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A Review of Neurodegenerative Diseases

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Abstract
In current studies, neurodegenerative disease research is more tremendous advances in two decades. These diseases occur when dysfunction of nerve cells in the brain or peripheral nervous system. While treatments may help reduce some of the physical or mental symptoms associated with neurodegenerative diseases. Several age-related neurodegenerative diseases occur they are Alzheimer's disease and Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias. Alzheimer's disease is the most common cause of dementia worldwide, with the prevalence continuing to grow in part because of the ageing world population. The pathogenesis of the neurodegenerative disease process is characterized by two hallmarks i.e β-amyloid plaque deposition and neurofibrillary tangles of hyperphosphorylated tau. Parkinson's disease (PD) is the second most common neurodegenerative disease, manifesting as a characteristic movement disorder with a number of additional non-motor features. The pathological feature of PD is the presence of intra-neuronal aggregates of α-synuclein (Lewy bodies). The movement disorder of PD occurs mainly due to loss of dopaminergic neurons of the substantia nigra, resulting in striatal dopamine depletion. At present no proven drugs or disease-modifying treatments for management of PD. Huntington's disease (HD) is a fully genetic neurodegenerative disease caused by a dominantly inherited CAG trinucleotide replicate growth in the huntingtin gene on chromosome 4. The prevalence of 10.6–13.7 individuals per 100000 in Western populations. It is categorized by cognitive, motor and psychiatric disturbance. Here, we discuss recent advances in our understanding of the clinical evaluation and treatment of neurodegenerative diseases, with updates regarding still in progress.

Keywords
Alzheimer's disease, Parkinson's disease, amyloid, Huntington's disease, neurodegeneration.

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INTRODUCTION
Neurodegenerative diseases occur when dysfunction of nerve cells in the brain or peripheral nervous system. while treatments may help reduce some of the physical or mental symptoms associated with neurodegenerative diseases. Several age-related neurodegenerative diseases occur mostly common diseases are Alzheimer's disease and Parkinson's disease. Others such as Huntington's disease, amyotrophic lateral sclerosis, frontotemporal dementia and the spinocerebellar ataxias.[1] These diseases are varied in their pathophysiology – with some causing impairments of memory and cognitive functions and others affecting a person's ability to move, speak and breathe.[2] NDDs are associated with the growth of misfolded proteins into microscopically visible aggregates in the brain. These aggregates contain fibrillar structures that are mainly composed of disease-specific misfolded proteins, such as a-synuclein in Parkinson's disease, amyloid-b

and tau in Alzheimer's disease, superoxide dismutase (SOD) in Amyotrophic lateral sclerosis (ALS), and mutant huntingtin in Huntington's disease[3]. Familial forms of these misfolding diseases often involve toxic gain-of-function mutations that increase misfolding and aggregation properties as well as the toxicity of the disease proteins. This is well illustrated by Huntington's disease, in which the expansion of a polyglutamine stretch within the huntingtin protein causes disease. In this several other polyglutamine diseases, there is a direct correlation between the length of the polyglutamine expansion and the aggregation and toxicity of disease proteins [4]. Additionally, there is an inverse correlation between the length of the polyglutamine stretch and the age-at-onset of disease [5]. Apart from the misfolding properties of the disease proteins and other inherited factors are predicted to modify the age-at-onset of these familial misfolding disease [6]. Non-familial forms of neurodegenerative diseases, which include the majority of cases of Parkinson's and Alzheimer's disease, typically develop in old age. In these sporadic cases, the characteristic aggregates in the brain are primarily composed of misfolded, but wild type, disease proteins. The cause of protein misfolding and pathogenesis in these non-familial forms remains elusive. One can speculate that several phenomena associated with old age, for example, cell shrinkage and a decline in protein quality control, could cause or contribute to protein misfolding and aggregation and thereby lead to disease [8]. These phenomena do not explain, however, why different people develop different protein-misfolding diseases in old age. Other disease-modifying factors are likely to play a role as well. Finding the genetic modifiers that influence protein misfolding and toxicity is, therefore, expected to expand our understanding of the molecular cause(s) of protein-misfolding diseases and could provide important cues for therapeutic strategies. In the present review, we have compiled data on the prevalence, pathogenesis, treatment with a special emphasis on neurodegenerative diseases.

EPIDEMIOLOGY

Neurological disorders are increasingly recognized as one of the most prevalent disorders with a high burden to the patients, their families and society. However, until recently there were no accurate estimates of the burden of neurological disorders on the global, regional, and national levels as well as their trends over the last 3 decades. This gap in the knowledge was filled in the recent series of 11 *The Lancet Neurology* papers on the prevalence, incidence, deaths, and disability-adjusted life years (DALYs; the sum of years of life lost and years lived with disability) of 15 neurological disorders in 195 countries from 1990 to 2016 derived from the Global Burden of Disease, Injuries, and Risk Factors 2016 Study (GBD 2016). [9]

Neurological disorders included in the analysis were tetanus, meningitis, encephalitis, stroke, brain and other nervous system cancers, traumatic brain injury, spinal cord injury, Alzheimer's disease and other dementias, Parkinson's disease, multiple sclerosis, motor neuron disease, idiopathic epilepsy, migraine, tension-type headache, and a residual category of other less common neurological disorders. Millions of Americans have Alzheimer's or other dementias. As the size and proportion of the U.S. population age 65 and older continue to increase, the number of Americans with Alzheimer's or other dementias will grow. This number will escalate rapidly in coming years, as the population of Americans age 65 and older is projected to grow from 55 million in 2019 to 88 million by 2050. [10,11]. This section reports on the number and proportion of people with Alzheimer's dementia to describe the magnitude of the burden of Alzheimer's on the community and health care system. The prevalence of Parkinson's disease, an estimated 7 to 10 million people worldwide have Parkinson's disease. The prevalence of the disease ranges from 41 people per 100,000 in the fourth decade of life to more than 1,900 people per 100,000 among those who are 80 and older. The incidence of the disease, or the rate of newly diagnosed cases, generally increases with age, although it can stabilize in people who are older than 80. An estimated 4 percent of people with Parkinson's are diagnosed before age 50. Men are 1.5 times more likely to have Parkinson's than women. In USA, about one million Americans are consider having Parkinson's compared to more than those affected by multiple sclerosis (MS), muscular dystrophy (MD), and amyotrophic lateral sclerosis (ALS). Every year more than 60,000 Parkinson's patients are diagnosed with America. In Canada, According to UCB, a global biopharma company focused on severe diseases with operations in approximately 40 countries, there are over 100,000 Canadians living with Parkinson's disease today, with about 6,600 new cases of Parkinson's diagnosed each year in Canada (based on an annual incidence of 20 new cases per 100,000 people). Overall, men are more likely to have the disease than women. The results are 0.3% of men compared to 0.2% of women in private households, and 6.6% of men vs. 4% of women in care facilities. In UK, The prevalence of Parkinson's in the U.K. is about

one in 500 people, with a total of about 127,000 people living with the disease. [12,13]

1. ALZHEIMER DISEASE

Alzheimer's is an age-dependent progressive neurodegenerative disorder. This is the most common type of dementia which is characterized by deteriorated memory; thinking and behaviour affect the daily social life of the person. There are two types of AD one is early-onset appears before age 60 and the other one is late-onset AD occurs at or above age 60.[14] Alzheimer's disease (AD) is a progressive neurodegenerative disorder which has the characteristic features of memory impairment, cognitive dysfunction, behaviour disturbances and deficits in activities of daily living [15]. Although the aetiology of the disease is still not very clearly known there are two major hypotheses which inadequately explain the molecular mechanism of AD, namely: the cholinergic hypothesis and the amyloid cascade hypothesis [16]. The cognitive dysfunction in AD is supposed to be a result of degeneration of cholinergic neurons in the basal forebrain and associated loss of cholinergic neurotransmission in the cerebral cortex and some other areas [17]. The enzyme acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) play an important role in the cholinergic deficit through enhanced degradation of the neurotransmitter acetylcholine (ACh). So, in most cases to improve neurotransmission and to alleviate cholinergic deficit, the focus is mainly on acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) [14]. According to the amyloid cascade hypothesis, AD is associated with the accumulation of β-amyloid (Aβ) fibrils and senile plaque in the brain parenchyma. Several studies have reported that increased oxidative stress has a potential role in the inflammatory processes that eventually lead to the lipid peroxidation and formation of Aβ [18]. Many studies have shown that increased level of free radicals and reactive oxygen species induced the degeneration of neurons [19, 20, 21].

1.1. Pathogenesis

Tau Protein: Tau is one of the microtubules associated with a protein that is thought to have a role in the stabilization of neuronal microtubules these, in turn, provide the track for intracellular transport. [22] The molecular mechanisms prevailing tau aggregation are mainly represented by some posttranslational modifications that structure modifying and conformational state. Hence, unusual phosphorylation of tau protein has gained consideration as crucial mechanisms that become tau protein in a pathological unit.[23] After neuronal damage, tau is released into extracellular space and may be increased in the cerebrospinal fluid (CSF). Elevated CSF levels of tau occur in parenchymal diseases, including neurodegenerative as well as vascular or inflammatory diseases.[24]

Oxidative Stress and β-amyloid: Oxidative stress plays a substantial role in the pathogenesis of AD, a damaging disease of the elderly. The brain is more susceptible than other organs to oxidative stress, and most of the neurons (lipids, proteins, and nucleic acids) can be oxidized in AD due to mitochondrial dysfunction, increased metal levels, inflammation and β-amyloid peptides. Oxidative stress participates in the development of AD by promoting amyloid -β deposition, tau hyper-phosphorylation and the successive loss of synapses and neurons.[25] The amyloid precursor protein observed in Alzheimer's disease pathology, suggests a time-course of plaque development beginning with neuronal amyloid precursor protein accumulation, then deposition into the extracellular space, subsequent processing by astrocytes or microglia, and resulting in beta-amyloid peptide accumulation in plaques.[26] APP can be proteolyzed directly by α-secretase and then γ-secretase, a process that does not generate amyloid-β, or reinternalized in clathrin-coated pits into another endosomal compartment containing the proteases BACE1 and γ-secretase. The latter results in the production of amyloid-β.[27]

1.2. Treatment

In pharmacological therapies, today various medications or drugs are available for Alzheimer's dementia to slow or stop the damage and destruction of neurons that cause Alzheimer's symptoms and make the disease fatal. The U.S. Food and Drug Administration (FDA) has approved six drugs for the treatment of Alzheimer's such as rivastigmine, galantamine, donepezil, memantine, memantine combined with donepezil, and tacrine (tacrine is now discontinued in the United States). With the exception of memantine, these drugs temporarily improve symptoms by increasing the number of chemicals called neurotransmitters in the brain. Memantine blocks certain receptors in the brain from excess stimulation that can damage nerve cells. The efficiency of these drugs varies from one person to other and is partial in time. Several factors give the difficulty of developing effective treatments for Alzheimer's. Biomarker tests will be essential to identify which individuals are in these early stages and should receive treatments when they are available. Biomarkers also will be critical for monitoring the effects of treatment. Already, biomarker tests are playing an important role in drug development because they enable researchers to recruit into clinical trials only those individuals with

the Alzheimer's brain changes that the drug has been intended to affect.[28] The most effective biomarker test or combination of tests may differ depending on the stage of the disease and other factors.[29]

Non-pharmacological therapies are those that do not involve medication. They have been studied in people with Alzheimer's dementia and in cognitively normal individuals who would like to prevent dementia or slow cognitive decline. The aim of this therapy to reducing behavioural symptoms such as depression, apathy, wandering, sleep disturbances, agitation and aggression. Examples include computerized memory training, listening to favourite music and incorporating special lighting to lessen sleep disorders. As with current pharmacologic therapies, non-pharmacologic therapies do not slow or stop the damage and destruction of neurons that cause Alzheimer's symptoms and make the disease fatal.[30]

Table 1: Drugs used for Alzheimer disease

S.No	Drugs name	Mechanism
1.	Acetylcholinesterase inhibitors	This class of drugs functions by inhibiting the neurotransmitter acetylcholine, which can improve brain performance [31]
2.	Modafinil	Central nervous system stimulants used for attention deficit disorder narcolepsy or excessive sleepiness which includes methylphenidate, atomoxetine, modafinil, armodafinil and the amphetamines [32]
3.	Clomethiazole (GABA agonists)	Neuroprotective agents inhibit reactions in the brain ischemic injury cascade which lead to neuronal death. GABA is a naturally occurring inhibitory neurotransmitter that increases chloride influx into the neuron and counteracts the toxic effects of glutamate [33]
4.	NMDA receptor antagonists	Continuous activation of NMDA receptors [34]
5.	Donepezil	Anti-dementia drugs [35]
6.	Omega-3 fatty acids	Plays a critical role in the development and function of the CNS.
7.	R-flurbiprofen (Flurizan)	reduces beta-amyloid

2.PARKINSON's DISEASE

Parkinson's has the second-highest occurrence neurodegenerative diseases of the nervous system. This disease affects about 4500000 people worldwide. In 2030, the number of affected people may be increased [36, 37]. Numerous studies advise that Parkinson's disease in elder ages if it is associated with ambient factors, although most cases of young people, there is a genetic factor. In addition, it has been examined that the disease affects about 50% more men than women [38]. Parkinson's disease belongs to a group of the disease characterized by muscle rigidity, tremor and hypokinesia.[39]. It is a progressive neurodegenerative disorder associated with age and affects mainly movement, so-called movement disorders. This disease is characterized by the loss of dopaminergic neurons of the nigrostriatal pathway with a consequent decrease in dopamine. On the other hand, the diminution of dopamine levels in the caudate and putamen of the basal ganglia leads to the appearance of a number of pathological manifestations, such as neuronal damage, depigmentation of the substantia nigra, and the presence of intracellular insertion in the dopaminergic neurons called Lewy bodies [40]. The finding of disease is based on clinical symptoms, such as the presence of a hypokinetic rigid syndrome characterized by the four cardinal motor signs: bradykinesia, stiff muscles, resting tremor, and impaired postural reflexes with locomotion difficulty [41, 42]. The loss of dopaminergic neurons to the striatum produces an imbalance between the dopaminergic pathway from the mesencephalon and the glutamatergic pathway from cortical, thalamic, and limbic areas. These effects are due to the lack of inhibition of dopaminergic receptor D2, which decreases the excitatory input stimuli to the cortex, resulting in the typical motor problems of the disease [43]. Thus, the pharmacological treatment of Parkinson's disease usually direct or indirect potentiation of dopaminergic activity or administration of anticholinergic drugs [44,45]. In addition to the effective treatments intended to reduce the development of the Parkinsons disease [46]. In addition, the clinical studies have established that inflammation may be involved in the aetiology of sporadic Parkinson's tendency because of the incidence of the disease is lower in patients that consume non-steroidal anti-inflammatory drugs.

2.1. Treatment

In worldwide Parkinson disease is the second most common neurodegenerative there is currently no cure for Parkinson's disease, but treatments are available to help relieve the symptoms and maintain your quality of life. Current treatments only improve some of the symptoms for a few years, but they become ineffective in the long run and do not stop the disease. Therefore, it is of utmost importance to develop therapeutic strategies that can prevent, stop, or cure Parkinson disease. The symptoms can be controlled using a combination of drugs, therapies and occasionally surgery. [47,48].

2.1.1. Supportive therapies: A number of therapies that can make alive with Parkinson's disease easier. Whether this therapy can be an effective treatment for people with brain or mental diseases e.g., dementia, Alzheimer's disease, Parkinson's disease [49-51].

2.1.2. Physiotherapy: in this therapy, to relieve muscle stiffness and joint pain through movement and exercise and also aims to make moving easier and improve your walking and flexibility. They also try to improve your fitness levels and your ability to manage things for yourself [52-54].

2.1.3. Speech Therapy: This therapy can improve the precision and volume of speech and provides instructions for better communication [55-57].

2.1.4. Drugs: Medication can be used to improve the main symptoms of Parkinson's disease, such as tremors (uncontrollable shaking) and movement problems. It is primarily associated with abnormal of dopamine in neurons within the midbrain resulting in Parkinson's disease. Dopamine is a neurotransmitter which conveys messages between neurons to ensure effective planning, initiation and maintenance of movement [58-60]. Most pharmaceutical treatment can focus on restoring the balance of dopamine and other neurotransmitters. Three main types of medication are commonly used. These are levodopa, dopamine agonists and monoamine oxidase-B inhibitors.

Levodopa: Most people with Parkinson's disease will eventually need to have a medication called levodopa. Levodopa is absorbed by the nerve cells in your brain and turned into the chemical dopamine, which is used to transmit messages between the parts of the brain and nerves that control movement. Increasing the levels of dopamine using levodopa usually improves movement problems. Levodopa is available in tablet or Capsule (Sinemet®) or liquid and is often combined with benserazide or carbidopa because the levodopa being metabolised in the bloodstream before it has reached into the brain [61-64]. Long term use of levodopa is also linked to problems such as uncontrollable, jerky muscle movements (dyskinesias) and 'on-off' affects-where the person suddenly switches between being able to move (on) and being immobile (off) [65-66].

Dopamine agonists: These drugs act as an agonist for dopamine in the brain and have a similar but milder effect compared to levodopa. Dopamine agonist available as a tablet, apomorphine can be injected subcutaneously. Sometimes, dopamine agonists are taken at the same time as levodopa as this allows lower doses of levodopa to be used. Possible side effects of dopamine agonists include nausea, vomiting, tiredness and dizziness [67-68]. Dopamine agonists can cause side effects including hallucinations and episodes of confusion, so they need to be used with care, particularly in old patients who are more susceptible. [69-71] .

Monoamine oxidase-B inhibitors: Selegiline and rasagiline are Monoamine oxidase B (MAOB) inhibitors are an alternative to levodopa for treating early Parkinson's disease. They block the effects of monoamine oxidase B. Both of these two drugs can improve the symptoms of Parkinson's disease. They can be used combined with levodopa or dopamine agonists. MAOB inhibitors can cause a wide range of adverse effects, including nausea, headache and abdominal pain [72-74].

Catechol-O-methyltransferase inhibitors: COMT inhibitors are enhancing Levodopa efficacy and half-life are also still being developed. Catechol-O methyltransferase (COMT) inhibitors are given for people in later stages of Parkinson's disease. They prevent levodopa metabolism by the enzyme COMT. COMT inhibitors can cause nausea, vomiting, diarrhoea and abdominal pain. Tolcapone is the COMT inhibitor used for Parkinson's disease. [75-76]

Anticholinergic drugs: Anticholinergic medicines block the action cholinergic neurotransmitter acetylcholine. They help to balance between the dopamine and acetylcholine. These medicines only help with tremor and are less effective [78].

2.1.5. Surgery: Most people with Parkinson's disease are treated with medication, although a type of surgery called deep brain stimulation is used in some cases [79].

The most common forms of surgery for Parkinson's disease are:

Thalamotomy: Surgical destruction of a tiny part of the brain (thalamus) to alleviate some forms of tremor.

Pallidotomy: The surgeon makes a lesion on a different part of the brain to alleviate dyskinesia (wriggling movements).[80]

3. HUNTINGTON DISEASE

A disease is a condition of the body associated with a defining set of deleterious symptoms, the disease phenotype. The rational identification of treatments and cures for human diseases is generally predicated upon an understanding of the disruption(s) in cellular and molecular pathways that cause the disease phenotype. This understanding is usually obtained from the observation of behavioural phenotypes and studies of abnormalities in the structure of organs, tissues and cells from diseased individuals.

Identification of disease-causing gene mutations for monogenic disorders can provide insight about the underlying functional disruption and, even in the absence of such insight, opens the way for the construction of disease models in experimentally tractable organisms. The study of such models facilitates the discovery of potential causes of disease phenotypes. They also provide platforms for validating these causes and for testing therapeutic approaches designed to obviate their deleterious effects.

Among the more common neurodegenerative diseases, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD), HD is unique in that most (~99%) individuals presenting with the HD phenotype have a mutation in the same gene. Although mutations that cause Alzheimer's, Parkinson's or ALS have been identified, there are several genes involved for each, and only 5–15% of patients carry a specific causative mutation.

As a very nearly monogenic disease with clear, defining phenotypes, HD is an attractive model in which to attempt to unravel the mechanism of disease causation as an approach to identifying therapeutic interventions capable of modifying the course of the disease and/or preventing its onset. In this article, we note some recent results impacting the status of this effort, summarize our view of the currently most promising approaches to treatments and a cure and comment on the research required to accomplish this goal.[81]

3.1. Causes

HD is a dominantly inherited disease caused, in most cases, by an expansion of a CAG repeat located in the DNA encoding the first exon of *HTT*. Most individuals with HD carry only one disease-causing (mutant) allele. [82,83] Nowadays, most disease-causing alleles of the HD gene occur on a common haplotype that is relatively rare in individuals of European descent and absent from several populations of Asian and African origins [84].

3.2. Phenotypes of Huntington disease

The defining phenotype of HD is generally considered to be chorea, involuntary movements, some dance-like, that occur in many parts of the body. Those with the disease often also display psychiatric symptoms, most commonly depression and irritability, as well as declines in cognitive abilities. It seems likely that people with HD have a variety of still-being-characterized behavioural changes; for example, recently, the occurrence of abnormal sleep patterns was documented in the laboratory, although patients and families usually complain of this symptom as well.

Post-mortem analyses of HD brains show massive degeneration of the striatum as well as the cortex with lesser, but still significant, changes in the hippocampus, hypothalamus and in other brain structures. In addition, recent results, using diffusion tensor imaging, emphasize the early occurrence of changes in white matter [85], and both positron emission tomography and biochemical studies demonstrate the presence of neuroinflammation in the HD brain [86]. Understanding the causes of these changes requires consideration of the roles of endogenous functional differences in the constituents of the brain. These include the roles of various glial cells (oligodendrocytes, astrocytes, microglia), endothelia and perivascular cells as well as potential influences from the periphery [87].

Biochemical studies of mRNA, protein and metabolite content in tissues from people with HD in the presence of many changes within the CNS. Recent results have emphasized changes beyond the striatum and cortex [88]. Many changes are also found in peripheral tissues including muscle [89], adipose tissue [90] and peripheral inflammatory cells. The HD gene encodes a large, 3144 amino acid long protein called 'Huntingtin', with roles in a variety of cellular functions, prominent among which are vesicle trafficking, energy production and transcription. The CAG repeat in the HD gene encodes a stretch of glutamine residues in the N-terminus of Huntingtin, beginning after the 17th amino acid. The mechanism by which the expressed expanded CAG repeats in *HTT* causes HD is only poorly understood. Still, most investigators consider the mutant Huntingtin protein with its expanded glutamine stretch the prime culprit, toxicity resulting from triplet repeat containing RNAs and/or dysregulation of antisense transcripts have not been fully explored.

3.3. Pathogenesis

Pathologically, HD is associated with diffuse loss of neurons, particularly involving the cortex and the striatum. Medium spiny neurons in the striatum that

contain γ-aminobutyric acid and enkephalin are affected early in the disease, and are the primary neurons targeted in HD. These neurons typically project into the lateral globus pallidus. Over time, the degenerative process progresses to involve the remainder of the basal ganglia with subsequent dissemination, including cortex and substantia nigra. Intranuclear and cytoplasmic inclusions of the *htt* gene aggregate can be demonstrated microscopically. Huntingtin is cross-linked with other soluble *htt* to form the inclusion bodies in neurons. It is not known if the accumulation of *htt* conglomerate results in cell death, or if the soluble form of the protein is the toxic form [91, 92]. Dopamine, glutamate, and γ-aminobutyric acid are thought to be the most affected neurotransmitters in HD and are currently the focus of pharmacotherapy (Table 2) [93-95].

Table 2: Neurotransmitters involved in the pathogenesis of Huntington's disease

S.No	Receptor	Location	Stage of disease
12	Adenosine A2A	Striatum, GPe	Preclinical to advanced
3	Cannabinoid	Striatum, GPe	Preclinical to advanced
4	Dopamine D_1	Striatum, substantia nigra	Clinical diagnosis to advanced
5	Dopamine D_2	Caudate, putamen	Prodromal
6	Dynorphin	Striatum	Emergence of dystonia
7	Enkephalin	Striatum	Emergence of chorea
8	GABA	Striatum	Advanced
9	Glutamate	Cortical	Preclinical to advanced
10	Substance P	Striatum	Emergence of dystonia

3.4. Treatment

Many agents and surgical procedures have been evaluated in HD for their efficacy in suppressing chorea, including dopamine-depleting agents, dopamine antagonists, benzodiazepines, glutamate antagonists, acetylcholinesterase inhibitors, dopamine agonists, antiseizure medications, cannabinoids, lithium, deep brain stimulation, and fetal cell transplantation [96–98]. Pharmacological interventions typically address the hyperkinetic movement disorders that may be associated with HD, such as chorea, dystonia, ballism, myoclonus, and tics. When choosing an intervention, providers should consider if there will be a positive or negative effect of the agent on psychiatric issues associated with HD, such as irritability, depression, anxiety, mania, apathy, obsessive–compulsive disorder, or cognitive decline. Adjunctive therapies, alternative and complementary therapies, behavioural plans, and cognitive interventions also may play a role in the symptoms of HD.

Several reviews have summarized the symptomatic treatment of chorea associated with HD. Overall, there is not enough evidence available to guide long-term symptomatic treatment in HD. Despite the lack of evidence, an American Academy of Neurology Guidelines publication was recently released recommending consideration of tetrabenazine (TBZ), amantadine, or riluzole if chorea requires treatment. Based on available evidence, the TBZ showed clear efficacy for the control of chorea, but "no statement can be made regarding the best medical practice for the control of motor and non-motor symptoms in HD".

TBZ is the only US Food and Drug Administration-approved drug for HD indicated for the treatment of chorea associated with HD. Other medications that are commonly considered when treating chorea include dopamine antagonists, benzodiazepines, and glutamate antagonists. Dopamine antagonists (neuroleptics) are perhaps the most commonly considered agents in the management of chorea and psychosis in patients with HD, but few double-blind, placebo-controlled studies evaluating the efficacy and safety of these agents have been published [99 - 100]. None of the typical neuroleptics has been found to be effective in reducing chorea in placebo-controlled trials. [101]. Apathy and akathisia, other potential adverse effects of the dopamine receptor blockers.

For patients with the akinetic form of HD (Westphal variant), antiparkinsonian medications, such as levodopa, dopamine agonists, and amantadine, may be beneficial [102]. Botulinum toxin injections can also be considered for focal dystonia associated with HD. Also there is a wide variety of behavioural and psychiatric issues that may be seen in HD, such as aggression, irritability, impulsiveness, depression, anxiety, apathy, mania, substance abuse, sexual dysfunction, and psychosis. Management outside of pharmacotherapy should be considered when possible, including environmental changes. Although commonly used in HD for depression, anxiety, obsessive-compulsive disorder symptoms and

apathy, there is no convincing evidence for the use of selective serotonin reuptake inhibitor, serotonin–norepinephrine reuptake inhibitor, or tricyclic or atypical antidepressant therapies in HD. Similar to other non-motor aspects of HD, treatment recommendations for irritability and obsessive–compulsive behaviours exist only as a paper-based opinion survey [103].

Table 3: Drugs used for the treatment of symptoms associated with HD

Symptoms	Drugs
No other symptoms	Tetrabenazine, amantadine, (riluzole)
Weight loss	Olanzapine, cannibinoids
Psychosis, aggression or impulsivity	Aripiprazole, haloperidol, olanzapine, risperidone, or other neuroleptic
Anxiety	Benzodiazepines
Depression	Aripiprazole and avoid tetrabenazine
Apathy	Amantadine or stimulating medications and avoid neuroleptics
Prominent dystonia	Amantadine, benzodiazepines, focal neurotoxin injection, and avoid neuroleptics
No response to pharmacotherapy	Deep brain stimulation

4. AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Motor Neuron Diseases (MNDs) are a group of progressive disorders that are invariably fatal and affect the motor system, involving the upper, lower motor neurons, or both. The most common entity under the umbrella of MNDs is Amyotrophic Lateral Sclerosis (ALS). ALS is a progressive neurodegenerative disease that affects both upper and lower motor neurons, with pathology spanning the primary motor cortex, corticospinal tracts, brainstem and spinal cord, and causing diffuse muscle weakness, atrophy, spasticity and eventually death, typically due to respiratory failure. Other, less common subtypes of MND include Progressive Muscular Atrophy (PMA), which affects only the lower motor neurons; Primary Lateral Sclerosis (PLS), which affects only the upper motor neurons; and Progressive Bulbar Palsy (PBP), which involves both upper and lower motor neurons but remains confined to bulbar muscles (i.e. brainstem centres responsible for facial movements, swallowing, speech, chewing and breathing). MNDs also include hereditary diseases such as Spinal Muscular Atrophy (SMA) and Spinal-Bulbar Muscular Atrophy (SBMA), etc. This review will focus mainly on ALS.[104] The incidence of ALS is estimated to be 1.7 cases per 100,000 per year,[105] with the cumulative lifetime risk of developing the disease by age 75 being approximately 1:1000.[106] The median age of onset is approximately 64 years for men and 67 for women with the male to female ratio estimated to be 1.8:1.ALS is associated with a family history in approximately 10–20% of cases. Familial ALS (FALS) is defined as the presence of a first-degree relative also affected by the disease and most commonly follows an autosomal dominant inheritance pattern. As many as one-third of familial ALS cases are caused by a recently discovered repeat expansion that is also linked to Frontotemporal Dementia (FTD), and hence, a careful family history exploring the presence of dementia syndrome and/or other neurodegenerative disorders in any family members should always be performed.[107]

4.1. Pathogenesis

A common feature of many neurodegenerative diseases characterized by neuronal dysfunction and eventual cell death is the accumulation of proteinaceous aggregates in cells throughout the nervous system. A protein called TDP-43 is the primary component of such aggregates in most ALS cases, including cases caused by *C9orf72*repeat expansions.[108] Notably, mutations in *TARDBP*, the gene that encodes the TDP-43 protein, have been discovered in sporadic and familial ALS, providing a direct link between TDP-43 abnormalities and neurodegeneration. How these abnormalities in TDP-43 cause neuronal loss is not yet definitely known but is likely to involve a combination of events. The TDP-43 inclusions may themselves be toxic, and they may also harm neurons by sequestering TDP-43 and preventing it from performing its usual functions in cells.[109]

Transactive response DNA-binding protein 43 is an RNA-binding protein with more than 6000 RNA targets in the brain; combined with its role in multiple steps of RNA processing, this suggests that disrupted RNA metabolism contributes to ALS pathogenesis. Further supporting this notion is the fact that mutations in *FUS,* heterogeneous nuclear ribonucleoproteins A1 and A2B1*,* TATA-box binding protein associated factor *15*, *and TIA1*, which also encode RNA-binding proteins, are implicated in the causation of ALS.[110] Stress granules are membrane-less, cytoplasmic organelles composed of mRNAs, translation initiation factors, 40S ribosomes, and RNA-binding proteins[111].

4.2. Symptoms

Symptoms occurring over a period of months and it is characterized by speech, breathing, or swallowing difficulty and weakness or loss of dexterity in one limb. Other features may include muscle wasting, muscle twitching (fasciculations), cramps, stiffness, and slowness. Fasciculations that are unaccompanied by wasting or weakness generally are due to benign causes rather than ALS. The bulbar disease can also manifest with voice hoarseness, sialorrhea, or "pseudobulbar affect," i.e. mood instability characterized by insuppressible crying or laughter in response to emotional stimuli. Weight loss can occur with bulbar dysfunction or respiratory involvement [112].

4.3. Treatment

The medications are available to slow the progression of ALS are limited, careful attention to breathing, nutrition, and patient mobility can have a positive impact on the course of the disease.

Riluzole (Rilutek®) is the only FDA approved drug for ALS and has been shown to prolong survival in ALS patients by three to six months. The modest benefit and high cost of the medication have limited enthusiasm for this treatment among some neurologists and patients, but the medication should be discussed with each patient. Riluzole is well tolerated overall, but patients should be monitored for liver toxicity. Elevation of hepatic enzymes to three to five times the upper limit of normal can occur but is typically self-limited and transient.[113] It is generally recommended to monitor liver enzymes at one week, one month and every six months after the initiation of riluzole, and to stop the drug if liver enzymes are elevated to more than five times the upper limit of normal. Riluzole typically is given at 50 mg twice per day. Traditional pharmacologic treatment of sialorrhea involves the use of anticholinergic agents, including glycopyrrolate (Robinul®), amitriptyline (Elavil®), benztropinemesylate (Cogentin®), trihexyphenidyl (Artane®), transdermal hyoscine (Scopolamine®), and atropine drops in mouth [114]. Common side effects include excessive drying of the nasopharynx, constipation, urinary retention, confusion, and sedation, particularly in the elderly. Other treatments include Botox injections and low dose radiation therapy to the salivary glands.

5. SPINOCEREBELLAR ATAXIA

Ataxia is defined as impaired coordination of voluntary muscle movement, is a physical finding, not a disease, and the underlying etiology needs to be investigated. Ataxia can be the patient's chief complaint or a component among other presenting symptoms. Ataxia is usually caused by cerebellar dysfunction or impaired vestibular or proprioceptive afferent input to the cerebellum. Ataxia can have an insidious onset with a chronic and slowly progressive clinical course (eg, spinocerebellar ataxias [SCAs] of genetic origin) or have an acute onset, especially those ataxias resulting from cerebellar infarction, haemorrhage, or infection, which can have a rapid progression with catastrophic effects. Ataxia can also have a subacute onset, as from infectious or immunologic disorders, which may have a limited window of therapeutic opportunities [115]. The following drugs are control the symptoms of ataxias, they are Amantadine, buspirone, baclofen, tizanidine, riluzole and varenicline.

6. SUMMARY AND CONCLUSION

Neurodegenerative diseases have long been distinct by the properties of the neuropathological lesions observed in the brain. We now know that these lesions are not just markers for neurodegenerative diseases but are tied intrinsically to their pathogenesis. Moreover, the striking similarities between many neurodegenerative diseases suggest common mechanisms in the aetiology of these disorders. The repeated theme of protein misfolding leading to amyloid formation and neurotoxicity is reinforced by a striking message from genetic studies. In each case of dominantly inherited neurodegeneration, the disease-causing mutations can be linked directly to amyloid formation. These clues have now come into sharp focus and neurodegenerative properties are better understood, and they have provided a strong rationale for the in vitro experiments, mouse models, and epidemiological studies that have gone a long way towards verifying this hypothesis. These experiments have laid a solid groundwork for a number of potential therapeutics that are now in preclinical and clinical development. Over the next five years, the efficacy of a large number of these drugs will be tested, and there is growing optimism that the results of these studies will confirm the current design of the aetiology and treatment of neurodegenerative diseases.

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