

DIFFERENT DRUG ACTIVITY AND MECHANISMS USED IN NEURODEGENERATIVE DISEASES

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ABSTRACT

Neurodegenerative diseases represent a spectrum of disorders that are characterized by the progressive destruction of cells and connections that make up the nervous system. These circumstances are hindering the existence of millions of individuals around the world, at last prompting the breakdown of the brain networks that are expected for human capability. The primary risk factor for the majority of primary neurodegenerative diseases is aging. In fact, it has been long believed that age-related changes in the brain make people more susceptible to neurodegeneration. Unfortunately, research for effective treatments is compromised due to lack of knowledge on the pathologic processes comprehensive these diseases and of dependable biomarkers. Clinical trials are challenging because they necessitate huge populations that must be monitored over extended periods of time, to record potential impacts on the course of the disease. These challenges lead to frequent failures and the waste of financial and human resources. New therapies can come from three main sources: synthesis, natural products, and existing drugs. This last source is known as drug repurposing, which is the most advantageous, since the drug's pharmacokinetic and pharmacodynamics profiles are already established, like cholinesterase inhibitors, NMDA receptor antagonists, and other medications, and the investment put into this strategy is not as significant as for the classic development of new drugs. Alternative study designs can be taken into consideration to

find disease modifiers and lower the costs of clinical studies, as research in this field must continue until a thorough understanding of fundamental pathologic processes is attained.

Keywords: *Alternative trials, Disease modification, Drugs and its MOA, Neurodegenerative Diseases, Symptomatic treatment, Therapeutic approaches.*

Introduction

As people age, the prevalence of neurodegenerative disorders including Parkinson's disease (PD) and Alzheimer's dementia (AD) rises. As a result, they will soon place a heavy load on aging populations similar to our own. The majority of neurodegenerative illnesses have unknown aetiologies and pathophysiologies, making them a scientific challenge. It is challenging but vital to create efficient remedies for illnesses whose causes are currently unknown. Neurodegenerative disease clinical trials necessitate a large number of patients to be monitored for an extended period of time, which makes the research extremely challenging to conduct and drives up expenses. While awaiting the elucidation of the processes underlying neurodegeneration, alternative study designs may be beneficial for identifying disease-modifying treatments. Current therapeutic approaches for the treatment of neurodegenerative diseases merely offer limited, and even worse, transient symptomatic benefits to patients, with no mitigation of the insidious loss of neuronal cells encountered in these conditions. Neurodegenerative diseases have a multifactorial pathoetiological origin, and it is not surprising that conventional drug-discovery approaches that embrace a 'one gene, one drug, one disease' philosophy may not offer the best pathway towards the development of much needed disease-modifying therapeutics for these diseases. Drugs that target only one protein are susceptible to resistance, one reason (among several others) being that even a single mutation in the target active site often substantially reduces compound binding affinity and, hence, efficacy. On the other hand, resistance to drugs that target multiple proteins would require the unlikely event of concurrent mutations appearing

in multiple protein targets. In view of these concerns, many clinicians and basic scientists have become persuaded that a strategy aimed at the simultaneous targeting of multiple proteins (and therefore etiologies) involved in the development of a disease should be more beneficial than the currently accepted 'silver bullet' approach. This approach may be useful in designing drug treatments for a range of diseases. Diseases of the CNS for which such an approach has been suggested include, among others, movement disorders, cognitive deficit disorders, negative symptoms in schizophrenia, Lewy body disease and depressive illness.

Ageing And Neurodegenerative Diseases

Life expectancy has increased during the past century due to improvements in healthcare and the development of better surroundings (Niccoli & Partridge, 2012). Since the primary risk factor for neurodegenerative illnesses is advanced age (Hou et al., 2019), the number of patients suffering from age-related primary neurodegenerative diseases, such as Alzheimer's disease (AD) (Hebert et al., 2010), Parkinson's disease (PD) (Poewe et al., 2017), or amyotrophic lateral sclerosis (ALS) (Talbot et al., 2016), rises sharply with any increase in the elderly population. In light of these recent shifts in the population, because primary neurodegenerative illnesses are expensive and significantly impact the quality of healthcare, they will have significant socioeconomic ramifications for healthcare systems. Life of those impacted and those who provide care, presenting a serious social emergency. It will take a more focused research strategy and innovative solutions to address these significant societal responsibilities (DiLuca & Olsen, 2014).

It makes natural that current medications are being evaluated for NDs given the increasing need for therapy and the potential benefits of drug repurposing. Drugs that have been repurposed for the most researched neurodegenerative diseases—Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS)—are included in this study (Figure 1).

The topic of drug repurposing with examples in NDs has been reviewed a few times, but no comprehensive review has been done for all of these diseases, which would provide a wider perspective and a better understanding of how these diseases might be related to one another.

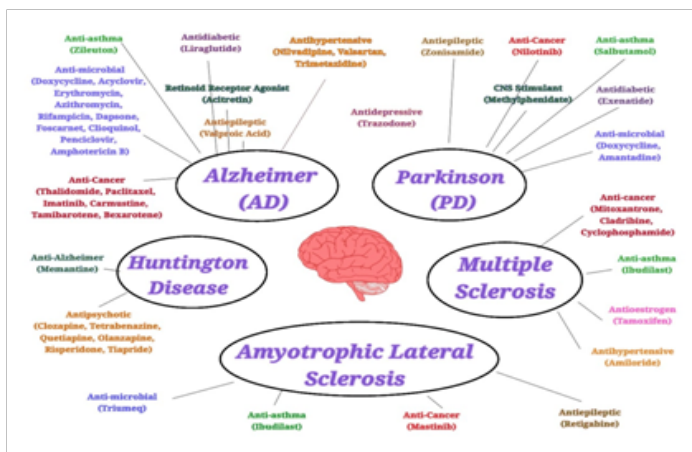


Fig. 1. Summary of the diseases and repurposed drugs presented in this review

Alzheimer's Disease

One of the most common NDs, AD accounts for 80% of dementia cases in the elderly. Progressive memory loss, learning difficulties, and a deterioration in behaviour and function are some of its signs. Although the exact origin of AD is still unknown, it is thought to be related to the build-up of amyloid plaques in the brain, which eventually causes the loss of neurons and synapses.

Since there is currently no known cure for AD, the medications used to treat it are primarily intended to address cognitive problems or other symptoms, and they work best when taken early. Interesting enough, galantamine is one medication sold to treat AD.

Parkinson's Disease

Affecting people all around the world, PD is the second most prevalent ND after AD. Although other neurotransmitter systems also seem to be impacted, the loss of dopaminergic neurons in the substantia nigra is believed to be the primary cause of Parkinson's disease's most well-known motor symptoms. It is increasingly recognized that Parkinson's disease (PD) includes a number of symptoms that are not related to motor function, including depression, sleep disturbances, and cognitive impairment. Deep brain stimulation and dopamine replacement are two effective treatments for Parkinson's disease (PD), despite the fact that there is currently no cure for the condition.

Amantadine is another medication in the antiparkinsonian arsenal that was repurposed, much like AD. Amantadine, a mild glutamate receptor antagonist that increases dopamine and blocks its reuptake, was actually initially created to treat influenza before being used to treat Parkinson's disease.

Huntington's Disease

HD is the most prevalent monogenical neurological illness in the developed world and is autosomal dominant. Dementia, behavioural and mental impairments, and involuntary choreatic motions are its hallmarks. It is caused by a genetic mutation that results in a mutant form of the multifunctional protein huntingtin. This form of the protein is toxic and causes malfunction and neuronal death. When HD first appears in adulthood, the symptoms worsen over time and eventually cause death within a few years. The only way to treat this illness is to manage its symptoms as there is currently no recognized cure.

Tetrabenazine, which functions as a mild blocker of D2 dopamine postsynaptic neurons and a high-affinity, reversible inhibitor of monoamine uptake of presynaptic neurons, was initially created as part of research to create simple compounds with reserpine-like antipsychotic action.

Multiple Sclerosis

MS is a central nervous system autoimmune disease. It is a

long-term, inflammatory disease in which there is variable destruction of the myelin and axons. It starts with treatable neurological impairments and progresses over time, but its course is uncertain. Although MS has no known cure, there are now approved treatments to lessen its symptoms and slow its progression.

Numerous anticancer medications have been modified to treat multiple sclerosis and its associated symptoms. An example of this is the synthetic chemical mitoxantrone, an anthracenedione that has been utilized as a wide-spectrum anticancer drug to treat acute leukemia, lymphoma, and breast and prostate cancer.

Amyotrophic Lateral Sclerosis

Death of the upper and lower motor neurons that govern voluntary muscles is a hallmark of ALS. It causes muscular atrophy, a condition in which muscles progressively weaken and shrink. Additional symptoms include breathing, swallowing, and speech difficulties, as well as twitching and stiffness in the muscles. About 10% of ALS cases are genetically inherited, with the majority of cases having an unknown aetiology.

Only two medications, riluzole and edaravone, are now available to slow the progression of ALS, however they cannot reverse symptoms once they have appeared. Nevertheless, some medications are currently being researched for their potential use in treating ALS.

Dog cancer is treated with the tyrosine kinase inhibitor mastitinib. Tyrosine kinase inhibitors may be effective against ALS because of the potential sensitivity of aberrant glial cells that proliferate in the disease. In the same rat model, mastinib was shown to enhance survival and decrease glial cell activation.

Table1

Summary of the the rapeutic approaches developed to target the biological path ways contributing to the pathogenesis of primary neurode generative disorders.

Disease	Target mechanism	Drug	Mechanisms of action
Alzheimer Disease (AD), ageing	Myelin	Clemastine fumarate	Binds to muscarinic receptor and activates OPC differentiation and myelination
Ageing		Metformin	AMPK inhibitor, restores OPC differentiation and remyelination
Ageing		LY294002	Modulator of PI3K-Akt-mTOR signalling modulator
Alzheimer Disease (AD)	Synaptic dysfunction	Levetiracetam	Inhibits calcium release intraneuronal deposits
AD		Bryostatin 1	Reverses synaptic dysfunction
AD, ASL		Masitinib	Activates PKC and regulates neurogenesis, axonal transport and synaptic plasticity
ASL		Riluzole	Tyrosine kinase inhibitor, Mast cell inhibition, reduces secretion of toxic mediators for synapses
ASL		Ceftriaxone	Inhibits glutamate release
AD		Cell-permeable peptides targeting ADAM10 trafficking	Up-regulation of glutamate transporter
HD			Blocks ADAM10 endocytosis, upregulating ADAM10 activity
			Inhibition of SAP97-mediated ADAM10 trafficking to synapse, decrease in ADAM10 activity

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AD AD	Gene expression: Transcriptional regulation and epigenetic mechanisms	Memantine Tubastatin ACY-1215 MPT0G211 5-Aroylindoles	Contrasts NF- κ B pro-inflammatory activity HDAC inhibitors: • Facilitate gene expression through chromatin remodelling • Restore memory function
Ageing, AD, ALS AD Ageing, AD, PD, HD AD	Autophagy	Rapamycin AUTEN-67 Metformin AUTOTAC	Blocks mTORC1 – Removing autophagy inhibition mTOR-dependent modulation of autophagy Activates AMPK promoting autophagy and blocking mTORC1 Removes protein aggregates using autophagy
AD PD PD, AD, ALS, HD AD AD AD, PD	Metabolic failure	MitoQ CoQ10 MitoVitE MitoTEMPOL Resveratrol Mdivi-1 Shikonin MCU inhibitors	Antioxidants: • Limit mitochondrial ROS production Antioxidant indirectly activating PGC-1 α Dpr1 inhibitor limiting mitochondrial division PKM2 modulator, an apoptotic break Limit mitochondrial calcium uptake
ALS AD, PD HD AD, HD, ALS, PD	CNS inflammation	Siponimod Fingolimod Natalizumab Minocycline	Limit immune cell infiltration in the CNS Anti-inflammatory (controversial results between pre-clinical models and clinical trials)

Treatment Of Neurodegenerative Diseases: An Unmet Need:

Neurodegenerative diseases are characterized by progressive neural loss, resulting in various clinical entities. These range from common conditions, such as Alzheimer's disease and Parkinson's disease, to less frequent disorders, including amyotrophic lateral sclerosis (ALS), progressive spinal muscular atrophies, and hereditary sensory-motor neuropathies. Despite many years of research and advancements in basic and clinical research, aetiology and pathogenesis of most of those conditions are still obscure. Dementia of Alzheimer type and Parkinson's disease are the most represented within the group in terms of prevalence and socio-economic burden. This is especially true for high-income countries with longer life expectancy, since PD and AD incidence increases with aging. Epidemiologic studies show that PD has an estimated prevalence between 65.6 (age under 65 years old) and 12 500 (age above 85 years old) per 100 000 and an estimated incidence between 5 (age under 65 years old) and 346 (age above 85 years old) per 100 000/year in Europe and AD has an estimated incidence of ~ 300 to 5600 per 100 000/year in USA, significantly increasing with age groups (from 65-69 to 90+ year). Similar figures are found in Europe for AD with incidence of 240 to 7020 per 100 000/year. AD and PD are very highly disabling conditions (AD is listed among the top 20 leading disabling conditions worldwide by WHO) for the affected subjects but also have a strong impact on their caregivers and to the local health system. Parkinson's disease and AD can therefore be considered as paradigmatic of all neurodegenerative diseases.

Developing a medicinal product able to cure neurodegenerative diseases is such a huge commitment that long time and hard work are still required for its achievement. There are many open questions that need to be answered, such as identification of plausible drug candidates, of reliable animal models with good predictive value to establish neuroprotection, identification of sensitive clinical endpoints and measurement tools, validation of biomarkers and design and execution of trials. Discussing all those issues is out of

the scope of this paper. Therefore, only some aspects will be addressed thereafter regarding the requirements of an effective treatment and on clinical trial designs.

And because the illness that bears his name was first reported by Aloysius Alzheimer in the early 1900s, who first described its histopathology. However, no remedy has been discovered as of yet for various ailments as well as for every neurodegenerative illness that still exists. In fact, there are now only symptomatic treatments—that is, therapies that can reduce the disease’s symptoms without halting or delaying its progression. Drugs used to treat Parkinson’s disease symptoms have an impact on the disease’s primary motor characteristics by reducing or normalizing tremor, bradikinesia (slowing of movements), and stiffness. Good efficacy is achieved in the initial months or years, but as time goes on, the effects of the medication diminish and nearly always, long-term treatment issues arise, making the patients’ quality of life extremely poor. Memory and other cognitive abilities can be somewhat restored by symptomatic therapy of mild or severe AD. Regretfully, the impact is fleeting and has a negligible effect size. Because no specific medicines have been approved for the other neurodegenerative illnesses yet, they are all undertreated. ALS is an example, as it has been shown that the anticonvulsant riluzole “extends life or the time to mechanical breathing for individuals suffering from amyotrophic lateral sclerosis. Riluzole prolongs the survival of ALS patients, according to clinical trials. For riluzole 100 mg/day and placebo, the median survival time was 13.5 months and 16.5 months, respectively. The clinical importance of this discovery is not striking, despite the fact that a 3-month survival difference was deemed statistically significant in this quickly evolving disease.

Another limitation of symptomatic drugs is that they frequently only address one symptom of illnesses that frequently exhibit several symptoms, which are caused by the degeneration of various neurotransmitter systems a variety of central nervous system regions. For example, not just the dopamine producing cells of the substantial Ingra pair’s compacts die in Parkinson’s disease (PD), for which only dopaminergic

drugs are available. Numerous symptoms could be caused by the death of other cells and neurotransmitter systems that dopamine replacement treatment cannot address.

Due to their complexity, neurodegenerative illnesses are extremely challenging to treat, and it is evident that symptomatic care alone is insufficient. Consequently, the objective would be a disease-modifying medication that could significantly slow—or even stop—the progression of the illness. It should be shown that a disease modifying technique has a lasting impact on the underlying illness process. A system that can stop pathological neuronal loss, or neuroprotection, is a component of the disease-modifying process rather than a replacement for it. A disease modification should indicate long-term alterations in the pathogenic process rather than transient effects like those associated with symptomatic medications.

Therapeutic approaches to modify gene expression in neurodegenerative disorders

Since targeting transcriptional regulators would cause a broad modulation of numerous impacted downstream processes, it may be advantageous in the fight against neurodegenerative diseases. This feature, however, also poses a possible warning since altering the transcription of multiple genes may be harmful because not all of them are involved in the pathogenesis. However, attempts have been made to investigate, develop, and test therapeutic strategies with the goal of altering mechanisms linked to transcription. Because there is so much evidence that CREB's functionality or expression is reduced in many diseases, it is one of the most sought-after targets in the therapy of neurodegenerative disorders. However, there are currently no medications that specifically boost CREB-dependent signaling. To restore its expression levels, a variety of tactics could be used, such as utilizing molecular biology or genetic techniques, or influencing its upstream signaling regulators. Because many neurodegenerative disorders are complicated and multivariate, medication research is likely to focus on targets other than the conventional actors linked to a particular disorder. In the treatment of AD, NF- κ B is an example of

these kinds of targets. Memantine, an FDA-approved therapy for AD, appears to inhibit NF- κ B's pro-inflammatory effects. Other anti-inflammatory medications are being evaluated in preclinical or clinical settings for their ability to disrupt NF- κ B (see to Sun et al., 2022).

A lot of work has gone into investigating HDAC inhibitors as potential treatments for neurodegeneration. By making the chromatin more conducive to transcription, HDAC inhibitors may widely promote gene expression by allowing for higher expression of maybe advantageous genes. Amyloid clearance is one instance of an AD-relevant mechanism that may be favorably controlled through HDAC regulation. In fact, amyloid clearance was enhanced in humanized cultured astrocytes or several animal AD models by pharmacological inhibition or genetic targeting of HDACs (Prasad & Rao, 2018; Su et al., 2021). Additionally, non-selective HDAC inhibitors effectively corrected neuronal structural abnormalities and memory performance in a mouse AD transgenic model (Ricobaraza et al., 2012). However, given the possible adverse consequences of non-selective inhibition as demonstrated by clinical research, caution should be exercised when following this course (Prince et al., 2009). The fact that all HDACs have a lot of structural similarities and are expressed in diverse organs and cell types has made it difficult to design and create selective HDAC inhibitors. However, given improved technological possibilities, it is highly probable that blocking a particular HDAC could be a promising treatment approach (Gupta et al., 2020). The selective inhibition of HDAC6 by tubastatin A, ACY-1215 (ricolinostat), MPT0G211, or 5-aroylindoles is a promising example. These drugs have demonstrated good outcomes in animal models of AD (Fan et al., 2018; Lee et al., 2018; Onishi et al., 2021) and are being evaluated in clinical trials for conditions other than neurodegeneration.

Cutting The Costs:

The persistent inability to create a novel treatment for neurodegenerative diseases is costly and discouraging. After a protracted and expensive development procedure, the vast majority of compounds under investigation rarely reach

signing up. No one has yet to hit the market out of the 509 compounds mentioned in a paper by Myoung-Ok Kwon and Paul Herrling that were in any stage of development up until June 2006. All of the products that were in Phase II or III at the time were probably discontinued because they were ineffective. Consequently, all of the financial and human resources that were invested were squandered. An average of \$1 billion is thought to be spent on clinical trials required to launch a new medication. The high expenses and potential for failure may make pharmaceutical companies hesitant to engage in this area.

The so-called adaptive design is a novel study design paradigm that has recently been proposed. It is believed to have the potential to significantly lower trial expenses while also improving trial outcomes. What makes it unique is in that, depending on the analysis of interim data, planned changes to one or more specific parts of the research design and hypotheses are permitted. A practical approach in this situation would be to “kill” the therapeutic compounds that don’t show promise in the early clinical stages before they move on to more costly stages of research. Patients’ safety would increase if useless medications were eliminated since they would be exposed to fewer ineffective therapies, the length of the research, and ultimately significantly reduce the expenses. However, determining what is and is not useless is essential since failing to do so could result in the irreversible discarding of agents that were mistakenly deemed useless. In contrast to standard efficacy studies, which test the null hypothesis that treatments are equivalent and reject it if one treatment is likely to be more effective than the other, so-called futility studies are intended to determine whether a treatment exhibits promise and will, therefore, result in outcomes that surpass a significant threshold. The main focus of these investigations is the threshold. If the threshold for futility is appropriately established, medications that surpass it may be deemed “non-futile drugs” and may move forward with confirmatory trials, whereas ineffective treatments shouldn’t be investigated further. Studies on futility have long been effectively employed in cancer research, but more lately, they have been given consideration in the field of

neurodegeneration. These are Phase II trials that typically compare one treated arm over a respectably brief length of time to a predetermined threshold value that represents a consistent clinical assessment.

Conclusions:

Neurodegenerative disease treatment presents difficult problems. These difficulties stem in part from the intricate pathophysiology that underlies the genesis of these illnesses. The effectiveness of a new strategy that claims to employ a single polypharmacological drug molecule—that is, one that affects many drug targets in the disease’s etiological pathway—may offer a new hope in treatment of many neurodegenerative diseases. Provide fresh promise for treating a variety of neurodegenerative illnesses, including those linked to cognitive loss. Future treatment plans for neurodegenerative disorders and the cognitive decline they cause may require a shift similar to an all-out strategy. The focus of drug development efforts will need to change from creating selective agents that only target one pathophysiological pathway to creating agents (like DMLs) that work through several mechanisms and are meant to address the disease state’s inherent complexity.

The main unmet medical need in neurodegenerative illnesses is a disease-modifying treatment that slows or prevents the progression of the illness. While aetiology or pathophysiology of these conditions are not entirely understood, efforts to create therapies that can influence the course of the disease must go on.

Innovative study designs like the delayed start and randomised withdrawal designs may be used in human clinical trials to assist distinguish between a medicinal agent’s symptomatic and disease-modifying effects. Another effective method to promote research in the field is through futility studies. Initiate neurological field by reducing the expenses associated with drug development programs.

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