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Neurodegeneration and Cognitive Decline: Causes, Consequences, and Treatment Approaches

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Abstract

Neurodegenerative diseases gradually destroy nerve cells, often leading to fatal outcomes. The phrase includes a wide range of clinical problems, such as a variety of Neurological conditions include movement disorders, like Parkinson's disease (PD) and progressive cognitive impairments, with Alzheimer's disease (AD) being the most common among them. A loss of neurones and synaptic connections, typically in later life, is a prevalent feature of Usually, the onset and development of clinical symptoms are directly correlated with the extent of neuronal death. Early in AD, the hippocampus – a part of the brain involved in declarative episodic memory experiences loss of neuro cells. Tremors, slow movement, and balance problems are the key signs of the condition. clinical trio of Parkinson's disease (PD), and they only show up when 70–80% of the dopaminergic neurones in the substantia nigra are gone.

Keywords: Neurodegeneration, neuroprotection, Alzheimer's disease, Parkinson's disease, epilepsy, stroke

INTRODUCTION

The goal of neuroprotection is to stop the loss of neurons and the degradation of existing ones by using various medications to block pathophysiological pathways that harm the nervous system [1]. The mechanisms and tactics used to protect the central nervous system (CNS) against damage resulting from acute (such as trauma or stroke) and chronic (Figure 1) (such as dementia, Parkinson's, Alzheimer's, epilepsy, etc.) [2]. Interestingly, metabolic disruption in the brain, spinal cord, and nerves is also a feature of these illnesses, which are not exclusive to neuronal cells [3]. Researchers are actively looking for useful biomarkers for early diagnosis and treatment interventions because the molecular pathways underlying these disorders are still mostly understood [4]. The role of miRNAs in post-transcriptional gene regulation adds to the complexity of neurodegenerative disorders, indicating a crucial epigenetic control system that might be involved in the emergence and possible management of various disorders [5].

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A common characteristic of neuroprotective diseases (NDs) is the activation of downstream pathways that trigger cellular death, such as pyroptosis and apoptosis, although the etiology of these disorders differs (Figure 2). These pathways are activated by neurotoxic chemicals that induce inflammation and/or malfunction of the mitochondria. Notably, such neurotoxic compounds are induced by dysregulation of NTs [6]. In the US, the frequency of neurodegenerative diseases (NDs) is rising. By 2050, 13.8 million people are expected to have Alzheimer's disease (AD) [7]. Additionally, the number of Parkinson's disease (PD) cases rose

between 1990 and 2019 [8]. As a neurological illness, AD gradually and irreversibly deteriorates memory, thinking, and ultimately the capacity to perform daily tasks. As a result, full-time care becomes necessary, and the condition primarily affects individuals over 65, though it can also strike younger people [9]. Neurotransmitter (NT) system rebalancing is a key component of FDA-approved treatments for AD and PD symptoms. Acetylcholine esterase inhibitors, are utilized to increase the amount of acetyl choline (ACh) accessible for signaling in AD patients [10]. Furthermore, levodopa (L-Dopa), dopamine (DA) agonists, and monoamine oxidase (MAO) inhibitors have been utilized therapeutically as main drugs for the treatment of Parkinson's disease (PD) symptoms [11].

Nutraceuticals and herbal medicine are significant and beneficial resources for neurological illness prevention as opposed to treatment [12]. Nutraceuticals and natural ingredients transfer their neuroprotective impact through distinct mechanisms. It is known that a wide range of chemical components interact with the GABAA receptor [13], for example, diterpenes and cyclodepsipeptides specifically block its activity [14]. Conversely, alkaloids positively regulate muscimol's binding to the GABA receptor complex [15, 16]. In a similar vein, some flavonoids have demonstrated a propensity to bind to the GABAA receptor's benzodiazepine region [17, 18]. Mono-amine oxidase-B (MAO-B) enzyme activity has been found to be inhibited by a number of plants, including *Arisaema amurense*, *Biota orientalis*, *Mentha arvensis*, *Salvia miltiorrhiza*, *Albizia julibrissin*, *Astragalus membranaceus*, and *Glycyrrhiza uralensis* [19].

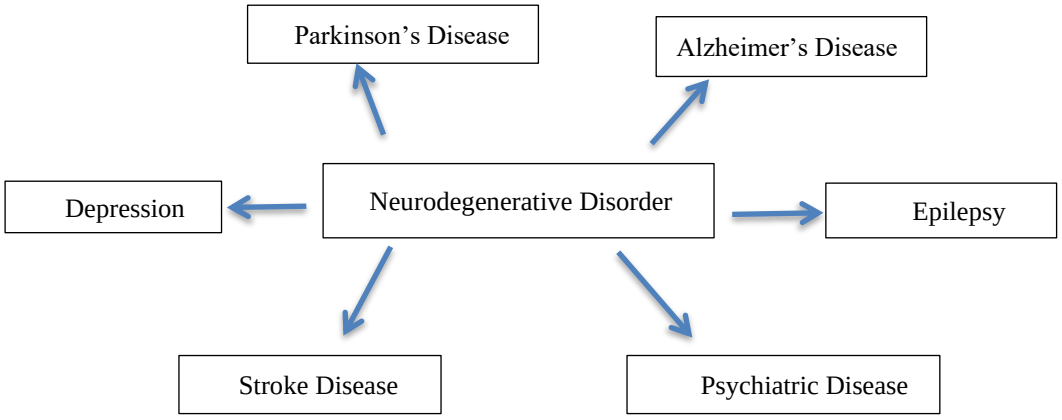

Figure 1. Different type of neurodegenerative disorders.

The pathogenesis of neurodegenerative disorders realize on oxidative stress. It functions as a possible cause of neuronal deterioration as well as one of its symptoms. Reactive oxygen species (ROS) and other free radicals are produced when neurons utilize a large amount of oxygen due to their high metabolic activity [20]. Furthermore, the high iron (Fe) concentration of the brain can act as a catalyst to create more harmful free radicals. This sensitivity is made worse by the relative lack of antioxidant defenses including glutathione peroxidase (GPx) and superoxide dismutase (SOD) [21].

These Neurodegenerative disorders (ND) are a group of diseases in which neurons in the central nervous system are damaged or die, resulting in serious disabilities and, in the worst cases, death. They are most commonly observed in older adults. However, disease occurrence could occur sooner. The number of cases increases day by day. Because the cause of NDs is unknown and no cure has been discovered, they are troublesome and can become a challenge. Nowadays, treatments are focused on symptom relief. Early recognition and supervision of ND will also hopefully evade health problems and reduce the threat of serious health issues [22].

ALZHEIMER'S DISEASE

The most common type of dementia is called Alzheimer's disease (AD), named for the German psychiatrist Alois Alzheimer. It is a slow-progressing neurodegenerative disease that leads to the

buildup of amyloid-beta peptide (Aβ) in the brain's most affected areas, including the medial temporal lobe and neocortical structures, resulting in neuritic plaques and neurofibrillary tangles [23]. The primary component of plaques is the neurotoxic peptide amyloid (Aβ), which is created when two enzymes, β-secretase (also referred to as BACE1) and γ-secretase (which involves four proteins, including presenilin), sequentially cleave a big precursor protein, APP. However, if α-secretase, rather than β-secretase, acts on APP first and cleaves it, Aβ is not produced. Tau, a microtubule associated protein (MAP) that binds microtubules in cells to support the neural transport system, makes up the majority of NFTs. Tau decouples from microtubules and congregates into tangles during AD development, which prevents transport and causes microtubule disintegration. Additionally, it is dependent on Tau phosphorylation [24].

Amyloid plaques, sometimes referred to as congophilic angiopathy or cerebral amyloid angiopathy (CAA), are extracellular deposits of Aβ in the brain parenchyma and cerebral blood arteries. Neurofibrillary tangles (NFTs) containing hyperphosphorylated tau proteins, along with neuronal and synaptic loss, mainly consist of paired helical filaments [25].

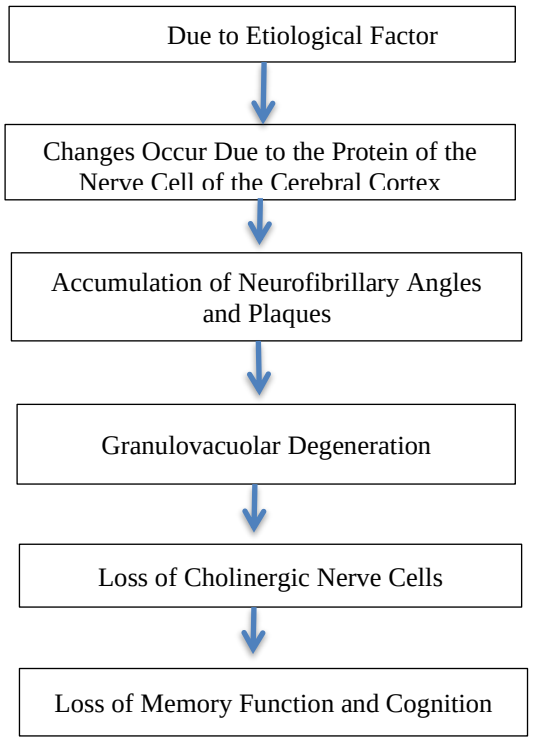

Figure 2. Etiology of loss of memory and cognition.

The clinical stages of Alzheimer's disease include: (1) the preclinical or presymptomatic stage, which can persist for several years or longer. This stage involves mild memory loss and early pathological changes in the cortex and hippocampus, but daily activities remain unaffected, and there are no noticeable clinical signs or symptoms of Alzheimer's disease [26–28]. (2) The mild or early stage of Alzheimer's disease is when symptoms begin to appear, including difficulty with daily tasks, loss of concentration and memory, disorientation in time and place, mood changes, and the onset of depression [29, 30]. (3) In the moderate stage of Alzheimer's disease, the condition spreads to the cerebral cortex, leading to worsening memory loss, difficulty recognizing family and friends, loss of impulse control, and trouble with reading, writing, and speaking [31]. (4) In the severe or late stage of Alzheimer's disease, the condition spreads throughout the entire cortex, causing a massive buildup of neuritic plaques and neurofibrillary tangles. This leads to severe functional and cognitive decline, where patients can no longer recognize their family, may become bedridden, and experience difficulties with swallowing and urination. Eventually, these complications result in death [32, 33].

Alzheimer's disease is a complex condition influenced by multiple risk factors, including aging, genetics, head injuries, vascular diseases, infections, and environmental exposures like heavy and trace metals (Table 1).

The exact cause of the pathological changes in Alzheimer's disease, including amyloid-beta buildup, neurofibrillary tangles, and synaptic loss, is still unknown. Several theories have been proposed to explain the cause of Alzheimer's disease, but two are widely considered primary: one suggests that impaired cholinergic function is a key risk factor, while the other points to abnormalities in amyloid-beta protein production and processing as the main trigger. At present, there is no widely accepted theory that fully explains the cause of Alzheimer's disease [34, 35]. Currently, there are about 24 million reported cases of Alzheimer's disease worldwide. By 2050, the total number of people with dementia is expected to four times.

Table 1. Drugs and their MOA used to treat Alzheimer's disease.

Drug	Class	Indication	Dosing
Donepezil	Cholinesterase inhibitors	Mild to severe cognitive impairment	After 4 to 6 weeks at 5 mg/d, titrate to 10 mg/d. There is insufficient data to recommend 23 mg/d for people who have been taking 10 mg/d for three months [36].
Galantamine	Cholinesterase inhibitors	Mild to moderate memory impairment	Regarding oral dose forms (tablets or oral solutions), Adults: Initially, take four milligrams (mg) twice daily. Once at least four weeks have passed, your doctor may raise your dosage to 8 mg twice day and ultimately to 12 mg twice daily [37].
Rivastigmine	Cholinesterase Inhibitor	Mild to Moderate Memory impairment	Take 1.5 milligrams (mg) twice daily. If necessary and as tolerated, your doctor may progressively increase your dosage. Typically, the dosage is limited to 6 milligrams administered twice daily [36].
Memantine	NMDA Receptor agonist	Moderate to severe memo ry impairment	5 mg before bed, increase by 5 mg per week to a maximum of 10 mg twice day [38].
Ginkgo biloba extract	Anti-oxidant	Mild cognitive impairment	120–240 mg po daily [36].
Tacrine	Reversible cholinesterase	Mild to moderate Alzheimer's disease	10–40 mg po four times daily [39].
Phenserine Cholinesterase inhibitor Investigational	Cholinesterase inhibitor	Investigational	–

PARKINSON'S DISEASE

In 1817, Dr. James Parkinson first described Parkinson's disease (PD) as "shaking palsy" [40]. Parkinson's disease (PD) is a movement disorder caused by the loss of dopamine-producing cells in the substantia nigra. However, from both a clinical and pathological perspective, Parkinson's disease is more complex than just the loss of dopamine-producing cells. In addition to the well-known motor symptoms, like slow movement, stiffness, tremors, and balance issues, Parkinson's disease also causes significant non-motor symptoms, including cognitive impairment, depression, hallucinations, autonomic dysfunction, and sleep disturbances. The Movement Disorder Society's recently updated diagnostic criteria for Parkinson's disease (PD) now emphasizes the importance of non-motor

symptoms. If non-motor symptoms do not appear within the first five years after diagnosis, it is considered a "red flag" [41]. Parkinson's disease (PD) affects the extrapyramidal system, which controls movement through the basal ganglia. It is marked by the loss of dopamine function, resulting in reduced motor abilities and the characteristic symptoms of the disease [42, 43].

In Parkinson's disease, dopamine loss in the striatum increases activity in the GPi/SNpr circuits, causing gamma-aminobutyric acid (GABA) dysfunction and leading to thalamic inhibition. As a result, the thalamus becomes less able to activate the frontal cortex, leading to reduced motor activity, which is a hallmark of Parkinson's disease. Therefore, restoring dopamine activity in the striatum by activating D1 and D2 receptors with dopaminergic therapies helps improve the motor symptoms of Parkinson's disease [44]. Additionally, the loss of dopamine not only reduces thalamic activation but also increases cholinergic activity, as dopamine normally helps inhibit it (Table 2) [45].

Table 2. Drugs and their mechanism to treat Parkinson's disease.

S.N.	Drugs	Class	Mechanism	Effect
1	Levodopa+Carbidopa	Dopamine precursor	Levodopa converts to dopamine	Increase dopamine level
2	Ropinirole	Dopamine agonist	Directly stimulates dopamine receptors	Activate dopamine receptor
3	Pramipexole	Dopamine agonist	Directly stimulates dopamine receptors	Activate dopamine receptor
4	Selegiline	MAO-B inhibitors	Blocks MAO-B enzyme	Increases dopamine availability
5	Entacapone	COOMP inhibitor	Blocks COMT enzyme	Increases dopamine level
6	Trihexyphenidyl, artane	Anticholinergic	block acetylcholine receptor	Relieves tremors and rigidity
7	Amantadine	NMDA receptor blocks	NMDA antagonists' receptors	Improves motor function
8	Istradefylline	Adenosine A2A receptor antagonist	Blocks adenosine A2A receptor	Reduces motor fluctuations
9	Tolcapones	COMT inhibitors	Block COMT enzyme	Increases dopamine level
10	Rasageline	MAO-B inhibitor	Blocks MAO-B enzyme	Increases dopamine level

Epilepsy

A person with epilepsy experiences frequent seizures, or convulsions, over time that impair a range of mental and physical abilities. Epilepsy is a chronic medical condition. An aberrant, excessive, hypersynchronous discharge of a population of cortical neurons results in a seizure, which is the clinical manifestation of the conditions [46, 47].

Seizures are classified into three categories:

1. *Focal (formerly called partial):* Focal seizures start in specific areas of one side of the brain.
2. *Generalized:* Generalized seizures originate from bilaterally distributed neuronal networks. A focused seizure may begin tiny and subsequently get larger.
3. *Epileptic spasms [48]:* Seizures may originate from both subcortical and cortex areas [49].

A seizure can be understood as an imbalance between the brain's normal excitatory (E) and inhibitory (I) signals. The brain's balance between activity and control (excitation and inhibition) can be upset by genetic or environmental factors. Genetic conditions that cause epilepsy include potassium channel mutations in benign familial neonatal epilepsy (BFNE), abnormal GABA receptor subunits in Angelman syndrome, and impaired synaptic connections in cortical dysplasia. A similar shift in circuit

function can result from acquired cerebral injuries (e.g., a structural alteration in the hippocampus circuitry after a prolonged febrile seizure or head trauma). Seizures are especially common in the developing brain for a range of physiological reasons (Figure 3, Table 3) [50].

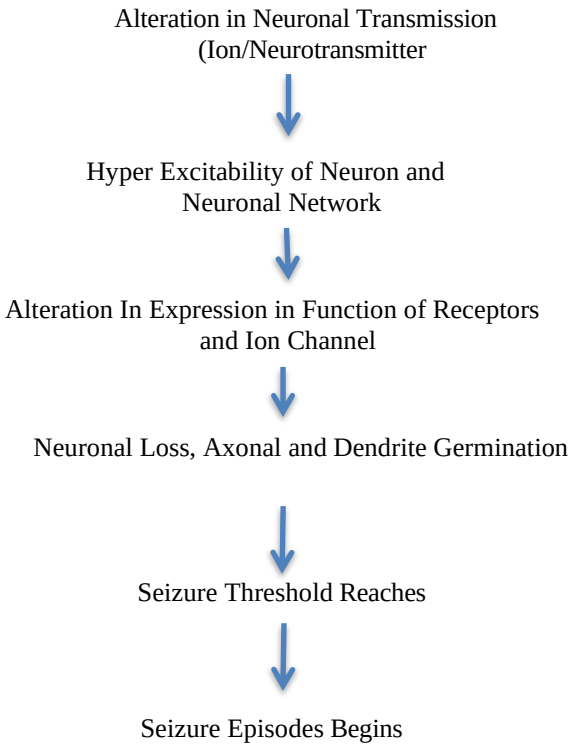

Figure 3. Mechanism of epilepsy.

Anti-epileptic medicines (AEDs) or anticonvulsive pharmaceuticals are considered the most essential therapy choice for epileptic seizures [51]. While these medications combat seizures through a variety of ways, the majority of them function as ion channel (sodium or calcium) or neurotransmitter (GABA) inhibitors. Bumetanide, felbamate, ganaxolone, regtibine, perampanel, and carbamazepine are a few AEDs [52].

Stroke

A stroke is a neurological condition caused by a blocked blood vessel. Blood clots can restrict blood flow, leading to artery blockages or vessel ruptures, which result in bleeding. During a stroke, a rupture in the brain's arteries cut off oxygen supply, causing brain cells to die suddenly. A stroke can also lead to dementia and depression [53, 54].

A stroke is a sudden condition that happens when blood flow to the brain is reduced. A hemorrhagic stroke happens when a blood vessel bursts, leading to bleeding in the brain. There are two types of hemorrhagic strokes: subarachnoid hemorrhage and intracerebral hemorrhage. In intracerebral hemorrhage (ICH), a blood vessel ruptures, causing blood to accumulate abnormally in the brain. The main causes of intracerebral hemorrhage (ICH) include high blood pressure, damaged blood vessels, and excessive use of blood-thinning medications. Subarachnoid hemorrhage happens when a cerebral aneurysm or head injury leads to bleeding in the space between the brain and its surrounding membrane [55, 56]. Ischemic stroke occurs when the brain doesn't receives enough blood and oxygen [57]. The

brain experiences thrombotic and embolic circumstances as a result of ischemic occlusion [58]. Atherosclerosis-induced arterial constriction impairs blood flow in thrombosis. Plaque accumulation will ultimately cause the vascular chamber to narrow and clot, leading to thrombotic stroke. An embolic stroke occurs when reduced blood flow to a brain region causes severe stress and leads to premature cell death (necrosis) (Figure 4) [59].

Table 3. Drugs with their MOA to treat epilepsy.

S. N.	Drug	Class	Mechanism	Effect	Dosing
1	Phenytoin Hydantoin	Imipramine derivative	Block sodium channels, stabilizes neuronal membranes	Reduces seizure frequency and severity	Initial: 100–200 mg/day, Maintenance: 300–400 mg/day
2	Carbamazepine	Imipramine derivative	Block sodium channels, inhibit glutamate release	Reduces seizure frequency and severity	Initial: 100–200 mg/day, Maintenance: 400–800 mg/day
3	Valproate	Fatty acid derivatives	Block sodium channels, enhances GABA	Reduces seizure frequency and severity	Initial: 10–15 mg/kg/day, Maintenance: 20–30 mg/kg/day
4	Lamotrigine	Triazine derivative	Block sodium channels, inhibit glutamate release	Reduces seizure frequency and severity	Initial: 25–50 mg/day, Maintenance: 100–200 mg/day
5	Topiramate	Fructose derivative	Block sodium channels, enhances GABA	Reduces seizure frequency and severity	Initial: 25–50 mg/day, Maintenance: 100–200 mg/day
6	Gabapentin	Aminoacid derivatives	Blocks calcium channel, enhance GABA	Reduces seizure frequency and severity	Initial: 100–300 mg/day, Maintenance: 900–1800 mg/day
7	Levetiracetam	Pyrolidine derivatives	Enhances GABA, blocks calcium channels.	Reduces seizure frequency and severity	Initial: 500–1000 mg/day Maintenance: 1000–3000 mg/day
8	Zonisamide	Benzisoxazole derivatives	Enhances GABA, blocks sodium channels	Reduces seizure frequency and severity	Initial: 100 mg/day, Maintenance: 200–400 mg/day
9	Oxcarbazepine	Imipramine derivative	Blocks sodium channel, inhibits glutamate release	Reduces seizure frequency and severity	Initial: 300–600 mg/day, Maintenance: 600–1200 mg/day
10	Lacosamide	Functionalized amino acid	Enhances sodium channel slow inactivation	Reduces seizure frequency and severity	Initial: 50–100 mg/day, Maintenance: 150–300 mg/day [53].

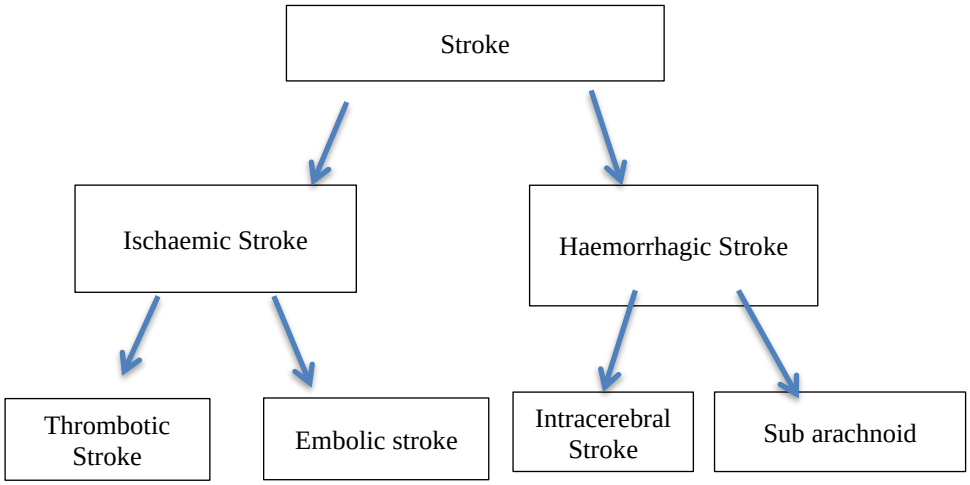

Figure 4. Mechanism of stroke.

Research on stroke in older individuals may not necessarily translate to younger patients due to differences in the nature and genesis of the disease, which affects treatment options and diagnostic evaluation. Younger stroke victims experience a disproportionately greater economic effect due to their disability during their prime years of productivity, as opposed to elder stroke sufferers. The rising number of strokes in younger people is a worrying trend [60].

Hemorrhagic and ischemic strokes have many risk factors, Additionally, risk factors can vary depending on the specific cause of an ischemic stroke. High blood pressure is a major risk factor for hemorrhagic stroke, but it also plays a role in atherosclerosis, which can lead to ischemic stroke. High cholesterol is a major risk factor for strokes caused by atherosclerosis in both extracranial and intracranial blood vessels [61].

Stroke risk factors fall into two categories: those you can change, modifiable factors: like diet and health conditions, and non-modifiable factors: those you can't, such as age and ethnicity. Stroke risk factors can also be categorized by time: short-term triggers like infections, sepsis, and stress; intermediate-term risks, such as high blood pressure and high cholesterol; and long-term factors like sex and ethnicity (Table 4).

Stroke risk factors in younger individuals are likely different from those in older patients [62, 63]. Stroke is a major and growing health concern worldwide. Worldwide, stroke is the top cause of physical disability in adults and the second leading cause of death in middle- to high-income countries. In these countries, the number of ischemic and hemorrhagic stroke cases has risen over the past decade to 85–94 per 100,000 people. However, the rate is much higher, at 1, 151–1, 216 per 100,000, among people over 75 years old. Moreover, 85% of all stroke-related deaths happen in low-income countries, which also account for 87% of the global impact of stroke measured by disability-adjusted life years (DALYs).

Table 4. Overview of Key Pharmacological Agents Used in Stroke Management: Mechanisms and Therapeutic Effects.

S. N.	Drug	Class	Mechanism	Effect
1	Tissue plasminogen activator, tPA activates	Serine protease	Converts plasminogen to plasmin, dissolving blood clot	Restore blood flow to ischemic brain tissue
2	Tenecteplase	Serine protease	Converts plasminogen to plasmin, dissolving blood clot	Restore blood flow to ischemic brain tissue
3	Aspirin	NSAIDs	Inhibit platelet aggregation	Prevent blood clot formation
4	clopidogrel	P2Y12 receptor inhibitor	Inhibits platelets aggregation	Prevent blood clot formation
5	Heparin	Inhibit thrombin and factor Xa	Inhibit thrombin and factor Xa	Prevent blood clot formation
6	Warfarin	Vitamin K antagonists	Inhibit vitamin K dependent clotting factors	Prevent blood clot formation
7	Edaravone	Free radical scavenger	Reduces oxidative stress	protect the neurons from damage
8	Citicoline	Cholinergic agent increases acetylcholine levels	Enhances cognitive function	Enhances cognitive function
9	lisinopril	ACE inhibitor	Lower blood pressure	Reduces risk of stroke

Psychiatric Disorders

Schizophrenia is one of the chronic illnesses with the worst prognoses among psychotic disorders. Due to the greater death rate of individuals with severe mental disorders compared to the general

population, healthcare systems worldwide face challenges in diagnosing and treating serious psychiatric illnesses like schizophrenia [64]. While atypical antipsychotics are useful in managing the symptoms of schizophrenia, no medication has been found to yet that can affect the disease's unclear pathogenetic core. Above all, treating patients with resistant schizophrenia – that is, the condition in which two antipsychotic medication trials have not resulted in remission – is a problem. Clozapine is the sole medication that works and is readily available in these situations [65]. Schizophrenia's positive symptoms include delusions and hallucinations, while negative symptoms involve apathy, flat affect, negative thoughts, social withdrawal, and cognitive or disorganized thinking [66]. Although the exact cause of schizophrenia remains unknown, researchers are exploring the neuroinflammatory and immunological hypothesis as a possible factor in its development [67]. Cytokines, which mediate neuroinflammation, also play a role in the generation, differentiation, and maturation of neurons (Table 5). Cytokine levels naturally fluctuate during key developmental stages when the prefrontal cortex undergoes significant changes. Interleukin (IL) levels peak during preschool years, while tumor necrosis factor-α (TNF-α) and Interleukin-6 (IL-6) reach their highest levels during adolescence [68].

Table 5. Pharmacological Classification and Clinical Effects of Selected Psychiatric Medications.

S. N.	Drug	Class	Mechanism	Effect
1	Risperidone	Atypical antipsychotic atypical antipsychotic	Dopamine and serotonin receptor antagonist	Reduces symptoms of schizophrenia and bipolar disorder, such as hallucinations and delusions
2	Olanzapine	Atypical antipsychotic	Dopamine and serotonin receptor antagonist	Reduces symptoms of schizophrenia and bipolar disorder, improves mood stability
3	Haloperidol	Typical antipsychotic	Dopamine receptor antagonist	Reduces agitation, aggression, and hallucinations in schizophrenia
4	Fluoxetine	SSRI	Increases serotonin level in brain	Improves mood, reduces symptoms of depression and anxiety
5	Venlafaxine	SSRI	Increases serotonin level in brain	Improves mood, reduces symptoms of depression and anxiety
6	Sertraline	SSRI	Increase serotonin and nor epinephrine level in the brain	reduces symptoms of depression and anxiety
7	Lithium Stabilizer	SSRI	Inhibit Norepinephrine reuptake norepinephrine level in the brain	reduces symptoms of depression and anxiety
8	Valproate	–	Mood stabiliser affects neurotransmitter release and ion channel	Stabilizes mood, reduces symptom of bipolar disorder and epilepsy Reduces anxiety and panic symptoms (69)
9	Alprazolam	Benzodiazepine	Enhances GABA activity	Stabilizes mood, reduces symptoms of bipolar disorder and epilepsy

CONCLUSIONS

The rising cases of neurodegenerative diseases have become a major concern. Finding effective treatments for these diseases is now more crucial than ever. strength of this review is comprehensive coverage of drug-based treatment options. Although there are many drug-based treatment options for neurodegenerative disorders, their potential side effects cannot be ignored. These medications offer only temporary symptom relief and do not prevent disease progression. Therefore, it is essential to find an alternative treatment that not only slows symptom progression but also has fewer side effects.

Neurodegenerative diseases affect people worldwide, causing brain cell death. Like Parkinson's disease, impact the basal ganglia, cause movement difficulties.

Other neurodegenerative diseases, such as Alzheimer's disease and Lewy body dementia, cause widespread brain cell death, leading to memory loss. This article does not cover some of the rarer types

of neurodegenerative diseases. Neurodegenerative diseases are devastating conditions with no cure yet, but researchers worldwide are actively working on treatments to help those affected. One promising treatment involves using stem cells to replace lost neurons. With so many brilliant researchers working on a cure, there is hope that effective treatments will be available soon.

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