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A REVIEW ON RECENT ADVANCE IN NEURODEGENRATIVE DISEASE

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ABSTRACT

We predict that global demographic shifts will make neurodegenerative diseases (NDs) a major concern for public health and medicine in the coming years. Degeneration or loss of neurons, which is mostly responsible for severe mental disease, is the primary manifestation of NDs. This degradation of neurons results in numerous neuropsychiatric issues and a person's long-term impairment. As the population ages, the prevalence of conditions such as Alzheimer's and Parkinson's is expected to rise significantly, placing increased pressure on healthcare systems. This urgent need for effective treatments and preventative measures will drive research and innovation in neurology and geriatric care. Additionally, the blood-brain barrier (BBB), a tight junction of the brain, has a protective function as a biological barrier that can keep toxins, medications, and other foreign substances out of the brain. But it's hard to get drugs to the brain in NDs (like MS, Alzheimer's, Parkinson's, etc.). The majority of the approved treatments for NDs only help with the symptoms that are linked to the condition. The BBB and drug-associated side effects are two reasons why the current treatments have not been able to stop the progression of NDs. The pathogenesis of NDs is incredibly complex, with numerous pathogenic processes. involved in the onset and progression; as a result, patients with ND have shown a restricted survival rate. Therefore, comprehending the precise process underlying NDs is essential to creating other strategies for raising the survival rates of ND patients. The current analysis clarifies the various cellular mechanisms behind NDs and innovative therapeutic approaches together with their clinical significance, which will help researchers come up with different ways to overcome the drawbacks of traditional ND treatments. The present project provides the potential to enhance NDs' treatment approach in the near future.

INTRODUCTION

Deliberate neuronal loss characterizes neurodegenerative diseases (NDs), which typically result in death (Gadhave et al., 2024; Lamptey et al., 2022a). According to Choonara et al. (2009) and Hui et al. (2023), they comprise progressive neuropsychiatric disorders, including Huntington's disease (HD), Alzheimer's disease (AD), Multiple Sclerosis (MS), Parkinson's disease (PD), Amyotrophic Lateral Sclerosis (ALS), and several other NDs. According to Pant et al. (2022) and Tanaka et al. (2020), NDs are frequently linked to the progressive loss of neurons and synaptic connections, which usually happens later in life. Depending on where neuronal death occurs in the brain (Fig. 1 A), many disorders can be identified by their distinctive symptoms (Gadhave et al., 2024). The patient's clinical prevalence and supporting magnetic resonance imaging (MRI) data are key factors in the diagnosis of NDs (Huang and Zhang, 2023). The onset and development of clinical symptoms are directly correlated with the extent of neuronal death. In ADs, neuronal loss appears early in the hippocampus, a brain region involved in declarative episodic memory (Jim´enez-Balado and Eich, 2021; Shankar and Walsh, 2009). Previous studies have indicated that the survival rate of NDs is restricted. According to Ding et al. (2022) and Huang et al. (2023), there were 10 million fatalities and 349.2 million cases of serious neurological illnesses globally in 2019. In terms of prevalence worldwide, these conditions came in second. Fig. 1B provides a summary of "Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019," 2022) discusses the incidence, prevalence, and consequences of major NDs. The most common cause of death among these conditions was AD, which was followed by memory loss and newborn dementia (Castelpietra et al., 2022). Although there are numerous approved treatments for NDs at the moment, the majority of them simply aid in the treatment of the related symptoms (Dnyandev Gadhave et al., 2023). The current treatments have not been able to manage the A poorer survival rate results from the advancement of NDs because of several difficulties with NDs medicines, including the blood-brain barrier (BBB) and numerous unintended side effects of existing medications (D. Gadhave et al., 2023, 2019; Niazi, 2023). Many researchers have highlighted the potential use of nanotechnology approaches to treat CNS conditions including NDs (Gadhave et al., 2021).

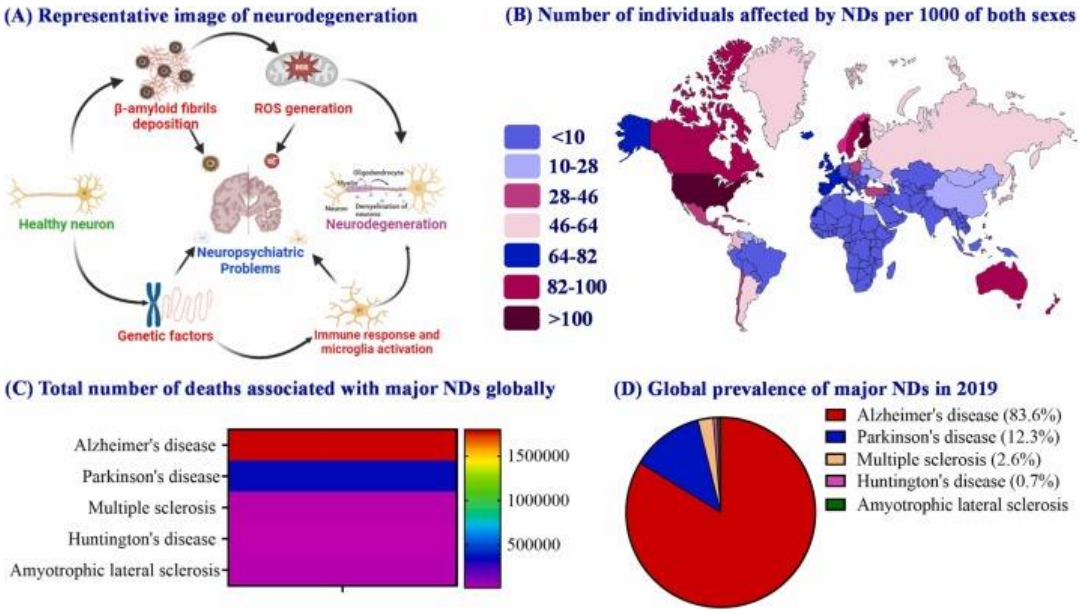

Fig. 1: (A) An illustration of neurodegeneration; (B) A map showing regional variations in the prevalence of NDs and the number of NDs affected per 100,000 individuals by country. According to the key, scores of less than 10, 10–28, 28–46, 46–64, 64–82, 82–100, and more than 100 affected individuals out of 100,000 are displayed in different colors. (C) A statistical depiction of the overall number of fatalities worldwide attributable to major NDs. (D) A statistical depiction of the major NDs' global prevalence percentage in 2019. The inadequacies of conventional treatments, comprehending the precise mechanism of NDs start, the advancement of biomaterials in treating NDS, and their therapeutic relevance are the main topics of the current review. It soon creates new opportunities to enhance the therapeutic properties of NDs.

Major types of neurodegenerative disorders (NDs)

Multiple sclerosis

The central nervous system (CNS), which includes the brain and spinal cord, is impacted by multiple sclerosis (MS), a chronic, immune-mediated neurological illness (Fig. 2). The hallmark of MS is the immunological system unintentionally targeting myelin, which surrounds nerve fibers as a protective layer (Goldenberg, 2012) (Lamptey et al., 2022) The underlying neurons become damaged as a result of inflammation and demyelination. Additionally, the normal transmission of electrical impulses throughout the nerves is disrupted by this illness. Multiple sclerosis symptoms can vary. significantly and include visual disturbances like double or blurred vision, muscle weakness, fatigue, impaired movement, sensory abnormalities including tingling or numbness, cognitive impairments impacting memory and focus, and coordination difficulties (Coles, 2015). Last but not least, secondary progressive MS (SPMS) starts off as RRMS before developing into a progressive phase characterized by worsening symptoms and impairment. The precise reason why MS occurs is still Uncertain, but thought to result from a complex interplay between environmental and genetic factors. Smoking, low vitamin D levels, and specific illnesses are examples of potential risk factors (Sugandhi et al., 2024). To make a diagnosis, neurologists frequently use a mix of clinical history, physical examination, MRI scans, and occasionally even spinal fluid studies (Omerhoca et al., 2018). As of this now, MS has no known cure. However, there are a number of treatment approaches that concentrate on managing symptoms, changing how the illness progresses, and improving MS patients' overall quality of life. Medications, therapy, and lifestyle changes are frequently employed. There are notable differences in how MS develops in different people. Understanding the fundamental causes of MS, developing innovative treatment options, and improving the general quality of life for those with the condition are the main goals of contemporary research (Eva et al., 2023) People who think they could have multiple sclerosis should visit medical experts almost once, especially neurologists, to obtain an accurate diagnosis. diagnosis and obtain the appropriate treatment. Prompt management and early discovery can greatly reduce symptoms and limit the disease's course. Beta-interferon, copolymer 1, and immunosuppressants like natalizumab and mitoxantrone are a few examples of medications.

Alzheimer’s disease

The progressive neurological condition known as Alzheimer's disease (AD) mostly affects the brain and causes memory loss, cognitive decline, and behavioral abnormalities. It is the main element causing In the elderly population, dementia (Lamptey et al., 2022b). The disease, which bears Dr. Alois Alzheimer's name, was initially described by him in 1906 AD and is typified by the buildup of aberrant protein aggregates in the brain. These include tau tangles and beta-amyloid plaques (Ow and Dunstan, 2014). These deposits cause cell death and the slow degradation of brain tissue by obstructing nerve cells' ability to send impulses normally (Breijyeh and Karaman, 2020).

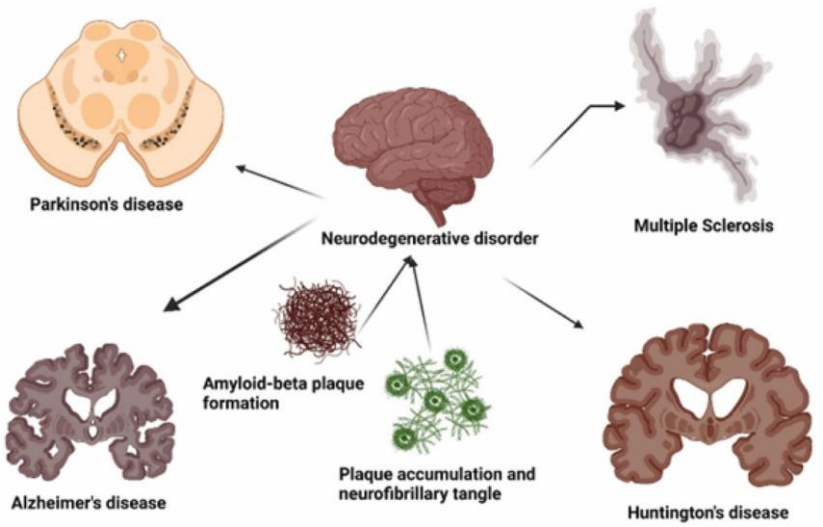

Fig. 2: Illustration of various neurodegenerative disorders such as Parkinson's disease, Multiple sclerosis, Alzheimer's disease, and Huntington's disease.

Functional restrictions. The patient's medical history should be carefully reviewed, cognitive tests should be performed, and any probable reasons of cognitive deterioration should be ruled out make the diagnosis. Cerebrospinal fluid (CSF) analysis and sophisticated imaging methods may also be employed in some situations. Three stages are commonly used to classify AD: mild (early stage), moderate (middle stage), and severe (late stage). Different levels of impairment and distinct symptoms further define each stage (Breijyeh and Karaman, 2020).

The treatment for AD is currently unknown. Nonetheless, drugs like memantine and cholinesterase inhibitors can effectively reduce symptoms and delay cognitive aging. Furthermore, additional therapeutic approaches including cognitive training and occupational therapy might also be helpful (Hogan et al., 2008).

The goal of current research is to comprehend the fundamental causes of AD and create efficient treatment plans. Notably, it has been observed that quick intervention and more knowledge improve the quality of life for both those with the illness and their caretakers.

In addition to affecting persons who have it, AD also significantly burdens those who care for them. Resources, education, and support groups are crucial for those who look after people with AD. Seeking medical guidance for a thorough diagnosis and suitable intervention should be a top priority for people with memory or cognitive impairments as well as their caretakers. More effective readiness and intervention techniques could result from early detection.

Parkinson's disease

One of the main characteristics of Parkinson's disease (PD), a neurological condition, is a progressive loss of motor ability. Parkinson's disease (PD) is frequently caused by a gradual loss of dopamine-producing neurons in the brain, especially in the substantia nigra (Hogan et al., 2008).

Neurotransmitters that control and synchronize certain muscle movements include dopamine (Gepshtein et al., 2014; Lamptey et al., 2022b). Although the exact etiology of Parkinson's disease is unknown, it is believed to be a result of a mix of environmental and genetic factors. These symptoms include bradykinesia, tremors, postural instability, stiffness, and a number of others (Khatri et al., 2020).

The goal of ongoing research is to create more potent treatment plans and get a deeper understanding of the fundamental processes that underlie PD. Increased consciousness is vital for prompt identification and action (Hughes, 1994). For a comprehensive assessment by a neurologist, people with Parkinson's disease symptoms or those who care for them should get medical help as soon as possible. Early identification and timely care can greatly enhance the quality of life for those with Parkinson's disease (PD) (Jankovic and Aguilar, 2008).

Amyotrophic lateral sclerosis

Since there is currently no available diagnostic test for ALS, the diagnosis is primarily made based on clinical symptoms and the methodical elimination of alternative conditions. Nerve and electromyography (EMG) Conduction studies are frequently used to assess how well motor neurons and muscles work. By lessening the damage done to motor neurons, the FDA-approved medication riluzole can slow the progression of ALS (Rg et al., 2012). According to Neupane et al. (2023), edaravone, an FDA-approved adjuvant drug, is used to treat ALS and can slow the progressive decline of physical ability. Unfortunately, there is currently no cure for ALS, and the majority of patients pass away from respiratory failure a few years after symptoms first occur. Presently, the focus is on understanding the underlying mechanisms of ALS and creating efficient treatment

plans. Increased awareness is essential for quick recognition and response. ALS is a crippling illness that poses major challenges for those who have it and their families. To properly manage the impacts of ALS on patients who have the condition, it is essential to provide assistance, assemble a team of experts from many sectors, and continuously carry out research (Hogden et al., 2017).

Huntington's diseases

A genetic and progressive neurological condition, Huntington's disease (HD) impacts a person's physical and mental well-being (Roos, 2010). A hereditary mutation in the huntingtin gene (HTT) causes the disorder by producing a faulty form of the (Hogan et al., 2008; Schulte and Littleton, 2011) huntingtin protein. This mutation causes certain parts of the brain to deteriorate, which leads to a number of mental, cognitive, and physical issues. Since HD is an autosomal dominant genetic disorder, the disease can originate from a single copy of the faulty gene in either parent. The mutation causes the CAG repeat in the HTT gene to expand (Saudou and Humbert, 2016). While there is no cure for HD, supportive care and symptomatic medicine can help manage symptoms. Drugs may be prescribed to lessen psychological issues and motor symptoms and improve the overall standard of living. To address the complex needs of individuals with HD, a multidisciplinary approach involving medical specialists such neurologists, psychiatrists, physical and occupational therapists, and genetic counselors is frequently required. Information on a person's risk of getting HD or passing it on may be obtained through genetic testing. It is recommended that those who are thinking about getting genetic testing seek genetic counseling in order to understand the potential consequences (McGarry et al., 2020). Important components of managing HD and addressing its complex effects on people's life include genetic counseling, prompt diagnosis, and thorough therapy (McGarry et al., 2020).

3. Major molecular mechanisms involved in NDs

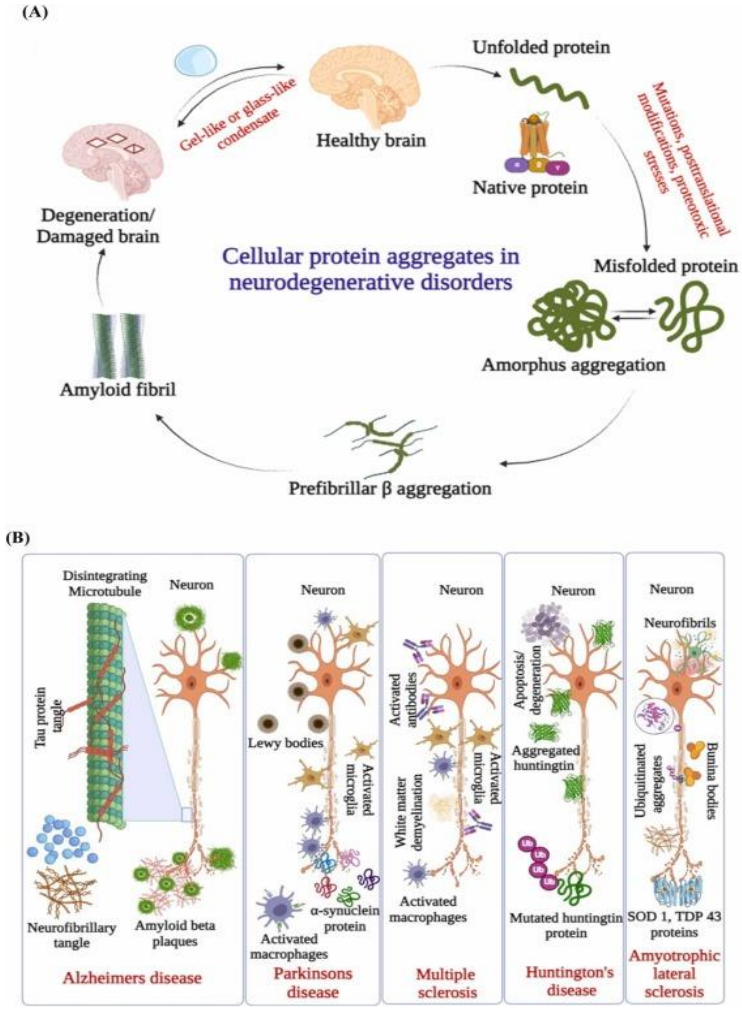

FIG. 3: Schematics show the steps involved in cellular protein aggregation associated with neurodegeneration: (A) represents the native structure of protein transformed in misfolding due to stresses, which impact amyloid protein fibrils and initiation of neurodegeneration. (B) Different proteins and their aggregates are involved in AD, PD, MS, HD, and ALS.

Reviews: trends in neurodegeneration research

An exclusive interview with Huda Zoghbi, a professor at the Baylor College of Medicine Departments of Pediatrics, Molecular and Human Genetics, Neurology, and Neuroscience, opens this issue that focuses on neurodegeneration. Huda is well known for her several innovative findings in the study of neurological disorders, not the least of which is her work clarifying the molecular mechanisms and genetic causes of Rett syndrome and spinocerebellar ataxia. The intricate mechanisms behind prevalent neurodegenerative illnesses have also been clarified by these discoveries. Huda highlights the experiences, mentors, and partnerships that influenced her research interests as she details her path from the clinic to the bench in this interview (Zoghbi, 2017). Then, Edward Lee and associates provide a "At a Glance" summary of RNA metabolism in neurodegenerative illnesses in this issue's review section (Liu et al., 2017). Recently, a number of neurodegenerative illnesses have been linked to altered RNA processing, primarily as a result of investigations using model systems. In addition to outlining possible treatment approaches to target these processes, this study and poster demonstrate how compromised RNA metabolism may be the underlying pathophysiology of neurodegeneration. The protein-level mechanisms that have long been linked to neurodegenerative and associated illnesses are summarized in an earlier DMM "At a Glance" poster by Julie Valastyan and Susan Lindquist (Valastyan and Lindquist, 2014).

New research: models, mechanisms and more

In their first of 10 new studies, Javier Fernández-Ruiz and associates apply previously published findings from a mouse model of familial ALS to a canine model of the illness (Fernández-Trapero et al., 2017). Dogs may have degenerative myelopathy, a neurological disease brought on by mutations in the superoxide dismutase 1 (SOD1) gene, which is also commonly mutated in human ALS. They tested for similar effects in the dog model after finding that cannabinoid receptor type-2 expression is elevated in human ALS and in a mouse model of ALS driven by SOD1 mutations. They discovered that dogs with degenerative myelopathy have higher levels of CB2 receptor expression in their spinal cords, which is in line with earlier findings (Fernández-Trapero et al., 2017). A unique structure, the neuromuscular junction is especially susceptible to neurodegenerative diseases. It does, however, have strong defences against harm and the ability to heal. In their latest DMM paper, Michela Rigoni and associates define the Schwann cell and neuron signalling events, components, and cross-talk necessary to support nerve regeneration in the face of peripheral neuropathies using an in vitro cellular model of the degenerative disease Miller Fisher syndrome (Rodella et al., 2017).

In addition to offering mechanistic understanding, defining the intrinsic cellular abnormalities that define a certain disease state may also operate as a biomarker for illness prediction based on patient cell analysis. Human mesenchymal stem cells (hMSCs) isolated from the bone marrow of sporadic ALS patients respond differently to DNA-damaging chemicals than do hMSCs from healthy participants, according to Miguel Weil and colleagues (Wald-Altman et al., 2017). The authors demonstrate that autophagy control is disrupted in cells from ALS patients and link this impairment to autophagy. These results support the idea that autophagy dysregulation plays a part in ALS and offer a possible biological biomarker for the illness.

Clinical relevance of novel ND therapies

To confirm the efficacy and therapeutic success of specially created innovative medicines, clinical research is necessary (Kumar et al., 2022). Considering the complexity of neurodegeneration disorders (NDs), the creation of disease-modifying therapies gives the biomedical community new hope for managing NDs successfully (Katsuno et al., 2012). The literature claims that improved therapies for NDs provide a number of benefits, such as high-quality care and cost-effectiveness (Kumar et al., 2022). But even with these developments, questions about the effectiveness and safety of these cutting-edge treatments still exist. In vivo applications, a large number of candidate compounds show little to no disease-modifying potential (Katsuno et al., 2012). Using Pittsburgh compound for positron-emission tomographic amyloid testing, patients receiving bapineuzumab demonstrated a greater reduction in amyloid and a drop in Patients with mild-to-moderate Alzheimer's disease participated in phase 2 clinical trials where CSF fluid phosphorylated tau, indicating target engagement and reduced neurodegeneration. Those who were given a placebo did not exhibit these same decreases. Code of trial NCT05541627 To evaluate safety, tolerability, and early efficacy signals, participants in an early apparent Phase I/II, open-label trial will receive a single intracerebral bilateral injection of AB-1001 into the striatum (caudate and putamen).

The main result incidences are treatment-emergent adverse events, dose-limiting toxicities, and serious adverse events (SAEs). the outcome MRI evaluations of the structural and volumetric elements of the brain regions affected by HD Since this information was not cited in any previous study or research publication, the formulations pertaining to Clinical Trials on Neurological Disorders (NDs) were only obtained from the Clinical Trials website It must be stated beneath the table that: On January 30, 2024, data was gathered from clinicaltrials.gov,

Future remarks

Finding potential candidates for neurodegenerative research remains a significant difficulty despite advances in biomedical science, molecular biology, genetics, and pharmaceutical sciences. medicinal. An in vitro cell culture, computational/in-silico, or in vivo/pre-clinical animal model is a clinically relevant disease model that

is necessary to comprehend the pathophysiology of the disease (Noble and Burns, 2010a).

There are currently mouse models that have undergone genetic modification to research neurodegenerative diseases. The extent to which these pre-clinical in vivo models can result in human translation and give us information that closely resembles real diseases varies widely, notwithstanding their benefits.

Human neuroprotective agent clinical research is difficult since it would be costly, time-consuming, and high-risk without readily quantifiable results.

The development of new therapeutic approaches will continually stall in the absence of a repeatable and informative model system of neurodegenerative disease (for example, one that includes several cell types in addition to mature neurons). Papageorgiou and Yiannopoulou (2013) New therapeutic strategies have been developed as a result of the identification of certain molecular targets. Gene treatments, such as RNA interference and CRISPR-Cas9 editing, have the potential to treat genetic abnormalities that underlie neurodegenerative diseases. With an emphasis on protein aggregation, Another area of active research is alpha-synuclein in Parkinson's disease and beta-amyloid in Alzheimer's disease (Nojadeh et al., 2023)

Table 1: Summarizes various novel therapies currently undergoing clinical trials for treating NDs. It confirms that most advanced therapies are in the initial phases of clinical trials, including phases 1, 2, and 3.

S. NO	DISORDER	TRIAL CODE	DELIVERY ROUTE	THERAPY	PHASE
1.	Alzheimer's Disease, Mild Cognitive Impairment	NCT05040217	Stereotaxic ally administration	A Clinical Trial of AAV2-BDNF Gene Therapy in Early Alzheimer's Disease and Mild Cognitive Impairment	1
2.	Huntington disease	NCT05541627	Bilateral injection	A Study to Evaluate AB-1001 Striatal Administration in Adults with Early Manifest Huntington's Disease	2
3.	PD	NCT01564992	Bilateral injection	Drug Interaction with Genes in Parkinson's Disease (DIGPD)	2
4.	Sanfilippo Type A Syndrome	NCT01474343	Intracerebral administration	Intracerebral Gene Therapy for Sanfilippo Type A Syndrome	1
5.	Human Prion diseases	NCT02837705	Intracerebral administration	Therapeutic Antibodies Against Prion Diseases from PRNP Mutation Carriers (PRNP)	2
6.	Parkinson Disease	NCT04167540	Bilateral image guided	infusion GDNF Gene Therapy for Parkinson's Disease	1
7.	Alzheimer's Disease	NCT03634007	Intrathecal administration	Gene Therapy for APOE4 Homozygote of Alzheimer's Disease	1
8.	Alzheimer's Disease	NCT00017940	Intrathecal administration	Gene Therapy (Human Nerve Growth Factor) for Alzheimer's Disease Clinical Trial	2
9.	Alzheimer's Disease	NCT05400330	Intrathecal administration	Long-Term Follow-up of Gene Therapy for APOE4 Homozygote Alzheimer's Disease (LEADLTFU	3
10.	Alzheimer's Disease s	NCT00663026	Subcutaneous injection	Study Evaluating Bapineuzumab In Alzheimer's Disease Subject	3
11.	Alzheimer's Disease	NCT00676143	IV infusion	Study Evaluating the Safety and Efficacy of Bapineuzumab in Alzheimer's Disease Patient	3
12.	Alzheimer's Disease	NCT00667810	IV infusion	Study Evaluating the Efficacy and Safety of Bapineuzumab in Alzheimer's Disease Patients	1
13.	Alzheimer's Disease	NCT00998764	Infusion	Long-Term Safety and Tolerability Extension Study of Bapineuzumab in Alzheimer's Disease Patients	2
14.	Alzheimer's Disease	NCT05821153	Subcutaneous injection	Low Dose IL2 Immunotherapy in AD	1
15.	Alzheimer's Disease	NCT00112073	IV	AAB-001 in Patients with Mild to Moderate Alzheimer's Disease	2
16.	Alzheimer's Disease	NCT05792163	Oral administration	A First Time in Human Study of SNP318 as a Treatment for Neurodegenerative Diseases Including Alzheimer's Disease	2

Table 2: FDA approved drugs for the treatment of ND's.

S. No	Disorder	Drug	Reference
1.	Alzheimer's Disease	Donepezil, rivastigmine, galantamine, Memantine	(Dur˜ aes et al., 2018)
2.	Parkinson's Disease	Levodopa, carbidopa, benserazide, tolcapone, entacapone, selegiline, rasagiline, amantadine	
3.	Huntington's Disease	Tetrabenazine	

CONCLUSION

Despite new discoveries that improve our understanding of how the disease progresses, the frequency of NDs is rising, and there are currently insufficient viable neuroprotective and neurorestorative treatments. creating a sense of urgency for the discovery of new drugs. Managing neurodegenerative diseases is made easier by advances in our knowledge of the different targets and intracellular and intercellular signaling pathways involved in neurodegenerative illness. In order to better understand the pathophysiology of diseases and highlight the connections between different factors, more research on neurodegenerative disorders must concentrate on better drug delivery techniques. elements include inflammation, genetic modification, and further neurochemical abnormalities. As the number of elderly people worldwide rises, so does the prevalence of neurodegenerative disease. As a result, giving patients practical methods to cure or prevent neurodegenerative disease is a major problem that researchers, physicians, that health officials are dealing with. Effectively addressing this challenge requires a thorough comprehension of the pathological processes underlying all neurodegenerative disorders, including those affecting the brain and visual system. In order to successfully monitor and cure NDs, future research should concentrate on linking molecular pathways to complex neurodegenerative diseases and investigating different approaches "not limited to pharmacological agents."

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