

# Recent Findings on the Effects of Pharmacological Agents on the Nerve Regeneration after Peripheral Nerve Injury

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**Abstract:** Peripheral nerve injuries (PNIs) are accompanied with neuropathic pain and functional disability. Despite improvements in surgical repair techniques in recent years, the functional recovery is yet unsatisfied. Indeed a successful nerve repair depends not only on the surgical strategy but also on the cellular and molecular mechanisms involved in traumatic nerve injury. In contrast to all strategies suggested for nerve repair, pharmacotherapy is a cheap, accessible and non-invasive treatment that can be used immediately after nerve injury. This study aimed to review the effects of some pharmacological agents on the nerve regeneration after traumatic PNI evaluated by functional, histological and electrophysiological assessments. In addition, some cellular and molecular mechanisms responsible for their therapeutic actions, restricted to neural tissue, are suggested. These findings can not only help to find better strategies for peripheral nerve repair, but also to identify the neuropathic effects of various medications and their mechanisms of action.

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## 1. INTRODUCTION

Peripheral nerve injuries (PNIs) have several causes like trauma and medical disorders and result in neuropathic pain and functional disability [1]. In contrast to the injuries of the central nervous system (CNS), in the PNIs, the damaged nerves will regenerate spontaneously to the extent restricted by the size of the nerve gap, neuroma and scar tissue formation [2]. Most traumatic nerve injuries need surgical repair to permit the regeneration of axons into the distal segment of the nerve [2]. However, the current state of research is a shift from primarily focusing on surgical repair methods to molecular mechanisms and new strategies influencing the key factors such as post-traumatic neuronal and glial cell death [3, 4], Schwann cell proliferation, migration and differentiation [5, 6], growth cone mobility [7], axonal outgrowth [8, 9] and orientation [10]. In this way, various types of conditioning treatments and extrinsic manipulations have been suggested, such as topical or systemic application of natural/or synthetic compounds [3, 11], electrical stimulation [12, 13], electromagnetic fields [14, 15], biological or non-biological scaffolds in combination with cells and/or neurotrophic factors [16-20] and gene therapy [21]. A combination of the above-mentioned methods is often used in experimental studies. Pharmacological agents have the advantage of accessibility and currently used for the treatment of PNIs in the

clinic [22, 23]. In this review article, we discuss the effects of selected pharmacological agents on the nerve regeneration after traumatic PNI in the animal studies evaluated by functional, histological and electrophysiological assessments (Fig. (1), Table 1). These medications were chosen on the basis of our laboratory's previous works in the field of peripheral nerve regeneration. These findings can not only help to find better strategies for peripheral nerve repair, but also to identify the neuropathic effects of various medications and their mechanisms of action.

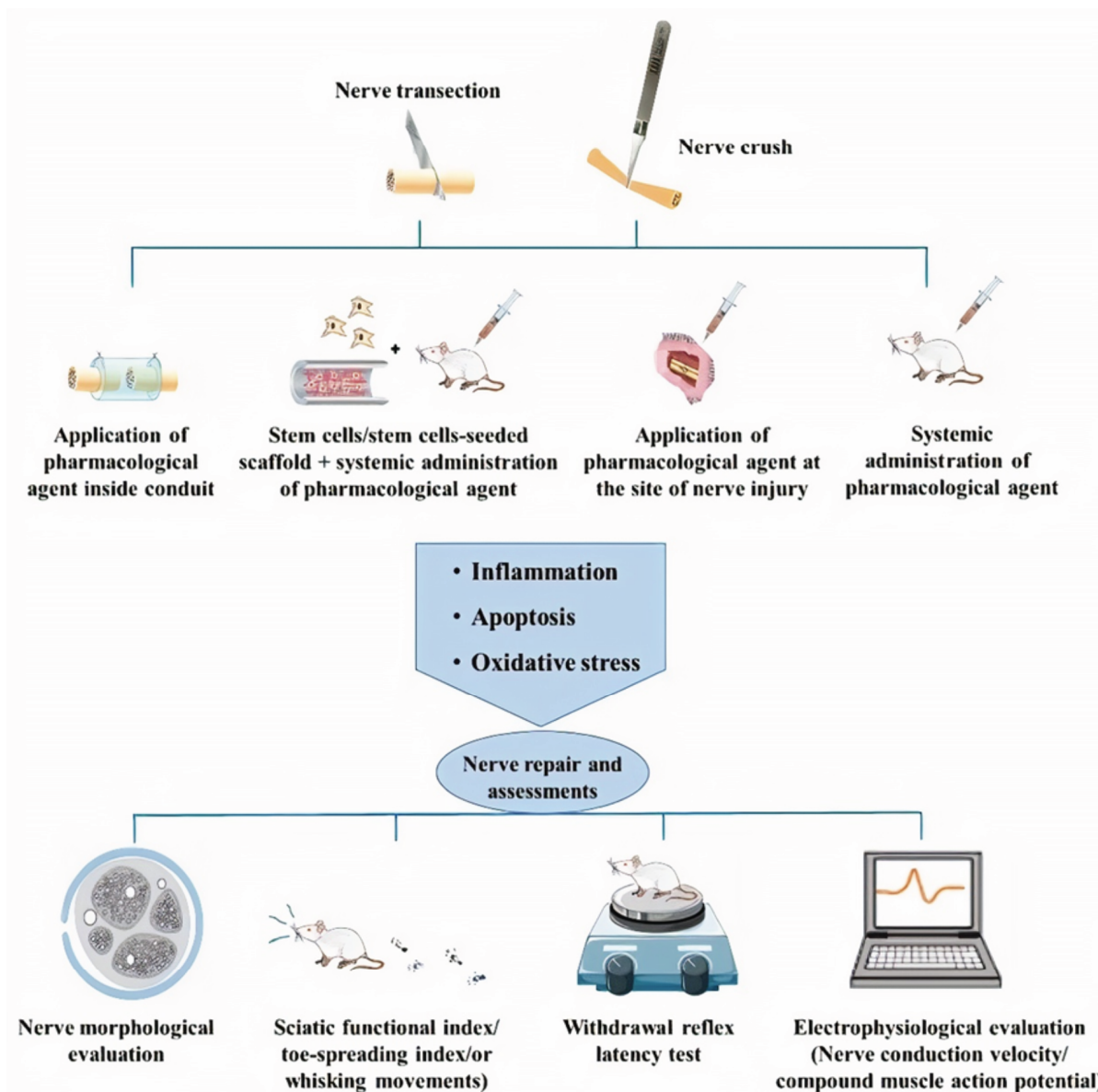
## 2. APPLICATION OF PHARMACOLOGICAL AGENTS AFTER SURGICAL REPAIR OF THE INJURED NERVE

### 2.1. Monotherapy (Pharmacotherapy)

#### 2.1.1. Dexamethasone

Dexamethasone is a potent anti-inflammatory glucocorticoid used for the treatment of acute spinal cord injuries [24]. Administration of this compound as topical (at doses of 1-4 mg/kg), systemic (2 mg/kg), or loaded in a silicone tube (0.1 mg/kg) improves the functional and morphological indexes of injured peripheral nerve [25-29]. A high dose of dexamethasone reduces the severity of Wallerian degeneration and delays the clearance of myelin debris after PNI [30]. Dexamethasone also has age-dependent effects on neuronal survival and functional recovery after facial nerve crush in mice [31]. According to a study, dexamethasone (1 mg/kg/day, for 7 days) slows functional recovery in the adult mice, while

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**Fig. (1).** *In vivo* study of the effects of the pharmacological agent on nerve regeneration after peripheral nerve injury. Two common models of traumatic peripheral nerve injury used in animal studies, including nerve crush and transection. Pharmacological agents, either alone or in combination with stem cells, are administered through different routes after / or before surgical repair of the injured nerve. They exert positive/or negative effects on nerve regeneration by influencing inflammation, apoptosis and oxidative stress. The success of nerve repair is evaluated by morphological, functional (motor and sensory) and electrophysiological assessments. (A higher resolution / colour version of this figure is available in the electronic copy of the article).

enhancing it in the juveniles after facial nerve crush. Moreover, neuronal survival is more decreased in juvenile mice than adults after treatment with dexamethasone [31]. Recent studies have shown that dexamethasone can act through mechanisms beyond anti-inflammatory action, such as upregulation of brain-derived neurotrophic factor (BDNF) [29], increasing the immunoreactivity of nerve growth factor (NGF) in nerve tissue [28], reducing fibrosis [28] and oxidative stress [32] after PNI. The other effects of dexamethasone on peripheral nerve tissue include being a potent comitogen for Schwann cell proliferation [33], increasing the viability of frataxin-depletion Schwann cells [34], inhibiting blood-nerve barrier disruption after sciatic nerve injury [35],

accelerating the time of initiation and the rate of myelin synthesis in Schwann cell/neuronal cocultures [36] and stimulating the transcription from the promoters of peripheral myelin protein-22 (PMP-22) and protein zero (P0) genes in Schwann Cells [37]. Although dexamethasone is widely used for the treatment of PNI in the animal studies, it can cause life-threatening side effects, either at high doses or after prolonged use [31, 38].

**2.1.2. Methylprednisolone**

Methylprednisolone is an intermediate-acting glucocorticoid widely used as a standard therapeutic agent for the treatment of spinal cord injury and idiopathic facial nerve

**Table 1. Summary of animal studies indicating positive (+) or negative (-) effects of pharmacological agents on the morphological, functional, and electrophysiological indexes of the injured peripheral nerve in adult animals.**

Application of pharmacological agents immediately after surgical repair of the injured nerve					
Medication	Nerve Injury Model	Route of Administration	Morphological Outcome	Functional Outcome	Electrophysiological Outcome
Dexamethasone	Sciatic nerve crush	Systemic (i.p.)	-[25]	+[25]	-
		Local	+[25, 29], -[28]	+[25, 29]	+[28, 29]
	Sciatic nerve transection	Local	+[27]	+[27]	-
	Facial nerve crush	Local	+[26]	+[26]	+[26]
Systemic (i.p.)		-[31]	-[31]	-	
Methylprednisolone	Sciatic nerve crush	Systemic (i.p.)	+[42, -50]	-	+[42]
	Sciatic nerve transection	Local	+[43, 49]	+[43, 49]	-
		Local	+[44]	+[44]	-
	Facial nerve crush	Systemic (i.p.)	-[44]	-[44]	-
		Systemic (i.m.)	+[48]	-	-
	Facial nerve transection	Systemic (i.m.)	-[46-48]	-	-[47]
Atorvastatin	Sciatic nerve crush	Systemic (oral)	+[59]	+[59]	+[59]
	Sciatic nerve transection	Systemic (i.p.)	-	+[61]	+[61]
	Facial nerve crush	Systemic (oral)	-	-[60]	-
Citicoline	Sciatic nerve transection	Local	+[77, 78]	+[77, 78]	+[77]
		Systemic (i.p.)	-	+[79, 80]	+[79, 80]
	Sciatic nerve crush	Local	-	+[81]	-
Acetyl-L-carnitine	Sciatic nerve transection	Systemic (i.p.)	+[88-90]	+[88]	-
		Local	+[91]	+[91]	+[91]
L-carnitine	Sciatic nerve crush	Systemic (oral)	+[93]	+[93]	-
	Sciatic nerve transection	Systemic (i.p.)	-[88]	-[88]	-
		Systemic (oral)	-[94]	+[94]	-
Memantine	Facial nerve crush	Systemic (i.p.)	-	+[96]	-
	Sciatic nerve crush	Systemic (i.p.)	-[97]	-[97]	-[97]
Riluzole	Sciatic nerve crush	Systemic (i.p.)	-[104]	-[104], +[105]	-[104]
	Facial nerve crush	Systemic (i.p.)	-[103]	-[103]	-
Application of pharmacological agents + stem cells immediately after surgical repair of the injured nerve					
Medication	Nerve Injury Model	Route of Administration	Morphological Outcome	Functional Outcome	Electrophysiological Outcome
Citicoline + bone marrow mesenchymal stem cells seeded on the decellularized nerve allograft	Sciatic nerve transection	Systemic (i.p.)	+[116]	+[116]	+[116]
Acetyl-L-carnitine + adipose-derived stromal cells seeded on the decellularized nerve allograft	Sciatic nerve transection	Systemic (i.p.)	+[20]	+[20]	+[20]
Dexamethasone + human mesenchymal stem cells seeded on a membrane	Sciatic nerve transection	Local	+[117]	+[117]	+[117]

(Table 1) contd....

Application of pharmacological agents in the delayed surgical repair of the injured nerve					
Medication	Nerve injury Model	Route of Administration	Morphological Outcome	Functional Outcome	Electrophysiological Outcome
Citicoline /or cytidine + choline	Sciatic nerve transection	Local	+ [78]	+ [78]	-
Mixture of acamprosate and ribavirin (NeuroHeal)	L3-L6 ventral root avulsion	Systemic (oral)	-	+ [123]	-
Methylprednisolone	Sciatic nerve transection	Systemic (i.p.)	+ [124]	-	-

<sup>i.p.</sup> and <sup>i.m.</sup> referred to intraperitoneal and intramuscular injection, respectively. Morphological outcome referred to morphometric parameters of the peripheral nerve (beyond fiber count) and dorsal root ganglion. Functional outcome referred to the sciatic functional index, withdrawal reflex latency and other indexes of functional recovery. Electrophysiological outcomes referred to each nerve conduction velocity, latency, and compound muscle action potential.

paralysis [39-41]. Unlike the positive effects of high doses of methylprednisolone (20, 30 and 160 mg/kg) on the nerve repair [42-45], the data on the effects of low doses of methylprednisolone (0.39 and 1 mg/kg) remains somewhat controversial [46-48]. Intramuscular administration of a low dose of methylprednisolone (1 mg/kg/day, for 2, 3 weeks and 2 months) has no effect on the nerve regeneration in the neurotomy model of facial nerve injury [46-48]; however, it increases nerve healing after compression of the facial nerve in the New Zealand rabbits [48]. Intraperitoneal injection of methylprednisolone (4 mg/kg, for 5 days) and topical application (20 mg/kg) of methylprednisolone-loaded hydrogel increases the expression of GAP-43 protein as a marker of regeneration and improves functional recovery after PNI [44]. The other effects of methylprednisolone include reducing the levels of nitric oxide (NO) and malondialdehyde (MDA) in the serum and nerve tissue [42, 45], increasing immunoreactivity for NGF and vascular endothelial growth factor (VEGF) in the endoneurium [42], and preventing the increase of endoneurial collagen fibers after PNI [47, 49]. Methylprednisolone (2mg/kg/day, for 14 days) also decreases Schwann cell atrophy, perineural granulation tissue and intraneural infiltration of inflammatory cells, despite increasing perineural inflammatory cells after sciatic nerve crush [50]. Also, an increase in scores of inflammation and fibrosis with chronic treatment by a low dose of methylprednisolone (0.5 mg/kg/day, for 4 weeks) has been reported [51].

### 2.1.3. Atorvastatin

Atorvastatin is a statin medication used for the treatment of hypercholesterolaemia [52]. Statins are inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG- CoA) reductase, the rate-limiting enzyme in the cholesterol biosynthesis pathway [53]. They exert the neuroprotective effects in neurodegenerative diseases such as Alzheimer's disease and multiple sclerosis [54, 55]. These effects have been attributed to the anti-inflammatory [56], anti-thrombotic [57], anti-excitotoxic [52], antioxidant [58] and immunomodulatory activities of statins [55]. Pretreatment with atorvastatin (5 mg/kg/day, for 1 week) improved the functional, electrophysiological, and morphological outcomes in a rat sciatic nerve crush model [59], while it (at the dose of 10 mg/kg) had no effect on the whisking recovery after facial nerve crush injury in the other study [60]. Atorvastatin treatment (5 mg/kg/day, for 14 days) after PNI also has improved the functional and electrophysiological outcomes yet [61]. On the other hand, atorvastatin treatment reduces oxidative stress [58, 59], apoptosis [59], matrix metalloproteinase ac-

tivity [59-62], inflammation [56, 59, 62, 63] and alleviates the disruption of the blood-nerve barrier at the early stage of nerve injury [59]. Moreover, atorvastatin upregulates the regeneration-associated genes, including growth-associated protein-43, myelin basic protein, ciliary neurotrophic factor, and collagen [59]. It also has a modulatory effect on the intracellular signalling molecules and transcription factors such as inhibiting extracellular signal-regulated kinase, AKT, signal transducer and activators of transcription-1, necrosis factor- $\kappa$ B and increasing activation of c-Jun N-terminal kinase, Smad2/3, and activating protein-1 [59]. It has been suggested that some effects of statins are due to the inhibition of isoprenylation of proteins (*e.g.*, Ras, Rho, Rac) involved in cellular signalling, proliferation and differentiation [64]. Conversely, epidemiological studies indicate that long-term use of statins is associated with peripheral neuropathy and myopathy [65-67].

### 2.1.4. Citicoline

Citicoline, also known as cytidine-5'-diphosphocholine (CDP-choline), is a natural intracellular precursor of phosphatidylcholine (PC), one of the most abundant phospholipids found in cell membranes [68]. Following injection or ingestion of citicoline in the rat, it is hydrolyzed into choline and cytidine, which enter cells separately and are used for intracellular synthesis of citicoline [69, 70]. It has therapeutic effects for neurological disorders [71-73] through increasing phospholipid synthesis and attenuating phospholipid destruction by reducing phospholipase A2 activity (PLA2) [74, 75]. PLA2 hydrolyzes phosphatidylcholine to lysophosphatidylcholine and arachidonic acid. The former can induce myelin breakdown and the latter involved in the induction of reactive oxygen species, lipid peroxidation and inflammatory responses [75, 76]. Local (78 mg/kg) or systemic (80 and 293 mg/kg) administration of each of citicoline, cytidine, choline or cytidine + choline, improves nerve regeneration and functional recovery after sciatic nerve injury in the rat [77-81]. These findings indicate that the beneficial effects of citicoline are likely to be mediated by its endogenous metabolites choline, cytidine, or both [78, 79]. Citicoline also reduces peripheral scar formation and nerve edema after sciatic nerve transection [77, 80].

### 2.1.5. L-carnitine

L-carnitine (levocarnitine; 3-hydroxy-4-N-trimethylaminobutyrate) is a naturally occurring compound with an obligatory role in the mitochondrial fatty acid metabolism [82]. It has neuroprotective effects in the CNS injury models

[83-85]. In the rodent intestines, L-carnitine undergoes extensive intracellular acetylation (50-60%) to generate the esterified carnitine, which can more readily cross the basolateral membrane [86, 87]. Long-term treatment with L-acetylcarnitine (50 mg/kg/day, for 2, 8 and 12 weeks) improves functional and histological outcomes and reduces muscle atrophy after PNI [88-90]. Acetyl-L-carnitine (1 ng) loaded in a chitosan conduit improved functional recovery and morphometric indexes of the injured sciatic nerve [91]. Moreover, acetyl-L-carnitine (100 mg/kg/day, for 15 days) prevents the induction of apoptosis in the distal segment of the ligated nerve by upregulation of XIAP [92]. L-carnitine (50 and 100 mg/kg/day, for 30 days) has also improved histological and functional outcomes after sciatic nerve crush in diabetic rats [93]. Another study has demonstrated that long-term treatment with L-carnitine (100 mg/kg/day, for 1 month) improves functional recovery and reduces inflammation, while short-term treatment (for 1 week) has no effect on the functional recovery after nerve transection [94]. Most of the above studies have reported the neuroprotective effect of acetyl-L-carnitine with its therapeutic effect at the doses of 50 and 100 mg/kg, which can be safe [88-90]. Meanwhile, some studies have demonstrated that L-carnitine (at doses of 50 and 100 mg/kg/day, for 15, 28 and 56 days) has no effect on nerve regeneration and apoptosis after the sciatic nerve injury [88, 92].

#### 2.1.6. Memantine

Memantine, as a derivative of amantadine, is non-competitive N-methyl-D-aspartate glutamate (NMDA) receptor antagonist that prevents excitotoxicity [95, 96]. Memantine (20 mg/kg/day, for 7 days) inhibited apoptosis and accelerated functional recovery after facial nerve crush [96], although it (5 and 10 mg/kg/day, for 7 days) had no effect on the histological outcome and functional recovery after sciatic nerve crush [97]. Intrathecal administration of memantine (200 µg) attenuates tactile allodynia and mechanical hyperalgesia induced by tight ligation of spinal nerves in the rats [98]. Pretreatment with memantine at a low dose (1.79 µg) prevents the induction of dynamic allodynia by blocking Kir2.1 channel and microglia activation in the spinal cord after spared sciatic nerve injury [99].

#### 2.1.7. Riluzole

Riluzole (2-amino-6-trifluoro-methoxy-benzothiazole) is currently the only clinically approved drug for the treatment of amyotrophic lateral sclerosis [100, 101]. The neuroprotective effects of riluzole are a result of blocking voltage-activated Na<sup>+</sup> channels and NMDA receptors and thereby reducing excitotoxicity [102]. Systemic administration of riluzole (4 mg/kg/day, for 4 weeks) had no effect on morphological and functional outcomes after facial nerve crush [103]. Moreover, another study has demonstrated that riluzole administration (4, 6 and 8 mg/kg/day, for 8 days) reduces functional, electrophysiological, and morphological outcomes after sciatic nerve crush [104]. Conversely, riluzole treatment (2, 4 and 8 mg/kg/day, for 3 days) has improved rat motor performance and coordination assessed in the open field and rotarod tests on the third day after sciatic nerve crush [105]. It was found that the administration of riluzole (4 and 16 mg/kg, for 2-3 weeks) increases the sur-

vival of neonatal and adult spinal motoneurons after axotomy [106-108]. It (0.1 µM) also enhances neurite outgrowth in terms of number, length and branch pattern in the adult L4 dorsal root ganglion culture after PNI [109]. Riluzole administration (4 mg/kg/day, for 5 days) attenuates the mechanical allodynia and thermal hyperalgesia through inhibiting the expression of P2X7 receptor (P2X7R) and microglial activation in the dorsal horn of spinal cord [110]. P2X7R is a microglia non-selective cation channel involved in the development of inflammatory and neuropathic pain and neuronal sensitization [111, 112].

#### 2.1.8. Combination Therapy (Stem Cells + Pharmacological Agent)

Stem cell therapy, in the form of cell transplantation or cell-seeded scaffolds for bridging the nerve gap, is the current method for repairing the injured nerves in the animal models [113]. These scaffolds have the advantages of removing the immunogenicity of the extracellular matrix and the seeded stem cells will eventually differentiate into Schwann cell-like cells [113, 114]. However, the survival of seeded or transplanted stem cells is yet a challenge [115]. Thus, the combination of stem cell therapy and pharmacotherapy may reduce the limitation of each strategy. In one study, administration of citicoline (200 mg/kg/day, for 2 weeks) in combination with bone marrow mesenchymal stem cells seeded on the decellularized nerve allograft improved morphological, functional and electrophysiological indexes of the injured sciatic nerve [116]. In the other study, administration of acetyl-L-carnitine (50 mg/kg/day, for 2 weeks) and adipose-derived stromal cells seeded on the decellularized nerve allograft led to regeneration across a 10-mm sciatic nerve gap, with results similar to those of the autografts in functional, electrophysiological, and histological assessments. In this study, acetyl-L-carnitine treatment attenuated apoptosis and upregulated the expression of NGF, BDNF, glial cell-derived neurotrophic factor (GDNF) and Schwann cell markers (S100 and P75) in the transplanted stem cells [20]. Moreover, local administration of dexamethasone (1 mg/kg) in combination with human mesenchymal stem cells seeded on a membrane has improved the histological, electrophysiological and functional outcomes (in comparison to each treatment alone) after sciatic nerve transection [117]. Lovastatin (5 and 10 µM) also enhances the differentiation of amniotic fluid stem cells to early Schwann cells in the culture. Treating stem cells with lovastatin upregulates Schwann cell markers (S100b and nestin) and lipogenic genes, including the low-density lipoprotein receptor (LDLR), HMG-CoA reductase and NAD(P) dependent steroid dehydrogenase-like (NSDHL) which play a role in myelin formation [118].

### 3. APPLICATION OF PHARMACOLOGICAL AGENTS IN THE DELAYED SURGICAL REPAIR

Most studies performed in the animal models of PNI are on the basis of immediate repair, while in the human PNIs, there is usually a delay between the nerve injury and surgical repair [119, 120]. This delay can be from a few days up to months and results in poor functional outcome [119, 121, 122]. This unsatisfied functional recovery indicates the necessity of the pharmacological interventions in the delayed

surgical repair and highlights the role of animal studies conducted in this field. In this regard, the local administration of citicoline /or cytidine + choline (78 mg/kg) improved morphological and functional outcomes when the surgical nerve repair was delayed for 3 days [78]. In the other study, oral administration of NeuroHeal, a mixture of acamprosate and ribavirin (2.2 and 1 mM, respectively, for 21 days or 6 months) enhanced motoneuron survival, nerve regeneration and the formation of functional neuromuscular junctions following detachment of L3-L6 ventral roots and reimplantation after a 2-week delay. NeuroHeal also reduced glial scar, muscular atrophy and accelerated nerve regeneration by activating the AKT pathway [123]. In addition, administration of methylprednisolone (2 mg/kg/day, for 2 weeks) during one month delayed nerve repair improved morphological indexes of the rat sciatic nerve [124].

## CONCLUSION

Pharmacological agents are cheap, accessible and non-invasive treatments that can be used in the first few hours after a PNI. They act in the forefront and the results of the other treatments depend on them. These medications may inhibit inflammation, oxidative stress and apoptosis and prevent deterioration of the injured nerves. In this regard, we suggest the administration of anti-inflammatory and CNS neuroprotective agents can be beneficial for peripheral nerve repair. However, timing, dose, route of medication administration and type of nerve injury should also be considered. Conversely, some pharmacological agents can cause neuropathy, accelerate nerve degeneration or delay regeneration. Administration of NMDA receptor antagonists has no or negative effects on the nerve repair in some studies. Also, it seems that the combination therapy (scaffold + stem cells + pharmacological agents) may be the best strategy for repairing nerve defects. However, the clinical application of this strategy still needs further research. On the other hand, the administration of pharmacological agents in the delayed repair is important since the regeneration capacity declines with delay in surgical repair. While most studies have focused on using pharmacological agents after the immediate surgical nerve repair, little is known about the effects of pharmacological agents on the delayed repair, which resembles delayed nerve repair in human. Then we suggest shifting future animal studies to this model, whose results are more translatable to the clinic. In conclusion, research in this area not only helps to find better strategies for peripheral nerve repair but also to identify the neuropathic effects of various medications and their mechanisms of action.

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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