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NEURODEGENERATIVE DISORDERS: A COMPREHENSIVE INSIGHT INTO CURRENT AND EMERGING THERAPEUTIC APPROACHES

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ABSTRACT

Neurodegenerative disorders (NDs) embrace a collective group of conditions portrayed by the gradual loss of neurons, leading to dementia, motor dysfunction, and other neurological defects. Major NDs include Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS), each carrying distinct clinical manifestations and pathogenic mechanisms such as protein aggregation, oxidative stress, and neuroinflammation. Globally, neurological diseases affect billions, with AD and PD reported as ubiquitous among other NDs, seemingly increasing in number with the progression of age. Though conventional drug therapies offer symptomatic relief, their effectiveness is hampered by limited brain drug delivery and the blood-CSF barrier, followed by different adverse reactions. Advanced therapeutic interventions, including monoclonal antibodies, precision medicine, advanced drug delivery systems, and gene and stem cell therapies, promise to slow disease progression. However, challenges, including late diagnosis and high out-of-pocket expenses, increase the risk of incidence. Emerging interventions like deep brain stimulation and novel site-specific drug delivery techniques show promise for PD and AD, as well as supportive care for less common NDs such as HD and FTD. Despite these advances, early diagnosis and effective disease-modifying treatments remain critical unmet needs in managing neurodegeneration at a global scale.

KEY WORDS: Alzheimer's Disease, Parkinson's Disease, Precision medicine, Targeted therapy, Deep brain stimulation

INTRODUCTION

Neurodegenerative disorders (NDs) refer to a wide class of slow-progressing disorders characterised by the gradual destruction of neurons, leading to cognitive deterioration, motor dysfunction, and other neurological symptoms. Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and Amyotrophic lateral sclerosis (ALS) are among the many disorders that fall under the division of neurodegenerative diseases. The term 'neuroprotection' refers to strategies and relative mechanisms that safeguard the central nervous system (CNS) from neuronal injuries caused by chronic or acute neurodegenerative diseases (NDs). [1]

As per WHO, approximately 1 in every 3 individuals is affected by some or the other type of neurological disorder, which amounts to almost 3 billion people worldwide. The prevalence of neurodegenerative diseases is anticipated to rise further by 2050, with an approximate of 139 million global cases of dementia reported.[2] Among all the NDs, Alzheimer's Disease is the most prevalent, with a prevalence of about 55 million people worldwide. It shows an incidence rate of 10 million new cases every year. [2] It is anticipated that the number of individuals with Alzheimer's disease would double by 2060, from 6.9 million in 2020 to around 14 million.[3] Parkinson's disease, which affects 10 million individuals, is a close second. Huntington's disease and amyotrophic lateral sclerosis are two other NDs that are very uncommon, with global prevalences of 2.7 and 5 per 100,000, respectively. [2]

NDs are characterized by their unique clinical appearances, affected brain areas, and underlying pathogenic mechanisms. For instance, Alzheimer's Disease is marked by memory loss and cognitive decline, associated with beta-amyloid plaques and tau tangles. Parkinson's Disease is concerned with tremors, bradykinesia, and stiffness due to dopamine-producing neuron degeneration. Huntington's Disease manifests as involuntary movements and cognitive deterioration arising from the repeated expansion of the CAG trinucleotide in the HTT gene. Amyotrophic Lateral Sclerosis is characterised by progressive muscle wasting and paralysis due to degeneration of motor neurons.[4] NDs have been discovered to be intimately related to ageing, which is described as a complicated physiological process that involves both morphological and biochemical changes that gradually unfold as we become older. Other etiological factors of NDs include hypertension, genetic and/or environmental factors, and infections. The chances of occurrence of aggregation of proteins, oxidative stress, loss of neurotransmitters, and inflammation increase with increasing age.[1]

ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) is a progressive and terminal neurodegenerative disorder that affects the hippocampus of the brain, leading to memory decline, cognitive disabilities, and behavioural abnormalities. AD is characterised by neuronal destruction and gradual deterioration of brain tissue.[6] The major pathophysiology that leads to the disease is the accumulation of Alpha-beta amyloid plaque in the brain, and the formation of neurofibrillary tangles due to hyperphosphorylation of tau protein. Plaque formation causes the hippocampal circuit disruption, leading to short-term memory. These changes progress with age, and hence the prevalence and incidence of the disease also increase with age.[5]

PARKINSON'S DISEASE

Parkinson's Disease (PD) is a gradual, slow-progressing movement disorder that mainly affects the neurons in the substantia nigra of the brain, leading to their destruction. The disease is manifested as tremors, bradykinesia, unsteady gait, muscle stiffness, and coordination difficulties. The primary risk factor for PD is considered to be ageing. In addition, various other etiological factors such as smoking, genetic mutations, and exposure to environmental toxins also contribute to the disease. In PD, due to destruction of the substantia nigra, there is a marked depletion in dopamine levels. Several mechanisms lead to the progression of PD. The major mechanism is the misfolding and aggregation of alpha-synuclein, a protein normally present in the brain, causing the formation of Lewy bodies. Another factor leading to PD is mutations in the PRKN gene.[6]

OTHER NEURODEGENERATIVE CONDITIONS

Other neurodegenerative diseases, such as Amyotrophic Lateral Sclerosis (ALS), Multiple System Atrophy (MSA), Frontotemporal Dementia (FTD), and Huntington's Disease (HD), share common pathophysiological features, such as progressive loss of selective neuronal populations, oxidative stress, neuroinflammation, impaired axonal transport, and accumulation of misfolded or aggregated proteins. Amyotrophic lateral sclerosis is caused by the degeneration of both upper and lower motor neurons, resulting from the mutation and aggregation of selective proteins like superoxide dismutase 1 (SOD1) and TAR DNA-binding protein 43 (TDP-43). Astrocytes, highly responsible for maintaining the BBB barrier integrity, constant blood flow, neurotransmitter levels, and providing structural rigidity to the neurons, play a toxic role here. MSA, a synucleinopathy like PD, features α-synuclein inclusions in neurons and glial cells, leading to neuronal damage and motor symptoms. FTD and HD also involve neuronal death due to protein accumulation, but affect distinct brain regions and functions. Overall, disrupted axonal transport, mitochondrial dysfunction, protein aggregation, and chronic neuroinflammation are considered the root causes of neurodegenerative disorders.[7]

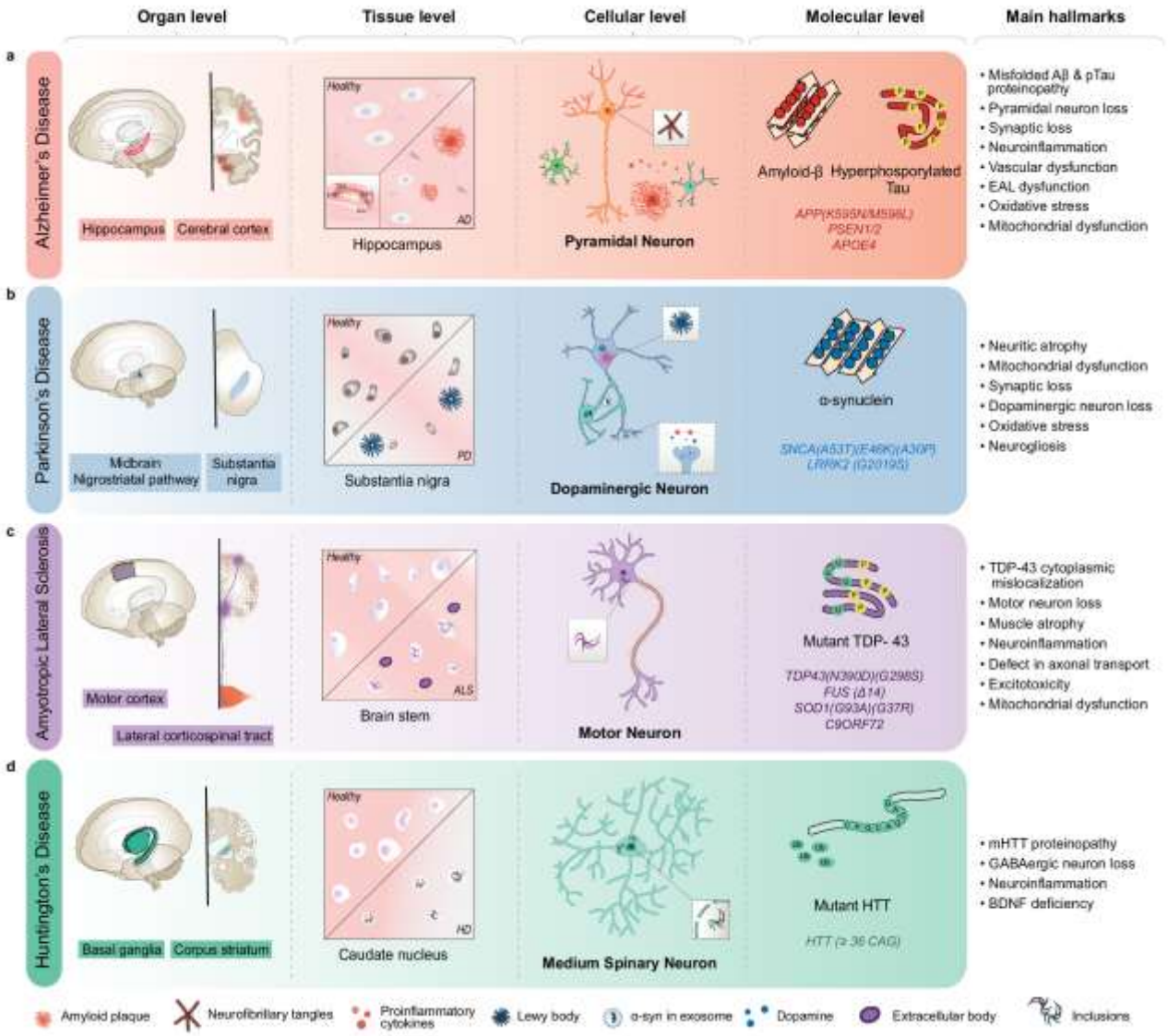

fig. 1: main hallmarks and pathophysiology of common neurodegenerative disorders.[8]

THERAPEUTIC INTERVENTION FOR ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive neurodegenerative disorder that is incurable. The treatment and therapeutic strategies for AD must be devoted to slowing the progression of the disease, managing the symptoms, and enhancing the quality of life in patients with AD. Combination therapy, rather than monotherapy, is more advantageous in improving patients' disease condition and reducing the burden of behavioural and social aspects on their lives. The primary objective is to improve cognition and memory by targeting various neuronal factors involved in the progression of the disease.[9]

CONVENTIONAL DRUG THERAPY

Several categories of drugs are used conventionally for the management of early or middle stages of AD cases. They are acetylcholinesterase (AChE) inhibitors (donepezil, galantamine, and rivastigmine) and NMDA receptor blockers (memantine). Other approved drugs are antipsychotics, natural nootropics (Ginkgo biloba, Ashwagandha, Brahmi), and disease-modifying immunotherapy.[4] Memantine is a noncompetitive NMDA receptor antagonist for the treatment of moderate to severe AD. It blocks the neurotoxic effects of glutamate and retards the disease progression

by saving the neurons from excitotoxicity.[10] Donepezil, rivastigmine, and galantamine are acetylcholinesterase inhibitors that enhance the levels of acetylcholine in the brain by inhibiting the AChE enzyme. As per various meta-analyses conducted, it has been reported that AChE inhibitors have an exceptionally beneficial effect on memory and cognition.[11] Donepezil and rivastigmine often only provide symptomatic relief without providing much neuroprotection. But on the contrary, the drug has been shown to slow down hippocampus atrophy in humans, suggesting a neuroprotective effect.[11]

Drawbacks Of Conventional Therapy

The conventional drug therapy for Alzheimer's disease exhibits various drawbacks. The foremost drawback is that the treatment only focuses on symptomatic relief rather than actually addressing the root cause. AD is often misdiagnosed or diagnosed at later stages when neurodegeneration has already transpired. The delayed diagnosis often leads to exacerbation of the disease, which cannot be treated effectively with conventional drugs. Another challenge is the blood-brain barrier that restricts the transport of the drug molecules from the blood to the brain, leading to therapeutic failure. The drug therapy often shows considerable side effects.[10] Acetylcholinesterase inhibitors exhibit side effects such as nausea, vomiting, tremors, insomnia, gastrointestinal distress, bradycardia, syncope, and even seizures. These effects are manifested primarily due to the overstimulation of peripheral cholinergic action and muscarinic receptors. The side effects of memantine include dizziness, headache, fatigue, abdominal pain, hypertension, confusion, etc. These drugs also happened to have a limited period of effectiveness owing to their short half-life. AD can adversely affect the quality of life of not just the diagnosed individuals but also their caregivers and families.[10] In many cases, the caregivers experience extreme levels of stress, anxiety, and distress caused by the patient's neuropsychiatric symptoms. AD also applies a huge financial burden on patients and caregivers on account of the cost of medications, medical care, and long-term care facilities.

The lack of efficient curative therapies and the challenge of correctly identifying AD in its early stages amply illustrate the necessity of putting preventative and neuroprotective measures into place to slow down the neurodegenerative process and lower the risk of AD. [12] Addressing these challenges needs innovative approaches in therapeutic development, including the requirement for precision medicines, targeted drug delivery, novel treatment techniques, and combination therapies.[10]

CURRENT THERAPEUTIC INTERVENTIONS

Despite the availability of conventional drugs such as acetylcholinesterase inhibitors and NMDA receptor blockers for the management of AD-related dementia, restricted penetration of the drug across the blood-brain barrier (BBB) and relapse of the disease due to ageing remain a challenge. While conventional therapies like tablets and capsules manifest significant oral bioavailability, factors such as systemic side effects, first-pass metabolism, and plasma protein binding cause a deterioration in their efficacy. To address these challenges, different advanced drug delivery systems (ADDS), genetic treatments, and targeted drug delivery can be employed. These delivery systems have several advantages over conventional delivery systems, as they can improve the pharmacokinetic parameters of the drug and can enhance the solubility or permeation characteristics of the drug across the BBB. In addition, these systems provide targeted delivery of drugs, thereby limiting the exposure of drug to systemic circulation and reducing adverse reactions.[9] The majority of the newer drugs target Aβ42 precursor protein, followed by APP,

MAPT, acetylcholinesterase (AChE), cholinergic receptor muscarinic 1 (CHRM1), NMDA receptor, tumor necrosis factor (TNF), 5-hydroxytryptamine receptor 6 (5-HTR6), 5-hydroxytryptamine receptor 4 (5-HTR4), glucagon-like peptide 1 receptor (GLP1R), insulin, sigma non-opioid intracellular receptor 1 (SIGMAR1), and sodium channel.[13]

Monoclonal Antibody Approach

Lately, monoclonal antibodies (mAbs) have sparked the hope for AD treatments.[13] The FDA has approved two disease-modifying monoclonal antibodies (MABs), including aducanumab and lecanemab.[9] Aducanumab is the first disease-modifying drug approved for AD patients, and was approved in June 2021. It is an IgG1 monoclonal antibody specific to extracellular Aβ plaques in the brain, which binds and helps in the destruction of the plaques.[5] Lecanemab shows enhanced selectivity for larger soluble beta amyloid protofibrils and regresses the progression of AD in both human and mice models.[9] Both these monoclonal antibodies target Aβ aggregates and reduce the plaque size. Donanemab is another monoclonal antibody that was approved by the FDA in 2024.[14]

Advanced Drug Delivery Systems

Advanced drug delivery systems have gained critical importance recently in the treatment and management of AD. Owing to an increase in neurodegenerative diseases, the challenge of delivering and releasing drugs into the brain is attracting much attention. Soft nanoparticles, such as liposomes and exosomes, are nanovesicles that have the potential to deliver drugs and genes across the BBB.[11] Inorganic nanoparticles like gold nanoparticles, iron nanoparticles, carbon dots, carbon nanotubes, cerium oxide nanoparticles, and organic/polymeric nanoparticles, such as nanoliposomes and nanomicelles, have been inspected for their efficacies in the treatment of AD. Nanoparticles have significant potential as carriers for drug delivery to enhance AD therapy and other diseases.[14] A wide range of natural and synthetic polymers is obtainable for developing nanoparticles, which are useful for targeted delivery.

Liposomes

Liposomes have been in research for more than five decades, to the point where they are well-established drug delivery vectors, resulting in the marketing authorization of several clinically approved liposomal-based products. Indeed, they offer great levels of biocompatibility and safety due to their resemblance to biological membranes. Sometimes, conventional liposomes cannot cross the BBB, but modifying their surface enables them to pass through and release the drug directly into the CNS.[12] Experiments identify the role of apolipoprotein E (ApoE) as a pivotal factor related to Aβ level and amyloid deposition in the progression of AD. Liposomes can be used to deliver plasmid-encoded ApoE2 (pApoE2) for the effective treatment of AD.

Exosomes

Exosomes are another innovative carrier method for the targeted delivery of drugs. Exosomes are considered more biocompatible, less immunogenic, and show an extended blood half-life when compared to liposomes. Generally, all exosomes contain non-coding RNAs, microRNAs, mRNAs, lipids, and proteins. There have been successful attempts where the exosomes loaded with siRNA are used for effective brain delivery [12]

NON-PHARMACOLOGICAL INTERVENTIONS

Nonpharmacological interventions for AD focus on improving cognitive function, enhancing overall well-being, and managing behavioural and psychological symptoms of the disease. Two essential nonpharmacological interventions for AD include cognitive stimulation and rehabilitation, as well as physical exercise and lifestyle modifications.[9]

Deep Brain Stimulation and Vagal Nerve Stimulation

Deep brain stimulation (DBS) is a surgical intervention used to stimulate a particular region of the brain specific to a given disease through electrodes implanted in that region by a pulse generator. In AD, the cholinergic nucleus of Meynert (Nucleus Basalis of Meynert) has undergone DBS in phase I clinical trials.[15] DBS has shown potential to decrease cognitive decline in mild to moderate AD. Vagal nerve stimulation (VNS) is another method used to stimulate the vagus nerve with a pulse generator and lead wire to stabilize irregular electrical activity in the brain. In AD, vagal nerve stimulation has been shown to increase catecholamine release in the hippocampus and neocortex. This procedure reduces neuroinflammation and enhances synaptic plasticity. It also improved cognition in AD patients.[10]

Cognitive Stimulation and Rehabilitation

Cognitive and rehabilitation programs focus mainly on engaging individuals with AD in activities that stimulate cognitive function, promote social interaction, and maintain overall cognitive abilities. CST helps improve memory, orientation, language comprehension, coping, and adaptation abilities; enables communication; lowers anxiety and sadness in patients; and ultimately improves the overall quality of life (QoL) of individuals with dementia.[10]

Physical Exercise and Lifestyle Modification

Regular physical exercise has been shown to have numerous positive effects on various bodily systems, including the immune, digestive, cardiovascular, and central nervous systems. As ageing plays a crucial role in the onset and progression of AD, physically active individuals tend to show decreased progression of AD. Physical activity has been demonstrated to improve memory and cognitive function, reverse the effects of ageing by reducing stress, anxiety, and depression, and enhance brain health.[10] Short-term resistance training improves cognitive function, decreases the accumulation of amyloid-β and hyperphosphorylated tau in the brain, and suppresses the production of the neuroinflammatory mediators IL-1β and tumor necrosis factor alpha. Dietary intake also contributes to combating the progression of AD symptoms. Several nutrients and food items, including omega-3 polyunsaturated fatty acids and vitamins such as vitamin D, complex B vitamins (B6, B12, and folate), and antioxidants (A, C, and E), have been studied and found to decrease the risk of cognitive impairment, dementia, and AD.[10]

EMERGING THERAPIES FOR ALZHEIMER'S DISEASE

Researchers are currently investigating new drug targets and therapies that modify the disease to tackle the root pathology of AD. [13] Many therapeutic agents that have shown potential in AD treatment and management are still undergoing clinical trials. Table 1 illustrates agents that are currently under investigation.

table 1. therapeutic agents that are under active investigation in different phases of clinical trials;

Therapeutic agent	Mechanism	Clinical trial phase
Semaglutide	GLP-1 agonist, and reduces neuroinflammation	Phase III
ALZ-801	Inhibits Aβ aggregation in individuals with the APOE4 genetic genotype	Phase III
Leuco-methylthioninium	Tau aggregation inhibition	Phase III
XPro1595	Neutralizes TNF-alpha receptor	Phase II
L-serine	Activation of glycine receptors, provides neuroprotection	Phase II
SAGE-718	NMDA receptor agonist	Phase II
OLX-07010	Prevent tau self-association	Phase I
ALZN002T	T-Cell activation, facilitates amyloid clearance	Phase I
Allopregnanolone	GABA-A receptor modulator, enhances neurogenesis	Phase I

THERAPEUTIC INTERVENTIONS IN PARKINSONS DISEASE

Parkinson's disease is a degenerative neurological condition that results in tremors, muscle rigidity, unsteady gait, and challenges with balance and coordination. It is the most common movement disorder among neurodegenerative diseases. Both genetic and non-genetic factors contribute to the development of PD.

There are two broad categories of therapies for PD: symptom-modifying therapy (SMT) and disease-modifying therapy (DMT). As the name suggests, SMT is used for managing motor symptoms, such as bradykinesia and tremors, whereas DMT focuses on slowing down the disease progression.[15] The first-line drug currently recommended for PD is levodopa combined with carbidopa, as this combination is very effective in controlling core motor symptoms such as tremors, muscle stiffness, etc., in individuals, especially those over 60 years of age. If levodopa is ingested alone, it breaks down in the bloodstream before crossing the brain, so levodopa is always given in combination [16]. Although currently approved treatments can dramatically improve the lives of people with PD in the first few years of disease diagnosis, they do not effectively treat the disabling nonmotor symptoms, nor do they address the underlying cause of the disease or the inevitable disease progression.

CONVENTIONAL APPROACHES IN PARKINSON'S DISEASE

Conventional treatment methods aim at providing symptomatic relief to the existing motor symptoms. The backbone of current PD treatment is dopamine-based preparations to meet dopamine insufficiency. Other than carbidopa-levodopa combinations, the following drugs are also used in the treatment of PD. Monoamine Oxidase is an enzyme that causes the uncontrolled breakdown of dopamine. So, MAO-B inhibitors like selegiline, rasagiline, etc., are introduced into therapy. Another category of drugs used to manage PD is COMT inhibitors such as entacapone, tolcapone, etc, but their effect is limited to specific symptoms. Anticholinergics are used especially in young patients at early stages of disease to relieve mild motor symptoms and movement disorders, and also play a major role in tremor-predominant PD. Examples of anticholinergics include benztropine, procyclidine, and Benzhexol. Amantadine, though initially developed as an antiviral drug, has been employed as a PD drug in recent years. Possible side effects include hallucinations, confusion, and impaired concentration.[17]

Antiparkinsonian agents tend to cause confusion and toxic psychosis in elderly patients. Therefore, it is commonly advised to maintain the treatment plan as straightforward as possible, as the chance of side effects is reduced when one or two medications are administered at higher doses versus a combination therapy involving lower doses.[18] Access to treatment is reduced by high out-of-pocket expenses for medications and advanced therapies like deep-brain stimulation. Though regular medications improve the quality of life of patients by reducing symptoms, the risk factors may overshadow the benefits over the course of time by disease progression and various side effects, including continuous fluctuation between on and off periods, dyskinesia, etc. [19] In addition to this, the physical and emotional strain faced by the caregivers of the patients is a matter of concern. The progressive nature of the disease escalates patient dependence, which amplifies caregiver burnout, affecting both their physical and mental health. Diminished quality of life in patients who are taking PD medications can be addressed through different methods, such as adjusting doses and switching medications, non-pharmacological interventions such as psychotherapy and mental health support, different kinds of rehabilitation activities, and occupational and speech therapies.

The existing medications have a lot of drawbacks, which may adversely affect the overall well-being of the patient. Here comes the importance of precision medicines. PD medications need to focus on both symptom management and disease control. A robust array of potential therapies is progressing for Parkinson’s disease. Certain drugs are being researched and developed that focus on different mechanisms, like alpha-synuclein aggregation, innovative drug delivery techniques, and more.

table.2: list of therapeutic agents under clinical trials

Therapeutic agent	Mechanism	Clinical trial phase
Istradefylline	Adenosine A2A receptor antagonist	Phase III
Safinamide	Monoamine oxidase B inhibitor, ion channel modulator, and dopamine uptake inhibitor	Phase III

Talampanel	AMPA receptor antagonist	Phase II
NS-2330	Dopamine agonist, dopamine uptake inhibitor, monoamine uptake inhibitor, and acetylcholine agonist	Phase II
ONO-2506	Astrocytic activation modulator and S-100 protein synthesis inhibitor	Phase II
Sarizotan	5-HT1A agonist and D3/D4 ligand	Phase II
Fipamezole	α2-Adrenergic receptor antagonist	Phase II
Besonprodil	NMDA receptor antagonist	Phase I

Precision medicines seek to move beyond "one size fits all" therapies by categorizing PD based on genetic mutations. (e.g., LRRK2, GBA, SNCA), molecular pathways, clinical features, and biomarkers enabling targeted interventions. Genetic discoveries have revealed several druggable targets that impact PD onset and progression. The two breakthroughs in parkinson's disease treatment include Magnetic resonance-guided focused ultrasound (MRgFUS) and Deep-brain stimulation (DBS).

TARGETED MEDICATIONS

Foslevodopa-Foscarbidopa Infusion Pump

Foslevodopa and Foscarbidopa are soluble prodrugs of both levodopa and carbidopa, respectively. The formulation of both is incorporated into an infusion pump, which delivers the drug continuously for 24 hrs. subcutaneously. This portable pump provides stable levodopa levels than oral levodopa and carbidopa, thus improving motor control. This prodrug gets converted to its active form once it reaches the body. The dose is determined by the neurologist and it differs from patient to patient to maximize the ON period and minimize the OFF periods. The preferred site for infusion is the abdomen. A new infusion has to be incorporated every third day.[19]

Amantadine Extended-Release Tablets

This drug, approved by the FDA, was initially used to control dyskinesia. Later, this drug received approval to be used as an adjuvant to levodopa for treating OFF periods (times of difficulty moving, walking, and speaking) and to manage levodopa-induced dyskinesia.[20]

COMT Inhibitors (Opicapone)

The COMT enzyme metabolizes levodopa in the body. So COMT inhibitors are given along with levodopa to decrease its breakdown and increase the amount reaching the brain. Opicapone is considered a more efficacious and better-tolerated COMT Inhibitor than entacapone.[21]

Drug Repurposing

Ambroxol, a prominent mucolytic expectorant, is gaining attention for its possible glucocerebrosidase-stimulating effects alongside its other properties, including the inhibition of sodium channels, alteration of calcium homeostasis, anti-inflammatory actions, and changes in oxygen radical scavengers. Ambroxol binds to the mutated Glucocerebrosidase enzyme (GCase) and stabilizes the GC protein, helping it to function correctly at cell lysosomes, resulting in the breakdown of the cells and clearing accumulated waste products and thereby counteracting disease progression.[22]

ADVANCED THERAPEUTIC INTERVENTIONS IN PARKINSON'S DISEASE

Magnetic Resonance- Guided Focused Ultrasound (MRGFUs)

This is one of the promising innovations in functional neurosurgery, especially in treating PD. This is mainly used in treating movement disorders and excessive tremor, especially tremor-dominant PD. In his technique, advanced ultrasound transducer emitters are used to focus multiple ultrasound beams on a definite brain target. This ultrasound radiations produce energy in the form of heat, which is capable of destroying the area of pathological invasion, and the magnetic resonance imaging provides detailed imaging to locate an accurate point and temperature monitoring. It is a non-invasive technique that requires no implantation or surgical openings. As other treatments for PD. This method cannot cure PD as a whole, but can ease the difficulties caused by PD motor symptoms and increase the quality of life of patients.[23]

Deep Brain Stimulation

Deep brain stimulation is a non-pharmacological treatment for Parkinson's disease, typically recommended for people with advanced PD when pharmacological options become less effective or cause problematic side effects. DBS is a surgical therapy that uses electrical stimulation delivered through implanted electrodes to specific regions in the brain to control certain motor symptoms.[24] There is a device similar to a pacemaker placed under the skin in the upper chest, which controls the amount of stimulation. Deep Brain Stimulation is used in a large number of conditions, including essential tremor, dystonia, obsessive-compulsive disorder, and to reduce seizures in hard-to-treat epilepsy.

EMERGING THERAPIES FOR PARKINSON'S DISEASE

Emerging therapies for Parkinson's Disease (PD) mainly focus on the parkin gene, primarily with the assistance of gene-based approaches, including gene replacement, gene supplementation, and gene editing (such as CRISPR-Cas9) to correct the dysfunctional parkin gene. These therapies accelerate disease progression by addressing the root genetic cause rather than just managing symptoms.

Gene And Stem Cell Therapy

These are the novel approaches that aim at restoring the dopamine-producing cells, replacing damaged neurons, or delivering genes that enable cells to produce dopamine. Gene therapy and stem cell therapy are still under investigation.[25] These treatments are varied and have a wide area of interest in the management of PD. They pledge to improve symptomatic treatment as well as progressive slowing down of the disease in the right patient group.

Alpha-Synuclein Targeting

The hallmark of PD is the accumulation of alpha-synuclein protein. There are different methods in targeting alpha-synuclein, including immunotherapy, i.e., by vaccines or antibodies, in clearing the protein aggregates and promoting its degradation by various processes, including autophagy. Alpha-synuclein functions normally in neurons, but in the case of PD, it misfolds and forms aggregates, forming Lewy Bodies. The aggregated alpha-synuclein deposits can result in mitochondrial dysfunction and oxidative stress, ultimately causing the loss of dopamine-producing neurons. [26]

TREATMENT STRATEGIES FOR OTHER NEURODEGENERATIVE DISEASES

Neurodegenerative disorders beyond Alzheimer's and Parkinson's diseases—namely Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), prion diseases, and multiple system atrophy (MSA)—pose major global public health challenges, with their prevalence and societal impact rising sharply as populations increase. Frontotemporal Dementia, Prion diseases, and related syndromes, though less common, add noticeably to the overall disease burden, especially in older adults. These conditions account for profound disability, loss of independence, and crippling expense. Current therapies for these disorders generally offer symptomatic relief. HD is managed with agents like tetrabenazine and antipsychotics, and ALS with riluzole and edaravone.[27] FTD is primarily treated through supportive psychiatric and behavioral care, and prion diseases through palliative measures. Innovative investigational approaches such as antisense oligonucleotide therapy, RNA interference, gene editing, stem cell transplantation, and immunotherapies targeting pathogenic proteins assure disease modification, but their practical level is constantly under challenge due to practical hurdles in delivering drugs across both the blood-brain barrier (BBB) and the blood-cerebrospinal fluid (CSF) barrier.[28] These barriers restrict the entry of most therapeutic agents into the central nervous system, which means that the promising treatments often fail in therapeutic efficiency or require invasive administration (intrathecal, intracerebral) or nanotechnological or molecular carrier strategies. Ultimately, it is this difficulty of CNS drug delivery, as well as significant diagnostic delays and limitations in accessing specialized care, that make the early diagnosis and treatment of neurodegenerative diseases difficult.

CONCLUSION

Neurodegenerative disorders (NDs) pose a crucial challenge in the global health arena. These conditions encompass Alzheimer’s Disease, Parkinson’s Disease, Amyotrophic Lateral Sclerosis (ALS), Huntington’s Disease, and various other diseases, among which the former two diseases remain the most prevalent. They feature a gradual but progressive neuronal destruction, varied clinical manifestations, and a substantial deterioration in the quality of life of affected individuals. The conventional therapy employed for the treatment and management of the disease delivers only symptomatic relief through mechanisms like acetylcholinesterase inhibition and dopamine replacement, while

failing to acknowledge actual causes of the disease, and other factors such as blood-brain barrier permeation difficulty, and side effects of the drugs. These limitations call for the need for innovative strategies such as precision medicines, targeted drug delivery, early diagnosis, use of advanced drug delivery systems, and techniques to enhance drug permeation through the blood-brain barrier. Many recent advancements in the field of ND treatment have shown positive effects. For AD, advanced drug delivery systems improve the permeation of drugs through the blood-brain barrier, enhancing the drug's efficacy. Monoclonal antibodies that target amyloid-beta aggregates, such as lecanemab and donanemab, are found to be highly efficacious in AD treatment. In case of PD, gene therapies, precision medicines, and state-of-the-art delivery techniques, including foslevodopa-foscarbidopa infusion pumps, aid in disease management, along with recent and emerging therapies to combat PRKN gene mutation and alpha-synuclein, the primary biomarkers of PD.

As we look into the prospects of management and treatment of neurodegenerative diseases, the success lies in integrative collaboration, rigorous research, and the application of precision medicines to individualize therapies as per the needs of the patient. By the incorporation of advanced strategies like stem cell therapies, genetic therapies, drug repurposing, and the use of non-invasive methods like magnetic resonance-guided focused ultrasound, there is an increased outcome that not only expands the life expectancy but also aids in the improvement of motor and cognitive functions. A comprehensive strategy that includes prevention, early intervention, and caregiver support will be crucial in diminishing the worldwide occurrence and effects of neurodegenerative diseases, nurturing optimism for better results in an aging demographic.

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