ABSTRACT

Neurodegenerative diseases are becoming more common as the global population ages. In many cases, they manifest themselves via mechanisms that are not fully understood, impairing memory, cognition, and movement. There is currently no cure for any neurodegenerative disease. Curable, and available treatments only manage symptoms or slow disease progression. As a result, there is an urgent need for new treatments for this type of disease, as stated by the World Health Organization. According to the organisation, neurodegenerative diseases that affect motor function will become the most common, In the next 20 years, it will be the second-leading cause of death. New therapies can emerge from three sources. Synthesis, natural products, and existing drugs are possible sources. Drug Repurposing is finding new use of an already existing drug. It offers affordable, cheap and faster treatment. Strategies such as in- silico models, data mining, artificial intelligence etc. help accelerate it. However, there are few barriers which need to overcome like legal and economic barriers. Collaboration between various sectors, awareness and encouragement can promote in flourishing of drug repurposing which holds a great future in the modern medicine sector.

INTRODUCTION

Neurodegenerative illnesses are becoming more common as the world's population ages, and it is predicted that by 2040, they will overtake cancer as the leading cause of death in developed countries. Neurodegenerative disorders are a type of central nervous system condition marked by cognitive, motor, and behavioural impairment. Alzheimer's disease and Parkinson's disease are the most common neurodegenerative dementia and movement disorder, respectively, while amyotrophic lateral sclerosis, Huntington disease, and vascular dementia are less common [1].

Neurodegenerative diseases are characterised by gradual nervous system failure and are both genetic and sporadic. Atrophy of the afflicted central or peripheral nervous system structures is frequently associated with these illnesses. Alzheimer's disease and other dementias, brain cancer, degenerative nerve disease, encephalopathies, epilepsy, genetic brain disorder, head and brain malformations, hydrocephalus, stroke, Parkinson's disease, Multiple sclerosis, Amyotrophic lateral sclerosis, Huntington's disease, and other diseases are among them[2].

The multifactorial nature of these illnesses is determined by common neuropathological hallmarks such as (a) aberrant protein dynamics with faulty protein function. Oxidative stress and free radicals; (b) degradation and aggregation (c) poor bioenergetics and mitochondrial dysfunctions (d) neuroinflammatory pro-inflammatory mediators[3].

One way to learn about how a disease works is to develop a model system that recapitulates the hallmark characteristics of the disease. Powerful experimental model organisms such as the mouse, fruit fly, nematode worm, and even baker's yeast have been used for many years to study neurodegenerative diseases and have provided key insights into disease mechanisms.

The ability to generate induced pluripotent stem cells (iPSCs) from differentiated human cells, which was just recently discovered, has allowed researchers to create patient-specific cell lines on a tissue culture dish, resulting in human models of human disease (Han).2011; et al.). There have been technological advancements recently that make it possible to cultivate these cells in three dimensions generate organoids that resemble a variety of human tissues, including the brain. Brain (Pasca et al., 2015; Marton and Pasca, 2016). Cell-cell interactions are possible in this three-dimensional brain organoid system A more complicated cytoarchitecture should be modelled and researched conventional tissue in greater detail and in more physiological situations Models of culturing using isolated cells.

The invention of a therapy for spinal muscular atrophy is one of the most inspiring success stories (SMA). SMA is a neuromuscular disorder caused by gene mutations that cause loss of function. The SMN1 gene is the most common cause of infant death .Ground breaking research into the disease's molecular mechanisms and the establishment of animal models (Hua et al., 2010, 2011) set the groundwork for future research the cornerstone for the current antisense clinical trials oligonucleotides (ASOs) as a therapeutic method for resolving a genetic problem repair the SMN protein's splicing problem and make it functional Research in this therapy method has been shown to be effective in animal model systems study (Hua et al., 2010; Hua et al., 2011) as well as two recent clinical trials in Children with SMA have shown that the method works[4].

Biomarkers in neurodegenerative [5]

In 1998, the National Institutes of Health's Biomarkers Definitions Working Group defined biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic response to a therapeutic intervention."

Biomarkers play a critical role in detecting both normal and pathological biological processes**.** Changes in pathology, biochemistry, and genetics can provide us with a wealth of information on the nature of an illness. A useful biomarker should be exact and dependable, able to differentiate between normal and interested disease, and differentiable amongst diseases. Biomarkers are seen to hold a lot of promise in terms of forecasting illness risk and assisting in disease treatment. In early disease detection and creating guidelines for the development of novel treatments.

Gene	Protein	Neurodegenerative disease
SNCA	Alpha-synuclein	monogenic PD
LRRK2	Leucine-Rich Repeat Kinase 2	Monogenic PD

PINK2	PTEN-induced kinase 1	monogenic PD
PARK2	Parkin	monogenic PD
DJ-1	DJ-1	monogenic PD
VPS35	Vacuolar protein sorting ortholog 35	monogenic PD
GBA	Glucocerebrosidase	PD (risk factor)
APP	Amyloid precursor protein	monogenic AD
PSEN1	Presenilin 1	monogenic AD
PSEN2	Prese.nilin 2	monogenic AD
APOE (ε4 allele)	Apolipoprotein-E	AD (risk factor)
TREM2	TREM2	AD (risk factor)
TARDBP	TDP-43	monogenic ALS
SOD1	Superoxide dismutase 1	monogenic ALS
FUS	Fused-in sarcoma	monogenic ALS
C9orf72	C9orf72	ALS (risk factor)
KIF5A	KIF5A	ALS (risk factor)

Biomarkers in exosomes associated with neurodegenerative disease

Name of disease	Source	Contents	Mechanism
Alzheimer's disease	Plasma and CSF	Aβ and NFT	Neuronal damage
Alzheimer's disease	Plasma	REST, HSF-1, Lamp 1 and IRS	Neuronal damage
Alzheimer's disease	Serum	miR-135a, miR-193b and miR-384	Neuronal damage
Parkinson's disease	CSF	α - SYN, DJ-1 miR-1, miR-485-5p, miR-153, miR-409-	Neuronal damage
Parkinson's disease	CSF	3p, miR-433, miR-136-3p, let-7g-3p, miR-19b-3p, miR-10a-5p, miR-132-5p, miR-370 and miR-873-3p	Neuronal damage
Prion Diseases	Plasma	PrPSc	Neuronal damage
Prion Diseases	Serum	miR-142-3p, miR-143-3p, miR-145a-5p, miR-451a, miR-146a-5p, miR-150-5p, miR-320, miR-let-7b, miR-141-3p, miR-429-3p and miR- 200 family	Neuronal damage
Amyotrophic lateral sclerosis	Peripheral blood and CSF	TDP-43	Neuronal damage and inflammation
Amyotrophic lateral sclerosis	Plasma	miR-183-5p, miR-9-5p, miR-193a-5p and miR- 15a-5p	Neuronal damage
Huntington's disease	Plasma	mHtt	Neuronal damage
Huntington's disease	Plasma	miR-877-5p, miR-223-3p, miR-30d-5p, miR-128, miR-22-5p, miR-223-5p, miR-222-3p, miR-338-3p, miR-130b-3p, miR-628-3p, miR-361-5p, miR-425-5p	Neuronal damage

Drug re-purposing [6]

Until the mid-1990s drug research heavily relied on the "one drug, one target" concept as the basic strategy for reducing the side effects of developed drugs, focusing on drug specificity and selectivity during the discovery process.

However, in recent years this concept has gradually given way to multitargeting pharmacology and the development of multifunctional ligands as a new strategy for reduced side effects and this is supported by the concept of Polypharmacology[7].

Polypharmacology is a strategy that employs one or multiple drugs to interact with multiple molecular targets toward a specific outcome. It is a concept based on great recent advances in areas, such as receptor dimerization (i.e., receptors coming together forming entities with distinct pharmacology; one drug, two targets), allosteric modulation (i.e., ligands causing target modulation after binding in secondary sites; two drugs, one target), and synergistic pharmacology (i.e., combination of drugs that have synergistic pharmacodynamics or pharmacokinetic efficacy; multiple drugs, multiple targets).

Based on the fact that a single drug can bind to, or affect the behaviour of, multiple and diverse molecular entities in a wide range of different cells and tissues resulting in a plethora of different biological effects, it is only natural to assume that one drug can be used therapeutically against different diseases. However, most of today's clinical drugs are used for different conditions; they affect one common molecular target but the effects are expressed in different tissues. For example, opioids bind to opioid receptors both in the nervous tissue and in the gut, resulting in two distinct biological effects (pain relief and reduced gastrointestinal motility), therefore they are used both against severe pain and diarrhoea. On the other hand, a smaller but significant number of clinical drugs are used for different conditions due to the fact that they bind to different molecular targets. One example is bromocriptine, which is used against acromegaly, Parkinson's and diabetes, since it binds to a large number of different receptors (i.e., dopamine, serotonin, alpha-adrenergic, and beta-adrenergic receptors). Drug repurposing or repositioning is the detection of novel indications for existing drugs in order to treat new diseases [8].

Drug repurposing offers drugs at a much cheaper, faster and accessible way to the patient population. The drug studied for repurposing are the shelved drugs which either could not made to the late phases of clinical trials or have failed in the market. Since the efficacy, safety and toxicity of the drug is already known, the initial phases of the clinical trials can be skipped which brings down the cost and duration of the clinical trials. It takes about 15 years to bring a new drug to the market whereas repurposed drug is cuts down both the duration (3 to 12 years) and costs. The challenges are to identify the right compound for the new purpose, to use the resources judiciously and to not fail again after bringing the failed drugs back into clinical trials.

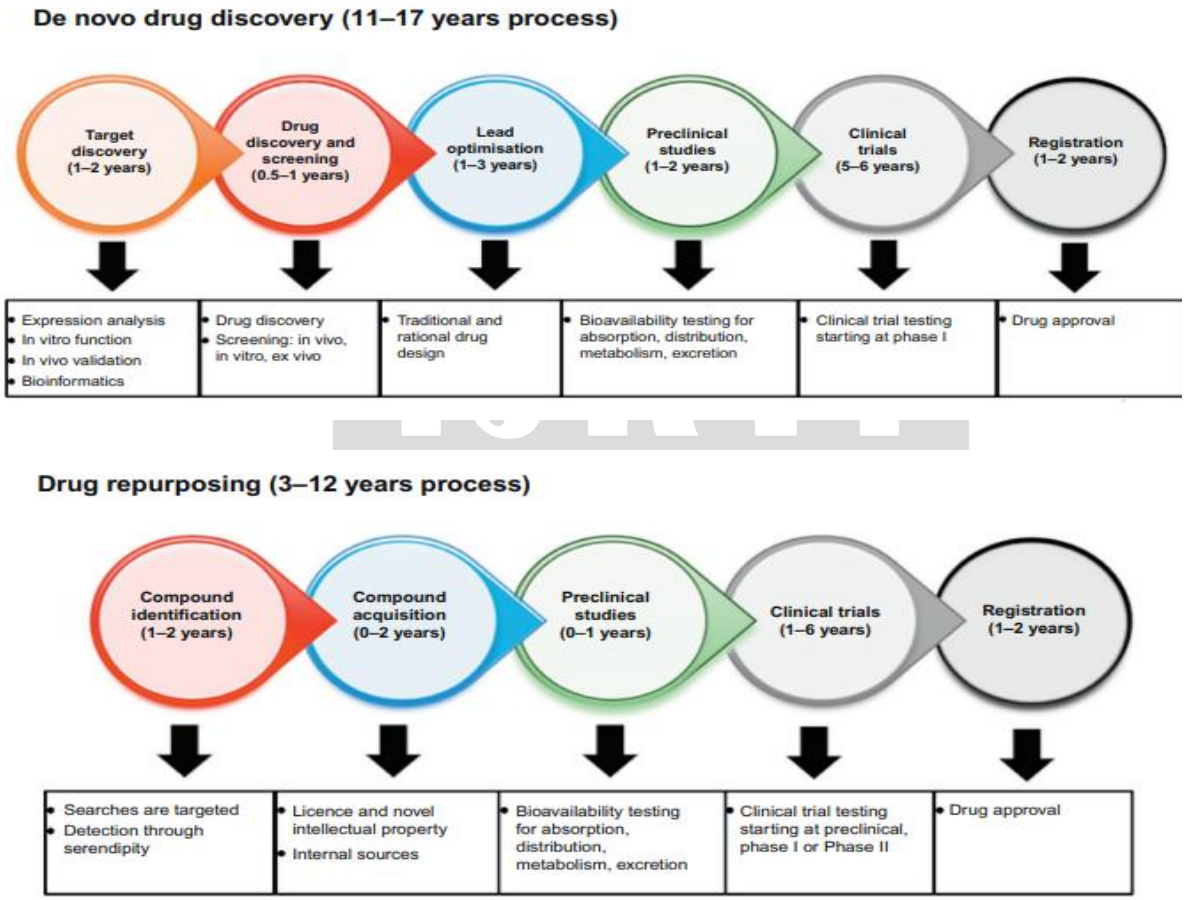

Fig. No. 1: De novo drug discovery

One of the most used strategies for drug repositioning is the in-silico screening of compound libraries in new targets. One remarkable example of drug repurposing is the drug thalidomide.

First used as an over-the-counter antiemetic for the treatment of pregnancy-associated morning sickness, it was quickly withdrawn after reports of teratogenicity and dysmyelia. However, in 1998, the Food and Drug Administration (FDA) approved thalidomide for the treatment of cutaneous manifestations of erythema nodosum leprosum. In 2006, thalidomide was approved for

the treatment of myeloma, due to its antiangiogenic properties. This example proves how important drug repurposing can be in drug discovery [9].

Strategies for accelerating drug repurposing

1. In-silico models- In-silico models or bioinformatics help in identifying the complex relationships among drugs, targets and diseases required for repurposing [10].

2. Target docking – Using high-throughput screening technologies to find out Polypharmacology compounds acting on multiple targets can cure multifactorial diseases like cancer, neurodegenerative diseases [11].

3. Artificial intelligence (AI)- AI improves access to data. Extensive data mining in literature to find out drug interactions, adverse effects, mechanism of actions, gene regulations can help accelerating drug development [12]. The side effect of one drug can be used as a treatment for another condition. If drugs have same adverse effects then they may work on same disease [13].

Pathway mining which involves identifying a specific pathway which is linked to different diseases and hence finding out drugs to hit that particular pathway for curing of diseases [12].

Neurodegenerative diseases (NDs) are age-dependent disorders, with very different pathophysiology's and a lack of understanding of the causes and mechanisms of these diseases, which leads to a lack of treatment. As the global population is increasingly becoming older, so is the prevalence of these diseases that impair the memory, cognition and movement [14]. The need for treatment for NDs is urgent, since the World Health Organization (WHO) predicts that in 20 years, NDs that mainly affect motor functions will overtake cancer to become the second-most prevalent cause of death, after cardiovascular diseases [15]. With the growing need for treatment for NDs, and the promise that drug repurposing poses, it makes sense that existing drugs are being tested for these diseases. This review comprises drugs that have been repurposed for Alzheimer's diseases (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS), the most studied neurodegenerative diseases [16].

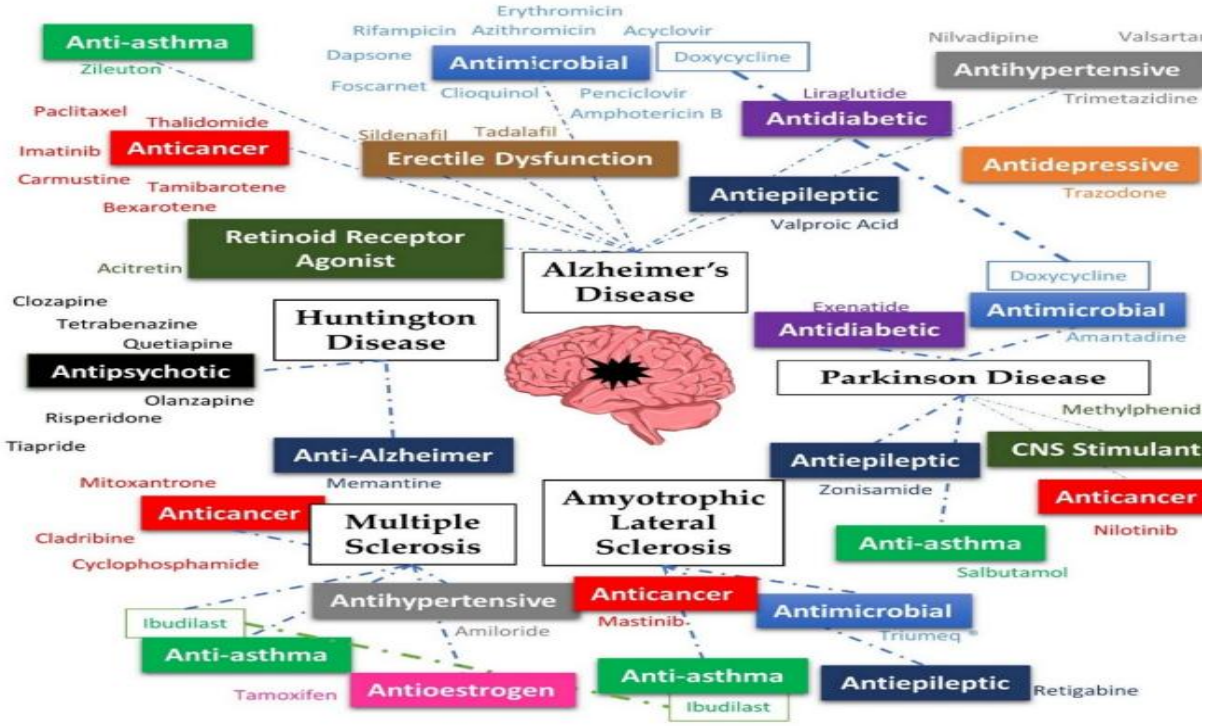

Fig. No. 2:

Alzheimer's Disease

Alzheimer's disease is one of the most common NDs, accounting for 80 percent of dementia cases in the elderly. Progressive memory loss, inability to learn, and a deterioration in behaviour and function are all signs. The aetiology of Alzheimer's disease is unknown, but it is thought to be related to the development of amyloid plaques in the brain, which eventually leads to neuronal and synaptic loss.[17].

There is currently no known cure for Alzheimer's disease, and the treatments used to treat the illness's cognitive manifestations or other symptoms are most effective when given early in the disease's progression.

Sl.no	Drugs	Class	Mechanism
1	Galantamine	Alkaloid	As it has a tertiary ammonium base, galantamine can easily penetrate the blood-brain barrier and inhibit brain acetylcholinesterase, which makes it particularly interesting used drugs for delaying the appearance of severe symptoms in patients suffering from AD [18].

2	Carmustine	Alkylating agent (nitrosourea)	n cells overexpressing amyloid-β protein precursor, carmustine showed a strong reduction in amyloid-β production, at a non-toxic dose [19][20].
3	Bexarotene	Anti-neoplastic agent	A retinoid X receptor antagonist, used to treat cutaneous T-cell lymphomas, has proven to be capable of reversing neurodegeneration, improve cognition and decreasing the levels of amyloid-β in mice overexpressing familial AD mutations [21].
4	Tamibarotene	Anti-neoplastic agent	A retinoic acid receptor agonist, approved in Japan for the treatment of acute promyelocytic leukaemia, is able to act on multiple pathways related to the pathophysiology of AD, such as reducing the secretion of proinflammatory cytokines and chemokines by brain cells, improving the behaviour in mice with accelerated senescence and decreasing cortical acetylcholine [22].
5	Imatinib	Tyrosine kinase inhibitor	Useful for the therapy of AD by two mechanisms: the reduction of amyloid-β and neuroprotection [23].
6	Paclitaxel	Antineoplastic agent	Among others it is also been studied as a potential treatment for AD [24][25].
7	Thalidomide	Immunomodulatory agent	It is also able to reduce hippocampal neuronal loss through the inhibition of the tumour necrosis factor-α [26].
8	Azithromycin Erythromycin	Macrolide antibiotic	Macrolide antibiotics, have shown inhibition of the amyloid precursor protein, resulting in the decrease of cerebral levels of amyloid-β [27].
9	Rifampicin	Anti-tuberculous	Effects in the reduction of amyloid-β fibrils, in a dose-dependent manner, probably due to the decreased production and increased clearance of amyloid-β [28][29][30].
10	Acyclovir Penciclovir Foscarnet	Anti-viral	Drugs have shown successful in reducing phosphorylated tau protein and amyloid-β in AD cell models, which can mean they are suitable for the treatment of AD [31].
11	Clioquinol	Antifungal agent	It has been shown to cause a delay in the formation of amyloid-β [32].
12	valproic acid	Anti-epileptic drugs	Have been suggested as a neuroprotective agent for AD, as it has shown reduced formation of amyloid-β plaques and improvement in memory deficits in transgenic mice [33].
13	Valsartan	Anti-hypertensive (Angiotensin receptor blocker)	The rationale behind the use of this class of drugs for AD comes from the fact that chronic adverse stress, one of the major environmental causes for the onset and progression of the AD. Reduced amyloid-β has been reported with in vitro and in vivo treatment of valsartan and this evidence suggests a reduction of dementia [34].
14	Nilvadipine	Antihypertensive (Calcium channel blocker)	Have shown to reduce the production, oligomerization and accumulation of amyloid-β in vitro, improve cell survival and reduce neurotoxicity, while having good blood-brain barrier penetration and increasing brain blood flow through its vasodilatory properties [35][36][37].

15	Trimetazidine	Anti-ischemic drug of the piperazine class	Its mechanism of action is diverse, ranging from increasing nitric oxide production, inhibiting cell apoptosis and being an antioxidant, which increases endothelial function. Apart from being able to pass through the blood-brain barrier, it can reduce the produce of free radicals, due to its antioxidant properties. It can also improve axonal regeneration and effective myelination in healthy and injured nerves [38][39].
16	Liraglutide	Antidiabetic (Glucagon-like peptide 1 analogues)	Drug Has been established brain penetration and shows physiological effects in the brain, improving learning, and reducing amyloid-β formation and brain inflammation [40].
17	Zileuton	Antiasthma drug	5-lipooxygenase is higher in AD patients, making it a promising target. In fact, studies with zileuton in mice showed a reduction in the deposition of amyloid-β [41].
18	Sildenafil Tadalafil	Erectile dysfunction drugs, Inhibitors of phosphodiesterase-5,	was successful in inhibiting neuroinflammation and was able to lower amyloid-β in aged mice models. also displayed cognition enhancement and neuroprotection, while penetrating the blood-brain barrier in high concentration enough to inhibit phosphodiesterase-5 more effectively [42].
19	Trazodone	Antidepressant	was successful in reversing eIF2α-P translational attenuation in in vitro and in vivo studies. Furthermore, it displayed neuroprotection, restoration of memory and prevented neurodegeneration [43].

Parkinsons disease

PD is the second-most common ND after AD, and affects populations worldwide. PD is most known for its motor symptoms, which are thought to arise primarily from the loss of dopaminergic neurons within the substantia nigra, although other neurotransmitter systems also appear to be affected [44]. It is now known that PD comprises several non-motor related symptoms, such as cognitive impairment, sleep disorders and depression. Even though PD has no cure, the current available treatments are efficacious and keep the disease managed, consisting of dopamine substitution and deep brain stimulation [45]. Similar to AD, there is also a drug in the antiparkinsonian arsenal that was itself repurposed: amantadine. In fact, amantadine was first developed to treat influenza, and was only later directed towards the treatment of PD as a weak glutamate receptor antagonist, increasing dopamine and blocking its reuptake [46].

Sl.no	Drugs	Class	Mechanism
1	Amantadine	Anti -viral	Drug act as a weak glutamate receptor antagonist, increasing dopamine and blocking its reuptake [46].
2	Nilotinib	Antineoplastic agent	It inhibits Abl phosphorylation, it increases α-synuclein degradation [47].
3	Doxycycline	Antibiotic agent	Drug has shown antioxidant activity and the ability to remodel early species of α-synuclein oligomers into non-toxic and non-seeding species. Furthermore, doxycycline has only been reported to bind to oligomeric species of α-synuclein; the physiological monomeric forms are preserved [48].
4	Zonisamide	Anticonvulsant	Zonisamide Inhibited monoamine oxidase-B enzyme were dopamine levels in the synaptic cleft stable and increases the effect of dopamine [49].
5	Selegiline	Antidepressant	Drug as shown to increases the activation of astrocytes after striatal injury [50].
6	Methylphenidate	Central nervous system stimulant	Methylphenidate acts through the blockage of presynaptic dopamine transporter and noradrenaline reuptake in the e striatum and the prefrontal cortex. Multiple studies with this drug have

			shown effective in reducing gait disorder of PD, as well as non-motor symptoms [51].
7	Exenatide	Anti-diabetic (Glucagon-like peptide-1 analogue)	It has been studied as a treatment for PD, and has shown neuroprotection and beneficial neuroplastic change that can delay or prevent disease progression [52].
8	Liraglutide	Incretin mimetics	Currently undergoing phase II clinical trials [53].
9	Salbutamol	anti-asthmatics	being the one capable of penetrating the blood-brain barrier and the study undertaken showed that drug was able to reduce the SNCA-mRNA and α-synuclein abundance [54].

Huntington's disease

HD is an autosomal dominant disease, and the most common monogenic neurological disease in the developed world. It is characterized by involuntary choreatic movements, behavioural and psychiatric disorders, and dementia. It occurs through a genetic mutation that originates a mutant form of the multifunctional protein huntingtin, which originates toxicity and leads to neuronal death and dysfunction. HD starts to manifest itself in adult life, and the symptoms progress until it leads to death within years. There is no known treatment for this disease, so the only option is the management of symptoms [55][56].

Sl.no	Drugs	Class	Mechanism
1	Tetrabenazine	Anti-psychotic	is a reversible vesicular monoamine transporter 2 (VMAT2) inhibitor which blocks the uptake of cytosolic monoamines and prevents dopamine release from synaptic vesicles [57].
2	Clozapine	Anti-psychotic	It displays a high affinity for the dopamine D1 and D4 receptors, with low antagonistic activity for the D2 dopaminergic receptors. Due to its low incidence of extrapyramidal side effects, it was suggested to be a good symptomatic drug for chorea, although clinical trials showed conflicting results [58].
3	Olanzapine	Antipsychotic	This drug has high affinity for serotoninergic receptor, but antagonizes dopamine D2 receptors [59].
4	Risperidone	Antipsychotic	Drug acts as a D2 receptor antagonist and a serotonin agonist. It showed beneficial effects on stabilizing motor decline and psychiatric symptoms [60].
5	Memantine	NMDA receptor antagonists	Memantine was studied for its efficacy in the treatment of HD, and it was noticed that it was able to decrease the vulnerability of neurons to glutamate-mediated excitotoxicity [61].

Multiple Sclerosis

MS is an autoimmune disease of the central nervous system. It is a chronic, inflammatory condition, where the myelin and the axons are destroyed in varying degrees. Its course is unpredictable, and is initially characterized by reversible neurological deficits, which over time become progressive. There is no cure for MS, but there are already therapies approved to reduce the symptoms and progression of the disease [62].

Sl.no	Drugs	Class	Mechanism
1	Mitoxantrone	Anticancer	Mitoxantrone is capable of inhibiting the activation of T-cells, stopping the proliferation of T- and B-cells, lowering antibody production and deactivating macrophages [63].
2	Cyclophosphamide	Anticancer	It acts as an immunosuppressive and immunomodulatory role. Explicitly, it acts in T- and B-cells, supressing cell-mediated and humoral immunity.it can also decrease the secretion of the pro-inflammatory T helper 1 cytokine interferon-γ and interleukin-12, while increasing the secretion of anti-inflammatory cytokines in the brain and blood [64].
3	Cladribine	Anticancer	Its mechanism of action is related to the decrease in circulating B- and T-lymphocytes. Additional

			mechanisms have been suggested, which is the induction of interferon-α producing myeloid dendritic cells, and the interference with the synaptic effects of interleukin-1β, leading to the conclusion that cladribine can also display neuroprotective properties [65].
4	Amiloride	Diuretics	Amiloride can block the neuronal proton-gated acid-sensing ion channel 1 (ASIC1), which is overexpressed in axons and oligodendrocytes in MS lesions, thus exerting its neuroprotective and myeloprotective effects. Furthermore, the fact that amiloride's protective effect happens downstream of inflammation constitutes an advantage, since it makes it active even on the onset of inflammation [66].
5	Ibudilast	Anti-inflammatory	In the brain, ibudilast can inhibit the release of the tumour necrosis factor from the microglia and the astrocytes, decreasing neuronal degeneration. Furthermore, it can protect astrocytes from apoptosis and inhibit oligodendrocyte apoptosis and demyelination, hence its usefulness in MS. Studies have shown its safety and tolerability, while reducing the rate of brain atrophy at a high dose [67].

Amyotrophic Lateral Sclerosis

ALS is a disease characterized by the death of upper and lower motor neurons, which control voluntary muscles. It leads to muscle atrophy, where muscles gradually become weaker, decreasing in size. Other symptoms are muscle stiffness and twitching, and difficulties in breathing, swallowing and speaking. The causes of ALS are of unknown aetiology in most cases, with about 10% being of genetic inheritance [68].

Sl.no	Drugs	Class	Mechanism
1	Masitinib	Tyrosine kinase inhibitor	It was proven that masitinib inhibited glial cell activation in the appropriate rat model and increased survival [69].
2	Ibudilast	Anti-inflammatory	it can protect astrocytes from apoptosis and inhibit oligodendrocyte apoptosis and demyelination, hence its usefulness in ALS [70].
3	Triumeq	Antiretroviral	Triumeq could suppress this genetic reactivation and may slow disease progression in patients with ALS[71].
4	Retigabine	Anti-epileptic	Drug is able to prolong motor neuron survival and decrease excitability, which is advantageous in the treatment of ALS, since it is believed that, in this disease, neurons are hyper-excitable, firing more than normal and ultimately leading to cell death. This drug is still under clinical trial for the treatment of ALS[71].

Conclusion:

As a result of the aforementioned data, it shows that drug repurposing can be an interesting source of candidates to treat diseases other than those for which they were originally used in therapeutics. It's also an appealing option because the costs of repositioning a drug are low.as the safety and tolerability have already been established, making clinical studies more cost-effective and necessitating smaller samples sizes and lowering the overall cost of clinical development.The neurodegenerative diseases discussed here are incurable and have a significant impact on the patients' overall quality of life. Examples of drug repurposing have demonstrated benefits primarily in symptom management and disease reversal. Unfortunately, no drug has yet been discovered that can completely reverse the mechanisms of neurodegeneration. However, several of the drugs discussed in this review are already in phase II and phase III clinical trials, implying that the arsenal against neurodegenerative diseases will be much larger in a few years than it is today.

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