Current Research in Pharmacology and Drug Discovery 2 (2021) 100012

Contents lists available at ScienceDirect

Current Research in Pharmacology and Drug Discovery

journal homepage: www.journals.elsevier.com/current-research-in-pharmacology-and-drug-discovery

Perspective insights of repurposing the pleiotropic efficacy of statins in neurodegenerative disorders: An expository appraisal

Aditi Bhat [a,1], Harshita Dalvi [a,1], Harsha Jain [a], Nagarjun Rangaraj [a], Shashi Bala Singh [b], Saurabh Srivastava [a,*]

[a] Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, 500037, India
[b] Department of Pharmacology and Regulatory Toxicology, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, 500037, India

ARTICLE INFO

Keywords:
Neurodegenerative disorders
Statins
Alzheimer disease
Parkinson disease
Huntington disease
Multiple sclerosis

ABSTRACT

Neurodegenerative disorders which affects a larger population pose a great clinical challenge. These disorders impact the quality of life of an individual by damaging the neurons, which are the unit cells of the brain. Clinicians are faced with the grave challenge of inhibiting the progression of these diseases as available treatment options fail to meet the clinical demand. Thus, treating the disease/disorder symptomatically is the Hobson's choice. The goal of the researchers is to introduce newer therapies in this segment and introducing a new molecule will take long years of development. Hence, drug repurposing/repositioning can be a better substitute in comparison to time consuming and expensive drug discovery and development cycle. Presently, a paradigm shift towards the re-purposing of drugs can be witnessed. Statins which have been previously approved as anti-hyperlipidemic agents are in the limelight of research for re-purposed drugs. Owing to their anti-inflammatory and antioxidant nature, statins act as neuroprotective in several brain disorders. Further they attenuate the amyloid plaques and protein aggregation which are the triggering factors in the Alzheimer's and Parkinson's respectively. In case of Huntington disease and Multiple sclerosis they help in improving the psychomotor symptoms and stimulate remyelination thus acting as neuroprotective. This article reviews the potential of statins in treating neurodegenerative disorders along with a brief discussion on the safety concerns associated with use of statins and human clinical trial data linked with re-tasking statins for neurodegenerative disorders along with the regulatory perspectives involved with the drug repositioning.

1. Introduction

Neurodegenerative disorders are marked off by the gradual damage or decay of neuronal cells impacting central and peripheral nervous systems (Prusiner, 2001). Nearly 1/6th of the world's population (around 1 billion people) suffers from neurodegenerative disorders. Over the past decade, there has been a surge in number of cases reported worldwide and they are statistically expected to increase in the near future. Neurodegenerative diseases on the other hand, impel an economic burden owing to their long-term treatment duration. Conventional treatments to date, are unsuccessful in preventing the progression of disease and have exerted meager symptomatic relief. There exists a grey zone due to ambiguous etiology and imprecise understanding of the biological markers of these disorders, making it difficult to design a drug (Shoulson, 1998). There has been a high failure rate reported with the human clinical trials as it involves longer treatment duration over a widely spread and genetically variable population. The preclinical trials are often faced with obstacles of having a validated animal model exhibiting required transgenic qualities (Stanzione and Tropepi, 2011). But on the brighter side, a large number of molecules in drug discovery pipeline are currently being investigated for their efficacy and therapeutic activity in the neurodegenerative area.

Most of the available approaches are not disease modifying rather they are aimed at reducing the symptoms. This non-availability of disease modifying agents is the major clinical setback for treating neurodegenerative disorders. Unfortunately, De-novo development of a drug would require huge investments and longer time with lower chances of approval. These problems compelled researchers and industrialists to shift their interest towards re-purposed drugs. Since re-purposed drugs

* Corresponding author. Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research (NIPER), Hyderabad, Telangana, 500037, India.
E-mail address: saurabh@niperhyd.ac.in (S. Srivastava).
[1] Aditi Bhat and Harshita Dalvi have contributed equally to this review article.

https://doi.org/10.1016/j.crphar.2020.100012
Received 1 October 2020; Received in revised form 15 December 2020; Accepted 18 December 2020

Abbreviations:

CNS	Central Nervous System
AD	Alzheimer's Disease
(Aβ)	Amyloid beta
APOE4	Apo-lipoprotein E−4
HMGCOA	3-hydroxy-3-methyl-glutaryl-Coenzyme A
LDL	Low Density Lipoprotein
VLDL	Very Low Density Lipoprotein
ROS	Reactive Oxygen Species
iNOS	Inducible Nitric Oxide synthase
BDNF	Brain Derived Neurotropic Factor
BBB	Blood Brain Barrier
STZ	Streptozotocin
PD	Parkinson's Disease
ETC	Electron Transport Chain
NF-kb	Nuclear factor kappa-light-chain-enhancer of activated B cells
TNF-alpha	Tumor Necrosis Factor
IL	Interleukins
6-OHDA	6-hydroxydopamine
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
NO	Nitric Oxide
CO-Q10	Coenzyme-Q10
HD	Huntington Disease
HTT	Huntingtin gene
COX	Cyclo-oxygenase
QA	Quinolinic acid
MS	Multiple Sclerosis
MRI	Magnetic Resonance Imaging
CK	Creatine kinase
CYP3A4	Cytochrome P 3A4
ANDA	Abbreviated New Drug Application
NDA	New Drug Application
GPCRs	G-Protein coupled receptors
ABC	ATP binding cassette
LRP1	LDL receptor related protein
24-OHC	24-hydroxy cholesterol
CSF	Cerebro Spinal Fluid
ETC	Electron Transport Chain
AMD	Age of Motor Diagnosis
DCL	Diagnostic Confidence Level
UHDRS	United Huntington's Disease Rating Scale
NMDA	N-methyl-D-aspartate
FPP	Farnesyl pyrophosphate
GGPP	Geranyl Geranyl Pyrophosphate
FDA	Food and Drug Administration

are already approved drugs for some other condition there are no major obstacles faced during their usage to target another indication. More recently, there is enormous interest in repositioning of drugs. In this regard, researchers have explored various drugs which can be re-purposed for treating neurodegenerative disorders (Hilbush et al., 2005). Drug repositioning comes with low risk to benefit ratio and offers advantages of low cost and a highly efficacious treatment option (Paranjpe et al., 2019). Statins are the wonder molecules that were discovered in 1976, and found its clinical application in 1986 when lovastatin became the first-marketed statin for treating hypercholesteremia (Endo, 2010; Tobert, 2003). Over the years of studies and discoveries in the field of science, statins were repurposed for multiple disease segments. Statins have shown to reap the potential benefits from repurposing in the segment of neurodegenerative diseases (Durães et al., 2018). Owing to their anti-oxidant, anti-inflammatory activities they exert pleiotropic effects in Alzheimer's Disease (AD) by reducing amyloid plaques and improving cognitive responses; decrease in the protein aggregation in Parkinson's Disease (PD) and by acting as a powerful antioxidant attenuating oxidative stress which is a causative factor for the neuronal damage. In case of Huntington Disease (HD), statins were shown to exert neuroprotective action and inhibited neuro-inflammation and supported re-myelination in Multiple Sclerosis (MS) (Cummings and Zhong, 2014). The article reviews the potential mechanism of actions of statins in neurodegenerative disorders along with the supporting clinical trial data. It also focusses on the safety concerns linked with usage of statins and regulatory perspective involved with re-profiling of statins in neurodegenerative disorders.

2. Statins as lipid lowering agents

There is an established and clear relationship between the concentration of cholesterol in the body and the occurrence of heart diseases. The translation of 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG CoA) to mevalonate is the vital step in the cholesterol biosynthetic pathway which is governed by the enzyme known as HMG CoA reductase. Drugs that particularly inhibit the HMG CoA reductase would inhibit the synthesis of cholesterol.

Statins cause competitive and reversible inhibition of the HMG CoA reductase enzyme leading to a decrease in the serum cholesterol levels which stimulate the increase in the expression of the gene controlling the Low Density Lipoprotein (LDL) receptors. The increased LDL receptors on the hepatocytes take up the free LDL and its precursors (like IDLP, VLDLP, etc.). Statins also inhibit the production of Apolipoprotein B-100 and effectively reduce the synthesis of lipoproteins that are rich in triglycerides. Thus, in a nut-shell, they increase the serum High Density Lipoprotein (HDL) concentration, and lower the LDL, and triglyceride concentrations which is briefly explained in (Fig. 1) (Stancu and Sima, 2001; Maron et al., 2000). Hence, they are prescribed on a large scale to treat hypercholesterolemia, dyslipidemia, hyperlipidemia, etc. They are either synthetically produced (like atorvastatin, pitavastatin, fluvastatin and rosuvastatin) or obtained as products from fungi (like lovastatin, simvastatin, pravastatin) (Stancu and Sima, 2001). Statins have a very similar structure to the endogenous substrate, HMG CoA. The affinity of the enzyme towards statins is much higher as compared to the natural substrate, which proves as the profit point for statins (Sirtori, 2014). They competitively bind to the enzyme and modify its active site and render

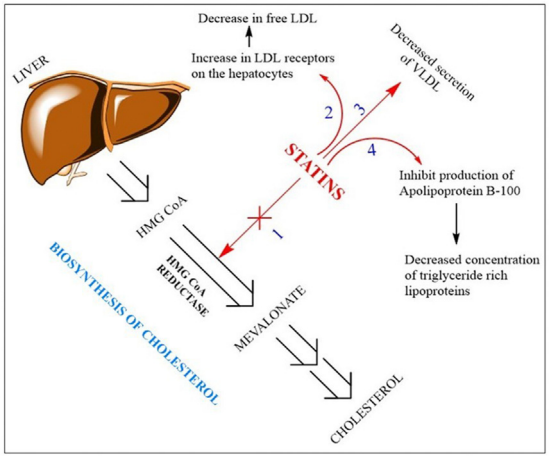

Fig. 1. Lipid lowering action of statins.

the enzyme inefficient (Stancu and Sima, 2001). In this way, statins reduce the cholesterol accumulation and have become the most prescribed medications for lowering the cardio-vascular risks. Apart from the above-mentioned properties, statins possess pleiotropic effects (i.e. anti-cancer, neuroprotective, atherosclerotic plaque stability, fibrosis, oxidative stress and inflammation). These multiple activities of statins had gained much attention and are in the limelight of research even now.

3. Cholesterol metabolism: a link to neurodegenerative disorders

Cholesterol is the chief component which is found abundantly in the brain compartment (Zhang and Liu, 2015). Brain is made of 25% of total body cholesterol of which major proportion is found in myelin sheaths covering the neurons. Cholesterol is responsible for carrying out crucial functions ranging from transport of essential molecules to neuronal growth and plasticity. Cholesterol homeostasis is the base of neuronal integrity because it establishes a perfect balance between cholesterol synthesis and its metabolism. Depletion in cholesterol reserves affects neuronal activities such as signal transmission and its survival as it deleteriously impacts several ion channels, G-Protein coupled receptors (GPCRs) which ultimately results in neurodegeneration (González-Guevara et al., 2020).

Cholesterol synthesis in the brain proceeds via the 25-step process called as de-novo synthesis, with acetyl-CoA as a starting component and involves various important intermediates. Astrocytes which are supporting cells surrounding neurons are the main depots where cholesterol is synthesized along with apolipoprotein E (APOE lipoproteins). This lipid cargo is exported with the help of ATP binding cassette (ABC) transporters to bind the LDL and LDL receptor related protein (LRP1) receptors present on the neuronal membrane. This internalized cholesterol lipoprotein is then used for neuronal growth and maintenance (Kang and Rivest, 2012).

Cholesterol metabolism in the brain is substantially different from that of plasma where the excess of cholesterol is metabolised by the 24-hydroxylase enzyme of CYP46A1 family to produce 24-hydroxy cholesterol (24-OHC), which is highly polar in nature (Benarroch, 2008). 24-OHC is the major metabolite of cholesterol degradation or breakdown which regulates the cholesterol homeostasis in the brain and crosses Blood Brain Barrier (BBB) and regulates the expression of APOE and ABCA1 genes via negative feedback mechanism. Raised levels of 24-OHC are attributed to various neurodegenerative disorders owing to its pro-oxidant activity which may be cytotoxic and bring about neuronal damage when present in excessive amounts (Doria et al., 2016). Levels of 24-OHC have been positively correlated with neuronal damage and neuroinflammation (Huang et al., 2019). In case of Alzheimer disease, mild cognitive impairment was linked with increased levels of 24-OHC in Cerebro Spinal Fluid (CSF) (Leoni et al., 2006). Similarly, in case of Parkinson disease, various studies have suggested that 24-OHC is the possible culprit for alpha-synuclein aggregation, which is the primordial cause of disease progression (Doria et al., 2016). In Multiple sclerosis, elevated levels of 24-OHC were found in CSF during the active and remission period of diseases suggesting that demyelination is a result of excess cholesterol metabolism (Leoni, 2009). Huntington disease on the other hand also suggested an impairment in cholesterol homeostasis (González-Guevara et al., 2020). Thus, cholesterol equilibrium within the brain region is of paramount importance for neuronal function. Loss in this balance is indicative of neurodegenerative disorders in individuals.

4. Statins in neurodegenerative disorders

The etiology of neurodegenerative disorders includes age, genetics and drugs as contributing factors. Statins being a cholesterol lowering drug aids in preventing cholesterol mediated Amyloid beta (Aβ) lesions in AD and α-synuclein aggregation in case of PD. The common phenomena associated with neurodegenerative disorders include imbalance in the oxidative cycle and result in the generation of Reactive Oxygen Species (ROS) which play key role in progression of neuronal diseases by creating oxygen deficit. (Berman and Bayati, 2018). Along with the oxidative stress, microglial activation generates pro-inflammatory cytokines such as IL-1β, IL-6, TNF-alpha, and various cytotoxic factors leading to cellular damage (Wang et al., 2015). Statins offer protection against oxidative stress and inflammatory cytokines owing to its anti-oxidant and anti-inflammatory actions, thereby improving symptoms of neurodegenerative disorders presenting the fruitful option of repurposing in neurodegenerative disorders. The role of statins in the Central Nervous System (CNS) disorders are elaborated in (Fig. 2).

Statins are a wide class of compounds bearing molecular entities having a wide range of physicochemical parameters which are elucidated in (Fig. 3). These molecular differences guide the selection of statins in a particular neurodegenerative disorder and helps in the formulation development of the same. As per previous reports and case studies it is advisable to prefer non BBB permeating drugs for not causing excessive cholesterol depletion which will lead to destruction of the myelin sheath of neurons (Caballero and Nahata, 2004). Various clinical studies have been performed to assess the role of statins in AD, PD, HD and MS and are listed in (Table 1).

4.1. Statins in Alzheimer's disease (AD)

AD is the most pervasive form of dementia and is exhibited by degeneration of neuronal cells heading to the loss of memory and transient decline in social and interpersonal behavioral skills. Currently 46.8 million people are experiencing AD and other forms of dementia. The histopathological hallmarks of AD encompass Amyloid beta (Aβ) plaques or lesions, and neurofibrillary tangles (Overmyer et al., 2000). Aβ are fractions of proteins which on aggregation form plaques or lesions generating cytotoxicity thereby disrupting cross talk between neuronal cells (Lukiw, 2012). Another protein named tau is responsible for the transportation of essential nutrients to the brain which experiences change in the protein morphology that disrupts the entire transport system impacting deleteriously on neuronal network (Goedert, 1993). These histopathological changes generate an overall oxidative stress and eventually lead to neuro-inflammation (Smith et al., 2000).

Number of studies suggest a positive association of cholesterol and risks linked with AD. Various animal studies reveal the formation of neuronal Aβ plaques with high dietary intake of cholesterol (Cucchiara and Kasner, 2001). Cholesterol levels are exacerbated by the over-expression of Apo-lipoprotein E−4 (APOE4) gene, which is observed in about 15% of population worldwide. Besides this, the substantial cholesterol environment ameliorates the activity of β secretase enzyme which generates Aβ lesions (Caballero and Nahata, 2004). Therefore, use of statins (cholesterol lowering drug) in the management of AD can prove beneficiary as they exhibit neuroprotective actions with pleiotropic efficacy in neural pathways linked to neurodegeneration. Simvastatin mediated attenuation of several inflammatory mediators, inhibition of microglial activation, Inducible Nitric Oxide synthase (iNOS) amelioration, Brain Derived Neurotropic Factor (BDNF) stimulation and inhibition of apoptosis are some of the mechanisms apart from inhibiting Aβ plaques which were postulated and observed during clinical studies (Manickavasagam et al., 2020). Several epidemiological data suggest a strong link between usage of statins and reduced risk of AD which are listed in (Table 2) (Appleby et al., 2013). The use of statins in AD portrayed significant behavioral outcomes in animal models such as enhanced memory retention and significant drop in transfer latency observed in the elevated plus maze model with long term treatment (120 days) of simvastatin in C57BL/6 mice model (Ghodke et al., 2012). Lovastatin ameliorated neurological outcomes in direction pointing towards the faster learning curve with overall progress in Morris water maze when animals took a direct path to reach to the hidden platforms suggesting definite memory retention (Zhao et al., 2010). Object location test is yet another kind of behavioral assessment test indicative of spatial memory and behavior of rodents towards the novel object, and its

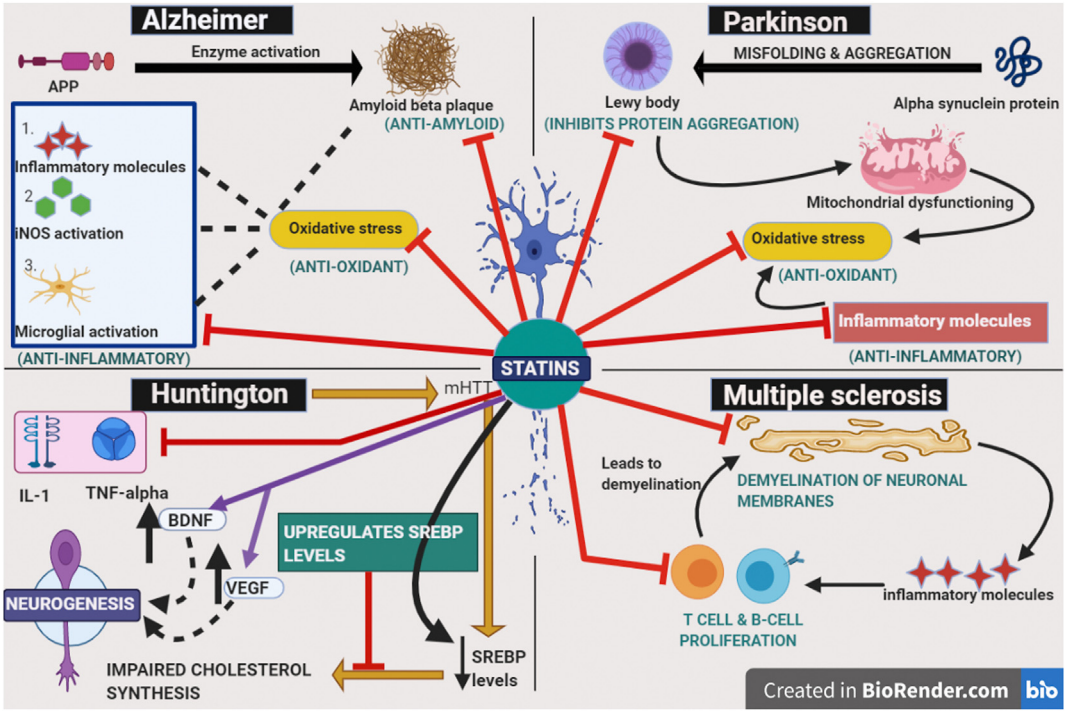

Fig. 2. A detailed representation of mechanism of action of statins in neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington disease and Multiple Sclerosis.

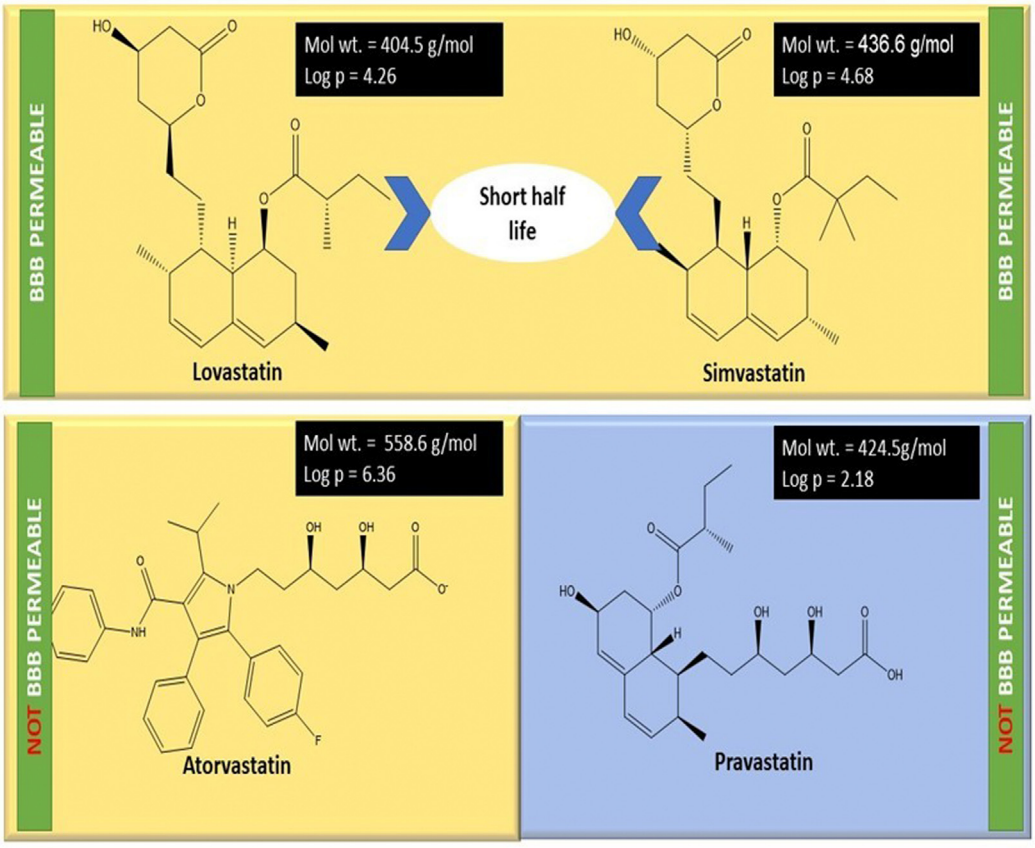

Fig. 3. Pharmacokinetic properties of lovastatin, simvastatin, atorvastatin and pravastatin.

Table 1
A Brief overview on the Clinical development of various statins on neurodegenerative disorders.

Drug/API	Approved indication	Status	Study details	ClinicalTrials.gov Identifier	Outcome
Simvastatin	Alzheimer's Disease	Completed	Evaluation of the potential role of simvastatin in treatment therapy.	NCT00486044	• Change in Cerebrospinal Fluid (CSF), Regional Cerebral Blood Flow on MRI and Beta-amyloid-42 was observed • There is decrease in Inflammatory markers • There are changes in the Cognitive Performance
Simvastatin	Alzheimer's Disease	Completed	Role of cholesterol lowering agent in Alzheimer's Disease to slow progression	NCT00053599	No study results are posted
Simvastatin	Alzheimer's Disease	Completed	Evaluation of the effects of simvastatin on biomarkers	NCT01142336	• Change from Baseline in Aβ42 was found in Cerebrospinal Fluid (CSF) at 1 Year • Change from Baseline in CSF Total Tau and CSF ptau181was observed at 1 Year
Simvastatin	Alzheimer's Disease	Completed	Evaluation of the effects of statins on beta-amyloid and cerebral perfusion for Alzheimer's Disease	NCT00939822	• Beta-amyloid-42 is a substance found in the plaques in the brain of subjects with AD and detected in CSF. • Beta-amyloid-42 has more potent cerebrovascular effects on individuals AD than other form of beta amyloid.
Simvastatin	Parkinson's Disease	Active	Study for the neuroprotective treatment for moderate Parkinson's Disease using simvastatin	NCT02787590	• Change in MDS-UPDRS (data related to patient's mood and mental state) was observed.
Simvastatin	Multiple Sclerosis	Recruiting	Investigation of simvastatin in secondary multiple sclerosis	NCT00647348	• Whole Brain Volume percentage change was observed. • Low disability and better progression in condition was observed.
Simvastatin	Multiple Sclerosis	Completed	Simvastatin as an add-on therapy to Interferon-β-1a for the management of relapsing-remitting multiple sclerosis	NCT00492765	No study results are posted
Simvastatin	Multiple Sclerosis	Recruiting	Study on simvastatin in management of secondary Multiple Sclerosis	NCT03896217	• Effect on cerebral blood flow and glutamate level using MRI technique was observed
Simvastatin	Multiple Sclerosis	Completed	EARLY IFNB-1a with simvastatin as combination therapy in Clinically Isolated Syndrome Suggestive of Multiple Sclerosis	NCT00146068	• Efficacy of combination study was observed
Lovastatin	Parkinson's Disease	Recruiting	Neuroprotective Treatment with lovastatin for Early Stage Parkinson's Disease	NCT03242499	• Change in MDS-UPDRS (data related to patient's mood and mental state) was observed.
Lovastatin	Alzheimer's Disease	Completed	Evaluation of effects of short-term statins and NSAIDs on Aβ level, in Alzheimer's Disease	NCT00046358	No study results are posted
Pravastatin	Alzheimer's Disease	Completed	Do HMG CoA Reductase Inhibitors Affect Aβ Levels?	NCT00303277	• Changes in CSF-beta levels and other biomarkers was seen
Pravastatin	Multiple Sclerosis	Completed	Evaluation of safety and efficacy of pravastatin in relapsing-remitting Multiple Sclerosis	NCT00200655	• Changes in the gadolinium positive lesions numbers (at 6th month in each group) was clearly seen.
Atorvastatin	Alzheimer's Disease	Completed	Safety and efficacy study of atorvastatin with a cholinesterase inhibitor in AD Patients.	NCT00151502	No study results are posted
Atorvastatin	Alzheimer's Disease	Completed	Lipitor for the management of Alzheimer's Disease	NCT00024531	No study results are posted
Atorvastatin	Alzheimer's Disease	Completed	Pilot study on cerebral and peripheral perfusion (CAPP)	NCT00751907	• Changes in regional cerebral flow and endothelial function was observed.
Atorvastatin	Alzheimer's Disease	Completed	A pilot study on the statins on cerebral blood flow and neuronal activity	NCT03411291	• Changes in the metabolite concentration in brain area and rate of perfusion in brain area was observed
Atorvastatin	Multiple Sclerosis	Completed	Lipitor therapy in subjects with clinically isolated syndrome having risk for Multiple Sclerosis	NCT00094172	• The occurrence of $\geq$ T2 lesions with or without gadolinium lesion (Gd+) enhancement or clinical exacerbation through 12 months.
Atorvastatin	Multiple Sclerosis	Completed	Study design to evaluate efficacy, safety and tolerability of atorvastatin at40 mg in subjects having relapsing-remitting multiple sclerosis	NCT01111656	• After 12 months of treatment proportion of patients with new lesions was calculated.
Atorvastatin	Multiple Sclerosis	Completed	Immunotherapy using BHT-3009 alone, or in combination with atorvastatin in subject showing multiple sclerosis	NCT00103974	• Safety and efficacy of BHT-3009 alone and when combined with atorvastatin in patients with multiple sclerosis was seen.

tracking in case of relocation. A 7-day treatment with 1 mg/kg of Atorvastatin or 10 mg/kg simvastatin enhanced the cognitive behavior of rodents proposing the elevated spatial memory retention power with use of statins (Zhao et al., 2010). These positive behavioral results suggest statins bear a significant repurposing rational to treat complex neurological disorders like AD and is a hot area of research.

In general, majority of the research focuses on positive effects observed with re-tasking of statins in animal models, but the safety data associated with long term usage of statins in wide population with several comorbidities still remains equivocal.

Repurposing statins hauls numerous loopholes including the elusive nature of the disease, insufficient knowledge of an exact mechanism, treatment duration and time of treatment initiation and genetic factors linked with it. Some studies report cognitive complications with the consumption of simvastatin and atorvastatin. Human clinical trials are less conclusive of re-profiling statins in AD and it requires extensive studies to analyze their effect without any confounding factors. More exhaustive research with concrete methodologies are needed to exemplify the cognition safety data of statins on their long-term usage for the treatment of AD.

4.2. Statins in Parkinson's disease (PD)

PD is a neurodegenerative disorder characterized by degeneration

Table 2a
Compilation of various human clinical studies demonstrating the role of statins in Alzheimer's disease.

Study carried out by	Outcome	Reference
Wolozin et al.	67% depletion in risk of AD in patients treated with statins along with noteworthy improvement in cognitive scores, correlating a pragmatic outcome.	Wolozin et al. (2000)
Lawrence T et al.	Lovastatin decreases serum Aβ in cognitively normal humans	Friedhoff et al. (2001)
Mitchel YB et al.	Simvastatin depletes plasma levels of APOE4 with senile plaques	Mitchel et al. (1995)
Jick H et al.	Simvastatin which showed 71% reduction in the likelihood of dementia/AD	Jick et al. (2000)

Table 2b
Various in-vitro studies demonstrating the role of statins in Alzheimer's disease.

Study carried out by	Outcome	Reference
Ramirez et al.	Pravastatin is more effective HMGCOA reductase inhibitor in neuronal cultures but simvastatin is better neuroprotectant even at low doses.	Ramirez et al. (2011)
Frears ER et al.	Lovastatin reduces production of senile plaques in *in-vitro* studies	Frears et al. (1999)

and deprivation of dopaminergic neurons in substantia nigra pars compacta heading to decline in the levels of dopamine (DA) (a neurotransmitter). The loss of DA leads to physiological abnormalities of tremors, rigidity and impaired motor movements. More than 10 million people are diagnosed with PD globally and it is becoming more prevalent every decade. The histopathological findings of PD include aggregation of the protein alpha synuclein termed as Lewy bodies, dysfunction of mitochondrial Electron Transport Chain (ETC), elevation of the proinflammatory mediators, and build-up of oxidative stress (Dexter and Jenner, 2013). *In vitro* studies suggest that cholesterol is a contributing factor in the aggregation of α-synuclein which further is associated with trail of events involving neural damage. Treatment with statins provides beneficial outcomes of decrease in neuronal α-synuclein aggregation. Lovastatin potentially decreased α-synuclein protein aggregation in the cell culture model of PD (Bar-On et al., 2008). Reducing cholesterol, changes the surface morphology and fluidity of the plasma membrane required for aggregation of the protein and thus prevents protein aggregation. Apart from preventing protein aggregation, Statins are powerful antioxidants, and exert anti-inflammatory activity on dopaminergic neurons thus maintaining oxidative balance (Carroll and Wyse, 2017).

Several studies were carried out to assess the activity of statins in amelioration of inflammatory molecules and suppression of microglial activation which are listed in (Table 3).

To evaluate neuroprotective effect of statin in 6-hydroxydopamine (6-OHDA) induced animal model of PD, various behavioral studies were performed to assess the improvement in locomotion that includes Amphetamine induced ipsilateral rotations, total locomotor activity and Rota rod performance. In the statin treatment group, it was observed that 2-week treatment of Atorvastatin (20 mg/kg) or Simvastatin (30 mg/kg) led to decrease in ipsilateral rotations, improved locomotor activity on day 7 and 14 of treatment and improved rota road performance (Kumar et al., 2012). Simvastatin also inhibited the down regulation of D1/D2 receptor thus preserving dopamine levels and helped in delaying the progression of disease (Kumar et al., 2012).

Although meta-analysis confirms modest protective action of statins in case of PD (Athauda and Foltynie, 2018) retrospective case studies suggest that previous studies were carried out at doses far exceeding human dose and are almost non-reproducible (Becker et al., 2008). It has been found in many studies that statins are associated with risk contributing to development of the PD itself and several cohort studies supports this contradictory claim. This inconsistency in findings is attributed to the dynamic nature of the lipid and statins when consumed for longer duration (Huang et al., 2015). Another claim opposing statin usage is inhibition of Coenzyme-Q10 (CO-Q10) (a ubidecarenone). CO-Q10 is synthesized in the human body following similar pathway of the cholesterol synthesis. CO-Q10 is responsible for mitochondrial ETC functioning and thus, low levels of CO-Q10 due to inhibition by the statins leads to mitochondrial impairment, thereby contributing to PD (Becker et al., 2008). Studies support that high levels of CO-Q10 delays PD and thus its supplementation along with statin therapy is needed. Also, Statins may affect CO-Q10 levels but does not produce deleterious effects which may worsen PD (Becker and Meier, 2009). More robust and exhaustive studies are needed for the assessment of the efficacy of statins in PD along with validation of the exact mechanism of statins considering no significant confounding factors are present. Till date, usage of statins in PD remains ambiguous and requires thorough investigations.

Table 3
Compilation of various pre-clinical studies demonstrating the role of statins in Parkinson's disease.

Study	Outcome	Reference
Pahan et al.	Lovastatin attenuated the Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-Kb), iNOS expression, Tumor Necrosis Factor (TNF-alpha), Inter Lukine (IL-6) and IL-1β inflammatory mediators in the rodent model	Carroll and Wyse (2017)
Kumar A et al.	simvastatin showed significant improvements in motor behavior, and suppression of NF-κB thus preserving dopaminergic neurons in the 6-OHDA induced PD model.	Kumar et al. (2012)
Selley ML	simvastatin prevented striatal depletion of dopamine and suppressed microglial activation in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced model of rat	Selley (2005)
Ghosh et al.	simvastatin (1 mg/kg) inhibited proinflammatory molecules and restored dopaminergic neurons and enhanced the locomotor functioning.	Ghosh et al. (2009)
Kumar, Sharma et al.	Combination of simvastatin and pravastatin inhibited glial cell activation, iNOS and TNF-alpha in MPTP model of PD	Kumar et al. (2012)

4.3. Statins in Huntington disease (HD)

Huntington disease (HD) is a genetically dominant autosomal neurodegenerative disease that is linked with chorea, neuropsychiatric symptoms, cognitive loss, and involuntary moment disorder. The major effects are pronounced because of discriminatory depletion of the medium spiny neurons in the striatum (Karasinska and Hayden, 2011). Huntingtin protein expression is ruled by the presence of the huntingtin gene. HD is produced because of abnormal expansion of the C-A-G (cytosine, adenine, guanine) trinucleotide repeat sequences in the huntingtin gene [HTT] which leads to production of mutant strain of the huntingtin protein (Leoni and Caccia, 2015). The mutant huntingtin protein has a stretched polyglutamine in the N-terminus of the protein. Individuals with more than 36 CAG repeats are prone to develop HD (Rubinsztein et al., 1996; Semaka et al., 2006). The toxicity produced by the mutant protein leads to the HD which is fatal in nature (Vonsattel and DiFiglia, 1998). In many studies it was concluded that the basic pathophysiology of HD involved neuro-inflammation, oxidative stress, mitochondrial malfunctioning and apoptosis. Neuronal death takes place due to the N-methyl-D-aspartate (NMDA) mediated cellular excitotoxicity, presence of reactive oxygen species and the production of oxidative stress. Existence of the reactive oxygen species plays a significant role in the disease progression of HD. The mutant HTT gene is incapable of reverting the oxidatively damaged DNA which leads to the aggregation of

cell debris (Sathasivam et al., 2013). Statins when given for the condition of HD will exhibit their metabolic activity (enhancement in the production of SREBP-2 gene leading to increase in cholesterol synthesis and transport of cholesterol from astrocytes into neurons), immunogenic activity (by lowering serum concentrations of TNF-alpha, IL-1 and reducing neuroinflammation), antioxidant activity (by upregulation of NO synthase), will maintain the order of the cell membrane and protect it against NMDA mediated cellular excitotoxicity, produce neurogenesis by stimulating and enhancing the vascular endothelial growth factor and BDNF and by causing down regulation of ABC transporters from macrophages (reducing the cholesterol efflux from macrophages) (González-Guevara et al., 2020; Karasinska and Hayden, 2011).Thus, it is fairly reasonable to state the repositioning of statins for HD and exploit their pleiotropic effect against inflammation and oxidative stress.

The time at which mutant gene carrier starts expressing the signs of HD is called as Age of Motor Diagnosis (AMD). The typical age at which the symptoms appear is around 30–50 years (Liu et al., 2015). A study was carried out to evaluate whether statin therapy can delay the AMD. They made use of the Enroll- HD dataset to collect patients with pre-motor HD (more than 36 CAG repeats) and with a Diagnostic Confidence Level (DCL) of less than 4. DCL is an indicative parameter of United Huntington's Disease Rating Scale (UHDRS), where a DCL of 4 means, it is 99% confirm that the individual has motor-manifest HD. They compared the data of 85 patients who received statins with 85 other patients who were off statin therapy. They concluded that in patients who were on statin therapy the time for the emergence of the HD symptoms was delayed with respect to patients who were devoid of statin therapy (Schultz et al., 2019).

Another study was performed to check the effect of simvastatin, atorvastatin, and rofecoxib in the rat model infused with malonic acid to induce HD like symptoms. Malonic acid causes mitochondrial dysfunction in the body and was used as oxidative stress inducer. Rofecoxib is a cyclo-oxygenase (COX) inhibitor and they are demonstrated to have neuroprotective actions. Thus, statins and COX inhibitor were studied to validate their effect in HD. It was successfully concluded that rofecoxib in combination with atorvastatin or with simvastatin was synergistically effective in animals treated with malonic acid to induce the behavioral, cellular and biochemical alterations seen in HD (Kumar et al., 2013).

The study performed to assess the efficacy of simvastatin as a neuroprotective agent in the quinolinic acid rat model reported a considerable decrease in the Quinolinic Acid (QA) lesion sizes in animals that were administered simvastatin as compared to animals that were administered vehicle and the frequency of surviving neurons was also more in animals treated with simvastatin. Simvastatin also showed negative-regulation of immunoreactivity for BaX (a pro-apoptotic factor) and positive-regulation of BcL-2 (anti-apoptotic factor) and the BaX/BcL ratio is critical for the survival and positive effect of statins. Simvastatin did not alter brain cholesterol levels, thus proving its positive effectivity. Thus, simvastatin was found effective in treating HD (Patassini et al., 2008).

There is marked reduction and dysfunction of cholesterol biosynthesis in HD. Hence, the utilization of cholesterol lowering compounds in such conditions is questionable. A study was carried out to evaluate the effect of cholesterol metabolism and statin therapy in the progression of HD. Cholesterol metabolism is hindered in HD and the available cholesterol gets accumulated in particular areas leading to an altered cellular distribution of cholesterol. Such areas of dense cholesterol accumulation are also called as lipid rafts which house NMDA receptors. Thus, the order of the membrane (fluidity of the membrane), which is governed by cholesterol concentration in the membrane, will determine the NMDA receptor mediated excitotoxicity of the cell. Simvastatin treatment lead to reduction in the order of plasma membrane, reduction in the lipid rafts and thus protected the cells from NMDA mediated excitation. It was also found that simvastatin did not reduce the total cholesterol levels in the body it just redistributed the available cholesterol to essential parts in the brain. Thus, it was proved that statins did not reduce the cholesterol levels in the brain. But we still need studies to render us sufficient safety data for usage of statins in HD (Thelen et al., 2006). Thus, there is an unmet need of effective clinical studies for validating the efficiency of statins in HD (Karasinska and Hayden, 2011; Valenza et al., 2005).

4.4. Statins in Multiple Sclerosis (MS)

An autoimmune condition of the central nervous system (CNS) that is characterized by demyelination as a result of neuro-inflammation, loss of neuromuscular performance and axonal damage is called as MS. It is more highly observed in young adults and more specifically in women aged between 20 and 50 years (Dendrou et al., 2015). CNS lesions are one of the distinctive features of MS. Inflammatory response is generated against the myelin antigens which is responsible for the disease progression. CD4 and CD8 cells in circulation, recognize the antigens and get activated. They penetrate the CNS, and the T-cells get reactivated and subsequently lead to demyelination and axonal damage. Thus, inhibition of reactivated T and B cells, inhibition of CNS infiltration and inflammation are possible ways to tackle the progression of MS (Ntolkeras et al., 2019). Statins inhibit the generation of mevalonate, the precursor for cholesterol production in the body. Thus, it inhibits the production of Farnesyl pyrophosphate (FPP) and Geranyl Geranyl Pyrophosphate (GGPP). FPP and GGPP are responsible for the isoprenylation and subsequent post-translational activation of Ras, Roh and Rac proteins. These activated proteins are involved in signal transduction, kinase activation, and transcription of proinflammatory cytokines, and chemokines. Thus, statins efficiently inhibit activation and proliferation of T cells, B cells and macrophages, reduces the expression of adhesion molecules and supports remyelination, etc. and thus can prove effective in treating MS either as monotherapy or in combination with already approved drugs for MS (Dendrou et al., 2015; Neuhaus et al., 2003; Pihl-Jensen et al., 2015).

In a study conducted to analyze the efficacy of lovastatin on patients with relapsing or remitting MS, no notable improvement was observed in the MRI, with respect to the gadolinium enhanced T1 lesions, and clinical data. But they were found to be safe for use and their data also suggested the immunomodulatory effects of statins (Sena et al., 2003). Another study was carried out to evaluate the utilization of simvastatin for MS. In this study the average of gadolinium improved lesions were found to drop down by 44% and the lesion volume was decreased by 41% when given simvastatin alone therapy when compared with pretreatment results. The safety of the drug was also confirmed. They observed the inhibitory effect of simvastatin on the inflammatory components involved in MS (Vollmer et al., 2004; Neuhaus et al., 2005; Wang et al., 2011). It is very clear that more clinical trials need to be conducted to analyze the complete potential of statins and their use in MS.

5. Safety concerns

Statins have a well-established safety profile, yet they show few side effects like abdominal pain, flu like symptoms, body rash, diarrhea, increased transaminase levels, nausea, etc. and some of the severe side effects of statins include, myalgia, rhabdomyolysis, hepatic toxicity, muscle toxicity, etc. (Stancu and Sima, 2001). The most typical adverse effect of statin therapy is myopathy which is identified by elevated levels of Creatine Kinase (CK) in the body (10-times higher than normal level) (Thompson et al., 2016). This effect is dose related and gets aggravated when concomitantly administered with drugs that hinder the metabolic fate of statins in the body (Golomb and Evans, 2008). Cytochrome P 3A4 (CYP3A4) is the major contributing enzyme responsible for metabolism of statins. Thus, drugs like erythromycin, cyclosporine, nefazodone, azole antifungals, etc. that are capable of inhibiting CYP3A4 may exasperate the condition (Schachter, 2005). Fibrates or niacin are capable of multiplying the risk of statin induced myopathy by a mechanism other

than rise in concentration of statin in the body (Saravi et al., 2017). If myopathy goes un-recognized and statin therapy is not discouraged then it leads to the development of rhabdomyolysis. The rate of occurrence of rhabdomyolysis in patients receiving cerivastatin therapy was very high, as compared to other statins, which led to the subsequent withdrawal from the market in 2001. Some deleterious effects have been observed with use of statins and their effect on cognitive responses (Caballero and Nahata, 2004). Lovastatin was shown to produce negative effect on the psychomotor speed (Cucchiara and Kasner, 2001). Nocturnal tumescence has also been reported with use of lovastatin and pravastatin (Caballero and Nahata, 2004).

The risk to benefit ratio of statins is very low and all the associated side effects can be reduced and eliminated by the careful administration of the right dose of the correct statin molecule. Frequent monitoring of the CK levels in the patients can help reduce the severe side effects (Weber et al., 2006).

6. Regulatory perspective

Statins which are mandated as HMG-CoA reductase inhibitor are hired to lower the blood cholesterol level which currently are also being utilised in the management of various other disorders owing to its flexible properties. Thus, the repurposing value of statins pose a higher importance. However, to be used as repurposed drug there are specific guidelines and detailed regulation to be followed. The development of repurposed drugs follows 505 (b) (2) approval pathway of Food, Drug and Cosmetic Act which is also known as hybrid NDA. It is a composite version of New Drug Application (NDA) and Abbreviated New Drug Applications (ANDA) under the Hatch-Waxman Amendment which came into force during 1984 (Johnston and Williams, 2002).

The 505 (b) (2) pathway enables the registration of those drug moieties for which minimum one study is mandatory for getting approval, that has not been carried out by the candidate. Therefore, candidate can partly entrust on already existing literature and the data provided by the Food and Drug Administration (FDA) based on the efficacy and safety of the approved drug obtained from clinical and preclinical studies along with their supplementary data. In addition to this, some supporting data are required to make it cost effective and less time consuming. Under this 505 (b) (2), applicant must disclose the novel route for administration or new disease indication of the repurposed drug and comparison profile with the primary route along with indication. This pathway assigns exclusivity of 3–5 years to the applicant if it is a new chemical entity which is more than what applicant will receive if filed for an ANDA approval (180 days only).

On another side, by European Medical Agency (EMA) in Europe, a parallel procedure for approval is regulated, which is under article 10 of directive 2001/83/EC (specifically articles 6, 8(3), 10(3) and 10(5)). Moreover, it does not allow the use of non-proprietary studies containing safety data and high-quality reports as a supportive data for application, which creates contrast to 505 (b) (2). Article 10 does not offer any basis to use non-proprietary studies. It does not accept any new drug only by its definition, or change in form from already approves listed drugs. EMA usually takes additional six months than that of FDA for approval of repurposed drugs. Furthermore, all applications must contain a risk management plan also.

Repurposing under 505(b) (2) application proffers benefits such as low drug developmental cost and time as preclinical and clinical data is available, low risk-benefit ratio along with high profit during the tenure of market exclusivity (Smith, 2011; Witkowski, 2011).

7. Conclusion

Apart from the lipid lowering activity of statins, they have shown significant positive outcomes in neurodegenerative disorders. The review briefly discusses the possible mechanism through which statins are reutilised for treating AD, PD, HD and MS. Statins predominantly exerts anti-oxidant and anti-inflammatory action, thereby acting as neuroprotectant maintaining oxidative balance. Moreover, human clinical trials portrayed a contradictory behavior especially in PD trial. Clinical trials failed to incorporate the various factors and confounding effects were observed. Lack of validated animal model led to confusing results in preclinical studies Therefore, a more exhaustive trial should be performed while taking all possible factors into consideration to achieve a robust data with proper methodologies. Repurposing however weighs some disadvantages, including shortage of the new molecular entities in pipeline and Intellectual Property related issues. Statins are accompanied with certain toxicity issues and safety concerns were discussed briefly in the review article. There exist still a need of good regulatory guidelines suggesting drug repositioning by various health authorities. Further research should propose complete knowledge of the efficacy of statins along with thorough information about the mechanism and pathways involved in disease progression of neurodegenerative diseases which will effectively reduce the economic burden on health care commodities and maximise healthcare outcomes.

Funding

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Aditi Bhat: Conceptualization, Writing - original draft, Methodology, Writing - review & editing, contributed equally to the script. **Harshita Dalvi:** Conceptualization, Writing - original draft, Methodology, Writing - review & editing, contributed equally to the script. **Harsha Jain:** Methodology, Writing - review & editing. **Nagarjun Rangaraj:** Writing - review & editing. **Shashi Bala Singh:** Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The authors would like to thank Department of pharmaceutics-NIPER Hyderabad for providing guidance and support while drafting of the review article.

References

Appleby, B.S., et al., 2013. A review: treatment of Alzheimer's disease discovered in repurposed agents. Dement. Geriatr. Cognit. Disord. 35 (1–2), 1–22. https://doi.org/10.1159/000345791.

Athauda, D., Foltynie, T., 2018. Drug repurposing in Parkinson's disease. CNS Drugs 32 (8), 747–761. https://doi.org/10.1007/s40263-018-0548-y.

Bar-On, P., et al., 2008. Statins reduce neuronal α-synuclein aggregation in in vitro models of Parkinson's disease. J. Neurochem. 105 (5), 1656–1667. https://doi.org/10.1111/j.1471-4159.2008.05254.x.

Becker, C., Meier, C.R., 2009. Statins and the risk of Parkinson disease: an update on the controversy. Expet Opin. Drug Saf. 8 (3), 261–271. https://doi.org/10.1517/14740330902859956.

Becker, C., Jick, S.S., Meier, C.R., 2008. Use of statins and the risk of Parkinson's disease. Drug Saf. 31 (5), 399–407. https://doi.org/10.2165/00002018-200831050-00004.

Benarroch, E.E., 2008. Brain cholesterol metabolism and neurologic disease. Neurology 71 (17), 1368–1373. https://doi.org/10.1212/01.wnl.0000333215.93440.36.

Berman, T., Bayati, A., 2018. What are neurodegenerative diseases and how do they affect the brain. Front. Young Minds. 6, 70. https://doi.org/10.3389/frym.2018.00070.

Caballero, J., Nahata, M., 2004. Do statins slow down Alzheimer's disease? A review. J. Clin. Pharm. Therap. 29 (3), 209–213. https://doi.org/10.1111/j.1365-2710.2004.00560.x.

Carroll, C.B., Wyse, R.K., 2017. Simvastatin as a potential disease-modifying therapy for patients with Parkinson's disease: rationale for clinical trial, and current progress. J. Parkinsons Dis. 7 (4), 545–568. https://doi.org/10.3233/JPD-171203.

Cucchiara, B., Kasner, S.E., 2001. Use of statins in CNS disorders. J. Neurol. Sci. 187 (1–2), 81–89. https://doi.org/10.1016/S0022-510X(01)00529-9.

Cummings, J.L., Zhong, K., 2014. Repackaging FDA-approved drugs for degenerative diseases: promises and challenges. Expert Rev. Clin. Pharmacol. 7 (2), 161–165. https://doi.org/10.1586/17512433.2014.884923.
Dendrou, C.A., Fugger, L., Friese, M.A., 2015. Immunopathology of multiple sclerosis. Nat. Rev. Immunol. 15 (9), 545–558. https://doi.org/10.1038/nri3871.
Dexter, D.T., Jenner, P., 2013. Parkinson disease: from pathology to molecular disease mechanisms. Free Radical Biol. Med. 62, 132–144. https://doi.org/10.1016/j.freeradbiomed.2013.01.018.
Doria, M., et al., 2016. Contribution of cholesterol and oxysterols to the pathophysiology of Parkinson's disease. Free Radical Biol. Med. 101, 393–400. https://doi.org/10.1016/j.freeradbiomed.2016.10.008.
Durães, F., Pinto, M., Sousa, E., 2018. Old drugs as new treatments for neurodegenerative diseases. Pharmaceuticals 11 (2), 44. https://doi.org/10.3390/ph11020044.
Endo, A., 2010. A historical perspective on the discovery of statins. Proc. Jpn. Acad. Series B. 86 (5), 484–493. https://doi.org/10.2183/pjab.86.484.
Frears, E.R., et al., 1999. The role of cholesterol in the biosynthesis of β-amyloid. Neuroreport 10 (8), 1699–1705 [DOI not available].
Friedhoff, L.T., et al., 2001. Treatment with controlled-release lovastatin decreases serum concentrations of human β-amyloid (A β) peptide. Int. J. Neuropsychopharmacol. 4 (2), 127–130. https://doi.org/10.1017/S1461145701002310.
Ghodke, R.M., Tour, N., Devi, K., 2012. Effects of statins and cholesterol on memory functions in mice. Metabolic Brain Dis 27 (4), 443–451. https://doi.org/10.1007/s11011-012-9343-5.
Ghosh, A., et al., 2009. Simvastatin inhibits the activation of p21ras and prevents the loss of dopaminergic neurons in a mouse model of Parkinson's disease. J. Neurosci. 29 (43), 13543–13556. https://doi.org/10.1523/JNEUROSCI.4144-09.2009.
Goedert, M., 1993. Tau protein and the neurofibrillary pathology of Alzheimer's disease. Trends Neurosci. 16 (11), 460–465. https://doi.org/10.1016/0166-2236(93)90078-Z.
Golomb, B.A., Evans, M.A., 2008. Statin adverse effects. Am. J. Cardiovasc. Drugs 8 (6), 373–418. https://doi.org/10.2165/0129784-200808060-00004.
González-Guevara, E., et al., 2020. Dysregulated brain cholesterol metabolism is linked to neuroinflammation in huntington's disease. Mov. Disord. https://doi.org/10.1002/mds.28089.
Hilbush, B.S., et al., 2005. New prospects and strategies for drug target discovery in neurodegenerative disorders. NeuroRx 2 (4), 627–637. https://doi.org/10.1602/neurorx.2.4.627.
Huang, X., et al., 2015. Statins, plasma cholesterol, and risk of Parkinson's disease: a prospective study. Mov. Disord. 30 (4), 552–559. https://doi.org/10.1002/mds.26152.
Huang, X., et al., 2019. Brain cholesterol metabolism and Parkinson's disease. Mov. Disord. 34 (3), 386–395. https://doi.org/10.1002/mds.27609.
Jick, H., et al., 2000. Statins and the risk of dementia. Lancet 356 (9242), 1627–1631. https://doi.org/10.1016/S0140-6736(00)03155-X.
Johnston, G., Williams, R.L., 2002. 505 (b)(2) applications: history, science, and experience. Drug Inf. J. 36 (2), 319–323. https://doi.org/10.1177/009286150203600210.
Kang, J., Rivest, S., 2012. Lipid metabolism and neuroinflammation in Alzheimer's disease: a role for liver X receptors. Endocrine Rev 33 (5), 715–746. https://doi.org/10.1210/er.2011-1049.
Karasinska, J.M., Hayden, M.R., 2011. Cholesterol metabolism in Huntington disease. Nat. Rev. Neurol. 7 (10), 561. https://doi.org/10.1038/nrneurol.2011.132.
Kumar, A., et al., 2012. Neuroprotective potential of atorvastatin and simvastatin (HMG-CoA reductase inhibitors) against 6-hydroxydopamine (6-OHDA) induced Parkinson-like symptoms. Brain Res. 1471, 13–22. https://doi.org/10.1016/j.brainres.2012.06.050.
Kumar, A., et al., 2013. Synergistical neuroprotection of rofecoxib and statins against malonic acid induced Huntington's disease like symptoms and related cognitive dysfunction in rats. Eur. J. Pharmacol. 709 (1–3), 1–12. https://doi.org/10.1016/j.ejphar.2013.03.042.
Leoni, V., 2009. Oxysterols as markers of neurological disease–a review. Scandinavian J. Clin. and Lab. Invest. 69 (1), 22–25. https://doi.org/10.1080/00365510802651858.
Leoni, V., Caccia, C., 2015. The impairment of cholesterol metabolism in Huntington disease. Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1851 (8), 1095–1105. https://doi.org/10.1016/j.bbalip.2014.12.018.
Leoni, V., et al., 2006. Are the CSF levels of 24S-hydroxycholesterol a sensitive biomarker for mild cognitive impairment? Neurosci. Lett. 397 (1–2), 83–87. https://doi.org/10.1016/j.neulet.2005.11.046.
Liu, D., et al., 2015. Motor onset and diagnosis in Huntington disease using the diagnostic confidence level. J. Neurol. 262 (12), 2691–2698. https://doi.org/10.1007/s00415-015-7900-7.
Lukiw, W.J., 2012. Amyloid beta (Aβ) peptide modulators and other current treatment strategies for Alzheimer's disease (AD). Expet Opin. Emerg. Drugs 17 (1), 43–60. https://doi.org/10.1517/14728214.2012.672559.
Manickavasagam, D., Lin, L., Oyewumi, M.O., 2020. Nose-to-brain co-delivery of repurposed simvastatin and BDNF synergistically attenuates LPS-induced neuroinflammation. Nanomed. Nanotechnol. Biol. Med. 23, 102107. https://doi.org/10.1016/j.nano.2019.102107, 102107.
Maron, D.J., Fazio, S., Linton, M.F., 2000. Current perspectives on statins. Circulation 101 (2), 207–213. https://doi.org/10.1161/01.CIR.101.2.207.
Mitchel, Y., et al., 1995. The effect of simvastatin on cerebrospinal fluid levels of apolipoprotein E in patients with Alzheimer's disease. Atherosclerosis 115, S113. https://doi.org/10.1016/0021-9150(95)96682-I.
Neuhaus, O., Archelos, J., Hartung, H., 2003. Statins in Multiple Sclerosis: a New Therapeutic Option? Sage Publications, Sage CA: Thousand Oaks, CA. https://doi.org/10.1191/1352458503ms952ed.
Neuhaus, O., et al., 2005. Putative mechanisms of action of statins in multiple sclerosis–comparison to interferon-β and glatiramer acetate. J. Neurol. Sci. 233 (1–2), 173–177. https://doi.org/10.1016/j.jns.2005.03.030.
Ntolkeras, G., et al., 2019. On the immunoregulatory role of statins in multiple sclerosis: the effects on Th17 cells. Immunol. Res. 1–15. https://doi.org/10.1007/s12026-019-09089-5.
Overmyer, M., et al., 2000. DNA fragmentation, gliosis and histological hallmarks of Alzheimer's disease. Acta Neuropathol. 100 (6), 681–687. https://doi.org/10.1007/s004010000228.
Paranjpe, M.D., Taubes, A., Sirota, M., 2019. Insights into computational drug repurposing for neurodegenerative disease. Trends Pharmacol. Sci. 40 (8), 565–576. https://doi.org/10.1016/j.tips.2019.06.003.
Patassini, S., et al., 2008. Effects of simvastatin on neuroprotection and modulation of Bcl-2 and BAX in the rat quinolinic acid model of Huntington's disease. Neurosci. Lett. 448 (1), 166–169. https://doi.org/10.1016/j.neulet.2008.10.023.
Pihl-Jensen, G., Tsakiri, A., Frederiksen, J.L., 2015. Statin treatment in multiple sclerosis: a systematic review and meta-analysis. CNS Drugs 29 (4), 277–291. https://doi.org/10.1007/s40263-015-0239-x.
Prusiner, S.B., 2001. Neurodegenerative diseases and prions. N. Engl. J. Med. 344 (20), 1516–1526. https://doi.org/10.1056/NEJM200105173442006.
Ramirez, C., et al., 2011. Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxicity and memory impairment. J. Alzheim. Dis. 24 (1), 161–174. https://doi.org/10.3233/JAD-2010-101653.
Rubinsztein, D.C., et al., 1996. Phenotypic characterization of individuals with 30–40 CAG repeats in the Huntington disease (HD) gene reveals HD cases with 36 repeats and apparently normal elderly individuals with 36–39 repeats. Am. J. Hum. Genet. 59 (1), 16 ([DOI not available]).
Saravi, S.S.S., et al., 2017. The beneficial effects of HMG-CoA reductase inhibitors in the processes of neurodegeneration. Metabolic Brain Dis 32 (4), 949–965. https://doi.org/10.1007/s11011-017-0021-5.
Sathasivam, K., et al., 2013. Aberrant splicing of HTT generates the pathogenic exon 1 protein in Huntington disease. Proc. Natl. Acad. Sci. Unit. States Am. 110 (6), 2366–2370. https://doi.org/10.1073/pnas.1221891110.
Schachter, M., 2005. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update. Fund. Clin. Pharmacol. 19 (1), 117–125. https://doi.org/10.1111/j.1472-8206.2004.00299.x.
Schultz, J.L., et al., 2019. Statin use and delayed onset of Huntington's disease. Mov. Disord. 34 (2), 281–285. https://doi.org/10.1002/mds.27591.
Selley, M.L., 2005. Simvastatin prevents 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine-induced striatal dopamine depletion and protein tyrosine nitration in mice. Brain Res. 1037 (1–2), 1–6. https://doi.org/10.1016/j.brainres.2004.02.083.
Semaka, A., et al., 2006. Predictive testing for Huntington disease: interpretation and significance of intermediate alleles. Clin. Genet. 70 (4), 283–294. https://doi.org/10.1111/j.1399-0004.2006.00668.x.
Sena, A., Pedrosa, R., Morais, M.G., 2003. Therapeutic potential of lovastatin in multiple sclerosis. J. Neurol. 754–755. https://doi.org/10.1007/s00415-003-1070-8.
Shoulson, I., 1998. Experimental therapeutics of neurodegenerative disorders: unmet needs. Science 282 (5391), 1072–1074. https://doi.org/10.1126/science.282.5391.1072.
Sirtori, C.R., 2014. The pharmacology of statins. Pharmacol. Res 88, 3–11. https://doi.org/10.1016/j.phrs.2014.03.002.
Smith, R.B., 2011. Repositioned drugs: integrating intellectual property and regulatory strategies. Drug Discov. Today Ther. Strat. 8 (3–4), 131–137. https://doi.org/10.1016/j.ddstr.2011.06.008.
Smith, M.A., et al., 2000. Oxidative stress in Alzheimer's disease. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1502 (1), 139–144. https://doi.org/10.1016/S0925-4439(00)00040-5.
Stancu, C., Sima, A., 2001. Statins: mechanism of action and effects. J. Cell. Mole. Med. 5 (4), 378–387. https://doi.org/10.1111/j.1582-4934.2001.tb00172.x.
Stanzione, P., Tropepi, D., 2011. Drugs and clinical trials in neurodegenerative diseases. Annali dell'Istituto superiore di sanità 47, 49–54. https://doi.org/10.4415/ANN_11_01_11.
Thelen, K.M., et al., 2006. Brain cholesterol synthesis in mice is affected by high dose of simvastatin but not of pravastatin. J. Pharmacol. Exp. Therapeut. 316 (3), 1146–1152. https://doi.org/10.1124/jpet.105.094136.
Thompson, P.D., et al., 2016. Statin-associated side effects. JACC (J. Am. Coll. Cardiol.) 67 (20), 2395–2410. https://doi.org/10.1016/j.jacc.2016.02.071.
Tobert, J.A., 2003. Lovastatin and beyond: the history of the HMG-CoA reductase inhibitors. Nat. Rev. Drug Discov. 2 (7), 517–526. https://doi.org/10.1038/nrd1112.
Valenza, M., et al., 2005. Dysfunction of the cholesterol biosynthetic pathway in Huntington's disease. J. Neurosci. 25 (43), 9932–9939. https://doi.org/10.1523/JNEUROSCI.3355-05.2005.
Vollmer, T., et al., 2004. Oral simvastatin treatment in relapsing-remitting multiple sclerosis. Lancet 363 (9421), 1607–1608. https://doi.org/10.1016/S0140-6736(04)16205-3.
Vonsattel, J.P.G., DiFiglia, M., 1998. Huntington disease. J. Neuropathol. Exp. Neurol. 57 (5), 369 ([DOI not available]).
Wang, J., et al., 2011. Statins for multiple sclerosis. Cochrane Database Syst. Rev. (12) https://doi.org/10.1002/14651858.CD008386.pub3.
Wang, W.-Y., et al., 2015. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann. Transl. Med. 3 (10) https://doi.org/10.3978/j.issn.2305-5839.2015.03.49.
Weber, M.S., et al., 2006. Statins in the treatment of central nervous system autoimmune disease. J. Neuroimmunol. 178 (1–2), 140–148. https://doi.org/10.1016/j.jneuroim.2006.06.006.

Witkowski, T.X., 2011. Intellectual property and other legal aspects of drug repurposing. Drug Discov. Today Ther. Strat. 8 (3–4), 139–143. https://doi.org/10.1016/j.ddstr.2011.06.007.

Wolozin, B., et al., 2000. Decreased prevalence of Alzheimer disease associated with 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors. Arch. Neurol. 57 (10), 1439–1443. https://doi.org/10.1001/archneur.57.10.1439.

Zhang, J., Liu, Q., 2015. Cholesterol metabolism and homeostasis in the brain. Protein & cell 6 (4), 254–264. https://doi.org/10.1007/s13238-014-0131-3.

Zhao, Z., et al., 2010. Lovastatin improves neurological outcome after nucleus basalis magnocellularis lesion in rats. Neuroscience 167 (3), 954–963. https://doi.org/10.1016/j.neuroscience.2010.02.054.