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Review Article

STATINS: A NEW THERAPEUTIC APPROACH FOR THE TREATMENT OF NEUROPATHIC PAIN

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ABSTRACT

Due to a lesion or chronic illness state that affects the somatosensory nerve system, Neuropathic Pain (NP) is a terrible ailment. NP has recently been a top problem for the pharmaceutical and medical industries. For the therapy of NP, stains may offer an additional source of illumination. By preventing 3-Hydroxy-3-Methylglutaryl-Coenzyme a (HMG-CoA), it prevents the rate-limiting step in cholesterol production. HMG-CoA reductase inhibitors, which have a pleiotropic impact in addition to the cholesterol-lowering effects of statins, have also been linked to neuropathic pain. According to reports, statins can worsen endothelial dysfunction by making more nitric oxide available. Antioxidant, antiproliferative, and immunomodulatory activities are known to exist in it. It primarily comes highly suggested for cardiovascular issues and helps to reduce inflammation. Atherosclerotic plaque is under its control. To the best of our knowledge, this subject has not yet been the subject of clinical research in humans. Up until now, most of the evidence pointing to a connection between statins and neuropathic pain has been speculative. As a result, this evaluation should be considered a synopsis of what is already known, what is being investigated, and where more research might be needed. This review assesses the statins for neuropathic pain in preclinical as well as clinical research.

Keywords: HMG-CoA, Disease of somatosensory nerve, Neuropathic pain, Statins

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INTRODUCTION

Pain is known to be an unpleasant sensory and emotional experience that is connected with actual and potential tissue damage [1]. In addition to posing challenges for patients and caregivers, chronic pain is often associated with several medical diseases and is associated with significant financial expenses for the public health system. The selections of articles for the current review were searched from specialized electronic databases (Range of years: 2001-2024) such as Elsevier, Pubmed, and Cambridge using the keywords statins, neuropathic pain, pain, pharmacokinetics and pharmacodynamics of statins, etc. Other selections include articles from Springer, information from Internet sources, and Online published articles. All literature searches provided an evidence that in order to treat chronic pain, it is necessary to first properly analyze or examine the patient to determine the type of pain he is experiencing and its cause. There are two categories for chronic pain: Nociceptive pain, which is distinguished from Neuropathic Pain (NP), is an acute form of pain that is brought on by chemicals, inflammation, or physical events in reaction to a particular circumstance [2]. Whereas NP arises as a consequence of any kind of lesion, trauma, surgery, and disease (diabetes, cancer), affecting the somatosensory system. However, the treatment of NP not only includes pharmacological but also non-pharmacological and interventional therapies [1].

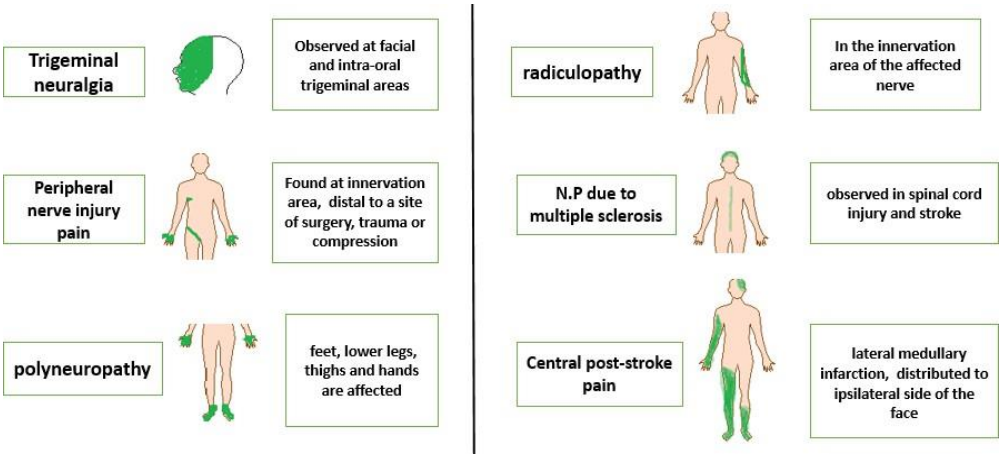

Fig. 1: Neuroanatomical distribution of pain symptoms

Numerous health issues that harm nerves are the root cause of NP. Diabetes, cancer, Parkinson's disease, sclerosis, strokes, spinal cord injuries, autoimmune disorders, and amyloidosis are possible causes of NP. Clinical problems like hypothyroidism, vitamin deficiency, and amyloidosis may also exist in association with NP. It might be the result of certain poisons that are preexisting in the body, such as lead, thallium, ethylene oxide, dinitrophenol, clioquinol, and arsenic. Fabry's disease and inherited sensory and autonomic neuropathy types 1 and 1B are additional causes of NP. Furthermore, NP can result from long-term usage of medications such as cisplatin,

disulfiram, ethambutol, isoniazid, nitrofurantoin, thalidomide, vincristine, chloramphenicol, metronidazole, and oxaliplatin [2]. Since different NPs influence different nerves and body parts, they are referred to by different names. The peripheral nerve system is impacted by peripheral neuropathy, which also affects the hands, legs, arms, and feet [3]. Diabetes is a prevalent cause of neuropathy worldwide. Diabetic neuropathy problems are neurodegenerative illnesses of the peripheral nervous system that impair the autonomic and sensory axons. They are often detected in 50% of persons with diabetes [4]. Diabetes mellitus raises the risk of cardiovascular disease, and one of the main consequences is cardiac autonomic neuropathy. Cardiovascular autonomic neuropathy is the result of any harm or injury to the autonomic nerve system in diabetics, and it is frequently accompanied by hypertension, arrhythmia, myocardial infarction, and even abrupt death [5]. Dental aches, also known as orofacial NP, are a typical side effect of periodontal and caries disorders, which are brought on by microorganisms that trigger inflammatory responses and expose primary afferent neurons to algogenic chemicals. These chemicals cause phenotypic and functional alterations in glial, immunological, and vascular cells that surround nerves.

Therefore, NP in the oral areas starts as a result of nerve trauma that occurs in an inflammatory environment [6]. Because of its great heterogeneity, NP still affects 1 in 10 people over the age of 30, yet accurate prevalence and incidence data are lacking. The World Health Organization estimates that 22% of people with incapacitating chronic pain are doing so because of this issue, which practically all doctors and other health professionals deal with [7]. Data obtained worldwide reported the prevalence of neuropathic pain at 10.3% in Morocco [8], 8% in the U. K. [9] 6.9% in France [10] 3.2% in Japan [11]. According to Van Acker, K., *et al.*,(2013), diabetic neuropathy was reported in around 17.9% of France [12], Jacovides, Andrew, *et al.*, (2014) reported 30.3% in South Africa [13] and Jambart, S., *et al.*,(2011) reported 53.7% in the middle east region [14]. These findings suggested that the NP is a global challenge. The hallmarks of NP are described as spontaneous pain, which gives persistent burning-like sensations and lancinating pain-like situations, whereas dysesthesias are characterized by abnormal and unpleasant sensations of shooting and lancinating, Parasthesias is also the feeling of unpleasant sensations like tingling [15]. Pain from non-painful stimuli due to heat, pressure, and touch is allodynia and hyperalgesia is an elevated response due to painful stimuli like form pinprick, heat, and cold, and delayed-type having explosive response due to the stimulus known as hyperpathia [16].

Therapeutic approaches for neuropathic pain

Neuropathic pain management emphasizes the treatment of symptoms of the pathological condition, mainly by relieving pain [17]. The results of the randomized controlled study indicated that a variety of lesions or diseases are the primary cause of pain in many individuals with neuropathic pain. Despite the fact that similar outcomes were seen in patients with postherpetic neuralgia or severe diabetic peripheral neuropathy. Here, the results also offered some insight into the bulk of pharmacotherapy. As first-line treatments for neuropathic pain, the Special Interest Group on Neuropathic Pain (NeuPSIG) recommended Tricyclic Antidepressants (TCAs), gabapentinoids, and selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRI). For peripheral neuropathic pain, powerful opioids (such as oxycodone and morphine) and Botulinum Toxin-A (BTX-A) were considered third-line treatments, while lidocaine, capsaicin, and tramadol were explored as possible second-line treatments [17, 18]. Standard analgesics like paracetamol, NSAIDs, or mild opioids typically do not affect people with neuropathic pain. Although there are numerous evidence-based treatments available for the patients, none of them can provide enough pain relief, and some even cause the patients to become intolerable to therapeutic levels [19].

Statins

Stains is a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor that is typically administered to reduce cholesterol synthesis, increase high-density lipoprotein, and lower levels of Low-Density Lipid (LDL). Inflammations, pro-inflammatory cytokines, and C-C-reactive protein levels are all reduced using them. The antioxidant properties of statins are well recognized, and they also enhance endothelial dysfunction and nitric oxide availability. However, they also have neuromodulatory effects and are mostly employed for cardiovascular problems and consequences [20, 21]. In the 1970s, the first statin was discovered, Compactin Later on it was named mevastatin and was identified as a secondary metabolite of fungi obtained from *Penicillium citrinium* that reduced the synthesis of cholesterol but unfortunately, it was discontinued due to its severe hepatotoxic effect. After that, another natural statin was isolated from *Aspergillus terreus,* which came out to be a more potent inhibitor with no side effects like hepatotoxicity; since then series of statins were discovered that is simvastatin, pravastatin, atorvastatin, cerivastatin, fluvastatin, pitavastatin, and rosuvastatin [22, 23]. Statins' typical mode of action essentially includes inhibiting HMG-CoA reductase, a rate-limiting enzyme required to the mevalonate pathway, to decrease the synthesis of cholesterol. Reduced production of hepatic cholesterol triggers the translocation of membrane-bound proteins that bind to sterol regulatory elements into the nucleus, which raises the number of LDL receptors on the surface of hepatocytes and promotes the removal of LDL cholesterol from the circulation [24].

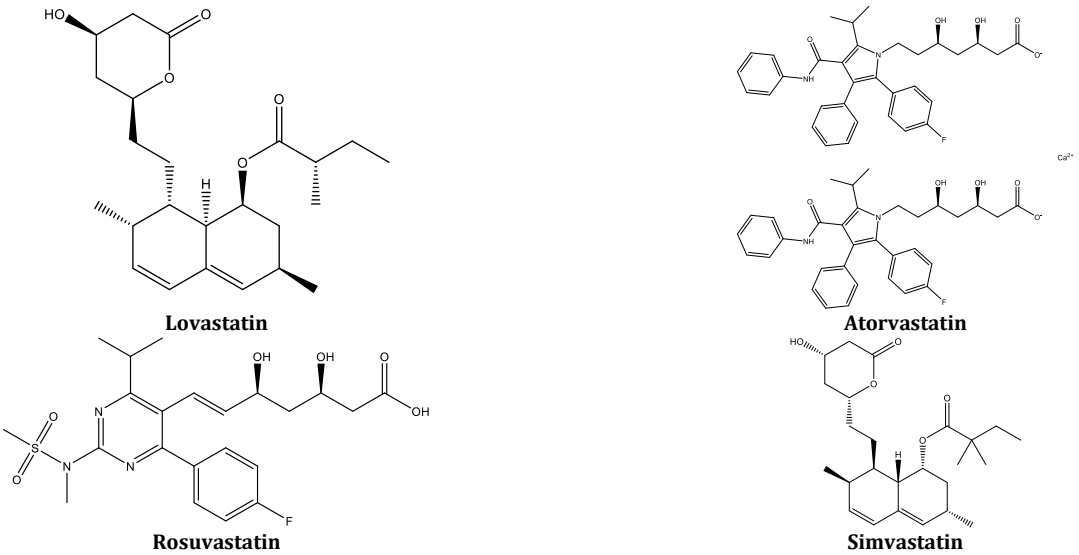

Fig. 2: Structures of statins

Statins decrease the superoxide anion synthesis by not allowing the prenylation of p21 Racprotein in endothelial cells. It also does not allow the oxidation of LDL by protecting the activity of the endogenous oxidant system, and when statins bind to the surface of lipoprotein to phospholipids, it prevents the diffusion of free radicals towards lipoprotein cores that are generated during oxidative stress that is they protect the lipoprotein from getting oxidized [25]. Other than that it also gives a pleiotropic effect that is suppression of inflammation, oxidative stress, and T-cell activation. Numerous pre-clinical and clinical investigations and studies offer proof that statins can control neuropathic pain. Nonetheless, several pre-clinical investigations have suggested numerous explanations for why statins reduce neuropathic pain. Several explanations have been proposed by studies, including increased expression of Endothelial Nitric Oxide Synthase (eNOS) and decreased expression of Inducible Nos (iNOS). Additionally, there is a decline in the expression of microglia and inflammatory mediators such as TNF-a, IL-6, and Interleukin-1b (IL-1b) [26].

Statins: chemical nature

The three components of the chemical structures of the statins—lovastatin, simvastatin, atorvastatin, and rosuvastatin-are analogs of the target enzyme substrate, HMG-CoA, which is a complexed hydrophobic ring covalently attached to substrate analog and primarily utilized for the statins' binding to the reductase enzyme. The ring's side groups provide information on the drugs' pharmacokinetics and solubility [27]. By attaching themselves to the enzyme's active site, the structures of statins sterically prevent the substrate from binding. The stiff, hydrophobic ring of the statins can adapt to the surroundings as a result of the enzyme's substrate-binding pocket undergoing rearrangement [28].

Pharmacokinetics of statins

Statins are most commonly prescribed lipid-altering therapy as they are a remarkably safe and well-tolerated class of drugs because statins are known to be highly selective inhibitors of HMG-CoA reductase and generally do not show any significant affinity toward other enzymes or receptor systems so at the site of action they do not easily interact with other drugs [29]. Statins even on long-term exposure, rarely show any adverse effects, are well tolerated, and have less interaction with other drugs, has been seeking a lot of attention for their use in neuropathic pain [30]. Although all statins have a common pharmacological target for sterol biosynthesis, they differ in terms of their pharmacokinetic profile and display variable dose-related lipid-modifying efficiency [31]. So, considering their pharmacokinetics profile (absorption, distribution, metabolism, and excretion of a given drug) statins are different in showing their half-life, systemic exposure, maximum plasma concentration (Cmax), bioavailability, protein binding, lipophilicity, metabolism, presence of active metabolites, and excretion routes [32]. Lovastatin, pravastatin, and simvastatin are derived from fungi, whereas fluvastatin, pravastatin, pitavastatin, and rosuvastatin are synthesized chemically, which is a synthetic compound [32]. Specifically, when taken orally, statins are delivered as active ß-hydroxy acid, which is readily absorbed and reaches its peak concentration in four hours [33]. The range of their absorption is 30% to 98%. The effects of food intake on the absorption of statins vary. For example, lovastatin is more effective when taken with food; however, the bioavailability of atorvastatin, fluvastatin, and pravastatin decreases with food, while simvastatin or rosuvastatin are not affected by food intake. Overall, there is not much interaction between food and the statins, so it is best to take them in the evening [34].

Most frequently prescribed statins have low bioavailability, displaying their extensive first-pass extraction. As statins affect the liver that is why first-pass uptake is more efficient than bioavailability [35]. Except for pravastatin, statins are highly coupled to plasma proteins, particularly albumin, and because of this high affinity for protein binding, systemic exposure to unbound, pharmacologically active drugs is minimal. Rosuvastatin and pravastatin, two hydrophilic statins, do not have widespread tissue distribution in the body because of low plasma protein binding, which causes unbound pravastatin to be highly concentrated in the bloodstream. Statins with a long onset of action are often unaffected by minor changes in unbound plasma drug concentration [36].

All the statins are highly hepatoselective; the inhibition of HMG-CoA reductase and their solubility profile makes them more hepatoselective as the lipophilic (Atorvastatin, fluvastatin, lovastatin, and simvastatin) statins through the passive diffusion via the hepatocytes and for the hydrophilic statins are a carrier-mediated mechanism that is responsible for first pass effect [36]. Statins easily get metabolized by the Cytochrome P450 (CYP450) family of enzymes, which is composed of over 30 isoenzymes and in those isoenzymes, CYP3A4 metabolizes several drugs in the human body, including the drugs of statins lovastatin, simvastatin, cerivastatin, and atorvastatin [37]. The major active metabolite of simvastatin is ß-hydroxy acid, its 6-hydroxy, 6-hydroxymethyl, and 6-exomethylene derivatives, and the major metabolite of atorvastatin is 2-hydroxy-and 4-hydroxy-atorvastatin acid and fluvastatin are mainly metabolized by the CYP2C9 isoenzymes. The other drugs of statins like pravastatin, pitavastatin, and rosuvastatin, do not go through metabolism by CYP450 pathways [38].

Table 1: Pharmacokinetic differences of statins

Parameters	Lovastatin	Simvastatin	Atorvastatin	Rosuvastatin	Fluvastatin	References
Bioavailability (%)	5	5	12	20	19–29	[39, 40]
Tmax(h)	2-4	1.3–2.4	2–3	3	0.5–1	
Cmax(ng/ml)	10-20	10–34	27–66	37	448	
Protein binding (%)	>95	94–98	80–90	88	>99	
Metabolism	CYP3A4	CYP3A4	CYP3A4	CYP2C9, 2C19(minor)	CYP2C9	
Metabolites	Active	Active	Active	Active(minor)	Inactive	
Solubility	Lipophilic	Lipophilic	Lipophilic	Hydrophilic	Lipophilic	
Elimination half-life(h)	3	2	14	19	1.2	
Urinary excretion (%)	10	13	2	10	6	
Fecal excretion (%)	83	58	70	90	90	

Only a very small portion of statin medications are excreted as parent pharmaceuticals; the bile is the primary route of elimination for statins following liver metabolization. Given the high risk of myopathy associated with statin use, manufacturers always advise against prescribing them to anyone who has liver disease. There is no plasma accumulation even after many doses, and all drugs—aside from atorvastatin—have incredibly brief elimination half-lives (between 0.5 and 3 h). As pravastatin remains in the body unaltered or as the parent drug, the kidneys and liver assist it in exiting the body. Due to competition for carrier-mediated transport across the bile canalicular membrane, drug interactions may happen at the excretion level [29].

Molecular targets of statin

Acute and chronic pain is caused by the activation of glial cells and neuroglial cells, which make up approximately 70% of the glial cells in the central nervous system. These cells include astrocytes, oligodendrocytes, and microglia. It is well known that macrophages are home to microglia. They are thought to react in the face of unfavorable circumstances such as trauma, ischemia, inflammation, infection, and nerve damage. Dorsal horn microglia in the spinal cord get activated in response to any type of peripheral nerve damage. Astrocytes are a particular kind of glial cell found in the brain and spinal cord. They are thought to play a significant role in

the process of brain and spinal cord healing and scarring because they are activated by an increase in Ca2+levels. The dorsal horn contains highly active astrocytes that react to pain by triggering local cellular connections that release neurotransmitters and neuromodulators such as glutamate, prostaglandin E2, and NO [30, 31]. According to M. Ohsawa, simvastatin was able to attenuate the activation of spinal astrocytes and microglia cells by inhibition of the RhoA/ROCK signaling pathway for the treatment of neuropathic pain [32] and even according to X. Chen simvastatin can inhibit the long term mechanical hyperalgesia within 7 day and also inhibited the expressions of Iba-1 and CD11 b that represent spinal microglia cells and p38MAPK expression that were enhanced due to formalin injection to induce neuropathic pain [33]. and according to W. Li rosuvastatin attenuated NP under morphine tolerance state and even inhibited the activation of astrocytes, which led to a decrease in the expression of TNFα and IL-1 [34].

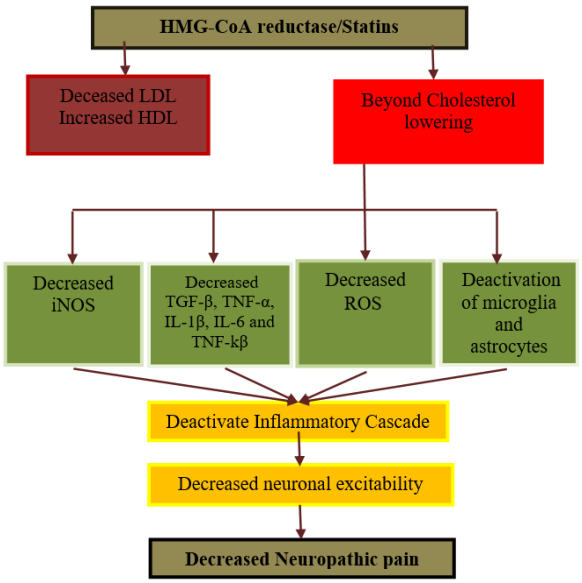

Fig. 3: Statins mechanism for attenuation of NP

Nitric oxide is a diffusible free radical that acts as a secondary messenger that is quite important for the regulation of certain activities in the human body. It balances the blood pressure, relaxes the smooth contraction, neuronal signaling, and activation of the immune system through the Cyclic Guanosine-3′,5′-Monophosphate (cGMP) pathway. It is generated endogenously from the L-arginine by a class of enzyme Nitric Oxide Synthases (NOSs). This enzyme NOS has three isoforms eNOS, iNOS, and neuronal NOS (nNOS). nNOS is present in the nervous system and skeletal muscles. NO is observed to possess a dual role of being both nociceptive and antinociceptive. In the brain, at a normal low concentration, it has a beneficial neuroprotective effect and it is generated by activation ofnNOSin a calcium/calmodulin (Ca2+/CaM)-dependent manner resulting in stimulation of Ca2+-permeable NMDA receptors. Production of NO results in downstream of NO, cGMP, and Protein Kinase G (PKG) signaling pathway and these regulate many neurotransmission and metabolic processes [35–37].

During any event of neural damage in the brain, the concentration of NO boosts to higher levels which is considered to be neurotoxic for the body. It leads to the production of Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS). The reaction between NO and superoxide ions causes the activation of Peroxynitrite (ONOO-) and peroxynitrous acid (ONOOH) free radicals that are dangerous for other reactive species, such as hydroxyl radicals and peroxides. These free radicals lead to oxidative stress which can cause DNA damage, lipid peroxidation, and damage to protein structure like aggregation or misfolding. A higher concentration of NO results in inflammation and degeneration of peripheral neurons resulting in NP [37].

According to H. Miranda, simvastatin was able to attenuate neuropathic pain and it also demonstrated its anti-inflammatory and antinociceptive properties in mice models. The mechanism behind this attenuation was through the inhibition of inflammatory cytokine and prostaglandin release and also by upregulating the expression of iNOS that inhibited the small G protein of the Rho family [38] and according to N. Pathakin increased levels of NO caused the development of neuropathic pain more precisely peripheral neuropathy and not only NO but also superoxide and peroxynitrite are also contributing to the same. In this research, atorvastatin was able to decrease the expressions of markers responsible for neuropathic pain [39].

Inflammatory, immunologic mediators or cytokines are becoming one of the interesting areas of research as they modulate neuronal plasticity and upregulate nociceptive transmission during neuropathic conditions. Cytokines are small intercellular regulatory polypeptides that originate from white blood cells and cells of the nervous system [40]. There are many different types of pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-17, that are increased in animal models of neuropathic pain [41]. Any damage or injury to peripheral nerves leads to neuropathic pain that occurs due to any injury or due to sensitization of neighboring axons or fire ectopically that they induce nociceptive signals to the central nervous system and elevated level of pro-inflammatory cytokines in the lesioned nerves alter the axonal properties. These pro-inflammatory cytokine interleukin-1b, IL-6, and Tumor Necrosis Factor-α (TNF-α) are formed and secreted under pathological conditions related to pain, hyperalgesia, tumor growth, and chronic inflammatory conditions. During these conditions, they are released from different types of cells like mononuclear cells, fibroblasts, synoviocytes, Schwann cells, and endothelial cells. In neuropathic pain conditions, they are present in DRG neurons and Schwann cells [42]. Interleukin-1b was the first known cytokine that have shown peripheral pain i. e. neuropathic pain in rodents. Its level was found during normal physiological conditions in the spinal cord but in any kind of nerve damage, their expression is usually upregulated. Same way TNF-α is also a kind of pro-inflammatory cytokine that is expressed during nerve injury or inflammatory conditions and in the classic model of neuropathic pain i. e. Chronic Constriction Injury (CCI) its levels are extensively elevated. Even exogenous administration of TNF-α induces allodynia among rodents [40]. According to L. W. Chu investigation, it has demonstrated that induction of neuropathic pain by CCI leads to an increase in the

expression of inflammatory cytokines but after the administration of atorvastatin it helped to reduce the expression of cytokines (TGF-ß, pIκB/IκB, nuclearNFκBCOX-2, EP1, EP4 and iNOS) and attenuated neuropathic pain conditions [43].

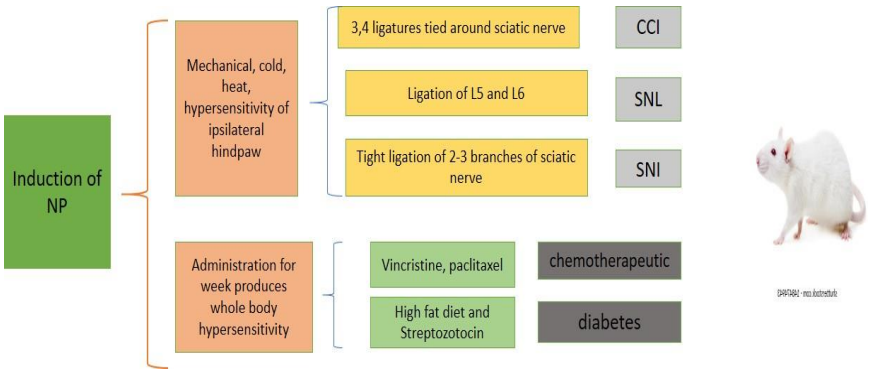

Fig. 4: Different preclinical models of NP

Table 2: Effect of statins on animals

Drug	Animals selected	Experimental period	Induction of NP	Dose selected	Findings of the research	Reference
Simvastatin	Male adult SD rats (200 to 225g)	7 d	Formalin	10µg	Attenuated NP through RhoA and p38 MAPK signaling pathway	[33]
Simvastatin	Male mice (20-30g)	7 d	Partial sciatic nerve injury	5µg	NP was reduced through RhoA/ROCK pathway	[32]
Simvastatin	CF-1male mice, (28–30g)	3 d	Acetic acid solution, formalin	3-100 mg/kg	Attenuated the NP by focusing on the activity of cytokine and nitric oxide.	[[38]
Simvastatin	Wistar albino rats (200-250g)	28 d	Vincristine	7.5,15 mg/kg	Lower dosages showed anti-inflammatory effects, reduced the mechanical hyperalgesia as well as cold allodynia	[50]
Simvastatin	Male Wistar rats (200g)	18 d	Injured sciatic nerve	2 and 80 mg/kg	Anti-inflammatory, antiallodynic and antinociceptive response	[51]
Simvastatin	MaleSD rats (180–200g)	21 d	Chronic constriction injury (CCI)	10 µl/d	Inhibited RhoA/lIMK/cofilin pathway	[52]
Atorvastatin	Male SD rats (250-300g)	14 d	CCI	10 mg/kg	Elevated the expression of VEGF, Akt, and eNOS, downregulated the levels of cytokines like iNOS, COX-2, and PGE2	[43]
Atorvastatin	Adult male albino wistar rats (180–250g)	14 d	CCI	3, 10, 30 mg/kg	Inhibiting oxidative stress and increasing the expression of MDA,O2, and protein	[39]
Atorvastatin	Adult male albino Wistar rats (180–250g)	14 d	CCI	3, 10, 30 mg/kg	• Inhibited the activation of glial cells like microglia and astrocytes • Decreased the inflammatory cytokines and expressions of MMP-2 and NGF • Down regulated tumor necrosis factor-α, interleukin1beta, prostaglandinE2.	[53]
Atorvastatin	Male SD rats (250-300g)	14d	CCI	10 mg/kg	• InhibitedpAkt/Akt, COX-2, iNOS, EP1, and EP4 release • Inhibited TNF-α and IL-1βlevelsinDRGandspinalcord	[54]
Rosuvastatin	Male SD rats (200-250g)	18 d	L5spinal nerve transection	10 mg/kg	• Reversed the morphine tolerance in the NP state • Reduced the expressions of cytokines and inhibited the activation of astrocytes, ERK42/44, and downregulated the release of TNF and IL-1	[34]
Rosuvastatin	Maleadult SD rats, (200-250g)	21 d	CCI	5,10 mg/kg	• Reduced hyperalgesia and allodynia • Decreases TNF-α,IL-6,and MDA inhibited	[55]
Rosuvastatin	CF-male mice, (28-30g)	14 d	Paclitaxel and partial sciatic nerve ligation	50 mg/kg	• Reduced the level of TBARS • Downregulated the expression of proinflammatory cytokines like IL-1ß, IL-6, IL-10,TNF-α, iNOS, and PGE2	[56]
Lovastatin	Male Swiss mice (20-25g) and male Wistar rats (200-250g)	24 h	Carrageenan	0.5, 1, 2, 5 and 10 mg/kg	Decreased the levels of TNF-α and nitric oxide	[48]
Lovastatin	MaleSprague-Dawley rats (300–350g)	14 d	CCI	50 µg/d	Inhibited the TLR4 signaling and blocked the LPS-induced TLR4 innate immune signaling	[57]
Lovastatin	Adult male wistar rats (250–300g)	9 w	Sciatic nerve crush injury	2 and 5 mg/kg	Restoreditsanti-inflammatory, immunomodulatory, and anti-oxidative properties.	[58]
Lovastatin	Adult male mice(22-25g)	4 d	Formalin	(1, 5,10, 20, 40, 80 and 100 mg kg	Inhibited by down-regulating the pain and inflammatory responses in inflammaed and neurogenic areas.	[59]

daily)

Reactive oxygen species (ROS) are produced during several degenerative neurological or in pain conditions [44]. They are essentially the metabolic byproducts of Oxidative Phosphorylation, a process that aids in preserving the body's redox balance. They can deal with redox-sensitive signaling pathways directly. In a healthy body, ROS production and exclusion are balanced, but in a stressful state, the body's natural balance is upset by mitochondrial fragmentation, which raises ROS production and causes NP and inflammation [45]. June Yowtak claims that in his study, he showed that ROS are responsible for maintaining neuropathic pain in mice and that ROS scavenger Phenyl N-tert-butylnitrone (PBN) was able to diminish its levels, proving that ROS are in fact to blame for NP [46]. Dario Siniscalco conducted a similar study to show the relationship between ROS and NP using a CCI model of mice that displayed neuropathic pain due to an increase in ROS production, while PBN decreased it [47]. Statins, such as lovastatin, are shown to be attenuating the NP and the ROS levels that were elevated due to carrageenan, which activated the inflammatory cascades. As inflammation is thought to be caused by an increase in ROS expression, lovastatin reduced the paw edema, demonstrating the anti-inflammatory action [48].

Clinical aspects

Some clinical trials have demonstrated the significance of statin in human patients suffering from neuropathic pain. Villegas-Rivera, G. *et al.*, demonstrated the therapeutic impact of Ezetimibe/Simvastatin (EZE/SIMV) and Rosuvastatin (ROSUV) on diabetic neuropathy individuals. It was a phase III randomized, double-blind, placebo-controlled clinical trial that was conducted at Therapeutics Institute, University of Guadalajara, Mexico. Out of 131 patients, around 74 were included and were assigned into three group treatments with a parallel sequence of 1:1:1. Patients were given a single dose once a day for 16 w of each treatment. The control group received a placebo. On the other hand, drug treatments were provided as EZE/SIMV at 10/20 mg, and ROSUV 20 mg. A combination of statins was given to reach similar effects without having adverse effects. There were inclusion and exclusion criteria, particularly people with diabetes mellitus and diabetes polyneuropathy were included and people suffering from renal or hepatic failure or are pregnant, breastfeeding, or suffering from neuropathy other than diabetes or were taking anti-oxidant and statins earlier were excluded. From 74 individuals, 24 were given a placebo 25 individuals received EZE/SIMV and the other 25 received ROSUV and one candidate from both EZE/SIMV and ROSUV was excluded due to myopathy. The results of the study, it has demonstrated that groups of EZE/SIMV and ROSUV had improved levels of LPO and Neuropathic Symptom Score (NSS). There were no changes in the neuropathic disability score (NDS), and other metabolic profiles i. e. glycemia and bilirubin. LDL and TG levels were all improved after 16 w of medication. From these studies, it was evident that statins (simvastatin and rosuvastatin) were effective in decreasing the incidence of neuropathic pain [49].

Another trial was conducted by N. Zangiabadi *et al.*, for patients having diabetic neuropathy and were treated with statins. A randomized, double-blind, placebo-controlled clinical trial was conducted for 6 mo on 40 individuals with confirmed Non-Insulin-Dependent Diabetes Mellitus (NIDDM) and with signs and symptoms of diabetic polyneuropathy and patients were excluded who were pregnant or having hepatic problems or is hypersensitive towards statins or were using statins prior to study or had any nerve injury or trauma in legs earlier. For 6 mo these individuals were treated with atorvastatin 20 mg every day and were advised to contact doctors in case of fever, weakness, or myalgia. However, due to certain reasons, few individuals left the study and only 32 patients completed the study. At the end of the study there were no changes in blood sugar, blood urea nitrogen, and cholesterol levels plus there was no side effect of atorvastatin among the patients. Considering the electrophysiological studies of Nerve Conduction Velocity (NCV) and F wave conduction velocity, there was a significant improvement by 5% was recorded. According to their conclusion, atorvastatin was beneficial for diabetic neuropathy and there were electrophysiological changes but that was short term; the effect started from the distal segment of nerves and extended proximally. However, this study required a larger sample size and more extended follow-up to provide more good and evident results [60].

Hernández Ojeda, Jaime, *et al.*,(2014) presented a randomized, double-blind, placebo-controlled Phase II study to examine the antioxidant effect of rosuvastatin in diabetic polyneuropathy subjects. In both the control and placebo group 17 subjects were kept who received 20 mg of rosuvastatin for 12 w. They stated that rosuvastatin improved diabetic neuropathy from 88% to 41% and even restored the symptoms of NP. Lipid peroxidation level decreased to 25.4±2 to 12.2±4.0 nmol/ml, concluding that stains have a beneficial effect on NP by attenuating the levels of lipid peroxidation and oxidative stress [61].

Combination therapy of statins

Combination therapy is beneficial for NP treatment, as they provide a better response to pain relief and reduce the chances of adverse effects. Various clinical data provide report regarding head-to-head assessments of combination and monotherapy, it easily characterizes symptom-specific combination therapies for individual suffering from neuropathic pain conditions. They even include combination therapies that explore non-drug domains like physical therapy, psychological coping, and biofeedback to assist functional restoration and they produce different and objective evaluation tools for clinical outcome assessment [62]. A combination method was used, according to Skiold, López-Canales Jorge *et al.* (2020), where rats were given vitamin B and statins. Vitamins B1, B6, and C were given along with pravastatin rosuvastatin (1, 3, 10, and 30 mg/kg), and analysis was done for both combination therapy and monotherapy. In comparison to solo therapies, the effective dose (ED30) of combination therapy was enhanced. According to this study, vitamin B works well with statins to manage discomfort of pain [63]. Souza, Luana Gabriel, *et al.* (2020) investigated the effects of simvastatin and photo-modulation (PBM) in Swiss mice with spinal nerve damage. For 28 d, PBM at 660 nm, 10 J/cm2, 30 mW, and 0.6 J per day was given to every mouse, along with 20 mg/kg of simvastatin and a combination of both. Based on the findings, they concluded that combination therapy improved the mice's sciatic functional index and their mechanical and thermal hyperalgesia [64].

A combination of morphine (10 mg/kg) and simvastatin (30, 60, 100, and 300 mg/kg, p. o.) was administered in the Mansouri, Mohammad Taghi, *et al.* (2015) trial. Information about morphine-induced tolerance and dependency in mice was supplied by this study. Here, morphine was found to have a significant reduction in the evolution of tolerance to its analgesic effect, and simvastatin was discovered to be an adjuvant therapeutic agent when used in conjunction with morphine [65].

Formulation of statins and patents

The optimal formulation is essential to guarantee that the active component of the medication enters the body at the right rate, in the right concentration, and for the intended use. Ala, Shahram, *et al.* (2017) investigated the possibility of reducing postoperative pain during bowel movements and during rest, as well as the requirement for analgesics following open hemorrhoidectomy, by applying 2% topical atorvastatin emulgel. Postoperative discomfort was decreased during rest and bowel movements in a 14-day randomized, placebo-controlled study, and the healing process after open hemorrhoidectomy was resumed [66]. The list of patents for the formulation of statins are listed below in table 3 [67-69].

Statins toxicity

Statin-Associated Muscular Symptoms (SAMSs) are another term for statin toxicity or intolerance. Type 2 diabetes mellitus, neurological

and neurocognitive consequences, hepatotoxicity, renal toxicity, and other disorders are among the serious side effects of statin medication [28]. Lovastatin, Simvastatin, and Atorvastatin are statins that are metabolized by CYP3A4, which increases their risk of interactions and toxicity. However, several statins have also been observed to not be metabolized by CYP3A4. Fluvastatin, rosuvastatin, pravastatin, and pitavastatin are a few examples of these statins. Muscle adverse effects associated with statins are poorly understood and may arise from a variety of factors. Strong evidence from numerous clinical trials has shown that statins, which are thought to decrease the accessibility of metabolites produced by the mevalonate pathway, are the cause of skeletal muscle damage [76, 77]. For liver damage with statins, a meta-analysis was carried out. As per the results of 13 trials taken together, there is no correlation between low-to-moderate dosages of pravastatin, lovastatin, and simvastatin with the risk of abnormal liver function tests. To prove that alternative statins have a comparable safety profile. For this report, more information is needed [78].

Table 3: Recent patents of formulation of statins

Year of patent application	Name of statins	Application number	Remarks about patent	References
2017	Atorvastatin	CN104306343A	• One type of atorvastatin calcium tablet lessened the issue of alkaline material • lessened stomach discomfort	[70]
	Atorvastatin calcium	CN104306343B	Developed tablet of micropill solid dispersion	[71]
		CN104546775A	• Solid dispersion mixture devoid of any basic or alkaline components • Fast release even after an accelerated stability study lasting six months.	[72]
2018	Rosuvastatin	CN105147636A	Capsules of rosuvastatin calcium with microcrystalline were determined to be more stable	[73]
		CN103690504A	Its solid dispersion tablet was stable at a temperature of 60 °C, a humidity of 92.5% for more than a week	[74]
2020	Simvastatin/ camsylate	JP2009521526B	The complex formulation was developed using amlodipine camsylate and simvastatin	[75]

CONCLUSION

Our research has shown that statins may be a novel therapeutic option for the management of neuropathic pain because they not only reduce peripheral and central hyperexcitability but also have anti-inflammatory properties, making them potential new candidates for the management of neuropathic pain. Statins have been shown to have two roles in NP. Numerous clinical studies indicate that statins both cause and contribute to np. Preclinical research reveals that statins have neuropathic pain-attenuating effects. Preclinical studies showing statins alleviate pain have primarily linked their benefits to decreased inflammation. However, in clinical research, statin side effects that cause discomfort may be outweighed by the changes that result from decreasing cholesterol. However, direct experimental studies are unable to account for the unique behavior of statins or the contradictory results about their role in neuropathy reported in the literature. Further research is needed to completely understand the binary behavior of statins in preclinical and clinical trials.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally. Bimlesh Kumar devised the project, the main conceptual ideas, wrote the article and the proof outline. Indu Melkani worked out almost all of the technical details and wrote the manuscript. Narendra Kumar Pandey developed the theoretical framework. Saurabh Singh discussed the results and commented on the manuscript. Dileep Singh Baghel contributed to the design and implementation of the research.

CONFLICTS OF INTERESTS

The authors have declared no conflict of interest.

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