anti-amyloidogenic activity, it can also prevent the aggregation and promote the clearance of A $\beta$  peptides and also inhibit Tau hyperphosphorylation, addressing the two major pathological hallmarks of AD [54,55]. In addition to these primary mechanisms, curcumin plays a crucial role in regulating several secondary processes involved in AD progression. It effectively combats oxidative stress by enhancing antioxidant defense mechanisms and

reduces neuroinflammation by modulating inflammatory mediators [54]. However, curcumin's application is severely constrained by its poor water solubility. To address this issue, Mathew et al. [54] created Tet-1 peptide-linked curcumin [5,54]. To enhance brain targeting, particularly given the restrictive nature of the BBB, the NPs were conjugated to the Tet-1 peptide, a neuropeptide known for its affinity for neurons and its retrograde transport capability. In vitro analyses demonstrated that the Tet-1-tagged PLGA–curcumin NPs exhibited strong anti-amyloid and antioxidant activities. Specifically, they could bind to amyloid plaques, inhibiting their aggregation and disrupting preformed aggregates, preserving the natural amyloid-clearing properties of unmodified curcumin. These NPs also showed no cytotoxic effects, suggesting their safety for neuronal applications. Notably, the addition of the Tet-1 peptide significantly enhanced the NPs' neuronal targeting efficiency in vitro, highlighting its potential as a delivery strategy for brain-targeted therapies [54].

In a related study by Garcia Alloza et al. [54], curcumin-loaded PLGA NPs were administered to the hippocampus and subventricular zone of adult rats, resulting in increased neurogenesis. Importantly, these NPs were shown to reverse learning and memory deficits in A $\beta$ -producing rats, suggesting not only a therapeutic effect but also a potential for functional brain recovery [5,54,56]. Taken together, these findings indicate that PLGA–curcumin NPs, particularly when functionalized with the Tet-1 peptide, represent a promising multifunctional therapeutic tool for AD. They maintain curcumin's intrinsic neuroprotective properties while overcoming delivery challenges, offering a novel approach for targeting neurodegeneration and promoting neural repair.

Considerable efforts have been devoted to developing nanocarriers capable of effectively delivering therapeutic agents across the BBB, a critical challenge in the treatment of NDs such as AD. One of these therapeutic agents, iA $\beta$ 5, has shown promising potential to inhibit A $\beta$  peptide aggregation. However, despite its efficacy, iA $\beta$ 5 and similar drugs face significant limitations in achieving optimal brain concentrations due to poor permeability through the BBB [57]. To address this limitation, one study proposed a novel drug delivery platform based on lactoferrin (Lf)-coated PEG-PLA NPs, referred to as Lf-PPNs functionalized with OX26 and DE2B4 monoclonal antibodies. The dual-targeting system enabled efficient BBB translocation and selective accumulation at A $\beta$  sites. Compared to non-functionalized NPs, Lf-PPNs achieved markedly higher cellular uptake and iA $\beta$ 5 delivery, highlighting the advantage of combining receptor- and antibody-mediated targeting to improve therapeutic efficacy in AD [58].

While the previously discussed work used PEG-PLA NPs functionalized with targeting ligands, another study explored the use of PEG-PCL PMs, functionalized with the OX26 monoclonal antibody to enhance BBB translocation and brain delivery of the neuroprotective peptide NC-1900. The optimized formulation (OX2634-PO) achieved the highest brain accumulation and permeability, significantly improving spatial learning and memory in rats compared to free NC-1900. These findings demonstrate that OX26-mediated PEG-PCL PMs effectively facilitate peptide delivery to the brain while maintaining therapeutic activity [48].

Zhang et al. [59] investigated the therapeutic effects of mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) engineered to overexpress miR-146a in experimental models of AD. Since miR-146a is a key regulator of inflammatory signaling pathways, the study aimed to determine whether miR-146a-enriched EVs could attenuate neuroinflammation and improve AD-related pathology. Engineered EVs were efficiently internalized by neural and glial cells and significantly reduced the expression of pro-inflammatory cytokines and microglial activation markers by modulating the NF- $\kappa$ B signaling pathway. In AD models, treatment with miR-146a-enriched EVs decreased neuroinflammation, reduced neuronal damage, and improved cognitive performance. The findings

highlighted the potential of engineered MSC-derived EVs as a targeted, cell-free therapeutic strategy for AD by modulating inflammatory pathways.

Musumeci et al. [60] developed an intranasal delivery platform based on PLGA NPs and NLCs loaded with a TRAIL-neutralizing monoclonal antibody for AD treatment. TRAIL (TNF-related apoptosis-inducing ligand) is a pro-inflammatory and pro-apoptotic cytokine implicated in A $\beta$ -induced neurotoxicity, neuronal apoptosis, and neuroinflammation in AD. The nanoformulations improved brain delivery and reduced limitations associated with BBB permeability. In vivo studies demonstrated reduced neuroinflammation, attenuation of amyloid-related pathology, and improved cognitive function in AD mice. The findings support TRAIL inhibition and intranasal nanocarrier-based delivery as promising therapeutic approaches for NDs.

Among the reviewed studies, PLGA-based NPs, particularly Tet-1-functionalized curcumin-loaded systems, appear among the most promising due to their multifunctional effects, including antioxidant, anti-inflammatory, anti-amyloid, and neurogenic activity, combined with improved neuronal targeting. PEG-based targeted nanocarriers showed superior BBB translocation and selective brain delivery. However, their greater formulation complexity may limit clinical translation. Engineered MSC-derived EVs demonstrated remarkable anti-inflammatory potential and natural biocompatibility, though challenges remain in scalability and standardization. In contrast, the intranasal PLGA/NLC anti-TRAIL system provided a non-invasive strategy to reduce neuroinflammation and improve cognitive outcomes. Overall, while each platform presents distinct advantages, PLGA-based NPs currently appear to provide the best balance between therapeutic efficacy, targeting capability, and translational potential for AD therapy.

Overall, these studies demonstrate that functionalized NP systems can improve BBB penetration and enhance therapeutic efficacy in AD models through distinct targeting strategies and mechanisms of action. While Tet-1-functionalized NPs mainly enhanced neuronal targeting, OX26- and lactoferrin-mediated systems facilitated BBB transcytosis and increased brain accumulation of therapeutic agents. In addition, some formulations primarily exhibited antioxidant and neuroprotective effects, whereas others focused on reducing A $\beta$  aggregation or promoting neurogenesis, reflecting the multifactorial nature of AD pathology. However, direct comparison between studies remains challenging due to differences in NP composition, surface functionalization, administration routes, and experimental models.

An increasing number of studies have been published in the past years, and their compilation is presented in Table 2.

**Table 2.** Preclinical investigations grounded on nanoformulations for the treatment of AD.

| Encapsulated Molecule | Nanocarrier | Therapeutic Outcomes                                               | Ref. |
|-----------------------|-------------|--------------------------------------------------------------------|------|
| Pomegranate           | SLNs        | Antioxidant and neuroprotective activity.                          | [51] |
| Curcumin              | PLGA NP     | Anti-amyloid and antioxidant activity.                             | [54] |
| iA $\beta$ 5          | PEG-PLA PM  | Inhibition of A $\beta$ peptides aggregation.                      | [57] |
| NC-1900               | PEG-PCL PM  | Neuroprotective effect.<br>Improved memory and cognitive function. | [48] |

|                            |           |                                                                                                                                                             |      |
|----------------------------|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Quercetin                  | Liposomes | Exhibits anti-amyloid and anti-cholinesterase properties. Enhances cognitive and memory functions. Ensures successful delivery of quercetin across the BBB. | [61] |
| Resveratrol                | SLNs      | Anti-amyloid activity.<br>Reduced oxidative stress.<br>Inhibits A $\beta$ formation in the brain.<br>Increase BBB permeability.                             | [62] |
| Epigallocatechin-3-gallate | PLGA      | Tau-aggregation inhibitors.<br>Anti-amyloid activity.<br>Increased drug permanence in the brain. Reduced neuroinflammation.                                 | [63] |
| Sesamol                    | SLNs      | Neuroprotective.<br>Mitigates learning and memory deficits.<br>Improved cognitive performance.                                                              | [64] |
| Camptothecin               | SLNs      | Anti-amyloid activity.<br>Enhanced penetration through BBB.                                                                                                 | [65] |
| Phytol                     | PLGA      | Attenuation of A $\beta$ accumulation.<br>Decreased ROS production, leading to enhanced neuroprotection in an in vivo AD model.                             | [66] |
| NAP                        | PEG-PLA   | Amelioration in learning impairment. Neuroprotective activity.                                                                                              | [67] |
| Zinc                       | PLGA      | Decreased formation of A $\beta$ plaques.<br>Attenuation of pro-inflammatory cytokine expression and preservation of synaptic density.                      | [68] |
| Donepezil                  | PLGA      | Development of a long-term donepezil DDS.                                                                                                                   | [69] |
| Estradiol                  | PLGA      | Improved neuroprotection.<br>Marked reduction in A $\beta$ immunoreactivity within the hippocampus.<br>Demonstrates neuroprotective effect.                 | [70] |

|                                                                                           |           |                                                                                                                                                                                                                                                                                                                                |      |
|-------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Vitamin D-binding protein                                                                 | PLGA      | Encapsulation of vitamin D-binding protein to prolong systemic half-life and improve therapeutic efficacy.<br>Inhibition of A $\beta$ polymerization and decreased cerebral accumulation of A $\beta$ plaques.<br>Notable amelioration of A $\beta$ -related neuroinflammation, neuronal degeneration, and cognitive deficits. | [71] |
| Galantamine                                                                               | SLN       | Memory restoration.<br>Offered approximately twice bioavailability to that of plain drug.                                                                                                                                                                                                                                      | [72] |
| Memantine                                                                                 | PLGA      | Improved spatial memory.                                                                                                                                                                                                                                                                                                       | [73] |
| Ferulic acid                                                                              | SLN       | Enhanced cognition.<br>Reduced oxidative stress and AChE activity in the cortex and hippocampus.                                                                                                                                                                                                                               | [74] |
| Vitamin B12                                                                               | Liposomes | Delaying the formation of A $\beta$ fibrils and disrupting mature fibrils.                                                                                                                                                                                                                                                     | [75] |
| Phosphatidic acid<br>Peptide derived from the receptor-binding domain of apolipoprotein E | Liposomes | Ameliorated mouse impaired memory.<br>Destabilize brain A $\beta$ aggregates and promote peptide removal across the BBB and its peripheral clearance.                                                                                                                                                                          | [76] |

### 5.2. PD Studies

Following previous discussion on the use of curcumin-loaded NPs for the treatment of AD, one study highlights its application in PD, further reinforcing curcumin's relevance across multiple NDs. Due to its potent antioxidant, anti-inflammatory, and neuroprotective properties, curcumin continues to emerge as a valuable therapeutic candidate for targeting key pathological mechanisms in the brain [38,54]. Its multifaceted action makes it particularly suitable for addressing the complex progression of neurodegeneration, although its clinical use has been hindered by poor oral bioavailability, attributed to its low aqueous solubility, limited absorption, rapid metabolism, and swift systemic elimination. To address this challenge, one study proposes a novel transdermal system combining curcumin-loaded SLNs with dissolving microneedle patches made of polymeric arrays, aiming to enhance curcumin's bioavailability and therapeutic potential in the treatment of PD by bypassing the gastrointestinal tract and hepatic first-pass metabolism [77].

The optimized formulation demonstrated good colloidal stability and the encapsulation efficiency reached 81.68%, suggesting effective incorporation of curcumin into the lipid matrix. In vivo neuroprotective activity was evaluated using a rotenone-induced PD model in Swiss albino mice. The microneedle-treated group exhibited significantly improved motor coordination and balance compared with the rotenone and orally treated groups. The improvement was statistically significant, indicating the superior efficacy of transdermal delivery via microneedles. Finally, a skin irritation study conducted on

Wistar rats showed no signs of erythema or edema following patch application, confirming the system's biocompatibility and safety [77]. In conclusion, the study demonstrates that transdermal delivery of curcumin via SLNs embedded in dissolving microneedle patches is a promising, minimally invasive strategy to enhance curcumin's bioavailability and therapeutic efficacy. This approach holds potential for future clinical applications in the management of NDs such as PD.

To solve several limitations of current therapies and improve the effectiveness of therapeutically relevant molecules (particularly antioxidants and neuroprotective agents), diverse PLGA NPs systems have been developed. Gambaryan et al. administered intranasally L-DOPA PLGA NPs in 6-hydroxydopamine (6-OHDA)-induced PD rats and observed improvements in the motor functions of the NP-treated animals and a prolonged effect in comparison to free L-DOPA [9,78]. This therapeutic strategy aimed at improving the efficacy of L-DOPA, one of the principal drugs used in the treatment of PD. While L-DOPA remains the most effective symptomatic treatment for PD, its clinical application is limited by several drawbacks. These include its short plasma half-life, reduced therapeutic effect over time, fluctuations in absorption, and the necessity for frequent dosing due to pulsatile stimulation of dopamine receptors. Furthermore, oral administration is hindered by the first-pass effect and can be complicated in PD patients suffering from dysphagia. To address these limitations, the researchers developed an NP-based delivery system in which L-DOPA is encapsulated in PLGA NPs, creating a formulation referred to as nano-DOPA. This formulation was designed for intranasal administration, offering several potential advantages: bypassing the gastrointestinal tract and hepatic metabolism [78].

Overall, these results highlight the superior and sustained efficacy of nano-DOPA in restoring motor function in PD. In contrast to standard intranasal L-DOPA, which was only effective acutely and subject to rapid therapeutic decline, nano-DOPA maintained high levels of motor performance, demonstrated a prolonged pharmacological effect, and reduced treatment frequency requirements [78].

While previous studies have explored the encapsulation of either curcumin or L-DOPA individually in NPs for PD treatment, a study innovatively combined both compounds in a single glutathione (GSH)-functionalized NP [79], aiming for neuroprotective and dopaminergic effects. This dual-delivery system enhanced brain targeting, drug stability and therapeutic potential. This study developed biodegradable NPs using the copolymer NH<sub>2</sub>-PEG-PCL to deliver L-DOPA and curcumin for the treatment of PD. To improve these NPs' ability to cross the BBB, their surfaces were coated with GSH, a molecule that can facilitate transport into the brain. The NPs produced had favorable physical properties, indicating good stability and uniformity. In vitro safety tests further confirmed the system's suitability for biological use. In summary, the study demonstrated that GSH-coated NH<sub>2</sub>-PEO-PCL NPs are stable, biocompatible, and capable of efficiently encapsulating and delivering both L-DOPA and curcumin [79].

Esteves et al. [80] investigated the therapeutic potential of small EVs enriched with miR-124-3p in experimental models of PD. Because miR-124-3p is known to regulate neuronal differentiation, neuroinflammation, and dopaminergic neuron survival, the researchers engineered mesenchymal stem cell-derived EVs to overexpress this microRNA and evaluated their effects both in vitro and in vivo. Treatment with miR-124-3p-enriched EVs promoted neuronal differentiation and significantly reduced inflammatory markers associated with microglial activation. In mouse models of PD, intranasal administration of the engineered vesicles increased dopaminergic neuronal survival, reduced neuroinflammation, and improved motor performance. Mechanistically, the therapeutic effects were associated with modulation of pathways involved in neurogenesis and inflammatory regulation. Overall, the study demonstrated that miR-124-3p-loaded EVs represent a

potential therapeutic strategy for PD by combining neuroprotective and anti-inflammatory effects.

Taken together, these studies on PD demonstrate that nanotechnology-based delivery systems can substantially enhance the therapeutic efficacy of neuroprotective and dopaminergic compounds by improving bioavailability, BBB penetration, and sustained drug release. Curcumin-loaded SLNs incorporated into dissolving microneedle patches demonstrated a promising minimally invasive strategy, significantly improving motor performance while overcoming curcumin's poor oral bioavailability. Intranasal PLGA nano-DOPA systems also showed notable advantages over free L-DOPA by providing prolonged therapeutic effects, improved motor recovery, and reduced dosing frequency, highlighting the benefits of NP-mediated dopaminergic delivery. More advanced multi-functional systems, such as GSH-functionalized NH<sub>2</sub>-PEG-PCL NPs co-loading L-DOPA and curcumin, combined neuroprotective and symptomatic approaches while enhancing BBB targeting and drug stability. In parallel, engineered EVs enriched with miR-124-3p demonstrated strong neuroprotective and anti-inflammatory effects, promoting dopaminergic neuron survival and improving motor outcomes by modulating neurogenesis and inflammatory pathways. Overall, while EV-based therapies showed high biological relevance and targeting potential, PLGA- and lipid-based NP systems currently appear more translationally feasible due to their stability, scalability, and effective improvement in both drug delivery and therapeutic efficacy in PD models.

Numerous studies have been conducted in the past years, and a summary of these can be found in Table 3.

**Table 3.** Preclinical investigations grounded on nanoformulations for the treatment of PD.

| Encapsulated Molecule    | Nanocarrier | Therapeutic Outcomes                                                                                                               | Ref. |
|--------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------|------|
| Curcumin                 | SLNs        | Antioxidant and anti-amyloid activity.                                                                                             | [77] |
| L-DOPA                   | PLGA        | Improved L-DOPA efficacy.                                                                                                          | [78] |
| L-DOPA, Curcumin         | PEG-PCL     | Improved neuroprotective and dopaminergic effects.                                                                                 | [79] |
| Tacrolimus and rapamycin | Liposomes   | Enhanced survival of grafted dopaminergic neurons and increased fiber outgrowth, contributing to improved management of PD.        | [81] |
| Ginkgolide B             | PEG-PCL     | Neuroprotective activity.<br>Controlled GB release.<br>Facilitated increased accumulation in the brain for effective PD treatment. | [82] |
| Catechin                 | Liposomes   | Attenuation of oxidative stress.<br>Reduced neuroinflammation.                                                                     | [83] |

|               |      |                                                                                                                                                                                                                           |      |
|---------------|------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Puerarin      | PLGA | Addressing puerarin's limited solubility and low oral bioavailability.<br>Enhanced brain concentrations of puerarin. Elevated dopamine levels in MPTP-treated mice accompanied by amelioration of behavioral impairments. | [84] |
| Rasagiline    | PLGA | Intranasal administration of rasagiline-loaded PLGA NPs achieves higher brain concentrations of rasagiline than intravenous delivery.<br>Improved bioavailability in the brain.                                           | [85] |
| Ropinirole    | PLGA | Reversal of PD-like neurodegenerative symptoms in the evaluated animal model.                                                                                                                                             | [86] |
| Nicotine      | PLGA | Potentiation of nicotine's neuroprotective effects.<br>Increased cerebral nicotine levels.<br>Reduction in several oxidative stress.<br>Restoration of dopamine levels.                                                   | [87] |
| MicroRNA- 124 | PLGA | Improvement in microRNA-124 stability and extension of its half-life.<br>Promotion of neuronal differentiation and stimulation of axonogenesis.<br>Improvement in PD motor symptoms.                                      | [88] |

### 5.3. HD Studies

In the following section, the focus will be on studies investigating NP-based delivery systems as potential therapeutic strategies for HD. The work of Joshi and co-workers [89] presents a novel and promising therapeutic strategy for HD caused by CAG repeat expansions in the HTT gene. This mutation leads to the production of mHTT with expanded PolyQ tracts, which tend to aggregate, causing cellular toxicity and neuronal dysfunction. In this study, the challenge of delivering peptide-based inhibitors of PolyQ aggregation across the BBB was addressed. Specifically, three peptides, QBP1, NT17, and PGQ9P<sub>2</sub>, known to inhibit PolyQ aggregation through different mechanisms, were incorporated into PLGA NPs [9,89]. To enhance brain targeting, the surface of the NPs was coated with polysorbate 80, which facilitated the crossing of the BBB. Functionally, the peptide-loaded NPs demonstrated dose-dependent inhibition of PolyQ aggregation in two cell models. This was accompanied by a significant reduction in visible aggregate formation, as assessed by fluorescence microscopy. Furthermore, in a *Drosophila* model of HD expressing

pathogenic PolyQ, the NPs improved motor performance in both larval and adult stages, highlighting their therapeutic potential *in vivo*. Importantly, the NP formulations exhibited excellent biocompatibility, showing no cytotoxicity in cell cultures or histopathological abnormalities in mice. Additionally, no adverse effects were observed in *Drosophila* models following treatment [89]. In conclusion, the study provides compelling evidence that PLGA-based NPs loaded with mechanism-specific peptide inhibitors offer a viable strategy for delivering therapeutic agents across the BBB to target protein aggregation in HD.

Bhatt et al. used SLNs to deliver rosmarinic acid (RA) (a caffeic acid derivative with antioxidant and anti-inflammatory properties) into the brain of 3-nitropropionic acid (3-NP)-lesioned rats [24,90]. Recognizing the limitations posed by the BBB for brain drug delivery, the researchers proposed intranasal administration as a non-invasive and efficient route for brain targeting. The optimized SLNs had a mean particle size of  $149.2 \pm 3.2$  nm, a ZP of  $-38.27$  mV (indicating good physical stability), and an encapsulation efficiency of  $61.9 \pm 2.2\%$ . The results indicated that intranasal administration of RA-loaded SLNs led to significant improvements in motor behavior and a reduction in oxidative damage in brain tissue. These outcomes were superior to those observed with both intravenous administration and unformulated RA. Furthermore, distribution studies showed that intranasal delivery led to greater drug accumulation in the brain. Pharmacokinetic analysis supported these findings, all indicating enhanced brain bioavailability through the nasal route [90]. In conclusion, the study demonstrates that intranasal administration of RA-loaded SLNs is a promising therapeutic strategy for the management of HD. The formulation offers multiple advantages, including non-invasiveness, targeted brain delivery, sustained drug release, and reduced systemic side effects.

Cano et al. [91] developed PEGylated PLGA NPs encapsulating epigallocatechin-3-gallate (EGCG) and ascorbic acid to improve neuroprotection in a mouse model of HD. Compared with free EGCG, the nanoformulation significantly reduced motor deficits, depression-like behavior, neuroinflammation, and striatal neuronal loss induced by 3-nitropropionic acid intoxication. The enhanced therapeutic efficacy was attributed to improved stability, antioxidant activity, and brain delivery of EGCG.

These preclinical studies in HD demonstrate that NP-based formulations can significantly enhance brain delivery and therapeutic efficacy of neuroprotective and anti-aggregation compounds. PLGA NPs loaded with PolyQ aggregation-inhibiting peptides demonstrated effective BBB penetration, reduced mHTT aggregation, and improved motor performance in HD models, supporting peptide-based nanotherapies as a targeted strategy against disease pathology. Similarly, intranasal RA-loaded SLNs showed enhanced brain accumulation, superior antioxidant effects, and improved motor outcomes compared with free drug administration, emphasizing the advantages of the nasal route for brain targeting. In parallel, PEGylated PLGA NPs co-encapsulating EGCG and ascorbic acid significantly attenuated motor deficits, neuroinflammation, and neuronal loss through enhanced antioxidant and neuroprotective activity. Overall, while peptide-loaded PLGA NPs offered a more disease-specific anti-aggregation approach, antioxidant-based SLN and PLGA systems demonstrated broader neuroprotective effects and may currently present greater translational feasibility due to their simpler formulation strategies and non-invasive administration routes.

Table 4 summarizes the studies that have emerged in the field over the past few years.

**Table 4.** Preclinical investigations grounded on nanoformulations for the treatment of HD.

| Encapsulated Molecule | Nanocarrier | Therapeutic Outcomes | Ref. |
|-----------------------|-------------|----------------------|------|
|-----------------------|-------------|----------------------|------|

|                 |      |                                                                                                                                                                                   |      |
|-----------------|------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Curcumin        | PLGA | Inhibit PolyQ aggregation.                                                                                                                                                        | [89] |
| Rosmarinic acid | SLNs | Enhanced brain-targeting efficiency.<br>Neuroprotective effect.                                                                                                                   | [90] |
| Thymoquinone    | SLNs | Effectively targets the brain and enables controlled drug release.                                                                                                                | [92] |
| Cholesterol     | PLGA | Exhibits superior BBB permeability, leading to enhanced cholesterol delivery to the brain. Promotes synaptic function and cognitive improvement in R6/2 mice, an HD animal model. | [93] |

#### 5.4. Clinical Trials

Unlike the previous studies, this work reports a clinical trial (NCT04445831) sponsored by AC Immune SA [94] to evaluate two Tau-targeted vaccines - ACI 35.030 and JACI 35.054 - in individuals with early AD. The Phase 1b/2a randomized, double-blind, placebo-controlled study aimed to assess safety, tolerability, and immunogenicity. Both vaccines, based on AC Immune's SupraAntigen® platform, use liposomal carriers displaying phosphorylated Tau peptides to enhance immune response while reducing neuroinflammation. Primary outcomes measured safety and tolerability, while secondary outcomes evaluated antibody responses to phosphorylated and aggregated Tau. This trial represents a key advancement in translating nanovaccine-based therapies to clinical evaluation in humans.

Exploratory analyses in the trial sought early signs of clinical efficacy and biomarker changes. The development of ACI 35.030 was supported by strong preclinical data, where its precursor (ACI 35) showed high immunogenicity and specificity for pathological Tau in transgenic Tauopathy mouse models. These studies demonstrated reductions in hyperphosphorylated and aggregated Tau, decreased neuroinflammation, and improved behavioral outcomes. The optimized ACI 35.030 formulation improved liposomal stability and consistency of the immune response. Preliminary clinical results indicated good tolerability for both vaccines, with only mild to moderate, non-treatment-related adverse events and no discontinuations. Overall, these findings validate the translational potential of preclinical results and highlight Tau-targeted vaccination as a promising therapeutic strategy for AD, warranting further evaluation in larger Phase 2 trials to assess clinical efficacy and biomarker modulation.

Another clinical trial, "Intranasal administration of allogenic adipose MSC-EVs in the treatment of mild to moderate dementia due to AD" (NCT04388982) [95] was a phase I/II study evaluating the safety and preliminary efficacy of intranasally administered allogenic adipose-derived mesenchymal stem cell exosomes (ahaMSCs-Exos) in patients with mild to moderate AD. Participants received different doses over 12 weeks, with follow-up extending to 48 weeks. The treatment was found to be safe and well-tolerated, with no reported adverse events. Notably, the medium-dose group showed improvements in cognitive function, as indicated by better scores on cognitive assessments, with sustained effects up to 36 weeks. However, no significant changes were observed in amyloid or Tau deposition, although a modest reduction in hippocampal atrophy was noted. Overall, the

results support the safety of this approach and suggest potential cognitive benefits, warranting further investigation in larger trials.

One of the clinical trials using NPs for treating AD, mentioned in Table 5, is titled “Biomarkers for Monitoring Dementia Progression” (NCT06855368) [96] and investigates the application of biomimetic anti-inflammatory NPs as an innovative approach to modulate neuroinflammation in AD. These NPs are engineered to promote a phenotypic shift of microglia from the pro-inflammatory (M1) to the reparative (M2) state, thereby attenuating neuro-inflammatory processes and supporting neuronal homeostasis. Their biomimetic and targeted design enables enhanced delivery efficiency, improved biocompatibility, and reduced off-target effects compared with conventional anti-inflammatory strategies [96]. Within the study, this nanotechnology approach is integrated with biomarker analysis and neurophysiological monitoring in both human participants and animal models, aiming to establish a mechanistic link between inflammation, disease progression, and therapeutic modulation. This strategy highlights the translational potential of nanomedicine in AD, offering a promising avenue for disease-modifying interventions that address neuroinflammation.

**Table 5.** Clinical trials associated with NDs—ClinicalTrials.gov (accessed on 9th of October 2025)

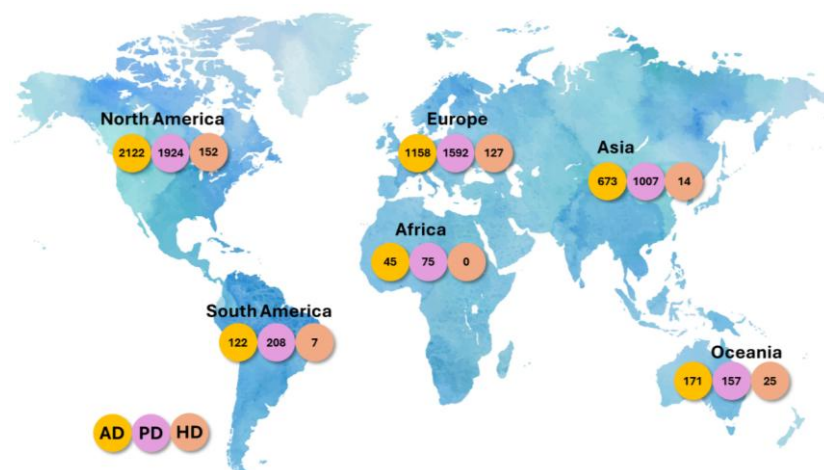
| Condition/Disease    | Number of Studies | Other Terms:  |          |           |
|----------------------|-------------------|---------------|----------|-----------|
|                      |                   | Nanoparticles | Vaccines | Liposomal |
| Alzheimer’s disease  | 3652              | 3             | 54       | 2         |
| Parkinson’s disease  | 4174              | 1             | 12       | 4         |
| Huntington’s disease | 266               | 0             | 0        | 0         |

The other clinical trial associated with AD is titled “Study of APH-1105 in Patients with Mild to Moderate Alzheimer’s Disease” (NCT03806478) and is a Phase 2 study assessing the safety, tolerability and efficacy of intranasal delivery of APH-1105 NPs in adults with mild to moderate AD [97]. This approach aims to enhance brain targeting, improve drug stability, and reduce systemic exposure, thereby potentially increasing therapeutic efficacy while minimizing adverse effects. By promoting  $\alpha$ -secretase-mediated non-amyloidogenic processing of APP, APH-1105 may reduce amyloid- $\beta$  formation and neurotoxicity. This study exemplifies the growing promise of NP-enabled delivery platforms to achieve targeted disease-modifying effects in Alzheimer’s therapy [97].

Furthermore, there is a clinical trial related to PD (Table 5) named “Efficacy of Nano-PSO in Parkinson’s Disease” (NCT05142085), which is a randomized, double-blind, placebo-controlled interventional study designed to evaluate the efficacy of a nanotechnology-based antioxidant (nano-PSO) in patients with PD. Patients receive either nano-PSO (nanodroplet formulation of pomegranate seed oil) or a placebo, with the main objective being to evaluate improvements in motor and non-motor symptoms and quality of life. Clinical assessments are complemented by neuroimaging analyses, including positron emission tomography, to investigate changes in presynaptic dopaminergic function. Overall, the study aims to determine whether this nanoformulation can provide neuroprotective effects and improve clinical outcomes in PD [98].

Until now, no clinical trials have investigated NP-based treatments for HD.

The results obtained when looking for clinical trials at ClinicalTrials.gov using “Condition/disease” “Alzheimer disease”, “Parkinson disease” or “Huntington disease” can be seen in Figure 8 and Table 5. When “Other terms” such as “nanoparticles”, “vaccines” or “liposomal” were added, the results were much lower (Table 5).



**Figure 8.** Number of clinical trials associated with the treatment of AD, PD and HD in the world—ClinicalTrials.gov (accessed on 9th of October 2025). Studies lacking geographical data are excluded from the counts and mapping. Regional counts may not equal global totals due to exclusion of studies without locations and potential duplication of studies with multiple locations across regions.

As shown in Figure 8, the largest number of clinical trials for these diseases occurs first in North America, then in Europe, and last in Africa. In North America and Oceania, the most tested disease is AD. In the other places, PD is the most tested disease. HD is the least studied disease, and it is worth noting that no clinical trials are currently taking place in Africa. For all the diseases, the country with the most trials was the United States.

### 5.5. Challenges

Despite significant progress in preclinical research, numerous NP-based systems have not achieved the same level of efficacy in clinical trials. Their limited clinical translation may result from several factors, including insufficient preclinical validation, inadequate therapeutic efficacy, and concerns about toxicity and safety. In addition, economic and manufacturing challenges, such as high production costs and complex formulation procedures, further limit their successful clinical application. Another major limitation is the reduced translational relevance of current experimental models. Conventional *in vitro* studies often fail to accurately replicate the complexity of human physiological conditions, whereas *in vivo* investigations rely primarily on transgenic rodent models that only partially recapitulate the pathological features of AD, PD, and HD. Although these models have been instrumental in advancing our understanding of disease mechanisms, they do not fully reproduce the complexity, heterogeneity, and age-related characteristics of human NDs. Emerging preclinical models, including patient-derived induced pluripotent stem cell (iPSC) models, human BBB organoids, microfluidic BBB systems, and larger-animal models, may provide greater translational relevance. Furthermore, methods used to evaluate drug distribution within brain tissue, including analysis of brain homogenates, are invasive, yield limited endpoint data, and often require large numbers of experimental animals [49].

## 6. Conclusions

NDs represent one of the greatest challenges in modern medicine, due to both their increasing prevalence in an aging global population and the lack of effective curative therapies. Current treatment strategies are primarily focused on symptom management, without directly targeting the underlying causes of neurodegeneration. In this context, advancements in nanotechnology, particularly the use of NPs as DDS, have emerged as a

promising therapeutic approach. NPs offer several advantages over conventional therapies, notably their ability to cross biological barriers, such as the BBB, to target the CNS directly and deliver bioactive compounds in a controlled, site-specific manner. The presented studies have shown encouraging results in preclinical models of AD, PD and HD using a variety of NPs, including LNP and PNP systems, that enhance bioavailability, reduce side effects, and improve the efficacy of antioxidant and neuroprotective compounds.

Although many of these advancements remain at the experimental stage, their level of translational maturity differs across NDs. Most NP-based strategies for AD have demonstrated promising in vitro and preclinical efficacy, with a limited number progressing to early-phase clinical evaluation. In PD, the available evidence is predominantly derived from in vitro and animal studies, with only one formulation reaching clinical investigation. For HD, research remains largely confined to in vitro and preclinical animal models, highlighting the need for further translational development. Continued development of this technology, combined with a deeper understanding of the molecular mechanisms of these disorders, could support the development of more effective therapeutic strategies aimed at delaying disease progression and improving patient outcomes and quality of life.

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## Abbreviations

The following abbreviations are used in this manuscript:

|           |                                       |
|-----------|---------------------------------------|
| 3-NP      | 3-nitropropionic acid                 |
| 6-OHDA    | 6-hydroxydopamine                     |
| A $\beta$ | Amyloid-beta                          |
| AChE      | Acetylcholinesterase                  |
| AD        | Alzheimer's disease                   |
| APP       | Amyloid Precursor Protein             |
| ARIA      | Amyloid-related imaging abnormalities |
| BBB       | Blood–Brain Barrier                   |
| BCSFB     | Blood cerebrospinal fluid barrier     |
| CAG       | Cytosine–adenine–guanine              |

|          |                                                                          |
|----------|--------------------------------------------------------------------------|
| CNS      | Central nervous system                                                   |
| CSF      | Cerebrospinal fluid                                                      |
| DDS      | Drug delivery system                                                     |
| EGCG     | Epigallocatechin-3-gallate                                               |
| EVs      | Extracellular vesicles                                                   |
| GSH      | Glutathione                                                              |
| HD       | Huntington's disease                                                     |
| HTT      | Huntingtin                                                               |
| iPSC     | Induced pluripotent stem cell                                            |
| L-DOPA   | Levodopa                                                                 |
| Lf       | Lactoferrin                                                              |
| Lf-PPNs  | Lactoferrin-coated poly(ethylene glycol)-Poly(lactic acid) nanoparticles |
| LNP      | Lipid-based nanoparticle                                                 |
| MAO-B    | Monoamine oxidase-B                                                      |
| mHTT     | Mutant huntingtin                                                        |
| MRI      | Magnetic resonance imaging                                               |
| MSC-EVs  | Mesenchymal stem cell-derived extracellular vesicles                     |
| ND       | Neurodegenerative diseases                                               |
| NFTs     | Neurofibrillary tangles                                                  |
| NLC      | Nanostructured lipid carriers                                            |
| NMDA     | N-methyl-D-aspartate                                                     |
| NP       | Nanoparticle                                                             |
| PD       | Parkinson's disease                                                      |
| PEG-PCL  | Poly(ethylene glycol)-poly( $\epsilon$ -caprolactone)                    |
| PEG-PLA  | Poly(ethylene glycol)-poly(lactic acid)                                  |
| PEG-PLGA | Poly(ethylene glycol)-poly(lactide-co- glycolic) acid                    |
| P-gp     | P-glycoprotein                                                           |
| PLA      | Poly(lactic acid)                                                        |
| PLGA     | Poly(lactic-co-glycolic) acid                                            |
| PM       | Polymersomes                                                             |
| RA       | Rosmarinic acid                                                          |
| SLN      | Solid lipid nanoparticle                                                 |
| SNCA     | Synuclein Alpha gene                                                     |
| TRAIL    | Tumor necrosis factor (TNF)-Related Apoptosis-Inducing Ligand            |
| WHO      | World Health Organization                                                |

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