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PHARMACOLOGICAL INTERVENSTION IN NEURODEGENERATIVE DISEASE

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1. ABSTRACT

Neurodegenerative diseases (NDDs), including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis, represent a group of disorders characterized by progressive neuronal loss and cognitive or motor dysfunction. Pharmacological interventions in NDDs aim to mitigate disease progression, alleviate symptoms, and improve quality of life. Current treatments are primarily symptomatic, with limited success in altering disease trajectory. In Alzheimer's disease, cholinesterase inhibitors (e.g., donepezil, rivastigmine) and glutamate regulators (e.g., memantine) offer modest cognitive improvements, while recent advances in disease-modifying agents, such as anti-amyloid antibodies (e.g., aducanumab), are being explored. In Parkinson's disease, dopaminergic therapies, such as levodopa and dopamine agonists, provide symptomatic relief, though motor complications, such as dyskinesia, are common over time. Newer approaches, including gene therapy and the use of neuroprotective agents (e.g., rasagiline, safinamide), aim to slow progression. In Huntington's disease, pharmacological options are more limited, with drugs like tetrabenazine addressing hyperkinetic movements but without effects on disease progression. In amyotrophic lateral sclerosis, riluzole and edaravone offer modest survival benefits, but there remains a significant need for more effective treatments. In parallel, the exploration of novel targets, including neuroinflammation, mitochondrial dysfunction, and protein aggregation, is opening new avenues for pharmacological intervention. Despite progress, the challenge remains to identify disease-modifying therapies that address the underlying pathophysiology and provide long-term benefits. Continued research into the molecular mechanisms of neurodegeneration is essential for developing more effective treatments for these devastating disorders.

KEYWORDS: Neurodegenerative disease, alzhiemer disease, Parkinson disease, hungtington disease, amyotrophic lateral sclerosis, drugs, blood brain barrier, nanotechnology, treatment.

2. INTRODUCTION

According to conventional definitions, neurodegenerative diseases (NDDs) are conditions characterized by a specific involvement of functional systems and a selective loss of neurons that determine clinical presentation. This concept has been broadened by thorough biochemical, genetic, and molecular Moreover, these proteins are accumulated by glial cells as well as neurons.

The idea of conformational disorders has been defined as a result of the involvement of protein.[1] This suggests that a normal protein's structural shape changes, leading to a change in function or possibly harmful intracellular or extracellular accumulation. Diseases that are inherited are associated with mutations in the encoding genes. Numerous ailments have been reclassified as a result of molecular pathological, genetic, and biochemical research, which has afar the creation of biomarkers or treatment plans.[2]

2.1. Common Neurodegenerative Conditions

Alzheimer Disease

The most prevalent neurological disease associated with aging is Alzheimer's disease (AD), which has short-term memory impairment as one of its early symptoms. Patients with AD experience substantial cognitive and memory impairment as the disease worsens. Neurofibrillary tangles (NFTs), which are made up of aggregates of hyperphosphorylated tau, and extracellular deposits in particular brain regions made up of aggregates of a little peptide known as Aβ are characteristics of AD.[3]

Parkinson Disease

Among neurodegenerative disorders, Parkinson's disease (PD) is the second most prevalent. Between 2 and 3 percent of people over 65 are impacted. Along with tremors or shaking, which typically start in the limbs, other signs of Parkinson's disease include altered posture and poor movement coordination (4). The striatal dopamine shortage brought on by neuronal death in the substantia nigra is the neuropathological characteristic of Parkinson's disease. The underlying molecular pathophysiology includes neuroinflammation, oxidative stress, mitochondrial dysfunction, and defective α-synuclein proteolysis.[4]

Huntington’s Disease

Huntington disease (HD) is an uncommon autosomal-dominant neurological illness that is inherited. It results from a single gene deficiency that gradually degenerates brain neurons that produce the huntingtin protein mutation (5).

Cognitive and motor impairments are caused by HD.[5]Peripheral IR increases the likelihood of developing type 2 diabetes in patients with HD.[6] Furthermore, a number of lines of evidence demonstrated that HD alters the metabolism of cholesterol within cells. Indeed, intercellular cholesterol transfer, neuronal excitotoxicity, and apoptosis are all impacted by the mutant huntingtin protein.[7]

Amyotrophic Lateral Sclerosis

The gradual and irreversible loss of motor neurons in the cerebral cortex, brain stem, and spinal cord is a feature of amyotrophic lateral sclerosis (ALS).[8] Within three to four years of the commencement of symptoms, the majority of individuals with this illness will pass away.[9] The exception is the well-known physicist Stephen Hawking, who lived

for more than 50 years after being diagnosed with ALS. As the name implies, ALS causes spinal cord scarring (lateral sclerosis) and muscular atrophy (amyotrophic).[10]

2.2. Current Burden And Treatment Gap

The pharmacological treatments available today have very little, if any, effect on changing the course of these diseases and only provide limited, temporary symptomatic improvements.

The traditional monofactorial strategy is ineffectual at reducing the progression of neuronal death because the pathophysiology of neurodegenerative illnesses is known to be multifactorial. Because changes in the number and affinity of receptors can impair the effectiveness of drugs that act on a single receptor, resistance is common. It would be more likely to be successful to combine behavioral and environmental changes with medications that target several different targets.

3. Pathophysiology of Neurodegenerative Disease

3.1 Molecular And Cellular Mechanism

Oxidative Stress

Interesting facets of the pathophysiology of neurodegenerative illnesses are suggested by the molecular mechanisms underlying them.[11,12] It seems that faulty protein processing,[11] genetic abnormalities,[13] misfolding and aggregation of different proteins,[12] inducing cellular apoptosis,[14] initiating mitochondrial dysfunction, producing free radicals, a and OS [12] are the main causes of neurodegeneration.

OS seems to play a major role in the pathophysiology of neurodegenerative disorders, according to new research.[12]

OS happens when the body's natural antioxidant defenses are unable to sufficiently offset the oxidant molecules it produces. Free radicals overpower the body's natural antioxidant defenses during OS episodes, which could have negative consequences. Although free radicals are physiologically typical byproducts of normal aerobic metabolism, they can be created in unusually high and dangerous quantities in pathological circumstances.[34] The notion that OS causes the emergence of neurodegenerative illnesses is supported by an increasing amount of data.[15,16,17] An increased concentration of free radicals above the threshold known to be harmful could be referred to as OS.[18] To put it another way, OS may result from weakened antioxidant defenses, increased formation of reactive oxygen species, or a combination of the two.[18] There are several theories regarding how this could happen. For instance, an excess of oxides may result from a mutation in SOD1.[19]

According to a different theory, OS may be encouraged by disturbed glutathione synthesis and homeostasis.[18] A comprehensive analysis of the mechanisms underlying neurodegenerative disorders discovered that the production of free radicals activated several harmful pathways linked to the emergence of neurodegenerative diseases through a variety of distinct methods.[20] These several processes may seven or more, engage in intricate and poorly explained interactions with one another. Neurodegeneration may be facilitated by the interaction of various systems rather than by any one mechanism acting alone.[20] Agents that can regulate the formation of free radicals would be a possible target for medication development to treat neurodegenerative diseases based on these theories.[20]

3.2. Protein Misfolding And Aggregation

A protein's structure determines its function, and accurate folding is a prerequisite for structure. At this stage, the misfolding process can produce loss-of-function and/or gain-of-function, which are two significant factors. The inability of misfolded proteins to carry out their intended activity results in loss-of-function, which can cause permanent cell malfunction and ultimately cell death. On the other hand, the gain-of-function Tau, β-amyloid, and α-synuclein are the main misfolded proteins implicated in the most common neurodegenerative disorders.

Beta Amyloid In Alzheimer

The extracellular space contains β-Amyloid inclusions, in contrast to other protein aggregates that are covered here. Nonetheless, there are similarities in the mechanisms of aggregate spread. Numerous investigations have previously demonstrated that introducing brain extracts from AD patients into transgenic mice's brains encourages β-amyloid aggregation and deposition in a way that is consistent with the presence of distinct β-amyloid strains.[21-23]

Comparable results were obtained using nonhuman Similar to prions, synthesized human β-amyloid aggregates may cause lesions in transgenic mice that expressed the human APP protein. Primates were also implanted with β-amyloid aggregates from human sick brains. In experimentally produced Alzheimer's disease. The propagation of prion-like protein inclusions in neurodegenerative diseases. aggregates are also seen to spread through axonally connected brain regions, leading to extensive areas such neocortical and subcortical regions.[24]

Alpha synuclein in Parkinson.

The primary constituent of Lewy's bodies, a feature of Parkinson's disease and associated disorders, is α-synuclein.

Pathologically distinct filamentous morphologies can be displayed by α-synuclein inclusions, indicating the possibility of distinct strains resulting in distinct illnesses.[3] Early in the disease, α-synuclein deposits typically show up in the peripheral and enteric nervous systems. According to this data, Parkinson's disease (PD) may have an extracellular origin, similar to the most well-known prion disease, mad cow disease, which is caused by eating contaminated meat from cattle. The development of the pathogenic form of α-synuclein is linked to the oxidative damage caused by the pesticide rotenone, which impacts mitochondria. This suggests that those exposed to this pesticide may be at risk for Parkinson's disease. D. Cell cultures and transgenic mouse models were also used to successfully address experimental cell-to-cell transmission of α-synuclein inclusions.[25] Synoptically linked neurons can disperse α-synuclein aggregates through retrograde transport, as determined by inoculation in the cortex or striatum, resulting in distinct patterns of dissemination, which is similar to the behavior seen for β-amyloid.[26]

Neuroinflammation

The body's normal, expected, natural, and adaptive response to injury is inflammation, which promotes both self-defense and the elimination of the damaging stimuli. Unbalances can harm host tissue and possibly result in organ malfunction, despite the fact that the inflammatory response is essential to the immune system.[27] Generally speaking, inflammation is only harmful when it doesn't go away in a timely manner.[28] A potentially preventable condition known as neuroinflammation happens when the central nervous system (CNS) and/or peripheral nervous system (PNS) become inflamed. This can pave the way for the emergence of chronic neurodegenerative disorders.[29]

4. Pharmacological Interventions In Alzheimer Disease

4.1. Cholinesterase Inhibitors

Moa

Some of the symptoms of Alzheimer's disease are brought on by a deficiency in acetylcholine generation in patients. Cholinesterase inhibitors raise acetylcholine levels by blocking the enzyme that breaks down acetylcholine in the synaptic cleft. Acetylcholinesterase and butyrylcholinesterase are the two types of the cholinesterase enzyme.

Cholinesterase inhibitors lessen the symptoms of Alzheimer's disease without stopping the illness's clinical development. They are regarded as symptomatic therapy in this sense. S. Anorexia, nausea, vomiting, diarrhea, abdominal pain, lightheadedness, exhaustion, and cramping in the muscles are examples of dose-dependent cholinergic adverse effects. Clinical practice advises that switching to a different cholinesterase inhibitor can be an option if side effects continue and the response is unsatisfactory. Adding memantine without stopping the original medicine is an additional option in the event of a poor clinical response.

Donepezil

The most widely used cholinesterase inhibitor in the world is donepezil. Acetylcholinesterase is inhibited by donepezil, which increases acetylcholine availability. A systematic review found that donepezil treatment significantly improved cognitive, global, functional, and behavioral measures in a dose-dependent manner in patients.[30] Anorexia, exhaustion, nightmares, nausea, vomiting, diarrhea, and dizziness were among the minor and temporary side effects.

Rivastigmine

a. Acetylcholinesterase and butyrylcholinesterase are both inhibited by rivastigmine. Both oral and transdermal forms are accessible. The goal of transdermal presentations is to reduce adverse effects and make administration easier for people who are less cooperative. Rivastigmine enhances cognitive, global, and functional outcome measures, but not behavioral ones, according to a systematic review.[31] Individuals taking 6–12 mg per day showed benefits. Anorexia, headache, syncope, nausea, vomiting, diarrhea, and dizziness were among the adverse effects.[31] With fewer adverse effects, the maximum transdermal rivastigmine dosage of 12 mg per day was just as effective as oral rivastigmine.[32,33]

Skin intolerance is linked to transdermal rivastigmine in certain people.[33]

Galantamine

By binding to nicotinic receptors and reversibly inhibiting acetylcholinesterase, galantamine increases the transmission of cholinesterase.[34] According to a Cochrane study, galantamine significantly affects behavioral, global, cognitive, and functional factors.[35] Galantamine, at 16–24 mg per day, demonstrated a noteworthy improvement in a trial involving Alzheimer's and mixed vascular dementia.[36]

Side Effect: Anorexia, nausea, vomiting, diarrhea, and dizziness are common cholinergic adverse effects.[34]

4.2. NMDA Receptor Antagonist

Cell death and excitotoxicity can result from damage caused by excitatory amino acid neurotransmitters, particularly glutamate.[24] The NMDAR is the receptor primarily implicated in excitotoxicity. Excessive Ca2+ entry into the cell due to overactivated NMDAR sites can produce reactive oxygen species and activate certain enzymes that cause cell death.

Crucially, however, adequate NMDA receptor activity is essential for the nervous system's regular operation since it largely facilitates physiological excitatory synaptic transmission in the brain.

4.3 Disease Modifying Therapies

According to earlier research on animals, blocking APP cleavage may be a target for altering the course of the disease.

Several targets that function in α-secretase and α-secretase have been identified. A γ-secretase inhibitor called semagacestat lowers the plasma levels of Aβ40/42. According to phase III investigations, semagacestat deteriorated cognitive performance and did not slow the course of the disease. The size of Aβ peptides varies, and Aβ42, which has 42 amino acids, is thought to be a more hazardous variant. Agents that decrease Aβ42, like tarenflurbil, can encourage the creation of shorter forms, which will slow the disease's course.

Regretfully, phase III investigations did not demonstrate any positive effects of tarenflurbil. APP cleavage can be shifted toward the production of nonamyloidogenic peptides by stimulating α-secretase. Drugs that boost α-secretase and decrease β-secretase activity are being studied.[34]

4.4.TauProteinInhibitor

Numerous circumstances can cause tau inclusions to develop, which are prevalent in the sick brain and seem to play a key role in neurodegeneration. Although it is unclear if tau aggregates can sustain themselves, mounting data indicates that tau inclusions exhibit a distribution pattern that is correlated with aging, indicating that the process begins in the transentorhinal cortex and progresses to the neocortex and hippocampal formation.[38] The various virulence grades are a consequence of being a transmissible agent, which aligns with the concept of prion strains. Different tau isoforms (at least six in humans) can cause strains in the case of tau.[39]

Table: comparison of drug mechanism,efficacyand side effect.

drug	Class and indication	Mechanism of action	Common adverse effect
Donepezil (FDA approved in 1996)	Cholinesterese inhibitor prescribed to treat symtoms of mild to modrate and modrate to seveare ad	Prevent brekdown of acetal choline in the brain	Nosia vomatting diarrhea
Galantamina (FDA iprove in 2001)	Cholinestares inhibitor prescrib to treat symtoms of mild to modrate ad	Preven the brekdown of acetal choline and stimulate nicotenic receptor to release more acetylcholinen in the brain	Nosia vomatting dirria affitide weight loss
Revastigment (FDA aprove in 2000)	Cholinestares inhibitor prescribe to treat symtoms of mild to modrate ad	Prevent the brekdown of acetyl choline and butyrylcholine in the brain	Nosia vomitting dirria loss of affitide weight loss muscle weeknes

5. Pharmacological interventions in Parkinson's disease

5.1 dopamine replacement therapy

Mechanism of action

Parkinson's disease is a long-term neurodegenerative condition marked by bradykinesia, postural instability, cogwheel rigidity, and resting tremor. There isn't a cure or treatment that modifies the sickness at the moment. Parkinson's disease causes movement disorders because the basal ganglia are not adequately stimulated by dopamine. The primary cause of this is the degradation of the substantia Negra's dopamine-producing neurons. There are also deficiencies in other

neurotransmitters, such as serotonin and norepinephrine. Within the basal ganglia, there are two main pathways: direct and indirect. The globus pallidus and substantia nigra receive inhibitory GABA and substance P efferent from the striatum, which receives inputs from the cerebral cortex in the direct pathway. The thalamic input to the cortex is affected differently by direct and indirect pathways. The pars compacta of the substantia nigra produces dopamine. Although dopamine operates through both direct and indirect channels, its loss causes the thalamic excitatory output to the cortex to decrease overall.[40]

Levodopa

The best pharmacological treatment for Parkinson's disease is levodopa.

In general, levodopa medication marked a significant advancement in the treatment of Parkinson's disease. Patients' quality of life has improved, and their mortality rate is nearly typical for the elderly. The majority of Parkinson's patients pass away from additional complications, such as infectious and cardiovascular illnesses. Postural instability is the cause of falls that result in hip fractures and is linked to a higher death rate . Levodopa produces a steady response, but over time, its effects diminish and there are variations in motor responsiveness. According to long-term research, levodopa should be added to therapy when the effects of selegiline and dopamine agonists are no longer sufficient.[40]

Before levodopa may get across the blood-brain barrier, the majority of it is digested. Levodopa is typically used in conjunction with a decarboxylase inhibitor for this reason, which lowers adverse effects and increases bioavailability by preventing peripheral conversion to dopamine.[34] Levodopa and decarboxylase inhibitors are most commonly associated with levodopa/carbidopa and levodopa/benderizine. In order to enhance therapeutic responsiveness and reduce plasma level fluctuations, controlled-release formulations have been created.[40] Levodopa's peripheral side effects include cardiac dysrhythmias, hypotension, nausea, and vomiting. To lessen negative effects, the dosage must be carefully titrated. Confusion, delirium, and behavioral abnormalities are the main adverse effects. Levodopa metabolites may cause damage to dopaminergic neurons, according to some unsubstantiated research.[41] Levodopa side effects include psychiatric disorders, swings, and dyskinesias. One example of a clinical fluctuation is on-off syndrome.

In this instance, the levodopa response's effective duration gets increasingly shorter. Levodopa treatment in the early stages of the disease raises the risk of side effects such fluctuations and dyskinesia.[40–42] A study examined whether levodopa/carbidopa/entacapone (Stalevo) delays the onset of dyskinesia in comparison to levodopa/carbidopa; nevertheless, the entacapone-treated group experienced a higher incidence of dyskinesia and a quicker time to onset than anticipated. Symptom management was somewhat improved by entacapone treatment. Entacapone is not now advised for early Parkinson's disease because of this.[40,42,43]

Dopamine agonist

Mechanism

Parkinson's disease is treated with dopamine agonists as an adjuvant.

Ergot alkaloids that function in postsynaptic receptors are accessible dopamine agonists.

They aid in the treatment of bradykinesia and stiffness. Less fluctuation occurs when levodopa and dopamine agonists are combined.[40,44] Before levodopa is needed, dopamine agonists can be used as monotherapy with moderate symptomatic effectiveness.[40] There was no evidence to support either of the initial ropinirole and pramipexole when

compared to initial levodopa in double-blind controlled studies. of these approaches over the other, despite the fact that dyskinesias were somewhat less common in groups receiving ropinirole and pramipexole.[40,44]

Mao-b inhibitors

Selegiline; Monoamine oxidase, type B (MAO-B) inhibitors like selegiline are believed to delay the course of Parkinson's disease. Dopamine availability is increased by MAO-B inhibition, which decreases dopamine breakdown.

Additionally, it shields neurons by preventing the generation of free radicals. Early in the course of the illness, selegiline can be administered to postpone the onset of dopaminergic medications.[40,42,43] According to a clinical study, the placebo group's levodopa dosages were 19% higher and their condition was 35% poorer than that of the selegiline-treated group after five years of concurrent therapy with levodopa. According to the majority of research, selegiline treatment that is started earlier and lasts longer tends to have better long-term results.[40]

Table: comparison of drugs, effect and side effect.

	Class	Agent	Use	Side effect
First line	Dopamine precursor	Carbidopa levodopa	Monotherapy to treat bradykinesia postural in stability and rigidity	Orthostatic hypotension dizziness headache dispersion dyskinesia
Second line	Dopamine agonist	Pramipexole ropinirole	Monotherapy or adjunct to levodopa to treat bradykinesia postural in stability and rigidity	Orthostatic hypotension drowsiness dizziness in somnia abnormal dream nausea constipation
	Monoamine oxidase inhibitor	Selegiline safinamide safinamide was approved recently in 2017	For of label use as monotherapies or adjunctive therapies with carbidopa levodopa	Hedac dizziness in somnia nausea hypotenstion sulfonamide can be increase level in enzyme
Third line	Antiviral	amantadine	Monotherapy or adjunctive therapy	Orthostatic hypotension syncope peripheral oedema avoids use to weeks before and to weeks after influenzas vaccine

6. Pharmacological Intervention In Huntington’s Disease

6.1 Dopamine Depleting Agent

Mechanism of Action

Autosomal dominant inheritance characterizes Huntington's disease, a neurological genetic condition. Middle-aged adults start to exhibit its symptoms, which include myoclonus, tics, chorea, dystonia, Parkinsonism, sadness, apathy, anxiety, irritability, psychosis, and cognitive decline. A mutant isoform of the protein Huntingtin (Htt) is produced as a result of genetic mutation.

Although huntingtin is linked to cell signaling, many people are poisoned by its mutant form kinds of brain cells (see to Chapter 9 for more details). Huntington's illness has no known cure. The only medication for Huntington's disease tics and chorea that has FDA approval is tetrabenazine. Myoclonus and dystonia may be treated with clonazepam. Certain drugs can be used to treat psychiatric problems. For depression, antidepressants such as mirtazapine are advised. For behavioral problems and psychosis, atypical neuroleptics are advised. The patient loses autonomy as the illness

worsens, making interdisciplinary caregiving essential. The effectiveness of phono audiologic, occupational, and physical therapy is supported by some data.[45]

6.2. Antipsychotic And Mood Stabilizers

Role In Treatment

The diagnosis of NDD increasingly relies on neuropsychiatric disorders. This is a reflection of the increasing awareness of the significance of NPS as indicators of neurological disorders and the distinct correlation between NPS and particular NDD. It is important to differentiate neuropsychiatric disorders from symptoms. Symptoms are personal experiences that are subjective in nature. Syndromes are groups of clinical characteristics, indicators, symptoms, or phenomena that make up a medical illness and are identified by a physician. The majority of the clinical characteristics included here are syndromes. Particular diagnostic standards have been established for agitation in cognitive diseases such as AD,[46] sadness in AD[47] apathy in AD and other NDD,[48] and psychosis in AD.[49] Psychosis[50] and depression[51] are criteria for particular neuropsychiatric disorders in PD.

The usual clinical approach to treating neuropsychiatric syndromes in NDD is to extrapolate from the use of psychotropic agents used in idiopathic psychiatric disorders for similar phenomena. Approved antidepressants are used for the treatment of depression in NDD; antipsychotics are used for the treatment of psychosis (hallucinations and delusions) and agitation in NDD; mood stabilizers are used in the management of agitation in NDD; In NDD, stimulants are recommended for apathy, hypnotics are used for sleep dysregulation, and anxiolytics are used for anxiety. This strategy is predicated on the approval of mood stabilizers for bipolar disorder, stimulants for attention deficit disorder, anxiolytics for generalized anxiety disorder, hypnotics for insomnia, antidepressants for the indication of major depressive disorder, and antipsychotics for schizophrenia or bipolar illness.

Olanzapine

In AD, olanzapine has been used to treat psychosis.[45] It has anticholinergic effects and raises the probability of anticholinergic delirium symptoms while also potentially impairing cognition.[51] The use of olanzapine to treat PD patients' delusions and hallucinations has made the condition worse.[52]

Risperidone

Alternatives for treating severe agitation, violence, and psychosis linked to AD where there is a risk of injury to the patient and/or others include atypically such as risperidone, olanzapine, and aripiprazole.[43–46] For patients with agitation, risperidone offers the strongest evidence of short-term effectiveness (6–12 weeks).[38] Even in individuals with AD who are severely impaired, risperidone is effective in managing agitation and aggression, according to a meta-analysis of four sizable placebo-controlled clinical trials.[47] Discontinuing risperidone was linked to a higher risk of relapse in AD patients with psychosis or agitation who had responded to treatment with the medication for 4–8 months.[48] When treating acute, treatment-resistant agitation in AD, risperidone may be a viable short-term solution. When agitation syndrome has progressed to a chronic state, it may also be helpful for long-term agitation management.

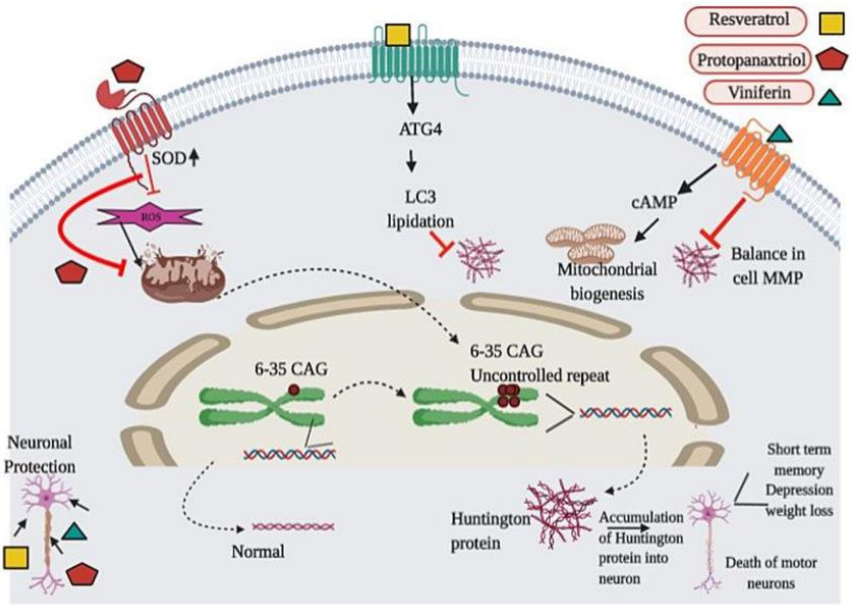
6.3. Emerging Therapeutics

Gene Silencing Therapies

Long CUG and CAG repeats in transcripts create hairpin structures that the ribonuclease dicer can use to create short RNA duplexes and initiate the RNA interference (RNAi) response . Dicer produces 21 nucleotide long fragments that

function as endogenous siRNAs and cause downstream silencing. Cell death is induced and 21 nucleotide long CAG-repeated small RNA levels are elevated by the enlarged htt exon-1 mRNA with 40 or more CAG repeats. Crucially, cell toxicity increases with the frequency of CAG repetitions.

Diagram



7. Pharmacological Interventions In Amyotrophic Lateral Sclerosis

Riluzole

At a dosage of 100 mg per day, the benzothiazole riluzole, which has ant glutaminergic qualities, has demonstrated a modest survival advantage (about three months) in patients without affecting muscle strength.[60,61] Riluzole's exact neuroprotective mechanisms are still unclear, however it has been suggested that it inhibits glutamate release in presynaptic terminals by blocking voltage-gated sodium channels, among other effects.[62] Riluzole has also been shown to interfere with intracellular processes that occur after transmitter binding at excitatory amino acid receptors, including OS,[63] and to impact the chloride, calcium, and potassium channels. Other research, however, has also demonstrated some of this compound's antioxidant qualities, which are mediated by the inhibition of phospholipase A activities[65] and protein kinase C activities,[64] which in turn reduce a wide range of oxidative damage. In keeping with its antioxidative properties, riluzole has also been demonstrated to reduce methylmercury-induced OS increasing intracellular glutamate levels, a precursor to GSH, and activating glutamate transporters to promote the elevation of GSH synthesis.[66,67] These several studies suggest that riluzole's beneficial effects might result from a combined impact on various targets, the exact nature of which is yet mostly unknown. Therefore, riluzole treatment was found to be ineffective in reversing the effects of ROS in SH-SY5Y cells carrying the G93A SOD1 mutation,[68] indicating that riluzole is unable to reverse chronic oxidative damage, even though it prevents cell death and regulates elevated ROS levels in parental SH-SY5Y cells.

Edaravone

In Japan, edaravone, the active component of Radical®, is a common free radical scavenger used to treat cerebral ischemia.[69,70] In cases of cerebral ischemia, edaravone protects patients' neurons by removing lipid peroxides and

hydroxyl radicals.[71,72] It has been suggested that edaravone, in addition to its radical scavenger activity, also prevents the opening of the brain's mitochondrial permeability transition pore (mPTP), albeit the precise mechanism of action is unknown This could be a factor in its neuroprotective properties [73]. As an extra neural defense mechanism against OS, other research also demonstrated that edaravone increased the expression of Prx2 in SH-SY5Y neuroblastoma cells, reversing the lethal effects of H2O2. By raising the protein levels of Nrf2, GPx, SOD, HO-1, and NQO1 (Figure 3), edaravone has also been demonstrated to strengthen antioxidant defense mechanisms and lessen the consequences of traumatic brain injury.[74]

Clinical Outcomes

The protective benefits of edaravone in neurons, microglia, astrocytes, and oligodendrocytes are further enhanced by its anti-inflammatory properties. In transgenic SOD1 mouse models of ALS, preclinical research showed that edaravone (ranging from 1.5 to 15 mg/kg) enhances motor function, delays the onset of symptoms, and reduces motor neuron degeneration. In an open-label phase II study involving 20 ALS patients, intravenous edaravone (30 mg or 60 mg/day) was found to be safe and well-tolerated. It also slowed the progression of the disease as indicated by the revised ALS functional rating scale (ALSFRS-R) score over the course of the six-month treatment period as opposed to the six months prior to edaravone administration.

7.3 Investigation Therapies

Stem Cell Therapy

Ongoing Trials And Challenges

Numerous claims of multi- or pluri-potency for cells of different origins, including amniotic fluid cells, umbilical cord blood cells, and the tiny vascular system cells known as multipotent adult progenitor cells, or MAPCs, have not really translated into the wide range of applications that were first anticipated. Autologous bone marrow stem cell trials are being investigated for a variety of illnesses, such as ischemic heart disease and stroke. But in the latter instance, the advantage has been linked to factual differences in the clinical data gathered rather than the cell therapy that was provided (Nowbar et al., 2014).

More recently, MSC trials for ulcerative colitis and ischemic stroke (Athersys), cardiac repair (three studies by Miltenyi Biotec; FBC Pharm cell, Korea; and Stempeutics Research), acute kidney injury (Allocure), ischemic stroke (Manipal Acunova, India), ARDS (China), critical limb ischemia (Raval et al., 2014), and MS (Spain) have failed or been terminated. Failures of clinical trials for MSC therapies have been common (Bersenev, 2015). Clinical trial failures are a fairly common occurrence in this initial wave of cell therapy trials involving autologous and allogeneic MSC products, though they are to be expected in the early stages of clinical research.

There is a registered phase I/II clinical trial in Russia that uses autologous MSC-derived neural cells (with "a matrix scaffold as necessary") in 30 patients with traumatic spinal cord injury, despite the lack of scientific evidence supporting the differentiation of MSCs into functional neurons (Averyanov, 2014). This trial, which started recruiting in July 2014, has not yet produced any findings; preclinical data supporting this questionable strategy were not presented.

One clinical trial utilizing undifferentiated and partially differentiated ESCs to treat cerebral palsy in children in India has been reported, with approval from a "national apex body" and a "independent ethics committee." This is in contrast to the care taken by others in the field to ensure the right cell type is used for transplantation (Shroff et al., 2014).

Numerous methods, including intramuscular or intravenous injection, were used to deliver the cells. Although it's possible that the procedures utilized killed the majority of the cells, transferring undifferentiated pluripotent stem cells is a potentially risky procedure that might have caused these kids to develop teratomas. For the field, these kinds of findings are highly worrying.

Gene Therapy

The gradual loss of motor neurons in the central nervous system (CNS) is the hallmark of ALS, a neuromuscular illness that often manifests as either bulbar-onset (affecting speaking and swallowing) or limb/spinal-onset (affecting arms and legs) muscle weakness and motor impairments.[75] In approximately 10% of ALS cases, familial inheritance is present.[76] Mutations in C9ORF72 (33.7%), SOD1 (14.8%), TARDBP (TDP-43; 4.2%), and FUS (2.8%) are the leading causes of familial ALS in people of European ancestry, whereas the remaining genetic drivers are unknown (44.5%)[77] Less is known about the genetics of familial ALS in people of Asian heritage, however SOD1 mutations account for the majority (30%). Mutations have been found in sporadic ALS cases in some of the recognized familial ALS genes, but about 95% of cases have no documented genetic connection.[28] ALS is characterized by ubiquitinated TDP-43 inclusions in motor neurons, which indicate a disruption in TDP-43 proteostasis. ALS patients have mutations that impair SOD1, an antioxidant-functioning enzyme. An increasing amount of data points to metabolic malfunction and reprogramming in ALS patients, particularly in relation to CNS glucose metabolism.[78]

Table Summary of als drugs, their mechanism and effectiveness

Table 1: Approve disease modifying treatments for amyotrophic lateral sclerosis.

	Riluzole	**edaravone**
dose	50 mg orally twice daily (suspention, tablet,or film)	60mg/day iv on 10 days/month
Mechanism of action	Glutamate inhibition	Free radical scavenger
Side effects	Anaphylaxis, hepatotoxicity,neutropenia,interstitial lung disease, and pneumonitis	Anaphylaxis,hypersensitivity,erthemamultiforme and intravenous adminisration complications
Efficacy in clinical trials	12-month survival was 74% with riluzole vs 58% with placebo	At 24 weeks decline on alsfrs was 249 points less with edaravone vs placebo

8. ADVANCES IN DRUG DELIVERY FOR NEURODEGENERATIVE DISEASE

8. Blood Brain Barrier Challenges

As a natural defense against circulating harmful or infectious chemicals, the brain's capillary micro vessels have developed to limit the flow of molecules and cells between the blood and the brain.

Tight junctions and adherent junctions between capillary endothelial cells created by cell adhesion molecules give the blood–brain barrier (BBB) its relative impermeability. Additionally, brain endothelial cells express large quantities of active efflux transport proteins, such as P-glycoprotein (P-gp, MDR-1, or ABCB1) and breast cancer resistance protein (BCRP, ABCG2), and have limited alternative transport pathways (such as fenestra, trans endothelial channels, and pinocytotic vesicles). The BBB is crucial for maintaining brain homeostasis, but it also poses a major challenge to the successful management of numerous brain disorders.[79,90]

The two main procedures utilized today to improve drug delivery to the brain are either globally through the bloodstream (by breaching the blood–brain barrier or employing targeted delivery techniques) or locally through the

BBB (for instance, by administering drugs via nasal sprays or direct injection. There are numerous strategies being developed to improve medicine delivery across the BBB, both by academia research teams in addition to biotechnology and pharmaceutical firms. Many steps in numerous research domains are needed to convert basic (academic) research into safe and efficient treatments for people with debilitating brain illnesses. Pharmacology and pharmacokinetics (drug delivery, neuroscience, and blood-brain barrier crossing), safety (toxicology, behavioral, route of drug administration, and chronic treatment), and pharmaceutical formulation (chemistry, manufacturing, control, analytics, and selection of appropriate nanocarriers) issues should all be coordinated and taken into consideration. Finding an effective vector for brain delivery that uses a physiological route mechanism to pass the blood-brain barrier is one of the main difficulties in the field of brain delivery. These vectors may take the shape of proteins, peptides, antibodies, or another particular formulation, like nanoparticles.

Intranasal Drug Delivery System

Intracellular and extracellular pathways allow medications that are delivered intranasally to enter the central nervous system (CNS) through the olfactory or trigeminal pathways. Olfactory or trigeminal sensory neurons absorb the medication through the intracellular route and send it to the olfactory bulb or the pons. The medication travels through the TJs, paracellular cleft, lamina propria, perineural space, and subarachnoid space via the extracellular pathway between the supporting cells. The medication molecules can enter the brainstem through the respiratory pathway [206,207]. In addition to the olfactory bulb or brainstem, the distal regions of the central nervous system are where intranasally given medications are mostly disseminated.

NANOTECHNOLOGY BASED APPROCHES

Nanoparticle And Liposome

Phospholipids, which have hydrophilic heads and hydrophobic fatty acid tails, make up the lipid-bilayer membrane structures of liposomes (Fig. 1A). In the middle of the 1960s, they were first applied to the research of biological membranes.[81,82] Since then, they have been used in many different fields, including the food industry, cosmetic formulations, medicine delivery, and diagnostic agents.[83,84,85] Food and Drug Administration has approved a few liposome-based medications.

Administration (FDA), and they can be purchased to treat a variety of illnesses.[86] Liposomes can transport both hydrophilic (in the core aqueous compartment) and hydrophobic (in lipid bilayers) substances because of their biphasic nature.[8]

Recently, the term "nanoliposome" was used to specifically refer to liposomes that are nanometric in size. The smaller size of nanoliposomes may result in a larger interfacial area of encapsulated compounds with biological tissues, which could increase the bioavailability of encapsulated compounds, even though liposomes and nanoliposomes share the same chemical, structural, and thermodynamic characteristics in general.[87] Because of the enhanced permeability and retention (EPR) effect, nanoliposomes can accumulate more in tumors, particularly when used to treat solid tumors.[87]

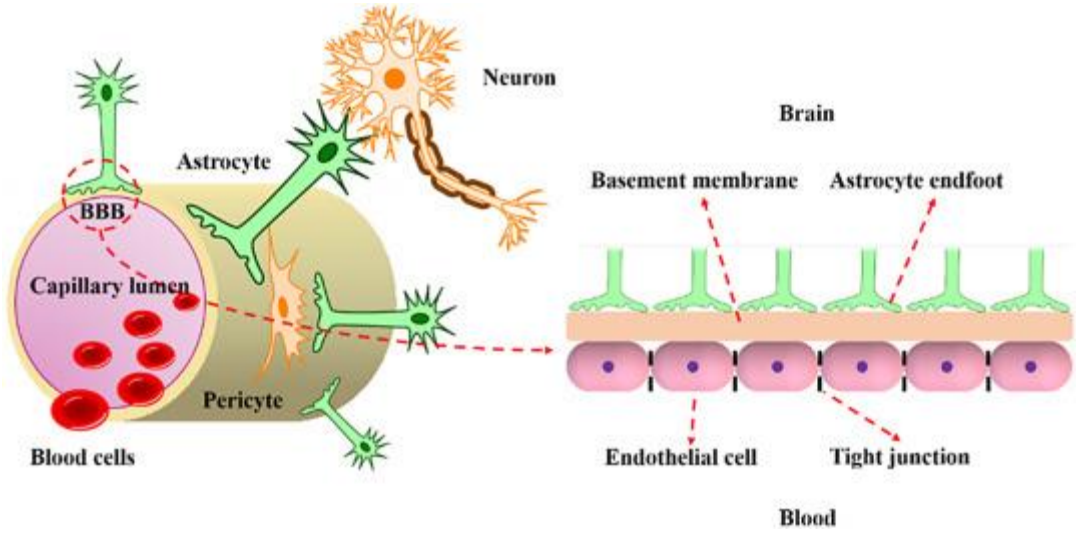
To create nanoliposomes in the aqueous solution, more energy must be input.[9] The most popular nanoliposomes include ether injection, sonication, extrusion, freeze-thaw, and microfluidization techniques for creating. Extrusion and sonication are frequently employed on a laboratory scale. Small nanoliposomes can be produced by extrusion filtration with high power, long duration, and small pore size. Industrial manufacturers frequently employ the microfluidization

approach, which uses high-pressure and high-force technologies with a device known as a microfluidizer to create a flow stream that passes through a narrow orifice to reduce liposome particle sizes. This method's noteworthy benefits include its large-scale nanoliposome preparation reproducibility, size adjustability, and lack of exposure to hazardous organic solvents.

Curcumin

The hydrophobic curcuminoid curcumin is found in turmeric, an Indian spice that is made from the herb Curcuma longa. Numerous positive effects, such as anti-inflammatory, anti-angiogenic, and antitumorigenic qualities, have been demonstrated for curcumin. It may also aid in the prevention or treatment of some chronic illnesses, such as diabetes, cancer, and cardiovascular disease.[88] Notwithstanding these benefits, curcumin is rapidly broken down by hepatic enzymes in both humans and laboratory animals, has low bioavailability, and is poorly soluble in water.[89] To get around these restrictions, biocompatible and biodegradable nanoparticles have been created. Curcumin's water solubility and chemical stability have been effectively enhanced by SLNs, nano emulsions, and PLGA nanoparticles.

DIAGRAM



9. Limitations and challenges in current pharmacological treatment

Pharmacological treatment for neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), faces numerous limitations and challenges. These diseases typically involve complex pathophysiology, and while drug therapies have shown some symptomatic benefits, they often fail to modify the underlying disease processes. Below are some of the key limitations and challenges in current pharmacological treatments, with references to relevant studies.

1. Limited Efficacy in Disease Modification

- **Current Treatments**: Most pharmacological treatments for neurodegenerative diseases primarily focus on symptomatic relief rather than modifying disease progression. For example:
  - In **Alzheimer's disease**, drugs like acetylcholinesterase inhibitors (donepezil, rivastigmine) and glutamate regulators (memantine) can alleviate cognitive symptoms but do not slow disease progression or target the underlying pathophysiological processes, such as amyloid-beta plaque deposition and tau tangles [Cummings et al., 2019].

- In **Parkinson's disease**, levodopa and dopamine agonists can reduce motor symptoms but lose effectiveness over time, and they do not address the progressive neurodegeneration of dopaminergic neurons.

Challenges: The pathophysiological mechanisms in neurodegenerative diseases are often poorly understood, which limits the ability to develop disease-modifying therapies. For instance, Alzheimer's involves complex interactions between amyloid plaques, tau tangles, inflammation, and oxidative stress, all of which remain challenging targets for pharmacological intervention [Cummings et al., 2021].

2. Side Effects and Toxicity

- Many current treatments have significant side effects. For example:
- **Levodopa** used in Parkinson's disease is effective for motor symptoms but can lead to motor fluctuations and dyskinesias (involuntary movements) after prolonged use.
- **Antipsychotic drugs**, used to manage behavioral symptoms in Alzheimer's and Parkinson's disease, can cause sedation, increased risk of falls, and even worsen cognitive decline [Ballard et al., 2009].
- The challenge is that neurodegenerative diseases often affect aging populations who may already be frail or have comorbidities, making them more vulnerable to adverse drug reactions.

3. Lack of Early Detection and Biomarkers

- The **timing of treatment** is crucial in neurodegenerative diseases. Most pharmacological treatments are initiated when the disease is already well-established, and irreversible neuronal damage has occurred. Early intervention, when neuronal damage is still reversible, is likely to be more effective, but early diagnosis remains a significant challenge.
- In Alzheimer's disease, biomarkers (such as amyloid PET scans and tau imaging) are being used to identify individuals at risk before clinical symptoms appear, but these tools are expensive, and not all patients with neurodegeneration show clear biomarker changes [Jack et al., 2018].

4. Genetic and Epigenetic Factors

- The role of **genetic** and **epigenetic** factors in neurodegenerative diseases is complex and not fully understood. While some genetic mutations (e.g., in the gene coding for α-synuclein in Parkinson's or APP mutations in Alzheimer's) provide insight into disease mechanisms, these are rare. For the majority of patients, disease is likely a mix of genetic predisposition and environmental factors.
- Understanding how these factors influence disease progression and how pharmacological interventions can modulate them is an ongoing challenge.

10. Future direction and emerging therapies

The future direction and emerging therapies for neurodegenerative diseases are evolving rapidly due to advancements in technology, molecular biology, and a deeper understanding of disease mechanisms. Neurodegenerative diseases like Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) remain major challenges, but several exciting avenues are being explored. Here’s a look at some of the most promising areas:

1. Precision Medicine and Biomarkers

- **Personalized Approaches**: Advances in genomics, proteomics, and metabolomics are enabling more personalized treatments for neurodegenerative diseases. Precision medicine involves tailoring treatment strategies based on genetic profiles, biomarkers, and specific disease pathways in individual patients.
- **Biomarker Development**: The identification and validation of biomarkers are crucial for early diagnosis, prognosis, and monitoring treatment response. In Alzheimer's disease, for example, blood-based biomarkers and imaging techniques such as amyloid PET scans are already becoming integral for diagnosis and tracking disease progression.

2. Gene Therapy

- **Gene Editing (CRISPR/Cas9)**: Gene-editing technologies like CRISPR/Cas9 hold potential to correct genetic mutations that cause neurodegenerative diseases, particularly those like Huntington's disease and certain inherited forms of ALS. However, challenges around delivery methods, off-target effects, and long-term safety remain.
- **Gene Silencing**: For diseases caused by dominant mutations (e.g., Huntington's disease), gene silencing technologies like antisense oligonucleotides (ASOs) are being developed to "turn off" the expression of toxic proteins. Recent success with ASOs in ALS and spinal muscular atrophy (SMA) has generated hope for broader applications.

3. Immunotherapy

- **Targeting Protein Aggregates**: In neurodegenerative diseases, misfolded proteins (like amyloid in Alzheimer's or alpha-synuclein in Parkinson's) accumulate in the brain and form toxic aggregates. Immunotherapies are being developed to target these misfolded proteins, either by stimulating the immune system or by introducing monoclonal antibodies.
  - **Alzheimer's Disease**: Drugs such as **Aducanumab** (approved by the FDA) aim to reduce amyloid plaques in the brain. Research into tau-targeted therapies is also progressing, given the importance of tau tangles in Alzheimer's pathology.
  - **Parkinson's Disease**: Immunotherapies targeting alpha-synuclein aggregates are being explored in clinical trials, aiming to slow disease progression or prevent neurodegeneration.

4. Stem Cell Therapy and Regenerative Medicine

- **Neurodegeneration**: Stem cell therapy holds promise for repairing or replacing damaged neurons. Induced pluripotent stem cells (iPSCs) can be derived from a patient's own cells and differentiated into neurons. These cells could potentially be used to replace lost or dysfunctional neurons in conditions like PD, HD, and AD.
- **Cell-based Therapies**: Research into using stem cells to replace dopaminergic neurons (as in Parkinson's disease) or to restore lost cognitive functions (as in Alzheimer's disease) is ongoing. Recent clinical trials using dopamine-producing cells from stem cells for Parkinson's disease are showing early promise

CONCLUSION

In conclusion, pharmacological interventions for neurodegenerative diseases aim to modify disease progression, alleviate symptoms, and improve patients' quality of life. While current therapies primarily focus on symptom management—such as cholinesterase inhibitors for Alzheimer's disease or levodopa for Parkinson's disease—there is a

growing emphasis on developing disease-modifying treatments that target the underlying pathophysiological mechanisms, such as protein aggregation, neuroinflammation, and neuronal degeneration.

Research into neuroprotective agents, gene therapies, and the modulation of specific molecular pathways holds promise, although many challenges remain, including the complexity of these diseases and the difficulty of delivering effective treatments to the brain. Personalized medicine, including genetic profiling and biomarker-driven therapies, may help to improve treatment outcomes in the future.

Despite progress, significant gaps remain in the development of truly effective pharmacological interventions. Ongoing clinical trials and advancements in neurobiology offer hope that more targeted, disease-modifying therapies will emerge, offering better outcomes for patients with these devastating conditions.

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