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Review Article

Nanotechnology-Based Drug Delivery Across the Blood-Brain Barrier in Neurodegenerative Diseases

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ABSTRACT

Background: Neurodegenerative diseases such as Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, and related dementias are major causes of progressive disability, dependency, caregiver burden, and long-term health-system pressure. Therapeutic development is limited not only by disease complexity but also by poor central nervous system delivery, as the blood-brain barrier restricts the entry of many hydrophilic drugs, peptides, proteins, antibodies, enzymes, and nucleic-acid-based therapies. Objective: This structured narrative review synthesized current evidence on nanotechnology-based drug delivery across, around, or through transient modulation of the blood-brain barrier in neurodegenerative diseases, with emphasis on carrier design, delivery mechanisms, disease-specific applications, translational readiness, safety limitations, and future research priorities. Methods: A structured narrative literature search was conducted using PubMed, Google Scholar, ScienceDirect, SpringerLink, Web of Science, and open-access biomedical repositories. Search terms combined concepts related to the blood-brain barrier, nanotechnology, nanoparticles, liposomes, lipid nanoparticles, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, exosomes, receptor-mediated transcytosis, intranasal delivery, focused ultrasound, Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, neuroinflammation, and neurodegeneration. Eligible sources included mechanistic studies, in vitro blood-brain barrier models, animal studies, early clinical studies, disease-focused reviews, and clinically relevant drug-delivery literature. Findings were synthesized narratively because the evidence was heterogeneous in platform type, disease model, payload, route of administration, outcome measure, and translational stage. Results: The evidence indicates that nanocarriers can improve several delivery-related barriers by protecting unstable payloads, increasing apparent brain exposure, prolonging circulation, supporting ligand-mediated targeting, enabling controlled release, and reducing some off-target effects. Receptor-mediated transcytosis, lipid and polymeric nanoparticles, exosome-based delivery, intranasal nanoformulations, and focused ultrasound-assisted blood-brain barrier opening were the most frequently discussed strategies. Alzheimer disease and Parkinson disease had the most developed preclinical evidence base, whereas Huntington disease and amyotrophic lateral sclerosis were supported mainly by conceptual and early preclinical delivery frameworks. Focused ultrasound-mediated blood-brain barrier opening had the strongest early human translational evidence, particularly in Alzheimer disease. However, most nanoparticle and exosome-based therapies remain preclinical, and evidence linking brain uptake to target engagement, long-term safety, and meaningful clinical outcomes remains limited. Conclusion: Nanotechnology-based blood-brain barrier delivery is a promising but not yet clinically established approach for neurodegenerative diseases. Future studies must move beyond proof of brain uptake and demonstrate active payload release, cell-specific target engagement, repeated-dose safety, scalable manufacturing, disease-stage specificity, and patient-relevant clinical benefit. Keywords: blood-brain barrier; nanotechnology; nanoparticles; neurodegenerative diseases; Alzheimer disease; Parkinson disease; exosomes; focused ultrasound.

INTRODUCTION

Neurodegenerative diseases are chronic, progressive disorders characterized by neuronal dysfunction, synaptic loss, protein misfolding, mitochondrial injury, oxidative stress, neuroinflammation, impaired proteostasis, and gradual loss of functional independence. Alzheimer disease and related dementias predominantly affect memory, language, behavior, and executive function, whereas Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, and other neurodegenerative disorders may present

with motor impairment, psychiatric symptoms, autonomic dysfunction, cognitive decline, and severe disability. The global burden of neurological disorders has increased substantially with population ageing and improved survival with chronic disease, making disorders of the nervous system a leading contributor to disability, dependency, caregiver strain, and long-term health-system pressure (1). Dementia alone affects tens of millions of people worldwide, with a large proportion of affected individuals living in low- and middle-income countries, where access to specialist diagnosis, disease-modifying therapy, rehabilitation, and caregiver support may be limited (2).

Although molecular understanding of neurodegeneration has advanced considerably, effective treatment remains difficult. Many available therapies are primarily symptomatic, and emerging disease-modifying approaches often show modest clinical benefit, require early diagnosis, or depend on sustained exposure in vulnerable brain regions. A major translational obstacle is the blood-brain barrier (BBB), a specialized neurovascular interface formed by endothelial cells with tight junctions, pericytes, astrocytic end-feet, basement membrane, neurons, microglia, transporters, and metabolic enzymes (3,4). The BBB preserves central nervous system homeostasis by regulating nutrient transport, ion balance, immune-cell trafficking, metabolic exchange, and xenobiotic entry. However, the same selective properties also restrict the brain penetration of many potentially useful therapeutic agents, particularly hydrophilic molecules, peptides, proteins, monoclonal antibodies, enzymes, nucleic acids, and other large biologics (5,6).

The BBB is not a passive anatomical wall but a dynamic and disease-responsive interface. Ageing, vascular injury, amyloid and tau pathology, alpha-synuclein accumulation, metabolic dysfunction, oxidative stress, and neuroinflammation can alter endothelial integrity, transporter expression, immune signaling, and pericyte-astrocyte regulation. In Alzheimer disease, BBB dysfunction has been linked with vascular injury, pericyte loss, impaired amyloid-beta clearance, altered transporter activity, and inflammatory signaling (5). These disease-related changes create both opportunities and risks for therapeutic delivery. Increased barrier permeability or inflammation may improve access for some therapeutic carriers, but may also increase the risk of edema, immune activation, nonspecific accumulation, and unpredictable biodistribution. Therefore, successful drug delivery in neurodegenerative disease requires more than simply increasing BBB permeability; it requires controlled, targeted, biologically compatible, and clinically meaningful delivery.

Nanotechnology has emerged as a promising strategy for addressing several pharmacological barriers that limit central nervous system therapy. Nanoscale carriers can be engineered to protect therapeutic payloads, improve solubility, prolong circulation, evade premature degradation, modify pharmacokinetics, display targeting ligands, respond to disease microenvironments, and release drugs in a controlled manner. Common platforms include liposomes, lipid nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, polymeric micelles, dendrimers, inorganic nanoparticles, exosomes, extracellular vesicles, and hybrid biomimetic systems (7-10). These systems may carry small molecules, antioxidants, anti-inflammatory agents, peptides, proteins, monoclonal antibodies, enzymes, plasmids, messenger RNA, small interfering RNA, microRNA, and imaging agents.

Several biological, physical, and route-based strategies have been investigated to cross, bypass, or transiently open the BBB. Receptor-mediated transcytosis uses endogenous endothelial transport pathways, including transferrin receptor, insulin receptor, low-density lipoprotein receptor-related protein 1, and related receptors, to shuttle therapeutic cargo across brain endothelial cells (11-13). Adsorptive-mediated transcytosis uses electrostatic interactions with the endothelial surface but may increase nonspecific uptake and toxicity. Intranasal nanodelivery may partly bypass the BBB through olfactory and trigeminal pathways, although mucociliary clearance, enzymatic degradation, limited dosing volume, and interindividual anatomical variation remain important constraints. Focused ultrasound with microbubbles can transiently and regionally open the BBB and has entered early human

studies in Alzheimer disease, making it one of the more clinically advanced BBB-modulation strategies (14-16).

Despite rapid growth in this field, translation remains uneven. Many nanocarriers show favorable brain uptake, biomarker modulation, or behavioral improvement in experimental models, but animal models often do not reproduce the chronicity, heterogeneity, comorbidity burden, and ageing-related vascular changes seen in human neurodegenerative disease. Moreover, reported brain accumulation may reflect fluorescence intensity, percentage injected dose, or tissue-level uptake without proving active payload release, cellular localization, target engagement, or durable clinical benefit. Prior reviews have often addressed nanomedicine, BBB biology, or individual carrier classes separately, but clinically oriented synthesis is still needed to integrate carrier design, BBB-crossing mechanism, disease-specific application, translational maturity, safety concerns, and evidence limitations in a single framework.

Therefore, this structured narrative review synthesizes current evidence on nanotechnology-based drug delivery across or around the BBB in neurodegenerative diseases. The review focuses on carrier classes, BBB-crossing mechanisms, disease-specific therapeutic applications, preclinical and early clinical evidence, translational readiness, and unresolved safety and manufacturing challenges. The objective is not to provide a pooled quantitative estimate of efficacy, but to present a clinically interpretable synthesis of how nanotechnology-based delivery strategies may address BBB-related therapeutic limitations in Alzheimer disease, Parkinson disease, Huntington disease, amyotrophic lateral sclerosis, and related neuroinflammatory neurodegenerative conditions.

METHODOLOGY

The reviewed evidence comprised foundational blood-brain barrier literature, broad nanomedicine and brain-delivery reviews, disease-focused reviews, mechanistic studies, in vitro blood-brain barrier model studies, animal studies, exosome-based nucleic-acid delivery studies, and early clinical studies of focused ultrasound-mediated blood-brain barrier opening. Because the available evidence differed substantially in carrier composition, payload type, disease model, route of administration, blood-brain barrier assessment method, outcome measure, and translational stage, findings were synthesized narratively rather than quantitatively. The strongest human translational evidence was identified for focused ultrasound-mediated blood-brain barrier opening in Alzheimer disease, whereas most nanoparticle, exosome, lipid, polymeric, and ligand-targeted systems remain supported mainly by mechanistic, in vitro, ex vivo, and animal evidence. Overall, the synthesis indicates that nanotechnology-based strategies can improve brain exposure, payload protection, targeting potential, and controlled delivery, but clinical efficacy in neurodegenerative diseases remains largely unproven.

Overview of the Evidence Landscape

The literature was organized into six major evidence domains: blood-brain barrier biology, receptor-mediated transport, lipid-based nanocarriers, polymeric and inorganic nanoparticles, exosome or extracellular-vesicle delivery, and route- or device-assisted strategies such as intranasal delivery and focused ultrasound. Across these domains, Alzheimer disease and Parkinson disease were the most frequently represented disease contexts, whereas Huntington disease and amyotrophic lateral sclerosis were addressed mainly through conceptual, mechanistic, or early preclinical delivery frameworks. Table 1 summarizes the scope and interpretive role of each evidence domain included in this structured narrative synthesis.

Table 1. Evidence Domains Included in the Structured Narrative Synthesis

Evidence Domain	Main Sources of Evidence	Disease Contexts Most Represented	Main Contribution to the Review	Translational Interpretation
Blood-brain barrier biology	Foundational BBB reviews and neurovascular biology literature	Broad CNS disease and neurodegeneration	Defines tight junctions, transporters, pericytes, astrocytic regulation, immune surveillance,	Provides mechanistic rationale for targeted or assisted delivery strategies

Evidence Domain	Main Sources of Evidence	Disease Contexts Most Represented	Main Contribution to the Review	Translational Interpretation
			and disease-related BBB dysfunction	
Receptor-mediated transcytosis	Mechanistic and transport-focused studies	Broad CNS delivery; Alzheimer and Parkinson disease applications	Explains use of transferrin receptor, insulin receptor, LRP1, and related endothelial pathways	Biologically plausible but highly dependent on ligand affinity, avidity, receptor saturation, and parenchymal release
Lipid-based nanocarriers	Carrier-specific reviews and preclinical studies	Alzheimer disease, Parkinson disease, neuroinflammation	Supports payload protection, solubility improvement, and flexible delivery of hydrophobic drugs or nucleic acids	Promising but limited by peripheral uptake, stability, and insufficient human neurodegenerative-disease data
Polymeric and inorganic nanoparticles	Preclinical and mechanistic studies	Alzheimer disease, Parkinson disease, experimental neurodegeneration	Demonstrates tunable size, charge, surface modification, release kinetics, and imaging or theranostic potential	Translation requires stronger long-term safety, reproducibility, and degradation data
Exosomes and extracellular vesicles	Mechanistic, preclinical, and review-level evidence	Parkinson disease, Alzheimer disease, gene-delivery concepts	Provides biological carrier framework for protein and nucleic-acid transport	Attractive but limited by heterogeneity, isolation challenges, cargo loading, purity, and safety concerns
Intranasal delivery and focused ultrasound	Route-based reviews, preclinical work, and early human studies	Alzheimer disease, Parkinson disease, broader neurological disorders	Explores BBB bypass or transient regional BBB opening	Focused ultrasound has the most advanced human evidence; intranasal delivery remains promising but variable

Blood-Brain Barrier Constraints Relevant to Nanodelivery

The blood-brain barrier restricts conventional central nervous system drug delivery through multiple anatomical, cellular, enzymatic, and transporter-mediated mechanisms. Tight endothelial junctions limit paracellular diffusion, while efflux transporters reduce intracellular accumulation of many drugs. Enzymatic metabolism and immune surveillance can degrade or clear therapeutic agents before they reach the intended brain compartment. In addition, protein corona formation after systemic administration may alter nanoparticle identity, biodistribution, ligand accessibility, and safety profile. These barriers are further complicated by disease-stage heterogeneity, because ageing, amyloid pathology, tau pathology, alpha-synuclein accumulation, vascular injury, oxidative stress, and neuroinflammation can alter barrier permeability and endothelial function.

Nanotechnology-based strategies attempt to overcome these barriers through carrier engineering, surface modification, receptor targeting, controlled release, immune evasion, and route-based enhancement. However, improved barrier crossing does not automatically indicate therapeutic success. Effective delivery requires that the carrier reach the relevant brain region, release an active payload, enter or affect the intended cell type, produce measurable target engagement, and do so without unacceptable neurovascular, immune, hepatic, renal, or systemic toxicity. Table 2 summarizes the main blood-brain barrier features relevant to nanodelivery and the corresponding nanotechnology-based responses.

Table 2. Blood-Brain Barrier Features and Nanotechnology-Based Delivery Responses

BBB Feature	Effect on Conventional Therapy	Nanotechnology-Based Response	Remaining Concern
Tight endothelial junctions	Limits passive paracellular diffusion, especially for hydrophilic and large molecules	Promotes transcellular transport, ligand-mediated uptake, intranasal bypass, or transient barrier opening	Barrier opening must be controlled, reversible, regional, and safe
Efflux transporters	Reduces brain exposure of many drugs after systemic administration	Encapsulation may protect payloads and alter transporter recognition	Released drug may still be actively effluxed from endothelial or brain cells
Enzymatic metabolism	Degrades peptides, proteins, nucleic acids, and labile small molecules	Nanocarriers protect unstable payloads during circulation and transport	Protection must be balanced with timely release at the target site
Endothelial glycocalyx and immune interface	Limits nonspecific contact and may promote clearance or immune recognition	Surface engineering, PEGylation, biomimetic coating, or exosome-based systems may reduce recognition	Complement activation, immune stimulation, and altered biodistribution remain possible
Protein corona formation	Changes nanoparticle surface identity after exposure to plasma proteins	Surface chemistry optimization may improve circulation and ligand accessibility	Corona may mask targeting ligands and reduce reproducibility
Disease-stage heterogeneity	BBB function differs across early, moderate, and advanced disease	Disease-responsive or stage-specific carriers may be developed	Human disease heterogeneity is greater than most experimental models
Regional BBB variability	Barrier permeability and transport differ across brain regions	Focused ultrasound and regional targeting may improve spatial precision	Regional delivery must match disease-relevant anatomy
Neurovascular vulnerability	Damaged or inflamed BBB may be more sensitive to intervention	Lower-dose, targeted, or reversible strategies may reduce injury	Edema, microhemorrhage, inflammation, and endothelial injury require monitoring

Nanocarrier Categories and Mechanisms of BBB Crossing

The reviewed literature supports several nanocarrier categories with distinct delivery mechanisms and translational limitations. Liposomes and lipid nanoparticles are among the most widely discussed systems because of their biocompatible composition, capacity to carry hydrophobic or nucleic-acid payloads, and broader manufacturing experience from non-neurodegenerative indications. Solid lipid nanoparticles and nanostructured lipid carriers are especially relevant for hydrophobic drugs and intranasal delivery, but may face challenges related to payload leakage, nasal clearance, and variable human nose-to-brain transport.

Polymeric nanoparticles provide greater control over particle size, surface charge, degradation, and release kinetics. They are attractive for sustained delivery and ligand modification but require careful evaluation of polymer toxicity, degradation products, residual solvents, reproducibility, and batch consistency. Inorganic nanoparticles, including gold and iron oxide platforms, may offer imaging, theranostic, or catalytic advantages, but long-term tissue retention and chronic neurotoxicity remain major translational concerns. Exosomes and extracellular vesicles provide a biological delivery framework with potential for nucleic-acid and protein transport, but clinical translation is limited by isolation methods, purity, yield, heterogeneity, donor-cell source, cargo-loading efficiency, and possible disease-signal transfer.

Table 3. Nanocarrier Categories, Payloads, BBB Strategies, and Translational Limitations

Carrier Category	Typical Payloads	BBB Delivery Strategy	Main Advantages	Key Limitations
Liposomes	Hydrophobic drugs, antioxidants, peptides, proteins, imaging agents	Surface ligands, adsorptive uptake, intranasal route, or FUS-assisted delivery	Biocompatible composition, flexible payload loading, established manufacturing experience	Stability problems, rapid clearance, limited brain specificity without targeting
Lipid nanoparticles	siRNA, mRNA, small molecules, anti-inflammatory agents	Ligand targeting, endocytic uptake, systemic or assisted delivery	Strong payload protection and nucleic-acid delivery potential	Peripheral liver and spleen uptake; limited disease-specific human CNS data
Solid lipid nanoparticles	Dopamine-related agents, antioxidants, hydrophobic drugs	Intranasal delivery, lipid-mediated transport, ligand modification	Good protection for hydrophobic payloads and possible controlled release	Payload leakage, nasal mucosal limitations, variable human delivery
Nanostructured lipid carriers	Hydrophobic and amphiphilic drugs	Intranasal or systemic delivery with surface modification	Improved loading capacity compared with some solid lipid systems	Stability, scale-up, and long-term safety need further evaluation
Polymeric nanoparticles	Curcumin, peptides, neuroprotective agents, genes, imaging probes	PEGylation, ligand targeting, receptor-mediated transport, controlled degradation	Tunable size, charge, release kinetics, and surface functionalization	Polymer toxicity, residual solvent, incomplete degradation, batch variability
Polymeric micelles	Poorly soluble drugs and hydrophobic compounds	Solubility enhancement and surface modification	Useful for hydrophobic drug delivery and small particle design	Stability after dilution and limited payload capacity may restrict use
Dendrimers	Small molecules, nucleic acids, anti-inflammatory agents	Multivalent ligand display and cellular uptake	Precise architecture and high functionalization capacity	Cationic toxicity and complex synthesis may limit translation
Inorganic nanoparticles	Gold, iron oxide, imaging agents, catalytic or theranostic payloads	Ligand targeting, imaging-guided delivery, photothermal or magnetic properties	High stability and imaging utility	Chronic tissue retention and neurotoxicity require careful assessment
Exosomes / extracellular vesicles	siRNA, miRNA, proteins, enzymes, anti-inflammatory cargo	Natural intercellular transport and engineered surface targeting	Biological compatibility and potential low immunogenicity	Isolation, purity, heterogeneity, loading efficiency, and disease-propagation risk
Hybrid biomimetic systems	Combined synthetic and biological payloads	Cell-membrane coating, ligand targeting, or immune evasion	May combine synthetic control with biological recognition	Regulatory complexity and reproducibility remain major barriers

Receptor-Mediated and Adsorptive Transcytosis

Receptor-mediated transcytosis is one of the most biologically attractive mechanisms for transporting nanocarriers across the blood-brain barrier because it exploits endogenous endothelial transport systems. The transferrin receptor, insulin receptor, and low-density lipoprotein receptor-related protein 1 are among the most frequently discussed targets. The evidence indicates that receptor selection, ligand affinity, particle size, ligand density, and avidity strongly influence uptake and brain delivery. High-affinity binding may increase endothelial uptake but can also trap particles within endothelial cells, limiting release into brain parenchyma. Conversely, low-affinity systems may fail to produce adequate

transport. This balance is especially important for chronic neurodegenerative diseases, where repeated dosing and long-term safety are required.

Adsorptive-mediated transcytosis offers a less receptor-specific mechanism through electrostatic interactions between positively charged carriers and the endothelial surface. While this may improve uptake, it also increases the possibility of nonspecific tissue distribution, cellular toxicity, plasma protein binding, and immune activation. Therefore, receptor-mediated approaches appear more selective in principle, but both receptor-mediated and adsorptive strategies require stronger evidence linking uptake to active payload release, target engagement, and functional benefit.

Table 4. BBB-Crossing Mechanisms and Their Interpretive Significance

Mechanism	Principle	Representative Application	Strength of Evidence	Main Translational Concern
Receptor-mediated transcytosis	Uses endogenous endothelial receptors to transport cargo across BBB cells	Transferrin receptor, insulin receptor, LRP1-targeted systems	Strong mechanistic rationale; substantial preclinical support	Ligand affinity, receptor saturation, endothelial trapping, and limited parenchymal release
Adsorptive-mediated transcytosis	Uses electrostatic interaction with endothelial surface	Cationic nanoparticles and surface-modified carriers	Mechanistically plausible; less specific than receptor targeting	Nonspecific uptake, toxicity, and peripheral tissue accumulation
Carrier-mediated transport enhancement	Uses endogenous nutrient or transporter pathways	Transporter-linked drug or carrier design	Selective in theory	Transporter competition and disease-related transporter variability
Intranasal nose-to-brain delivery	Attempts to bypass BBB via olfactory and trigeminal pathways	Intranasal lipid or polymeric nanoformulations	Promising in preclinical studies and route-based reviews	Mucociliary clearance, dosing volume, enzymatic degradation, and human anatomical variability
Focused ultrasound-mediated BBB opening	Uses ultrasound and microbubbles to transiently open BBB regionally	Alzheimer disease BBB opening and antibody-delivery studies	Most advanced early human evidence among BBB-opening approaches	Requires procedural control, imaging guidance, safety monitoring, and repeat-dose validation
Exosome-mediated biological transport	Uses extracellular vesicle communication pathways	siRNA, miRNA, protein, or anti-inflammatory cargo delivery	Strong conceptual and preclinical appeal	Heterogeneity, isolation, purity, cargo loading, and unwanted biological signaling

Disease-Specific Synthesis

Alzheimer disease represented the most developed disease context in the reviewed literature. Nanotechnology-based approaches in Alzheimer disease target amyloid-beta aggregation, tau pathology, oxidative stress, synaptic injury, neuroinflammation, vascular dysfunction, and impaired clearance pathways. Curcumin nanoparticles, anti-amyloid ligand-modified systems, polymeric carriers, lipid carriers, exosomes, and focused ultrasound-assisted delivery have all been explored. However, most nanoparticle-based Alzheimer disease evidence remains preclinical. The strongest human translational evidence relates to focused ultrasound-mediated blood-brain barrier opening, including studies demonstrating reversible regional BBB opening and early combination approaches with anti-amyloid therapy.

In Parkinson disease, nanotechnology-based delivery has focused on dopaminergic replacement strategies, alpha-synuclein modulation, mitochondrial dysfunction, oxidative stress, iron-related injury, and neuroinflammation. Dopamine-loaded nanoparticles and exosome-based siRNA delivery are notable examples of preclinical approaches. These studies support the plausibility of improving brain delivery and functional outcomes in experimental models, but human efficacy remains unproven.

Huntington disease and amyotrophic lateral sclerosis were less mature areas in the reviewed evidence. For Huntington disease, the rationale for nanoparticle and exosome-based nucleic-acid delivery is strong because mutant huntingtin expression is a central molecular target. However, delivery to the striatum, neuronal specificity, long-term gene modulation, and safety remain unresolved. For amyotrophic lateral sclerosis, nanotechnology-based approaches include antioxidant carriers, anti-inflammatory delivery, and nucleic-acid delivery concepts, but the evidence remains less developed than in Alzheimer and Parkinson disease. Targeting motor neurons, spinal cord regions, and diffuse neuroinflammatory processes remains a major barrier.

Table 5. Disease-Specific Applications and Translational Readiness

Disease Context	Main Therapeutic Targets	Nanotechnology-Based Approaches	Evidence Pattern	Clinical Readiness
Alzheimer disease	Amyloid-beta, tau, oxidative stress, synaptic dysfunction, vascular injury, neuroinflammation	Curcumin nanoparticles, anti-amyloid ligand particles, liposomes, polymeric carriers, exosomes, FUS-assisted delivery	Large preclinical literature; early human evidence mainly for focused ultrasound-mediated BBB opening	Promising but mostly preclinical; FUS is early clinical
Parkinson disease	Dopamine deficit, alpha-synuclein aggregation, mitochondrial dysfunction, iron stress, oxidative injury, neuroinflammation	Dopamine-loaded nanoparticles, antioxidant carriers, deferoxamine nanoparticles, exosomal siRNA	Animal studies report improved delivery or functional effects; human nanocarrier efficacy remains unproven	Preclinical to early translational
Huntington disease	Mutant huntingtin expression, striatal degeneration, gene-silencing targets	Nanoparticle and exosome-based nucleic-acid delivery concepts	Strong conceptual rationale but limited disease-specific translational evidence	Primarily preclinical
Amyotrophic lateral sclerosis	Motor-neuron injury, neuroinflammation, oxidative stress, genetic targets	Lipid or polymeric nucleic-acid delivery, antioxidant nanocarriers, exosome approaches	Less mature than Alzheimer and Parkinson disease; spinal cord and motor-neuron targeting remain difficult	Primarily preclinical
Neuroinflammation-linked neurodegeneration	Microglial activation, cytokine signaling, oxidative stress, immune dysregulation	Anti-inflammatory nanoparticles, exosome-based delivery, lipid and polymeric carriers	Biologically plausible across disorders, but disease-specific outcomes vary	Preclinical and hypothesis-generating

Representative Evidence Matrix

Representative sources were grouped according to their methodological role and contribution to the synthesis. Foundational BBB studies established the structural and functional basis for selective CNS delivery. Receptor-mediated transport studies clarified why ligand choice, receptor affinity, and avidity are central to nanocarrier performance. Focused ultrasound studies provided the most direct early human evidence for reversible BBB opening in Alzheimer disease. Carrier-specific reviews and preclinical studies supported the potential of lipid, polymeric, inorganic, and exosome-based systems, but also highlighted the need for stronger safety and target-engagement evidence.

Table 6. Representative Sources and Their Contribution to the Narrative Synthesis

Reference Range	Evidence Type	Disease / Scope	Delivery Strategy	Main Contribution
3-6	Foundational BBB reviews	CNS drug delivery and neurovascular biology	BBB structure, transporters, endothelial regulation	Established why barrier selectivity limits CNS therapy and why targeted or assisted transport is needed
7-10	Broad nanomedicine and BBB-delivery reviews	Neurological and neurodegenerative diseases	Nanoparticles, brain-targeted systems, stimuli-responsive platforms	Summarized major nanoscale approaches to BBB crossing and CNS delivery
11-13	Receptor-mediated transport reviews and studies	BBB transport mechanisms	Transferrin receptor, insulin receptor, LRP1, receptor-mediated transcytosis	Showed that receptor choice, ligand affinity, and avidity influence uptake and parenchymal delivery
14-16	Early clinical focused ultrasound studies	Alzheimer disease	MR-guided focused ultrasound with microbubbles	Demonstrated reversible regional BBB opening and early clinical feasibility
17-21	Carrier-specific and route-based reviews	Neurological disorders, Alzheimer disease, Parkinson disease	Liposomes, lipid carriers, intranasal nanoformulations	Supported carrier-dependent advantages and limitations of route-specific delivery
22	Preclinical Alzheimer disease study	Alzheimer disease models	Curcumin nanoparticles	Reported improved stabilization and BBB-related delivery potential for a poorly soluble neuroprotective compound
23	Preclinical Parkinson disease study	Parkinsonian rats	Dopamine-loaded nanoparticles	Reported functional recovery linked to trans-BBB delivery of dopamine-loaded nanoparticles
24	Preclinical targeting study	Brain delivery	Gold nanoparticles conjugated with transferrin receptor-targeting peptide	Supported ligand-mediated brain delivery of inorganic nanoparticles
25	Preclinical exosome study	Parkinson disease-related alpha-synuclein pathology	Systemic exosomal siRNA delivery	Reported reduction of alpha-synuclein aggregates in transgenic mice
26-28	Exosome and Alzheimer-focused reviews	Neurodegenerative diseases	Exosomal delivery and targeted nanoparticles	Highlighted promise and technical barriers for biological nanocarriers
29-32	Mechanistic and translational BBB-delivery literature	Brain diseases and drug delivery	Transferrin targeting, focused ultrasound, BBB regulation	Strengthened mechanistic interpretation and translational context

RESULTS

Outcome-Domain Synthesis

Across the evidence base, the most consistently favorable findings related to brain uptake, payload protection, prolonged circulation, and improved formulation properties. Nanocarriers were repeatedly described as useful for protecting labile payloads such as peptides, proteins, siRNA, mRNA, and poorly soluble small molecules. Lipid and polymeric systems showed particular relevance for hydrophobic drugs and nucleic-acid payloads, while exosomes were attractive for biological cargo delivery.

However, evidence for target engagement was less consistent. Many studies demonstrated carrier presence in the brain or improved behavioral outcomes in animal models, but fewer established whether the active drug was released in the correct brain compartment, entered the relevant cell type, and modulated a disease-specific molecular target. Functional outcomes were most commonly reported in selected preclinical models, but these outcomes should not be interpreted as evidence of clinical disease modification. Human safety data were most developed for focused ultrasound-mediated BBB opening, whereas long-term safety evidence for repeated systemic nanocarrier dosing in neurodegenerative disease remains limited.

Table 7. Outcome-Domain Synthesis Across Nanotechnology-Based BBB Delivery Strategies

Outcome Domain	Overall Direction of Evidence	Interpretation	Remaining Evidence Gap
BBB crossing / brain uptake	Generally favorable in preclinical studies when carriers are targeted or route-enhanced	Nanocarriers can improve apparent brain exposure compared with free drug in selected models	Brain uptake does not prove parenchymal delivery, cell-specific uptake, or active payload release
Payload protection	Consistently favorable for labile molecules and poorly soluble compounds	Encapsulation protects peptides, nucleic acids, proteins, and hydrophobic drugs from degradation or poor solubility	Release kinetics at the target site require stronger demonstration
Circulation and biodistribution	Often improved through surface engineering or PEGylation	Longer circulation may increase opportunity for BBB interaction	Liver, spleen, immune-system uptake, and protein corona effects remain major concerns
Receptor targeting	Mechanistically strong and supported by experimental evidence	Ligand modification can increase endothelial interaction and transcytosis potential	Endothelial trapping, receptor saturation, ligand masking, and disease-stage variability remain unresolved
Target engagement	Variable and inconsistently reported	Some studies link delivery with molecular or pathological markers	Future work should connect dose, brain concentration, cellular localization, molecular effect, and clinical outcome
Behavioral / functional outcomes	Favorable in selected animal studies	Experimental recovery supports biological plausibility	Animal behavioral improvement may not translate to human neurodegenerative disease
Clinical safety	Most developed for focused ultrasound-mediated BBB opening	Early human FUS studies support feasibility of reversible regional opening	Long-term repeat-treatment safety and nanocarrier-specific safety remain insufficient
Manufacturing feasibility	More advanced for lipid and polymeric systems than for exosomes or hybrid carriers	Some platforms benefit from broader pharmaceutical manufacturing experience	Sterility, scale-up, stability, batch consistency, and regulatory classification remain challenges
Clinical efficacy	Not established for most nanocarrier platforms in neurodegenerative disease	Current evidence supports promise rather than proven therapeutic benefit	Randomized clinical trials with meaningful endpoints are needed

Translational Maturity of Delivery Strategies

The evidence suggests a gradient of translational maturity across delivery platforms. Focused ultrasound-mediated BBB opening appears most advanced clinically, particularly in Alzheimer disease, because early human studies have demonstrated regional and reversible BBB opening. However, this does not yet establish broad therapeutic efficacy and requires further evaluation of repeated procedures, cognitive outcomes, imaging biomarkers, adverse events, and combination with disease-modifying therapies.

Lipid-based and polymeric nanocarriers have stronger pharmaceutical-development foundations than many biological carriers because of broader manufacturing familiarity, flexible formulation properties, and extensive preclinical testing. Nevertheless, neurodegenerative-disease-specific clinical translation remains limited. Exosome-based delivery is highly attractive for biological cargo, especially nucleic acids and proteins, but manufacturing standardization remains a central obstacle. Inorganic nanoparticles offer imaging and theranostic potential but require more rigorous long-term retention and toxicity evaluation before repeated use in chronic neurodegenerative disease.

Table 8. Translational Maturity and Development Barriers

Strategy	Current Translational Position	Main Strength	Main Barrier to Clinical Translation
Focused ultrasound with microbubbles	Early human evidence, especially in Alzheimer disease	Regional, reversible BBB opening under imaging guidance	Procedural complexity, repeat-treatment safety, and proof of clinical benefit
Receptor-targeted nanoparticles	Strong mechanistic and preclinical rationale	Biological specificity through endogenous transport pathways	Ligand optimization, endothelial trapping, receptor saturation, and reproducibility
Liposomes and lipid nanoparticles	Advanced platform experience outside neurodegeneration; mostly preclinical in neurodegenerative disease	Flexible payload loading and biocompatibility	Peripheral uptake, limited CNS specificity, and limited human disease-specific efficacy data
Solid lipid nanoparticles and nanostructured lipid carriers	Preclinical and route-based development	Useful for hydrophobic drugs and intranasal formulations	Payload leakage, nasal variability, stability, and clinical validation
Polymeric nanoparticles	Strong preclinical engineering flexibility	Tunable release, size, charge, and ligand functionalization	Polymer toxicity, degradation, residual solvents, and batch consistency
Inorganic nanoparticles	Preclinical and imaging-oriented development	Stability, imaging, and theranostic potential	Long-term tissue retention and chronic neurotoxicity
Exosomes and extracellular vesicles	High biological interest but technically immature	Natural intercellular transport and nucleic-acid/protein delivery potential	Isolation, purity, yield, cargo loading, heterogeneity, and regulatory complexity
Intranasal nanoformulations	Promising noninvasive route; mostly preclinical	Potential partial BBB bypass and reduced systemic exposure	Mucociliary clearance, low dosing volume, anatomical variability, and inconsistent delivery

Safety and Risk Synthesis

Safety concerns differed by carrier class and delivery mechanism. Synthetic nanoparticles may accumulate in liver, spleen, kidney, or brain tissue, depending on composition, size, surface charge, and clearance pathway. Cationic surfaces may improve uptake but can increase cytotoxicity and immune activation. PEGylation may prolong circulation but does not eliminate immune or protein-corona-related concerns. Polymeric carriers require careful assessment of degradation products, residual solvents, and chronic inflammatory potential. Inorganic particles raise concerns about long-term retention, oxidative stress, mitochondrial injury, and delayed neurotoxicity.

Exosome-based systems present a distinct safety profile. Although they may be less immunogenic than some synthetic particles, their biological complexity introduces concerns about donor-cell source, unwanted protein or RNA cargo, pathogen safety, batch heterogeneity, and possible transfer of pathological signals. Focused ultrasound involves procedural risks rather than conventional systemic carrier toxicity. Potential concerns include excessive BBB opening, edema, microhemorrhage, inflammatory response, and unintended regional injury if acoustic exposure is not precisely controlled.

Table 9. Safety Concerns by Delivery Platform

Platform / Strategy	Main Safety Concerns
Liposomes and lipid nanoparticles	Infusion reactions, complement activation, liver/spleen uptake, limited CNS specificity
Solid lipid nanoparticles / nanostructured lipid carriers	Payload leakage, mucosal irritation, systemic lipid accumulation
Polymeric nanoparticles	Polymer toxicity, degradation products, residual solvents, local inflammation
Dendrimers	Cationic surface toxicity, membrane disruption, immune activation
Inorganic nanoparticles	Long-term tissue retention, oxidative stress, mitochondrial toxicity, delayed neurotoxicity
Exosomes / extracellular vesicles	Heterogeneity, unwanted biological cargo, pathogen safety, disease-signal transfer
Receptor-targeted carriers	Receptor saturation, off-target uptake, altered endogenous ligand transport
Focused ultrasound with microbubbles	Edema, microhemorrhage, excessive BBB opening, inflammatory response
Intranasal nanoformulations	Nasal irritation, mucociliary clearance, variable absorption, limited dose volume

Integrated Narrative Synthesis

The overall synthesis indicates that nanotechnology-based delivery across or around the blood-brain barrier is scientifically plausible and technically diverse, but not yet clinically established for most neurodegenerative disease indications. The field has advanced beyond the simple concept of increasing BBB permeability toward more sophisticated strategies involving receptor targeting, controlled release, payload protection, biological carriers, regional BBB opening, and route-based bypass. These strategies are particularly relevant for therapeutic classes that are otherwise difficult to deliver to the brain, including antibodies, enzymes, peptides, proteins, oligonucleotides, siRNA, mRNA, and poorly soluble small molecules.

Among the strategies reviewed, focused ultrasound-mediated BBB opening currently has the strongest early human translational support, especially in Alzheimer disease. Its main advantage is regional and reversible modulation of the BBB under imaging guidance. However, focused ultrasound is a delivery-enabling method rather than a disease-modifying treatment by itself. Its clinical value depends on whether it can safely and repeatedly improve delivery of therapeutic agents and produce meaningful biomarker or clinical outcomes.

Receptor-mediated transcytosis remains one of the most rational biological approaches for systemic nanocarrier delivery. However, receptor targeting is technically complex. Delivery success depends not only on whether a carrier binds an endothelial receptor, but also on whether it avoids lysosomal degradation, escapes endothelial trapping, releases cargo beyond the vascular compartment, and reaches the intended neural or glial target. This makes ligand affinity, ligand density, particle size, avidity, and disease-stage-specific receptor expression central design variables.

Lipid and polymeric nanocarriers are among the most practically developable platforms because they can be engineered for payload protection, surface modification, and controlled release. Their major challenge is that improved formulation performance does not necessarily translate into brain-specific delivery. Peripheral uptake by the liver, spleen, and immune system remains a recurring limitation. For chronic neurodegenerative diseases, repeated dosing, cumulative toxicity, and long-term biodistribution are more important than short-term proof of uptake.

Exosomes and extracellular vesicles offer a biologically attractive alternative because they are naturally involved in intercellular communication and can carry nucleic acids, proteins, and regulatory molecules. Their potential is particularly relevant for diseases in which gene regulation or protein modulation is central. However, their clinical development is constrained by manufacturing complexity, heterogeneity, purification challenges, uncertain cargo loading, and safety concerns related to unwanted biological signaling.

Across diseases, Alzheimer disease and Parkinson disease currently have the strongest evidence base for nanotechnology-based BBB delivery, largely because they have clearer molecular targets and more extensive preclinical models. Huntington disease and amyotrophic lateral sclerosis remain important but less developed applications. For these disorders, the therapeutic rationale for gene or nucleic-acid delivery is strong, but anatomical targeting, cell specificity, disease-stage selection, and safety remain unresolved.

A recurring limitation across the evidence is the overreliance on uptake or biodistribution outcomes without sufficient demonstration of pharmacodynamic target engagement. Future studies should move beyond showing that nanocarriers reach brain tissue and should demonstrate that the active payload is released at the intended site, enters the relevant cell population, modulates the target pathway, improves disease-specific biomarkers, and produces durable functional benefit without unacceptable toxicity. Therefore, the current evidence supports cautious optimism: nanotechnology may substantially improve central nervous system delivery, but its clinical value in neurodegenerative disease will depend on stronger translational evidence connecting delivery, target engagement, safety, and patient-relevant outcomes.

DISCUSSION

This structured narrative review synthesized current evidence on nanotechnology-based strategies for delivering therapeutic agents across, around, or through transient modulation of the blood-brain barrier in neurodegenerative diseases. The principal finding is that nanotechnology provides a scientifically plausible and technically diverse framework for improving central nervous system drug delivery, particularly for therapeutic agents that are otherwise limited by poor solubility, enzymatic degradation, rapid systemic clearance, efflux transport, or inadequate brain penetration. Lipid-based carriers,

polymeric nanoparticles, receptor-targeted systems, exosomes, intranasal nanoformulations, and focused ultrasound-assisted delivery each address different aspects of the blood-brain barrier problem. However, the evidence remains uneven across platforms and diseases. Most nanoparticle and exosome-based strategies are supported mainly by mechanistic, in vitro, ex vivo, and animal studies, whereas the most mature early human evidence relates to focused ultrasound-mediated blood-brain barrier opening in Alzheimer disease (14-16).

The findings are consistent with foundational blood-brain barrier literature showing that the neurovascular unit is a selective, regulated, and disease-responsive interface rather than a simple anatomical wall (3-6). This distinction is clinically important because increasing blood-brain barrier permeability alone is not sufficient for effective therapy. A successful delivery system must protect the payload, reach the relevant brain region, cross or bypass endothelial barriers, avoid premature clearance, release the active therapeutic agent, achieve cellular or molecular target engagement, and maintain an acceptable safety profile during repeated or chronic use. The reviewed evidence supports the view that nanocarriers can improve several of these pharmacological steps, particularly payload protection, solubility enhancement, circulation time, and apparent brain exposure (7-10). Nevertheless, these properties should not be interpreted as proof of disease modification unless they are linked to pharmacodynamic target engagement and clinically meaningful outcomes.

Receptor-mediated transcytosis remains one of the most biologically rational approaches for systemic brain delivery because it uses endogenous endothelial transport pathways such as the transferrin receptor, insulin receptor, and low-density lipoprotein receptor-related protein 1 (11-13). However, the evidence also indicates that receptor targeting is not a simple matter of adding a ligand to a nanoparticle surface. Binding affinity, avidity, particle size, ligand density, receptor saturation, protein corona formation, and disease-related changes in receptor expression may all determine whether a carrier is transported into the brain parenchyma or trapped within endothelial compartments. Therefore, receptor-mediated delivery should be evaluated not only by endothelial uptake or whole-brain accumulation, but also by released payload concentration, cell-specific localization, target modulation, and safety after repeated exposure.

Lipid-based nanocarriers, including liposomes, lipid nanoparticles, solid lipid nanoparticles, and nanostructured lipid carriers, appear especially attractive because they can encapsulate hydrophobic drugs, protect nucleic acids, and support surface modification. These systems also benefit from broader pharmaceutical manufacturing experience in non-neurodegenerative indications. However, their translation to chronic neurodegenerative disease remains limited by peripheral uptake in the liver and spleen, variable brain specificity, stability concerns, and incomplete evidence of long-term safety. Similarly, polymeric nanoparticles offer considerable engineering flexibility through control of size, surface charge, biodegradation, and drug-release kinetics, but polymer toxicity, residual solvents, degradation products, and batch reproducibility require careful evaluation before clinical application in older and medically complex populations.

Exosomes and extracellular vesicles represent a biologically attractive delivery strategy because they naturally participate in intercellular communication and can transport proteins, RNA, and other regulatory molecules. This makes them particularly relevant for diseases where gene regulation, protein aggregation, or inflammatory signaling are central therapeutic targets. Preclinical evidence, including systemic exosomal siRNA delivery for alpha-synuclein pathology, supports their conceptual promise (25). However, exosome translation remains technically demanding. Isolation methods, donor-cell source, cargo loading, yield, purity, heterogeneity, storage conditions, and unwanted transfer of biological signals remain major barriers. Unlike synthetic nanoparticles, exosomes are not uniform chemical products; they are complex biological preparations, and this increases both their therapeutic appeal and their regulatory complexity (26,27).

Focused ultrasound-mediated blood-brain barrier opening currently appears to have the strongest early human translational evidence among the reviewed delivery-enabling strategies. Studies in Alzheimer disease have demonstrated that magnetic resonance-guided focused ultrasound with microbubbles can achieve reversible regional blood-brain barrier opening, and early work has explored its combination with anti-amyloid therapy (14-16). This approach is clinically important because it offers spatially targeted, image-guided modulation of the barrier rather than relying solely on systemic nanoparticle biodistribution. However, focused ultrasound is a delivery platform, not a disease-modifying treatment by itself. Its ultimate clinical value will depend on whether it can safely and repeatedly improve delivery of effective therapeutic agents, produce biomarker changes, and translate into durable cognitive, functional, or disease-modifying benefits.

Across disease contexts, Alzheimer disease and Parkinson disease currently have the most developed nanotechnology-based delivery literature. Alzheimer disease studies commonly target amyloid-beta, tau, oxidative stress, neuroinflammation, synaptic injury, and vascular dysfunction, whereas Parkinson disease applications focus on dopaminergic delivery, alpha-synuclein aggregation, mitochondrial dysfunction, iron-related injury, and neuroinflammation. Huntington disease and amyotrophic lateral sclerosis remain less mature application areas, although the rationale for nucleic-acid, gene-silencing, antioxidant, and anti-inflammatory delivery is strong. In these conditions, delivery challenges are compounded by the need for disease-region specificity, neuronal or glial targeting, spinal cord or striatal distribution, long-term gene modulation, and safety in progressive neurodegenerative settings.

A recurring limitation in the evidence base is the reliance on delivery metrics without adequate linkage to target engagement. Many experimental studies report brain uptake, fluorescence intensity, tissue distribution, or behavioral improvement, but fewer demonstrate active payload release in the intended brain compartment, uptake by the relevant cell population, modulation of a disease-specific molecular target, biomarker improvement, and durable functional benefit. This distinction is critical because a carrier detected in brain tissue may be intravascular, perivascular, trapped in endothelial cells, taken up by off-target cells, or unable to release the payload at a therapeutic concentration. Future studies should therefore integrate pharmacokinetic and pharmacodynamic endpoints, including systemic dose, brain concentration, cellular localization, release kinetics, target engagement, biomarker response, functional outcome, and toxicity.

Safety is especially important because neurodegenerative diseases often require chronic or repeated treatment in older patients with vascular disease, metabolic comorbidities, polypharmacy, and altered immune function. Potential safety concerns include complement activation, infusion reactions, endothelial injury, edema, microhemorrhage, hepatic and splenic accumulation, renal clearance burden, microglial activation, oxidative stress, mitochondrial toxicity, off-target gene effects, and delayed tissue retention. Platform-specific safety evaluation is therefore essential. Lipid systems, polymeric carriers, inorganic nanoparticles, exosomes, intranasal formulations, and focused ultrasound-assisted delivery each carry different risk profiles and should not be discussed as a single uniform intervention.

This review has several limitations. First, it was conducted as a structured narrative review rather than a registered systematic review; therefore, no PRISMA flow diagram, exhaustive study count, formal risk-of-bias assessment, or meta-analysis was performed. Second, the literature is heterogeneous across diseases, experimental models, carrier systems, payloads, administration routes, and outcome measures, limiting direct comparison across platforms. Third, much of the evidence remains preclinical, and animal models may overestimate delivery efficiency, safety, or functional benefit in human neurodegenerative disease. Fourth, publication bias is likely because successful delivery studies are more likely to appear in the literature than negative, neutral, or toxicity-focused studies. Fifth, because this review prioritized mechanistic relevance, translational importance, and representative evidence, it should be interpreted as a clinically oriented synthesis rather than an exhaustive systematic inventory.

Future research should move from proof-of-uptake studies toward translationally complete delivery evidence. Studies should include standardized nanoparticle characterization, ligand-density reporting, protein-corona assessment, human-relevant blood-brain barrier models, direct comparison of targeted and non-targeted systems, repeated-dose toxicology, sex- and age-aware experimental designs, and pharmacokinetic-pharmacodynamic modeling. For Alzheimer disease, future work should connect delivery with amyloid, tau, neuroinflammation, synaptic, vascular, and neurodegeneration biomarkers. For Parkinson disease, studies should focus on alpha-synuclein modulation, dopaminergic function, mitochondrial injury, oxidative stress, and motor or non-motor outcomes. For Huntington disease and amyotrophic lateral sclerosis, priority should be given to cell-specific nucleic-acid delivery, disease-region targeting, long-term safety, and clinically meaningful functional endpoints. Manufacturing research should address sterility, scalability, storage stability, reproducibility, cost, and regulatory classification, particularly for exosome-based and hybrid biomimetic systems.

CONCLUSION

Nanotechnology-based drug delivery across or around the blood-brain barrier offers a credible and rapidly advancing strategy for addressing one of the major therapeutic barriers in neurodegenerative diseases. Receptor-targeted nanoparticles, lipid and polymeric carriers, exosomes, intranasal nanoformulations, and focused ultrasound-assisted delivery each provide distinct opportunities for improving brain exposure, payload protection, controlled release, and regional or biological targeting. However, current evidence supports cautious optimism rather than confirmed clinical efficacy. Most nanoparticle and exosome platforms remain preclinical or early translational, while focused ultrasound-mediated blood-brain barrier opening has the strongest early human evidence, particularly in Alzheimer disease. Future progress will depend on demonstrating not only brain entry, but also active payload release, cell-specific target engagement, long-term safety, scalable manufactuing, disease-stage selection, and meaningful clinical benefit.

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