WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Advances in Therapeutic Strategies for Neurodegenerative Diseases with a Focus on Parkinson's Disease: Pharmacological, Non-Pharmacological, and Emerging Interventions

Mr. Vishal Chauhan[1], Dr. Sonali Uppalwar[2]

IDEAL INSTITUTE OF PHARMACY, POSHERI, WADA, MAHARASHTRA, INDIA,MUMBAI UNIVERSITY

ABSTRACT :

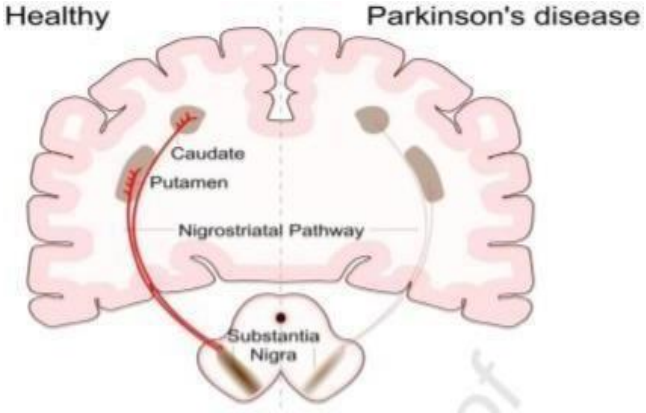
Millions of people worldwide are impacted by neurodegenerative diseases (NDDs), which progressively harm neurones and impair cognitive function. The urgent need for therapies that can preserve and restore the neurological system is highlighted by the fact that current medications mostly manage symptoms rather than reducing or preventing the progression of the disease. Novel strategies for treating the underlying causes of neurodegeneration include gene therapy, stem cell therapy, immunotherapy, and neurotrophic agents.

Although preclinical and early clinical research is showing promising results, there are still issues with making sure these medicines are targeted, safe, and successful. A summary of current pharmacological and non-pharmacological approaches is also included in the review, which highlights their limited capacity to change long-term results.The blood–brain barrier, a strictly regulated opening that shields the brain but also keeps many treatments from getting there, is another significant barrier. Treatment advancement depends on removing this obstacle. For significant advancements in NDD care, ongoing innovation and research are essential.

INTRODUCTION

The central nervous system's (CNS) most vulnerable organ is the brain. It facilitates learning and memory, interprets information from sensory receptors throughout the body, and performs ongoing maintenance to guarantee appropriate and effective operation.[1] Neurological problems now make up around 6.3% of the global disease burden as the world's population ages. Consequently, these disorders have grown to be significant causes of disability, frequently necessitating long-term care and intensive medical intervention.[2] Neurodegenerative diseases (NDDs) are a diverse group of disorders affecting millions worldwide. They are marked by the slow, progressive loss of neurons in the central or peripheral nervous system, making neurodegeneration the core feature driving their symptoms and impact.[3,4] One of the main causes of neuronal damage is oxidative and nitrosative stress, which is brought on by an excess of reactive oxygen and nitrogen species as well as compromised cellular antioxidant defences. The onset and progression of neurodegenerative illnesses are significantly influenced by this damage.[5] Conventional therapies, such as levodopa for Parkinson's disease or cholinesterase inhibitors for Alzheimer's disease, help control symptoms but do not stop the illness's
progression. New medications that target detrimental protein aggregation have been inspired by recent discoveries about neurodegenerative processes.[6] Huntington's disease (HD) currently has no known cure. Medication and supportive care are the mainstays of treatment to help control symptoms. Researchers are aggressively searching for a solution for this difficult illness, even though there are a number of treatments available to address particular symptoms.[7] The blood-brain barrier (BBB), which is composed of cells including astrocytes, neurones, and tight junctions, is a robust, semi- permeable barrier that controls the transport of nutrients while shielding the brain from dangerous substances.[8,9] To target medications without damaging healthy cells, efficient drug delivery devices are required. Despite their stability, there are still issues with large- scale manufacturing, quality assurance, safety, and how they affect the brain after passing across the blood-brain barrier.[10,11,12] Implant-based therapy and the use of biomaterials, including hydrogels, loaded with anticancer medications to effectively target afflicted areas are examples of modern treatments for neurodegenerative illnesses.[13,14]

Figure. 1: PD hallmarks and used in pre-clinical animal trials of PD



Alzheimer's disease

Alzheimer's disease, which affects over 5 million Americans, is characterised by memory loss, brain shrinkage, tau tangles, amyloid plaques, oxidative stress, reduced acetylcholine, and metal accumulation.[15,16] Cholinesterase inhibitors, which increase acetylcholine but can induce nausea, vomiting, and bowel problems, and Namenda, a
glutamate regulator that improves memory and learning but can cause headaches, constipation, disorientation, and dizziness, are used to treat Alzheimer's.[16]

Huntingtons disease

An genetic neurological condition, Huntington's disease often manifests in midlife. It results in dementia, altered mood and behaviour, and erratic, jerky movements that interfere with day-to-day functioning.[17] A mutation in the HTT gene on chromosome 4 that results in unusually long CAG repeats is the cause of Huntington's disease. This results in an enlarged HTT protein that destroys nerve cells by clumping and misfolding.[18] The brain gradually shrinks with Huntington's disease, and important medium spiny neurones are lost in the striatum, particularly in the caudate nucleus and putamen. Additionally, patients have thinning in certain cortical areas of the brain.[19]

Parkinson's disease

About 10 million people worldwide suffer with Parkinson's disease, which is brought on by Lewy body protein aggregates and the death of dopamine neurones in the substantia nigra. Temporary symptom relief is offered by medications such as L-Dopa, dopamine agonists, and enzyme inhibitors.[16,20]

Stroke

Every year, over 800,000 people suffer from stroke, a dangerous and expensive illness. It happens when the brain's blood arteries get clogged or bleed, killing brain cells and perhaps resulting in permanent impairment or even death.[21] Personalised rehabilitation, such as speech therapy for language impairments, is the mainstay of stroke treatment.
Patients who receive treatment within four hours may occasionally require emergency operations, such as blood clot removal techniques like angioplasty.[16,22]

Current therapies for neurodegenerative disorders

Treatment for neurodegenerative illnesses including ALS, Parkinson's, and Alzheimer's is difficult. This section examines contemporary pharmacological and non-drug therapy, emphasising their advantages, drawbacks, and new research findings.

Pharmacological interventions

Alzheimer's disease:
Cholinesteraseinhibitors: The primary goal of Alzheimer's therapy is to reduce symptoms. In mild to severe cases, cholinesterase inhibitors such as galantamine, rivastigmine, and donepezil temporarily improve thinking and memory by increasing brain signalling.[23] These medications, nevertheless, provide few advantages and do not halt the advancement of the illness. Some patients may find it difficult to tolerate side effects like slowed heart rate and digestive problems.[23]

NMDA receptor antagonists:

An NMDA receptor blocker called memantine is used to treat Alzheimer's disease cognitive symptoms. With little chance of slowing the course of the illness, it primarily relieves symptoms.[24] Memantine may help moderate to severe Alzheimer's patients after six months, according to studies, although its impact on cognition in mild to moderate cases—including vascular dementia—is yet unknown.[24]

Dopaminergic therapy in Parkinson's disease

The goal of Parkinson's treatment is to increase dopamine levels in the brain. The best treatment for managing symptoms related to movement is levodopa plus carbidopa.[25] Long-term use, however, may result in involuntary motions and movement fluctuations. Furthermore, non-motor problems like memory loss, mood disorders, and psychiatric disorders frequently do not improve with these treatments.[25]

Antipsychotic medications

Antipsychotic medications are frequently used to treat behavioural and psychiatric symptoms in neurodegenerative illnesses. These medications can be helpful, but they can also have adverse effects include drowsiness and mobility issues.[26]

Non-pharmacological interventions

For those with neurodegenerative diseases, non-pharmacological methods can greatly enhance their quality of life.

Physical and occupational therapy:

For patients to preserve their freedom, lessen mobility issues, and enhance their general wellbeing, physical and occupational therapy are crucial.[27] These treatments can be particularly beneficial for those suffering from neurodegenerative diseases such as Parkinson's disease. However, access to specialised rehabilitation programmes can occasionally be restricted, and their efficacy can vary from person to person.[28]

Cognitive training and behavioural interventions:

Programmes for cognitive training, such as mental stimulation and memory exercises, have been developed to help people with Alzheimer's disease think and remember better.[29]

Types of stem cells that have been considered for use in treating neurodegenerative diseases

Embryonic Stem Cells (ESCs):

These cells, which originate from embryos, have the capacity to differentiate into several cell types, including neurones. However, due of possible hazards like tumour development and moral issues with using human embryos, their usage is debatable.[30,31]

Induced Pluripotent Stem Cells (iPSCs):

An approach that circumvents certain ethical issues is induced pluripotent stem cells (iPSCs), which are produced by reprogramming adult cells to function like embryonic stem cells. However, research is currently ongoing about their safety and efficacy in treating neurodegenerative illnesses.[30,31]

Mesenchymal Stem Cells (MSCs):

An approach that circumvents certain ethical issues is induced pluripotent stem cells (iPSCs), which are produced by reprogramming adult cells to function like embryonic stem cells. However, research is currently ongoing about their safety and efficacy in treating neurodegenerative illnesses.[30,32]

Gene therapy for neurodegenerative diseases

Gene therapy has the potential to treat neurodegenerative disorders by protecting neurones and correcting disease pathways, however there are still issues with delivery efficiency, specificity, long-term effects, and safety.[33] Delivering genetic material into target cells, where it is absorbed, transported, and expressed, is how gene therapy operates. Understanding the mechanisms by which DNA is transported into cells by both viral and non-viral carriers is essential to the success of gene therapy.[34]

Types of gene therapy :

Each of the various methods used in gene therapy has advantages and disadvantages of its own and is intended to address particular genetic disorders. These are a few of the primary forms of gene therapy.

1. **Gene addition therapy:**

This method replaces a defective gene in cells with a healthy copy. It is frequently used to treat genetic problems brought on by mutations in a single gene.[35]

2. **Gene editing:**

Certain genes in a cell can be precisely altered using gene editing. It can help treat genetic problems by correcting mutations, adding new genes, or changing existing ones.[35]

3. **Gene silencing:**

This technique turns off particular genes using tiny interfering RNAs, or siRNAs. It helps treat genetic problems brought on by hyperactive genes.[35]

4. **Gene correction therapy:**

This method aims to correct the mutations that lead to a hereditary illness. These mutations can be fixed by editing a cell's DNA using methods like CRISPR-Cas9.[35]

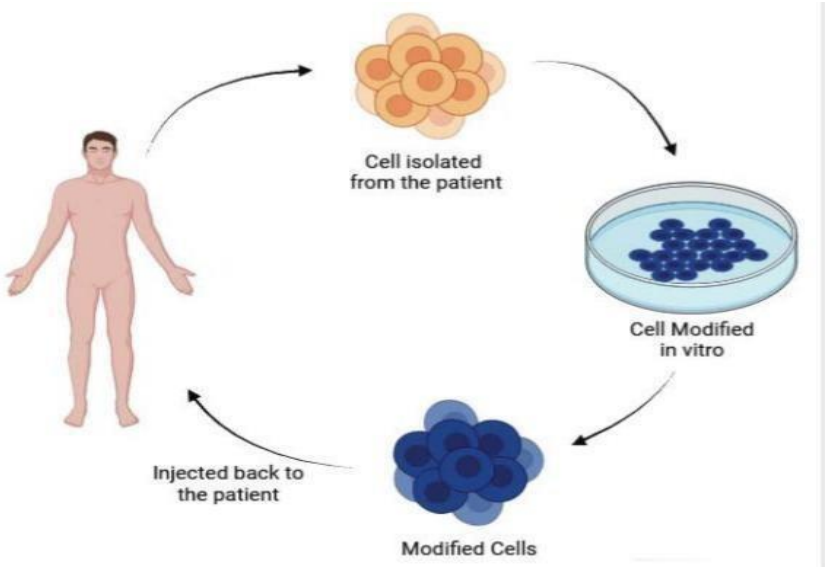


Figure 2: Gene Therapy Process.

Immunotherapy:

Due to increased longevity, neurodegenerative illnesses are a global health concern; nevertheless, there are currently no treatments that alter the course of the disease. Direct immunotherapy slows or stops the expression of illness by targeting misfolded proteins in the brain.[36] Immunotherapy reduces the accumulation of dangerous proteins in the brain. The first Aβ-focused experiment switched from active to passive immunisation in the vaccine design. Abnormal protein clumps are widespread in neurodegenerative illnesses like Alzheimer's, and the majority of treatments target Aβ, however some also target α- synuclein.[37]

Conclusion :

Pharmacological, non-pharmacological, and sophisticated molecular techniques are among the fast developing therapeutic treatments for Parkinson's disease and kindred neurodegenerative illnesses. While physical, occupational, and cognitive interventions improve quality of life and maintain functional independence, traditional therapies generally concentrate on symptom management. Gene therapy, stem cell therapy, and immunotherapy are examples of emerging medicines that have the ability to address fundamental illness pathways, offering hope for disease change rather than just symptom reduction. Notwithstanding encouraging developments, obstacles still exist, such as inconsistent individual reactions, safety issues, and restricted access to specialised treatments. To optimise effectiveness and enhance results for people with these crippling illnesses, more research and individualised strategies are crucial.

REFERENCE:

1) Abbott NJ, Pizzo ME, Preston JE, Janigro D, Thorne RG. The role of brain barriers in fluid movement in The CNS: is there a 'glymphatic' system? Acta Neuropathologica 2018;135:387-407.
2) Misra A, Ganesh S, Shahiwala A, Shah SP. Drug delivery to the central nervous system: a review. J Pharm Pharm Sci 2003;6:252-73.
3) Wilson DM 3rd, Cookson MR, Van Den Bosch L, Zetterberg H, Holtzman DM, Dewachter I. Hallmarks of neurodegenerative diseases. Cell 2023 Feb 16;186(4):693-714. Doi: 10.1016/j.cell.2022.12.032. PMID: 36803602.
4) Merelli A, Czornyj L, Lazarowski A. Erythropoietin: a neuroprotective Agent in cerebral hypoxia, neurodegeneration, and epilepsy. Curr Pharm Des. 2013;19(38):6791-801. Doi: 10.2174/1381612811319380011. PMID: 23530506.
5) Melo A, Monteiro L, Lima RM, Oliveira DM, Cerqueira MD, El-Bachá RS. Oxidative stress in neurodegenerative diseases: mechanisms and Therapeutic perspectives. Oxid Med Cell Longev. 2011;2011:467180. Doi: 10.1155/2011/467180. Epub 2011 Nov 24. PMID: 22191013; PMCID: PMC3236428.
6) Poddar KM, Chakraborty A, Banerjee S. Neurodegeneration: Diagnosis, Prevention, and Therapy. Oxidoreductase 2021.https://www.Researchgate.net/publication/349117125_Neurodegeneration Diagnosis_Prevention_and_Therapy
7) Rojas NG, Cesarini ME, Peker G, Andres G, Prat D, Luis Etcheverry J. Review of Huntington's Disease: From Basics to Advances in Diagnosis And Treatment. J Neurol Res. 2022; 12(3):93-113. https://www. Neurores.org/index.php/neurores/article/view/721/701
8) Oller-Salvia B, Sánchez-Navarro M, Giralt E, Teixidó M. Blood–brain barrier shuttle peptides: an Emerging paradigm for brain delivery. Chemical Society Reviews 2016;45:4690-707.
9) Dong X. Current strategies for brain drug delivery. Theranostics 2018;8:1481.
10) Zhang T-T, Li W, Meng G, Wang P, Liao W. Strategies for transporting nanoparticles across the blood– Brain barrier. Biomaterials science 2016;4:219-29.

11) Saeedi M, Eslamifar M, Khezri K, Dizaj SM. Applications of nanotechnology in drug delivery to the Central nervous system. Biomedicine C Pharmacotherapy 2019;111:666-75.

12) Teleanu D, Chircov C, Grumezescu A, Volceanov A, Teleanu R. Blood-Brain Delivery Methods Using Nanotechnology. Pharmaceutics 2018;10:269.

13) Vashist A, Kaushik A, Vashist A, Bala J, Nikkhah-Moshaie R, Sagar V, et al. Nanogels as potential drug Nanocarriers for CNS drug delivery. Drug discovery today 2018

14) Ran W, Xue X. Theranostical application of nanomedicine for treating central nervous system Disorders. Science China Life Sciences 2018:1-8

15) Roney C, Kulkarni P, Arora V, Antich P, Bonte F, Wu A, et al. Targeted nanoparticles for drug delivery Through the blood–brain barrier for Alzheimer's disease. Journal of controlled release 2005;108:193-214.

16) Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle- mediated brain drug Delivery: overcoming blood–brain barrier to treat neurodegenerative diseases. Journal of Controlled Release 2016;235:34-47

17) Roos RAC. Huntington's disease: A clinical review. Orphanet J Rare Dis. 2010; 5(1):1-8. https://ojrd.biomedcentral.com/ Articles/10.1186/1750-1172-5-40

18) Huntington Disease Article 2024. https://www.statpearls.com/ ArticleLibrary/viewarticle/23053

19) Rojas NG, Cesarini ME, Peker G, Andres G, Prat D, Luis Etcheverry J. Review of Huntington's Disease: From Basics to Advances in Diagnosis And Treatment. J Neurol Res. 2022; 12(3):93-113. https://www. Neurores.org/index.php/neurores/article/view/721/701

20) Soni S, Ruhela RK, Medhi B. Nanomedicine in central nervous system (CNS) disorders: a present and Future prospective. Advanced pharmaceutical bulletin 2016;6:319.

21) Lucas SM, Rothwell NJ, Gibson RM. The role of inflammation in CNS injury and disease. British Journal of pharmacology 2006;147:S232-S40.

22) Amor S, Puentes F, Baker D, Van Der Valk P. Inflammation in neurodegenerative diseases. Immunology 2010;129:154-69.

23) Birks JS, Harvey RJ. Donepezil for dementia due to Alzheimer's Disease. Cochrane Database Syst Rev. 2018 Jun 18;6(6):CD001190. Doi: 10.1002/14651858.CD001190.pub3. PMID: 29923184; PMCID: PMC6513124.

24) Areosa SA, Sherriff F, McShane R. Memantine for dementia. Cochrane Database Syst Rev. 2005 Jul 20;(3):CD003154. Doi: 10.1002/14651858. CD003154.pub4. Update in: Cochrane Database Syst Rev. 2006;(2):CD003154. PMID: 16034889.

25) Connolly BS, Lang AE. Pharmacological treatment of Parkinson disease: A review. JAMA. 2014 Apr 23-30;311(16):1670-83.Doi: 10.1001/ Jama.2014.3654. PMID: 24756517.

26) Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R; DART-AD investigators. The Dementia antipsychotic withdrawal trial (DART-AD): long-term followUp of a randomised placebo-controlled trial. Lancet Neurol. 2009 Feb;8(2):151-7. Doi: 10.1016/S1474-4422(08)70295-3. Epub 2009 Jan 8. PMID: 19138567.

27) Slade SC, Underwood M, McGinley JL, Morris ME. Exercise and Progressive Supranuclear Palsy: the need for explicit exercise reporting. BMC Neurol. 2019 Nov 29;19(1):305. Doi: 10.1186/s12883-019-1539- 4. PMID: 31783740; PMCID: PMC6884751

28) Tomlinson CL, Herd CP, Clarke CE, Meek C, Patel S, Stowe R, Deane KH, Shah L, Sackley CM, Wheatley K, Ives N. Physiotherapy for Parkinson's Disease: a comparison of techniques. Cochrane Database Syst Rev. 2014 Jun 17;2014(6):CD002815. Doi: 10.1002/14651858.CD002815.pub2. PMID: 24936965; PMCID: PMC7120367.

29) Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive Rehabilitation for mild to moderate Alzheimer's disease and vascular Dementia. Cochrane Database Syst Rev. 2013 Jun 5;2013(6):CD003260. Doi: 10.1002/14651858.CD003260.pub2. PMID: 23740535; PMCID: PMC7144738.

30) Sakthiswary R, Raymond AA. Stem cell therapy in neurodegenerative Diseases: From principles to practice. Neural Regen Res. 2012 Aug 15;7(23):1822-31. Doi: 10.3969/j.issn.1673-5374.2012.23.009. PMID: 25624807; PMCID: PMC4302533.

31) Varma SK, Hyder MK, Som S, Dhanabal S. Stem cell therapy: in treatment Of neurodegenerative diseases. J Stem Cell Res Ther (Edmond). 2018; 4(1). https://medcraveonline.com/JSRT/JSRT-04-00105.php

32) Sivandzade F, Cucullo L. Regenerative Stem Cell Therapy forNeurodegenerative Diseases: An Overview. Int J Mol Sci. 2021 Feb 22;22(4):2153. Doi: 10.3390/ijms22042153. PMID: 33671500; PMCID: PMC7926761.

33) Zu H, Gao D. Non-viral Vectors in Gene Therapy: Recent Development, Challenges, and Prospects. AAPS J. 2021 Jun 2;23(4):78. Doi: 10.1208/ S12248-021-00608-7. PMID: 34076797; PMCID: PMC8171234.

34) Vaughan EE, DeGiulio JV, Dean DA. Intracellular trafõicking of plasmids For gene therapy: mechanisms of cytoplasmic movement and nuclear Import. Curr Gene Ther. 2006 Dec;6(6):671-681. Doi: 10.2174/ 156652306779010688. PMID: 17168698; PMCID: PMC4400175.

35) Kanter J, Falcon C. Gene therapy for sickle cell disease: where we are now? Hematology Am Soc Hematol Educ Program. 2021 Dec 10;2021(1):174-180. doi: 10.1182/hematology.2021000250. PMID: 34889358; PMCID: PMC8791177

36) Morgan D. Immunotherapy for Neurodegenerative Disorders. Oxford University Press. 2016; 1.

37) Kwon S, Iba M, Kim C, Masliah E. Immunotherapies for Aging-Related Neurodegenerative Diseases-Emerging Perspectives and New Targets. Neurotherapeutics. 2020 Jul;17(3):935-954. Doi: 10.1007/s13311-020- 00853-2. PMID: 32347461; PMCID: PMC7222955.