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Gene Therapy Approaches in Neurodegenerative Diseases: An Overview

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Abstract:
Neurodegenerative diseases are a major challenge in modern neuroscience. Disorders such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and Amyotrophic Lateral Sclerosis (ALS) cause serious nerve cell damage and gradual loss of body functions. Because many of these diseases are linked to faulty genes, gene therapy has gained attention as a possible way to slow or change disease progression.
In Alzheimer's disease, gene therapy focuses on delivering genes like ApoE and BDNF to reduce harmful amyloid plaques and support nerve cell survival. Parkinson's disease studies mainly use viral vectors to deliver genes that increase dopamine production and improve movement. Huntington's disease treatment aims to silence the defective HTT gene using RNA-based methods and gene editing tools. In ALS, therapies target genes such as SOD1 and C9orf72 to protect motor neurons.
Modern tools like viral vectors, CRISPR-Cas9, and antisense therapies show strong potential. However, challenges such as safe delivery, side effects, immune reactions, and ethical issues remain. Overall, gene therapy offers hope for more personalized and effective treatments for neurodegenerative diseases.

Keywords: *Neurodegenerative diseases, Alzheimer disease, Parkinson disease, Huntington disease, ALS, Gene therapy etc.*

Introduction:

Over two decades have passed since the death of Jesse Gelsinger a relatively healthy 18 years-old volunteer for a gene therapy trial likely due to a fatal immune response triggered by adenovirus vectors. The intervening years have seen public outcry, soul searching, regulatory reforms, and even professional shunning of gene therapy researchers and advocates. Yet, work in the arena continued, including strategies to mitigate the viral vector-induced activation of immune responses that ultimately took Jesse's life.[1] Gene therapy for neurodegenerative disorders has made straightforward progress.[2] Even if scientific research has made great progress over the last decade in identifying pathogenic mechanisms and treatment strategies, neurological disorders affecting the central nervous system (CNS) are still incompletely understood. Most neurodegenerative conditions currently have no definitive cure, and available therapies are often limited in their effectiveness. Reasons are certainly multifold and include the complexity of the CNS, the limited regenerative capacity of the tissue, and the difficulty in conveying conventional drugs to the organ across the blood-brain barrier (BBB). The BBB expresses a selective permeability for molecules that possess a limited range of molecular weight and lipophilicity, preventing the entry of large-molecule drugs and of the majority of small-molecule drugs.[3]

Neurodegenerative diseases (NDDs) are a group of disorders affecting the nervous system, marked by their high prevalence and significant impact on patient health. These diseases typically lack curative treatment and have a poor prognosis, leading to progressive disability and reduced life expectancy.[4]One great mystery for most neurodegenerative diseases is the onset of clinically manifest symptoms, as pathological alterations usually occur long before symptoms start to develop. The prevalence of these largely age-dependent disorders is increasing, partly due to the aging population, which in turn places a major economic burden on health care services.[5] Although each disease has a unique biological mechanism, they all result in progressive nervous system damage. This damage commonly involves neuron loss, failure of axonal repair, breakdown of myelin, and both structural and functional defects in nerve cells. These leads to cause Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis, and amyotrophic lateral sclerosis (ALS).[6] Idiopathic Parkinson's disease (PD) impacts over one million people in the USA alone, with 1% of individuals older than 60 likely to develop PD, whereas an estimated 5.7 million Americans of all ages are living with Alzheimer's dementia.[7]

Importantly, neurodegenerative diseases manifest in an abnormal buildup of proteins in the brain/tissue, i.e.-amyloid in AD, misfolded Huntington protein in HD, aggregation of ubiquitinated proteins in amyotrophic lateral sclerosis, Tau and-amyloid accumulation in MS plaques, -synuclein accumulation in PD, and Tau neurofibrillary tangles in traumatic brain injuries. Evidence suggests that the spread of misfolded protein from cell-to-cell significantly contributes to the progression of disease.[8] Gene therapy is especially attractive because it can provide long-lasting or even permanent benefits, which is important for isolated organs such as the eye, inner ear, and central nervous system (CNS). These tissues are difficult to treat since many drugs cannot cross natural protective barriers like the blood-brain barrier, blood-retina barrier, or blood-cerebrospinal fluid barrier. In addition, gene therapy can address targets that do not respond well to conventional drugs by either suppressing harmful gene activity or increasing the expression of missing or defective genes. This approach allows direct correction or regulation of disease-causing genetic changes. With advances in genome editing and vector layout, both viral vectors including adeno-associated viruses (AAVs) and lentiviruses and non-viral systems have emerged as promising equipment for targeted transport to neural tissues. Additionally, a large number of capsids can be employed across species to favourably target multiple tissues and cells within the CNS including oligodendrocytes, astrocytes and neurons. [2, 6]

Appropriate gene therapy parameters, however, depend on disease pathogenesis and the temporal evolution of the pathological phenotype. Another important aspect is control over when and where a therapeutic gene is active. Timing determines whether gene expression is constant or regulated, while location determines if expression is limited to specific brain regions or cell types. Focal neurosurgical delivery of gene therapy vectors circumvents the blood–brain barrier and allows for therapy to be specified to anatomical regions of interest, avoiding exposure to other brain areas in which trans gene expression is not necessary or is undesired.[7]

Viral and non-viral based gene therapy:

Human and animal vectors efficaciously regulate transgenes that manifest therapeutic antibodies, small interfering RNA, and mRNA in unhealthy cells. Adeno-associated viruses (AAVs) are widely used in treating neurodegenerative disorders. They can effectively target not only astrocytes but also oligodendrocytes using different capsid types. Advances in AAV design and non-viral delivery methods have shown strong safety profiles and widespread gene expression. Recent studies have reported promising results across several neurodegenerative diseases.[9]

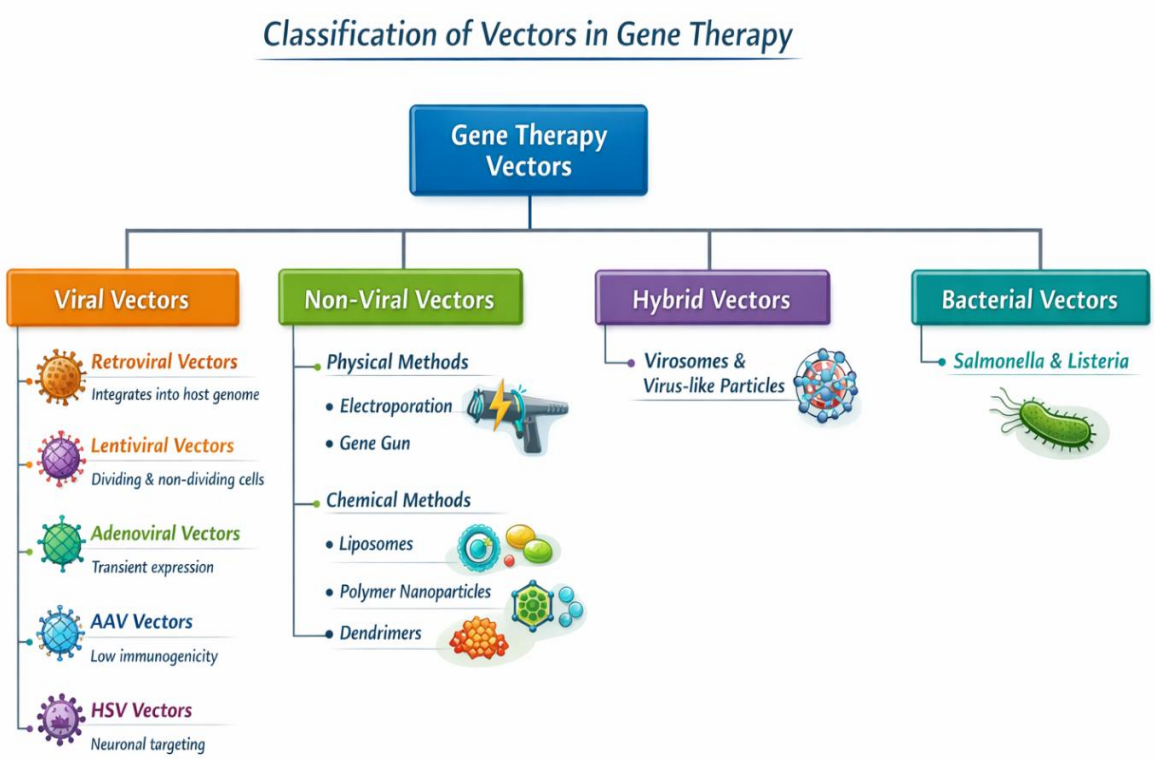

Figure 1: Classification of vectors in gene therapy

Viral gene therapy:

Independent of their origin, order, and family, viruses has evolved very fine strategies to reach and penetrate specific cellular targets. Their use in gene therapy lies in their innate ability to deliver and express genetic information into host cells.[4] Viral vectors are central to modern gene delivery because they efficiently introduce therapeutic genes into target cells. Among them, AAVs are the most broadly utilized in neurological gene therapy due to their low immunogenicity, sustained gene expression, and capability to cross the BBB. Gene therapy using viral vectors especially those based on adeno-associated viruses (AAVs) has shown promise in treating neurodegenerative diseases, particularly in clinical trials. Adeno-associated viruses (AAVs) are small, non-enveloped, single-stranded DNA viruses belonging to the Parvoviridae family. Despite their limited cargo size, they are considered highly suitable for CNS therapy due to their safety, ability to infect both dividing and non-dividing cells, and capacity for long-term gene expression. Over 150 clinical trials have successfully used AAV vectors, demonstrating good safety and meaningful clinical benefits in various genetic disorders. Their effectiveness depends largely on their serotype, which influences key factors like tissue targeting (tropism), distribution in the body, and resistance to immune system neutralization. The AAV genome contains only three genes, replication (rep), assembly (aap), and capsid (cap), necessary for viral replication, integration, and packaging. There are several AAV serotypes and their role. These are over 100 known AAV variants, including 13 main serotypes (AAV1-AAV13) derived from humans and non-human primates. Each serotype behaves differently in the body. Among them, AAV2 is one of the most studied due to its safety and long-lasting gene expression in neurons. It has been used in several clinical studies and is considered a strong candidate for treating neurodegenerative conditions. For example, AAV2 carrying the nerve growth factor (NGF) gene has shown therapeutic benefits when injected directly into the brain for Alzheimer's-related dementia.

Different AAV serotypes have unique properties:

-AAV4 targets ependymal cells lining the brain's ventricles, making it useful for therapies involving the cerebrospinal fluid.

-AAV9 and AAVrh10 can cross the blood-brain barrier (BBB), a major hurdle in delivering therapies to the central nervous system (CNS).

-AAV-PHP.B, a newly engineered capsid, can deliver genes to over 50% of neurons and astrocytes after intravenous injection, showing the power of capsid design in improving delivery efficiency.

In contrast, adenoviruses (Advs) are larger viruses (70-100 nm) that do not integrate their genes into the host genome. While they offer short-term gene expression and a good safety profile, their strong immune response limits their use in CNS therapies. Some studies have explored Advs for neurodegenerative diseases, but results are limited and show only mild side effects.

Retroviruses and lentiviruses (LVs), on the other hand, integrate their genetic material into the host genome, allowing for long-term gene expression. However, this raises concerns about potential genetic damage, so their use must be carefully controlled. One notable clinical trial used an LV-based therapy called ProSavin to treat advanced Parkinson's disease (PD). It aimed to restore dopamine production and improve motor function, showing safety and potential benefits in all treated patients. Lentiviral vector, derived from human immunodeficiency virus, offer the gain of stable integration into the host genome, making them appropriate for long-term expression in dividing and non-dividing cells.

However, worries regarding insertional mutagenesis and oncogenicity require caution vector engineering and safety checks. [3, 6, 9]

Non-viral gene therapy:

Viral vectors have traditionally been central to gene delivery strategies, but their use is constrained by issues such as immune activation, limited genetic cargo capacity, and difficulties in scalable production. These drawbacks have led to an increased focus on non-viral delivery systems, particularly for neurological applications, due to their improved safety profile and adaptability. Lipid nanoparticles (LNPs) are at the forefront of this research, offering advantages in biocompatibility, ease of modification, and the ability to carry various nucleic acids including mRNA, Siena, and plasmid DNA. Their successful use in mRNA COVID-19 vaccines has accelerated interest in applying LNPs to brain-targeted therapies, where functionalization with targeting ligands or peptides capable of crossing the blood–brain barrier (BBB) can significantly improve delivery efficiency. Similarly, polymer-based carriers such as Possible spelling mistake found. (PEI) and poly (lactic-co-glycolic acid) (LPGA) enable high gene loading and controlled release, although cytotoxicity especially with higher molecular weights remains a limiting factor. Dendrites, with their highly branched and tunable surface chemistries, show promise in targeting neural tissues while minimizing systemic toxicity. Another emerging platform involves twosomes, which are endogenous extracellular vesicles that naturally traverse the BBB and provoke minimal immune responses. Genetically or chemically engineered twosomes are being studied as potential carriers for therapeutic RNA's and proteins, supporting the development of cell-free, personalized approaches to neurodegenerative diseases. Despite these advances, the efficiency of non-viral vectors remains challenged by biological barriers: extracellular degradation of nucleic acids in circulation and intracellular entrapment in endosome compartments before nuclear access. Various strategies have been employed to address these challenges, including regulation to enhance systemic stability, and possible spelling mistake found. materials that respond to intracellular conditions such as low pH or reductive environments to trigger targeted release. Linkers like pH-sensitive acetyl bonds and cytosol-reducible disulfide bridges have also shown promise in enhancing nuclear delivery. Continued optimization of these non-viral platforms is essential for realizing their full therapeutic potential in treating neurological disorders.[3, 6]

Alzheimer's disease:

Alzheimer's disease (AD) is the major cause of age-related dementia, which affects more than 40% of people over the age of 85 year.[5] The accumulation of β-amyloid plaques and neuronal loss in the brain are two of the distinct pathological features of this neurodegenerative disease. Tau tangles and amyloid deposits. The primary symptom of AD is progressive cognitive decline, which is often accompanied by memory loss is the first sign. The patient's personality and conduct progressively change as the illness gets worse, and in the later stages, they may undergo more significant changes. Throughout the duration of the sickness, they require a great deal of assistance from loved ones and caregivers. The stages of the illness have been illuminated by recent advancements in gene therapy, as well as molecules like NGF, MAPT, APP, TREM2, TRIM11, and ApoE, which have little experimental treatment for AD. They could be promising therapeutic targets due to their important role in the beginning and progression of AD.[10]

Over the past twenty years, there has been a focus on the function of these molecules in the causes of the illness. For many years, the amyloid cascade hypothesis has been the focus of research into the pathogenesis of AD. However, the finding of modifications to three autosomal dominant genes: APP on chromosome 21, PSEN1 on chromosome 14, and PSEN2 on chromosome has dramatically changed the study paradigm. Later genome-wide association research GWAS has identified additional SNP locations linked to AD as well as the risk gene for ApoE4. These genes find proteins that play a role in the various biological mechanisms of AD that might be targets for future modification. Recent GWAS has led to the discovery of scores of risk sites, such as ApoE, for which there is strong evidence of functionality. TREM2, SORL1, ADAM10, SPI1, CR1, BIN1, and ABCA7. The ApoE4 isoform, in particular, has been extensively studied in unique disease model. A recent study found that the biological form of the Klotho hormone reduces the likelihood of developing AD in those who have ApoE4. Furthermore, a heterozygous KL-VS (KL VSHET+) genotype status was suggested. lower load of A protein and AD are linked to the Klotho variant known as KL-VS. Patients' cognitive decline was observed in a different clinical experiment. The potential function of ApoE4 in AD was examined in greater detail measure from several perspectives. The connection between REST, a crucial regulator of neural differentiation, and the ApoE4 genotype considers the energy metabolism breakdown in Alzheimer's patients. In addition to the phenotype it causes may have a regulatory function over metabolism. These metabolic changes have also been linked to gender inequalities. A benefit is that there is only one nucleotide difference between ApoE4 and its allele ApoE3. Therefore, induction is feasible it changes in individual nucleotides, particularly with the PE method. TREM2, the activating receptor found on myeloid cells, is Alzheimer's and Parkinson's diseases share a shared genetic site. Mice lacking TREM2 exhibit elevated neurodegeneration, which may be caused by it. It can be related to microglial activation. We developed a single-App knock-in model mouse that expressed a humanized Aβ in a recent experiment. In addition, the native murine App gene contains two or three clinically pathogenic mutations. The mechanism behind these is described below. Surprisingly, we found that mice with an App knock-in that had the 3′-UTR and the last two introns (intron 16, 17) eliminated did not show Aβ. Substantial drop in APP expression at both the transcriptional and translational level, leading to deposition or negative effects at any age translational levels. We were able to conclude from the data that modifications in these regions of the App gene affect Aβ deposition by changing the APP gene is expressed in Alzheimer's disease. GWAS has identified additional risk loci in addition to those that have been extensively researched. Several studies have included peripheral tissues (like skin tissue) to continue to demonstrate in cellular/animal models analysis. It remains, though, to establish the pathogenic importance of these novel genes in Alzheimer's disease.[11]

Parkinson's disease:

Parkinson's disease (PD), a prevalent neurodegenerative illness, affects more than 4.5 million people in the United States who are over 50 years. The number will have doubled by 2030. The incidence rate among those over 65 is between 1% and 2% by means of PD. Over the past fifteen years, genetic studies have transformed our understanding and categorization of neurodegenerative illnesses as well as other conditions like PD. Some of the 16 distinct PARK locations are now located on autosomal dominant genes, such as SNCA. The majority of autosomal recessive genes, including PRKN, DJ-1, and PINK1, are only discovered in isolated cases. PD is the most common term for the alpha synuclein Lewy body (LB) pathology that affects individuals who have mutations in the SNCA, LRRK2, and GBA genes. There are various kinds of PD. Nonetheless, tau or TDP-43 pathology can also be seen in certain instances of PD associated with mutations in the LRRK2 gene (G2019S, R1441C). Furthermore, the susceptibility of some of these genes varies, as seen by the variations in the LRRK2 G2385R and R1628P variants. Several ethnic groups have linked the SNCA and GBA genes to significant risk factors for Parkinson's disease (PD).[12]

Although Parkinson's disease is common, there are few known genetic risk factors. The primary symptoms of Parkinson's disease (PD) are tremors, hypokinesia, and stiffness, which are mostly brought on by the death of motor neurons in the brainstem. Dopaminergic cells make up the pars compacta of the substantia nigra (SN), which causes an imbalance between excitation and inhibition. The existing treatments, such as nigrostriatal projection pathways 82, only target symptoms and have many undesirable adverse effects. The course of the illness is unaffected. Gene therapy has long been viewed as a possible way to treat the localized aspect of SN pathology in PD. Therapy that uses a range of strategies to address neurotransmitter imbalances, neuronal survival, or genes exclusively related to the condition. Gene therapy with AAV has been utilized to increase dopaminergic signals in PD. The rate-limiting enzymes that control the dopamine production pathway, tyrosine, and GTP cyclohydrolase1 (GCH1) are the three. The last step of the enzymatic mechanism is the decarboxylation of aromatic amino acids by the aromatic amino acid decarboxylase (AADC) and hydroxylase (TH). The synthesis of dopamine. The safety and consistent expression of AAV2-AADC ithas been demonstrated in clinical trials for up to four years. The symptoms improved somewhat. In NHPs, targeted AAV2-AADC distribution was employed in conjunction with real-time MRI guidance acceptable and secure. In the gene therapy known as ProSavin, lentiviruses are used to deliver all three rate-limiting enzymes (TH, DDC, and AADC). Phase 1/2 trials demonstrated that the AADC and GCH1 were well tolerated, but follow-up studies revealed only modest improvements in motor function. The expression of synuclein is directly correlated with the SNCA gene, which is also one of the most significant predictors of behaviour a rare kind of Parkinson's illness (PD).[11] It includes those over 65 and is expected to increase dramatically in the next years genetic early. The identification of several PARK loci, including autosomal dominant ones, has altered the categorization of PD in research. The SNCA gene, which codes for alpha-synuclein, is just as important as other genes like LRRK2 that have mutations were the first to be associated with familial PD, particularly with the genomic and point mutations at the A53T, A30P, and E46K loci duplication and triplication events. [12]

The essential role of alpha-synuclein in the progression of the disease. Both spontaneous and acquired PD share the same pathological characteristics. The protein is implicated in the production of Lewy bodies, which are defined by aggregates of misfolded alpha-synuclein is a significant factor in neurodegeneration. Recent studies have advanced our knowledge of the presynaptic activity of alpha-synuclein evaluating its function in nuclear occurrences and transfer mechanisms. The architecture of the nuclear envelope shifts, the nuclear circularity gets better, and the expression or mutation of SNCA increases. Their finding that alpha-synuclein influences a cell's susceptibility to stress. The primary regulator of nucleocytoplasmic transport is the Ras-related nuclear protein (RAN), which binds and sequesters RAN in its mutant forms. As a result, its capacity to move essential nuclear proteins, such as DNMT3A, is reduced, which leads to fewer nuclei. The reduced overall DNA methylation and the position of DNMT3A point to the unique epigenetic process at work.[13] These results support the growing body of evidence pointing to a potential link between nucleocytoplasmic transport disruptions and the development of Parkinson's disease. Tauopathies, Huntington's disease, and ALS/FTD are a few examples of neurodegenerative illnesses that share a similar root cause. Protein mis-localization and nuclear envelope defects are shown by protein localization and nuclear homeostasis. Our knowledge of PD is now cantered on epigenetic regulation. Further research has yielded additional information. Additional evidence of stress response and intracellular signaling pathways may be found in the autosomal dominant genes VPS35 and EIF4G1as the traffic problem worsens. According to the literature, the pathophysiology of Parkinson's disease may be influenced by synaptic trafficking and other variables. Nuclear dysregulation, which provides innovative therapeutic approaches for addressing nucleocytoplasmic transport and dysfunction. Protein transport and epigenetic repair mechanisms mediated by RAN.[12]

Amyotrophic lateral sclerosis:

Lou Gehrig's disease, also known as amyotrophic lateral sclerosis (ALS), is a progressive neurological illness marked by the progressive death of nerve cells in the brain and spinal cord. The most prevalent adult onset of ALS occurs when nerve cells gradually die. The upper and lower motor neurons in the brain and spinal cord are affected by this motor neuron illness, but not by anything else. Neuroanatomical regions can also be impacted. The nerve cells that control movement, known as motor neurons, are destroyed by ALS. Voluntary muscular contractions. The brain loses its capacity to start and control muscular activity as the motor neurons die reduces. Symptoms like hyperreflexia and spasticity are caused by the degeneration of the upper motor neurons, whereas the loss of Progressive muscle weakness, cramps, fasciculations, muscle wasting, and paralysis are all symptoms of lower motor neuron dysfunction with genetic

and environmental variables both likely contributing to its etiology, ALS is still not well understood pathogenesis. Muscle atrophy, muscle weakness, and speech and swallowing problems are common symptoms of this illness and respiratory difficulties. It can be divided into two groups: familial ALS and sporadic ALS. The diagnosis of since there is no diagnostic test for ALS, its diagnosis is mostly based on clinical symptoms and the methodical elimination of other conditions. Electromyography (EMG) and nerve conduction studies are commonly used to assess this condition. The efficiency of muscles and motor neurons the progression of may be slowed down by riluzol, a medication that has been approved by the FDA by lessening the damage done to motor neurons. Edaravone, a supportive drug approved by the FDA, is prescribed for the management of ALS and may slow the slow decline of physical capabilities. An ND called ALS causes a continuous and progressive weakening of the muscles in the arms, legs, and respiratory system. At present, no established cure exists for this disease. Although there are obvious reasons for ALS, 3% of patients suffer from a hereditary form (FALS) that is phenotypically similar to the sporadic disease. A mutation in SOD1 that causes an overabundance of harmful oxygen radicals leads to FALS, and there are also notable elevated amounts of plasma glutamate in those with ALS. Gene therapy for ALS, based on the genotypes and phenotypes, employs micro RNA against superoxide dismutase 1 (SOD1) to cause the breakdown of its mRNA and a glutamate transporter gene (excitatory amino acid) acid transporter 2 [EAAT2]), which eliminates extra glutamates in microenvironments.[14]
10% of ALS cases are familial, and the causative genetic alterations are generally inherited in a Mendelian autosomal dominant fashion. As a result, the majority of ALS cases are the main causes of ALS are still unknown, and cases are believed to happen randomly. Similar to many other NDDs, ALS is presently incurable. The primary disease-causing genes in ALS are C9orf72, SOD1, FUS, TARDBP, and TBK1. Due to the majority of cases of ALS being sporadic, there is not a significant genetic component several cell and animal models. The CRISPR system, which is mediated by the adeno-associated virus (AAV), has been used to target SOD1 for disruption. SOD1, which results in lower amounts of SOD1 protein in the spinal cord and less muscular atrophy in mice. The average lifespan of mice increased by 28-30 days as a result of improved motor function. In addition to other animal studies, SOD1 deletion was also noted. Approximately 10-20% of fALS patients and 1-2% of sALS patients have mutations in SOD1. The majority of SOD1 mutations change the structure of the protein, resulting in an increase in neurotoxicity ASO injection. A transgenic rat model harboring mutant human SOD1 showed reduced SOD1 levels and increased lifespan when SOD1 was introduced into the CSF. Intrathecal delivery of ASO-SOD1 was well tolerated in fALS patients with SOD1 during a Phase 1 clinical trial. A follow-up Phase 1/2 experiment revealed that the CSF SOD1 protein content decreases in response to ASO-SOD1 therapy, and a Phase 3 trial demonstrated that the CSF SOD1 protein level is reduced by ASO-SOD1 treatment. Additionally, RNAi and CRISPRs have been used to inactivate the aberrant SOD1. IV administration of AAV9 in a transgenic SOD1 mouse, SOD1 shRNA lowered SOD1 levels, slowed disease progression, and increased lifespan. Disrupting SOD1 expression using CRISPR further enhanced motor function and extended the lifespan of mutant SOD1 mice. In a recent proof-of-concept experiment, miRNAs targeting SOD1 were administered intrathecally in two SOD1-ALS mice using AAVs. Post-mortem examination of one patient revealed suppression of SOD1 in the spinal cord, proving that it is possible to do so. A newly discovered pathogenic factor is the hexanucleotide repeat of G4C2 in C9orf72. The pathway through which it causes disease is unknown intricate. The researchers discovered that deleting C9orf72 exacerbated the axonal flaws, which led to higher cell apoptosis. Although recent research indicates that the CRISPR/Cas system can completely remedy this pathogenic increase in expression. Additionally, it has been reported that C9orf72 has an impact on the effectiveness of the gene editing procedure and DSB repair. The pathogenic impact may be achieved by influencing the mitochondrial Ca2+ absorption deficit and GluA Q/R site RNA editing. Additionally, it has been reported that KIF5A is linked to the cytoskeletal abnormalities seen in ALS. Nevertheless, more thorough research is needed. The potential gene therapy for ALS may involve changes in the presently inadequate GWAS-identified sites.[11] mRNA processing (up frameshift protein 1 [UPF1] and adenosine deaminase acting on RNA 2 [ADAR2]) as well as blocking of neuronal cell death (vascular endothelial growth factor [VEGF], IFG1, GDNF, BDNF, hepatocyte growth factor [HGF]) peroxiredoxin 3, astrocyte elevated gene 1 [AEG-1], regulator of calcineurin 1 [Rcan1], colony-stimulating factor 3 [CSF3][PRDX3], and nuclear factor [erythroid-derived 2]-like 2 [NFE2L2]. In particular, the clinical trials for ALS, which apply stem cells that express BDNF or GDNF. [14]

Huntington's disease:
Huntington's disease (HD) is a progressive and inherited neurological ailment that impacts both the mind and the body. An individual's characteristics, with an average age of onset of 40. HD is a heritable triad duplication complaint of the CNS, in which the condition results from an inherited mutation in the huntingtin gene (HTT), which causes the improper repetition of particular gene sequences. The production of an erroneous version of the huntingtin protein. The mutant huntingtin protein (mHtt) is harmful and gradually kills cells, harming neurons in the brain. Furthermore, this mutation causes certain areas of the brain to degenerate, resulting in a vibrant performance physical, mental, and psychological issues.[14,15] It's a unique ailment that affects 5-10 persons out of every 100,000 the Caucasian community. Only five of the cases involved juvenile forms, which are rare. Although there are differences between individuals, a combination of motor, cognitive, and psychological symptoms typically defines them. Motor symptoms may be broken down into the choreiform motions and gait abnormalities that typically manifest earlier in the course of the illness and motor impairments resembling bradykinesia and severity that are seen in post-stage patients. Cognitive problems may be detected up to ten years before public opinion, with the flaws becoming more evident as the complaint progresses. Cognitive problems are one of the deficiencies is retardation and a decline in both focus and inner harshness. Additionally, there may be emotional deficits or psychiatric symptoms. HD cases are consistently depressed and display symptoms of apathy, perversity, impulsivity, and other characteristics, as noted in advance social disinhibition. The

neuropathology of HD is distinguished by the malfunction and death of particular neurons in the brain. Specifically, the neurons of the striatum are the most prone to die.[16]

Health care professionals such as neurologists, psychiatrists, physical and occupational therapists, and inheritable counsellors are always there testing for HD that is inheritable may provide insight into the complex circumstances of those who have the illness. The individualities suggest that inheritable testing should be advised to assess the existing's vulnerability to contracting or spreading the illness. Gain a deeper understanding of the potential effects by conducting further research experiments to obtain inheritable assurance. A greater understanding of the elementary processes of HD is sought, as well as practical rehabilitation strategies or solutions. Additionally, improving understanding is crucial for helping those who have been affected as well as their families; and encouraging research and development access to services. HD poses major difficulties for both the complainant and their relatives inheritable timely and reassuring advice, along with thorough therapy, are essential fundamentals in running HD and treating its diverse effects on human life.[15]

The mutation that causes HD is an aberrant increase in a CAG duplication in the brain. The HTT gene, which codes for huntingtin (HTT), a massive protein consisting of 3,144 amino acids. The CAG duplication in HTT canons for apolymorphic polyglutamine (polyQ) stretch. In the non-HD population, the CAG sequence is repeated between 9 and 35 times, with an average standard of between 17 and 20 renewals. An HD outcome is achieved with a CAG expansion of more than 35 reprises. There are very few carriers that have between 36 and 40 renewals. The 39 CAG renewals have a reduced penetration and occur later in the course of the complaint than those with 40 or more CAG reprises. The age at which the ailment first appears is as comparable to the length of the CAG expansion as juvenile onset is related. HTT brings approximately 75 or more reprises. HD is autosomal dominant. Homozygous instances, though uncommon, exhibit the same symptoms, age at onset as heterozygotes, but the course of the condition may be more severe. An aberrant polyQ expansion has been established to be including a number of spinocerebellar ataxias, it is the cause of eight additional neurodegenerative disorders. The loss of particular neurons is associated with a change in a different protein under conditions that are characterized by little overlap between the brain areas impacted by these vibrant disorders.[16]

Gene therapy for various neurodegenerative diseases:

a) Gene therapy for Alzheimer's disease:

One of the frequent types of progressive neurodegenerative illness, announcement complaint is marked by neuroinflammation. Neurodegeneration that causes madness and a low quality of life.[17] The actuality of amyloid- beta peptide and the individual criteria for announcement are neurofibrillary befuddlements (NFT), which are defined by phospho- tau protein.[18] Besides this, NFTs are distinguished by the presence of phospho- tau protein. The functions of tau proteins, amyloid beta (Aβ) peptides, NFTs, astrogliosis, microglia activation, and changes in brain structure and function are all significant. Neurotransmitters are a confounding factor in the etiology of Alzheimer's complaint.[19] Gene remedy has demonstrated encouraging results in the treatment of the condition. Operation and treatment of the prognostic and side goods of announcement. The cause has been linked to whim-whams growth factor (NGF), for the conflation of choline acetyl transferase, which is essential to the product of acetylcholine that sustains the condition of literacy and memory.[20] In announcement exertion of NGF is down regulated, hence gene transfer with the help of the functionality of NGF is frequently restored by retroviruses, which also save functional homeostasis.[21] Other than that, in addition to the retrovirus, AVV was also employed to bring the down regulated NGF back over.[22,23] Neprilysin (NEP), a neutral endopeptidase, is set up. The NEP enzyme, which occurs naturally in the healthy brain, breaks down the abnormally produced Aβ peptides.[24] The quantum of NEP enzyme decreases during announcement. Because the position is down regulated, lentivirus with the neprilysin protagonist gene has been used to increase it displayed notable neuroprotection.[25] In announcement, a lack of the NGF peptide has been proved; as a result, the administration of using AAV to deliver the gene for this growth factor greatly reduced the cognitive and learning impairments.[26] The gene silencing fashion, in which RNAi was used to target the CDK5 gene, redounded in advance in the remedy of announcement. This gene promotes tau phosphorylation by producing kinase enzymes, therefore silencing it to protein.[27, 28] As a result, by lowering tau, gene remedy has demonstrated significant neuroprotection and neurorestoration in announcement through protein phosphorylation and by enhancing spatial memory and literacy.

b) Gene therapy in Parkinson's disease:

The substantia nigra (SN) region is where the dopaminergic neuron in PD degenerates, which is a neurodegenerative illness.[29] Causes dementia, cognitive impairment, and locomotor dysfunction, when pharmacotherapy was used to improve. It boosted the dopamine level in the mesolimbic region but not in the nigrostriatal region, which is why it showed up as aberrant impulse control.[30] In addition, it was discovered that a number of enzymes and co-factors essential for genetic anomalies prevented the production of dopamine.[31] As a result, gene therapy was employed to address this by employing the equine infectious anaemia virus as a vector for this issue.[32] The genes in charge of improving the manufacture of tyrosine hydroxylase, aromatic amino acid decarboxylase, and GTP cyclohydrolase1. The nigrostriatal area markedly reduced the functional deficit and re-established normal dopaminergic activity production.[33,34] The conclusion of this study prompted the start of clinical trials in phases I and II.[35] In the pharmacotherapeutic technique, which involves using GABA agonists, has demonstrated encouraging results in controlling the PD by controlling the synaptic activity. However, this method employs standard injection into the thalamic area, which is very painful and has demonstrated poor patient compliance.[36] Additionally, it was discovered that the enzyme glutamate decarboxylase (GAD) is responsible for the synthesis of glutamate-derived GABA.[37] In PD,

the patient has a deficiency of GAD; hence gene therapy is used to de liver the AAV2.A vector carrying the GAD gene. The study's findings also resulted in the start of a phase II clinical trial, during which the discovery was made. More than 36% of patients experienced improvement.[38] However, these two gene therapy approaches enhanced the quality of patient lives. Although they had no discernible impact on the rehabilitation of dopaminergic neuronal loss, they did have an impact on the lives of patients. Considering the prior study's restriction was that the NTRN gene was delivered by gene therapy using an AAV2 vector, which is responsible for producing neurturin. Neurturin is a neuroprotective substance that shields the dopaminergic neuron from degeneration in PD and aims to prevent neurodegeneration and neuro-restoration in PD. The study's findings resulted in the following: The start of the phase II study, and perhaps in the future, NTRN may represent a step forward in the therapy of neurological illnesses.

Gene therapy in Amyotrophic lateral sclerosis:

The loss of motor neurons is a hallmark of the fatal motor neuron degenerative condition known as amyotrophic lateral sclerosis (ALS). The progressive atrophy of the muscles of the limbs, trunk, chest, and abdomen, resulting in muscle weakness, is its typical hallmark. Within three to five years after the onset of symptoms, weakness, stiffness, and eventually death due to respiratory failure.[39] The gene responsible is now being studied. The main targets of ALS treatment are the SOD1 mutations, the C9orf72 hexanucleotide repeat extensions, and the ATXN2 trinucleotide sporadic illness with unknown genetic component, FUS mutations, and expansions. Recent clinical breakthroughs have highlighted particular delivery methods for gene regulation, such as CRISPR, RNAi, and ASOs. These strategies specifically highlight the altered SOD1 and C9orf72 genes.[40, 41] Mutations in superoxide have been discovered to cause, about 10 to 20 percent of instances of familial inherited ALS are caused by dismutase (SOD1).[42] Later research validates these results.[43] Changes in protein conformation, followed by induction, are noticeable when there are mutations in the SOD1 gene, protein aggregation and aberrant motor neuron activity.[44] The purpose of ASOs targeting SOD1 (ASOs-SOD1) is to lower the expression of SOD1, which is promising for slowing the course of ALS and increasing patient survival during clinical treatment, is being studied treatment.[45] Moreover, CRISPR and shRNA targeting SOD1 to be transported by the AAV9 vector (AAV9-SOD1 shRNA) AAV9 can be used to target Cas9 at SOD1, which can lower the amount of mutant SOD1 protein and enhance motor function as well as extending survival in mouse models of ALS.[46,47] Two individuals with fALS caused by one of the patients with a SOD1 mutation had an intrathecal injection of AAV vectors that produced miRNAs that targeted SOD1. The other had a little gain in right leg strength,[48] while the first was seen to have a consistent ALS Functional Rating Score. According to the results, SOD1 may be a viable target for treatment for ALS.

Gene therapy for Huntington disease:

A vector carrying the gene for fibroblast growth factor (FGF) and nerve growth factor (NGF) has been used for the therapy and management of HD and also used to demonstrated considerable progress [49]. Recently, the implantation of cilliary neurotrophic factor (CNTF) generating according to the preclinical research, fibroblasts have been shown to alleviate the behavioural abnormalities. [50, 51] Other than that, Neurotrophic factors, which demonstrated improvement, were also delivered by implantation, lentivirus, and AAVin behavioural and anatomical irregularities. [52, 53] In addition, using RNAi to silence the Huntington gene revealed decreased Huntington expression, which lessens the causes of HD.[54] HD is a neurodegenerative disorder that is autosomal dominant. A main consequence of an enhanced cytosine-adenine-guanine (CAG) (trinucleotide repeat) in the huntingtin (HTT) gene is the onset of disease. The production of a poisonous mutant HTT (mHTT) protein that is the clinical signs of HD include cutting-edge motorcognitive loss, psychological abnormalities, and dysfunction.[55] The main goal of gene therapy for HD is to silence or decreasing the expression of the mutant HTT gene. The use of RNAi techniques is one well-researched strategy, made up of siRNAs and quick hairpin RNAs to specifically destroy HTT mRNA.[56] ASOs directed towards HTT have moreover, scientific tests have been enhanced, and some candidates have shown a decrease in mHTT protein levels in cerebrospinal fluid.[57] More recently, the CRISPR/Cas9 age has seen the implementation of the technique to remove or interrupt the enhanced CAG. The HTT gene has repeats that might offer a unique therapeutic approach.[58] However, despite these advances, it is still necessary to have a high level of care. Ensuring long-term protection and effectiveness, minimizing off-target effects, and attaining allele specificity are still difficult, especially for treatments that include irreversible gene modification.[59]

Table 1:**Illustrates the key gene targets, manipulation techniques, & delivery strategies used in gene therapy for major neurodegenerative diseases.**

Disease	Target gene (s)	Manipulation technique	Delivery method
Alzheimer's	ApoE, BDNF, APP	AAV vectors, CRISPR, ASOs	Intracranial/AAV
Parkinson's	TH, AADC, GAD	AAV2 vectors, lentiviral therapy	Substantia nigra delivery
Huntington's	HTT	CRISPR-Cas9, RNAi, ASOs	Striatal injection
ALS	SOD1, C9orf72	Gene silencing, ASO therapy	Systemic/AAV9 delivery

Gene editing technologies in neurological disorders:

The landscape of molecular medicine has changed due to gene modification, which allows for targeted alteration of disease linked genetic sequences. In neurological diseases, where pathogenic mutations are frequently the root cause of disease progression, Targeted modification instruments, such as CRISPR/Cas9, which is the most researched, can produce long-lasting therapeutic outcomes. The programmable nature and great efficiency of the gene-altering device are the reason for this. It uses a guide RNA to direct the Cas9nuclease to specific DNA sequences, allowing for site-specific se double strand breaks and then repair or gene disruption. Models of Huntington's disease, ALS, and Alzheimer's disease have been used to study CRISPR-based procedures in their entirety, either fix mutations or silence harmful genes. Additional gene-modifying structures include zinc finger nucleases and transcription activators, such as effector nucleases, that are more difficult to design but provide too much specificity in comparison to CRISPR architectures. Recent advancements, like base editors and high editors, offer even greater precision by facilitating nucleotide conversions without causing double-strand breaks, which reduces the likelihood of off-target effects. Although integrated with sophisticated transportation systems, those tools have the potential to develop one-time treatments for inherited diseases and neurological diseases that were acquired.[11]

Gene expression:
Introducing genes from outside the body into the central nervous system is the simplest method for gene therapy. The genes that are delivered can help recover the loss of gene functionality caused by pathogenic mutations, such as the SMN1 gene related to spinal muscular atrophy type 2. Alternatively, genes can provide neurotrophic factors that encourage the survival of neurons, as seen in conditions like Alzheimer's and Parkinson's disease; or they can supply metabolic enzymes to correct neurotransmitter imbalances, as in the case of Parkinson's disease.[60]

DNA editing:
DNA editing tools can manipulate gene expression or correct pathogenic mutations, and are starting to enter the clinic. In general, there are two crucial rudiments DNA-binding disciplines that fete specific genomic sequences, and nucleases that induce double-stranded breaks (DSBs). DSBs are repaired by non-homologous end- joining (NHEJ) which is an endogenous error-prone process leading to sequence insertions and elisions (INDELs) in the reading frame that generally create frameshift mutations and unseasonable termination codons(PTCs), eventually knocking out the targeted gene. Alternately, in the presence of an exogenous template, native homology dependent form (HDR) mechanisms can be exploited to fit asked sequences or point mutations into the host genome. The three main DNA- editing nucleases such as zinc cutlet nucleases (ZFNs), recap activator- suchlike effector nucleases (TALENs), and CRISPR- associated nucleases.[60]

ZFNs and TALENs:
A ZFN is emulsion protein with two functional disciplines, a DNA-binding sphere composed of three to six zinc fritters each feting three DNA base-dyads in the host genome and a DNA-adhering sphere of the endonuclease Fok1. As Fok1 is functional as a dimer, two ZFNs are designed to bind contrary beaches of the targeted genomic DNA, which allow the Fok1 disciplines to dimerize and stick DNA. TALEN contains a series of recap activator- suchlike effectors (TALEs) and the Fok1 DNA-fractionalization sphere. Each TALE polypeptide comprises 33-34 amino acids, of which remainders 12 and 13 fete a specific DNA- base, allowing targeted DNA- list by opting a combination of modular TALEs.[61]

CRISPR:
CRISPR Clustered regularly interspaced palindromic reprise (CRISPR) was first described in 1987 and its gene editing capability verified in mortal cells in 2013. CRISPR exists in 40 bacteria and 90 archaeal genomes and functions as an adaptive vulnerable defence system. The CRISPR system can specifically capture gene sequences conterminous to protospacer conterminous motif (PAM) for fractionalization using Cas nuclease into spacer parts deduced from the exogenous genome. Spacers are latterly incorporated into the CRISPR locus of host cells, separated by palindromic sequences, and ultimately transcribed to CRISPR RNA (crRNA) with spacer characteristics. CrRNA dyads with overrunning foreign gene sequences in a reciprocal manner. contemporaneously, Cas nuclease destroys target DNA and completes the entire vulnerable response. By landing exogenous gene parts from overrunning phages, contagions and plasmids and incorporating them into host genomic loci, the CRISPR/ Cas system sustains acquired vulnerable function. Type II CRISPR/ Cas9 composed of Cas9 endonuclease, crRNA and trans- cranking crRNA (tracrRNA) is the most generally used system in inheritable engineering. Cas nuclease is the core functional element of the CRISPR system. TracrRNA and precursor crRNA (pre-crRNA) bind via base pairing, are trimmed by RNaseIII, self-folded into a partial double- stranded RNA structure, and interact with Cas9 to form a complex with DNA fractionalization capability. The crRNA- tracrRNA duplex functions as a single companion RNA (sgRNA) that effectively dyads with the target sequence. After binding to the target point, Cas9 undergoes conformational changes and induces DSBs 3 4 nucleotides upstream of PAM. disciplines in Cas9 not only interact with the PAM motif but also help with sgRNA list to the target sequence. Compared with ZFN and TALEN, the editing horizon of CRISPR is elevated from protein to RNA and specialized difficulties from design to assembly are greatly simplified. In terms of target recognition, particularity is advanced and list is more stable. In addition, Cas9 acts as monomer in discrepancy to FokI, which only cleaves DNA in a dimeric form. Still, CRISPR does not alter the nature of HR induction through DSBs. In fact, NHEJ is a more current pathway for DSB form in the entire cell cycle. Although NHEJ impediments (e.g., Scr7) and HR promoters (e.g., Cas9-

RecA emulsion protein) are anticipated to ameliorate the effectiveness of HR, CRISPR technology requires farther enhancement to ameliorate the delicacy of gene editing.[11]

CRISPR-mediated canonical applications- NHEJ and HDR:
Unlike TALENs and ZFNs, which employ amino acids to guide their action. The CRISPR system uses a specially created guide-RNA to direct a Cas9 nuclease, which is the nuclease, to certain locations in the host DNA. The existence of PAM (protospacer adjacent motif) sites that are distributed throughout is another condition the genome 24. The guide-RNA for the most widely used Cas9-Streptococcus pyogenes Cas9, often known as SpCas9includes a trans-activating CRISPR RNA (tracrRNA), which interacts with a genomic target sequence, and a CRISPR RNA (crRNA), which identifies the genomic target sequence, are both components of the CRISPR RNA (crRNA)attracts Cas9. INDELs often modify the reading frame and cause nonsense mutations after Cas9-induced DSBs and NHEJ-mediated repair. Most of the time, mRNAs carrying the mutated PTCs are destroyed by nonsense-mediated decay (NMD), an installation of a PTC. Endogenous surveillance system that causes the protein to be lost. In theory, CRISPR-guided HDR may be employed to through 'donor-templates', introduce any desired point mutations or insertions into the native genome. But in the majority of cells, HDR. The frequency of mediated repair is lower than that of NHEJ, which reduces recombination. Furthermore, during mitotic, HDR occurs spontaneously recombination, which is restricted to post-mitotic neurons, while methods are being worked out to enhance HDR brain efficiency 25. One approach involves editing HDR in an ex-vivo environment before transplanting the treated cells in vivo, which is a potential course of action. A legitimate gene therapy approach for sickle cell disease is stem cell transplantation. Stem cell transplantation in sickle cell disease has been studied in clinical trials. Given the nature of neurodegenerative illnesses, the usefulness of this method seems restricted.[60]

CRISPR-mediated transcriptional modulation:
In CRISPRi (inhibition), a catalytically dead Cas9(dCas9) or a nickase Cas9(nCas9)-only able of generating single-beachfront breaks is fused with recap repressors to inhibit gene recap. suppression can also be achieved by enzymes that modify histones and alter chromatin structure by epigenome editing. Since dwindling gene expression is a logical strategy for numerous neurodegenerative conditions for case inordinate α- synuclein, APP, tau and Huntingtin has been intertwined this is a promising approach. still, important issues similar as safety and efficacity still need to be addressed. CRISPRa (activation) is similar strategy to spark endogenous genes by fusing dCas9 or nCas9 to recap activators or epigenome modulators. Though these large Cas9- effector proteins in CRISPRi poses a challenge for AAV- packaging and clinical development, this can be overcome by using the lower SaCas9. [62]

RNA editing:
Author handwriting RNA- grounded editing alters gene expression at the paraphrase position. Since RNA is flash, there's lower threat of endless injurious goods, which is a significant remedial appeal of this technology. still, the need for repeated administration generally by intrathecal injections is challenging in the clinical setting. Though antisense oligonucleotides (ASOs) were described over 40 years ago, clinical operation of RNA- grounded rectifiers suffered multitudinous lapses due to limited efficacity, lack of particularity, and injurious off target goods.[63]still, multitudinous advances in chemical variations, delivery vehicles, and RNA- editing tools have converted the field, leading to several remedial agents that are in the clinic. RNA-grounded editing technologies have been reviewed lately, and then we bandy two strategies applicable to neurodegenerative conditions.[60]

Current treatment paradigm:
Current treatment approaches for neurodegenerative illnesses only target a small segment of the population and concentrate solely on symptom relief, without addressing the underlying causes of the disease. This results in the victims' permanent disability or death. Currently, the Food and Drug Administration (FDA) has authorized the use of acetylcholine esterase inhibitors [Donepezil (Aricept), Rivastigmine (Exelon)] as palliative treatment. These medications alleviate symptoms and slow the course of the illness, but they are not effective in treating it over the long term. Levodopa, which is used in conjunction with carbidopa (Sinemet) in the treatment of PD, crosses the blood-brain barrier and undergoes decarboxylation to produce dopamine. Levodopa improves dopamine levels in the substantia nigra and reduces all clinical symptoms of Parkinsonism for the first few years, but its efficacy wanes with prolonged use. Dopamine agonists [Pergolide (Permax), Bromocriptine (Parlodel)] are also widely used in practice, however they have several adverse effects, including cardiovascular and endocrine problems. Overactivity in dopaminergic nigrostriatal pathways causes HD. As a result, the treatment for HD uses medications that block dopamine receptors [e.g., phenothiazines (Haldol, Trilafon)] or deplete central monoamines [e.g., Reserpine (Serpadil)] to impair dopaminergic transmission. A number of immuno-suppressors are used in the treatment of MS, which helps to speed up recovery from relapse and slow down the progression of the disease. Some of the medications used to treat relapse re-emittance MS include prednisone, which reduces inflammation and prevents MS relapse; Ocrelizumab, which treats primary progressive MS; and several other medications, such as Tysabri, natalizumab, which causes immune cells to enter the brain; mitoxantrone and alemtuzumab, which suppress the immune system; glatiramer acetate; beta-interferon, which modulates the immune system; and Ocrelizumab, which neutralizes antibodies.[8]

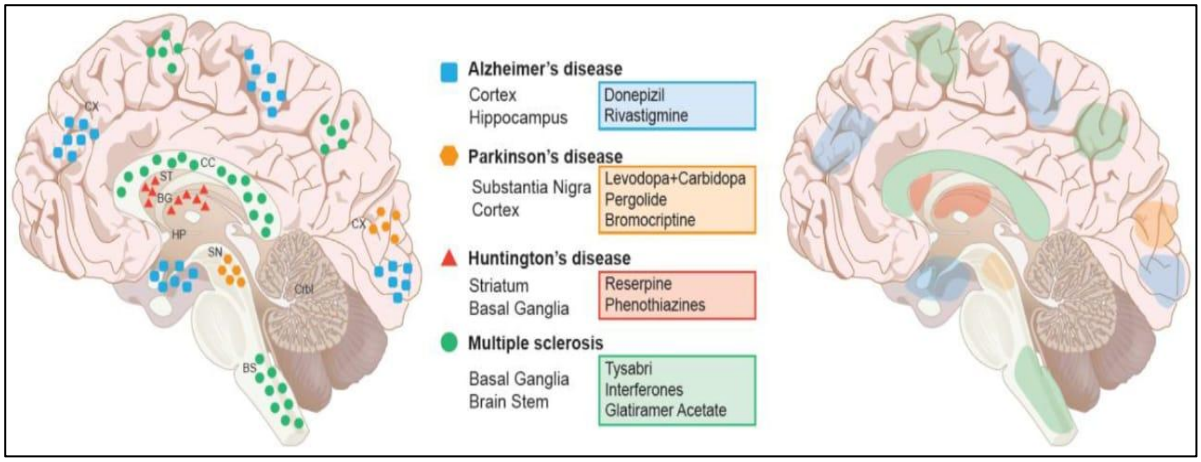

Figure 2: Major Neurodegenerative diseases, their associated regions, and current therapeutic interventions

Challenges and future prospects:

Despite significant advancements in biomedical science, molecular biology, genetics, and pharmaceutical research, numerous challenges continue to hinder progress in neurodegenerative disease (ND) research and therapeutic development. The lack of clinically relevant and reproducible disease models remains a major bottleneck, as current in vitro, in silico, and in vivo (genetically modified rodent) models only partially mimic human pathophysiology, thereby limiting translational potential. Clinical evaluation of neuroprotective or disease-modifying agents in humans is high-risk, costly, and time-consuming due to ethical constraints and the absence of easily measurable clinical outcomes. Additionally, neurodegeneration involves multiple cell types beyond mature neurons, yet existing models often fail to capture this cellular complexity. While currently available therapies for most NDs are largely symptomatic with very few disease-modifying options, recent progress in understanding molecular triggers and disease pathways offers new hope. Gene therapy, once considered impractical for widespread CNS pathology, is now emerging as a feasible approach due to advanced vector technologies and genome-editing tools. These innovations hold promise for both inherited and sporadic NDs, yet major obstacles persist especially in achieving safe and efficient gene delivery across the blood-brain barrier (BBB), optimizing drug lipophilicity and molecular weight, and ensuring rigorous safety evaluations of gene manipulation technologies. Thus, the future prospects lie in developing more predictive multicellular disease models, improving CNS delivery systems, fostering transparent interdisciplinary collaboration, and refining gene-based therapeutic strategies to transform the clinical management of neurodegenerative diseases.[1, 15, 60]

Conclusion:

Neurodegenerative disease research has made substantial progress in recent years, yet the path to effective clinical translation remains challenging. The current limitations in available disease models especially their inability to fully replicate human molecular and cellular complexity continues to hinder the development of reliable therapeutic strategies. Ethical constraints, high clinical trial costs, and the absence of robust biomarkers further complicate the evaluation of neuroprotective or disease-modifying agents. Although most existing treatments remain largely symptomatic, advances in genetics, molecular biology, and vector engineering have reshaped the therapeutic landscape. Gene therapy, once thought impractical for CNS disorders, is now becoming a realistic intervention due to improvements in genome-editing platforms and delivery systems. However, major barriers still persist, particularly in achieving safe and targeted delivery across the blood–brain barrier and ensuring long-term safety of gene manipulation technologies. Therefore, the future of neurodegeneration research lies in developing highly predictive multicellular models, integrating computational and stem cell-based platforms, enhancing BBB-crossing delivery technologies, and promoting interdisciplinary collaboration. By addressing these critical gaps, the field may progress toward true disease-modifying interventions and a more personalized, mechanism-based clinical management of neurodegenerative disorders.

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