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Review Article

Beneficial Effects of Statins on Seizures Independent of Their Lipid-Lowering Effect: A Narrative Review

Arash Amanlou[1], DVM; Ehsan Nassireslami[2,3], PhD; Ahmad Reza Dehpour[1,4], PhD; Amir Rashidian[1,4], PhD; Mohsen Chamanara[2,3], PhD

[1]Experimental Medicine Research Center, Tehran University of Medical Sciences, Tehran, Iran;
[2]Department of Pharmacology, School of Medicine, AJA University of Medical Sciences, Tehran, Iran;
[3]Toxicology Research Center, AJA University of Medical Sciences, Tehran, Iran;
[4]Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Correspondence:
Mohsen Chamanara, PhD;
School of Medicine, AJA University of Medical Sciences, Fatemi-Gharbi St., Etemad Zadeh St., P.O. Box: 14117-18541, Tehran, Iran
Tel/Fax: +98 21 43822401
Email: chamanaramohsen@gmail.com
Amir Rashidian, PhD;
Experimental Medicine Research Center, Tehran University of Medical Sciences, Poursina St., Keshavarz Blvd., P.O. Box: 13145-784, Tehran, Iran
Tel/Fax: +98 21 66402569
Email: amirrashidian@yahoo.com
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Abstract

Among the many types of central nervous system (CNS) disorders, seizures and epilepsy severely affect the quality of life and routine daily activity of the sufferers. We aimed to review research studies that investigated the effect of statins on the prevention and treatment of seizures and epilepsy. Both animal models and human studies were included in this review. This article starts with a brief introduction about seizure, its prevalence, treatment, and various animal models of seizures and epilepsy. Next, we discuss statin's mechanism of action, side effects, and effects on neurological disorders with a specific focus on seizures. Finally, the effects of different types of statins on seizures are compared. The present review gives a better understanding of the therapeutic effects of statins on neurological disorders in animal models and human studies. This permits researchers to set up study designs to resolve current ambiguities and contradictions on the beneficial effects of statins on neurological disorders.

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What's Known

- Seizures and epilepsy severely affect the routine daily activity of the sufferers. Over 75% of patients with epilepsy do not receive proper therapy and medications due to treatment inefficacy or drug resistance.
- Studies suggest that statins, primarily used as a lipid-lowering drug, may have beneficial effects on neurological diseases.

What's New

- The effect of statins on seizures is independent of their cholesterol-lowering properties, which is partially due to the involvement of the nitric oxide pathway.
- Statins' primary mechanism of action is by reducing the expression levels of tumor necrosis factor-alpha, and interleukin-1, as well as inflammatory mediators produced in the brain.

Introduction

Among the many types of central nervous system (CNS) disorders, seizures and epilepsy have a drastic impact on the quality of life of the sufferers, and their routine daily activities are subject to limitations. People with a history of brain diseases such as traumatic brain injuries, brain tumors, and stroke have between a 10% and 30% higher risk of developing seizures and epilepsy.[1] Worldwide, more than 70 million people suffer from epilepsy, of which about 90% live in developing countries. It is estimated that about 75% of patients with epilepsy do not receive proper therapy and medications. Infection of the CNS and brain injury can cause epilepsy. Some of the known risk factors for epilepsy are strokes, vascular malformations, and a family history of seizures. Conditions associated with epilepsy are autism, migraine, depression, and cerebral palsy, as well as viral infections, and parasitic diseases.[2] There are many seizure classifications, including that of the International League Against Epilepsy (ILAE), which categorizes seizures into three types, namely seizures with focal onset, generalized onset, and unknown onset. In the case of seizures with focal onset, patients can be aware or have impaired awareness during the onset of

motor or nonmotor symptoms.[3] The etiology of epilepsy is categorized into six subgroups, namely genetic, infectious, immune, metabolic, structural, and unknown.[4]

Treatment

Seizures are treated using different types of drugs, each with a different mechanism of action. However, not all types of seizures can be treated with medication. Therefore, the development of alternative treatments is essential.[5] Drugs that are generally prescribed for different types of seizures include benzodiazepines, carbamazepine, clobazam, clonazepam, ethosuximide; felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital; phenytoin, pregabalin, primidone, rufinamide, tiagabine, topiramate, valproic acid, vigabatrin, and zonisamide.[4, 5] Patients taking any of these drugs may experience one or more side effects to varying degrees, such as ataxia, dizziness, headache, nausea, rash, tremor, vomiting, weight loss or gain, and so on. Moreover, some of these side effects are specific to some of the above-mentioned drugs.[5] Factors that influence therapeutic efficacy are age, sex, type of epilepsy and its etiology, family history, and medication history.[4] Anti-epileptic drugs target the mechanisms causing epilepsy, including variations in Ca^{2+} concentrations, the elevation of postsynaptic glutamate receptors, reduction of gamma-aminobutyric acid, and changes in K^+ and Na^+ levels.[5]

Animal Models

Different animal models are used to simulate seizures and epilepsy in humans, including methods such as chemo-convulsive stimulants, electrical stimulation, and genetic models. Some of the well-known animal models are corneal kindling in mice, pentylenetetrazole (PTZ), pilocarpine, and amygdala kindling. The pilocarpine-induced status epilepticus (SE) rat model is a simulation of temporal lobe epilepsy (TLE), widely used as an experimental model to study how SE affects the brain, which regions are mainly affected, and the mechanisms involved.[6, 7] Maximal electroshock (MES) and 6 Hz electrical stimulation are the two rodent models to simulate seizures in humans. PTZ is applied through intraperitoneal or intravenous injection to induce seizures in mice.[7] In the case of pilocarpine-induced SE rat models, the most affected regions in the hippocampus with significant cell loss include the hilus of the dentate gyrus (DG) and pyramidal cell layer (cornu ammonis 1 [CA1] and cornu ammonis 3 [CA3]).[6] Another model used to simulate TLE is the kainic acid (KA) model in rats. Both pilocarpine and KA models cause limbic SE and tonic-clonic seizures.[8] Similar to the KA model, the amygdala kindling rat model is a chronic seizure model for the simulation of TLE.[7]

Statins

3-hydroxy-3-methylglutaryl-coenzyme a (HMG-CoA) reductase inhibitors, better known as statins, are lipid-lowering drugs used in patients at risk of cardiovascular diseases. They are also used for different types of neurological disorders such as epilepsy, Parkinson's disease, multiple sclerosis, depression, dementia, stroke, Alzheimer's disease, cerebral ischemia, tumors, and trauma. Commercially available statins are atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, rosuvastatin, and simvastatin.[9-12] Lovastatin reduces neuronal cell death in the CA1 region of the hippocampus caused by pilocarpine-induced SE.[6] Pravastatin has relatively mild protein binding (50%) compared to 90-98% for other statins. Rosuvastatin and pravastatin are hydrophilic, whereas atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin are lipophilic. Statins are primarily cleared through fecal and less through renal secretion.[12]

Mechanism of Action

Statins' primary mechanism of action is to decrease low-density lipoprotein levels through inhibition of the enzyme HMG-CoA.[11] The effect of statins mainly occurs in the liver by lowering the production of cholesterol.[13, 14] In addition to inhibiting HMG-CoA reductase, statins are used as anti-inflammatory and neuroprotective drugs.[15] Another mechanism of action of statins is inhibition of the mevalonate pathway by preventing the conversion of HMG-CoA to mevalonate.[16] Anti-inflammatory and anti-atherosclerotic effects are the two major pleiotropic effects of statins. Chronic statin therapy can halt neuron apoptosis, as in dopaminergic neurons, due to its anti-inflammatory and anti-oxidative stress properties. Statins also interact with dopaminergic neurotransmitters and affect cholinergic, serotoninergic, and glutamatergic neurotransmitters.[17] The anti-atherosclerotic effect of statins is explained by their effect on endothelial cells, vascular smooth muscle cells, platelets, and immune cells.[18] Statins have also been widely used in the treatment of graft-versus-host disease (GVHD), systemic lupus erythematosus, multiple sclerosis, and rheumatoid arthritis. However, the effect of statin therapy in different diseases depends on the type of statin used.[19]

Statins have anti-oxidant effects by reducing reactive oxygen species (ROS) and their immunomodulatory properties.[20] They also have antithrombotic and endothelial stabilizing properties.[21] Statins are believed to play a role in coagulation procedures by decreasing platelet aggregation, reducing thrombin formation, and enhancing clot lysis.[20] One of the important pleiotropic effects of statins is increased nitric oxide (NO), which leads to increased cerebral perfusion. They also inhibit isoprenylation of RhoA GTPase, which in turn increases NO production by endothelial nitric oxide synthase (eNOS). Activation of nuclear factor-kappa B (NF-kB) will be inhibited, which affects inflammatory gene transcription.[20] In addition to affecting cholesterol levels, statins can upregulate eNOS, also known as NOS3 expression.[22] Some studies reported the beneficial effect of statins in patients with Alzheimer's disease.[22, 23] There is an association between ischemic stroke, the bioavailability of NO, and the activity of statins. Statins can help patients at risk of vascular-related disease by reducing the risk of ischemic stroke. Some experimental research indicated the protective effects of statins in acute cerebral ischemia.[22] Statins alter the expression of eNOS, and its pleiotropic effects have some benefits for the cardiovascular system.[24] Pravastatin, a type of statin, can reduce C-reactive protein levels.[25]

Side Effects

The beneficial effects of statins in the prevention of various diseases have been widely reported, and many patients around the world consider statins to be a safe drug with minimum side effects. However, some patients prematurely discontinue statin therapy due to certain adverse side effects.[26, 27] Some of these side effects could be due to the general health of patients or may not occur until prolonged use. The side effects could also be due to the interaction of statins with other medications. Physicians should pay attention to these issues and consider prescribing other statins or drugs.

Among some of the known anti-epileptic drugs, the most prevalent side effects are drug interactions, sedation, amnesia, hair loss, nervousness, paresthesia, and tingling of extremities.[28] Several predisposing factors are involved in the adverse effects of statins, such as genetic mutations related to mitochondrial dysfunction, sex, and statin dose-dependent effect. Moreover, underlying diseases (e.g., diabetes), metabolic syndrome risk factors, thyroid, and other diseases should be considered.[9] Myalgia is the most common side effect of statins with a prevalence ranging from 1% to 10%. One of the most severe side effects is rhabdomyolysis. However, it is very rare with a prevalence of less than 0.1%.[11] Risk factors associated with statin-related myopathy include alcohol abuse, hypothyroidism, and polypharmacy. Other risk factors associated with statins toxicity include age over 80, female sex, and diseases such as chronic liver disease, diabetes, and chronic kidney disease. Liver damage is another reported side effect of statins that might affect 1% of patients.[11]

Some statins are diabetogenic, and the risk of diabetogenicity increases in patients taking higher doses. Of the statins, only pitavastatin does not increase the risk of diabetes. Drugs that interact with cytochrome p450 may interact with statins, giving patients the best medication with lower side effects.[11] Moreover, statins inhibit the synthesis of isoprenoids.[29] Statins are also associated with musculoskeletal side effects. In this regard, myositis is less common than myalgia, as it increases creatine kinase. Pitavastatin is commonly prescribed in Asia, and thus the reported data may not be generalized to a larger population. Besides, the prevalence of these side effects varies greatly due to the different methods of data collection, and how the studies were conducted. Therefore, the choice of prescribing statins cannot just be based on the reported prevalence rates of side effects. Considering a cost-benefit analysis approach, it is evident that statins are safe for the majority of patients, and the disadvantages associated with risk factors are much lower than the protective benefits of statin therapy.[11]

Depending on patients' condition and their response to a single drug, polytherapy based on different treatment strategies should be considered.[30] Sometimes two drugs are combined to lower the individual drug dosage (i.e., reduce their side effects) or to reduce treatment costs. In addition, prescribing different drugs with different mechanisms of action may yield better results. In situations when monotherapy fails, physicians may opt for polypharmacy drug treatment.[30] Rhabdomyolysis is one of the most serious adverse effects of statin therapy, which at times could be fatal.[9, 31] Statin-related myopathies usually occur when statins are prescribed in high doses or combined with other drugs that share the same metabolic pathway, e.g., nicotinic acid and fibrates (especially gemfibrozil). Knowledge of drug interactions, and their specific metabolic pathway, as well as choosing the right treatment program will deliver the best outcome and provide more comfort to patients.[9, 31, 32]

Effects on Neurological Disorders

The role of statins in certain diseases is not well-understood yet. However, some of the suggested mechanisms may be beneficial to patients and their illnesses. Statins can reduce the inflammatory response and secondary injury caused by acute ischemia.[22, 23] Inflammation is one of the consequences of epilepsy.[33] Excitotoxicity is a condition caused by the overstimulation of glutamate receptors, which is responsible for neuronal death in some neurological diseases such as epilepsy and Alzheimer's disease.[10] Some reports stated the therapeutic potential of statins in CNS diseases such as epilepsy, multiple sclerosis, depression, dementia, and stroke. However, the exact mechanism, pathway, and how statins protect the brain against diseases are not clear. More investigation is required to fully understand the role of statins in helping patients with CNS-related diseases to provide them with optimal therapeutic intervention.[12]

Some studies reported the beneficial effect of statins in diseases such as depression and schizophrenia. In contrast, other studies claimed that statin therapy did not have any benefits for patients suffering from neurological disorders and neurodegenerative diseases.[34] Different statins can influence the expression of various genes.[23] Statin therapy may help patients with cognitive disorders by increasing the expression of nerve growth factors. However, current data are limited to *in vitro* and *in vivo* studies, and the results of some clinical trials have shown no beneficial effect of statins on cognition. As for Alzheimer's disease, several *in vitro* and *in vivo* studies have reported that statin therapy helps patients with this disease provided that at the start of the treatment the patient is not of old age, and there is no evidence of cognitive disorders. The suggested mechanism of action of statins in Alzheimer's disease is by reducing neuroinflammation, reactive oxygen species (ROS), and amyloid-β production, while increasing amyloid-β degradation. However, it seems that the results of these studies depend on the setup of the experimental model and should be interpreted with caution.[12] Among all statins, atorvastatin seems to reduce the risk of Parkinson's disease by preventing dopaminergic neurons from deterioration. However, the reported effect is not significant.[35] The suggested statins' mechanism of action in Parkinson's disease is the reduction of NO, ROS, neuroinflammation, neuronal loss, NF-kB activity, and lipid peroxidation. Despite the availability of various *in vivo* and *in vitro* studies, clinical trials should be performed to confirm the primary data.[12] Results of retrospective cohort studies on both ischemic and hemorrhagic strokes indicated that statins can reduce the risk of acute symptomatic poststroke seizures.[36] Various *in vivo*, *in vitro*, and meta-analysis studies, as well as randomized controlled trials showed the beneficial effect of statins on stroke. The suggested mechanism of action in stroke is by reducing NO, ROS, and modulation of eNOS.[12] In multiple sclerosis, it is believed that statins reduce the modulation of NF-kB activity. However, some *in vivo* and *in vitro* studies have reported contradictory results.

Effect on Seizures

GABAergic reduction and elevated glutamatergic activity are the two mechanisms that cause brain damage and neuronal cell death in seizures.[37] The nitrergic system is believed to be involved in the effect of statins on epilepsy.[33] A previous study reported the neuroprotective properties of statins. Besides reducing cholesterol levels, the effect of statins can be associated with an increase in NO production. In the treatment of patients with statins, improvement of endothelium is one of its initial effects. Different statins require different treatment periods before any effect could be observed.[22] While statins reduce blood lipids, their effect and mechanism of action on CNS seem to be independent of their cholesterol-lowering property, or at least it is not the early mechanism of action. It is believed that statins have pleiotropic effects. For example, an animal study showed that statins lowered cholesterol levels in the brain cerebral cortex. However, simvastatin did not significantly reduce cholesterol levels in the mice treated group compared to the control group. In contrast, mice receiving pravastatin showed significantly lower cholesterol levels in the brain that the control group.[23]

Mossy fiber sprouting (MFS) in the DG is correlated with the frequency of spontaneous recurrent seizures and the severity of TLE.[38] The exact molecular mechanism of MFS is, however, not fully understood. Collapsing responsive mediator protein-2 (CRMP-2) is responsible for axonal growth and neuronal polarity in the hippocampus. After inducing a seizure in rats, there was an increase in the expression levels of glycogen synthase kinase-3 beta (GSK-3β) and CRMP-2. It was shown that the administration of lovastatin reversed this effect and led to a significant reduction of the area of MFS in the DG and CA3 region of the hippocampus. Lovastatin modified the GSK-3β pathway and inhibited MFS following pilocarpine-induced SE.[38]

Effects of Different Types of Statins on Seizures

Animal models and clinical studies have shown the neuroprotective properties of statins. For example, it was shown that atorvastatin inhibited KA-induced apoptosis (table 1). In addition, atorvastatin attenuates seizure activities, neuronal cell death in the hippocampus, pro-inflammatory gene expression, and infiltration of monocytes. It was shown that the CA1 and CA3 regions of the hippocampus in the rat brain were less damaged by atorvastatin pretreatment in KA-induced seizures.[15] In SE and traumatic brain injury, the DG and CA3 regions of the hippocampus are most affected. A previous animal study on post-traumatic brain injury reported that atorvastatin and simvastatin increased neurogenesis in the DG, reduced delay in neuronal cell death in the CA3 region of the hippocampus, and improved spatial learning in rats.[39] Another study showed that statins inhibit KA-induced seizures and associated inflammation and hippocampal cell death. KA is a model used to simulate TLE and excitotoxic neurodegeneration.[15] Another study on the effect of statins on the cerebral cortex of mice reported that 21 days of treatment with lovastatin, simvastatin, and pravastatin significantly altered the expression of 15 genes. The results showed that simvastatin altered 38 genes followed by lovastatin (26 genes), and pravastatin (21 genes). These genes were grouped into three main categories, namely signaling, trafficking, and cell growth. By determining which genes play a more important role in which diseases, novel drugs can be developed to effectively alter gene expression in patients with various other diseases.[23]

Simvastatin

It has been reported that simvastatin can suppress chronic TLE after KA-induced SE.[40] Treatment with simvastatin reduces the expression of tumor necrosis factor-alpha (TNF-α) and interleukin (IL-1β). However, it does not change the expression of interleukin-6 (IL-6) in the hippocampus. Simvastatin also reduces the frequency of abnormal spikes in the electroencephalography of rats with SE.[40] In another seizure model (picrotoxin-induced seizure in mice), administration of simvastatin (10 mg/Kg) significantly reduced the duration and the number of mice showing signs of seizures.[37] Simvastatin doses of 10, 20, and 40 mg/Kg reduced the total amount of abnormal pyramidal cells in the CA1 and CA3 regions of the hippocampus compared to picrotoxin.[37] Another study showed that atorvastatin protected both male and female mice (C57BL/6 mice) against PTZ-induced seizures on day 14 after SE. However, the effect was subtle.[41]

Simvastatin is a lipophilic statin that can cross the blood-brain barrier. However, atorvastatin is shown to be ineffective in electrically-induced seizure models. On the other hand, in a chemically-induced seizure, atorvastatin exhibited anticonvulsant effects. Chronic administration of low doses of atorvastatin (maximum of 10 mg/Kg) inhibited KA- and PTZ-induced seizures. In contrast, acute atorvastatin therapy at a dose of 50 mg/Kg exhibited proconvulsant effects. Higher doses of atorvastatin (80-100 mg/Kg) are shown to be effective against audiogenic seizures.[42] Among all statins, simvastatin can most efficiently protect memory impairment and KA-indued excitotoxicity. In the second place, lovastatin prevents seizures and histopathological signs of excitotoxicity. It was reported that only simvastatin and lovastatin have some neuroprotective effects. In contrast, atorvastatin, fluvastatin, and pravastatin did not present such an effect.[10]

Fluvastatin

Fluvastatin is shown to be ineffective in inhibiting KA- and PTZ-induced seizures. While some statins exhibit anticonvulsant effects, some others may present proconvulsant effects. This determines which statins can stimulate seizures. Proconvulsant effects of statins are determined in experimental animal models of seizures. Pending further studies for confirmation, the dosage and the method of treatment (chronic or acute) with statins determines whether a statin is anticonvulsant, proconvulsant, or has no effect at all. In KA-induced seizures in mice, acute treatment with atorvastatin 50 mg/Kg or pravastatin 50 mg/Kg exhibited proconvulsant effects. Oral administration of lovastatin at sub-chronic doses of 50 and 100 mg/Kg showed a proconvulsant effect on AY9944-induced atypical absence seizures in rats.[42]

Lovastatin

In vitro studies on cultured hippocampal neurons indicated that lovastatin reduced the neuronal cell death caused by glutamate.[15] Experimental animal models showed that lovastatin reduces excitotoxicity caused by pilocarpine-induced epilepsy. This occurs by increasing the synthesis of interleukin-10 (IL-10) and decreasing pro-inflammatory cytokines in the hippocampus.[43]

Lovastatin reduces inflammatory mediators produced in the hippocampus. The inflammatory response impacts the lower body temperature and reduces oxidative stress associated

Table 1: A list of neuroprotective properties of statins in animal models

Authors	Study type	Experimental model	Type of statin and dosage (mg/Kg)	Measured outcomes	Main results
Rangel et al.[6]	Animal (rats)	Pilocarpine-induced status epilepticus	Lovastatin (20)	Normal cell population in hippocampal pyramidal cell layer and the dentate hilus using histological evaluation.	Lovastatin showed neuroprotective properties after pilocarpine-induced status epilepticus in rats.
Ramirez et al.[10]	Animal (mice)	Kainic acid-induced seizures	Simvastatin (50), Lovastatin (50), Fluvastatin (50), Atorvastatin (50), Pravastatin (50)	Behavioral studies (memory), histopathological evaluation of the hippocampus post kainic acid administration, statins effect on limbic structures of the cortex post kainic acid administration.	Lovastatin and simvastatin may have therapeutic properties in some neurological disorders (e.g., Alzheimer's disease) where the impairment of memory and excitotoxicity is an essential part of the disease.
Lee et al.[15]	Animal (rats)	Kainic acid-induced seizures, excitotoxicity induced by glutamate or kainic acid in cell culture studies	Atorvastatin (10 mg/Kg/day/oral) for seven days, Lovastatin (cell culture)	Anti-excitotoxic and anti-seizure properties of statins in kainic acid-induced seizures and anti-excitotoxicity in cell culture studies.	Atorvastatin reduced the activity of seizures, death of the hippocampus neurons, infiltration of monocytes, and the expression of the pro-inflammatory genes. Lovastatin lowered the excitotoxicity induced by glutamate or kainic acid in the cultured hippocampal neurons.
Khoshnoud et al.[29]	Animal (mice)	PTZ-induced seizures, maximal electroshock-induced seizures	Atorvastatin (2, 4, 8, and 16)	Onset time of seizures and protection from hindlimb tonic extension and death in pentylenetetrazole model and protection from hindlimb tonic extension in maximal electroshock model.	Atorvastatin showed anti-seizure properties in pentylenetetrazole-induced seizures, but not in maximal electroshock-induced seizures.
Kesim et al.[37]	Animal (mice)	Picrotoxin-induced seizures	Simvastatin (10, 20, 40)	Quantity and length of picrotoxin-induced seizures in mice and irregular pyramidal cell numbers in CA1 and CA3 regions of the hippocampus.	Simvastatin lowered the quantity and length of picrotoxin-induced seizures in mice and irregular pyramidal cell numbers in CA1 and CA3 regions of the hippocampus.
Lee et al.[38]	Animal (rats)	Pilocarpine-induced status epilepticus	Lovastatin (20)	Behavioral seizure evaluation, western blotting for antibody detection, histopathological assessment in the dentate gyrus, CA1, CA3, and whole-cell patch-clamp recording.	GSK-3b and CRMP-2 expression are increased after seizure induction, and lovastatin reduces their expression. Lovastatin also lowered mossy fiber sprouting in the dentate gyrus and CA3 region of the hippocampus.
Xie et al.[40]	Animal (rats)	Kainic acid-induced status epilepticus	Simvastatin (1 mg/Kg/day) for three days	Expression of cytokines, reactive astrocytosis, and neuronal cell loss.	Simvastatin blocked IL-1β, TNF-α, reactive astrocytosis, mossy fiber sprouting, and lowered neuronal cell loss in the hippocampus.
Oliveira et al.[47]	Animal (mice)	Pilocarpine-induced status epilepticus	Atorvastatin (10, 100) for 14 days	Behavioral changes (open field test and object recognition test), pro-inflammatory markers (IL-1β, IL-6, TNF-α, IL-10, and INF-γ).	Atorvastatin increased IL-10 and reduced IL-1β, IL-6, TNF-α, IL-10, and INF-γ both in basal and statue epilepticus-induced levels.

Gouveia et al.[43]	Animal (rats)	Pilocarpine-induced status epilepticus	Lovastatin (20) for 15 consecutive days, twice a day	mRNA expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and anti-inflammatory cytokine IL-10.	Administration of lovastatin decreased the synthesis of inflammatory mediators and increased anti-inflammatory cytokine (IL-10).
Gouveia et al.[44]	Animal (rats)	Pilocarpine-induced status epilepticus	Lovastatin (20)	Kinin B1 and B2 receptors, body temperature, interleukin-1β, IL-6, and TNF-α.	Lovastatin decreased the hyperthermia caused by status epilepticus. RT–PCR showed that lovastatin significantly reduced mRNA expression of IL-1β, IL-6, TNF-α, and kinin B1 receptors in rats receiving pilocarpine for status epilepticus induction.
Citraro et al.[48]	Animal (rats)	Genetic animal model of absence epilepsy	Simvastatin (10 mg/Kg/day) for 17 consecutive weeks, Pravastatin (10, 30 g/Kg/day) for 17 consecutive weeks, Atorvastatin (5, 10 mg/Kg/day) for 17 consecutive weeks	Depressive-like behavior using forced swimming test, anxiety levels using open field test, and levels of serum cholesterol.	Early long-term statin therapy resulted in anticonvulsant properties, a decreased immobility time in the forced swimming test, and a lower anxiety level in an open field test. Not effective in acutely established absence seizures.
Shafaroodi et al.[45]	Animal (mice)	Pentylenetetrazole-induced seizures, electroshock-induced seizures	Atorvastatin (10, 20)	Threshold of seizures and death.	Atorvastatin had an anticonvulsant effect in both PTZ and electroshock model.
Uzum et al.[46]	Animal (rats)	Pentylenetetrazole-kindled rats	Atorvastatin (5 mg/Kg/day) for four weeks or daily	Memory impairment using the passive avoidance test, EEG alterations.	Atorvastatin in PTZ-kindled rats enhanced memory and learning.
Stepien et al.[49]	Animal (mice)	Maximal electroshock-induced seizures	Atorvastatin (80) acute treatment for seven consecutive days, Fluvastatin (80) acute treatment for 7 consecutive days	Tonic hind limb extension in the maximal electroshock-induced seizures model, chimney test to investigate the adverse effects of co-administration of statins with anticonvulsant drugs, the total concentration of anticonvulsant medications in the brain, long-term memory using passive avoidance test.	Long-term atorvastatin therapy reduces the anticonvulsant effect of carbamazepine, and acute therapy with fluvastatin can enhance the anticonvulsant effects of valproate and carbamazepine. Co-administration of valproate with atorvastatin (both acute and chronic treatment) and fluvastatin (chronic treatment) causes long-term memory impairment.
Johnson-Anuna et al.[23]	Animal (rats)	Gene expression	Lovastatin (100) for 21 days, Pravastatin (100) for 21 days, Simvastatin (100) for 21 days	Gene expression, statin, and cholesterol levels in the cerebral cortex of the brain.	Statins change the expression of genes in the cerebral cortex of the brain and reduce the cholesterol levels in the cerebral cortex of the brain.
Lu et al.[39]	Animal (rats)	Traumatic brain injury	Atorvastatin (1 mg/Kg/day) for 14 days, Simvastatin (1 mg/Kg/day) for 14 days	Histological evaluation using immunohistochemistry staining, Morris water navigation task for memory studies, neuronal cell loss, angiogenesis, and new cell formation.	Statins may be beneficial in the treatment of traumatic brain injury.

with brain ischemia. Lovastatin also reduces hyperthermia in SE. Statins are also able to prevent neuronal cell death from prolonged SE. They also reduce seizure-related behavior due to KA-induced seizures. In rats with SE treated with Lovastatin, a significant decrease in mRNA expression of IL-6, IL-1β, TNF-α, and kinin B1 receptors has been reported.[44] In another animal study, administration of lovastatin in pilocarpine-induced SE showed a reduction in neuronal cell death in the CA1 region of the hippocampus. Since cell death is the most damaging effect of SE, any drug that can prevent or reduce it is noteworthy.[6]

Atorvastatin

Based on the results of two seizure models in mice (electroshock-induced seizure model and intraperitoneal injection of PTZ), it was shown that acute treatment with atorvastatin decreased tonic seizure and increased clonic seizure threshold.[45] An experimental study on PTZ kindled rats showed that administration of atorvastatin improved learning and memory functions.[46] In another study, following pilocarpine-induced ES, treatment of male and female mice (C57BL/6) with atorvastatin reduced the level of interferon-γ in a dose-dependent manner. However, atorvastatin was effective only in 100 mg/Kg doses in male mice and 10 and 100 mg/Kg doses in female mice.[47] Atorvastatin reduces mRNA expression of inducible nitric oxide synthase, TNF-α, and IL-1β in the hippocampus. Furthermore, the administration of atorvastatin reduced inflammation by infiltration of ectodysplasin-1 positive cells and the expression of cytokines.[15] A previous study found that early chronic treatment of six months old Wistar Albino Glaxo rats with atorvastatin (5 mg/Kg/day) and pravastatin (10 mg/Kg/day) did not show anticonvulsant effects. However, treatment with atorvastatin (10 mg/Kg/day) and pravastatin (30 mg/Kg/day) could lower the development of absence seizures following the termination of treatment after one month.[48]

Different Types of Clinical Studies

A study of patients with first-time ischemic stroke, with no history of epilepsy, reported that statin therapy reduced the risk of poststroke early-onset seizures (table 2).[50] Results of a cohort study showed that statins could reduce the risk of death in patients with SE.[51] Although infrequent, seizures after a stroke can be life-threatening.[52] Based on the results of two experimental seizure models in animals (PTZ and MES), it was shown that atorvastatin had anti-seizure effects in the PTZ model, but not in the MES model. In cultured brain cells (microglia and astrocytes) and endothelial cells, statins can present anti-inflammatory and vasoprotective effects.[29] In a mice MES model, acute treatment with fluvastatin 80 mg/Kg for seven days elevated anticonvulsant effects of carbamazepine and valproate by reducing ED.[49, 50]

It is reported that ionizing radiation may cause epilepsy. In a study of patients with nasopharyngeal carcinoma, statins reduced the risk of post-radiation epilepsy compared to those not receiving statins.[53] Statins improved blood flow and had beneficial effects in patients with cerebral ischemic stroke.[54] The neuroprotective effect of statins is believed to be through cholesterol-dependent and -independent mechanisms (pleiotropic effects).[54] Pleiotropic properties of statins include elevation of NO production and reduction of neuroinflammation, neurotoxicity, and oxidative stress.[45] A cohort study showed that statins may reduce the risk of poststroke epilepsy (PSE) after an intracranial hemorrhage, especially in medium-high level severity.[55] Statin therapy in mice models showed a decrease in IL-1β, IL-6, and TNF-α but an increase in IL-10 and eNOS levels.[56]

Not all studies have reported the beneficial effects of statins in patients at risk of epilepsy. A study of two propensity score (PS)-matched cohorts of statin and non-statin users showed the beneficial effects of statins on the risk of being diagnosed with epilepsy.[57] As for seizures, a study reported that statin use in patients with glioblastoma (a malignant brain tumor) was associated with decreased occurrence of seizures.[58] It is also reported that treatment with high-dose statins can reduce the risk of post-stroke seizures.[59] Simvastatin 40 mg is reported to be more effective than 20 mg in decreasing the occurrence of PSE. Moreover, early initiation of statin use was associated with a lower risk of developing PSE.[60] However, a retrospective cohort study in Taiwan reported that statins had no significant effect in preventing PSE.[61] A study of 1,051 patients reported that statin therapy reduced the risk of early-onset seizures, late-onset seizures, and PSE, and the reduction was even more significant at higher dosages. In addition, it was reported that the risk of developing PSE was lower in the case of long-term statin therapy.[59] The results of a case study in Canada showed that statins could reduce the risk of hospitalization due to epilepsy. However, the results need to be substantiated, since the research was a nested case-control study.[62]

A cohort study comprising 477 patients showed that the prevalence of PSE was higher in patients receiving lower doses of simvastatin,

Table 2: A list of clinical studies on the administration of statins in epileptic patients

Authors	Study type	Number of patients	Type of statin	Measured outcomes and Main results
Borger et al.[21]	Retrospective (patients undergoing isolated valve surgery)	4,216	N/A	Cardiac output syndrome, undergoing concomitant coronary artery bypass grafting, mean EuroSCORE predicted risk of mortality.
Guo et al.[50]	Cohort	1,832	Atorvastatin, Rosuvastatin, Simvastatin	Early use of statins reduced the risk of early poststroke seizures.
Sierra-Marcos et al.[51]	Cohort	427	Simvastatin, Atorvastatin, Pravastatin	Exposure to statins before a status epilepticus episode is related to decreased mortality risk, suggesting a possible anti-epileptogenic role.
Rong et al.[53]	Retrospective	532	N/A	In patients with nasopharyngeal carcinoma, early statin therapy may lower the risk of post-radiation epilepsy.
Etminan et al.[62]	Nested case-control study	150,555	Atorvastatin, Lovastatin, Cerivastatin, Fluvastatin, Pravastatin, Simvastatin, Rosuvastatin	Statin therapy may lower the risk of hospitalization because of epilepsy.
Lin et al.[55]	Cohort	7,435	Atorvastatin, Rosuvastatin, Lovastatin, Pitavastatin, Fluvastatin, Simvastatin, Pravastatin	Post-stroke, but not pre-stroke, statin use was associated with a reduced risk of post-stroke epilepsy.
Trivedi et al.[57]	Propensity score-matched cohorts	43,438	Simvastatin, Atorvastatin, Pravastatin, Rosuvastatin	Statin therapy had no significant effect in patients with epilepsy.
Henker et al.[58]	Cohort	224	Simvastatin, Pravastatin, Atorvastatin	Statin therapy reduced the number of seizures. The necrosis (size and amount) was significantly lower in seizures caused by glioblastoma.
Li et al.[59]	Cohort	1,051	Atorvastatin, Rosuvastatin, Simvastatin	High-dose statin therapy can lower the risk of post-stroke seizures. There is a lower risk of post-stroke seizures with chronic statin therapy.
Vitturi et al.[60]	Prospective cohort	477	Simvastatin (40, 20 mg), High potency statins	Patients receiving statins (e.g., simvastatin) were less likely to suffer from post-stroke epilepsy compared to those who did not. Statin therapy in an adequate dose may reduce the risk of post-stroke epilepsy.
Hsieh et al.[61]	Retrospective cohort	18,957	Atorvastatin, Rosuvastatin, Fluvastatin, Simvastatin, Lovastatin, Pravastatin	In relation to epilepsy, no significant differences were found between non-statin and statin users. Male patients using statins had a lower risk of post-stroke epilepsy mortality compared to non-statin users. Statins had a modest effect in preventing post-stroke epilepsy.
Matsubara et al.[63]	Retrospective study	4,595	Pitavastatin, Atorvastatin, Simvastatin, Rosuvastatin, Pravastatin	Statins significantly reduced the risk of early-onset seizures in patients with acute ischemic stroke.
Guo et al.[64]	Meta-analysis of cohort studies	26,042	Atorvastatin, Simvastatin	Statin therapy could be considered as one of the preventive medications for individuals at risk of seizures and epilepsy.

as well as those who did not receive statin therapy. It is suggested that statin therapy after stroke may lower the risk of PSE.[60] A study performed in Taiwan showed that statins had a modest effect in preventing PSE. However, the results were not significant compared to non-statin users. Pending confirmation, they also reported that statin therapy reduced PSE mortality in men.[61] Another study reported that early statin administration to patients with acute ischemic stroke reduced the risk of early-onset seizures.[63]

Discussion

The effects of statins on different neurological disorders have been investigated in several *in vitro* and *in vivo* studies as well as clinical trials and cohorts. Apart from lipid-lowering capacity, it is suggested that statins have beneficial effects on neurodegenerative disorders such as seizures, epilepsy, Alzheimer's disease, Parkinson's disease, multiple sclerosis, and stroke. However, there is a need for detailed clinical studies to further explore these additional effects. Conflicting results on the effect of statins on seizures and epilepsy have been found. Some studies reported its beneficial effects, while some others claimed modest or non-significant effects in combating seizures. It is also suggested that the observed improvements are not due to the neuroprotective properties of statins.[41] Such inconsistencies could be the result of the heterogeneity in parameters used in the respective studies. For example, when animal models are employed, the outcome of a cohort study is influenced by parameters such as animal sex, types of treatment (acute or chronic), drug dosage, study design, sample size, confounding variables, and many other factors. In addition, findings from animal model studies are not necessarily similar to those in humans. Despite great efforts by researchers for accuracy and precision in animal models, ultimately, these models only mimic certain aspects of a disease found in humans. Therefore, it is logical to expect contradictory results on the effect of statins.

Conclusion

Given the beneficial effects of statins as part of a therapy for neurodegenerative disorders, further studies on this subject are justified. It is evident that statins are safe for the majority of patients, and the protective benefits of statin therapy outweigh the disadvantages associated with risk factors.

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Author's Contribution

A.A: Design and data acquisition, analysis and interpretation; E.N and M.CH: Design and data analysis and interpretation; A.R.D, A.R: Data analysis and interpretation. All authors contribute in writing the manuscript; All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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