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Review article

Clinical gene therapy development for the central nervous system: Candidates and challenges for AAVs

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ABSTRACT

Many diseases affecting the central nervous system (CNS) are deadly but less understood, leading to impaired mental and motor capabilities and poor patient prospects. Gene therapy is a promising therapeutic modality for correcting many genetic disorders, expanding in breadth and scope with further advances. This review summarizes the candidate CNS disorders for gene therapy, mechanisms of gene therapy, and recent clinical advances and limitations of gene therapy in CNS disorders. We highlight that improving delivery across CNS barriers, safety, monitoring techniques, and multiplexing therapies are predominant factors in advancing long-term outcomes from gene therapy.

1. Why gene therapy for CNS diseases?

Many central nervous system (CNS) disorders have genetic causes, resulting in faulty neurological function [1]. These diseases impair a wide range of mental and motor functions and diminish the quality of life. Conventional pharmaceuticals generally induce transient effects because they do not target the underlying causes of disease. In contrast, gene therapy is versatile in correcting genetic mutations and modulating host protein production to treat diseases with long-lasting or even curative effects by nucleic acid delivery [2]. Recent developments in gene-editing technologies, including DNA and RNA targeting, transcriptional control, and base and prime editing, create unprecedented opportunities for correcting genetic mutations [3,4].

One major challenge for gene therapy is delivery across the blood-brain barrier (BBB) or blood-spinal cord barrier (BSCB), physical barriers between blood vessels and CNS parenchyma that prevent most molecules from entering the brain. The BBB blocks approximately 98% of small-molecule drugs and almost all large-molecule drugs from entering the brain tissue, significantly hampering most CNS treatments [5]. BBB-crossing advances include the evolution of recombinant adeno-

Abbreviations: AADC, aromatic L-amino acid decarboxylase; AAV, adeno-associated virus; ALS, amyotrophic lateral sclerosis; APOE, apolipoprotein E; ASO, antisense oligonucleotide; ATXN2, ataxin 2; BBB, blood-brain barrier; BSCB, blood-spinal cord barrier; CDKL5, cyclin-dependent kinase-like 5; CNS, central nervous system; CRISPR, clustered regularly interspaced short palindromic repeats; CSF, cerebrospinal fluid; DRPLA, dentatorubral-pallidoluysian atrophy; FTD, frontotemporal dementia; FUS, Focused ultrasound; FXTAS, fragile X-associated tremor/ataxia syndrome; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; GAG, glycosaminoglycan; GAN, giant axonal neuropathy; GBA, glucocerebrosidase; GCH, guanosine triphosphate cyclohydrolase; GDNF, glial cell line-derived neurotrophic factor; ICis, intracisternal; I.C.V., intracerebroventricular; IPa, intraparenchymal; I.T., intrathecal (lumbar); I.V., intravenous; LacNAc, sulfated *N*-acetyllactosamine; MAO, monoamine oxidase; miRNA, microRNA; MLD, metachromatic leukodystrophy; MPS, mucopolysaccharidosis; MRgFUS, magnetic resonance imaging-guided focused ultrasound; MRI, magnetic resonance imaging; MSA, multiple system atrophy; NCL, neuronal ceroid lipofuscinosis; NGF, nerve growth factor; NTN, neurturin; PDHD, pyruvate dehydrogenase deficiency; Put, putamen; rAAV, recombinant adeno-associated virus; RNAi, RNA interference; siRNA, short-interfering RNA, small interfering RNA; SMA, spinal muscular atrophy; SMARD, spinal muscular atrophy with respiratory distress; SNc, substantia nigra pars compacta; SOD1, superoxide dismutase 1; Str, striatum; TDP-43, TAR DNA binding protein 43; TERT, telomerase reverse transcriptase; TH, tyrosine hydroxylase; Th, thalamus; VTA, ventral tegmental area; ZFN, zinc-finger nuclease.

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associated virus (rAAV) capsids that more efficiently cross the BBB, such as rAAV9 and rAAV-PHP variants [6]. These developments have prompted significant and renewed preclinical and clinical interest in developing and translating gene therapies for many challenging CNS diseases without adequate treatments or cures.

In this review, we will focus on the viability of both rare and more prevalent diseases for gene therapy and the current status of gene therapy studies in clinical trials. We highlight the need to refine tools for safe, targeted, and monitored gene delivery. This review should be a concise guide for researchers in studying the evolving landscape of gene therapy for CNS diseases. We offer a list of potential disease candidates for designing new CNS-targeted gene therapies, illustrate the current environment of CNS gene therapies both in the clinic and in human trials, and underscore significant needs in the field in general and for specific diseases.

2. Barriers and advances in molecular delivery to the brain

The major biological barriers that limit therapeutic delivery within the CNS include the endothelial BBB and BSCB. Among other properties, both barriers express important tight junction proteins such as claudin-5 and claudin-11, respectively, and their role in maintaining junctional integrity and molecular exclusivity have been intensely studied and discussed in recent reviews [7–10]. In summary, the BBB and BSCB inhibit molecular transport from the blood to the brain and spinal cord, respectively.

In the case of intrathecal injections, delivery via the CSF may occur via diffusion or glymphatic flow through perivascular spaces. However, drug accumulation in the brain may decrease due to the diffusion and dilution of CSF from the brain to the blood, and drugs within the CSF must also cross the pia mater, whose vasculature may have its own unique barrier, before reaching the brain [11]. At the same time, diffusion of drugs from the CSF to the brain is inversely proportional to the square of diffusion distance. Injecting small molecular drugs into the lateral ventricle of primates showed a logarithmic decrease of drug accumulation for each mm from the brain's surface at an initial concentration of only 1% of the CSF concentration [12]. Consequently, the drug distributed to only the ependymal surface of the brain after intraventricular injection. Other routes, such as the lumbar puncture, may also be inefficient in delivering therapeutics across barriers, despite being one of the simplest routes of drug administration [13]. In a primate study, a single intrathecal injection of either adeno-associated virus 9 (AAV9) or engineered rAAV2 hybrid led to the transduction of about 2% of brain and spinal cord cells [14].

However, the most common delivery modality is via intravenous injection. It is commonly misunderstood that breaching the BBB's endothelial barrier may provide direct access to the brain parenchyma, but in reality, drugs must breach a "tripartite barrier" containing the endothelial glycocalyx, astrocyte end-feet, and a basement membrane [15]. Each plays an essential role in maintaining molecular exclusivity: astrocytic cells form a "second-barrier" known as the glia limitans [16,17], whereas the glycocalyx maintains blood vessel integrity, comprising of proteoglycan and its linked glycosaminoglycan (GAG) chains forming restrictive mechanical and charge-based barriers [18].

Since repeated injections are not viable due to possible immune responses [19], there are significant needs for rAAV variants that can effectively cross barriers and transduce the CNS, which are being heavily investigated [20–22]. For instance, in the brain, delivery across the BBB or BSCB of anti-amyloid beta monoclonal antibodies and other gene therapy products was restricted to just 0.1%–0.2% of the plasma concentration [23,24]. Some studies have shown that the transport and transduction efficiency of AAV9, a neuron-transducing AAV, may not be efficient enough and must be administered at high doses of over 10^{14} vg/kg to transduce 20% of neurons [20,25]. Although Zolgensma is approved for Spinal Muscular Atrophy (SMA), it requires a high dosage of 1.1×10^{14} vg/kg of self-complementary AAV9 due to these deficiencies [26]. Such high doses can lead to toxicity in the liver and dorsal root ganglia [27]. Other risks include immune responses after multiple injections and permanent transgene integration into the human genome, particularly in the liver [19,28].

BBB/BSCB crossing advances include the evolution of recombinant adeno-associated virus (rAAV) capsids that more efficiently cross the BBB, such as rAAV9 or rAAV-PHP variants [6]. These developments have prompted significant and renewed preclinical and clinical interest in developing and translating gene therapies for many challenging CNS diseases without adequate treatments or cures, though with some difficulties. Therefore, intense efforts have been made to develop new delivery systems to bypass or temporarily overcome these barriers; however, most efforts focus on the blood-brain and blood-spinal cord barriers [5,29–31].

A handful of BBB modulation techniques are available for patients in the clinic. Focused Ultrasound (FUS) is a BBB-opening method that uses ultrasound waves to cause mechanical- or thermal-mediated opening on local brain tissue without surgical intervention [32]. High ultrasound frequencies combined with intravenously injected microbubbles induce cellular cavitation, which has been successful in the clinic for delivering chemotherapeutics (NCT01698437, NCT03626896, NCT05615623), delivering contrast agents, and facilitating interventions in neurodegenerative diseases such as Alzheimer's (NCT02986932), Parkinson's diseases, and ALS (NCT03347084, NCT05469009, NCT02343991) [33–35]. Hyperosmolar modulation using mannitol has also been used in clinical settings; however, it requires an arterial intervention as a mode of delivery [36]. Hyperosmolar techniques induce indiscriminate BBB opening and may cause sterile inflammation, innate immune responses, seizures [37], and systemic neurotoxicity, especially when used with chemotherapeutics such as cisplatin, bleomycin, and 5-fluorouracil [38]. Bypassing the BBB without disruption has been implemented via Trojan-horse antibodies that, when surface-linked to peptides and therapeutic-containing liposomes, allow gene and protein delivery by receptor-mediated transcytosis [29,39,40]. Such novel technologies may prove valuable in advancing efficient BBB/BSCB-modulating tools for molecular delivery.

3. CNS diseases for gene therapy

First, we provide an overview of genetic CNS diseases to define their scope and what would make them viable for gene therapy. Table 1 delineates CNS diseases with extensive research for gene therapy treatment, including the disorders, identified genetic targets, and affected CNS regions. Fig. 1 summarizes the prevalence, survival, genetic causes, and areas within the CNS affected by neurological diseases (see Table 2 for further details, resources, and references). Among these diseases, 17 out of 32 diseases are rare and monogenic (having only one genetic cause), most occur in <0.001% of the global population (Fig. 1A), and many are highly lethal (Fig. 1B). This monogenicity simplifies the design process in identifying causation and therapeutic targets. Further, if the area of pathology is highly localized, this would improve the viability of a disease for gene therapy by localized delivery.

However, CNS diseases differ in their location in the CNS, which may impact strategies for delivering therapeutics. Some disease effects are localized to specific CNS structures, while others are diffusely distributed throughout the CNS (Fig. 1C). For example, motor neuron diseases, such as amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), result from mutations in cells most often within the spinal cord, while lysosomal storage disorders like gangliosidoses impact the whole CNS. Some sites are more viable than others for therapy delivery. To deliver gene therapeutics to affected CNS regions, the field has used several routes of therapeutic administration, including intraparenchymal (direct injection into the CNS tissue), cerebrospinal fluid (into the ventricles, the cisterna magna, or the spinal canal), and intravenous methods (Fig. 1D). Preclinical studies have also explored other routes, such as intramuscular [184] and intranasal [185] methods,

Table 1
CNS disease candidates and genetic targets for gene therapy. (*Monogenic, †Each type is monogenic to the corresponding gene listed in the table. For example, CLN1 disease's sole cause is mutations in the *CLN1* gene, etc.) Note: We define primarily CNS-affecting diseases that have shown or will soon show translation to human clinical trials as candidates within the scope of this review. If the gene therapy clinical trials have been suspended or terminated (ex. Charcot-Marie Tooth disease), therapies must significantly address hurdles in non-CNS delivery, or the only data for translational gene therapy research to the clinic has not yet been publicly released (such as the case for drug development companies), we do not include such diseases within our scope of candidates.

Disease	Gene	Region in CNS	Reference
Lysosomal Storage Disorders			
Canavan disease	*ASPA**	Brain (whole)	[41]
GM1 and GM2 Gangliosidoses	*GLB1** (GM1); *HEXA** (GM2, Tay-Sachs variant), *HEXB** (GM2, Sandhoff variant), *GM2A** (GM2, AB variant)	Brain (whole), spinal cord	[42,43]
Krabbe disease (GLD)	*GALC**	White matter in brain and spinal cord	[44]
Metachromatic leukodystrophy (MLD)	*ARSA, PSAP*	Brain (whole), spinal cord	[45]
Mucolipidosis type IV	*MCOLN1**	Brain (whole), spinal cord	[46,47]
Mucopolysaccharidosis (MPS)	*IDUA** (MPS I), *IDS** (MMPS II), *SGSH** (MPS IIIA), *NAGLU** (MPS IIIB), *HGSNAT** (MPS IIIC), *GNS** (MPS IIID)	Brain (whole), spinal cord	[48]
Neuronal ceroid lipofuscinosis (NCL)	*PPT1** (NCL1), *TPP1** (NCL2), *CLN3** (NCL3), *CLN5** (NCL5), *CLN6** (NCL6), *MFSD8** (NCL7), *CLN8** (NCL8), *CTSD** (NCL10), *ATP13A2** (NCL12); non-adult-onset forms*, †	Brain (varies depending on NCL type), spinal cord	[49]
Niemann-Pick disease type C1	*NPC1**	Brain (whole), spinal cord	[50,51]
Other Metabolic Disorders			
Aromatic L-amino acid decarboxylase (AADC) deficiency	*DDC**	Brain (cerebrum, hypothalamus basal ganglia)	[52,53]
CDKL5 deficiency disorder	*CDKL5**	Brain (cerebrum, cerebellum), spinal cord (anterior horns)	[54]
Dentatorubral-pallidoluysian atrophy (DRPLA)	*ATN1**	Brain (cerebellum, brainstem, possibly cerebrum)	[55]
Pyruvate dehydrogenase deficiency (PDHD)	*PDHA1, PDHB, DLAT, DLD, PDHX, PDP1*	Brain (cerebrum, cerebellum, brainstem)	[56]
Transport Disorders			
Dravet Syndrome	*SCN1A, SCN1B, HCN1, KCN2A, GABRA1, GABRG2, STXBP1*	Brain (cerebrum, cerebellum, brainstem)	[57,58]
Menkes Disease	*ATP7A**	Brain (cerebrum, cerebellum)	[59]
Prion Disease			
Familial prion disease	*PRNP**	Brain (varies)	[60]
Transcription Factor Disorders			
FOXG1 syndrome	*FOXG1**	Brain (corpus callosum, cerebrum, white matter)	[61]
Rett syndrome	*MECP2, CDKL5, FOXG1*	Brain (whole), possibly spinal cord	[62,63]
Other Developmental Diseases			
Angelman syndrome	*UBE3A* and other unknown genes	Brain (whole), spinal cord	[64,65]
Fragile X syndrome	*FMR1**	Brain (whole), possibly spinal cord	[66,67]
Neurodegenerative Disorders			
Alexander disease	*GFAP**	Brain (cerebral white matter, medulla oblongata), spinal cord (cervical white matter)	[68]
Alzheimer's disease	*APP, PSEN1, PSEN2,* and other genes	Brain (cortex, hippocampus)	[69–72]
Amyotrophic lateral sclerosis (ALS)	*C9orf72**, *SOD1**, *TARDBP**, *FUS**, *Matr3, Kif5a, Pfn1,* and other genes (May also be multigenic)	Brain (motor neurons, brainstem), spinal cord (motor neurons)	[73,74]
Fragile X-associated tremor/ataxia syndrome (FXTAS)	*FMR1**	Brain (whole, especially cerebellum), spinal cord	[75]
Friedreich ataxia	*FXN**	Brain (cerebellum, pyramidal tracts), spinal cord	[76]
Frontotemporal dementia (FTD)	*MAPT, GRN, C9orf72, VCP, TARBP, FUS, CHMP2B,* and other genes	Brain (cerebrum, possibly cerebellum and/or brainstem), possibly spinal cord	[77–79]
Giant axonal neuropathy (GAN)	*GAN, DCAF8*	Brain (whole), spinal cord	[80,81]
Huntington's disease	*HTT**	Brain (basal ganglia)	[82]
Leigh Syndrome	*SURF1, MT-ND3, MT-ND5, PDHA-1,* and other genes	Brain (basal ganglia, brainstem, cerebral white	[83]

(*continued on next page*)

Table 1 (*continued*)

Disease	Gene	Region in CNS	Reference
		matter, thalamus, cerebellum), spinal cord	
Multiple system atrophy (MSA) (genetic variant)	*COQ2* and other genes	Brain (basal ganglia, cerebellum, brainstem), spinal cord	[84,85]
Parkinson's disease	*LRRK2*, *PARK7*, *PINK1*, *PRKN*, *SNCA*, and other genes	Brain (basal ganglia)	[86,87]
Spinal muscular atrophy (SMA)	*SMN1**	Brain (motor neurons, brainstem), spinal cord (motor neurons)	[88]
Spinocerebellar ataxia 1 (SCA1)	*ATXN1**	Brain (cerebellum, brainstem), spinal cord	[89]
Spinocerebellar ataxias 2, 23	*ATXN2** (SCA2), *PDYN** (SCA23)	Brain (cerebellum, brainstem, cerebrum), spinal cord	[90–92]
Spinocerebellar ataxias 3, 21	*ATXN3** (SCA3), *TMEM240** (SCA21)	Brain (whole), spinal cord	[93–95]
Spinocerebellar ataxias 5, 11, 14, 15, 19/22, 26, 28, 29, 31, 37, 38, 41, 43–45, 47, 48	*SPTBN2** (SCA5), *TTBK2** (SCA11), *PRKCG** (SCA14), *ITPR1** (SCA15, SCA29), *KCND3** (SCA19, also known as SCA22), *EEF2** (SCA26), *AFG3L2** (SCA28), *BEAN1*, *TK2* (SCA31), *DAB1** (SCA37), *ELOVL5** (SCA38), *TRPC3** (SCA41), *MME** (SCA43), *GRM1** (SCA44), *FAT2** (SCA45), *PUM1** (SCA47), *STUB1** (SCA48)	Brain (cerebellum)	[96–114]
Spinocerebellar ataxias 6–8, 10, 13, 17, 27	*CACNA1A** (SCA6), *ATXN7** (SCA7), *ATXN8*, *ATX8OS* (SCA8); *ATXN10** (SCA10)	Brain (cerebellum) (Possibly more)	[101,115–121]
	*KCNC3** (SCA13), *TBP** (SCA17), *FGF14** (SCA27)		
Spinocerebellar ataxias 34, 36, 40, 43	*ELOVL4** (SCA34); *NOP56** (SCA36); *CCDC88C** (SCA40) *CACNA1G** (SCA42)	Brain (cerebellum, brainstem)	[122–125]
Spinocerebellar ataxia 12 (SCA12)	*PPP2R2B**	Brain (cerebellum, cerebrum)	[126]
Spinocerebellar ataxia 18 (SCA18)	*IFRD1**	Brain (cerebellum), spinal cord	[127]
Autosomal recessive spinocerebellar ataxias 14, 24	*SPTBN2** (SCAR14), *UBA5** (SCAR24)	Brain (cerebellum)	[128,129]

though these are beyond the scope of this review. Recent FDA-approved therapies under clinical trials utilize intraparenchymal, intrathecal (into cerebrospinal fluid), and intravenous delivery routes most often, with disease localization repeatedly guiding choice of administration route.

4. Gene therapeutic mechanisms and AAV as the current primary carrier

Among the various techniques devised to correct phenotypes resulting from deficient genes, delivering replacement genes and using antisense oligonucleotides (ASOs) to target RNA are the most common approaches for CNS gene therapeutics, with RNA-interfering technology having been only recently approved for clinical use in the CNS [186]. Though RNA therapies such as ASOs are sometimes not considered gene therapy, we include them due to their instrumental roles in treating CNS diseases. In comparison, DNA delivery is often implemented due to longer-lasting effects, though RNA-mediated therapies are safer by manipulating protein production without affecting host DNA.

First, RNA-mediated technologies focus on modifying host RNA processes. ASOs are modified to prevent mRNA translation by physically blocking translation, tagging mRNA for degradation, or altering mRNA splicing [187]. These strands target and bind to complementary sequences and can initiate RNA degradation by recruiting RNase H enzymes [188]. This is useful in suppressing mutant forms of protein without permanently impacting the genome. In addition, ASOs can be modified to alter pre-mRNA splicing instead [189]. However, since this is an RNA approach, the therapy must be given repeatedly for continued effect, as ASOs eventually degrade, and therapeutic effects diminish, compared with the lasting effects of replacement gene therapy. A different RNA-modulating mechanism is via RNA interference (RNAi), in which small, double-stranded RNA molecules silence target RNA translation [190]. RNAi uses conserved Argonaute (Ago) proteins to bind to interfering RNA sequences to trigger the degradation of complementary RNA targets [191].

Most CNS-targeted gene therapies employ viral rAAV carriers to enhance cargo delivery in clinical trials. Since rAAVs are the primary carrier choice in current clinical research, we will focus on AAVs, even though the current FDA-approved RNA techniques for the CNS use non-viral or naked RNA delivery. rAAVs are the top choice for CNS gene therapy due to their low toxicity and low potential for DNA integration into the host genome, though effects from gene therapy are potentially long-lasting [192,193]. Wild-type AAVs rely on infection from other

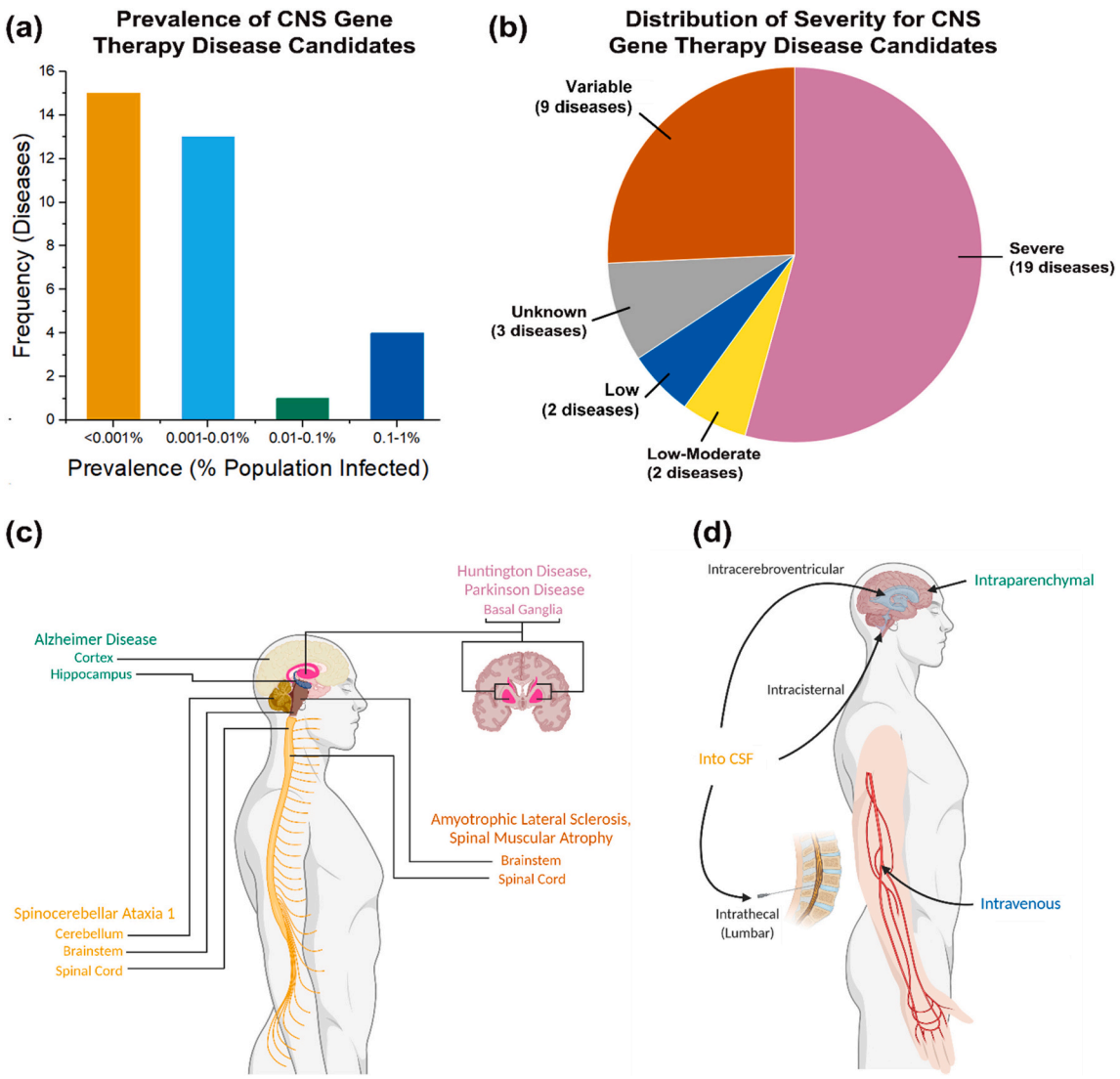

Fig. 1. Prevalence, lethality, and CNS distribution of gene therapy-viable CNS diseases as well as clinical administration routes for CNS gene therapies. (a) Prevalence of gene therapy-viable CNS diseases among the total population (Based on Table 1). $N = 33$ diseases. Canavan disease and familial prion disease were excluded because worldwide prevalence is unknown for these diseases. (b) Lethality of gene therapy-viable CNS diseases. Lethality is defined as the likelihood of death because of a particular disease, not counting the length of time until prospective death. Low lethality is defined as within 0–20% of patients with a disease having shortened lifespans due to the disease in question, low-moderate as 21–40%, moderate lethality as 41–60%, moderate-severe as 61–80%, and severe as 81–100%. Certain diseases have variable lethality due to variance in phenotypes. $N = 35$ diseases. Spinocerebellar ataxias are grouped into one category due to insufficient data in singular subtypes or autosomal recessive types. Specific prevalence of each disease, designations of lethality, and sources for this data are delineated in Table 2. (c) Anatomical regions of focus and degeneration for various CNS diseases. (d) Diagram of injection sites for different administration routes used in clinical trials: intraparenchymal, into the CSF (intracisternal, intracerebroventricular, intrathecal/lumbar), and intravenous.

viruses (primarily adenoviruses) present within a host to activate; thus, they are non-pathogenic, unlike lentiviruses or adenoviruses [194]. After infection, the viral vector is usually left as an episome (non-integrating gene) within the host nucleus to replicate by endogenous DNA replication mechanisms [192].

AAVs depend on cell membrane receptors for uptake, and different serotypes are uptaken from different receptors and cell types due to the variation in rAAV capsid configurations [195,196]. For example, rAAV9 capsids primarily bind to the galactose receptor, which functions to uptake sugars [197]. AAVrh.10 primarily binds to sulfated *N*-acetyllactosamine (LacNAc), with unknown biological role [198]. Some AAVs have both primary and secondary receptors. AAV2 has been shown to localize primarily to heparan sulfate receptors and secondarily to integrin, laminin, and fibroblast growth factor receptors [199–201]. It is unclear if AAV9, the most prominent AAV, has secondary receptors. CNS localization may be further enhanced by tailoring the capsids and transgenes for more specific targeting and expression, respectively, though transduction can be spread further due to axonal transport, especially for AAV9 [202].

Despite rAAV's significant advantages, some preclinical CNS gene therapies use non-viral carriers, which can have better in vivo stealth capabilities, are easily modified, may not trigger immune responses, and have higher gene capacity [203]. However, current non-viral carriers have made limited progress in the CNS area, presumably due to their low transfection efficiency compared to viral carriers, though further preclinical research is underway to improve transfection rates [204–206]. Alternatively, therapies may be delivered by different viruses with larger carrying capacities, such as lentiviruses, retroviruses, or adenoviruses [207]. Yet, these other viral options may induce significant immune responses or cause insertional mutagenesis after gene integration into the host genome [208].

Table 2
Classifications of prevalence and lethality of CNS diseases. Prevalence is defined as the percent of the total global population who has the disease in question. In cases when sources list a range of values for prevalence, the average is calculated for the table. Lethality is defined as the likelihood of death because of the particular disease, not counting the length of time until prospective death. Low lethality is defined as within 0–20% of patients with a disease having shortened lifespans due to the disease in question, low-moderate as 21–40%, moderate lethality as 41–60%, moderate-severe as 61–80%, and severe as 81–100%. Certain diseases have variable lethality due to variance in phenotypes. Spinocerebellar ataxias are grouped into one category due to insufficient data in singular subtypes or autosomal recessive types.

Disease	Average Prevalence (%)	Lethality	Reference
Lysosomal Storage Disorders			
Canavan disease	Unknown	Low-Moderate	[130,131]
GM1 gangliosidosis	0.0005	Variable	[42,132]
GM2 gangliosidosis	0.0007	Severe	[133]
Krabbe disease (GLD)	0.001	Variable	[134,135]
Metachromatic leukodystrophy (MLD)	<0.003	Variable	[45,136]
Mucolipidosis type IV (MLIV)	<0.001	Unknown	[46]
Mucopolysaccharidosis type I (MPS I)	0.0008	Variable	[48]
Mucopolysaccharidosis type II (MPS II)	0.0006	Severe	[48,137]
Mucopolysaccharidosis type III (MPS III)	0.0008	Severe	[48,138]
Neuronal ceroid lipofuscinosis (NCL)	0.001	Severe	[139,140]
Niemann-Pick disease type C1 (NPC1)	<0.001	Severe	[141]
Other Metabolic Disorders			
Aromatic L-amino acid decarboxylase (AADC) deficiency	<0.000002	Unknown	[53]
CDKL5 deficiency disorder	0.002	Unknown	[142]
Dentatorubral-pallidoluysian atrophy (DRPLA)	<0.00004	Severe	[143,144]
Pyruvate dehydrogenase deficiency (PDHD)	0.0001	Variable	[145–147]
Transport Disorders			
Dravet syndrome	0.003	Low-Moderate	[148,149]
Menkes disease	0.0006	Severe	[150–152]
Prion Disease			
Familial prion disease	Unknown	Severe	[60,153,154]
Transcription Factor Disorders			
FOXG1 syndrome	<0.001	Severe	[61]
Rett syndrome	0.0004	Variable	[155]
Other Developmental Diseases			
Angelman syndrome	0.006	Low	[156,157]
Fragile X syndrome	0.012	Low	[67,158]
Neurodegenerative Disorders			
Alexander disease	<0.00004	Severe	[159,160]
Alzheimer's disease (AD)	>0.381	Severe	[161,162]
Amyotrophic lateral sclerosis (ALS)	0.004	Severe	[163,164]
Fragile X-associated tremor/ataxia syndrome (FXTAS)	0.229	Severe	[165–167]
Friedreich ataxia	<0.003	Severe	[168,169]
Frontotemporal dementia (FTD)	0.231	Severe	[170]
Giant axonal neuropathy (GAN)	<0.001	Severe	[171,172]
Huntington's disease (HD)	0.003	Severe	[173,174]
Leigh syndrome	0.003	Variable	[175,176]
Multiple system atrophy (genetic variant) (MSA)	0.003	Severe	[177,178]
Parkinson's disease (PD)	0.133	Severe	[179,180]
Spinal muscular atrophy (SMA)	0.001	Variable	[181]
Spinocerebellar ataxias (SCAs)	0.002	Variable	[182,183]

5. The current status of clinical development in CNS gene therapy

In treating CNS diseases, the FDA has approved multiple gene therapies, which encompass viral delivery of replacement genes or delivery of RNA-altering agents (Table 3). With the former, the gene of interest is inserted into a vector and delivered to the target tissue to recover protein function with a more permanent, one-time treatment [209]. With the latter RNA therapies, nucleic acids modulate host RNA and protein production to affect therapeutic outcomes. Unlike DNA therapy, RNA therapy presents no risk of modifying host DNA but requires multiple injections, with antisense oligonucleotides (ASOs) ranging from every two weeks to every four months [189,210,211] and the short-interfering RNA (siRNA) given every three weeks [212]. Among currently available gene therapy treatments, RNA therapies have significant precedence in safely modulating host RNA for curative gene therapies for CNS diseases, and rAAV-delivered DNA therapies are implemented in numerous clinical trials in the field.

Currently, 24 ongoing clinical trials employ BBB-penetrating rAAV serotypes (i.e., rAAV9 and rAAVrh.10) to treat the CNS [198] (Table 4). 20 of these trials deliver into the cerebrospinal fluid (CSF) to avoid systemic exposure or due to limitations in the rAAV serotype employed (i.e., inability to cross the BBB). Based on delivery methods used in clinical trials for CNS treatments, rAAV9 is of high interest because it penetrates the BBB when administered intravenously, though intrathecal or intracisternal injections are also frequently used to reduce systemic exposure, especially to the liver (Fig. 2) [217]. Other rAAV serotypes, such as rAAV2 and rAAV8, cannot cross the BBB and have also been administered into the CSF in clinical trials (Table 4) [218,219]. For localized delivery into specific brain regions, such as the putamen or substantia nigra, intraparenchymal administration has been performed using stereotactic injections to maximize local delivery without systemic exposure. However, there are risks associated with the surgical procedure, including possible infection, hemorrhage, and imbalances in intracranial pressure [220]. Despite these risks, intraparenchymal injections are still used to achieve therapeutic effect with lower virus titers with fewer risks of off-target effects. Technologies are being optimized to improve the safety and accuracy of stereotactic injections [221].

Next, we explore the prospects of several CNS diseases (both rare and more common types) in the clinical trial pipeline, including AADC (aromatic L-amino acid decarboxylase) deficiency, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and spinal muscular atrophy. We first introduce the scope for these diseases, currently available treatments, and what these treatments lack. Then, we explain the clinical trials for gene therapy underway to treat this disease and summarize their limitations.

5.1. *AADC deficiency*

5.1.1. *The disease*

AADC (aromatic L-amino acid decarboxylase) deficiency is a rare, monogenic, and well-characterized disease. In AADC deficiency, a *DDC* gene mutation results in the expression of defective AADC enzymes. These enzymes mediate the production of the neurotransmitters dopamine and serotonin, which play critical roles in neurological development, cognition, coordination, and autonomic function [222]. Ensuing deficiencies in dopamine and serotonin swiftly result in impaired motor function, with symptoms beginning at about 3 months old [223]. Less than 150 people worldwide are affected by this disease, and no approved treatments induce significant benefits to patients [53]. However, dopamine agonists, monoamine oxidase (MAO) inhibitors, and pyridoxine derivatives may be used to alleviate disease symptoms. Dopamine agonists mimic dopaminergic effects by binding to dopamine receptors to activate the same pathways. MAO inhibitors block the MAO enzyme from breaking down dopamine and serotonin, extending the lifetime and use of these neurotransmitters [224]. Pyridoxine

Table 3
FDA-approved gene therapy for the CNS.

Treatment Mode	Name (Drug Name)	Specific Mode	Delivery Route	Target Disease	Time Approved	Reference
AAV	Luxturna (voretigene neparvovec-rzyl)	rAAV2	Intraparenchymal (retinal)	Leber congenital amaurosis	December 2017	[213]
	Zolgensma (onasemnogene abeparvovec-xioi)	rAAV9	Intravenous	Spinal muscular atrophy	May 2019	[214]
RNA	Vitravene (fomivirsen)	ASO	Intraparenchymal (retinal)	Cytomegalovirus retinitis	August 1998	[215]
	Spinraza (nusinersen)	ASO	Intrathecal	Spinal muscular atrophy	December 2016	[216]
	Milasen	ASO	Intrathecal	Batten Disease/CLN2 (only one specific mutation)	January 2018	[189]
	Onpattro (patisiran)	Lipid complex siRNA	Intravenous	Hereditary transthyretin-mediated amyloidosis	August 2018	[186]

Table 4
Current clinical trials using AAV-mediated gene therapy to treat CNS diseases. Note: I.T., I.C.V., and ICis all administer into the CSF, but in different locations. (*microRNA delivery; †ZFN delivery for gene editing.)

Disease	Method	AAV Serotype	Gene	NCT No.	Phase(s)
Alzheimer's disease	IPa	AAV2	*BDNF*	NCT05040217	I
	ICis	AAVrh.10	*APOE2*	NCT03634007	I
	I.V., I.T.	Unknown	*TERT*	NCT04133454	I
AADC deficiency	IPa (SNc, VTA)	AAV2	*DDC*	NCT02852213	I
	IPa (Put)	AAV2	*DDC*	NCT01395641	I, II
	IPa (Put)	AAV2	*DDC*	NCT02926066	II
	IPa (Put)	AAV2	*DDC*	NCT04903288	II
Canavan Disease	I.C.V.	AAV/Olig001	*ASPA*	NCT04833907	I, II
	I.V.	AAV9	*ASPA*	NCT04998396	I, II
FTD	ICis	AAV1	*GRN*	NCT04747431	I, II
	ICis	AAV9	*GRN*	NCT04408625	I, II
GM1 Gangliosidosis	I.V.	AAV9	*GLB1*	NCT03952637	I, II
	ICis	AAVrh.10	*GLB1*	NCT04273269	I, II
GM2 Gangliosidosis	IPa (Th), ICis, I.T.	AAV8	*HEXA, HEXB*	NCT04669535	I
	I.T.	AAV9	*HEXA, HEXB*	NCT04798235	I, II
GAN	I.T.	AAV9	*GAN*	NCT02362438	I
Huntington's Disease	IPa (Str)	AAV5*	*HTT*	NCT04120493	I, II
MPS	I.V.	AAV2/6†	*F9, IDS, IDUA*	NCT04628871	NA
	ICis	AAV9	*IDS*	NCT03566043	I, II
	ICis, I.C.V.	AAV9	*IDS*	NCT04571970	I, II
	ICis, I.C.V.	AAV9	*IDS*	NCT04597385	NA
	ICis	AAV9	*IDUA*	NCT03580083	I, II
	I.V.	AAV9	*NAGLU*	NCT03315182	I, II
	I.V.	AAV9	*NAGLU*	NCT04655911	NA
	I.V.	AAV9	*SGSH*	NCT02716246	I, II
	I.V.	AAV9	*SGSH*	NCT04088734	I, II
	I.V.	AAV9	*SGSH*	NCT04360265	NA
	IPa	AAVrh.10	*SGSH*	NCT03612869	II, III
MSA	IPa (Put)	AAV2	*GDNF*	NCT04680065	I
NCL	I.T.	AAV9	*MFSD8*	NCT04737460	I
	I.T.	AAV9	*CLN3*	NCT03770572	I, II
	I.T.	AAV9	*CLN6*	NCT04273243	NA
Parkinson's disease	IPa (Put)	AAV2	*GDNF*	NCT04167540	I
	IPa (Put)	AAV2	*DDC*	NCT03562494	II
	IPa (Put)	AAV2	*DDC*	NCT03733496	NA
	ICis	AAV9	*GBA1*	NCT04127578	I, II
SMA	I.T.	AAV9	*IGHMBP2*	NCT05152823	I, II
	I.V., I.T.	AAV9	*SMN*	NCT04042025	IV
	I.V.	AAV9	*SMN*	NCT03421977	NA

derivatives are precursors to supplement pyridoxal 5′-phosphate activity as a cofactor for AADC to synthesize dopamine and serotonin [53].

5.1.2. Gene therapy development

Clinical trials have demonstrated efficacy in treating AADC deficiency with DNA therapy locally injected into the brain. Three different groups studying AADC deficiency treatments have completed their studies. These groups intraparenchymally delivered rAAV2 to three segments of the brain: the putamen, substantia nigra, and/or ventral tegmental area (Fig. 3). The putamen and substantia nigra are portions of the basal ganglia that host dopaminergic neurons, whose dopamine plays significant roles in motor control [225]. The ventral tegmental area resides in the midbrain and possesses dopaminergic neurons regulating motivation, as well as GABAergic neurons to regulate sleep and inhibit dopaminergic signals [226,227]. Injection into these different sites helped in understanding the safety of these delivery routes.

rAAV2 capsids delivered the human AADC gene (*DDC*) with CMV promoter within the transgene. Chien et al. (Phase I/II, NCT01395641) (Table 4) reported the efficiency and safety of an rAAV2 therapeutic (1.81×10^{11} vector genomes per patient) delivered into the putamen of 10 children aged 1.67–8.42 years. These children experienced improved

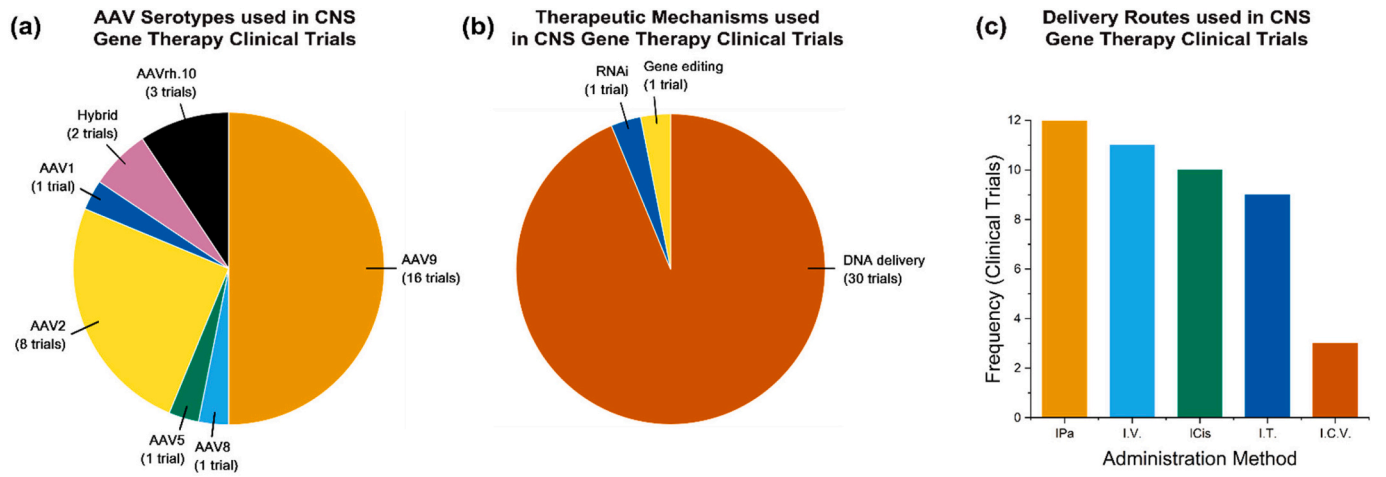

Fig. 2. Summary of gene therapies applied to treat CNS diseases under clinical trials using AAV carriers. (a) Percentage of therapies using different AAV serotypes. *N* = 32. (b) Percentage of therapies delivering corrective DNA, RNA interference molecules, or gene editing agents for therapeutic effect. N = 32. (c) Bar graph listing the frequency of certain administration routes used for CNS gene therapy clinical trials. Note: The total does not add to 32 trials because some trials use more than one administration route. Clinical trials in which a sponsor/investigator uses a particular treatment for an indicated disease are only counted once, and subsequent trials to further test the same treatment method for the same disease or disease subtype are not counted. All data was obtained from clinicaltrials.gov, clinical trial sponsors, or clinical trial contacts.

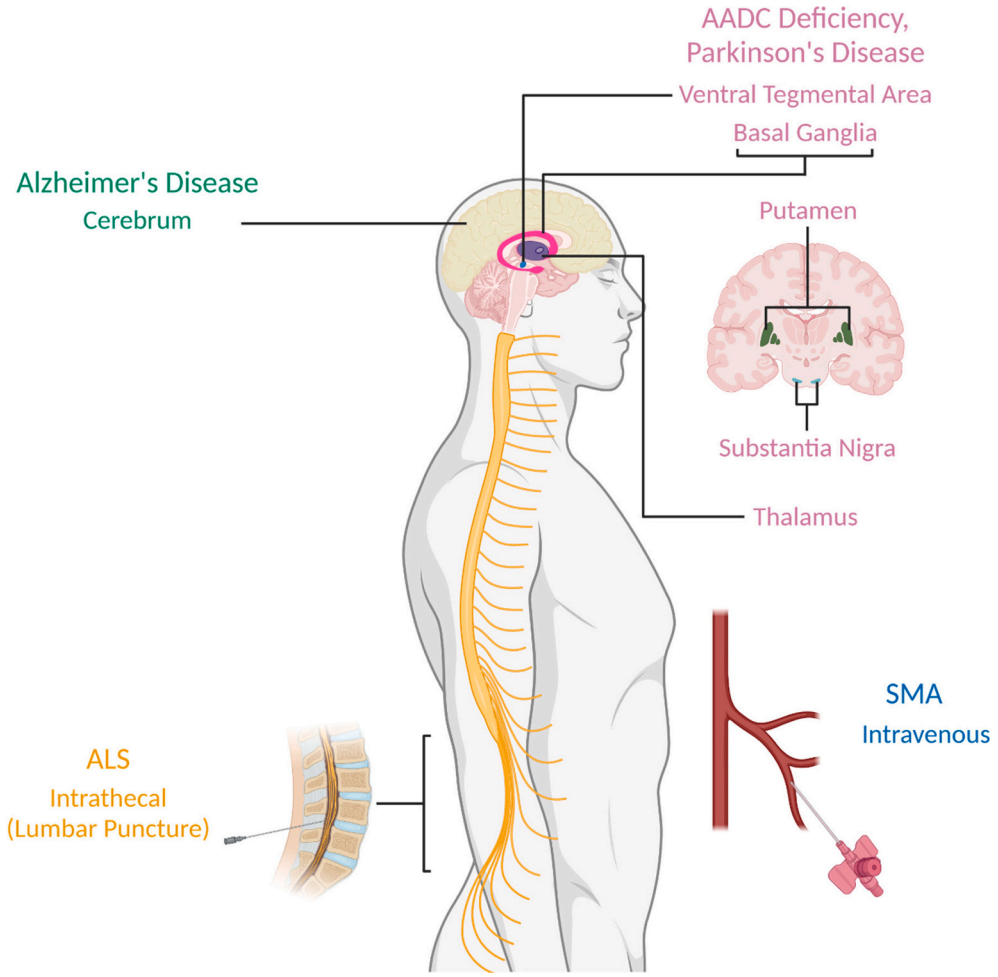

Fig. 3. Regions of therapeutic administration in clinical trials for Alzheimer's disease, AADC Deficiency, Parkinson's disease, ALS, and SMA.

motor function and increased dopamine production, particularly in the youngest patients [228]. The following Phase II trial further evaluated safety and efficacy in more patients with escalated dosage (NCT02926066) (2.37×10^{11} vector genomes per patient), which resulted in motor and cognitive improvements sustained 5 years after treatment with minimal treatment-associated complications [229].

Another Phase II trial funded by a different sponsor will follow a similar protocol while using an MR-compatible cannula (NCT04903288) (1.8×10^{11} vector genomes per patient). Another group, Kojima et al. (Phase I/II, UMIN000017802), conducted a trial to inject rAAV2-AADC (2.00×10^{11} vector genomes per patient) into the putamina of 6 patients [230]. This group was generally older (4–19 years old) and more diverse, though all showed improved motor function after treatment, with older patients experiencing slower motor recovery than younger ones. The last group, Pearson et al. (Phase I, NCT02852213), investigated the delivery of rAAV2-AADC (1.30×10^{11} vector genomes per patient) into the substantia nigra and ventral tegmental areas of the brain in 7 children aged 4.5–9 years old [231]. These patients showed varying levels of motor recovery after treatment and increased brain AADC activity. This trial demonstrated both safety and efficacy, despite possible risks in intraparenchymal injection of rAAV-AADC into the substantia nigra, including dopamine overexpression and induced stress responses [232].

These trials inject rAAV-AADC into different sites to balance safety in avoiding dopamine overexpression and motor improvement. Between these completed trials, Chien et al. specifically injected into the putamen to avoid dopamine. Kojima et al. also performed intraputaminal injections to ensure motor improvement, since motor projections from the cortex occur in the putamen [230]. Pearson et al. delivered to the substantia nigra and ventral tegmentum to rescue neurotransmitter production in multiple midbrain pathways and spread the therapeutic to other regions via anterograde axonal transport [231]. Despite the risks of dopamine overexpression in the substantia nigra, Pearson et al.'s trial still yielded safe, effective results with no severe adverse effects related to the procedure. Further, although clinical trials for intraparenchymal rAAV2-AADC demonstrated both safety and efficacy in children, future studies could develop dopaminergic neuron-targeting therapeutics that require less invasive administration, either by BBB-crossing agents or intrathecal agents.

5.2. Alzheimer's disease

5.2.1. The disease

Unlike AADC deficiency, Alzheimer's disease (AD) impacts about 33–38.5 million people worldwide [161] and is a more complex disease that is difficult to treat due to multiple, less understood disease pathways [233]. AD primarily affects older individuals and leads to progressive memory loss and cognitive impairment. Alzheimer's is characterized by neurofibrillary tangles and excessive amyloid-beta peptides, mainly in the cerebral cortex and hippocampus, causing neuronal death [234].

Mechanisms for AD pathology are not fully understood. Several hypotheses implicate the involvement of multiple proteins. For instance, excess amyloid precursor protein and amyloid beta lead to increased neurotoxicity by the formation of amyloid plaques and toxic accumulation of heavy metals [235,236]. Increased tau proteins correlate with worsened motor function due to the aggregation and formation of neurofibrillary tangles from microtubules, causing neurotoxicity by changing the cytoskeleton, axonal transport, and mitochondrial function [237]. Additionally, a lack of antioxidants in AD pathology has been hypothesized to result in reactive species, further exacerbated by dysfunctional mitochondria [238]. Further, decreasing cholinergic activity due to neurodegeneration is thought to result in cognitive dysfunction [239]. Current treatments for AD use cholinesterase inhibitors to reduce the breakdown of cholinergic neurotransmitters and reduce symptoms in mild to moderate AD [240]. Still, this treatment does not halt or reverse progression.

5.2.2. Gene therapy development

Gene therapies for AD in clinical trials target multiple proteins implicated in AD directly or indirectly. Human apolipoprotein E (APOE) is a fat-binding protein that transports cholesterol and binds to amyloid beta to facilitate its uptake and can cause neurotoxic aggregation [241]. A Phase I trial (NCT03634007) tests whether conversion of APOE4 to APOE2-APOE4 may safely alleviate AD (Table 4). In an alternative approach, a different Phase I trial (NCT04133454) used telomerase, which protects from DNA shortening and reverses detrimental age-related effects by maintaining genome integrity [242]. This Phase I trial is underway to test whether AAV-mediated *TERT* delivery to upregulate telomerase reverse transcriptase (TERT) may prevent, delay, or reverse AD pathology. Clinical trials also test the viability of nerve growth factor (NGF), which regulates neurons and ensures their survival by stimulating cholinergic function (Phases I and II) [243]. In a different trial, investigators studied the in vivo injection of rAAV2 carrying *NGF* into the cerebrum (Fig. 3) of two patients 56 and 78 years old (Phase I NCT00087789) [244] and 26 patients in a subsequent trial (Phase II NCT00876863) (2.00×10^{11} vector genomes per patient, CAG promoter) [243]. Despite tolerance toward treatment from the Phase I in vivo trial, the Phase II trial showed no treatment benefits in cognition, dementia ratings, impression of psychometric change, or improvement of daily living 24 months after treatment.

Many of these recent trials use gene delivery because most curative agents, such as NGF, cannot cross the BBB [243]. Moreover, delivering a gene encourages the production of the desired agent without requiring constant invasive re-administration. Though preclinical studies have shown promising results, recent clinical trials in gene therapy have shown no clinical benefit after translation from animal models [243,245–248]. Implementing carriers such as AAV9 (as opposed to AAV2) that improve CNS transduction by axonal transport may improve genetic delivery and increase the effectiveness of upregulated molecules [202]. Additionally, since AD is heterogeneous, a multipronged approach addressing different mechanisms of action may be necessary to treat this disease. Further, tailorable, personalized treatment may be preferable since AD genotypes differ between patients. For example, individuals with the *APOE ε4* allele are at higher risk for AD due to APOE-mediated cholinergic atrophy than those with *ε3* and *ε2* alleles [241].

5.3. Amyotrophic lateral sclerosis (ALS)

5.3.1. The disease

Amyotrophic lateral sclerosis (ALS) is another neurodegenerative disease wherein motor neurons progressively deteriorate. It affects 46,500–295,000 people around the world [249]. Efforts to treat ALS have also met difficulty due to disease multicausality. Genetics influence risks for ALS, and about 20% of familial ALS cases are caused by mutations in the *SOD1* (superoxide dismutase 1) gene, which normally destroys reactive oxygen species and protects against oxidative stress [250,251]. Yet only 10% of ALS cases are familial; therefore, SOD1 treatments would exclude 98% of individuals with ALS [250,252]. Current treatments for ALS include Rilutek (riluzole), a pharmaceutical that prolongs survival by interfering with excess glutamate causing excitotoxicity [253] but cannot reverse motor neuron degeneration, and Radicava (edaravone), an antioxidant that counteracts oxidative stress in ALS to slow disease progression.

5.3.2. Gene therapy development

There are multiple pathways to target in ALS, and current clinical efforts focus on RNA therapies with varying success. For example, a Phase I trial using ASOs is recruiting for treatment with BIIB105/ION541, by Ionis Pharmaceuticals™ (NCT04494256). This trial would measure the safety, tolerability, and pharmacokinetics of the intrathecally administered ASO targeting ataxin 2 (ATXN2) RNA, which could help treat the majority with sporadic, non-familial forms of ALS. ATXN2 regulates TDP-43 (TAR DNA binding protein 43), a protein whose mutant forms influence ALS development by forming insoluble aggregates in brain and spinal cord neurons [254]. However, direct knockdown of TDP-43 may impair its critical functions of transcriptional repression and DNA repair; thus, an alternative way to regulate its

aggregation, such as by modulating ATXN2, is preferable [255]. Other trials used RNA therapies to target SOD1 mRNA. Miller et al. conducted a Phase I/II clinical trial (NCT02623699) for the ASO drug, tofersen (20, 40, 60, or 100 mg per patient), which targets SOD1 mRNA for degradation [256]. This group gave 48 participants (mean age 48.1–51.2 years) graded doses of tofersen via intrathecal lumbar puncture (Fig. 3), noting maximal decreases in CSF SOD1 levels 85 days post-treatment with the highest dose. A different group, Mueller et al., used rAAV encoding miRNA to similarly target SOD1 mRNA (4.20×10^{14} vector genomes per patient intrathecally). They observed lower levels of SOD1 in their first patient's spinal cord compared with the control, but the second patient did not show clinical benefit, as his overall motor function worsened over time since before therapy [257].

Alternative targets for familial ALS include the *C9ORF72* (the most common locus for familial ALS), *TARDBP* (coding TDP-43 for transcriptional repression and DNA repair), and *FUS* (coding for a ribonucleoprotein involved in transcriptional activation [258]) genes [259]. *C9ORF72* regulates vesicle trafficking and lysosomal degradation, and dysfunctional C9ORF72 causes neuroinflammation, issues with clearing protein aggregates, disrupted RNA processing, and TDP-43 aggregation [260]. FUS regulates RNA metabolism and splicing, and mutant FUS can result in neurotoxicity [261]. However, the mechanisms for this dysfunction and the roles of other proteins must be further elucidated.

Despite recent clinical studies, treatments addressing sporadic ALS are needed. Targeting *ATXN2* and different pathological cascades may be vital in treating this disease, particularly since *ATXN2* is a common gene for ALS susceptibility [262]. Given that sporadic ALS has no genetic causes, regulating deficient or overexpressed molecules, such as CHMP7 overaccumulation in motor neurons for both sporadic and familial forms, may alleviate the disease [263]. Further, the true cause of ALS is unclear for most patients [249]. Therefore, robust elucidation and testing for these causal molecules and understanding their roles in the disease are paramount. Albeit beneficial, most approved treatments have shown only an extension of lifetime and not complete reversal of the disease. Moreover, one-time treatments using DNA-based therapy may have better potential for lasting therapeutic effects over current clinical approaches using RNA-based therapeutic mechanisms.

5.4. Parkinson's disease

5.4.1. The disease

Parkinson's disease (PD) also has multiple causal roots, complicating curative efforts and efforts to understand disease mechanisms; moreover, current treatments for PD can be improved to increase efficacy. PD is associated with the degeneration of dopaminergic neurons within the basal ganglia, specifically in the substantia nigra [207] (Fig. 3). About 9.4 million worldwide have PD [264], and PD's multigenic, environmental, and epigenetic factors result in different phenotypic outcomes [265]. Treatments for PD include dopamine agonists, anticholinergics, dopamine enzyme inhibitors, and the clinical standard, enzyme replacement by levodopa [266]. Dopamine agonists mimic dopaminergic action by binding to and activating dopamine receptors [267]. Anticholinergics help control tremors and compensate for the dopaminergic/cholinergic neurotransmitter imbalance in PD by blocking cholinergic receptors from firing cholinergic neurological signals [268]. Enzyme inhibitors prevent dopamine breakdown by interrupting enzyme-initiated dopamine metabolism [269]. Levodopa can alleviate motor symptoms as the precursor to dopamine but can cause side effects such as psychosis, depression, and peripheral neuropathy [270,271]. Continued levodopa use leads to swinging phases of energy and lethargy and may cause psychological dependence; reducing dosage may induce withdrawal symptoms such as muscular pain, rigidity, and fever [272,273]. Additionally, the enzyme needed to convert levodopa to dopamine, AADC, gradually dwindles as the disease progresses. Although levodopa is the most effective treatment for PD symptoms, this drug does not slow disease progression [266].

5.4.2. Gene therapy development

Three primary directions exist for PD gene therapy: protecting neurons in the substantia nigra, inhibiting the subthalamic nucleus (within the basal ganglia) by gamma-aminobutyric acid (GABA) signaling, and increasing dopamine production [207]. The first approach can be implemented by increasing the expression of neurotrophic factors such as glial cell line-derived neurotrophic factor (GDNF) and neurturin (NTN). By protecting the dopaminergic neurons in the substantia nigra, which are the most susceptible to degeneration in PD, disease progression may be delayed. The second approach hypothetically reduces brain activity that inhibits movement by modulating GABA signaling; however, the effect of changing GABA in PD is unclear, as there is conflicting evidence as to whether GABA is beneficial or detrimental in PD [274,275]. The last may be addressed by modulating the expression of tyrosine hydroxylase (TH), AADC, and guanosine triphosphate cyclohydrolase (GCH), which are instrumental in dopamine production [207]. TH plays a vital role in dopamine synthesis by catalyzing the first rate-limiting tyrosine-to-levodopa reaction step, and supplementing deficient TH in PD alleviates one of the bottlenecks in dopamine production [276]. In the next step, AADC catalyzes levodopa conversion to dopamine. Lastly, GCH converts guanosine triphosphate to tetrahydrobiopterin, a cofactor for TH and dopamine synthesis [276,277]. By modulating the production of these three molecules simultaneously, insufficient dopamine production may be more effectively reversed than by modulating one molecule alone.

So far, clinical trials test both RNA and DNA therapies directly injected into the brain and focus on safety and tolerability, though results have output limited efficacy. Ongoing clinical trials have not posted full details of experimental setups or results but currently test or recruit for an ASO-based approach to modulate LRRK2 mRNA (leucine-rich repeat kinase 2, Phase I NCT03976349); safety and efficacy of rAAV-based methods (Table 4) for GDNF, AADC, and GBA1 (glucocerebrosidase); and maximizing dopamine production (Phase I/II NCT03720418, NCT01856439). Additional completed or terminated trials include a safety and efficacy study for rAAV2-NTN (Phase I/II NCT00985517); safety and efficacy studies for rAAV2-GAD (increasing glutamic acid decarboxylase upon transduction) (Phase I NCT00195143, Phase II NCT00643890); and studies for safety and dose evaluation for maximizing dopamine production (Phase I/II NCT00627588). Among completed trials, Bartus et al. found reasonable safety and tolerability toward rAAV2-NTN (9.40×10^{11} or 24.0×10^{11} vector genomes per patient, CAG promoter) delivered into the putamen and substantia nigra (Fig. 3) of PD patients (age 42–63 years) in a preliminary trial, and the follow-up double-blinded trial reported similar results for 2-year safety [278]. Christine et al. (NCT01973543) used MRI to guide rAAV2-AADC delivery ($\leq 1.50 \times 10^{12}$ or $\leq 4.70 \times 10^{12}$ vector genomes per patient, CMV promoter) into the putamen of patients (average age 57.4–58.4 years) and found that intraparenchymal injections were well tolerated [279]. The Unified Parkinson's Disease Rating Scale and time without abnormal movement improved depending on the dosage. Regarding a different method, Neurologix ultimately terminated its clinical trials for rAAV2-GAD for financial reasons, though its first Phase I trial (1×10^{11}, 3×10^{12}, or 1×10^{12} vector genomes per patient, CAG promoter) demonstrated safety and tolerance of intrathalamic rAAV2-GAD among PD patients (53–67 years old) [280]. In another trial, Palfi et al. used a lentivirus to package genes for TH, AADC, and cyclohydrolase 1 to maximize the conversion of levodopa to dopamine in the striatum of PD patients (48–64 years) (Phase I/II NCT00627588, NCT01856439) (1.90×10^{7}, 4.00×10^{7}, or 1.00×10^{8} transducing units per patient, CMV promoter) [281]. Results showed safety and tolerance toward treatment with motor improvement in all patients, but no continued trials for the agent are underway. The group chose to improve the transgene to achieve optimal dopamine replacement and demonstrated significant improvements in motor function in a primate PD model [282]. A Phase I/II trial (NCT03720418) is ongoing for this improved lentiviral agent to assess safety and tolerability in PD

patients.

Since PD is not monogenic, ongoing work focuses on improving treatment efficacy and addressing multiple biological pathways for PD, such as by modulating TH, AADC, and cyclohydrolase 1. Clinical trials have shown safety for different gene therapy treatments: rAAV2-NTN, rAAV2-AADC, and rAAV2-GAD. Further refinement and optimization are tested to improve effectiveness, including using rAAV9 instead of rAAV2 (NCT04127578) to enhance CNS transduction or fusing transgenes to create an optimized cassette (NCT03720418) and maximize the protein production [283]. Further, specific molecular effects on disease states, such as that of GABA, need to be elucidated to verify the correlation between PD severity and molecular activity.

5.5. Spinal muscular atrophy

5.5.1. The disease

Gene therapies for spinal muscular atrophy (SMA) have met better success, though there are still gaps in the current field of treatments. In SMA, mutations in *SMN1* cause motor neurons to degenerate primarily in the spinal cord, and SMA affects approximately 80,000–160,000 people worldwide [181]. Current treatments for SMA include Spinraza (nusinersen), an ASO administered intrathecally every four months to alter *SMN2* RNA splicing and increase normal SMN (survival of motor neuron) protein [211]; Zolgensma (onasemnogene abeparvovec), a one-time replacement *SMN1* gene delivered by intravenous rAAV9 [26]; Evrysdi (risdiplam), an RNA splicing modifier taken orally every day to increase SMN production by *SMN2* [284]; and muscle relaxants.

5.5.2. Gene therapy development

Clinical trials for SMA gene therapies include long-term follow-up studies for Zolgensma (NCT04042025, NCT03421977), verification of safety and efficacy for intrathecal rAAV9-IGHMBP2 to increase helicase production (NCT05152823), and an analysis of functional effects of Spinraza (NCT04576494) (Table 4). Several trials for Zolgensma recently concluded, though no data has yet been released for many. In a Phase I trial (NCT02122952), Zolgensma was intravenously delivered in children (0.9–7.9 years old) with SMA type 1 (SMA1). Children receiving the full dose (2.00×10^{14} vector genomes per patient, CAG promoter) had comparable survival to healthy children and experienced improved motor function over the control group after 24 months [285]. In a Phase III trial (NCT03461289), a larger group of children (average age 4.1 years) with SMA1 from Italy, the United Kingdom, Belgium, and France received intravenous Zolgensma (1.10×10^{14} vector genomes per patient, CAG promoter) [286]. These children had better survival and significant motor improvement over the untreated cohort. A similar study was run in the United States (NCT03306277) (average age 3.7 years), yielding similar results (1.10×10^{14} vector genomes per patient, CAG promoter) [287]. Therefore, this method may be effective in treating SMA1.

Although the FDA has already approved several treatments for SMA, a one-time curative treatment applicable for patients of all ages is not currently available, as Zolgensma is only given to patients under two years old [26]. The clinical trial testing rAAV9-IGHMBP2 (NCT05152823) aims to treat spinal muscular atrophy with respiratory distress type 1 (SMARD1), which is caused by mutant *IGHMBP2* instead of *SMN1*; thus, the mechanism of approach is similar to Zolgensma by aiming to provide a replacement gene via rAAV delivery. Though, the treatment age range is slightly broader than Zolgensma's, as the eligible ages for this study are 2 months to 14 years old. Combinatory therapies are also being tested: Biogen is recruiting for a Phase IV trial (NCT04488133) to investigate whether Spinraza after Zolgensma therapy will further improve patient prospects. Another gap in current treatments is a lack of regenerative treatment; increased SMN protein production improves motor neuron survival but does not regenerate those that have already deteriorated, a significant obstacle in treating older patients. Because of this gap, more comprehensive newborn screening for SMA and better early diagnoses are critical to best use the optimal treatment window (younger as opposed to older) [288].

6. Concluding remarks and future perspectives

Gene therapies are transforming current treatment strategies for genetic disorders by using versatile genetic tools for precise gene manipulation. The growth and maturation of these molecular tools have revolutionized gene therapy toward promising clinical outcomes for CNS disorders. Although gene therapies have shown efficacy for rare and monogenic diseases with clear therapeutic targets, there is a significant need to address a broader percentage of affected patients with rare diseases. Furthermore, treating more common CNS diseases with less clearly characterized disease mechanisms remains challenging. We summarize four key challenges and future perspectives to advance gene therapy over the next decade. These include overcoming barriers to CNS delivery (such as the BBB); developing methods to monitor gene therapy; improving safety for gene therapy, such as by addressing immunogenicity and toxicity; and advances in gene therapy that will enhance efficacy for future treatments.

First, gene therapy for the CNS needs better delivery, such as by overcoming the BBB and BSCB, since they represent the most significant barriers to CNS therapeutics [289]. The BBB/BSCB consists of multiple components, including astrocyte end-feet, tight junctions, basal membrane, and a low density of transcytotic receptors on vascular endothelial cells, restricting the passage of both drugs and toxins in blood to brain tissue [5]. Several methods have been developed to improve carrier delivery and locally overcome the BBB or BSCB. Carrier modification may be implemented to overcome the BBB by virus capsid evolution, such as in the development of rAAV.PHP.eB from rAAV9 [290]. In designing intravenous delivery vehicles, researchers should consider the CRITID delivery cascade: circulation in systemic blood, receptor recognition to cells along the BBB or BSCB, intracellular transport, targeting the appropriate cell population, internalization, and drug release [291]. Other delivery techniques may also be exploited, such as exploring administration through the CSF, using more natural delivery vehicles such as exosomes and extracellular vesicles, or tuning release to specific organelles or brain microenvironments [292]. Alternatively, various burgeoning methods regulate the BBB/BSCB, such as MRI-guided focused ultrasound (MRgFUS) with intravenously injected microbubbles [35]. In particular, the MRgFUS procedure has been performed on human subjects with promising safety profiles. Other approaches, including the use of lasers, have been developed to locally increase BBB permeability, though these require further clinical characterization [30,293]. Additional translation and adoption would require a better understanding of the brain's response to BBB/BSCB opening and gene therapy delivery efficiency.

Second, approaches to monitoring gene therapy in clinical applications are needed. Currently, the NIH Somatic Cell Genome Editing Consortium has put forth a plan to validate gene editing by implementing new technologies to track edited cells in vivo as well as by developing new animal and human models [294]. Such improvements to experimental models will aid in improving the prospects of translation to human applications. Countless platforms have seen efficacy in animal models, only to yield no benefits to humans in clinical trials, such as the case of many efforts in treating Alzheimer's disease. Testing treatments in non-human models may result in treatments that are effective only in those models; thus, improving disease models to have closer analogs to the human disease state is instrumental in enhancing translatability. Moreover, although assays are commercially available for assessing in vitro and ex vivo transduction and in vivo host responses, research is underway to improve methods for monitoring the causes and effectiveness of gene therapies. However, there is a need to robustly track in vivo gene editing and its therapeutic benefit in the clinic.

Thirdly, safety considerations for gene therapy during therapeutic

design and characterization need to be addressed. First, the immunogenicity associated with viral gene therapy needs to be better understood, especially in humans. With 20–90% of people having preexisting antibodies against AAVs, depending on the serotype [295], this is a pressing problem, as antibodies can neutralize the virus and hamper gene therapy efficacy [296]. There is a significant need to better understand, assess, and mitigate rAAV-associated immunogenicity. Enhancing assays for neutralizing antibodies would improve assessments to better characterize host antibody responses [297]. Moreover, approaches such as carrier surface modifications are of high interest in improving therapeutic delivery to the CNS while minimizing the immune response [298]. Antibody-cleaving enzymes may also be implemented to reduce levels of neutralizing antibodies [299]. Second, toxicity must be avoided, particularly in the liver and dorsal root ganglia [27]. Adverse events from clinical trials have revealed AAV-related toxicities and carcinogenesis at high rAAV doses ($\geq 1 \times 10^{14}$ vector genomes); thus, safety must improve by increasing rAAV effectiveness at lower doses [300]. Techniques devised to overcome the BBB, such as organ- and cell-specific targeting and BBB modulation, may be instrumental in lowering the effective dose necessary for therapeutic effect and decreasing systemic exposure [301–303]. Based on the FDA's findings, improving targeting and packaging efficiency during the rAAV manufacturing process would also help enhance therapeutic effectiveness [300].

Currently, most approaches focus on one genetic origin for monogenic and rare diseases. Many of these diseases are not well characterized, so areas of dysfunctionality may be unclear for more complex disorders, such as spinocerebellar ataxia 13. On the other hand, more prevalent CNS diseases such as Alzheimer's and Parkinson's have complex and less clear genetic targets. Our analysis from Table 1 and Fig. 1 shows that these more common CNS diseases are polygenic and involve multiple disease pathways, begging further characterization for disease mechanisms. Multiple transgenes may be packaged into viruses larger than AAVs to treat complex disorders. Alternatively, CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) may cut multiple DNA or RNA targets by packaging small targeting molecules together. One primary issue with multiplexing may be packaging limitations for rAAVs [304], though preclinical research has attempted to split CRISPR single-base editors into multiple rAAV vectors, resulting in significant therapeutic gene editing with no significant increases in off-target editing [196]. These base editors were split specifically at points that allowed intein-mediated trans-splicing to reassemble the pieces into the full-length editor. Several targeting RNAs for CRISPR may also be packaged into one rAAV vector, improving prospects for multiplexing with gene editing [305]. Therefore, research addressing disease mechanisms, validated therapeutic targets, and approaches toward multiplexed genome engineering may significantly move the field forward. Further, treatment approaches should be developed to stratify patients for specific gene therapy modalities based on the disease subtype.

CRediT authorship contribution statement

Tiffany W. Leong: Conceptualization, Formal analysis, Data curation, Investigation, Visualization, Writing – original draft. **Arindam Pal:** Visualization, Writing – original draft, Writing – review & editing. **Qi Cai:** Writing – review & editing. **Zhenghong Gao:** Investigation, Writing – review & editing. **Xiaoqing Li:** Writing – review & editing. **Leonidas Bleris:** Writing – review & editing. **Heather N. Hayenga:** Investigation, Writing – review & editing. **Zhenpeng Qin:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors declare no competing interests that could have influenced the work reported in this review.

Data availability

Data will be made available on request.

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