WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
Coden USA: WJPRAP Impact Factor 8.453
Volume 14, Issue 23, 547-574. Review Article ISSN 2277–7105

"CLINICAL FEATURES AND DIAGNOSTIC APPROACHES IN MAJOR NEURODEGENERATIVE DISEASES: AN UPDATED REVIEW"

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Article Received on 30 Oct. 2025,
Article Revised on 20 Nov. 2025,
Article Published on 01 Dec. 2025,
https://doi.org/10.5281/zenodo.17747987

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How to cite this Article: Ajeet Singh, Prashant Mishra, Rishabh Maurya, Tanushka Singh, Dr. Manju Pandey, Sarita Singh. (2025). Clinical Features And Diagnostic Approaches In Major Neurodegenerative Diseases: An Updated Review. World Journal of Pharmaceutical Research, 14(23), 547–574.
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ABSTRACT

There are numerous clinical questions that do not have simple answers, even for well-trained medical professionals. The diagnostic instrument frequently used to evaluate cognitive impairment in neurodegenerative diseases is founded on established clinical criteria. However, differentiating between disorders can be quite challenging, particularly in the early stages or with atypical presentations. This issue becomes particularly significant when there is still a chance to apply an appropriate treatment. To resolve this challenge, doctors must have access to a variety of diagnostic tests, such as neurofunctional imaging, which provide greater specificity in clinical evaluations. Nonetheless, the reliability of these diagnostic tests can vary, so the diagnostic validity of a specific investigation must be determined by comparing the results obtained from "true" criteria to the "gold standard" or reference test. While pathological analysis is deemed the gold standard for a wide range of diseases, it cannot be utilized for neurological processes. Other methods may offer potential solutions, including clinical follow-up of patients, the creation of a data bank, or the implementation of computer-aided diagnostic algorithms. Neurodegenerative diseases are a prevalent source of morbidity and cognitive dysfunction in the elderly population. Most healthcare providers who work with older adults are not adequately trained to identify these conditions, aside from the well-known Alzheimer's disease (AD). its variants, progressive supranuclear palsy (PSP),

corticobasal degeneration (CBD), Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA), and Huntington's disease (HD). For each condition, we present a brief overview of the epidemiology, defining clinical symptoms and diagnostic criteria, relevant imaging and laboratory features, genetics, pathology, treatments, and differential diagnosis.

KEYWORDS: Neurodegenerative, Alzheimer's disease, epidemiological data, neuroimaging, Huntington's disease.

1. INTRODUCTION

Neurodegenerative disease (ND) is a prevalent and increasingly significant cause of mortality and morbidity across the globe, particularly among older adults. The individual neurodegenerative disorders are varied in their clinical presentations and the underlying physiological mechanisms, although they often share common features. The precision of diagnosis is crucial, as it allows for more accurate prognostication and frequently guides specific treatment and management strategies. In this review, we present a brief overview of several of the most common neurodegenerative diseases especially those related to cognitive impairment and explore their clinical features and diagnosis, epidemiology, imaging findings, genetic aspects, relevant laboratory tests, differential diagnosis, and treatment options. This review is not designed to provide a comprehensive overview of each diagnosis but rather to offer a basic background and encourage further exploration.[1] The molecular pathological classification is cantered on distinguishing between synaptic, intracellular, and extracellular protein accumulations. The subcellular location of intracellular deposits (such as nuclear, cytoplasmic, or cell process) is also of great significance. A variety of new antibodies have been developed for immunohistochemistry, which illustrate novel immunostaining patterns. Nevertheless, in terms of diagnostic classification, not every protein immunoreactive morphology is acknowledged. Although morphological criteria are predominantly employed for disease subtyping, biochemical and genetic analyses are often necessary as complementary assessments to immunohistochemistry. It is important to note that there exist certain forms of neurodegenerative diseases, such as hereditary spastic paraplegia or some variants of spinocerebellar ataxia, where no specific protein inclusions can be identified using the currently available methods.[2] In this study, we analyse the relationship between depressive symptoms and neurodegenerative disorders from a clinical standpoint, concentrating on the depressive symptoms noted in principle neurodegenerative diseases.

Notably, in neurodegenerative diseases, depression may emerge as an early symptom and can frequently be the predominant manifestation, particularly in the early phases of degenerative brain processes. These depressive symptoms are crucial in medical practice since they can be the most significant concern raised by patients or caregivers. Additionally, they influence the quality of life of patients and have been correlated with heightened caregiver burden, more rapid progression of disability and functional decline, along with earlier institutionalization and mortality.[3]

1.2 Concepts of Disease Classification

Classification of neurodegenerative diseases is based on the following.

1. Clinical manifestations determined by the anatomical area indicating neuronal dysfunction.
2. Proteins that exhibit various biochemical modifications and accumulate in neurons or glial cells (intracellular), or in extracellular regions. Thus, anatomical, cellular, and protein vulnerability patterns can be outlined in neurodegenerative diseases.

1.3 Anatomic involvement and clinical symptoms

Clinical classification is advantageous when emphasizing the early symptoms. Combinations of clinical manifestations may occasionally be recognized as an early characteristic and frequently during the advancement of the disease. The following classifications of clinical manifestations are distinguished:

1. Cognitive decline, dementia, and modifications in high-order brain functions. The anatomical structures involved consist of the hippocampus, entorhinal cortex, limbic system, and neocortical areas. Frontotemporal dementia is correlated with the degeneration of the frontal and temporal lobes (frontotemporal lobar degeneration: FTLD)
2. Movement disorders include hyperkinetic and hypokinetic movement disorders, symptoms related to cerebellar dysfunction or the engagement of the upper and lower motor neurons. The most significant anatomical regions involved in movement disorders are the basal ganglia, thalamus, brainstem nuclei, cerebellar cortex and nuclei, motor cortical areas, and lower motor neurons of the spinal cord.[4]

1.4 Molecular pathologic classification

The entire range of protein deposits can only be visualized through immunohistochemistry. The diagnostic method concentrates on differentiating synaptic, intracellular, and extracellular protein accumulations. It is important to identify the subcellular location of the

intracellular deposits—whether they are nuclear, cytoplasmic, or neuritic (axonal or dendritic), or present in cellular processes (for example, in astrocytes). At present, not all protein deposit morphologies are considered in disease classification. This is attributed to the development of many new antibodies, and the diagnostic criteria have not been revised to incorporate new immunostaining patterns. Biochemical and genetic analyses are frequently required as complementary assessments to immunohistochemistry. Morphological criteria are predominantly employed for disease subtyping. There are a few exceptions where biochemical alterations or even gene polymorphisms are also factored into subtyping (Kovacs, 2016). Importantly, hereditary forms have been described for all neurodegenerative proteinopathies, thus genetic analysis and a detailed family history are recommended for comprehensive disorder characterization.[5] The following proteins are associated with most sporadic and genetic adult-onset neurodegenerative diseases (Kovacs et al., 2010):

1. The microtubule-associated protein tau, encoded by a single gene (MAPT) on chromosome 17q21.
2. Ab, which is cleaved from a large transmembrane precursor protein known as amyloid precursor protein.

   The APP gene has been located in the centromeric region of chromosome 21q.
3. a-synuclein is produced by a single gene (SNCA) found on chromosome
4. The prion protein (PrP) is a protein consisting of 253 amino acids, encoded by the PRNP gene situated on chromosome 20
5. The transactive response (TAR) DNA-binding protein 43 (TDP-43) is a highly conserved nuclear protein, encoded by the TARDBP gene located on chromosome 1.
6. FET proteins encompass the fused-in sarcoma (FUS), Ewing sarcoma RNA-binding protein 1 (EWSR1), and TATA-binding protein-associated factor 15 (TAF15) (Neumann et al., 2011). The most studied among these is FUS, a protein that is 526 amino acids long and encoded by a gene on chromosome 16.[6]
7. Additionally, there are other proteins primarily associated with hereditary disorders. These include proteins encoded by genes related to neurologic trinucleotide repeat disorders, neuroserpin, ferritin-related neurodegenerative diseases, and familial cerebral amyloidosis.

Neurodegenerative disease groups are classified according to the main protein deposits found in the nervous system. Thus, we can identify tauopathies, alpha-synucleinopathies, TDP-43 proteinopathies, FUS/FET proteinopathies, prion diseases, trinucleotide repeat disorders,

neuroserpinopathy, keratopathy, and cerebral amyloidosis This terminology overlaps with clinicopathologic descriptions, such as the classification of FTLD (refer to Chapters 25 and 26). Alzheimer's disease is often discussed separately because it is characterized by the pathological accumulation of both amyloid-beta and tau proteins. An increase in biochemical modifications of these proteins has been reported in neurodegenerative conditions (Kovacs, 2016). Understanding these modifications is crucial for elucidating the pathogenesis of neurodegenerative diseases and for developing biomarkers. In neuropathology, the most significant step is to evaluate the localization and distribution of proteins (Kovacs and Budka, 2010). Extracellular or vascular deposits consist of those that show immunoreactivity for amyloid-beta or prion protein. Additionally, disease-associated prion protein demonstrates a synaptic deposition pattern. Proteins that accumulate intracellularly include tau, alpha synuclein, TDP-43, FUS/FET proteins, as well as those associated with trinucleotide repeat disorders or rare hereditary diseases. Regarding protein distribution, it is of utmost importance to note that many protein deposits exhibit a hierarchical involvement of brain regions, which has significant implications for clinicopathologic correlation, as it allows for the differentiation between early and late stages or phases of specific diseases. In conclusion, the evaluation of the most common neurodegenerative conditions necessitates differentiation based on the predominance of extra- or intracellular protein deposits and the assessment of stages and phases in a growing number of disorders.[7]

Table 1: Comprehensive Table of Dementia & Movement Disorders.

Category	Subtype / Variant	Description (Brief)
Alzheimer's Dementia	Amnestic	Predominantly memory impairment
	Non-amnestic	Language, visuospatial, or executive dysfunction more prominent than memory
	Frontal-variant AD	Behavioral and executive dysfunction resembles FTD
	Corticobasal syndrome (AD pathology possible)	Asymmetric rigidity, apraxia, cortical sensory loss
	Posterior cortical atrophy	Visual processing deficits, visuospatial issues
Dementia with Lewy Bodies (DLB)	—	Fluctuating cognition, visual hallucinations, parkinsonism
Frontotemporal Dementia (FTD)	Behavioral-variant FTD (bvFTD)	Personality change, disinhibition, apathy
	Primary Progressive Aphasia (PPA)	Progressive language impairment
	Nonfluent / Agrammatic Variant PPA (naPPA)	Effortful speech, grammar errors
	Semantic Variant PPA	Loss of word meaning, fluent but empty

	(svPPA)	speech
	Logopenic Variant PPA (lvPPA)	Word-finding pauses, impaired repetition
Corticobasal Syndrome (CBS)	—	Asymmetric parkinsonism, apraxia, dystonia
Progressive Supranuclear Palsy (PSP) – Related Syndromes	PSP-Richardson Syndrome	Early falls, gaze palsy, axial rigidity
	PSP-Parkinsonism	More tremor, better levodopa response
	PSP with Pure Akinesia with Gait Freezing	Marked gait freezing, little tremor/rigidity
	PSP with Progressive Apraxia of Speech	Speech production difficulty, motor speech issues
Rapidly Progressive Dementia (RPD)	—	Fast cognitive decline (weeks–months), e.g., CJD
Hypokinetic Movement Disorders	Bradykinesia	Slowness of movement
	Hypokinesia	Reduced amplitude of movement
	Akinesia	Absence of movement
	Rigidity	Increased tone, resistance to passive movement
	Rigid-akinetic syndromes	Dominant rigidity & akinesia (e.g., PSP-RS)
	Freezing	Sudden inability to start/continue movement
	Stiff muscles	Increased muscle tone
Hyperkinetic Movement Disorders	Tremor	Rhythmic oscillatory movement
	Myoclonus	Sudden, brief jerks of muscle groups
	Chorea	Irregular, dance-like movements
	Ballism	Flinging, violent movements (proximal muscles)
	Athetosis	Slow, writhing movements
	Tics / Stereotypies	Repetitive, suppressible (tics) or automatic (stereotypies)
	Startle Syndrome	Exaggerated motor response to stimulus
	Restless Legs Syndrome	Urge to move legs, worse at rest/night
	Ataxia & Dysmetria	Incoordination & impaired targeting movements
	Akathisia	Inner restlessness, need to move

1.5 Pathophysiology of Neurodegenerative Diseases

1.5.1 Multiple sclerosis

Multiple Sclerosis (MS) is an immune-mediated disorder of the central nervous system (CNS) marked by significant myelin degeneration.[8] Myelin, an electrically insulating substance, plays a crucial role in stabilizing and organizing the axonal cytoskeleton.[9] When axons undergo demyelination, it severely impairs the propagation of neuronal signals, resulting in various mental and physical symptoms This impairment can significantly affect daily functioning. Consequently, those affected may face numerous challenges in both cognitive and physical domains.[10] Multiple Sclerosis (MS) generally presents in adults in their late 20s or early 30s, leading to depression in more than half of the cases.[11] This illness

affects over 2.5 million individuals in North America and Europe.[12] The precise cause of MS is still unclear, but it is believed to result from both genetic and environmental factors. For instance, some genes that heighten the risk of MS are associated with the immune molecule major histocompatibility complex (MHC) class II. Environmental factors encompass exposure to microbes, stress, and smoking.[13] Furthermore, a deficiency in vitamin D due to reduced sunlight exposure could raise the likelihood of developing MS.[14]

Numerous studies indicate that multiple sclerosis (MS) is a disease driven by inflammation, with the immune system playing a pivotal role.[15] It is marked by the activation of CD8+ cytotoxic T cells that specifically attack neurons and facilitate axonal transection. Additionally, a CD4+ T-cell response is observed during the damage caused by MS, which prompts the release of various inflammatory mediators and toxic substances. Furthermore, the inflammatory microenvironment within the central nervous system (CNS) is rich in proteolytic enzymes, cytokines, and free radicals, all of which may contribute to both direct and indirect demyelination of axons.[16] Indirect demyelination encompasses the loss of protective myelin, mitochondrial dysfunction, and the release of nitric oxide, all of which can adversely affect axonal survival.[11,16] Various pharmacotherapies, including glatiramer acetate, natalizumab, and mitoxantrone, have demonstrated effectiveness in reducing the symptoms of this disease. However, many of these medications can lead to negative side effects such as skin irritation, liver damage, and hypertension. Therefore, it is essential to conduct more research to develop innovative treatment strategies for MS. The advancement of immune-mediated, viral, and genetic models of this disease may provide insights into its characteristic features and help in identifying therapeutic targets.

1.5.2 Parkinson’s Disease

Parkinson's disease (PD) is a type of neurodegenerative disorder that presents with motor symptoms such as tremors and rigidity, as well as neuropsychiatric disturbances that can influence the patient's speech, mood, and behavior. It ranks as the most prevalent neurodegenerative disease after Alzheimer's disease (AD) and usually affects people between the ages of 50 and 60.[17] Multiple studies have shown that Parkinson's Disease (PD) is linked to the neurodegeneration of neurons due to inflammation in the central nervous system (CNS).[18] It is believed that both immune system activation and inflammatory mechanisms significantly contribute to the development and advancement of PD. In this condition, inflammation in the periphery triggers the activation of microglia, which subsequently leads

to the neurodegeneration of neurons in the substantia nigra, a brain region associated with motivation and reward.[19] Additionally, PD is linked to the activation of lymphocytes within the CNS. Research indicates that a majority of PD patients exhibit markedly elevated levels of cytokines such as IL-1β, TNF-α, and interleukin-2 (IL-2), along with an increased presence of CD4+ and CD8+ T lymphocytes, suggesting heightened inflammation and an activated immune response.[20]

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At present, several animal models are being used to explore the pathophysiology of Parkinson's Disease (PD), and they have proven to be quite beneficial in understanding the molecular mechanisms related to this illness.[21] One of the most prevalent neurotoxin animal models is the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced mouse model, which simulates the biochemical changes that take place in PD.[21,22] MPTP specifically targets the neurons associated with PD, resulting in the apoptosis of dopaminergic cells in the substantia nigra. Furthermore, MPTP disrupts mitochondrial respiration, which can lead to cytotoxic effects. Other animal models include the 6-hydroxydopamine (6-OHDA) rat, characterized by the destruction of the dopaminergic pathway in the substantia nigra. The creation of both genetic and chemically induced models could help scientists clarify the neurobiological mechanisms involved in PD and identify new therapeutic strategies.

1.5.3 Alzheimer's Disease

Alzheimer's disease (AD) is the most prevalent type of neurodegenerative disorder, marked by a decline in short-term memory. It primarily impacts those aged 65 and older, with a higher occurrence in women compared to men. Additional symptoms of AD encompass irritability, heightened stress levels, and mood disorders.[23] While there is no definitive cure for Alzheimer's Disease (AD), most individuals affected by it rely on pharmaceutical and psychological therapies that can help mitigate some of their symptoms. On a molecular scale, AD results from the accumulation of beta-amyloid and tau amyloid proteins in the brain.[24] The buildup of these amyloid proteins increases brain toxicity and is a pivotal event that triggers neuronal degeneration. Additionally, there is mounting evidence that links AD with neuroinflammation and heightened immune system activity.[25] For instance, during an inflammatory response, the activation of microglia and astrocytes can lead to an increase in beta-amyloid protein production.[25] Moreover, research has shown that individuals with AD have significantly higher levels of pro-inflammatory cytokines, including TNF-α, TGF-β, and interleukin-6 (IL-6), compared to healthy individuals, indicating the crucial role of inflammation in the pathophysiology of AD.[26] Other inflammatory factors, such as the complement system, pentraxin acute-phase proteins, and neuronal-type nicotinic acetylcholine receptors, also play a vital role in the progression of AD.[25] While there is no definitive cure for Alzheimer's Disease (AD), many patients turn to pharmaceutical and psychological therapies that may help alleviate some of their symptoms. On a molecular scale, AD is driven by the accumulation of beta-amyloid and tau proteins in the brain. This build up increases brain toxicity and is a pivotal event that leads to neuronal degeneration. Additionally, there is mounting evidence that links AD with neuroinflammation and heightened immune system activity. For instance, during an inflammatory response, the activation of microglia and astrocytes can elevate the production of beta-amyloid protein. Moreover, research has indicated that individuals with AD have significantly higher levels of pro-inflammatory cytokines such as TNF-α, TGF-β, and interleukin-6 (IL-6) compared to healthy individuals, underscoring the critical role of inflammation in the pathophysiology of AD.[27] Other inflammatory factors, including the complement system, pentraxin acute-phase proteins, and neuronal-type nicotinic acetylcholine receptors, also play a vital role in the advancement of AD. A variety of animal models have been utilized to explore the pathogenic and neurological mechanisms of AD, with the goal of identifying new therapeutic targets . Both natural and genetic models of this disease are being extensively researched to gain a deeper understanding of its neuropathological features. AD can also be induced in animals by

administering chemical compounds or pharmaceutical agents directly into the brain.[28] One study has indicated that the intracerebroventricular infusion of beta-amyloid peptides into rats can lead to progressive brain dysfunction and neurological damage akin to that seen in AD patients.[29]

1. The concept of multi proteinopathies

Neurodegenerative proteinopathies often demonstrate a high frequency of co-occurrence). Therefore, in addition to the signature lesions of a disease, further pathological changes can be found within the same brain in reality, the aging brain reveals a broad spectrum of proteinopathies with varying combinations, which hinders the translation of disease subtyping into biomarkers that are easily interpretable in clinical settings. The threshold for cognitive impairment might be reached due to a significant amount of a single disease or through the simultaneous presence of neuropathological changes that are not alone sufficient to cause dementia. This multiproteinopathy is linked to several gene mutations (for example, bAPP mutation Ab, tau, and also with a synuclein pathology or PRNP mutations in combination with tau or a-synuclein pathology.[30]

2. Current Advancement of Diagnosis of Neurodegenerative Diseases

3.1 Amyloid imaging

Extracellular accumulations of Amyloid-beta (Ab) plaques are recognized as one of the defining pathological markers of Alzheimer's disease (AD) and can be visualized in vivo through positron emission tomography (PET). To this day, international guidelines recommend the use of Ab-PET during the diagnostic assessment of patients with suspected AD, especially in instances of atypical clinical presentations or in younger patients.[30] Ab PET delivers binary information regarding the presence of amyloid burden in the brain, yet it does not permit the classification of the disease stage.[7, 8] Beyond the typical amnestic syndrome seen in AD, the following atypical variants are best characterized: visuospatial and visuo-perceptual syndromes in posterior cortical atrophy.[31]

3.2 Tau imaging

Numerous disease entities fall under the umbrella of tauopathies. This includes Alzheimer's disease, progressive supranuclear palsy, corticobasal degeneration, and various forms of frontotemporal lobar degeneration, all characterized by the presence of intraneuronal tau deposits. These disorders not only lead to clinically distinct syndromes but also differ significantly in terms of the underlying tau pathology. This includes variations in splicing

isoforms, different histopathological forms of aggregation, and the types of affected cells.[32] Recently, in vivo PET imaging of tau tangle pathology with several tracers (e.g., AV-1451, THK-5351) has demonstrated promising results. According to initial studies, Tau-PET may be less sensitive than Ab-PET for the early diagnosis of Alzheimer's disease. However, it may allow for the documentation of the onset of actual neurodegenerative damage and could be valuable for differential diagnosis. Since tau pathology appears to be more closely related to the site and extent of neuronal injury than amyloid pathology in Alzheimer's disease, it may represent a superior tool for monitoring disease progression and therapy.[33]

3.3 FDG

In addition to the detection of underlying pathology with Amyloid- and Tau-PET, imaging of the cerebral glucose metabolism with FDG-PET is a well-established method to assess the extent and spatial distribution of neuronal injury. FDG-PET can be considered a universal tool for imaging neurodegeneration as it provides information on ‘where the disease is’ and ‘how extended the disease is’, and thus, in a single examination allows detection, staging and characterization of mostly all types of neurodegenerative disorders. It does not, however, yield reliable information on the underlying neuropathology. In summary, FDG measures the consequence rather than the cause of disease.[34]

3.4 Structural MRI

The wide-ranging diagnostic potential of MRI is invaluable for eliminating non neurodegenerative origins of cognitive impairment (for instance, cerebrovascular, inflammatory, or neoplastic disorders) Concerning neurodegenerative conditions, MRI detects regional atrophy patterns that are thought to develop later in the disease trajectory. Currently, we are in a favourable position to utilize a comprehensive array of imaging techniques, which allow us to capture significant pathologies related to neurodegeneration in vivo. In this report, we highlight a group of representative patients exhibiting various clinical presentations and at different stages of their diseases who underwent multimodal imaging, including FDG-PET, Ab-PET, Dopamine-transporter imaging, Tau-PET, and structural MRI in our facility, to showcase the complementary advantages of the imaging approaches used.[35]

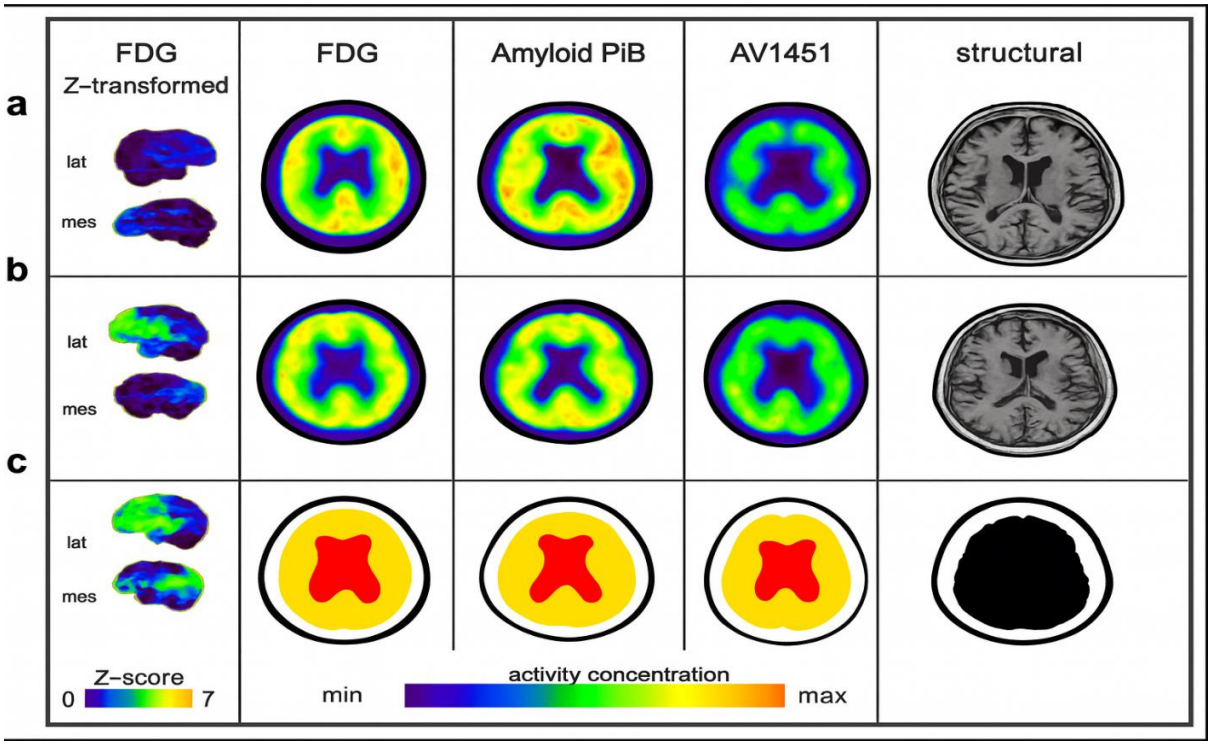

Figure 1: Structural Images of MRI Scanning.

3. DISCUSSION

Structural and molecular imaging plays a significant role in the diagnostic evaluation of patients exhibiting dementia symptoms. On one hand, FDG is commonly utilized at most PET centers, while on the other hand, there are three FDA-approved F-18-labeled Ab-tracers, making these diagnostic options accessible to a wide range of patients. Nevertheless, both FDG and Ab-PET have not yet attained the level of clinical acceptance for diagnostic use that is already established for FP-CIT-SPECT and structural MRI. In the early detection of neurodegenerative diseases, Ab-PET provides essential insights into the general presence of cerebral amyloid deposition at very early, even preclinical stages of the disease, which other biomarkers, such as FDG-PET and cerebrospinal fluid analysis, fail to deliver. Furthermore, Ab-PET is beneficial in the differential diagnosis of atypical clinical presentations of cognitive decline. In this regard, Ab-PET facilitates the identification of disorders with unusual clinical manifestations in the presence of AD pathology and the exclusion of AD pathology in neurodegenerative disorders that clinically resemble AD symptomatology. It is important to note that Ab-PET alone does not distinguish between AD and DLB, as Ab pathology can also be found in some DLB patients. However, these disease entities can be differentiated through dopamine transporter imaging.[36]

Table. No. 2

Panel	FDG (Z-Transformed)	FDG PET	Amyloid PiB PET	FP-CIT (DAT SPECT)	Structural MRI	Interpretation
a	Shows cortical hypometabolism patterns (blue–yellow map)	Mild–moderate posterior & temporal hypometabolism	Significant amyloid deposition (yellow–red)	Preserved DAT in striatum	Mild cortical atrophy	Typical Alzheimer's disease pattern
b	Asymmetric frontal/temporal involvement	Frontal-dominant hypometabolism	Mixed or low amyloid signal	Reduced DAT uptake (putamen/caudate)	Moderate atrophy	Lewy body dementia / FTD overlap
c	Diffuse cortical hypometabolism	Severe global hypometabolism	High amyloid positivity	Moderate DAT reduction	Marked cortical atrophy	Advanced Alzheimer's / Mixed dementia

In the follow-up care of Alzheimer's Disease (AD), FDG-PET is capable of monitoring the degree of neuronal damage over time, while Ab PET cannot differentiate between various stages of the disease due to an early plateau, it is understood that Tau-PET provides similar insights into the disease stage in cortical amyloid deposits.[37] Presently of AD as FDG-PET, while also being able to indicate the spread of the underlying pathology in AD. In the pursuit of therapies that directly address amyloid pathology, there have been only limited achievements recently. In addition to some failures in the later phases of clinical trials for Ab-targeting therapies, the monoclonal antibody aducanumab has been shown to slow cognitive decline and reduce Ab-load in the brain, as assessed by PET in patients with prodromal or mild AD.[38] Nevertheless, while PET serves as a practical method for measuring Ab-load, it comes with a caveat; the PET signal may be affected by tissue perfusion, which requires non-standard PET protocols to reliably quantify Ab-load over time as a measure of treatment response.[39]

4. Preventing neurodegenerative disease

As people age, the majority of illness increasingly impacts systems that have a limited ability to repair or sustain themselves. Neurons, being post-mitotic, are particularly susceptible in this aspect, resulting in a growing incidence of neurodegenerative diseases as the average age of the population rises. For individuals facing a decrease in movement, limb atrophy, tremors, or memory issues, the emergence of symptoms seems to indicate the start of the underlying condition, and people frequently attempt to connect the cause to recent occurrences—'It all started after the operation', 'I was fine until I had a bad cold'. The body's extraordinary ability to buffer and adapt to changes suggests that neurodegeneration actually begins well before the first symptoms are noticed. In Parkinson's disease, 90% of neurons in the

substantia nigra have already been lost by the time the disease is diagnosed.[16] In Alzheimer's, there exists a lengthy presymptomatic prodrome[17] In this month's publication, Jun Liu and colleagues[18] highlight the increased levels of free water in the substantia nigra among patients suffering from idiopathic REM sleep behaviour disorder (RBD). Why is this important? RBD can be seen as an early indicator of Parkinson's disease, potentially manifesting a decade or more before the classic triad of tremor, rigidity, and bradykinesia appears. Understanding the pathogenic processes at such an early stage indicates the potential for early intervention, which could help prevent the development of full-blown symptoms. The prevention of neurodegenerative diseases would provide significant advantages to society; however, while it may seem achievable for prevalent conditions like Alzheimer's disease, the prevention of less common neurodegenerative diseases poses challenges. Although these conditions are rare on an individual basis, they collectively represent a considerable disease burden, making prevention an essential focus.[40]

The initial challenge lies in the issue of frequency. Encouraging a population to modify its diet and increase physical activity is reasonable for a prevalent condition like heart disease. However, for a condition such as ALS, which has a lifetime risk of 1 in 300, or even less common diseases like progressive supranuclear palsy, the burden of changing one’s lifestyle does not align with the disease's risk. This makes such interventions impractical on a population scale unless they can be integrated with risk prevention strategies for other diseases, in which case the intervention is already being implemented. Recent findings indicate that cardiovascular risk serves as an independent risk factor for ALS or Alzheimer’s disease, which fits into this framework[41] One possible approach is to enhance the population's predisposition to neurodegenerative diseases, thereby creating a cohort with a medium risk of illness. Nevertheless, screening for uncommon diseases presents challenges, as the false positive rate is closely associated with the frequency of the disease and the test's accuracy. Testing the entire population at birth through whole genome sequencing, for instance, may initially seem like a sensible method to pinpoint individuals at risk for monogenic neurodegenerative disorders. However, the variability in gene penetrance and genetic pleiotropy diminishes the test's accuracy, rendering this strategy unreliable. Despite a relatively high false positive rate, individuals who receive a positive screening result could be directed towards lifestyle recommendations. This is particularly relevant for complex diseases with a polygenic foundation, where a polygenic risk score or a similar measure can help identify those at risk of developing the disease[42] The second challenge stems from the

assumption that detecting markers indicative of future neurodegenerative disease symptoms suggests that prevention is feasible. While this assumption is likely correct, it is essential to keep in mind that the mechanisms behind disease progression may not align with those of disease onset, indicating that risk factors may not be the solution for prevention. Therefore, we need research to clarify what propels neurodegeneration once it has commenced, as well as what instigates it. Although genomics research is already quite advanced, there is a significant lack of understanding regarding environmental and lifestyle risk factors. This is partly due to the genome being vast yet finite, presenting a technical hurdle. Conversely, environmental risk factors encompass an almost limitless area of inquiry, hindered by challenges such as recall bias and the requirement for extensive longitudinal studies. To navigate these issues, epidemiologists have created innovative approaches, including Mendelian randomization.[43]

5. Current and old Treatment of neurodegenerative disease

Drug repurposing, often referred to as drug repositioning or drug reprofiling, is a growing trend in the field of drug discovery. This process involves identifying new therapeutic uses for existing medications, and it is one of the primary strategies, alongside synthesis and natural products, for discovering small molecule leads for novel therapeutic applications. Recently, there has been a surge of interest in drug repurposing, particularly in the context of new combination therapies or in addressing diseases that lack adequate clinical solutions, such as orphan and neglected diseases.[44] Neurodegenerative diseases (NDs) are disorders that depend on age, characterized by diverse pathophysiology's and a significant lack of understanding regarding their causes and mechanisms, resulting in limited treatment options. As the global population ages, the prevalence of these diseases, which affect memory, cognition, and movement, is also increasing.[45] The urgency for treatment for NDs is critical, as the World Health Organization (WHO) forecasts that in two decades, NDs primarily impacting motor functions will surpass cancer to become the second leading cause of death, following cardiovascular diseases.[46] Given the rising demand for treatment for NDs and the potential of drug repurposing, it is logical that existing medications are being evaluated for their efficacy against these diseases. This review focuses on drugs that have been repurposed for Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease. Despite the existence of several reviews on drug repurposing, particularly in the context of NDs, a thorough review that encompasses all these diseases collectively is still lacking. Such a

review would provide a more expansive perspective and enhance our understanding of the interconnections among these diseases.[47]

Table 3: Summary of the diseases and repurposed drugs presented in this review.

1. Alzheimer's Disease

Drug Class	Drug Examples
Antimicrobial	Erythromycin, Azithromycin, Acyclovir, Doxycycline, Dapsone, Foscarnet, Ciloquinol, Penicillovir, Amphotericin B
Retinoid Receptor Agonist	Acitretin
Erectile Dysfunction	Sildenafil, Tadalafil
Antiepileptic	Valproic Acid
Antidiabetic	Liraglutide, Exenatide
Anticancer	Paclitaxel, Thalidomide, Imatinib, Carmustine, Tamibarotene, Bexarotene
Anti-Alzheimer	Memantine

2. Parkinson's Disease

Drug Class	Drug Examples
Antidiabetic	Exenatide
Antimicrobial	Doxycycline, Amantadine
Antiepileptic	Zonisamide
CNS Stimulant	Methylphenidate
Antiasthma	Salbutamol
Anticancer	Nilotinib

3. Huntington Disease

Drug Class	Drug Examples
Antipsychotic	Clozapine, Tetrabenazine, Quetiapine, Olanzapine, Risperidone, Tiapride

4. Amyotrophic Lateral Sclerosis (ALS)

Drug Class	Drug Examples
Anticancer	Mastinib
Antiasthma	Ibudilast
Antimicrobial	Triumeq
Antiepileptic	Retigabine

5. Multiple Sclerosis

Drug Class	Drug Examples
Anticancer	Mitoxantrone, Cladribine, Cyclophosphamide
Antihypertensive	Amiloride
Anti-asthma	Ibudilast
Antiestrogen	Tamoxifen

6. Additional Drug Categories from the Diagram

Drug Class	Drug Examples
Anti-Ashtma	Zileuton, Ibudilast, Salbutamol
Antimicrobial	Multiple (listed above)
Antidepressant	Trazodone
Antihypertensive	Nilvadipine, Valsartan, Trimetazidine
Erectile Dysfunction	Sildenafil, Tadalafil

a. Alzheimer's Disease

AD is recognized as one of the primary neurodegenerative diseases, responsible for 80% of dementia cases among the elderly. Symptoms include a gradual deterioration of memory, difficulties in learning, and a decline in both behavior and functionality. Although the precise cause of AD is not completely understood, it is believed to be associated with the buildup of amyloid plaques in the brain, leading to the eventual loss of neurons and synapses.[48] At present, there is no established cure for Alzheimer's Disease (AD), and the medications utilized for this condition primarily aim to alleviate cognitive symptoms or other manifestations, proving to be more effective when given in the early stages.[49] Interestingly, one of the medications marketed for AD treatment, galantamine, was originally repurposed. This alkaloid, derived from Galanthus species, gained attention when it was discovered that it could inhibit muscle acetylcholinesterase, making it a promising candidate for treating myopathies and peripheral neuropathies, as well as for reversing neuromuscular blockade following anaesthesia, due to galantamine's (1) ability to enhance nerve impulse transmission. With its tertiary ammonium structure, galantamine (1) can readily cross the blood-brain barrier and inhibit brain acetylcholinesterase, which adds to its appeal.[50] Research into the therapeutic effects of galantamine began in the 1980s for AD treatment, and it was incorporated into the anti-Alzheimer's treatment options in 2000; it continues to be one of the most frequently prescribed medications for delaying the onset of severe symptoms in AD patients.[50]

Table 4: Drug Repurposing Table for Neurodegenerative Diseases (29 Drugs).

No.	Drug Name	Drug Class	Neurodegenerative Target	Status
1	Memantine	Anti-Alzheimer	Alzheimer's Disease	(***)
2	Acitretin	Retinoid Receptor Agonist	Alzheimer's	(**)
3	Doxycycline	Antimicrobial	Alzheimer's / Parkinson's	(**)
4	Liraglutide	Antidiabetic (GLP-1 agonist)	Alzheimer's	(**)
5	Exenatide	Antidiabetic	Parkinson's	(**)
6	Valproic Acid	Antiepileptic	Alzheimer's / Huntington	(**)
7	Amantadine	Antimicrobial/Antiparkinson	Parkinson's	(***)

8	Zonisamide	Antiepileptic	Parkinson's	(***)
9	Methylphenidate	CNS Stimulant	Parkinson's	(**)
10	Salbutamol	Anti-asthma	Parkinson's	(*)
11	Nilotinib	Anticancer (TKI)	Parkinson's	(**)
12	Mastinib	Anticancer	ALS	(**)
13	Ibudilast	Anti-asthma	ALS	(**)
14	Retigabine	Antiepileptic	ALS	(***)
15	Triumeq	Antimicrobial (HIV combo)	ALS	(*)
16	Mitoxantrone	Anticancer	Multiple Sclerosis	(***)
17	Cladribine	Anticancer	Multiple Sclerosis	(***)
18	Cyclophosphamide	Anticancer	Multiple Sclerosis	(***)
19	Amiloride	Antihypertensive	Multiple Sclerosis	(**)
20	Tamoxifen	Antiestrogen	Multiple Sclerosis	(*)
21	Clozapine	Antipsychotic	Huntington's Disease	(***)
22	Tetrabenazine	VMAT2 Inhibitor	Huntington's Disease	(***)
23	Quetiapine	Antipsychotic	Huntington's Disease	(***)
24	Olanzapine	Antipsychotic	Huntington's	(***)
25	Risperidone	Antipsychotic	Huntington's	(***)
26	Tiapride	Antipsychotic	Huntington's	(***)
27	Sildenafil	Erectile Dysfunction	Alzheimer's	(**)
28	Tadalafil	Erectile Dysfunction	Alzheimer's	(*)
29	Paclitaxel	Anticancer	Alzheimer's	(*)

- **Clinically Approved (*):** 15 drugs**
- **Under Clinical Studies ():** 10 drugs**
- **Preclinical (*): 4 drugs**

Research has been conducted to determine if cancer medications can be repurposed for treating Alzheimer's disease (AD). The basis for this concept lies in the observation that cancer and neurodegenerative diseases may share similar signaling pathways, including mitochondrial dysfunction, oxidative stress, impaired cellular metabolism, and the formation of misfolded proteins. It has been noted that breast cancer survivors who underwent chemotherapy exhibit a reduced risk of developing AD in later life compared to a control group.[51] Carmustine (2), a nitrosourea used as an alkylating agent in brain cancer treatment, is a small, lipophilic, and non-ionized molecule, allowing it to cross the blood-brain barrier effectively.[52] In cells that overexpress the amyloid-β protein precursor, carmustine (2) demonstrated a significant decrease in amyloid-β production at a non-toxic dosage.[21] Bexarotene (3), a retinoid X receptor antagonist utilized for treating cutaneous T-cell lymphomas, has shown the ability to reverse neurodegeneration, enhance cognitive function, and lower amyloid-β levels in mice with familial AD mutations.[53] Tamibarotene (4), a retinoic acid receptor agonist approved in Japan for acute promyelocytic leukemia treatment, can influence various pathways associated with AD pathophysiology, such as diminishing the

release of pro-inflammatory cytokines and chemokines from brain cells, improving behavior in mice with accelerated aging, and reducing cortical acetylcholine levels.[54] Imatinib (5), a tyrosine kinase inhibitor authorized for chronic myelogenous leukemia and other tumors, has been proposed as a potential treatment for AD through two mechanisms: lowering amyloid-β levels and providing neuroprotection. Nevertheless, imatinib (5) faces challenges due to its limited ability to penetrate the blood-brain barrier and its rapid efflux by P-glycoprotein (P-gp).[55] Antimicrobials have been investigated for their potential effectiveness in treating Alzheimer's disease (AD) and its associated symptoms. Both azithromycin (8) and erythromycin (9), which are macrolide antibiotics, have demonstrated the ability to inhibit amyloid precursor protein, leading to reduced levels of amyloid-β in the brain. Tetracyclines have also been shown to diminish the formation of amyloid-β, enhance its susceptibility to trypsin digestion, and promote the breakdown of pre-existing fibrils. Additionally, they have been found to lower oxidative stress, indicating a diverse mechanism of action. Doxycycline (10) has exhibited promise in this area, both on its own and when used alongside rifampicin (11).[56] Rifampicin (11), commonly prescribed for Mycobacterium infections, has been observed to reduce amyloid-β fibrils in a dose-dependent manner, likely due to decreased production and enhanced clearance of amyloid-β.[57] Dapsone (12), an antibiotic for leprosy, gained attention in the 1990s when a lower incidence of dementia was reported among leprosy patients treated with dapsone (12). Conflicting evidence regarding dapsone's (12) ability to reduce senile plaques led to the theory that this could serve as a protective factor against amyloid accumulation. This theory was further supported by research indicating similar occurrences of AD in leprosy and tuberculosis patients, despite the differing proportions of patients receiving drug treatments in both groups.[58] Antiviral medications such as acyclovir (13), penciclovir (14), and foscarnet (15) have proven effective in lowering phosphorylated tau protein and amyloid-β in AD cell models, suggesting their potential for AD treatment.[59] Amphotericin B (16), an antifungal agent, has been shown to delay the formation of amyloid-β.[60]

b. Huntington’s Disease

Huntington's disease (HD) is an autosomal dominant disorder and the most prevalent monogenic neurological condition in developed countries. It is marked by involuntary choreatic movements, as well as behavioral and psychiatric issues, alongside dementia. The disease arises from a genetic mutation that produces a mutant variant of the multifunctional protein huntingtin, resulting in toxicity that causes neuronal death and dysfunction. HD

typically begins to present symptoms in adulthood, with a progression that ultimately leads to death within a few years. Currently, there is no known cure for this condition, leaving symptom management as the only viable option.[61]

Tetrabenazine was initially created as part of research focused on developing simple compounds that exhibit reserpine-like antipsychotic properties. It functions as a high-affinity, reversible inhibitor of monoamine uptake in presynaptic neurons and serves as a weak blocker of D2 dopamine postsynaptic neurons. The results of antipsychotic studies involving this compound were inconclusive, leading to its repurposing for conditions characterized by abnormal, involuntary hyperkinetic movements, such as Huntington's disease (HD). Moreover, tetrabenazine (37) is considered safer for use in HD compared to dopamine receptor blockers, as it has never been reported to induce dyskinetic symptoms.[62] Consequently, other medications with dopamine antagonistic properties have been evaluated for HD treatment. One such example is tiapride (38), a D2 receptor antagonist utilized as an antipsychotic. In Europe, selegiline (33) is commonly chosen for managing Huntington's chorea.[63] Clozapine (39), a neuroleptic medication prescribed for schizophrenia, exhibits a strong affinity for dopamine D1 and D4 receptors while demonstrating minimal antagonistic activity against D2 dopaminergic receptors. Due to its low occurrence of extrapyramidal side effects, it has been proposed as a suitable symptomatic treatment for chorea, although clinical trials have yielded mixed outcomes.[64] Olanzapine (40), another antipsychotic, is frequently prescribed for addressing the motor and behavioral symptoms associated with HD. This medication has a high affinity for serotonin receptors but antagonizes dopamine D2 receptors. It is also regarded as safe and well-tolerated, making it a recommended option when irritability, sleep disturbances, and weight loss are present, in addition to chorea.[65] The antipsychotic risperidone (41), which is used to treat schizophrenia and bipolar disorder, functions as a D2 receptor antagonist and a serotonin agonist, thus making it applicable for treating HD chorea as well. It has demonstrated positive effects in stabilizing motor decline and alleviating psychiatric symptoms.[66]

c. Multiple Sclerosis

Multiple Sclerosis (MS) is an autoimmune disorder affecting the central nervous system. This chronic inflammatory condition leads to varying degrees of destruction of myelin and axons. The progression of the disease is unpredictable, initially presenting with reversible neurological deficits that gradually become progressive. While there is currently no cure for

MS, several therapies have been approved to alleviate symptoms and slow disease progression.[67] A wide range of anticancer medications have been repurposed for managing MS and its associated symptoms. One such example is the synthetic compound mitoxantrone an anthracene Dione recognized as a broad-spectrum antitumor agent utilized in the treatment of breast and prostate cancer, acute leukemia, and lymphoma.[68] Mitoxantrone (44) has also received approval for MS treatment, particularly due to its immunosuppressive characteristics, which are linked to unpredictable responses of central nervous system T- and B-cells to antigens, myelin damage caused by macrophages, and axonal injuries. Mitoxantrone (44) can inhibit T-cell activation, halt the proliferation of T- and B-cells, reduce antibody production, and deactivate macrophages. Additionally, mitoxantrone (44) has shown high tolerability.[69] The alkylating agent cyclophosphamide (45) is employed in treating various solid tumors and is approved for leukemia, lymphomas, and breast carcinoma, among others. It is associated with nitrogen mustards and binds to DNA, disrupting mitosis and cell replication, primarily targeting rapidly dividing cells. Its application in MS arises from cyclophosphamide (45) being capable of performing both immunosuppressive and immunomodulatory functions. Specifically, it acts on T- and B-cells, suppressing both cell-mediated and humoral immunity. Research has also indicated that cyclophosphamide (45) can reduce the secretion of the pro-inflammatory T helper 1 cytokine interferon-γ and interleukin-12, while enhancing the release of anti-inflammatory cytokines in the brain and bloodstream. Furthermore, it transforms T-lymphocytes into a less inflammatory phenotype. Cyclophosphamide (45) can penetrate the blood-brain barrier, demonstrating good bioavailability in the central nervous system, allowing it to exert its immunomodulatory and immunosuppressive effects, thereby stabilizing and preventing disease progression. The medication ibudilast (48) has received approval in various countries for treating bronchial asthma and cerebrovascular disorders. It functions by inhibiting phosphodiesterases, which are recognized for their anti-inflammatory properties, and can also obstruct the synthesis mechanisms of leukotrienes and nitric oxide, both of which are associated with multiple sclerosis (MS). In the brain, ibudilast (48) can prevent the release of tumor necrosis factor from microglia and astrocytes, thereby reducing neuronal degeneration. Additionally, it offers protection to astrocytes against apoptosis and inhibits the apoptosis of oligodendrocytes and demyelination, which underscores its relevance in MS. Research has demonstrated its safety and tolerability, while also showing a reduction in the rate of brain atrophy at elevated doses.[71]

d. Amyotrophic Lateral Sclerosis

ALS is a condition marked by the degeneration of both upper and lower motor neurons, which are responsible for controlling voluntary muscles. This results in muscle atrophy, where the muscles progressively weaken and shrink in size. Additional symptoms include muscle stiffness, twitching, and challenges with breathing, swallowing, and speaking. The origins of ALS are largely unknown, with approximately 10% attributed to genetic factors.[72] While some medications are currently under research for potential treatment of ALS, only two drugs, riluzole and edaravone, are available at present to slow the disease's progression, though they do not reverse symptoms once they appear.[73] Masitinib is a tyrosine kinase inhibitor that is utilized in cancer treatment for dogs. Its application in ALS is based on the premise that the abnormal glial cells that proliferate in this condition may respond to tyrosine kinase inhibitors. Research has demonstrated that masitinib (49) effectively inhibited glial cell activation in a suitable rat model and improved survival rates

An antiretroviral medication, Triumeq®, utilized for anti-HIV therapy, was investigated for its potential in treating ALS. This interest stems from the observation that ALS patients exhibit serum levels of reverse transcriptase similar to those found in HIV-infected individuals, along with the detection of a human endogenous retrovirus in the brains of ALS patients. Given these findings, anti-HIV medications may offer benefits for ALS. Triumeq® combines dolutegravir (50), an integrase inhibitor, with abacavir (51) and lamivudine (52), both antiretrovirals, and has demonstrated safety and tolerability in ALS patients.[75] Retigabine (53), an approved epilepsy medication, functions by binding to voltage-gated potassium channels, enhancing the M-current, and resulting in membrane hyperpolarization. This action allows Retigabine (53) to extend the survival of motor neurons and reduce excitability, which is beneficial in treating ALS, as neurons in this condition are thought to be hyper-excitable, firing excessively and leading to cell death. Currently, this drug is undergoing clinical trials for ALS treatment.[75] Tamoxifen (54), an antioestrogen drug sanctioned for breast cancer chemotherapy and chemoprevention, was serendipitously repurposed for ALS treatment after neurological improvements were noted in ALS patients with breast cancer who were treated with tamoxifen (54). Its neuroprotective effects have been previously documented and seem to be linked to the inhibition of protein kinase C, which is overexpressed in the spinal cords of ALS patients. Additionally, tamoxifen (54) has been shown to modulate a proteinopathy associated with ALS, acting as an autophagy

modulator.[76] All the compounds discussed in this chapter have been subjected to clinical trials for ALS treatment, as this disease has garnered significant attention in recent years.

5. Failed Repurposing

Despite numerous successful instances of drug repurposing, it is equally true that many attempts at repositioning have not succeeded. A drug may seem promising based on computational studies or in vitro assays, yet fail to demonstrate any activity in vivo, resulting in the discontinuation of its investigation for new applications. This was the situation with latrepirdine, an anti-histamine medication that received approval in Russia for treating allergy-related rhinitis, which was later considered for repurposing in Alzheimer's Disease (AD) and Huntington's Disease (HD). Although a clear mechanism of action was never definitively established, it was noted that it could modulate the activity of channels and neurotransmitters, effectively blocking amyloid-β toxicity, among other effects.[77] Notably, while phase II trials indicated improvements in AD patients compared to placebo, phase III trials did not reveal significant changes in the progression of the disease . A similar outcome was observed in phase III trials for HD[78] Simvastatin and atorvastatin, medications prescribed for hypercholesterolemia, have also been explored for repurposing in AD. This hypothesis arose from the notable correlation between AD and cardiovascular diseases. Research indicated that statins could provide various benefits, including lowering amyloid-β levels and enhancing neuroprotection. Nevertheless, neither drug demonstrated efficacy in treating AD.[79] Selective serotonin reuptake inhibitors, which are commonly used as antidepressants, have also been studied to evaluate their effectiveness in treating Alzheimer's disease (AD). Nortriptyline and paroxetine initially showed improvements in cognitive functions; however, subsequent assessments concluded that there was no enhancement in cognitive behavior even after these medications addressed mood disorders.[80] The antimicrobial ceftriaxone seemed promising in phase II trials for treating amyotrophic lateral sclerosis (ALS), yet it did not demonstrate clinical efficacy in phase III trials.[81] Initially, cladribine was rejected as a repurposed treatment for multiple sclerosis (MS) before it received approval. These instances suggest that while drug repurposing has shown potential in uncovering new treatments for neurodegenerative diseases (ND), the journey to approval can be fraught with challenges, often resulting in the abandonment of repurposing efforts.[82]

6. CONCLUSION

Neurodegenerative diseases represent a group of complex, slowly advancing disorders that cause neuron loss and impair cognitive, motor, and behavioral functions. Conditions such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Multiple Sclerosis, frontotemporal dementia, among others, vary in their symptoms, yet they often exhibit shared pathological traits—especially the abnormal accumulation of proteins like tau, amyloid-beta, α-synuclein, TDP-43, and FUS. The early symptoms are frequently mild and can overlap with other conditions, making it challenging for clinicians to achieve an accurate diagnosis. As a result, modern diagnostic tools, including amyloid PET, tau PET, FDG-PET, structural MRI, dopamine transporter imaging, and neurofunctional scanning, are becoming crucial. These imaging techniques not only support early detection but also help differentiate between similar disorders, monitor disease progression, and evaluate treatment responses. Preventing neurodegenerative diseases continues to be a challenge; however, examining early biomarkers such as REM sleep behavior disorder in Parkinson's disease or initial amyloid deposition in Alzheimer's suggests that interventions could be feasible well before the onset of symptoms. Gaining insights into lifestyle, genetic, and environmental factors will further aid in crafting preventive measures. In summary, progress in molecular pathology, imaging techniques, and genetics has greatly enhanced our capacity to diagnose and comprehend neurodegenerative diseases. Ongoing research is crucial for developing effective therapies, pinpointing early indicators, and ultimately preventing or mitigating disease progression, thereby enhancing the quality of life for millions of individuals affected by these conditions.

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