

Non-surgical therapies for peripheral nerve injury

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Background: Non-surgical approaches have been developed to enhance nerve recovery, which are complementary to surgery and are an adjunct to the reinnervation process.

Sources of data: A search of PubMed, Medline, CINAHL, DH data and Embase databases was performed using the keywords 'peripheral nerve injury' and 'treatment'.

Areas of controversy: Most of the conservative therapies are focused to control neuropathic pain after nerve tissue damage. Only physical therapy modalities have been studied in humans and their effectiveness is not proved.

Growing points: Many modalities have been experimented with to promote nerve healing and restore function in animal models and *in vitro* studies. Despite this, none have been actually translated into clinical practice.

Areas timely for developing research: The hypotheses proved in animals and *in vitro* should be translated to human clinical practice.

Keywords: peripheral nerve injury/conservative management/non-surgical treatment/nerve recovery/enhance reinnervation

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Introduction

Peripheral nerve injuries (PNI) are common and have marked impact on the everyday life of the population at large. Thirty percent of these injuries arise from lacerations by sharp objects and long bone fractures,¹ and in the remaining penetrating injuries, crush, ischemia, traction, electric shock and vibration play a role.² Approximately 100 000 patients undergo peripheral nerve surgery in the USA and Europe annually.³ Severe nerve injury has a devastating impact on patients' quality of life.

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The primary goal of nerve repair is to allow reinnervation of the target organs by guiding regenerating sensory, motor and autonomic axons into the environment of the distal nerve with minimal loss of fibers at the site of repair.⁴ Many factors have to be taken into consideration when trying to predict the outcome of peripheral nerve repair, including type, location and extent of nerve injury; timing of surgery; type of repair; proper alignment of fascicles; surgical technique and patient comorbidities.⁵

In the last century, much has been learnt of peripheral nerve pathophysiology.⁶ The introduction of microsurgical nerve repair has been a breakthrough.⁷ Nerve allografting made it possible to bridge large nerve defects,⁸ which was previously unachievable with application of standard autografting methods.⁸ Tubularization techniques can eliminate the morbidity of autograft harvesting, and provide comparable outcomes in short nerve gap repair.⁹ However, despite meticulous surgical techniques and different repair methods, fully functional outcome, especially of motor function, is rarely achieved.¹⁰

Non-surgical approaches have been developed to enhance nerve recovery.^{11,12} These are complementary to surgery, and are an adjunct to the reinnervation process.^{13,14}

We review the literature on experimental non-surgical approaches for PNI recovery in human, animals and *in vitro* studies.

Material and methods

A search of PubMed, Medline, CINAHL and Embase databases was performed using the following keywords ‘peripheral nerve injury’ and ‘treatment’ on the 1 January 2011.

Scientific articles reporting *in vitro*, animal and human studies were suitable if detailing a non-surgical, conservative or adjuvant therapy in a peripheral nerve injury. Their bibliographies were thoroughly reviewed by hand to identify further related articles. To be included, the study had to be a prospective clinical study, a randomized controlled trial, a non-randomized clinical trial or a prospective case series. There had to be a well-described intervention in the form of application, the treatment, the source, the hypothesis, the method of administration and the target cell or nerve. The outcomes had to be reported in terms of (i) molecular changes, myelination or nerve regeneration *in vitro* studies, (ii) histological changes, electrophysiological reinnervation or functional outcomes in animal studies, and (iii) time of nerve regeneration, motor or sensory function.

We thus identified 54 of 479 studies which investigated the use of non-surgical treatments in PNI (Fig. 1).^{15–31} Of the 54 studies, 11 were undertaken *in vitro*, 39 in animal models and 4 in humans (Tables 1–3).

Exclusion criteria

Studies in language other than English, French, Italian, Spanish and Portuguese, pain therapies, spinal cord injuries and results published as abstracts only were excluded from the present study.

In vitro studies

Changes in the nerve at the site of injury begin almost immediately. Within hours after injury, the axons will sprout into multiple regenerating axons,^{32,33} and Schwann cells (SCs) play an important role in nerve regeneration at the site of injury. SC develop protein complexes that serve as physical conduits that guide axons to their targets. The rate of axon regeneration is limited by the extension of these SC processes

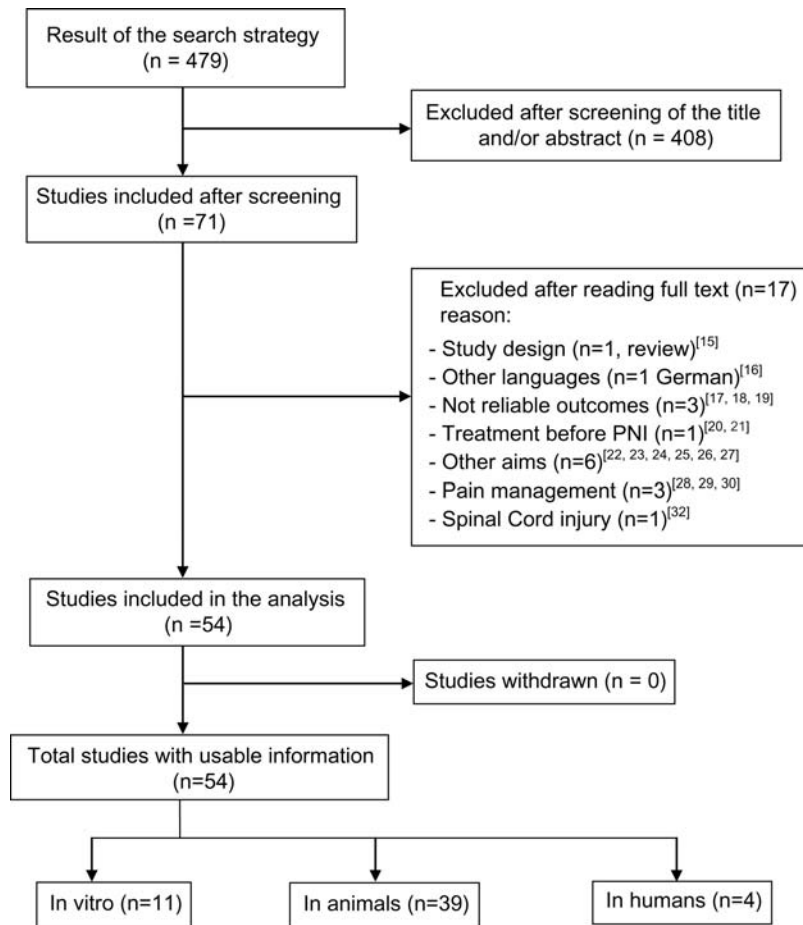


Fig. 1 Diagram flow

Table 1 *In vitro* studies (*n* = 11).

Schmitte <i>et al.</i> ³⁵	SC	Artificial biohybrid transplant	Transplanted canine SC contribute to the formation of bands of Büngner and are located in close vicinity to GAP-43 expressing regenerating nerve fibers. This provides first evidence that transplanted genetically modified SC do successfully integrate into the host tissue where they could actively contribute to the regeneration process.
Wan <i>et al.</i> ³⁶	Neurons and SC	Co-culture subjected to electrical stimulation (ES)	The ES of the site of nerve injury potentiated axonal regrowth and myelin maturation during peripheral nerve regeneration. The myelination progress was mediated via enhanced brain-derived neurotrophic factor signals, which driving the promyelination effect on SCs at the onset of myelination.
Liu <i>et al.</i> ³⁷	SC	Matrix metalloproteinases (MMPs) inhibitor	MMPs inhibitor enhanced division of cultured primary SCs. The administration immediately after rat sciatic nerve crush and daily thereafter produced increased nerve regeneration and growth-associated expression. After MMP inhibition, myelin basic protein mRNA expression and active mitosis of myelin-forming SCs were reduced.
Peng <i>et al.</i> ⁴⁰	Wharton's jelly-derived mesenchymal stem cells (WJMSCs)	WJMSCs source of Schwann-like cells	The differentiated WJMSCs secreted and expressed neurotrophic factors, including brain-derived neurotrophic factor, NGF and neurotrophin-3. The neurite outgrowth was significantly higher than the control medium and undifferentiated WJMSCs group.
Magill <i>et al.</i> ⁴²	Glial cell line-derived neurotrophic factor (GDNF)	Expression of GDNF after nerve crush injury	Peripheral delivery of GDNF resulted in earlier regeneration following sciatic nerve crush injuries than that with central GDNF delivery. Treatment with neurotrophic factors such as GDNF may offer new possibilities for the treatment of peripheral nerve injury.
Matsuse <i>et al.</i> ³⁹	Human umbilical cord-derived mesenchymal stromal cells (UC-MSCs)	To induce UC-MSCs to differentiate into cells with SC properties (UC-SCs)	Immunohistochemistry and immunoelectron microscopy demonstrated myelination of regenerated axons by UC-SCs. Cells with SC properties and with the ability to support axonal regeneration and reconstruct myelin can be successfully induced from UC-MSCs to promote functional recovery after peripheral nerve injury.

Walsh <i>et al.</i> ³⁸	Skin-derived precursor cells (SKPs)	SKPs source of transplantable cells	Immunohistology showed survival of both cell types and early regeneration in SKP-seeded grafts was comparable to those seeded with SCs. Histomorphometrical and electrophysiological measurements showed significant improvement as compared with diluent controls. Eight weeks after implantation, morphological analysis revealed that LCL, MCL and HCL controlled-release nerve conduits were similar to autograft treatment in numbers and area of myelinated axons. A high concentration of NGF at 5–10 days in LCL groups is needed in bridging a 15-mm peripheral nerve injury.
Chang ⁴⁶	NGF	NGF release characteristics among controlled-release nerve conduits	Plain electrospun fibers can help in peripheral nerve regeneration; however, the synergistic effect of an encapsulated growth factor facilitated a more significant recovery.
Chew <i>et al.</i> ⁴³	GDNF	GDNF encapsulated in aligned biodegradable polymeric fibers	Endothelin treatment of PC12 does not cause upregulation of heat shock proteins. Regulation of heat shock proteins after nerve injury is not likely due to endothelin signaling.
Klass <i>et al.</i> ⁴⁷	Tissue culture model for the sciatic nerve (PC12 cells)	Potential regulation of heat shock proteins by endothelin.	Amplitudes of distally evoked compound muscle action potentials are increased significantly faster after axonal injury in mice treated with fasudil compared with controls. Histological analysis shows that fasudil treatment increases the number of regenerating axons with large diameter.
Hiraga <i>et al.</i> ⁴⁸	Rho-kinase inhibitor, fasudil	RhoA/Rho-kinase as a molecular target to enhance axonal regeneration	

Table 2 Studies in animals ($n = 39$).

Câmara <i>et al.</i> ⁷⁰	Rat sciatic nerve	Low-intensity laser therapy (904 nm)	The low-intensity laser therapy group showed an increased number of SC, myelinic axons with large diameter and neurons than the control with a significant level.
Haastert-Talini <i>et al.</i> ⁵⁵	Rat sciatic nerve	Low-frequency electrical stimulation	Combining low-frequency electrical stimulation to nerve autotransplantation, silicone tubes filled of SC or tubular grafts with fibroblast growth factor showed a high rate of nerve regeneration.
Kosins <i>et al.</i> ⁸⁵	Rat sciatic nerve	Immunological demyelination	Immunological demyelination enhanced regeneration in the peripheral nerve system. The axon count, axon density and nerve fiber diameter within the region of acute crush injury was improved.
Luria <i>et al.</i> ⁸⁶	Rat sciatic nerve	Glatiramer	Regenerated axons partially derived from the proximal motor axons. A single treatment with glatiramer acetate resulted in accelerated functional and histological recovery after sciatic nerve crush injury. The role of T-cell immunity in the mechanism of glatiramer acetate was suggested by the partial and late response found in the T-cell-deficient rats.
Joung <i>et al.</i> ⁷¹	Rat sciatic nerve	Neuregulin 1	Promoted nerve regeneration in the histology of axons, Schwann cells and increased expression of neurofilaments, GAP43 and S100 in the distal stump. Sensory and motor functions were significantly improved in treated animals in behavioral tests.
Yin <i>et al.</i> ¹²⁰	Rat sciatic nerve	Erythropoietin	Increase in the axon diameter, myelin thickness and total number of nerve fibers as well as the degree of maturity of regenerated myelinated nerve fibers in comparison with those rats not treated with EPO.
Li <i>et al.</i> ⁸⁸	C57BL/6 mice	Apolipoprotein E mimetic peptide (COG112)	There was no significant difference in the motor function between the two groups at 4 weeks. COG112 promoted axonal regrowth after 2 weeks of treatment by elevating the markers of axon regeneration and remyelination, and thickening the myelin sheaths.
Gu <i>et al.</i> ⁷⁵	Rat	Transplant fetal neural stem cells (NSCs)	COG112 significantly promoted axon elongation in primary dorsal root ganglion cultures from rat pups.
Apel <i>et al.</i> ⁷³	Rat	IGF-1	Electrophysiological analysis and retrograde tracing manifested that the neural pathway between muscle and differentiated neurons was integrity. Fetal NSCs transplanted into peripheral nerves could differentiate into neurons and form functional NMJs with denervated muscle.
			IGF-1 significantly improved axon number, diameter and density. IGF-1 also significantly increased myelination and SC activity and preserved the morphology of the postsynaptic neuromuscular junction.

Mehanna <i>et al.</i> ⁹⁴	Mouse femoral nerve	Alpha 2,8 polysialic acid (PSA)	Retrograde tracing of regenerated motoneurons and morphometric analyses showed that motoneuron survival, motoneuron soma size and axonal diameters were not affected by treatment with the PSA mimetic. However, remyelination of regenerated axons distal to the injury site was considerably improved by the PSA mimetic indicating that effects on SCs in the denervated nerve may underlie the functional effects seen in motor recovery. SC proliferation <i>in vivo</i> was enhanced in both motor and sensory branches of the femoral nerve by application of the PSA mimetic.
Wilson <i>et al.</i> ⁹⁷	Rat sciatic nerve	Acetyl-L-carnitine (ALCAR)	ALCAR not only increases the number of regenerating nerve fibers but also morphologically improves the quality of regeneration and target organ reinnervation.
Sharma <i>et al.</i> ⁵⁸	Rat facial nerve	Electrical stimulation (ES) + testosterone propionate (TP)	The two treatments differentially enhance facial nerve regenerative properties, whereby ES reduced the delay before sprout formation, TP accelerated the overall regeneration rate and the combinatorial treatment had additive effects.
Pan <i>et al.</i> ⁷⁸	Rat sciatic nerve	Amniotic fluid mesenchymal stem cells (AFS) + hyperbaric oxygen (HBO)	AFS in combination with HBO augment peripheral nerve regeneration, which may involve the suppression of apoptotic death in implanted AFS and the attenuation of an inflammatory response detrimental to peripheral nerve regeneration.
Pan <i>et al.</i> ⁷⁹	Rat sciatic nerve	AFS + granulocyte-colony stimulating factor (G-CSF)	Crush injury-provoked inflammation was attenuated in groups receiving G-CSF but not in AFS only group. In transplanted AFS, marked apoptosis was detected and this event was reduced by G-CSF treatment. Increased nerve myelination and improved motor function were observed in AFS transplanted, G-CSF administrated and AFS/G-CSF combined treatment groups.
Pan <i>et al.</i> ⁸⁰	Rat sciatic nerve	Natto/AFS/Natto + AFS	Significantly, the combined treatment showed the most beneficial effect. Administration of Natto suppressed the inflammatory responses and correlated with decreased AFS and SC apoptosis.
Lu <i>et al.</i> ⁵⁷	Rat sciatic nerve	ES	The combined therapy caused the most significantly beneficial effects. The group receiving ES, especially at 1 mA had significantly shorter latency, larger amplitude, larger area of the evoked muscle action potentials and faster conduction velocity compared with the controls. However, ES at 4 mA provoked adverse responses to the function recovery of regenerated nerves in the kinematic gait analysis.
Wei <i>et al.</i> ¹⁰⁰	Rat sciatic nerve	Lumbricus extract	ES appears to have a detrimental effect on the regeneration process. For nerve function index value, for conduction velocity, for the number of regenerated myelinated nerve fibers, treatment group is higher than the control group at weeks 2 (3) and 6.
Padilla-Martin <i>et al.</i> ⁹⁹	Rat sciatic nerve	Glycine intravenous	Glycine was effective in the morphologic regeneration and functional recovery of the sciatic nerve postinjury in Wistar rats with 1 month administration.

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Table 2 Continued

Pan et al. ¹⁰²	Rat sciatic nerve crush injury	Fermented soybeans (natto)	Increased functional outcome such as sciatic nerve functional index, angle of ankle, compound muscle action potential and conduction latency were observed in natto-treated group. Prolonged prothrombin time and reduced fibrinogen but did not change activated partial thromboplastin time and bleeding time. Decreased injury-induced fibrin deposition. The increased production of TNF-alpha and apoptosis were attenuated by natto treatment.
Wei et al. ¹⁰¹	Rat sciatic nerve	Hedysari polysaccharide	HPS was able to enhance sciatic function index (SFI) value, tibial function index (TFI) value, peroneal nerve function index (PFI) value, conduction velocity, and the number of regenerated myelinated nerve fibers.
Asensio-Pinilla et al. ⁶⁰	Rat sciatic nerve	Electrical stimulation (ES) and exercise	Groups that received acute ES and/or were forced to exercise in the treadmill showed higher levels of muscle reinnervation and increased numbers of regenerated myelinated axons when compared to control animals or animals that received chronic ES.
Elfar et al. ⁸⁹	Rat sciatic nerve	Erythropoietin	The maintenance of activity helps to prevent the development of hyperreflexia. The sciatic function index was 60% better in the erythropoietin-treated mice at 7 days postinjury ($P < 0.05$). Although the group that had been given the erythropoietin immediately postinjury showed the best enhancement of recovery, the timing of the administration of the drug was not critical. Histological analysis demonstrated enhanced erythropoietin-receptor positivity in the nerves that recovered fastest, suggesting that accelerated healing correlates with expression of the receptor in nerve tissue.
Delaviz et al. ⁷⁶	Rat sciatic nerve	Olfactory ensheathing glia (olfactory mucosa transplant)	The total number of Dil-labeled motoneurons in the ventral horn (L4–L6) and the sciatic function index scores were significantly higher in the group of rats that received olfactory mucosa rather than respiratory mucosa.
Cámara-Lemarroy et al. ⁸⁷	Rat sciatic nerve crush injury	Celecoxib (COX-2 inhibitor)	Celecoxib had beneficial effects on sciatic function index, with a significantly better score on Day 7.
Chabas et al. ⁹⁸	Rat peroneal nerve	Peroneal nerve autograft + vitamin D2	Vitamin D2 significantly increased axogenesis and axon diameter, improved the responses of sensory neurons and induced a fast-to-slow fiber tpe transition of the Tibialis anterior muscle.
Jankowski et al. ¹⁰⁴	Mouse saphenous nerve	Sox11 siRNA	Analysis of Sox11 RNAi-injected nerves showed that regeneration of myelinated and unmyelinated axons was inhibited. All neurons in ganglia of crushed nerves that were Sox11 immunopositive showed colabeling for the stress and injury-associated activating transcription factor 3.

Zuijendorp <i>et al.</i> ¹⁰⁵	Rat sciatic nerve	Regenerating agents (OTR4120) adhesion tissues	<p>No significant difference in conduction capacity between the RGTA and the control group.</p> <p>The static footprint analysis demonstrates no improved or accelerated recovery pattern.</p> <p>The mean pullout force of the RGTA group (67 ± 9 g) was significantly ($P < 0.001$) lower than that of the control group (207 ± 14 g).</p> <p>The RGTAs strongly reduce nerve adherence to surrounding tissue after nerve crush injury.</p>
Panseri <i>et al.</i> ⁸²	Rat sciatic nerve	Electrospun tubes (bioscaffolds)	<p>Electrospun tubes induced nervous regeneration and functional reconnection of the two severed sciatic nerve tracts.</p> <p>Myelination and collagen IV deposition have been detected in concurrence with regenerated fibers.</p> <p>Reinnervation of the target muscles in the majority of the treated animals.</p>
Rochkind <i>et al.</i> ⁶⁸	Rat sciatic nerve	Laser phototherapy	<p>Positive somatosensory-evoked potentials at 3 months: 70% laser group >40% non-irradiated rats.</p> <p>More intense axonal growth.</p>
Grasso <i>et al.</i> ⁹⁰	Rat sciatic nerve	rHuEPO or darbepoetin alfa	<p>Darbepoetin alfa shortened the duration of peripheral nerve recovery' and facilitated recovery from the neurological and electrophysiological impairment following crush injury significantly better than rHuEPO.</p> <p>The administration of erythropoietin in its long-lasting recombinant forms affords significant neuroprotection in peripheral nerve injury models and may hold promise for future clinical applications.</p>
Hess <i>et al.</i> ⁸⁴	Primates ulnar nerve	Autografts, fresh allografts, cold-preserved allografts (CPA), CPA seeded with SCs	<p>Cytokine production in response to cold-preserved allografts and cold-preserved allografts seeded with autologous SCs was similar to that observed for autografts. SC-repopulated cold-preserved grafts demonstrated significantly enhanced fiber counts, nerve density and percentage nerve ($P < 0.05$) compared with unseeded cold-preserved grafts at 6 months after reconstruction.</p>
Zou <i>et al.</i> ¹⁰³	Mouse	Tissue plasminogen activator	<p>Tissue plasminogen activator increased the number of macrophages and induced MMP-9 expression at the injury site, coincident with reduced collagen scar formation and accelerated clearance of myelin and lipid debris after treatment.</p>
Kadoya <i>et al.</i> ⁹³	Rat sciatic nerve	Oxidized galectin-1	<p>The recovery curves of toe spread in the test group showed a statistically significant improvement of functional recovery after Day 21 by the application of oxidized recombinant human galectin-1/Ox compared with the control group. This functional recovery was supported by histological analysis.</p>
Rovak <i>et al.</i> ⁷⁴	Rat peroneal nerves	Vascular endothelial growth factor (VEGF-165)	<p>Two-centimeter nerve gaps were created in rat peroneal nerves and repaired with either peripheral nerve autografts, acellular peripheral nerve isografts or VEGF-165-treated acellular peripheral nerve isografts.</p> <p>In the absence of any cellular elements, VEGF-impregnated acellular peripheral nerve grafts do not demonstrate enhanced axonal elongation, as noted by relatively few axons at the distal nerve graft coaptation site.</p>

Continued

Table 2 *Continued*

Rochkind <i>et al.</i> ⁸³	Rat 2 cm sciatic nerve defect	Composite neurotube + survival factors	Electrophysiological study indicated compound muscle action potentials in 9 of 12 rats, 2–4 months after peripheral nerve reconstructive surgery. Beginning of re-establishment of active foot movements at fourth month after surgery.
Kalmar <i>et al.</i> ¹⁰⁶	Rat sciatic nerve (sensory system)	BRX-220 (co-inducer of heat shock proteins)	Treatment did not prevent the emergence of mechanical or thermal hyperalgesia. However, oral treatment for 4 weeks lead to reduced pain-related behaviour suggesting either slowly developing analgesic actions or enhancement of recovery processes. Treatment with BRX-220 promotes restoration of morphological and functional properties in the sensory system following peripheral nerve injury. Increase in the total numbers of regenerated myelinated nerve fibers and reinnervated muscle fibers. Motor function and plateau levels faster with VA > control. No differences in motor function.
Cui <i>et al.</i> ⁹⁵	Rat sciatic nerve	Valproic acid (VA)	In 5-mm nerve defects, the quality of nerve regeneration was similar to that of the control group. For 10-mm nerve defect, nerve regeneration was inferior to that of the control group. Chitosan-collagen film degraded at 12 weeks postoperatively. Higher sciatic function index, toe spreading reflex, amplitude and velocity of MCAP and NCAP, mean axon count above the lesion for thick myelinated fibers (>6.5 μ m), mean axon count above the lesion for thin myelinated fibers (2–6.5 μ m) for MS > control. Acetylcholine esterase examination showed that the MS could significantly increase the number of the motor neurons, but there was no significant difference in the number of the motor neurons between the treatment side and the normal side ($P > 0.05$).
Wei <i>et al.</i> ¹⁰¹	Rat sciatic nerve	Chitosan	Allogeneic SCs were rejected by 6 weeks, whereas syngeneic SC could still be identified. Equally enhanced the axonal regeneration distance but the quantity of axons was greater using syngeneic SC. Allogeneic SC did not induce deleterious immune response. SC continued to express phenotypic markers of non-myelination and these were highest in conduits with allogeneic SC. Neither NT3, nor NGF-treatment significantly enhanced motor recovery as examined by gait analysis. At the end of 12 weeks of behavioral testing, there was no difference in motor recovery. Regenerated sciatic nerves from NT3-treated animals had slightly more axons than control- or NGF-treated animals.
Bannaga <i>et al.</i> ⁶⁴	Rat sciatic nerve	Magnetic stimulation (MS)	Treatment of animals with DEDC caused a significant delay in functional recovery, which was accompanied by poor histological and electrophysiological outcome. Prooxidant effect of DEDC is quite evident from a significant decrease in vitamin E levels.
Mosahebi <i>et al.</i> ⁸¹	Rat sciatic nerve	Allogenic vs. syngeneic SCs	
Young <i>et al.</i> ⁷²	Rat sciatic nerve	NGF and neurotrophin-3 (NT3)	
Tariq <i>et al.</i> ¹⁰⁷	Rat sciatic nerve	Diethylidihio-carbamate (DEDC)	

Table 3 Studies in humans ($n = 4$).

Rochkind <i>et al.</i> ⁵⁹	Laser phototherapy	Rat/ <i>in vitro</i> /humans	The function of denervated muscles can be restored, not completely but to a very substantial degree. It has an immediate protective effect. It maintains functional activity of the injured nerve for a long period, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord and significantly increases axonal growth and myelination.
		<i>In vitro</i>	In cell cultures, laser irradiation accelerates migration, nerve cell growth and fiber sprouting.
Gordon <i>et al.</i> ¹³	Low-frequency electrical stimulation (LFES)	Median nerve (carpal tunnel syndrome)	Similar effects in animals and humans. The application of LFES significantly accelerated nerve regeneration.
		Rat femoral nerve	The mechanisms of action of electrical stimulation likely operate through up-regulation of neurotrophic factors and cyclic adenosine monophosphate.
Rochkind <i>et al.</i> ⁶⁹	Low-power laser irradiation	Incomplete peripheral nerve and brachial plexus injury	Motor function at 6 months: the recruitment of voluntary muscle activity was higher in the laser group than in the control group.
Hao <i>et al.</i> ¹¹²	Acupuncture	Peripheral nerve injury (54 cases -54 controls)	No differences in sensory function. Total effective rate of 92.6% in contrast to the 55.6% for the controls. Nerve injuries should be treated as early as possible. The radial nerve and the common peroneal nerve recovered faster than others. Cases not surgically explored recovered faster than those that were. Patients with prompt propagation of the needling sensation recovered significantly faster than those with slow propagation.

rather than by axonal growth.³⁴ For extended nerve defects, bridging with an autologous nerve transplant is the gold standard therapy, but has the disadvantage of donor-site morbidity. Natural or artificial nerve conduits could support nerve regeneration over longer distances and obviate the risk of rejection and immunosuppression. Schmitte *et al.*³⁵ described an artificial biohybrid nerve transplant, which combines a synthetic conduit with autologous SC genetically primed to express regeneration-promoting proteins. After the manipulation of the SC, they successfully integrated into the host tissue where they could actively contribute to the regeneration process. Wan *et al.*³⁶ co-cultured the neurons and the SC of a sciatic nerve of rats after a crush injury. The culture was subjected to 1 h of continuous electrical stimulation. A potentiated

regrowth and myelin maturation was evident in the group receiving electrical stimulation than the controls. The myelination was mediated via enhanced brain-derived neurotrophic factor signals.³⁶ Other ways to modulate the SC signalling and mitosis could be through the action of the matrix metalloproteinases.³⁷ Liu *et al.*³⁷ tested the hypothesis that the administration of matrix metalloproteinases inhibitor stimulated mitosis in the SC and advanced nerve regeneration. The study³⁷ established novel roles for matrix metalloproteinases in peripheral nerve repair via control of SC mitosis, differentiation and myelin protein mRNA expression.

Other sources of transplantable cells to enhance nerve regeneration have been proposed. Skin-derived precursor cells are an easily accessible source of autologous stem cells with the ability to secrete bioactive neurotrophins, acting as functional SC.³⁸ In a rat sciatic nerve gap of 12 mm, after 4 weeks immunohistology showed survival of both cell types, and early regeneration in skin-derived precursor cells seeded grafts was comparable to those seeded with SCs.³⁸

Human umbilical cord-derived mesenchymal stromal cells were effective for axonal regeneration comparable to that of human SC based on histological criteria and functional recovery.³⁹ Immunohistochemistry and immunoelectron microscopy also demonstrated myelination of regenerated axons by human umbilical cord-derived mesenchymal stromal cells.³⁹ Wharton's jelly-derived mesenchymal stem cells have recently shown promising results,⁴⁰ being able to differentiate into SC in terms of morphologic features, phenotype and function.

Changes in the levels of neurotrophins within both the proximal and distal stump also occur. Neurotrophin 4/5 mRNA in the distal stump is increased, as well as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF). In sensory nerves, neuropeptides such as substance P decrease, whereas vasoactive intestinal peptide and cholecystikinin increase.⁴¹ Magill *et al.*⁴² evaluated the levels of GDNF using histomorphometry and muscle force and power testing after a rat sciatic nerve crush, and confirmed the increased levels at 2 weeks, but no differences with the controls at 6 weeks. When GDNF was encapsulated in a biodegradable protein polymeric composite, after 3 months of bridging, a 15-mm sciatic nerve gap of both substances acted synergistically.⁴³

NGF is secreted by SC after axotomy,^{44,45} but at 3 weeks its levels decrease. Different lag-time of pulse-released NGF within polycaprolactone conduits showed bioactivity of the NGF by neurite outgrowth of PC12 cells.⁴⁶ With a high concentration of the NGF within low crosslink controlled-release nerve conduits made it possible to bridge a 15 mm rat sciatic nerve defect.⁴⁶

Heat shock proteins and endothelin are upregulated after peripheral nerve injury. Heat shock proteins are important in neuroprotection after a variety of stresses or injuries, but their regulation has not been systematically studied in peripheral nerves. Using a tissue culture model for the sciatic nerve (PC12 cells), Klass *et al.*⁴⁷ found that endothelin treatment did not cause up-regulation of heat shock proteins.

After nerve transection, the distal segment undergoes a slow process of degeneration known as Wallerian degeneration. This process starts immediately after injury and involves myelin breakdown and proliferation of SC. These proliferating SC organize themselves into columns, and the regenerating axons associate with them by growing distally in between their basal membranes. RhoA, a key regulator of neurite elongation after nerve injury, is activated in motoneurons. Its effector, Rho-kinase, retards axon regeneration. Hiraga *et al.*⁴⁸ employed fasudil, a Rho-kinase inhibitor, finding an increased number of regenerating axons with large diameter, without suppressing the myelination of regenerating axons. Given these findings that benefit the maturity of axons, Rho-kinase could be a practical molecular target in peripheral neuropathies.⁴⁸

Animal studies

Physical therapies

A peripheral nerve injury produces degeneration of the distal axon to the injury, retrograde degeneration of their corresponding neurons of the spinal cord, followed by a very slow regeneration. Recovery may eventually occur, but it is slow and frequently incomplete. The secondary effects of peripheral nerve injury are muscle wasting and a high incidence of pressure sores. Therefore, numerous attempts have been made to enhance and/or accelerate the recovery of injured peripheral nerves and decrease or prevent atrophy of the corresponding muscles. Electrical stimulation produces neurobiological effects, such as relieving pain in the region of head and face⁴⁹ and restoring movement and function in individuals with spinal cord injury.^{50,51} It can directly exert effects on regenerating neural tissues in a well-controlled experimental environment.⁵² Low-frequency electrical stimulation holds promise to accelerate nerve regeneration after injury.^{53–55} However, a high frequency of electrical stimulation may increase failure of nerve regeneration.⁵⁶ Therefore, electrical stimulation could have a positive or negative impact on peripheral nerve regeneration depending on the current power of the electrical stimulus.⁵⁷

Electrical stimulation with testosterone propionate⁵⁸ has differential effects on gene expression, with electrical stimulation leading to early

but transient upregulation. Also testosterone propionate produces late but steady increases in mRNA levels. In comparison to individual treatments, the combinatorial treatment strategy has the most enhanced effects on the transcriptional program activated following the injury.⁵⁸

The short-term application of low-frequency electrical stimulation of proximal peripheral nerve stumps prior to end-to-end coaptation or tubular bridging of small distances has been reported to increase preferential motor reinnervation and functional motor recovery in animal models and human patients undergoing carpal tunnel release surgery.⁵⁹ Haastert-Talini *et al.*⁵⁵ studied the effects of the low-frequency electrical stimulation on three different reconstruction approaches: nerve autotransplantation, silicone tubes filled with SC, and tubular grafts containing fibroblast growth factor. In all instances, the combination showed a high rate of nerve regeneration, and in the nerve autotransplantation and the tubular graft groups, the construct functionally reconnected to the target muscle.

With electrical stimulation and exercise,⁶⁰ rats that received acute electrical stimulation and/or were forced to exercise on the treadmill had higher levels of muscle reinnervation and increased numbers of regenerated myelinated axons when compared with control animals or animals that received chronic electrical stimulation. Combining electrical stimulation after suture repair with treadmill training significantly improved muscle reinnervation during the initial phase. The facilitation of the monosynaptic H reflex in the injured limb was reduced in all treated groups, suggesting that maintenance of physical activity helps to prevent the development of hyperreflexia.

In veterinary medicine, electrodiagnostic evaluation of peripheral nerve disorders is mostly achieved by electrical stimulation of peripheral nerves,⁶¹ but little is known about magnetic nerve stimulation in animals. With electrical stimulation, current is passed into the body via needle electrodes. In magnetic stimulation a brief magnetic pulse induces a current in conductive tissues.⁶² Magnetic stimulation provides a non-invasive and almost painless alternative to electrical nerve stimulation. The disadvantages of the technique are (i) problems in obtaining a consistent supramaximal response as compared to the response obtained after electrical stimulation and (ii) defining the exact site of localisation.⁶³

Magnetic stimulation⁶⁴ could enhance functional recovery, and has a considerable effect in the management of the peripheral nerve injury. However, there was a non-significant trend of increasing the number of motor neurons ($P > 0.05$) in rats after a crushed sciatic nerve.⁶⁴

Low-power laser irradiation (laser phototherapy) enhances and/or accelerates the recovery of injured peripheral nerves, and decreases or prevents atrophy of the corresponding muscles.⁶⁵ Although a

pioneering report on the effects of laser phototherapy on the regeneration of traumatically injured peripheral nerves was published in the late 1970s,⁶⁶ only since the late 1980s scientific interest was shown in this therapeutic approach for neural rehabilitation.^{67,59}

Laser phototherapy was applied to rat-denervated muscle to estimate biochemical stimulus on cellular and tissue levels, and on rat sciatic nerve model after crush injury, direct or side-to-end anastomosis and neurotube reconstruction.⁶⁸ Nerve cells growth and axonal sprouting were investigated in embryonic rat brain cultures. Animal outcomes proved the basis for future human randomized control trials measuring the effectiveness of 780-nm laser phototherapy.⁶⁹ A recent study analyzed the influence of the low-intensity laser therapy in regeneration of the sciatic nerve in rats.⁷⁰ Although the wavelength of the laser used in that investigation, 904 nm, differed from the study of Rochkind *et al.*,⁶⁹ they also found positive effects in the regeneration of the injury nerve.

Growth factors

Schwann cells play an important role in axon regeneration. The rate of axon regeneration is limited by the extension of these SC processes rather than by axonal growth.³⁴ Joung *et al.*,⁷¹ based on the hypothesis that Neuregulin 1 and epidermal growth factor receptor signaling pathways control SC during axonal regeneration, investigated whether a persistent supply of recombinant Neuregulin 1 to the injury site could improve axonal growth and recovery of sensory and motor functions in rats during nerve regeneration. Transduction of the concentrated form of Neuregulin 1 into an axotomy model of sciatic nerve damage induced an effective promotion of nerve regeneration, as shown by histological features of the axons and SC, as well as increased expression of neurofilaments, growth associated protein-43 (GAP-43) and S100 in the distal stump of the injury site. This result was consistent with longer axon lengths and thicker calibers observed in the treated animals. Furthermore, sensory and motor functions were significantly improved in treated animals when evaluated by a behavioral test.⁷¹

Changes in the levels of neurotrophins within both the proximal and distal stump take place after a nerve injury. NGF is secreted by SC after axotomy,^{44,45} but at 3 weeks its levels decrease. Chang⁴⁶ demonstrated *in vitro* that a high concentration of NGF within low crosslink controlled-release nerve conduits made possible to bridge a 15 mm rat sciatic nerve defect.⁴⁶ However, a continuous supply of NGF and neurotrophin-3 did not improve long-lasting anatomical or functional outcomes in rats 12 weeks after sciatic nerve transection.⁷²

Some neurotrophic factors decline with age, and the insulin-like growth factor 1 (IGF-1) is one of them.⁷³ Apel *et al.*⁷³ showed that in

young and aged rats, the continuous deliver of IGF-1 to the site of nerve repair, compared with saline, significantly improved axon number, diameter, density, myelination and Schwann cell activity and preserved the morphology of the postsynaptic neuromuscular junction.

Growth factors can be applied locally or added to grafts. In a 2 cm peroneal nerve gap in rats, Rovak *et al.*⁷⁴ compared the effects of a peripheral nerve autograft, an acellular peripheral nerve isograft and an acellular peripheral nerve isografts supplemented with human recombinant vascular endothelial growth factor (VEGF-165). Even though nerve autografting is still the gold standard for nerve gap repair, shorter defects up to 3 cm can be repaired with natural or artificial conduits.⁵ At the proximal nerve gap coaptation site, there was a statistically significant ($P < 0.05$) increase in the total number of axons and percent neural tissue in the VEGF-treated acellular nerve graft group, compared with the acellular peripheral nerve isograft and autograft groups. At the distal coaptation site, the total number of axons and percent neural tissue was significantly less than the autograft group. Rovak *et al.*⁷⁴ concluded that, in the absence of any cellular elements, the vascular endothelial growth factor did not enhanced axonal elongation.

Cell sources

Injuries to peripheral nerves result in progressive skeletal muscle atrophy and poor functional recovery. Transplanting neural stem cells into peripheral nerves can induce differentiation into neurons and delay muscle atrophy. However, the mechanisms are not clear.⁷⁵ Gu *et al.*⁷⁵ demonstrated in rats that fetal neural stem cells transplanted into peripheral nerves could differentiate into neurons and form functional neuromuscular junctions with in denervated muscle. This could be beneficial for the treatment of muscle atrophy after peripheral nerve injury.

Based on the hypothesis that olfactory ensheathing glia has neuroprotective effects in spinal cord injury, Delaviz *et al.*⁷⁶ tested the possible beneficial results in a transected sciatic nerve. The rats receiving olfactory mucosa transplantation showed better outcomes in functional recovery and axonal regeneration than those who received respiratory mucosa. Radtke *et al.*⁷⁷ supported the hypothesis that the transplantation of myelinating-forming cells, such as SCs or olfactory ensheathing cells were capable of bridging the repair site by establishing an environment permissive to axonal regeneration. However, the use of olfactory ensheathing cells has only been proved in animals and the evidence in peripheral nervous system is experimental.⁷⁷

Another cell source used in animal studies has been amniotic fluid mesenchymal stem cells. As the pro-inflammatory environment of an

injured tissue could lead amniotic fluid mesenchymal stem cells to apoptosis, Pan *et al.*⁷⁸ administered hyperbaric oxygen to a rat-crushed sciatic nerve that was embedded in a fibrin glue rich of amniotic fluid mesenchymal stem cells. The authors⁷⁸ evaluated the beneficial effect of hyperbaric oxygen on the transplanted amniotic fluid mesenchymal stem cells. Crush injury resulted in production of inflammatory cytokines, deposits of inflammatory cytokines and associated macrophage migration chemokines that were attenuated in groups receiving hyperbaric oxygen but not in the amniotic fluid mesenchymal stem cells-only group. Amniotic fluid mesenchymal stem cells transplant increased nerve myelination and improved motor function. Significantly, the amniotic fluid mesenchymal stem cells/hyperbaric oxygen combined treatment showed the most beneficial effect.⁷⁸

Amniotic fluid mesenchymal stem cells harbour the potential to improve peripheral nerve injury by inherited neurotrophic factor secretion, but present the drawback of short-term survival after transplantation. Pan *et al.*⁷⁹ evaluated whether granulocyte-colony stimulating factor (G-CSF), given its anti-inflammatory and anti-apoptotic effects, could augment the neuroprotective properties of transplanted amniotic fluid mesenchymal stem cells against peripheral nerve injury. The combined treatment showed the most beneficial effect.⁷⁹

Another way of attenuating inflammatory cytokines and prevent the apoptosis of the transplanted stem cells in a sciatic nerve crush injury is administering fermented soybeans (Natto) to transplanted amniotic fluid mesenchymal stem cells.⁸⁰

The immediate availability of autologous SC in the reconstruction of a peripheral nerve defect remains a challenge. If allogeneic SC could equally enhance the axonal regeneration without deleterious immune response, the transplantation of syngeneic SC would compensate the longer preparation time in culture of the autologous SC.⁸¹ The results in rats are encouraging, but further clinical studies are needed.

Bioscaffolds

Consistent loss of nervous tissue in PNI may impair movements of patient by interrupting their motor-sensory pathways. In the last few decades, tissue engineering has opened the door to new approaches. However, most of them make use of rigid channel guides that may cause cell loss from the lack of physiological local stresses exerted over the nervous tissue during patient's movement. Electrospun tubes⁸² are promising scaffolds for functional nervous regeneration. They can be knitted in meshes and various frames depending on the cytoarchitecture of the tissue to be regenerated. The versatility of this technique gives room for further scaffold improvements, such as tuning the mechanical properties of the tubular structure or providing biomimetic

functionalization. Moreover, these guidance conduits can be loaded with various fillers, including collagen, fibrin or self-assembling peptide gels or loaded with neurotrophic factors and seeded with cells. Electrospun scaffolds can also be synthesized in different micro-architectures to regenerate lesions in other tissues such as skin and bone.⁸²

Based on tissue-engineering technology, Rochkind *et al.*⁸³ described a biodegradable composite neurotube containing viscous gel with survival factors, neuroprotective agents and SCs. The bioscaffold served as a regenerative environment for repair.

An option for nerve gaps beyond 3 cm could be the cold-preserved allografts seeded with autologous SCs.⁸⁴ Hess *et al.*⁸⁴ used autologous tissue in the reconstruction of an extensive ulnar nerve injury in primates as a safe and effective alternative.

Other proteins/molecules

Based on the physiology of nerve recovery after an injury, Kosins *et al.*⁸⁵ caused an experimental immunological demyelination in 10 sciatic rat nerves. An epineural injection of complement proteins plus antibodies to galactocerebroside resulted in demyelination, but was followed by a faster and improved SC remyelination compared with the control group. The regenerated axons partially derived from the proximal motor axons.⁸⁵

The delivery of factors to the site of injury and their dosage regimen have been major problems in this field of research. Neuroprotective therapy is aimed at boosting the beneficial autoimmune response to injury-associated self-antigens. Immune cells play a role in the regulation of motor neuron survival after a peripheral nerve injury, and the antigen glatiramer acetate is known to affect T-cell immunity on peripheral nerve regeneration.⁸⁶ Based on this hypothesis, Luria *et al.*⁸⁶ found that a single treatment with glatiramer acetate resulted in accelerated functional and histological recovery after sciatic nerve crush injury.

Related to the inflammatory response, the cyclooxygenase-2 (COX-2) is strongly upregulated around the nerve injury site. After an experimental study in rats, the anti-inflammatory drug celecoxib is suggested to be considered in the treatment of PNI.⁸⁷

Considering that cholesterol and lipids are needed for reconstructing myelin sheaths and axon extension, Li *et al.*⁸⁸ supported the hypothesis that supplementation with exogenous apolipoprotein (apoE) mimetics could be a strategy for restoring lost functional and structural elements following nerve crush. The postinjury treatment with apoE-mimetic peptide promoted axonal regrowth after 2 weeks of treatment compared with the control group. The morphometric analysis showed an

increased thickness of myelin sheaths, an increased clearance of myelin debris and the markers of axon regeneration and remyelination.⁸⁸

Erythropoietin may have neuroprotective, and perhaps have neurotrophic roles^{89,90} in acute sciatic nerve crush injury. This protective effect could have clinical relevance, especially since it was detectable even when erythropoietin had been administered up to 1 week after injury.⁸⁹ Still, darbepoetin alfa, the long-lasting derivate of recombinant human erythropoietin (rHuEPO), showed faster recovery of neurological function with weekly administration than the rHuEPO treatment.⁹⁰

Many experiments have been undertaken using different factors to facilitate better or faster nerve stump growth: NGF, platelet growth factor, hyaluronic acid, leukemic inhibiting factor and GABA^{91,92} oxidized galectin-1.⁹³

Another organic molecule implicated in nervous system development and repair is the alpha 2.8 Polysialic acid, a carbohydrate attached to the glycoprotein backbone of the neural cell adhesion molecule. The application of functional polysialic acid considerably improved the remyelination of regenerated axons distal to the injury site, indicating that effects on SCs in the denervated nerve may underlie the functional effects seen in motor recovery.⁹⁴

Valproic acid⁹⁵ enhanced recovery by promoting neurite outgrowth, activating kinase pathway and increasing growth cone in neuroblastoma cells.

Acetyl-L-carnitine prevented neuronal loss by increasing their aerobic capacity.^{96,97}

Vitamin D2 stimulated axon regeneration when added to a nerve autograft in rats.⁹⁸

Glycine is an inhibitory neurotransmitter in the brain stem and spinal cord, and it also plays a critical role as a modulator of NMDA receptors.⁹⁹ After the administration of glycine, a damaged nerve showed similar characteristics to a healthy nerve.

In traditional Chinese medicine, *Lumbricus* has been used to promote nerve function for hundreds of years, based on the idea that earthworms regenerated amputated parts of their body if the nervous system was intact.¹⁰⁰ *Lumbricus* extract promoted the regeneration of PNI in rats, with a higher nerve function index value, conduction velocity and number of regenerated myelinated nerve fibers than the control group.¹⁰⁰

In rats, the aqueous extract of *Radix Hedysari* Prescription is beneficial, suggesting the potential clinical application of *Hedysari* polysaccharides for the treatment of peripheral nerve injury in humans.¹⁰¹

The oral intake of the Japanese natto (fermented soybean) had the potential to augment regeneration in peripheral nerve injury, given its

similar biological activity to tissue-type plasminogen activator (t-PA) that mediated by the clearance of fibrin and decreased production of TNF- α .¹⁰² Acting directly in the photolytic cascade by the administration of exogenous tPA, Zou *et al.*¹⁰³ promoted axonal regeneration and remyelination prevention of collagen scar formation.

Other animal studies focus on the role of transcription factors, such as Sox11, in the functional and anatomical recovery after a PNI.¹⁰⁴ The application of polymers as regenerating agents (OTR4120) mimic stabilizing and protective properties, and reduce nerve adherence to surrounding tissue after nerve crush injury.¹⁰⁵ BRX-220 is a co-inducer of heat shock proteins that promoted restoration of morphological and functional properties in the sensory system.¹⁰⁶

Although most studies are based on products that hypothetically enhance the process of reinnervation, there are fewer that did not show any satisfactory results.

Diethyldithiocarbamate is known for its multiplicity of action that exerts both pro- and antioxidant effects. In PNI, the exposure to diethyldithiocarbamate adversely affected recovery.¹⁰⁷

To bridge the nerve defects, a chitosan-collagen film has also been used.¹⁰⁸ It did not show any superiority to the control end-to-end anastomosis, and its degradation at 12 weeks made it useless.

Human studies

Physical therapies

Low-power laser irradiation (laser phototherapy) alters nerve cell activity, inducing upregulation of several neurotrophic growth factors and extracellular matrix proteins, which support neurite outgrowth.¹⁰⁹ A possible molecular explanation was provided by demonstrating an increase in GAP-43 immunoreactivity in the early stages of rat sciatic nerve regeneration after phototherapy.¹¹⁰ Snyder *et al.*¹¹¹ showed that phototherapy upregulates calcitonin gene-related peptide mRNA expression in facial motor nuclei after axotomy. By altering the intensity or temporal pattern of injury-induced CGRP expression, phototherapy could optimize the rate of regeneration and target innervations and neuronal survival of axotomized neurons.¹¹¹

In cell cultures, laser irradiation accelerates migration, nerve cell growth and fiber sprouting (Rochkind *et al.*⁵⁹).

In denervated muscles, animal studies suggest (Rochkind *et al.*⁵⁹) that the function of denervated muscles can be partially preserved by temporary prevention of denervation-induced biochemical changes. The function of denervated muscles could be restored to a very

substantial degree by laser treatment initiated at the earliest possible stage postinjury.⁶⁵

In a pilot, clinical, double-blind, placebo-controlled randomized study in patients with incomplete long-term peripheral nerve injury, 780 nm laser irradiation progressively improve peripheral nerve function, which lead to significant functional recovery ($P = 0.0001$).⁶⁹ No statistically significant difference was found in sensory function. Electrophysiological analysis also showed statistically significant improvement in recruitment of voluntary muscle activity in the laser-irradiated group ($P = 0.006$), compared with the placebo group.⁶⁹

In peripheral nerve injury, laser phototherapy has shown an immediate protective effect. It maintains functional activity of the injured nerve for a long period, decreases scar tissue formation at the injury site, decreases degeneration in corresponding motor neurons of the spinal cord and significantly increases axonal growth and myelination.⁶⁵

Gordon *et al.*¹⁴ has also shown promising results in animal models using low-frequency electrical stimulation for only 1 h, as it significantly accelerated regeneration through speeding of axon growth across the injury site. They carried out a randomized controlled trial in patients who had experienced substantial axonal loss in the median nerve from severe compression in the carpal tunnel. They demonstrated that effects similar to those observed in animal studies could also be attained in humans.¹⁴

Acupuncture has been a traditional Chinese practice of stimulating nerve regeneration. Hao *et al.*¹¹² performed a case-control study in patients suffering from PNI in different locations. Fifty-four patients were treated by electric acupuncture and compared with 54 controls who received supportive medication. The changes after treatment were observed chiefly by electromyography, while sensory and motor improvements were also recorded as auxiliary indicators. Acupuncture was effective in 50 patients (92.6%) in contrast to the 30 controls (55.6%). The patients in the acupuncture group were significantly better than those in the control group; nerve injuries should be treated as early as possible; the radial nerve and the common peroneal nerve recovered faster than others; cases not surgically explored recovered faster than those that were, and patients with prompt propagation of the needling sensation recovered significantly faster than those with slow propagation.

The relationship of proprioceptive (kinesthetic) feedback to motor physiology lead Brudny *et al.*¹⁸ to perform a prospective case study for 3 years of 114 patients with various manifestations of disturbed neuro-motor control. EMG feedback induced significant functional recovery.

However, we did not include this study given the heterogeneous group over all feedback therapy.

Discussion

The strategies for nerve regeneration include a variety of surgical procedures, grafting, new biologically based technologies and tissue engineering.¹⁰

In the management of nerve injuries, most of the published studies focus on bridging methods and nerve conduits.⁵ Conservative therapies aim to control neuropathic pain after nerve tissue damage.

Research has focused on conservative therapies to enhance nerve regeneration. Few studies have been performed^{59,69,14,112} in humans. All experiments with physical therapy modalities, and their effectiveness are not proved. Laser phototherapy has been studied in relative depth, but the studies involve small cohorts of patients, different nerves and etiology of injury.^{113,59} The indications for laser phototherapy are disparate, being used in multiple dermatological pathologies, in cosmetics, and in lung and airway problems.^{114,115} It is a non-invasive treatment, with minimal side effects,¹¹⁶ but high-quality studies are needed to assess its role in this field.

Most experiments are performed in animal models. Physical therapies, growth factors, cell sources and some proteins intervene at the lesion site, since the location is usually promptly available at the time of nerve repair. An advantage of animal models is the opportunity to perform controlled experiments, but the therapies used in each study have been only compared with a control group and not against each other. It is difficult to measure superiority given the lack of a standard design: structuring the samples, animal model, type of injury, time of recovery; and also a lack of a standard reporting. Although each of the hypotheses is proved in animals, translation to clinical practice in humans is missing.

In vitro investigations concentrate on genetically modified cell sources^{35,39,40} and neurotrophic factors^{42,43,46} to bridge extensive nerve defects. They also study the endogenous response to nerve injury^{47,37} and the mechanisms of cell differentiation to provide a more accessible source of nerve cells,³⁸ and molecular targets to enhance axonal regeneration.⁴⁸ *In vitro* studies are helpful to understand the molecular pathways that follow nerve damage and localize targets as potential neuroprotectants. However, their evidence is still poor, their results are not reliable and their clinical application is limited.

Other reviews on PNI management are mostly based on experiments in animals, or *in vitro* and usually focus on specific areas of research:

new sources of neural stem cells,¹¹⁷ new tissue engineering approaches¹¹⁸ and neuropathic pain management.¹¹⁹ This systematic review provides a comprehensive view of the non-surgical modalities investigated to date in the field of PNI, reporting evidence from *in vitro*, animals and human studies.

Many modalities have been proposed to promote nerve healing and restore function. Despite this, essentially none has been actually translated into clinical practice. PNI is still an unsolved issue with a marked impact on everyday life of patients, and economic relevance to society. There is a wide field of research to deepen, and future quality clinical studies are needed to provide acceptable scientific evidence.

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