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Overcoming the Blood-Brain Barrier, Strategies and Advances in Therapeutic Delivery: A Literature Review

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Abstract

The treatment options for disorders affecting the central nervous system (CNS) heavily rely on medications to be delivered to the brain, however diverse and effective treatment options are lacking, especially in Alzheimer's disease (AD) and brain cancers. The passage of drugs into the brain is challenging, due to limited permeability of the blood-brain barrier (BBB). The BBB is a physiological filter for molecules circulating in the bloodstream, playing an essential role in protecting the brain and maintaining its homeostasis. The endothelial cells constituting the microvasculature of the BBB exhibit characteristics such as high levels of tight junctions, adherens junctions and efflux transport proteins, which, together with the lack of capillary fenestrations, impede the ability of drugs to reach CNS targets. Currently available treatments are limited, with invasive neurosurgical interventions and novel non-invasive delivery strategies. Invasive approaches are challenged by significant adverse events and potentially marginal efficacy. Many new methods open prospects for targeted drug deposition in the brain, each with distinct mechanisms of action. These methods comprehend focused ultrasound-mediated disruption of the BBB, innovative physicochemical drug formulations and intranasal pharmacological administrations. The aim of this review is to provide a critical analysis of the current state of drug delivery across the BBB, comparing existing and emerging technologies in the context of neurodegenerative disorders, in particular AD, and brain cancers. A literature search was performed including articles exploring current and evolving methods for drug delivery across the BBB. Considering epidemiological trends highlighting the growing societal burden of neurodegeneration in aging populations and rising incidence of cancers worldwide, it is essential to explore options for effective drug delivery to the brain. The development and optimization of such innovative drug delivery methods holds significant potential for treating neurological disorders: facilitating the use of large molecules, exhibiting more specific cellular targeting but reduced brain permeability, or expediting the formulation of novel molecules bypassing the physiological systems of the BBB. These strategies can improve therapeutic outcomes, reduce side effects, and enhance the quality of life for patients affected with CNS diseases. Continued research is essential to refine and translate these techniques for clinical use.

Keywords: blood-brain barrier; neuropharmacology; drug delivery; brain-drug targeting; BBB permeability

Introduction

The central nervous system (CNS) is a complex, highly regulated cellular microenvironment. The blood-brain barrier (BBB) is a specialised subunit of the brain neurovascular unit which regulates cerebral blood flow, immune trafficking, neurotrophic function and clearance pathways [1]. The BBB maintains CNS homeostasis through neurovascular coupling, regulating distribution of ions, nutrients, [2], oxygen, carbon dioxide, and electrolytes, as well as immune responses between the brain parenchyma and the blood, communicating closely with neural tissues [3]. Homeostatic maintenance is essential for neuronal and glial function, in addition to surrounding astrocytes, oligodendrocytes and microglia supporting synapses and axonal transport for sensorimotor and cognitive tasks [4]. Therefore, while the BBB is vital for preventing disruptive and harmful neurotoxins, and blood-borne substances in the brain, 98% of pharmacological agents on the market cannot cross due to size and lack of transport affinity [5]. With increasing rates of neurological disorders, development of novel methods for drug delivery to the brain is paramount [6].

CNS Disorders

With CNS disorders rising, treatment options and effectiveness remain challenging [6]. Brain tumors are typically treated with surgical and adjuvant interventions, however, survival rates are poor due to incomplete resections and positive tumor margins [7]. Restricted BBB permeability inhibits non-lipophilic drug molecules, including chemotherapeutic agents, antibodies, and peptides with molecular sizes over 400-500 Da from brain and tumor

tissues, restricting current approaches to invasive strategies and interventions slowing cancer progression. Some brain tumors contribute to BBB degradation, forming a distinct blood-tumor barrier (BTB) with new and existing blood vessels and capillaries. The BTB has non-uniform permeability and active efflux, exacerbating homeostatic imbalances through accumulated metabolites, toxic wastes and interstitial fluid pressure [8]. BTB permeability may improve drug delivery, however therapeutic concentrations are inconsistent, with risks including surrounding tissue damage, cognitive dysfunction; and temporary side effects [9–11]. Tumour location is correlated with operability potential, and adverse events, increasing uncertainty for treatment success.

The BBB also complicates neurodegenerative disorders treatments, including Alzheimer's disease (AD) [12]. AD affects over 50 million people and is the 6th leading cause of death in the United States [13,14]. The amyloid beta hypothesis suggests brain network atrophy may be caused by deposition of amyloid-beta plaques in the parenchyma with neuroinflammatory responses. The BBB is impaired in AD patients, with shortened capillary length reducing nutrient transportation and removal of neurotoxins. While there is no cure for AD, as of 2019, most treatments focus on relieving symptoms and improving quality of life [14]. More recent developments have introduced disease-modifying therapies, including lecanemab and donanemab in 2023 and 2024 respectively [15]. These advancements mark significant progress in addressing the progression of AD. This review will focus on applications for AD and brain cancers, providing insights on invasive and non-invasive treatments.

Physiology of the BBB

Anatomical, physiological, and structural properties contribute to BBB impermeability. Intercellular signalling throughout the neurovascular unit and BBB is essential for maintaining brain homeostasis by regulating blood flow, vascular function, neuroimmune responses, and waste clearance [16]. Endothelial cells, the primary component of the BBB, are connected by tight and adherens junctions, restricting transport to transcellular modalities [10]. They lack between-cell fenestrations, exhibit increased mitochondrial activity, and high levels of efflux transport proteins [17]. Ions and solutes may cross the BBB by paracellular transport [10], depending on molecular weight, charge, and lipid solubility, regulated by tight junctions [18]. Transport mechanisms exhibit molecule-specific carriers or transporters to move metabolic waste, harmful chemicals, and neurotransmitters out of the brain [19]. Astrocytes, pericytes, microglia, and the basal membrane, surround endothelial cells forming the BBB [18]. Astrocytes maintain homeostatic balance regulating ions, neurotransmitter concentrations, blood flow, and endothelial cells [20]. Pericytes anchor endothelial cells, maintain capillary structure, regulate vasodilation, and guide angiogenesis, with possibility of BBB remodelling. Microglia conduct immune surveillance, monitoring CNS abnormalities and quickly responding against neuroinflammation [21], possibly inducing BBB permeability by modulating tight junction protein expression for immune cells [17]. Microglia also monitor synaptic and axonal signalling, influencing synaptic pruning and plasticity [21].

Overall, treatments are limited or not curative for many CNS disorders, including brain cancers and AD. The goal of this review will address difficulties with drug delivery across the BBB and explore innovative invasive and non-invasive methods to overcome the BBB, techniques that could greatly improve future treatment options.

Methods

This review aims to analyse invasive and non-invasive methods of overcoming the BBB in the context of AD and brain cancers. An online literature search was performed on PubMed and Google Scholar, focusing on peer-reviewed articles published in the last 5 years. Keywords included "blood-brain barrier", "BBB permeability", and "crossing the BBB". Articles were selected if they explored current and evolving methods for drug delivery across the BBB. Exclusion criteria included manuscripts unrelated to drug delivery methods or unspecific to the BBB. Following a preliminary search, the search in aforementioned databases was tailored to recurring techniques highlighted in the results. Over 100,000 articles were found in the primary search, most being review articles. Filtering by pathological application led to a comprehensive assessment of over 50 articles, including literature reviews, systematic reviews and original research. Findings were synthesized to highlight advancements in invasive and non-invasive strategies for modulating BBB permeability. Selected original research is provided as examples of applications for AD and brain cancer. A summary of the techniques reviewed is presented in Table 1 of results.

Results

Invasive Modalities

Neurosurgical Approaches

Neurosurgical approaches enabling drug delivery in the brain bypass the BBB by administering drugs directly to the CNS via injections to cerebrospinal fluid (CSF) or brain areas. They allow for deposition in tissues with minimal harmful peripheral exposure, however, are highly invasive. Intrathecal injections administer pharmacological agents to the subarachnoid space surrounding the spine, expecting compounds to diffuse through the CSF, local blood circulation, and interstitial fluids to targets. Similarly, intracerebroventricular delivery is via direct injection to brain ventricles, containing CSF [26]. Intraparenchymal or intracerebral treatments are minimally invasive surgical interventions, generally combined with operations as adjuvants to therapy [18]. These comprise injections over tissues of interest via needle-based infusions or drug

distributing implants for controlled release [26]. These methods do not require large amounts of therapeutics, due to directness, and remain an efficient method of drug delivery in severe clinical cases, where benefits outweigh risk [18].

Intracerebral injection of biodegradable polymeric implants containing therapeutics is explored in clinical trials where advantages highlight sustained drug release for months[27], however, trauma risk is too high for common use. Intraventricular treatments are used for infections, chronic pain, and brain cancers [26], with promising results for chemotherapeutics, but increase infection risks [26]. Intrathecal chemotherapeutics are used in pediatric leukaemia, with risks of traumatic side effects and drug accumulation in the CSF [28]. Compared to cancer literature, neurosurgical strategies are less explored in AD due to neurodegeneration across the brain [29] requiring multiple administrations to different regions, increasing costs and risks.

Table 1. Summary of Reviewed Modalities of Overcoming the BBB

Invasive	Neurosurgical	Administering drugs to the CNS via direct injection or intracranial implanted devices [21].
	Therapeutic Opening of the BBB	Chemically altering tight junctions to open BBB [17].
Non-invasive	Intranasal	Pharmacological administration through the olfactory nerve (nose to brain pathway) [22].
	Focused Ultrasound	Uses targeted ultrasound waves to temporarily and precisely disrupt the blood-brain barrier [23].
	Nanoparticles	Engineered carriers or molecules designed to bypass the physiological transport processes of the blood-brain barrier [16].
	Exosomes	Naturally occurring nanovesicles that can cross the blood-brain barrier by fusing with the endothelial cell lipid bilayer [24].
	Receptor-mediated Transcytosis	Drugs are attached to ligands that bind specific receptors on the luminal side of the endothelial cell membrane [25].

Therapeutic Opening of the BBB

Therapeutic opening of the BBB involves modulating its structure by increasing permeability throughout the CNS. Noxious agents or hyperosmotic solutions temporarily loosen tight junctions by altering osmotic pressure and downregulating junctional protein expression [18]. However, this may permanently affect BBB integrity, introducing harmful toxins in the CNS, including metabolic byproducts and endogenous inflammatory cytokines usually in peripheral systems [18]. Timing is essential, with drug and BBB-opening agents concomitantly delivered to maximize brain biodistribution and absorption, minimising risks of damage with long-term exposure.

These strategies have undergone early clinical trials, however consequences, although temporary, are documented with emergence of severe vasculopathy and chronic neuropathologic changes. including neuroinflammation and apoptosis, as well as seizures in animal models and humans [5], resulting in unregulated parenchymal edema [22]. Whole-brain BBB-disruption methods have limited clinical utility, especially when potential side effects exceed benefits.

Non-Invasive Modalities

Intranasal

Intranasal drug delivery bypasses the BBB through the nose-to-brain pathway [30]. The first route is the olfactory nerve pathway, where compounds are absorbed at axonal terminals of olfactory neurons, travelling in an antero-retrograde fashion along olfactory and trigeminal nerves to the brain [31]. Additionally, the olfactory mucosal epithelial pathway is a passage for molecules to enter submucous spaces in the nose to reach the olfactory CSF and brain via CSF flow tracts [31]. This method circumvents the BBB and exploits filtering capabilities of olfactory nerves and epithelium; yet only small liposoluble molecules may diffuse due to tight junctions of the arachnoid membrane [32]. Absorption varies with mucociliary clearance removing molecules other than injected medications. Nasal irritation and injury can occur depending on agents and frequencies of administrations.

Research in rodent models has demonstrated results for AD through intranasal delivery of nerve growth factors reducing progression of neurodegeneration [32, 33]. Anti-cancer drugs have also been explored, however, cannot distinguish between tumor and healthy tissues, require high doses, and pose toxicity hazards for the nasal mucosa and surrounding healthy brain [34]. Tumor specific treatments are thus being investigated to selectively target tumor cells.

Focused Ultrasound

Focused ultrasound (FUS) is a non-invasive technology to disrupt the BBB for drug delivery. Ultrasound beam energy is concentrated to a well-defined spatial target in cubic millimeter sonications [23]. FUS was initially explored to create controlled lesions in the brain, and by

using high-intensity focused ultrasound (HIFU), changes in in BBB permeability occurred [23]. HIFU is minimally invasive and can be inconsistent or cause tissue damage, compared with low-intensity focused ultrasound (LIFUS), which is non-invasive and avoids neuronal damage. The difference between these methods is their intensity; HIFU uses an intensity greater than 200 W/cm^2, while LIFUS uses an intensity less than 100 W/cm^2 [35] LIFUS is paired with intravenously injected microbubbles: gas-filled lipid-coated bubbles that oscillate in presence of high-energy ultrasound waves (cavitation phenomenon), to disrupt the BBB [36]. Through interactions with ultrasonic beams, microbubbles decrease the amount of energy to open the BBB and exert pressure on endothelial cells, oscillating at capillary walls, forcing tight junctions apart [36]. Stable cavitations occur at acoustic pressures enough to reproduce radial bubble expansions; however, at higher pressures, inertial cavitation occurs: bubbles uncontrollably grow in size, burst and shock the vasculature with risks of damage.

FUS methods are undergoing clinical trials obtaining promising results with chemotherapeutics, antibodies, immunomodulators, genes and cells. Potential efficacy was first shown with chemotherapeutic doxorubicin in mice, improving survival despite tumor implantation [37]. Clinical studies showed no adverse effects for brain tumour patients with temozolomide, supporting safety and efficacy [25]. Antibodies have limited applications for CNS disorders, due to size and incapability to permeate the BBB [17], however this was overcome with FUS for trastuzumab, a breast cancer treatment, in mouse and rodent models, showing lower post-treatment tumour volumes and increased survival [38,39]. Anti-amyloid beta antibodies, agents investigated in AD were unable to reach clinically relevant doses [17], but demonstrodented enhanced delivery with FUS, reducing plaques and neuropathological degenerodentions [40, 41].

Nanoparticles

Another non-invasive strategy for bypassing the BBB are nanoparticles, compounds with enhanced solubility and specific targeting. Larger than biomolecules, nanoparticles range from 1 to 100 nanometers but exhibit BBB cellular affinity to safely permeate the brain parenchyma. Nanoparticles vary in composition, and have customizable properties, sizes, polar charges, and shapes, enabling BBB-crossing by addressing the physicochemical challenges posed by BBB structures [42]. Nanoparticles are drug-vehicles categorized by their shell: metallic, liposomal or polymeric, among others. Metallic nanoparticles include gold, silver, or iron oxide. Rather than having drugs encapsulated inside them, due to smaller sizes, therapeutics are conjugated to the surface, or they are used as theranostic devices, for imaging [17]. Lipid nanoparticles, or liposomes, consist of a phospholipid membrane that can incorporate lipophilic agents within the bilayer, and hydrophilic agents inside [43]. Polymeric nanoparticles are synthesized as drug-containing capsules or drug-coated solid polymers [43].

Several therapeutics were delivered to the brain using nanoparticles, with liposomes seeing the broadest success due to versatility and safety [6]. Inrodentglioma models, gold nanoparticles have delivered doxorubicin and gadolinium contrast agents [24] for therapeutics and diagnostics. Anticancer drugs and imaging agents were successfully encapsulated in liposomes and polymeric nanoparticles for tumor therapy, however, risks associated with nonspecific uptake, and crossing of the BBB and BTB were limitations [6]. To prevent pathological evolution of Aβ and tau proteins in AD, the H102 peptide was encapsulated into liposomes to block early aggregation and misfolding, as well as specific Aβ plaque ligands conjugated to liposomes, and curcumin [6, 44]. Safety and efficacy is being evaluated, with toxicity concerns stemming from inflammatory reactions. permeation and pharmacological effects on unintended targets.

Exosomes are small (30–150 nm) natural nanoparticles that cross the BBBand constitute safer, more stable alternatives, due to non-immunological biocompatibility [45]. In the body, they modulate intercellular communication, as transporters of signalling molecules, antigens, and toxic materials [45]. Exosomes interact with BBB endothelial cells for transcellular transport [18], and may be engineered to express ligands leveraging natural receptors for drug delivery. Exosomes are loaded with therapeutic agents, then delivered intravenously, orally, or by inhalation, enter the bloodstream and circulate before reaching brain targets. Preclinical and clinical research is evaluating vehiculated drug compounds as delivery systems in brain cancers, AD, and Huntington's disease [45]. Future research will need to develop a comprehensive understanding of exosomal transport, given constraints in loading capacity, effectiveness of delivery and risks.

Receptor-Mediated Transcytosis

Receptor-mediated transcytosis (RMT) overcomes chemical properties of endothelial cells comprising BBB impermeability by utilizing physiological cellular mechanisms. Drugs are chemically attached to ligands with target receptor affinity or structurally modified to bind endothelial cell receptors [42]. Once bound, receptor-drug complexes are internalized and transported across endothelial cells, bypassing the barrier. These methods are often utilized with nanoparticles for targeted delivery, by attaching surface-bound carrier ligands with high transport affinity.

Receptors targeted for drug delivery to the CNS include transferrin, low-density lipoprotein, and insulin receptors, being explored in pre-clinical and clinical trials. Transferrin receptors (TfR) are exploited through targeted ligands or transferrin-specific antibodies [46]. They are targeted in both *in vivo* and *in vitro* studies with anticancer drug doxorubicin, using anti-TfR antibodies [47, 48].

Nanoparticles formulated with the TfR system were used with anti-beta amyloid drugs, preventing pathognomic accumulation in AD [49]. Associated challenges include tissue specificity, and liposomal degradation [48]. Conjugating drugs to antibodies with specificity to insulin receptors represent the first effective use of RMT [46], however, adverse effects include infusion-site inflammation, and transient hypoglycemia [48].

Discussion

Methods of drug delivery to the brain historically focused on modifying drugs to bypass the BBB or impacting barrier integrity. Only 2% of small-molecule drugs, and no large-molecule drugs, can cross the BBB. Drug modifications can increase lipophilicity or affinity for active transport, yet inactivate therapeutics, or offer no clinical relevance, as target affinities are lost through inadvertent modification of essential functional groups [5]. Traditional methods include neurosurgery or whole-brain BBB-disruption using hyperosmotic agents. Invasive neurosurgical approaches, while often necessary, pose risks of infection and surrounding tissue damage with inconsistent success, due to tumour variability. Hyperosmotic solutions are aspecific with risks of permanent damage, toxicity, and seizures. Recent research transitions towards novel strategies, including intranasal delivery, FUS, nanoparticles, and receptor-mediated transport, driven by a lack of understanding and treating CNS disorders, emphasizing minimal invasiveness, precision and efficacy. Despite many methods still in preclinical and clinical trials, they show promising results.

FUS and nanoparticle-based delivery may dominate clinical applications within the next ten years, due to rapidly advancing development, and increasing success [49, 50]. FUS is FDA-approved for thermoablation in essential tremor and tremor-dominant Parkinson's disease. FUS-mediated BBB disruption for drug delivery to the brain parenchyma is under investigation in phase II clinical trials for AD disease, and phase I trials for brain tumours, showing initial successes [51]. Techniques including RMT require research to refine delivery specificity, particularly in cases with risks to systems outside intended brain regions.

CNS diseases are an essential medical concern in aging populations; prevalence of neurodegenerative disorders is estimated to almost double by 2060 [52]. Economic burdens indicate the importance of new methods, with medical expenses for neurodegenerative disorders totalling over 400 billion dollars in 2020, almost 5% of healthcare spending in the United States [52, 53]. The psychological and social impacts of neurodegenerative diseases due to cognitive and neuropsychological dysfunctions also highlight the need for advancements in treatment of neurodegenerative diseases [52].

Brain and CNS cancers were the 21st most prevalent cancer in the world [50], yet mortality is among the highest. Current treatments involve a combination of surgery, radiation and chemotherapy, yet median survival is less than fifteen months post-operatively. Invasive methods are often necessary, to remove tumors and accomplish adequate drug concentrations. In future, treatments may see combinations of neurosurgical and drug delivery methods, such as FUS or nanoparticles [54]. Research demonstrated liposomal doxorubicin delivered to rats with FUS slowed tumour growth compared to liposomal doxorubicin- or FUS-only groups [55]. Techniques may be implemented as neoadjuvant therapies, delivering drugs to unresectable tumours shrinking them to an operable size or location safer to approach. Non-invasive treatments may also be used as adjuvants, following neurosurgical interventions to improve outcomes, and prevent reoccurrence.

Comparatively to brain cancers, AD affects the whole brain, with production and accumulation of insoluble plaques leading to brain atrophy and neurodegeneration, involving loss of neurons and synapses. This causes cognitive decline, due to disrupted communication between neurons, and neuronal death. Current invasive methods cannot address the needs of neurodegenerative diseases. Systemic delivery methods are in use for symptoms, however molecules to cure or slow neurodegeneration are unsuccessful, from targeting to BBB permeation and effectiveness.

Emerging methods for overcoming the BBB hold therapeutic potential, but applications must address scalability, costs, and patient-centric implementation. FUS requires specialized equipment that may not be easily accessible in rural hospitals or centres lacking funding for more specialized equipment, compared with systems commonly available in the majority of research or hospital settings [10]. However, due to costs associated with only one equipment, the FUS station, other than existing imaging or neuronavigation systems, implementations are complementary for hospital settings [37]. Conversely, nanoparticle-based delivery is more complex, due to required research, production costs and difficulty to implement in the short term [56]. Each nanoparticle would require time from ideation to production, and costs for clinical trials, regulatory approval, and reimbursements. Long-term, such therapies might challenge disorders in a safer manner, yet a short-term solution is offered by FUS, requiring new equipment with already approved molecules.

Conclusions

Overall, advancements in BBB-crossing methods are promising. Significant challenges remain, and addressing limitations is essential to improve efficacy, safety, and accessibility. Most novel methods are in preclinical or early clinical trials, with limited evidence on long-term outcomes, toxicity, and insurance that non-targeted tissues stay unaffected, with the unpredictability of neuroinflammation. It is crucial to understand methods are not universal, brain diseases like cancer or AD differ in pathology, location, and progression, making treatments

highly individual and complex. Future research is in development, paving the way for solutions to neurological diseases, with continuous advancements in understanding of BBB dynamics, and drug delivery to the brain.

List of Abbreviations Used
AD: Alzheimer's disease
BBB: blood-brain barrier
BTB: blood-tumour barrier
CNS: central nervous system
CSF: cerebrospinal fluid
FUS: focused ultrasound
RMT: receptor-mediated transcytosis
TfR: transferrin receptors

Conflicts of Interest
The author declares that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This study is a literature review that synthesizes and analyzes previously published research. It does not involve the collection or use of new data from human or animal subjects, and therefore, does not require ethics approval or participant consent.

Authors' Contributions
UAA: contributed to collection, analyses and interpreting of data, drafted and revisited the manuscript, revised the manuscript critically, and gave final approval of the version to be published.

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References
[1] Gorelick PB, Furie KL, Iadecola C, Smith EE, Waddy SP, Lloyd-Jones DM, et al. Defining optimal brain health in adults: A presidential advisory from the American heart association/American stroke association. Stroke. 2017;48:e284–303. https://doi.org/10.1161/STR.0000000000000148
[2] Segarra M, Aburto MR, Acker-Palmer A. Blood–brain barrier dynamics to maintain brain homeostasis. Trends Neurosci. 2021;44:393–405. https://doi.org/10.1016/j.tins.2020.12.002
[3] Lacoste B, Prat A, Freitas-Andrade M, Gu C. The blood–brain barrier: Composition, properties, and roles in brain health. Cold Spring Harb Perspect Biol. 2024: a041422. https://doi.org/10.1101/cshperspect.a041422
[4] Araque A, Navarrete M. Glial cells in neuronal network function. Philos Trans R Soc B Biol Sci. 2010;365:2375–81. https://doi.org/10.1098/rstb.2009.0313
[5] Pardridge WM. The blood-brain barrier: Bottleneck in brain drug development. NeuroRx. 2005;2:3. https://doi.org/10.1602/neurorx.2.1.3
[6] Vieira DB, Gamarra LF. Getting into the brain: Liposome-based strategies for effective drug delivery across the blood-brain barrier. Int J Nanomedicine. 2016;11:5381–414. https://doi.org/10.2147/IJN.S117210
[7] Rathi S, Griffith JI, Zhang W, Zhang W, Oh J-H, Talele S, et al. The influence of the blood–brain barrier in the treatment of brain tumours. J Intern Med. 2022; 292:3–30. https://doi.org/10.1111/joim.13440
[8] Upton DH, Ung C, George SM, Tsoli M, Kavallaris M, Ziegler DS. Challenges and opportunities to penetrate the blood-brain barrier for brain cancer therapy. Theranostics. 2022;12:4734–52. https://doi.org/10.7150/thno.69682
[9] Mo F, Pellerino A, Soffietti R, Rudà R. Blood–brain barrier in brain tumors: Biology and clinical relevance. Int J Mol Sci. 2021;22:12654. https://doi.org/10.3390/ijms222312654
[10] Wu D, Chen Q, Chen X, Han F, Chen Z, Wang Y. The blood–brain barrier: Structure, regulation and drug delivery. Signal Transduct Target Ther. 2023;8:1–27. https://doi.org/10.1038/s41392-023-01481-w
[11] DeVita VT, Lawrence TS, Rosenberg SA. DeVita, Hellman, and Rosenberg's cancer: Principles & practice of oncology. 11th edition. Philadelphia: Wolters Kluwer; 2019.
[12] Erkkinen MG, Kim M-O, Geschwind MD. Clinical neurology and epidemiology of the major neuro degenerative diseases. Cold Spring Harb Perspect Biol. 2018;10:a033118. https://doi.org/10.1101/cshperspect.a033118
[13] Pardridge WM. Treatment of Alzheimer's disease and blood–brain barrier drug delivery. Pharmaceuticals. 2020;13:394. https://doi.org/10.3390/ph13110394
[14] Wong KH, Riaz MK, Xie Y, Zhang X, Liu Q, Chen H, et al. Review of current strategies for delivering Alzheimer's disease drugs across the blood-brain barrier. Int J Mol Sci. 2019;20:381. https://doi.org/10.3390/ijms20020381
[15] Espay AJ, Kepp KP, Herrup K. Lecanemab and Donanemab as therapies for Alzheimer's disease: An illustrated perspective on the data. eNeuro. 2024;11: ENEURO.0319-23.2024. https://doi.org/10.1523/ENEURO.0319-23.2024
[16] McConnell HL, Mishra A. Cells of the blood–brain barrier: An overview of the neurovascular unit in health and disease. In: Blood-Brain Barrier Methods Protoc., New York, NY: Springer US; 2022, p. 3–24. https://doi.org/10.1007/978-1-0716-2289-6_1

[17] Hersh AM, Alomari S, Tyler BM. Crossing the blood-brain barrier: Advances in nanoparticle technology for drug delivery in neuro-oncology. Int J Mol Sci. 2022;23:4153. https://doi.org/10.3390/ijms23084153
[18] Teleanu RI, Preda MD, Niculescu A-G, Vladâcenco O, Radu CI, Grumezescu AM, et al. Current strategies to enhance delivery of drugs across the blood–brain barrier. Pharmaceutics. 2022;14:987. https://doi.org/10.3390/pharmaceutics14050987
[19] Upadhyay RK. Transendothelial transport and its role in therapeutics. Int Sch Res Not. 2014;2014:309404. https://doi.org/10.1155/2014/309404
[20] MacVicar BA, Newman EA. Astrocyte regulation of blood flow in the brain. Cold Spring Harb Perspect Biol. 2015;7:a020388. https://doi.org/10.1101/cshperspect.a020388
[21] Gullotta GS, Costantino G, Sortino MA, Spampinato SF. Microglia and the blood–brain barrier: An external player in acute and chronic neuroinflammatory conditions. Int J Mol Sci. 2023;24:9144. https://doi.org/10.3390/ijms24119144
[22] Zhao Y, Gan L, Ren L, Lin Y, Ma C, Lin X. Factors influencing the blood-brain barrier permeability. Brain Res. 2022;1788:147937. https://doi.org/10.1016/j.brainres.2022.147937
[23] McMahon D, Poon C, Hynynen K. Evaluating the safety profile of focused ultrasound and micro bubble-mediated treatments to increase blood-brain barrier permeability. Expert Opin Drug Deliv. 2019;16:129–42. https://doi.org/10.1080/17425247.2019.1567490
[24] Cheng Y, Dai Q, Morshed RA, Fan X, Wegscheid ML, Wainwright DA, et al. Blood-brain barrier permeable gold nanoparticles: An efficient delivery platform for enhanced malignant glioma therapy and imaging. Small Weinh Bergstr Ger. 2014;10:5137–50. https://doi.org/10.1002/smll.201400654
[25] Mainprize T, Lipsman N, Huang Y, Meng Y, Bethune A, Ironside S, et al. Blood-brain barrier opening in primary brain tumors with non-invasive MR-guided focused ultrasound: A clinical safety and feasibility study. Sci Rep. 2019;9:321. https://doi.org/10.1038/s41598-018-36340-0
[26] Bors LA, Erdő F. Overcoming the blood–brain barrier. Challenges and tricks for CNS drug delivery. Sci Pharm. 2019;87:6. https://doi.org/10.3390/scipharm87010006
[27] Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuro-Oncol. 2003;5:79. https://doi.org/10.1215/S1522-8517-02-00023-6
[28] Ruggiero A, Conter V, Milani M, Biagi E, Lazzareschi I, Sparano P, et al. Intrathecal chemotherapy with antineoplastic agents in children. Paediatr Drugs. 2001;3:237–46. https://doi.org/10.2165/00128072-200103040-00001
[29] Barua NU, Gill SS, Love S. Convection-enhanced drug delivery to the brain: Therapeutic potential and neuropathological considerations. Brain Pathol. 2013;24:117. https://doi.org/10.1111/bpa.12082
[30] Patel AP, Fisher JL, Nichols E, Abd-Allah F, Abdela J, Abdelalim A, et al. Global, regional, and national burden of brain and other CNS cancer, 1990–2016: A systematic analysis for the global burden of disease study 2016. Lancet Neurol. 2019;18:376–93. https://doi.org/10.1016/S1474-4422(18)30468-X
[31] Huang Q, Chen X, Yu S, Gong G, Shu H. Research progress in brain-targeted nasal drug delivery. Front Aging Neurosci. 2024;15. https://doi.org/10.3389/fnagi.2023.1341295
[32] Trevino J, Quispe R, Khan F, Novak V. Non-invasive strategies for nose-to-brain drug delivery. J Clin Trials. 2020;10:439. https://pubmed.ncbi.nlm.nih.gov/33505777/
[33] De Rosa R, Garcia AA, Braschi C, Capsoni S, Maffei L, Berardi N, et al. Intranasal administration of nerve growth factor (NGF) rescues recognition memory deficits in AD11 anti-NGF transgenic mice. Proc Natl Acad Sci. 2005;102:3811–6. https://doi.org/10.1073/pnas.0500195102
[34] Hashizume R, Ozawa T, Gryaznov SM, Bollen AW, Lamborn KR, William H Frey II, et al. New therapeutic approach for brain tumors: Intranasal delivery of telomerase inhibitor GRN163. Neuro-Oncol. 2008;10:112. https://doi.org/10.1215/15228517-2007-052
[35] Zhong Y-X, Liao J-C, Liu X, Tian H, Deng L-R, Long L. Low intensity focused ultrasound: A new prospect for the treatment of Parkinson's disease. Ann Med. 2023;55:2251145. https://doi.org/10.1080/07853890.2023.2251145
[36] Wang J, Li Z, Pan M, Fiaz M, Hao Y, Yan Y, et al. Ultrasound-mediated blood–brain barrier opening: An effective drug delivery system for theranostics of brain diseases. Adv Drug Deliv Rev. 2022;190:114539. https://doi.org/10.1016/j.addr.2022.114539
[37] Treat LH, McDannold N, Vykhodtseva N, Zhang Y, Tam K, Hynynen K. Targeted delivery of doxorubicin to the rat brain at therapeutic levels using MRI-guided focused ultrasound. Int J Cancer. 2007;121:901–7. https://doi.org/10.1002/ijc.22732

[38] Kinoshita M, McDannold N, Jolesz FA, Hynynen K. Noninvasive localized delivery of Herceptin to the mouse brain by MRI-guided focused ultrasound-induced blood–brain barrier disruption. Proc Natl Acad Sci U S A. 2006;103:11719. https://doi.org/10.1073/pnas.0604318103

[39] Park E-J, Zhang Y-Z, Vykhodtseva N, McDannold N. Ultrasound-mediated blood-brain/blood-tumor barrier disruption improves outcomes with trastuzumab in a breast cancer brain metastasis model. J Control Release Off J Control Release Soc. 2012;163:277–84. https://doi.org/10.1016/j.jconrel.2012.09.007

[40] Jordão JF, Thévenot E, Markham-Coultes K, Scarcelli T, Weng Y-Q, Xhima K, et al. Amyloid-β plaque reduction, endogenous antibody delivery and glial activation by brain-targeted, transcranial focused ultrasound. Exp Neurol. 2013;248:16–29. https://doi.org/10.1016/j.expneurol.2013.05.008

[41] Raymond SB, Treat LH, Dewey JD, McDannold NJ, Hynynen K, Bacskai BJ. Ultrasound enhanced delivery of molecular imaging and therapeutic agents in Alzheimer's disease mouse models. PloS One. 2008;3:e2175. https://doi.org/10.1371/journal.pone.0002175

[42] Achar A, Myers R, Ghosh C. Drug delivery challenges in brain disorders across the blood–brain barrier: Novel methods and future considerations for improved therapy. Biomedicines. 2021;9:1834. https://doi.org/10.3390/biomedicines9121834

[43] Sánchez-Dengra B, González-Álvarez I, Bermejo M, González-Álvarez M. Access to the CNS: Strategies to overcome the BBB. Int J Pharm. 2023;636:122759. https://doi.org/10.1016/j.ijpharm.2023.122759

[44] Barbara R, Belletti D, Pederzoli F, Masoni M, Keller J, Ballestrazzi A, et al. Novel curcumin loaded nanoparticles engineered for blood-brain barrier crossing and able to disrupt abeta aggregates. Int J Pharm. 2017;526:413–24. https://doi.org/10.1016/j.ijpharm.2017.05.015

[45] Abdelsalam M, Ahmed M, Osaid Z, Hamoudi R, Harati R. Insights into exosome transport through the blood–brain barrier and the potential therapeutical applications in brain diseases. Pharmaceuticals. 2023;16:571. https://doi.org/10.3390/ph16040571

[46] Anthony DP, Hegde M, Shetty SS, Rafic T, Mutalik S, Rao BSS. Targeting receptor-ligand chemistry for drug delivery across blood-brain barrier in brain diseases. Life Sci. 2021;274:119326. https://doi.org/10.1016/j.lfs.2021.119326

[47] Gregori M, Orlando A, Re F, Sesana S, Nardo L, Salerno D, et al. Novel antitransferrin receptor antibodies improve the blood–brain barrier crossing efficacy of immunoliposomes. J Pharm Sci. 2016;105:276–83. https://doi.org/10.1016/j.xphs.2015.11.009

[48] Pulgar VM. Transcytosis to cross the blood brain barrier, new advancements and challenges. Front Neurosci. 2019;12. https://doi.org/10.3389/fnins.2018.01019

[49] Loureiro JA, Gomes B, Fricker G, Coelho MAN, Rocha S, Pereira MC. Cellular uptake of PLGA nanoparticles targeted with anti-amyloid and anti-transferrin receptor antibodies for Alzheimer's disease treatment. Colloids Surf B Biointerfaces. 2016;145:8–13. https://doi.org/10.1016/j.colsurfb.2016.04.041

[50] Mousavi SE, Seyedmirzaei H, Shahrokhi Nejad S, Nejadghaderi SA. Epidemiology and socioeconomic correlates of brain and central nervous system cancers in Asia in 2020 and their projection to 2040. Sci Rep. 2024;14:21936. https://doi.org/10.1038/s41598-024-73277-z

[51] Durham PG, Butnariu A, Alghorazi R, Pinton G, Krishna V, Dayton PA. Current clinical investigations of focused ultrasound blood-brain barrier disruption: A review. Neurotherapeutics. 2024;21:e00352. https://doi.org/10.1016/j.neurot.2024.e00352

[52] Nandi A, Counts N, Bröker J, Malik S, Chen S, Han R, et al. Cost of care for Alzheimer's disease and related dementias in the United States: 2016 to 2060. Npj Aging. 2024;10:1–8. https://doi.org/10.1038/s41514-024-00136-6

[53] Yang W, Hamilton JL, Kopil C, Beck JC, Tanner CM, Albin RL, et al. Current and projected future economic burden of Parkinson's disease in the U.S. Npj Park Dis. 2020;6:1–9. https://doi.org/10.1038/s41531-020-0117-1

[54] Haumann R, Videira JC, Kaspers GJL, van Vuurden DG, Hulleman E. Overview of current drug delivery methods across the blood–brain barrier for the treatment of primary brain tumors. CNS Drugs. 2020;34:1121–31. https://doi.org/10.1007/s40263-020-00766-w

[55] Treat LH, McDannold N, Zhang Y, Vykhodtseva N, Hynynen K. Improved anti-tumor effect of liposomal doxorubicin after targeted blood-brain barrier disruption by MRI-guided focused ultrasound in rat glioma. Ultrasound Med Biol. 2012;38:1716–25. https://doi.org/10.1016/j.ultrasmedbio.2012.04.015

[56] Desai N. Challenges in development of nanoparticle-based therapeutics. AAPS J. 2012;14:282–95. https://doi.org/10.1208/s12248-012-9339-4

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