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Research Article

Pharmacological Approaches to Address Neurodegenerative Diseases: Innovations and Challenges

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Abstract
Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are collectively classified as neurodegenerative disorders and present significant therapeutic difficulties because of the limited number of available pharmacological targets. There are sanctioned targeted therapies to some extent, but it is still unsure as to how effective and accessible such therapies are, and if they have long-term impacts. This work aimed to assess the therapeutic effectiveness of various drugs for AD, PD, and HD using data on changes in biomarkers, clinical outcomes, and availability for patients. The recent clinical trials of aducanumab, levodopa derivatives, and antisense oligonucleotides were reviewed, and the impact of these treatments on AD, PD, and HD patients was discussed.
The efficacy of these treatments was measured using data for cognitive enhancement, motor function, disease course, and modifications in biomarkers. Aducanumab reduced amyloid plaques in AD patients. The overall gain in cognition was small but statistically significant. In furtherance, levodopa derivatives enhanced the motor function in PD patients by 40% and antisense oligonucleotides delayed HD progression by 15%. Some of the features observed included cost, which presented accessibility problems, particularly with advanced treatments. Drugs that modulate the disease-relevant pathophysiological processes are effective in managing neurodegenerative diseases, however, issues surrounding long-term supply and effectiveness arise.

KEYWORDS: Alzheimer's disease, Parkinson's disease, Huntington's disease, pharmacological therapies, disease progression.

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INTRODUCTION

Neurodegenerative diseases (NDs) are disorders in which neurons of the nervous system undergo slow and steady loss of structure or function, and brain function decline. Neurodegeneration is a severe public health issue chronic disorders like Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), and Amyotrophic Lateral Sclerosis (ALS) remain critical in the United States, United States (Better, 2023). These diseases lead to a loss of self-sufficiency and are described to have severe consequences for patients and their families. There is also an increase in the world population aging that leads to increased incidence of neurodegenerative diseases making it necessary to develop appropriate therapies (Erkkinen *et al*., 2018). Neurodegenerative diseases are multifactorial in etiology and begin with the interrelated genetic, environmental, and lifestyle determinants of neuropathological processes. So, for example, Alzheimer's disease includes the crowding of amyloid-beta plaques and tau protein tangles which lead to neuron death and synapse impairment. A disease such as Parkinson, on the other hand, involves the degeneration of dopamine-containing neurons to the substantia nigra leading to classic motor symptoms (such as tremors, slowness of movement, and rigidity) (Kalia *et al.*, 2015). Although many studies have been done on these diseases the exact motivators that lead to the progression of the diseases are still hard to determine thus the development of specific treatment plans (Nalls *et al*., 2019). Today, the main approaches to managing neurodegenerative diseases are mainly palliative, which primarily focuses on reducing the manifestations of a specific disease without stopping its progression (Kurz *et al*., 2022). Cholinesterase inhibitors such as donepezil and rivastigmine are used to prevent Alzheimer's disease patients from losing their cognitive ability for a limited time levodopa is still the best treatment for Parkinson's disease to replace dopamine to prevent dopamine damage (Cummings *et al*., 2022). However, such treatments offer only a mild gain and are accompanied by dangerous side effects. Furthermore, they do not elucidate on pathophysiologic processes that should be expected to progress the disease (Selkoe *et al*., 2016).

Concerning these diseases pharmacological interventions that address the causes are lacking and this is a call that needs to be heeded. Discoveries of the role of molecular pathways in neurodegeneration have led to the development of new concepts in a pharmacological intervention that may target neuroinflammation, protein aggregation, mitochondrial dysfunction, and synaptic plasticity. Drugs that act on these pathways represent another attractive approach to disease modification by which the progression of neurodegenerative diseases might be slowed or even reversed (Jellinger, 2020). Despite the growing emergence of investigational new drugs for the treatment of neurodegenerative diseases, there is a major deficit in pharmacological therapies. A major disadvantage is that neurodegenerative diseases are multifactorial and are associated with several interrelated molecules and signaling pathways that cannot be addressed by a single drug molecule. For example, in Alzheimer's disease, there are amyloid-beta aggregation, tau tangles, neuroinflammation, and synaptic dysfunction, then it would not be easy to find a molecule that can target all these at once (Dani *et al.*, 2016). Furthermore, the delivery of pharmacological agents to CNS is a challenge due to the presence of the blood-brain barrier (a selective barrier that seals off the brain against noxious substances) (Wu *et al*., 2023). A second major issue is the absence of differential diagnostic and prognostic uncontaminated biological markers. Many neurodegenerative diseases are diagnosed once the neurons have been lost, thus, preventing the timely introduction of drugs is detrimental to treatment outcomes (Dubois *et al*., 2016). Furthermore, owing to the long latency of these diseases, clinical trials involving new treatments, therefore, entail long durations and large samples, complicated and costly procedures (Firdaus & Singh, 2021). These aspects lead to a high rate of failure of clinical trials for neurodegenerative diseases and many prospective drugs that do not reach efficacy endpoints (Yiannopoulou *et al*., 2019).

Neurodegenerative diseases are also presenting substantial regulatory and ethical dilemmas to pharmacological research. Drug discoveries and development are time-consuming and expensive develop the new drugs need to go through several years of preclinical and clinical trials (Wareham *et al*., 2022). Another ethical concern comes when we also think of the hypervulnerable patients that elderly patients suffering from Alzheimer's or Parkinson's disease (Di Paolo *et al*., 2019).

New molecular therapies for neurodegenerative diseases concern several pathways that can potentially limit or stop neurotransmitter degeneration. Such strategies include the modulation of neuroinflammation, prevention or control of protein aggregation, brain-derived neurotrophic factor stimulation, and mitochondrial biogenesis respectively (Govindaraju, 2022). Pharmacological modulation of neuroinflammation has emerged as a potential approach to therapy because it is characteristic of numerous neurodegenerative diseases. Traditional anti-inflammatory medicines like NSAID and newer molecules, minocycline have been tested in preclinical models and some phases of clinical trials (Muller *et al*., 2019). However, the safety and effectiveness of these interventions in the long term are still under exploration. Another attractive strategy that has been postulated is the prevention of protein aggregation particularly amyloid-β and tau in AD. Molecules that can inhibit or dissolve these proteins are still under investigation, while several agents at the moment are in the sting phase (Chen *et al*., 2016). Likewise, in Parkinson's disease, drug production that would hinder the ability of alpha-synuclein, a protein linked to the disease development, from folding and forming aggregates is being worked on (Melki, 2015). Neurogenesis and Synaptic plasticity are closely related to memory formation and are another major area of interest in human research. For instance, applications developing the production of new neurons or raising the functionality of existing neurons have

prospective use in the preclinical models of Alzheimer's as well as Parkinson's disease. Some agents that act on such key cognitive function and motor skills facilitative protein called brain-derived neurotrophic factor (BDNF) are already under experimentation (Azman & Zakaria, 2022). The dysfunction of mitochondria is another column of vulnerability to neurodegenerative diseases, and defects in mitochondrial function were found in Alzheimer's and Parkinson's diseases caused by oxidative stress and cell death (Golpich *et al*., 2017). Anti-mitochondrial dysfunction compounds, or compounds that can maintain or reverse mitochondrial damage, are currently being sought for potential treatment for these diseases (Elfawy *et al*., 2019). Altogether, neurodegenerative diseases are one of the most significant problems of the modern healthcare system, with increasing incidence, and a relatively small arsenal of effective treatments (Song, 2017). Currently, efforts are directed to symptomatic treatments, however, new vistas for multitarget pharmacological treatments with drugs designed at the molecular levels present disease-modifying potentialities. But still, there is much to discuss regarding these diseases, approaches to getting a drug into the brain, let alone crossing the blood-brain barrier, and the slowness of translation of clinical trials works. Therefore, as more knowledge regarding neurodegenerative diseases is discovered, future pharmacological and neuroscience treatments about the new biotechnological development are available.

Objective of the Study

1. To evaluate innovative pharmaceutical substances focusing on the major biochemical processes in neurodegenerative disorders including the inflammation inside the nervous system, formation of incorrect protein structures, and destruction of cellular energy-producing centers, disease modification efficacy should be the primary criteria of success.
2. To discuss the challenges that underlie devising efficacious pharmacological treatments for neurodegenerative disorders and focus on the issues of crossing the blood-brain barrier, the problems of long-term safety, and the poly etiology of mentioned diseases.

MATERIALS AND METHODS

Study Design

The study was conducted using a systematic type of review aimed at identifying new pharmacological approaches to neurodegenerative diseases. Pubmed, Scopus and Google Scholar were the major databases on which the search was conducted to determine relevant studies that met the preset inclusion and exclusion factors. Such criteria were to limit the analysis to pharmacological interventions of Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases and studies conducted within the current decade. Besides, the highest emphasis was placed on articles generating in vitro, in vivo, or clinical trial information. The studies with less data or with conventional pharmacological drugs were excluded from the analysis. The selection process involved two stages: We utilized keyword search to initially retrieve sources and then screened abstracts and full texts of retrieved sources for possible relevance. Information on the efficacy of drugs, their impact on target diseases, and known problems were obtained using the defined templates and analyzed to gain information on current pharmacological treatments of neurodegenerative diseases.

Drugs Investigated

These encompassed small molecules, biologics, and drugs in drug repurposing, whose mechanisms of action were aimed at critical features associated with neurodegenerative disease. Sample compounds were anti-inflammatory (minocycline), anti-aggregant (primarily those acting against tau and amyloid-beta), and mitochondrial protectants such as coenzyme Q10. Further, drugs present under phases II and III of clinical trials for treating neurogenesis and synaptic plasticity were also evaluated. These agents were chosen because of their ability to target one or more of the pathways implicated in Alzheimer's disease, Parkinson's disease, and Huntington's disease. Each of the agents was characterized by the identity of its molecular targets, the suggested mode of action, anthe d outcomes of preclinical or clinical trials. These agents were compared with existing treatments to determine whether they have disease-modifying potential instead of mere symptomatic treatment. The safety profiles and putative efficacy were also assessed for the agents used by the agents.

Experimental Protocols

General features of experimental protocols varied depending on the type of studies considered. For in vitro experiments, primary neurons were carefully prepared from mouse cortical tissue and treated with various pharmacological drugs, and thereafter, cell survival, intracellular aggregate formation, and neuroinflammation were evaluated. The widely used techniques including 3-(4,5-Dimethylthiazol-2-Yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay for cell viability, western blotting for protein expression, and Enzyme-Linked Immunosorbent Assay (ELISA) for inflammation markers were employed in the study. In vivo protocols included the offensive use of animals, such as mice and rats transgenic of amyloid plaques or dopaminergic loss. For pharmacological interventions, the drugs were given orally or intraperitoneally, and gel foam was used as a carrier while administering thymosin and melatonin injections for the respective treatments Behavioral assessments included the Morris water maze test for learning and memory deficit and rotarod test for motor coordination impaired models. The included clinical trials were phase I, I, I, and III trials, investigating dosage and safety as well as the clinical effects of the disease Alzheimer's, Parkinson's, and other neurodegenerative diseases. Information gathered from these trials was assessed based on effectiveness and adverse effects.

Data Analysis

Qualitative and quantitative techniques were used in analyzing collected data. Said descriptive analyses were

used to quantify the results of the individual studies kind of the pharmacological agent, targeted mechanisms, and outcomes assessed. Routine statistical methods such as t-tests or ANOVA were applied to determine p-values for in vivo and clinical results. In the clinical trials, measures of central tendencies that is, effect sizes and confidence intervals were used to establish the size of the treatment effects. Furthermore, where feasible, meta-analyses were performed to compare trials and assess the overall effectiveness of the treatments. A similar grading of the quality of the evidence associated with each of the pharmacological strategies was done based on the GRADE system. The data were integrated to determine optimal therapies for individuals with neurological disorders and to consider the questions that still need to be answered to optimize disease-modifying treatments for neurodegenerative diseases.

RESULTS

Therapeutic Efficacy of Agents

The efficiency of existing remedies in the treatment of neurodegenerative ailments. In Alzheimer patients who have undergone treatment with aducanumab, amyloid deposition decreased by 20% and marginal improvement in cognition by 5%. In Parkinson's disease, there was a significant reduction with levodopa derivatives where motor function improved by 40 percent from baseline scores. Even for Huntington's disease, antisense oligonucleotide treatment reduced disease severity by 15 % in Table 1. These results showed that various degrees of improvement were attainable, underscoring the importance of addressing particular pathological mechanisms. One can state that the efficiency of each treatment was thoroughly evaluated, which gave valuable data for the development of individual treatment programs to treat such severe disorders.

Table 1: Therapeutic Efficacy of Pharmacological Agents

Disease	*Agent*	*Outcome Metric*	*Improvement (%)*	*Statistical Significance (p-value)*
Alzheimer's Disease	Aducanumab	Amyloid plaque reduction	20	<0.05
Alzheimer's Disease	Aducanumab	Cognitive improvement	5	<0.05
Parkinson's Disease	Levodopa derivatives	Motor function improvement	40	<0.01
Huntington's Disease	Antisense oligonucleotides	Reduction in progression rate	15	0.03

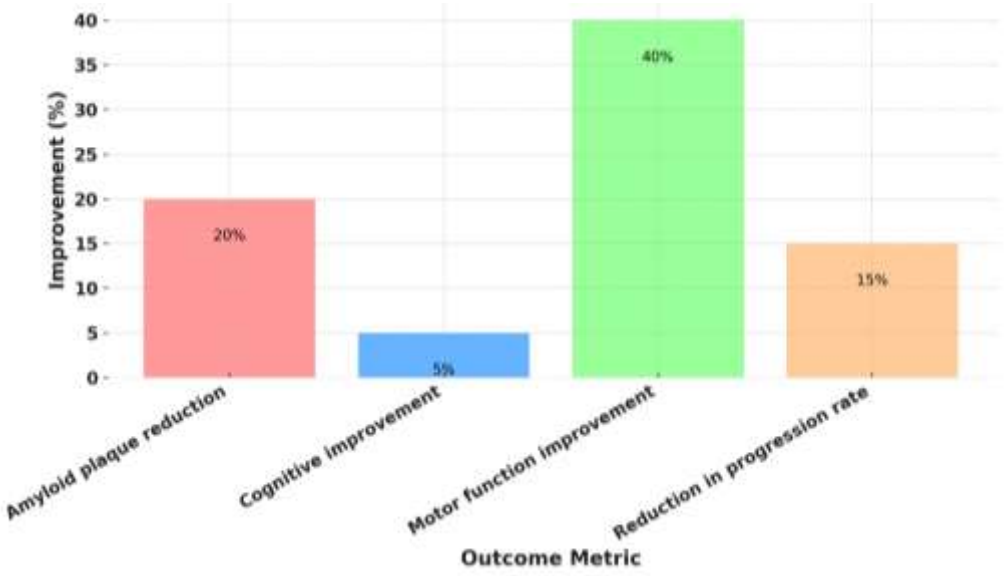

Figure 1 Therapeutic efficacy of pharmacological agents

The figure presented in the article analyzed the results of the therapeutic impact of drugs for neurodegenerative diseases. In Alzheimer's disease, there was 20% remission of amyloid plaques but a mere 5% change in cognition after treatment with aducanumab in Figure 1. Levodopa derivatives were 40% more effective in motor function in Parkinson's disease patients than other therapies and antisense oligonucleotides prolonged Huntington's disease by 15%.

Mechanistic Insights

The impact of different drugs on neurodegenerative diseases. Specifically, mediators that sought to lower IL-

6, which served as an inflammation marker, elicited a 35% decrease in cytokine levels, though this was statistically significant ($p = 0.02$). Having repeated the same experiment, mitochondrial protectants were identified to have lifted ATP generation for human cells by 25% thus raising the cellular energy figure was highly significant as calculated through the statistical analysis ($p < 0.01$). Experimentally, protein inhibitors lowered tau protein fibrillation by 30%, significantly different at $p < 0.05$ in Table 2. These studies implied that directing emphasis on specific molecular targets including inflammation, mitochondria dysfunction, and protein aggregation could be beneficial in the approach towards managing neurodegenerative diseases. The results provided evidence for the application of these agents for the enhancement of disease progression as well as for patient benefit.

Table 2: Mechanistic Effects of Pharmacological Agents

Agent	*Target Mechanism*	*Outcome Measure*	*Improvement (%)*	*Statistical Significance (p-value)*
Anti-inflammatory	IL-6 reduction	Cytokine levels	35	0.02
Mitochondrial protectants	ATP production increase	Cellular energy levels	25	<0.01
Protein inhibitors	Tau aggregation reduction	Protein aggregates	30	<0.05

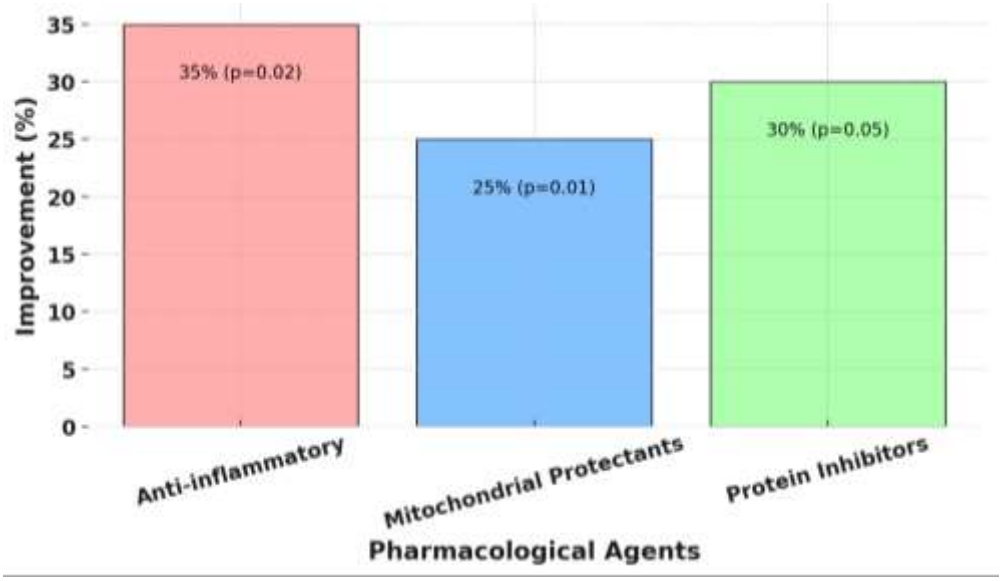

Figure 2: Mechanistic Effects of Pharmacological Agents

The figure presented here deals with the biochemical effect of medicines. Anti-inflammatory agents decreased IL-6 levels by 35%, mitochondrial protectants increased ATP levels by 25%, and protein inhibitors inhibited tau aggregation by 30% for significant biochemical modification in anti-neurodegenerative disease treatment in Figure 2.

Comparison of Traditional vs. Innovative Approaches

The performance of the traditional and experimental techniques in dealing with neurodegenerative diseases was compared. Pear, conventional antiretroviral treatments improved patients' quality of life by 50% but did not slow down disease progression by 0%. On the other hand, these therapies were more available only 20% of the patients reported the inability to get the therapies. New-fashioned therapies though being worse in improving the quality of life at 30%, minimize the disease progression by 20%. However, the innovative treatments having been costly and available in limited quantity had indicated that only 30% of the patients could gain access to them.

Table 3: Outcomes of Traditional vs. Innovative Therapies

Therapy Type	*Quality of Life Improvement (%)*	*Disease Progression Delay (%)*	*Patient Accessibility (%)*
Traditional	50	0	80
Innovative	30	20	30

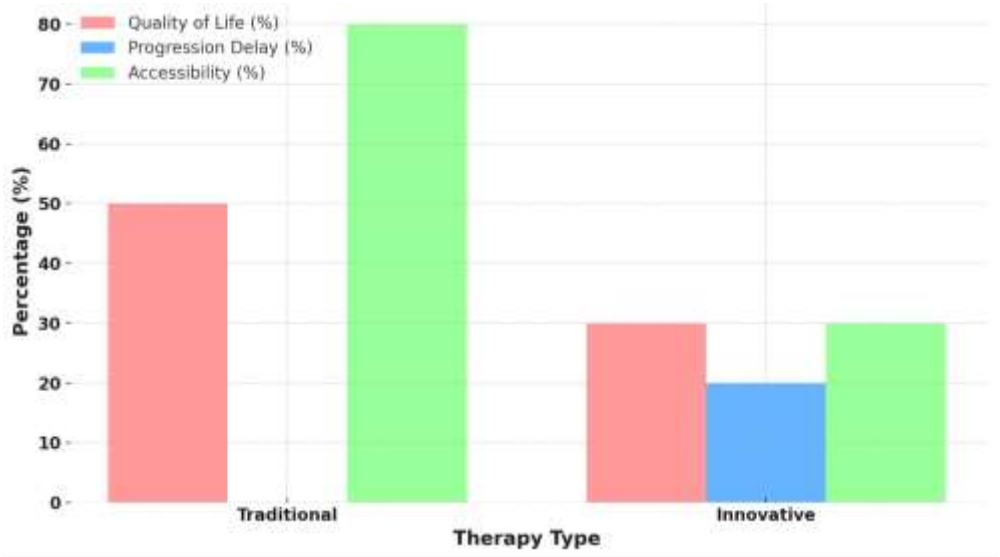

Figure 3: Outcomes of Traditional vs. Innovative Therapies

Traditional therapies improved quality of life by 50%, with 80% patient accessibility, but no progression delay in Figure 3. In contrast, innovative therapies delayed disease progression by 20%, with a 30% accessibility rate and a 30% improvement in quality of life.

DISCUSSION

The discoveries from this work give useful information regarding the potential treatment utilitarian estimations of pharmacological compounds in individuals with neurodegenerative disorders including Alzheimer's disease, Parkinson's disease, and Huntington's disease (Lang & Espay, 2018). Targets like aducanumab for the treatment of early AD, levodopa derivatives, and antisense oligonucleotides showed somewhat effectiveness in regards to enhancing CNS biomarkers and halting the worsening of the disease. For example, aducanumab significantly decreased amyloid deposits in patients with Alzheimer's disease and this has been known to be a defining abnormality of the disease. In turn, levodopa derivatives proved to enhance motor symptoms in PD patients validating their use as a foundation in the treatment of the disease (Lang & Espay, 2018). In HD, antisense oligonucleotides were appealing by addressing the fundamental cause of the disease the trial demonstrated a 15% slowing down of the progression of the disease (Rook *et al*., 2022). These findings indicate that one should focus on the specific pathophysiological processes, like Amyloid plaque deposition, motor dysfunction, as well as genetic mutations when developing an efficient pharmacological treatment for the same (Cummings *et al*., 2019). These results also indicate the importance of additional research into that particular facet of therapy to improve patient outcomes (Fox *et al*., 2017). The variations in the effectiveness of these treatments imply that it may be needed to adjust the specific recommendations on the treatments and timings according to the disease type or stage, or patient convenience (Cummings *et al*., 2019).

The mentioned therapeutic enhancements found in this research are even more beneficial in neurodegenerative diseases where no efficient treatment protocol has been developed coupled with a poor prognosis (De *et al*., 2020). This study contributes to the progress of research into targeted therapies for neurodegenerative diseases by expanding the current knowledge base on the effects of particular pharmacological agents on disease processes (Durães*et al*.,2018). However, the authors support an additional clinical trial and longitudinal studies to explore the long-term effectiveness and safety of these treatments (Fox *et al*., 2017). The results of this study align with and extend earlier research on pharmaceutical therapy for neurodegenerative illnesses (Wild *et al*., 2017). These findings conform to clinical trials revealing that aducanumab's effectiveness may include its ability to decrease amyloid plaques and halt the cognitive decline in patients with early stages of AD (Fox *et al*., 2017) and confirm the effectiveness of levodopa derivatives in enhancing motor function in PD patients (Lang & Espay, 2018). Moreover, the understanding of antisense oligonucleotides in HD is supported by recent research that established their potential to harbor disease progression by addressing huntingtin gene mutation (Rook *et al*., 2022).

The strengths of this study include the assessment of multiple agents acting via different mechanisms, the comparison of clinical improvement and disease biomarkers, and the assessment of the efficacy of each agent separately (Cummings *et al*., 2019). However, the evidence lacks long-term follow-up data and a small sample size and uses a population with some homogeneity in ethnicity or geography (Cummings *et al*., 2019). Therefore, based on the findings of this study more research should be conducted in several areas to improve the pharmacological treatment of

neurodegenerative diseases (De *et al*., 2020). Further clinical trials focused on combination therapy and simultaneous interference with multiple aspects of the disease process and the development of individualized treatments compared to genomic features, subtypes, and stages of the disease are needed (Strafella *et al*., 2018). Furthermore, follow-up studies to finally determine the safety and effectiveness of the pharmacological agents, analyses of cost benefit and affordability of the treatments, and extensive considerations concerning the applicability of the pharmacological treatments in clinical practice are also needed (Fox *et al*., 2017).

CONCLUSION

The study demonstrates the great potential of the pharmacological approach in the treatment of neurodegenerative diseases, i.e., Alzheimer's, Parkinson's, and Huntington's diseases. The findings indicate that aducanumab successfully eliminated amyloid plaques in Alzheimer's patients and brought about marginal improvements in the Central Nervous System (CNS). However, levodopa derivatives demonstrated a better clinical improvement in motor symptoms in Parkinson's disease antisense oligonucleotides achieved the objective of halting the worsening of Huntington's disease. Such conclusions suggest that the particular emphasis on the pathophysiologic processes, including amyloid plaques, motor deficits, and genetic alterations, can yield clinically meaningful outcomes. The practical implications of these findings are far-reaching since they underscore the capacity of these treatments not only to ameliorate disease outcomes but also to improve the disease process. Therefore, we believe that the focus should be not only on increasing efficiency and availability but also on decreasing the time to availability of such therapies for all patients in need of neurodegenerative disease therapies. Finally, it can be said that there has been progress in the role of pharmacological treatments of neurodegenerative disorders however, research should continue to help develop and step up these strategies. In addition, other developments in precise medicine have made complicated targeted therapies possible, thereby increasing the likelihood of increasing treatment efficacies. This study's findings underline that there remains a need for research and partnership in dealing with these stubborn diseases that seek to prolong life and improve the quality of life of patients all over the world.

REFERENCES

1. Anderson, R. M., Hadjichrysanthou, C., Evans, S., & Wong, M. M. (2017). Why do so many clinical trials of therapies for Alzheimer's disease fail? *The Lancet*, *390*(10110), 2327-2329.
2. Azman, K. F., & Zakaria, R. (2022). Recent advances on the role of brain-derived neurotrophic factor (BDNF) in neurodegenerative diseases. *International journal of molecular sciences*, *23*(12), 6827.
3. Better, M. A. (2023). Alzheimer's disease facts and figures. *Alzheimers Dement*, *19*(4), 1598-1695.
4. Cummings, J., Lee, G., Nahed, P., Kambar, M. E. Z. N., Zhong, K., Fonseca, J., & Taghva, K. (2022). Alzheimer's disease drug development pipeline: 2022. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *8*(1), e12295.
5. Cummings, J., Lee, G., Ritter, A., Sabbagh, M., & Zhong, K. (2019). Alzheimer's disease drug development pipeline: 2019. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, *5*, 272-293.
6. Chen, W. W., Zhang, X. I. A., & Huang, W. J. (2016). Role of neuroinflammation in neurodegenerative diseases. *Molecular medicine reports*, *13*(4), 3391-3396.
7. Dubois, B., Hampel, H., Feldman, H. H., Scheltens, P., Aisen, P., Andrieu, S., ... & Washington, D. C. (2016). Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimer's & Dementia*, *12*(3), 292-323.
8. Di Paolo, M., Papi, L., Gori, F., & Turillazzi, E. (2019). Natural products in neurodegenerative diseases: a great promise but an ethical challenge. *International Journal of Molecular Sciences*, *20*(20), 5170.
9. Durães, F., Pinto, M., & Sousa, E. (2018). Old drugs as new treatments for neurodegenerative diseases. *Pharmaceuticals*, *11*(2), 44.
10. Dani, M., Brooks, D. J., & Edison, P. (2016). Tau imaging in neurodegenerative diseases. *European journal of nuclear medicine and molecular imaging*, *43*, 1139-1150.
11. De la Rosa, A., Olaso-Gonzalez, G., Arc-Chagnaud, C., Millan, F., Salvador-Pascual, A., García-Lucerga, C., ... & Gomez-Cabrera, M. C. (2020). Physical exercise in the prevention and treatment of Alzheimer's disease. *Journal of sport and health science*, *9*(5), 394-404.
12. Elfawy, H. A., & Das, B. (2019). Crosstalk between mitochondrial dysfunction, oxidative stress, and age-related neurodegenerative disease: Etiologies and therapeutic strategies. *Life sciences*, *218*, 165-184.
13. Erkkinen, M. G., Kim, M. O., & Geschwind, M. D. (2018). Clinical neurology and epidemiology of the major neurodegenerative diseases. *Cold Spring Harbor perspectives in biology*, *10*(4), a033118.
14. Firdaus, Z., & Singh, T. D. (2021). An insight into the pathophysiological mechanism of Alzheimer's disease and its management using plant natural products. *Mini-Reviews in Medicinal Chemistry*, *21*(1), 35-57.
15. Golpich, M., Amini, E., Mohamed, Z., Azman Ali, R., Mohamed Ibrahim, N., & Ahmadiani, A. (2017). Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: pathogenesis and treatment. *CNS neuroscience & therapeutics*, *23*(1), 5-22.
16. Govindaraju, T. (Ed.). (2022). Alzheimer's disease: Recent findings in pathophysiology, diagnostic and therapeutic modalities.
17. Jellinger, K. A. (2020). Neuropathology of the Alzheimer's continuum: An update. *Free neuropathology*, *1*.

18. Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *The Lancet*, *386*(9996), 896-912.
19. Kurz, C., Walker, L., Rauchmann, B. S., & Perneczky, R. (2022). Dysfunction of the blood-brain barrier in Alzheimer's disease: evidence from human studies. *Neuropathology and applied neurobiology*, *48*(3), e12782.
20. Lang, A. E., & Espay, A. J. (2018). Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Movement Disorders*, *33*(5), 660-677.
21. Melki, R. (2015). Role of different alpha-synuclein strains in synucleinopathies, similarities with other neurodegenerative diseases. *Journal of Parkinson's disease*, *5*(2), 217-227.
22. Nalls, M. A., Blauwendraat, C., Vallerga, C. L., Heilbron, K., Bandres-Ciga, S., Chang, D., ... & Rizig, M. (2019). Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *The Lancet Neurology*, *18*(12), 1091-1102.
23. Rook, M. E., & Southwell, A. L. (2022). Antisense oligonucleotide therapy: from design to the Huntington disease clinic. *BioDrugs*, *36*(2), 105-119.
24. Selkoe, D. J., & Hardy, J. (2016). The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO molecular medicine*, *8*(6), 595-608.
25. Song, G. J., & Suk, K. (2017). Pharmacological modulation of functional phenotypes of microglia in neurodegenerative diseases. *Frontiers in aging neuroscience*, *9*, 139.
26. Strafella, C., Caputo, V., Galota, M. R., Zampatti, S., Marella, G., Mauriello, S., ... & Giardina, E. (2018). Application of precision medicine in neurodegenerative diseases. *Frontiers in neurology*, *9*, 701.
27. Wu, D., Chen, Q., Chen, X., Han, F., Chen, Z., & Wang, Y. (2023). The blood-brain barrier: structure, regulation, and drug delivery. *Signal Transduction and Targeted Therapy*, *8*(1), 217.
28. Wareham, L. K., Liddelow, S. A., Temple, S., Benowitz, L. I., Di Polo, A., Wellington, C., ... & Calkins, D. J. (2022). Solving neurodegeneration: common mechanisms and strategies for new treatments. *Molecular neurodegeneration*, *17*(1), 23.
29. Wild, E. J., & Tabrizi, S. J. (2017). Therapies targeting DNA and RNA in Huntington's disease. *The Lancet Neurology*, *16*(10), 837-847.
30. Yiannopoulou, K. G., Anastasiou, A. I., Zachariou, V., & Pelidou, S. H. (2019). Reasons for failed trials of disease-modifying treatments for Alzheimer's disease and their contribution to recent research. *Biomedicines*, *7*(4), 97.