

Acute spinal cord injury: Pathophysiology and pharmacological intervention (Review)

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Abstract. Spinal cord injury (SCI) is one of the most debilitating of all the traumatic conditions that afflict individuals. For a number of years, extensive studies have been conducted to clarify the molecular mechanisms of SCI. Experimental and clinical studies have indicated that two phases, primary damage and secondary damage, are involved in SCI. The initial mechanical damage is caused by local impairment of the spinal cord. In addition, the fundamental mechanisms are associated with hyperflexion, hyperextension, axial loading and rotation. By contrast, secondary injury mechanisms are led by systemic and cellular factors, which may also be initiated by the primary injury. Although significant advances in supportive care have improved clinical outcomes in recent years, a number of studies continue to explore specific pharmacological therapies to minimize SCI. The present review summarized some important pathophysiologic mechanisms that are involved in SCI and focused on several pharmacological and non-pharmacological therapies, which have either been previously investigated or have a potential in the management of this debilitating injury in the near future.

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1. Introduction

Spinal cord injury (SCI) is caused by a degenerative loss of motor, sensory and autonomic function (1). As a result, trauma occurs either due to partial or complete damage to the spinal cord (2). It poses physical, psychosocial and vocational implications for patients and caregivers alike. SCI can therefore pose a threat to the health of the patient. Long-time treatment, cost of care and economic losses can affect the patients and their families, raising social and physiological issues. Typically, >50% of patients may not regain their normal function and daily life (3). Healthy young individuals of 15-25 years are most commonly affected; because of this, SCI is a serious worldwide health concern (3). Extensive attempts for SCI treatment have so far been aimed at developing treatments for SCI effects (1). However, an active or permanent cure in the treatment of this condition has yet to be developed.

Central nervous system function cannot be regained following SCI and this is a crucial clinical concern (4). For a number of years, researchers and clinicians have been trying to determine various viable options based on the pathophysiology of SCI to improve neuronal function. This has led to efforts aimed at developing pharmacological treatments for SCI to reduce neuronal damage and improve neuronal function (5). Several pharmacological and non-pharmacological treatments show improvement or even recovery of motor functions and minimization of neurological damages (2,6). In particular, preventing secondary injury, enhancing regeneration and replacing destroyed spinal tissue are the current primary aims to treat SCI (7). Additionally, some potential pharmacological candidates including minocycline, are already being studied in clinical trials for the treatment of SCI (8).

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2. Pathophysiology of SCI

The mechanism of primary and secondary damage following SCI. Spinal cord compression is the most frequent mechanism of SCI and can continue after the injury (9). Penetrating injuries and strain to the neural tissues or vascular structures are caused by dislocation, flexion, extension or distraction forces related to rotation (9). Other mechanical damage to bone structures and ligaments can result, or consequences related to compression can give rise to hematomas in the spinal cord channel (10). Bleeding during spinal trauma begins during the early period of SCI and is later followed by the interruption of blood supply (11). Hypoxia and local ischemic infarction are both consequences of the disruption of blood flow following SCI (12). Specifically, these two conditions damage the grey matter, where metabolic function is high. Neurons in the damaged area are physically fractured and the myelin thickness is reduced (13). In addition, deterioration in neuronal transmission can be augmented by edema and the accumulation of macrophages in the damaged tissue (14).

Secondary damage can be initiated by primary damage, whereas a number of pathophysiological mechanisms can come into play even hours and days after developing SCIs (15). The most notable mechanism is a lack of energy due to ischemia and impaired perfusion at the cellular level (16). Ischemia can result immediately after traumatic SCI and, if left untreated, additional damage may commence within the first 3 h and continue for at least 24 h (8,17). Several crucial changes are found, such as hemorrhage, demyelination, edema, and cavity formation with axonal and neuronal necrosis, as well as a series of pathological changes in the nerve tissues following SCI, which can further increase infarction (18). High levels of glutamate can cause excitotoxicity, oxidative damage and ischemia, while Ca^{2+} -dependent nitric oxide synthesis can cause secondary spinal cord damage (19,20). Following secondary injuries, increased free radical damage and lipid peroxidation in the cell membrane and secondary injury signaling cascades at the injured tissue areas can eventually lead to neuronal death (12,21).

Nevertheless, extensive experiments show that the spinal cord has excellent healing properties (22). Proper blood flow is an essential factor in ensuring that progressive tissue damage precedes and promotes necrosis during the healing process (23). SCI is therefore regarded as a pathological condition involving injury to the nerve tissue. Pathological cascades, ranging from atrophy to apoptosis or necrosis, can be result in the deterioration of neurons in the brain due to local injuries to the spinal cord (6). The axons in the injured area may be regenerated due to the well-vascularized astrocytic environment (24). Secondary injury may also cause neuronal death (25). Insight into the mechanisms of secondary damage can be useful in developing advanced therapies. Systemic and local effects contribute to the development of secondary damage (15).

Systemic factors. Systemic factors causing acute SCI include hypotension resulting from neurological shocks, minimized cardiac output and respiratory failure (9). In such cases, the supply of essential metabolites and oxygen to the nervous tissue is restricted. Low blood pressure must be promptly

controlled in patients with spinal shock (19,26). Since perfusion pressure is mainly related to systemic blood pressure, damage to the spinal cord is aggravated (26,27). Hence, issues arising in the cardiopulmonary system are liable to increase the severity of SCI by damaging the spinal cord (18). Normal blood pressure must be maintained to avoid intramedullary hyperemia and hemorrhage (28). In addition, post-traumatic hypotension can occur following SCI and last for a few days or even months (29). In animal models, blood transfusion and dopamine can provide normotension, which can lead to an increase in blood flow to the spinal cord (23). However, since the local micro-circulation is affected, the functions of the spinal cord cannot be improved.

Inflammatory responses. Peripheral immune cells, including macrophages, neutrophils and T cells, can initiate an inflammatory response following SCI, which may gradually increase within a few days (22). Macrophages and neutrophils can cause the growth of lesions and lead to tissue damage (Fig. 1) (30). The release of inflammatory cytokines (TNF, IL-1, IL-6 and IL-10) and macrophages results in inflammatory reactions and subsequent pathological changes to the microglia (4). The lesion sites exhibit an increase in the levels of several inflammatory mediators including leukotrienes, bradykinin, prostaglandins, platelet-activating factors and serotonin (4). Central nervous system (CNS) inflammatory responses may be promoted by several cytokines, chemokines, oxygen, nitric oxide and other nitrogen-containing molecules (31). IL-10 is a neuroprotective cytokine and can improve motor function (32). The inflammation levels are significantly decreased in an animal model after 30 min of IL-10 administration (8).

Free radicals. The generation of free radicals should be inhibited to maintain cell viability (33). The activity of the endogenous antioxidant system is reduced by aging and has a substantial impact on SCI (34). Previous studies revealed that cyclosporin A, vitamin E and selenium are effective in the management of SCI (35,36). In addition, lipid peroxidation in SCI is inhibited by melatonin, mexiletine, thiopental and propofol (34,37,38).

Excitatory amino acids. There is a direct influence of the excitatory neurotransmitter in the spinal cord by *N*-methyl-D-aspartate (NMDA) receptors (39). Studies reveal that blocking the NMDA receptor results in protection from secondary damage due to trauma and ischemia in animal models (39,40). NMDA antagonists can significantly improve neurological functions and decrease the incidence of edema (41,42). Magnesium ions can block the ion channels of the NMDA receptors (14). A previous study identified a reduction in the injured area and indicates that functional improvement can be achieved by the administration of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) antagonists (32). Glutamate is an important excitatory neurotransmitter located in the CNS. Neuronal damage occurs due to the overactivation of the glutamate receptors (43). Shortly following SCI, there is an increase in the levels of excitatory amino acids, including glutamate and aspartate (44). The extracellular excitatory amino acids reach toxic levels within 15 min of injury to the spinal cord and can last ≤ 120 min (45).

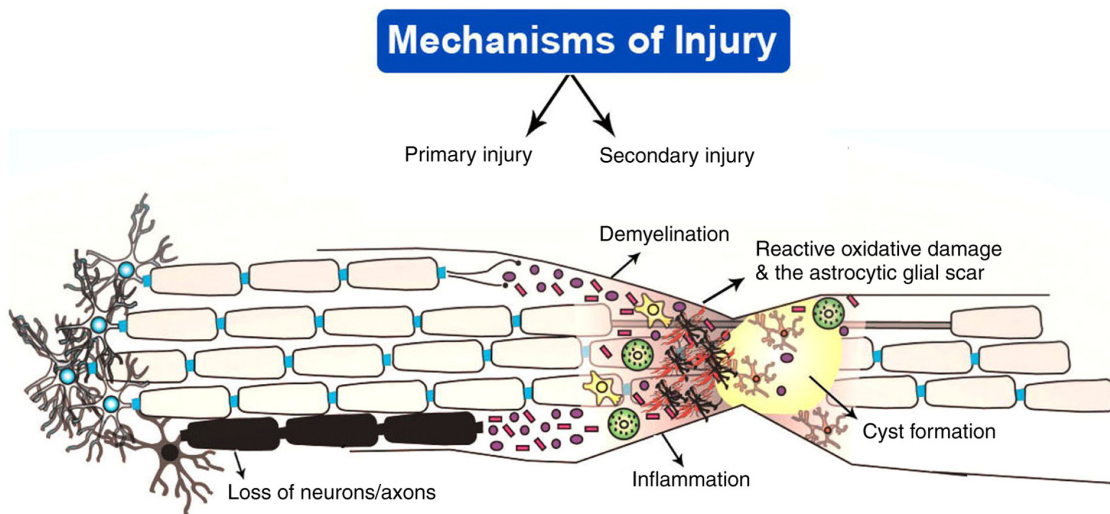


Figure 1. Pathophysiology of primary and secondary injury during spinal cord injury.

Apoptosis. Apoptosis is activated following SCI due to the release of inflammatory cytokines and free radicals, which lead to inflammation and excitotoxicity (46). Between 3 h and 8 weeks following SCI, apoptosis occurs in the areas surrounding the injured spinal cord tissue (47). Several studies indicate that after a few weeks of injury, demyelination is intensified by apoptosis of the oligodendrocytes (47,48). David *et al* (48) report that oligodendrocytic changes occur in response to SCI. Furthermore, apoptosis adversely affects the situation by increasing neuronal loss. Other studies reveal that apoptosis results in deterioration of the microglia and enhances secondary inflammatory injury (15,49). Previous studies also show that several caspase components are activated following SCI (48,50). Several stimuli are known to activate three major apoptosis pathways through caspases (51). Apoptosis is induced in specialized cells, including neurons, astrocytes, oligodendrocytes and microglia (48). Therefore, neuronal protection is a crucial and challenging concern, as neurons in the spinal cord cannot be reproduced. Based on the regenerative ability of the glial cells, preventing glial death can enhance neuronal protection by two mechanisms (52). In the first mechanism, glial cells provide neurotrophic and metabolic support to the injured neurons to promote recovery (53). The second mechanism is based on the ability of glial cells to scavenge apoptotic mediators, including cytokines, and prevent the leak of free radicals from dying cells, which are toxic to the adjacent cells (54).

Opiate receptors. Opioid peptides are locally released during SCI (55). The hypothesis that endogenous opioids may have a significant role in the mechanism of secondary injury has been proven by previous studies that show that blocking the opiate receptors protects against cellular damage as well as preventing release of cellular contents (56,57). Previous research also indicates that the administration of non-selective antagonists, such as naloxone, improves blood flow and clinical outcomes in patients following acute SCI (58-61).

Local vascular effects. Severe SCI causes a substantial decrease in blood supply, resulting in the initiation of ischemia

following the trauma (62). When the spinal cord autoregulation is disrupted, abnormal changes in systemic hemodynamics may be reflected in blood flow in the spinal cord (63). Therefore, the ischemia produced by SCI is enhanced by systemic hypotension and hypoxia. The transportation of glucose and oxygen to tissues and ATP generation are substantially reduced due to ischemia (63). The exact cause of post-traumatic ischemia remains to be elucidated (2). However, focal narrowing of sulcal arterioles and intramedullary capillaries, fragmentation, aneurysmal dilatation or occlusion have been reported in experimental studies (64,65). A study demonstrated progressive vascular damage in a spinal cord contusion injury model for the first time (66). The uptake of Evans blue increases by ~76% in the injury area at 24 h compared with those at 2 h (67). Low pH of tissue due to lactic acidosis, as well as the accumulation of fibrin and platelets that cause congestion of venous stasis, may contribute to ischemia (68). In addition, ischemia is caused by the damaging of capillary endothelium, edema, petechial hemorrhages and vasoactive cytokines (69). Under these conditions, the systems adopt anaerobic respiration. Various pathophysiological processes can be affected by ischemia and activation of anaerobic respiration (70). Edema is formed at the injured area and around peripheral tissues due to proteinaceous leakage from intrinsic spinal cord veins (71). Spinal cord pressure is increased by edema and the disruption of blood flow of the spinal cord occurs (72). Magnesium can diminish edema and vascular permeability in SCI (71).

Abnormal changes in the concentration of electrolytes are observed following spinal cord trauma (14,73,74). Formation of glutamate and free radicals is significantly increased due to ischemia-reperfusion injury (75). Antagonism of glutamate in endothelium can prevent the devastation of the blood spinal cord barrier. Evidence demonstrates that glutamate receptor blockers improve neurological results in SCI (60). Magnesium ions can decrease the lipid peroxidation process via the antagonism of glutamate receptors (76). Calcium ions can also serve a role in cell death, as calcium ions can activate phospholipases, proteases and phosphorylases in cells (77). Another experimental study reported that calcium channel blockers can significantly prevent secondary SCI (77). Extensive

experimental studies suggest that blood flow to the spinal cord is improved by those agents, such as gacyclidine, which have significantly positive activity on healing (18,77,78).

3. Pharmacological drugs used for the treatment of SCI (Table I; Fig. 2)

Cyclooxygenase (COX) inhibitors. COX inhibitors are a preferred choice for the treatment of SCI in the damaging secondary pathway (79). Ibuprofen and meclofenamate are two common non-steroidal anti-inflammatory drugs that can be applied to maintain spinal cord blood flow following SCI in an animal model (80,81). The combination of a thromboxane inhibitor with a prostacyclin analogue shows a similar effect (82). In a rat model, COX-2 expression levels are greatly augmented in the injured spinal cord tissue following contusion injury and the pharmacological inhibition of COX-2 isoform enhances functional results in moderately acute spinal injuries (80,83). Although the widespread use and clinical applications of COX-1 or COX-2 inhibitors for SCI in humans have not yet been indicated in the aforementioned previous studies, their wide use as well as application in the musculoskeletal and rheumatologic conditions assuages several of the safety and pharmacokinetics concerns.

Glutamate receptor antagonists. Activation of NMDA and non-NMDA can serve a crucial role in the excitotoxic damage following SCI (84). Along with traumatic disorders, non-traumatic CNS disorders have quickened the development of associated pharmacological interventions. NMDA-receptor antagonists, including MK801 and gacyclidine, demonstrate substantial neuroprotective effects following SCI in animal experiments (76). The development of NMDA-targeting systemic clinical therapies and applications has been impeded by the extensive distribution of glutamate and its receptor throughout the entire human CNS, which makes it a challenge to avoid possible side effects (76,85). Gacyclidine, an NMDA receptor antagonist, has been evaluated in France in a phase-II double-blind, randomized evaluation of 280 patients with SCI (86). However, this study reveals no remarkable improvement in American Spinal Injury Association (ASIA) scores compared with placebo treatment. White matter glial loss is reduced and locomotor function can be improved by focal microinjections of NBQX, an AMPA receptor blocker, into the injured spinal cord areas after blunt injury (87). Unfortunately, this invasive form of receptor antagonism has not been developed into pharmacological therapies due to several side effects (87). Magnesium is an NMDA receptor antagonist that reduces excitotoxicity and inflammatory factors (88). However, cerebrospinal fluid levels are increased by the combination of magnesium and polyethylene glycol (PEG) without large doses of magnesium (86). The enhancement of tissue sparing and the action of magnesium produces an improvement of functional motor recovery with PEG in the treatment of SCI in animal models (86). However, a phase I/II clinical trial for the combination of magnesium and PEG was ended in 2015, due to several difficulties in enrolling patients.

Ion channel antagonists. Calcium channel blockers display significant effects on reducing the pathological influx of

calcium into cells via non-glutamate receptors (78). However, the potent physiological impacts of calcium blockers are regulated via their pharmacological activity on vascular smooth muscle, rather than inducing calcium flux across neuronal and glial cell membranes (78). In experimental SCI models, nimodipine (NDP) can improve spinal blood flow and rescue hypoperfusion (77). NDP administration can significantly improve neurological recovery following spinal cord trauma or ischemia (Table I) (89). NDP was first studied in France in a potential randomized clinical trial of 160 patients within 8 h of injury: Methylprednisolone (MPSS), NDP 0.15 mg/kg/h for 2 h, then 0.03 mg/kg/h for 7 days; both MPSS and NDP or placebo (90-92). Studies demonstrate that blood flow and neurological recoveries are promoted by dopamine, adrenaline, NDP and dextran following SCI (77,93-95). It is difficult to prove any firm effects in neurological outcomes after 1 year of injury. The administration of calcium channel blockers in acute SCI raises concerns regarding the potential for systemic hypotension that, in the context of the injured spinal cord, could be harmful due to autoregulation (18). The administration of sodium channel blockers notably improves the neuroprotection of white matter and functional outcomes with microinjections of tetrodotoxin after blunt experimental SCI (96). Even though surgery is required, similar neuroprotective effects have been observed for the administration of riluzole, another sodium channel blocker, after a clip compaction injury to a rodent spinal cord (97). The US Food and Drug Administration has recently approved riluzole for the treatment of amyotrophic lateral sclerosis. Notably, riluzole has an important role in protecting against excitotoxic cell death by blocking the sodium channel in the injured neurons constraining the presynaptic toggle of glutamate (97). Neuronal loss and cavity size have been reduced in SCI animal models (98). A significant improvement of sensorimotor and results of electrophysiological were demonstrated in a previous study (66). A phase-I trial has been completed in which 36 patients (50 mg orally every 12 h for 14 days) participated (99). This study demonstrates a substantial increase in motor recovery following cervical injury at 3 months compared with matched registry control patients. Enhanced motor scores were not observed at 6 months follow-up. Regarding the neurological results, an improvement in ASIA motor score was demonstrated in patients with cervical SCI treated with riluzole compared with non-riluzole-treated patients. Although a transient increase in liver enzyme levels was found, a number of pharmacokinetics and toxicity effects have not been investigated (99). Nevertheless, the therapeutic application of riluzole has yet to be documented. Further studies should be carried out for its therapeutic use in patients with SCI. A phase-II/III multicenter randomized controlled trial of riluzole is currently underway by the AO Spine North America Research Network (100).

Blocking potassium channels may be a potential therapeutic target for the treatment of SCI. A patient with chronic SCI taking 4-aminopyridine (4-AP) demonstrated an increase of the axonal regeneration with mild levels of recovery (101). Similarly, an animal model of SCI supports the potential effects of 4-AP on blocking the fast potassium channels. 4-AP exhibits the most significant improvement in conduction in chronic SCI (102). Fampiridine is a fast potassium channel blocker, which has completed phase-II clinical trials and

Table I. Potential pharmacological therapies for SCI.

First author(s), (year)	Potential agents	Pharmacological effects	(Refs.)
Damon <i>et al</i> (2018), Chaves <i>et al</i> (2018), Sohn (2018)	Cyclooxygenase inhibitors	Inhibit inflammation and neuronal cell death and enhance functional outcomes	(80,81,83)
Wang <i>et al</i> (2015), Kim <i>et al</i> (2017), Mori <i>et al</i> (2018), Chen <i>et al</i> (2018)	Glutamate receptor antagonists (MK801 and gacyclidine)	Exert neuroprotective effects, reduce neuronal cells and cavity formation and improve functional outcomes.	(76,86-88)
Cheng <i>et al</i> (2018), Chu <i>et al</i> (2018), Ko <i>et al</i> (2018), Fehlings <i>et al</i> (1989), Rosenberg <i>et al</i> (1999), Caglar <i>et al</i> (2019), Verma <i>et al</i> (2019), Nagoshi <i>et al</i> (2015), Fehlings <i>et al</i> (2016), Grijalva <i>et al</i> (2010), Page <i>et al</i> (2018), Darlington (2000), Hayes (2011), Proks <i>et al</i> (2002), Kurland <i>et al</i> (2013), Caffes <i>et al</i> (2015)	Ion channel antagonists	Exert neuroprotective effects, reduce water contents in the injured areas and improve functional outcomes.	(79,93-107)
Anwar <i>et al</i> (2016), Bracken <i>et al</i> (1985), Sayer <i>et al</i> (2006), Bracken <i>et al</i> (1990), Bracken <i>et al</i> (1997), Bracken (2012), Bowers <i>et al</i> (2016), Ferrara <i>et al</i> (2019)	Corticosteroids	Reduce various cellular stress and immune-regulated neuronal phagocytosis, inhibit neuronal cell death and improves axonal regeneration and enhance motor function recovery.	(113-120)
Resnick 2013, Mojtabedzadeh <i>et al</i> (2019), Inoue <i>et al</i> (2014), Hawryluk <i>et al</i> (2015)	Vasoactive drugs	Improve blood circulation and axonal regeneration and enhance motor function recovery.	(123-126)
Yakovlev and Faden (2004), Knoblauch <i>et al</i> (2004), Thomas <i>et al</i> (2013), Hall and Springer (2004)	Caspase inhibitors	Exert neuroprotective effects, inhibit excessive inflammation and neuronal loss and improve functional recovery.	(127-130)
Zhang <i>et al</i> (2019), Elmore (2017), Scholz <i>et al</i> (2015), Tikka and Koistinaho (2001), Wells <i>et al</i> 2003, Curtis <i>et al</i> (2018), Casha <i>et al</i> (2012)	Minocycline	Inhibits inflammation and neuronal loss and improves axonal regeneration and motor functions.	(132-138)
Barros <i>et al</i> (2016), Marcon <i>et al</i> (2010), Badhiwala <i>et al</i> (2018), Geisler <i>et al</i> (1991)	Monosialotetrahexosylganglioside	Exerts neuroprotective effects, enhances neuronal plasticity and regeneration and improves axonal regeneration and motor recovery.	(139-142)
Awad <i>et al</i> (2015), Ma <i>et al</i> (2017), Teng <i>et al</i> (1998), Wu <i>et al</i> (2011), Gupta <i>et al</i> (2017), Clarke <i>et al</i> (2001), Raballo <i>et al</i> (2000), Zhou <i>et al</i> (2018), Ko <i>et al</i> (2018), Wu <i>et al</i> (2008)	Fibroblast growth factors	Exert neuroprotective effects and educe neuronal motor loss and improve functional recovery.	(144-153)

Table I. Continued.

First author(s), (year)	Potential agents	Pharmacological effects	(Refs.)
Nishio <i>et al</i> (2007), Derakhshanrad <i>et al</i> (2018), Koda <i>et al</i> (2018)	Granulocyte colony-stimulating factor	Exerts neuroprotective effects and reduces inflammation, inhibits neuronal cell death and cavity formation and improves axonal regeneration and functional outcomes.	(155-157)
Kitamura <i>et al</i> (2007), Ohta <i>et al</i> (2018), Kitamura <i>et al</i> (2011)	Hepatocyte growth factor	Promotes neuronal survival, decreases lesion size and oligodendrocytes, inhibits neuronal loss and enhances axonal regeneration and functional recovery	(158-160)
Iannitti <i>et al</i> 2016, Yiu and He (2006), Liebscher <i>et al</i> (2005), Freund <i>et al</i> (2007), Wiessner <i>et al</i> (2003), Zörner and Schwab (2010)	Anti-Nogo-A antibody	Promotes neuroprotection and inhibits neuronal loss. Improves axonal regeneration micro-environment, plasticity and functional outcomes.	(167-172)
Kawakami (2013), Liu <i>et al</i> (1991), Sharkey and Butcher (1994)	Neuroimmunophilin ligands (Cyclosporin A and FK-506)	Exert immunosuppressive effects, reduce inflammation and neuronal cell death, improve functional outcomes	(173-175)
Barritt <i>et al</i> (2006), Caggiano <i>et al</i> (2005), Iaci <i>et al</i> (2007), Iseda <i>et al</i> (2008), Kwok <i>et al</i> (2008), Grimpe and Silver (2004), McRae and Porter (2012), Moon <i>et al</i> (2001), Bradbury <i>et al</i> (2002), Wang <i>et al</i> (2011), Hu <i>et al</i> (2018), Rosenzweig <i>et al</i> (2010), Lawrence and Kuypers (1968), Nout <i>et al</i> (2012)	Chondroitinase ABC	Inhibits inflammation and neuronal loss, improves myelination and number of axons, promotes corticospinal cord and sensory axons regeneration and functional outcomes	(189-202)

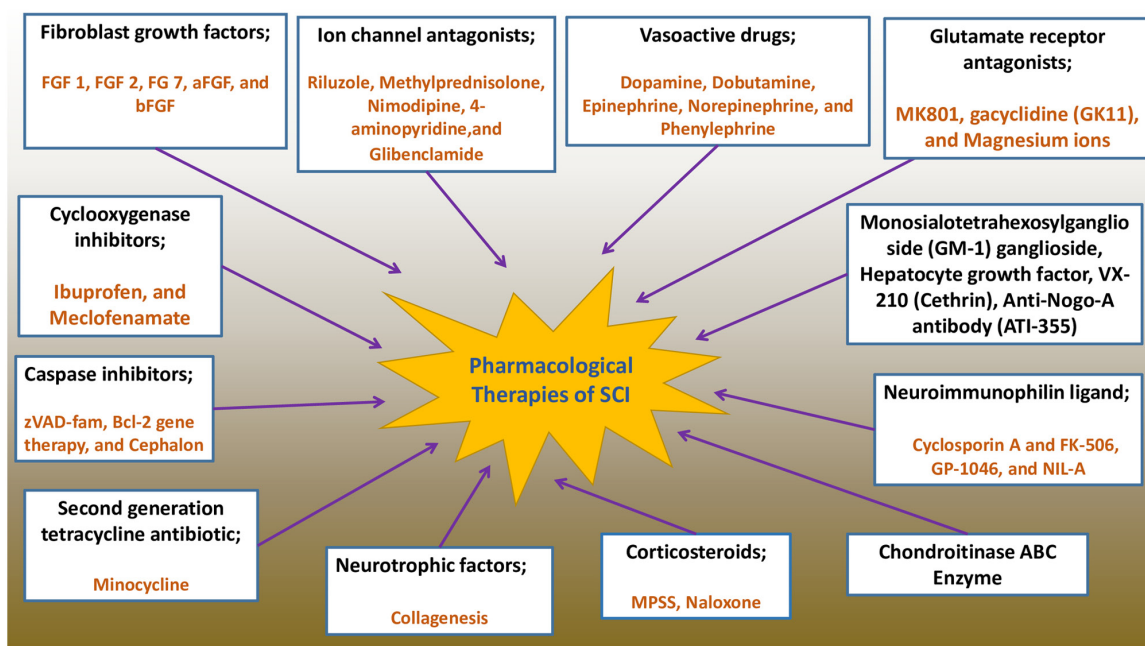


Figure 2. Different type of pharmacological drugs used for the treatment of SCI. SCI, spinal cord injury; FGF, fibroblast growth factor; a, acidic; b, basic.

is co-developed by Elan and Acorda Therapeutics (103). In some small clinical trials, chronic SCI patients with incomplete injury have demonstrated improved patient satisfaction, quality of life scores, sensory and motor scores, decreased spasm and increased amplitude following fampiridine administration (103,104). In addition, this potent drug has good tolerance and few side effects (102). In another study, patients treated with 4-AP exhibit less impact on functional status (104). This beneficial mechanism demonstrates that potassium channel blockade enhances axonal transmission between demyelinating nodes, and enhances neuronal and neuromuscular transmission in the preserved axons (103). Thus, further investigations in greater detail are urgently required to explore the potential benefits of potassium channel blockers in improving axon conduction in patients with the chronic injury. If more axons are retained in the acute phase following SCI, the potential of this treatment may be more substantial.

Glibenclamide (GLC) is a sulfonylurea receptor 1-regulated, transient receptor potential cation channel subfamily M member 4 channel, Ca^{2+} -activated, non-specific cation channel blocker that is commonly used to treat diabetes by increasing insulin release (105). It exhibits substantial neuroprotective effects in ischemic hemorrhagic stroke and traumatic brain injury models (106,107). GLC reduces hemorrhagic necrosis, edema and inflammation in SCI (108,109). In animal models, GLC reduces hemorrhage at 24 h after injury and minimized the lesion size at 1-6 weeks (110). GLC treatment significantly improves functional recovery following SCI within 6 weeks. In one animal study, the improvement of bilateral injury (33% reduction in lesion size) was more limited compared with unilateral injury (57% reduction in lesion size) at 6 weeks following GLC treatment (111). These findings illustrate that the severity of the damage may play significant roles in the functional recovery outcomes. In conclusion, GLC can be potentially useful in the treatment of SCI.

Corticosteroids. The National Acute Spinal Cord Injury Study (NASCIS) is a large randomized clinical trial of SCI, which has investigated the therapeutic role of corticosteroids (CSs) in SCI and produced high-quality data (112). CSs can significantly reduce various cellular stresses, including oxidative stress associated with hypoperfusion, calcium influx and excitotoxicity, and immune-regulated neuronal phagocytosis in the injured spinal cord (113). All NASCIS trials have yet to demonstrate benefits ascertained by primary outcome measures.

Numerous investigations reveal the potential effects of CSs. NASCIS-I published a paper in 1984, compared low-dose and high-dose MPSS (100 mg bolus and 100 mg/day vs. 1,000 mg bolus and 1,000 mg/day) following SCI (114). No significant differences in neurological improvement were observed in this study, but high-dose MPSS administration can increase several physical complications including gastrointestinal bleeding, sepsis, wound infection, pulmonary embolism and even mortality (115). Notably, a placebo was not provided in the NASCIS-I study, because CS was considered effective and to not apply them raised ethical concerns. NASCIS-II assessed high-dose MPSS within 24 h of SCI compared with naloxone, opioid antagonists and placebo (115,116). A pre-planned subgroup analysis illustrated that the patients administered with MPSS within 8 h of injury could demonstrate substantially enhance motor function recovery. NASCIS-III assessed MPSS and tirilazad mesylate (21 aminosteroids with antioxidant effect) within 8 h after injury and is the first NASCIS study to use functional measurement results. CS (30+5.4 mg/kg) were compared at 24 and 48 h with tirilazad mesylate (2.5 mg/kg every 6 h) at 48 h. Subgroup analysis demonstrated that patients who received MPSS bolus 3 to 8 h after injury and were infused within 48 h exhibit improved neurological functions within 1 year. Following this study, MPSS was recommended for 24 h in patients treated within 3 h of injury and 48 h in patients treated within 3-8 h of injury. The treatment of acute

SCI with MPSS is still controversial. Recent guidelines give first-class evidence against the application of CSs in SCI (117).

A randomized controlled trial reported that MPSS administration within 8 h of injury is significantly effective in SCI (118). This study demonstrated the lack of other therapeutic strategies and MPSS is the only drug to be investigated in phase-III trials. Notably, a previous study also suggested that CS administration has limited efficacy and increases several physical complications, including septicemia and pneumonia (119). A study of 77 patients with SCI demonstrates that despite limited risk and efficacy, most patients prefer to take CS (120). By contrast, 59.4% of the patients considered that the chance of neurological recovery was improved and that it was worth using CS. Only a few (1.4%) hypothesized that it was inappropriate to use CS. These findings should be explored by health practitioners caring for the treatment of SCI patients. The upcoming AO Spine-guidelines for the management of acute SCI will reinstate the NASCIS-II dosing of MPSS administered within 3 to 8 h after injury to level-III treatment strategy (121).

Vasoactive drugs. Primary supportive care during acute SCI maintains spinal cord perfusion and oxygenation. Injuries above the T6 vertebra can cause sympathetic nerve damage and neurogenic shock. Liquid administration and vasoactive drugs are widely used in the treatment of SCI (122). Following volume resuscitation, vasoactive drugs can be used to increase blood pressure, aimed at improving spinal cord perfusion (123). Patients with acute SCI can limit tolerance for intravascular volume expansion in the context of impaired sympathetic outflow. Several pharmacological agents, including dopamine (1-10 mg/kg/min), dobutamine (5-15 mg/kg/min), epinephrine (1-8 mg/min), norepinephrine (1-20 mg/min) and phenylephrine (10-100 mg/min), can be considered (124). Norepinephrine and dopamine result in vasoconstriction and enhance cardiac activity. Inoue *et al* (125) found that dopamine is most commonly used as a vasoactive drug, followed by epinephrine, phenylephrine, norepinephrine and vasopressin. The study suggested that both dopamine and phenylephrine administration can increase cardiovascular complications. Patients with a mean arterial pressure >85 mm Hg enhance their ASIA-score recovery (126). This study also suggests that this important therapeutic strategy might be effective soon after injury.

Caspase inhibitors. Following traumatic SCI, the preservation of axons can significantly enhance their overall function, even in a small number. Studies have demonstrated that the activity of caspase-1 and caspase-3 in neurons and non-neuronal cells increases following SCI (127,128). Treatment using a broad-spectrum caspase inhibitor, such as Z-VAD-FMK, can reduce the area of post-traumatic injury and neurological deficit, as the therapeutic window of Z-VAD-FMK is extended by 9 h following transient (30 min) cerebral ischemia (128). It can be inferred that this treatment regimen may have a neuroprotective effect and prolong the therapeutic window of the drug following SCI. Bcl-2 gene therapy and cephalon, a protease/calpain inhibitor, have completed pre-clinical studies and appear beneficial to patients with SCI (129,130). However, targeting long-term delayed caspase activation in oligodendrocytes may also be a potential treatment, as it may save the

degenerated white matter and significantly improve patient prognosis.

Minocycline (MIN). MIN is a tetracycline antibiotic and previous studies have shown that it exhibits significant neuro-protective activities in Huntington's disease and multiple sclerosis (131,132). MIN can significantly impede the activation of IL-1 β , TNF- α , COX-2 and MMPs following SCI (132). In addition, MIN administration can substantially hinder the expression of caspase-1 and caspase-3 levels following SCI (133). MIN also inhibits inducible nitric oxide synthase, leading to microglial activation following SCI (134). MIN protects neurons from glutamate excitotoxicity at the injured spinal cord tissue area (135). Thus, MIN is a useful drug, since it targets multiple processes involved in mediating cell death and prevents the progression of secondary injury following SCI. A previous study demonstrated that MIN can enhance significant long-term functional outcomes in a mouse model (136). MIN-treated mice showed continual and substantial improvements over a 4-week recovery period. MIN administration could significantly enhance the Basso, Beattie, and Bresnahan scores at 20 days post-injury. In the injured mouse model of SCI, consistent weight support and considerable plantar stepping were found, while some mice indicated evidence of forelimb-hindlimb coordination. MIN could also improve neurological and histological outcomes, impede neuronal and oligodendroglial apoptosis, minimize microglial activation and inhibit inflammation in animal SCI models (131). MIN significantly reduces the lesion size and promotes tissue sparing following acute SCI (131). Patients with acute incomplete cervical SCI can benefit from early MIN administration (128). These findings were supported by a phase-II clinical trial where a 14-point ASIA motor score recovery was achieved compared with the placebo (137). The development of a phase-III trial entitled 'Minocycline in Acute Spinal Cord Injury' has been driven by these initial outcomes and was evaluated for 7 days (compared with placebo) using an intravenous administration of MIN (138).

Monosialotetrahexosylganglioside (GM-1). The glycosphingolipid GM-1, stimulates tyrosine kinase receptors, which increases neuronal plasticity and regeneration (139). Successful tissue sparing has been developed to study neuroprotection in an animal model of SCI (42,140). A successfully completed phase-II trial shows enhanced 1-year ASIA motor scores after daily administration of GM-1 for 18-32 days post-injury (141). Additionally, a landmark trial indicates a substantial improvement in ASIA motor score and Frankel grade following GM-1 administration in 37 patients with SCI (142); lower limb function was markedly improved at 48 h following treatment with GM-1. Thus, this study demonstrated that GM-1 serves an important role in the repair of neurons. Although these initial findings led to a large-scale phase-III trial involving >750 patients in 28 centers, the major findings of the study failed to meet the primary outcomes (2-point improvement in the improved Benz walking scale) (137). The two groups showed a substantial improvement in bowel/bladder recovery and sacral function, as well as a remarkable improvement in functional independence scores and an enhanced Barthel index. Intensive physical therapy was also combined with pharmacological

therapy to improve the prognosis of patients in the study. A valid criticism of this study is the delayed therapeutic effects of GM-1 treatment, as most of the patients received MPSS for the first time in their clinical treatment (137). Meta-analyses to evaluate the potential therapeutic benefits of GM-1 in the treatment of SCI failed to support its extensive use (136,142).

Fibroblast growth factors (FGFs). FGFs are heparin-binding proteins that have significant neuroprotective activity against excitotoxicity and in impeding the generation of oxygen free radicals (143). FGFs determine the fate of neuronal cells, including migration and differentiation (144,145). The administration of FGFs can reduce neuronal motor loss and improve respiratory deficits (146,147). A phase-I/II trial of an FGF analog is successfully completed (148). Several growth factors possess neuroprotective effects and can enhance functional recovery in SCI (144). FGF1 administration can improve the survival and growth of various neuronal cell types, including neocortical, hippocampal, cerebellar, dopaminergic, isolated sensory neuronal and spinal cord cells (145,149). In addition, basic FGFs and/or keratinocyte growth factor possess significant neuroprotective effects in SCI (150). Although preliminary studies of FGFs in animals are obligatory and essential, reviews on SCI should focus more on human trials (151). Ko *et al* (152) were the first to demonstrate a clinical trial involving a patient suffering from chronic SCI, who was treated with four survival nerve grafts coupled with fibrin glue containing acidic FGF (aFGF). The authors suggest that patients with acute SCI can significantly enhance functional recovery from their wheelchair-bound status and independently ambulate using a walker, 2.5 years after surgery (152). The authors also report that ASIA motor and sensory scores are significantly enhanced in postoperative functional status patients compared with presurgical patients. Wu *et al* (153) conducted a clinical trial on nine patients with cervical SCI, who received direct spinal cord implantation of fibrin glue containing aFGF for >6 months. The 6-month postoperative follow-up indicated a marked enhancement in the ASIA motor and sensory scale scores of patients. After 3 years, the authors published an open-labeled, prospective, uncontrolled human clinical trial involving 60 patients with SCI (comprising 30 cervical and 30 thoracolumbar SCIs) and significant improvement in ASIA motor and sensory scale scores was observed in these patients at 24 months, following FGF treatment (147). Detailed studies are required to explore the potential therapeutic effects and long-term outcomes.

Granulocyte colony-stimulating factor (G-CSF). G-CSF is a cytokine glycoprotein located in numerous tissues in the body. Several studies report that G-CSF can significantly promote the proliferation, survival and mobilization of neuronal cells (147-149). Increasing evidence suggests that G-CSF can enhance neurogenesis, reduce apoptotic-mediated neuronal death, and reduce TNF- α and IL-1 β expression levels at the injured spinal cord area (154-156). White matter sparing and improved hind-limb function are the positive effects associated with this therapy (154). Non-randomized phase-I/IIa trials have indicated ASIA grade improvement, without any adverse effects, associated with G-CSF therapy (155-157). However, additional randomized controlled trials are needed to establish

the potential therapeutic benefits of G-CSF in SCI. Recently, a phase-III clinical trial of G-CSF in Japan has been completed, but the results are pending.

Hepatocyte growth factor (HGF). HGF, found in mesenchymal cells, induces cell growth and motility (150). HGF administration can enhance neuronal survival, decrease lesion size and reduce the production of oligodendrocytes in rodent models (158). Furthermore, HGF treatment markedly improved hand dexterity in a primate model of cervical SCI (159,160). A recent study showed that the specific receptor, c-Met, of HGF increases sharply while the upregulation of endogenous HGF is relatively weaker in a rat model with acute SCI (161). By injecting an HGF expression vector into the spinal cord of rats, the survival rate, angiogenesis and axon regeneration of neurons and oligodendrocytes following SCI show significant improvement. The injured area shows reduction and functionality is restored (161). The exogenous administration of HGF in acute SCI can reduce the activation of astrocytes, reduce the formation of glial scars, exert anti-inflammatory effects and reduce the infiltration of leukocytes (161). Recombinant human HGF (intrathecal rhHGF) injection improves the neurological functions following cervical contusion in non-human primates (160). Based on these findings, a phase-I/II clinical trial of intrathecal rhHGF conducted between June 2014 and May 2018 involving patients with acute cervical SCI revealed that the patients had a Frankel score of A/B1/B2 72 h after the initial injury (160).

VX-210 (Cethrin). The p-signaling pathway is detrimental to axonal regeneration and neurite growth (162). In a rodent model of SCI, p-mediated inhibition of axonal growth enhances neuronal regeneration and recovers the motor function induced by C3 transferase (Cethrin), a toxin produced by *Clostridium botulinum* (163). During decompressive surgery in the acute phase, Cethrin is injected into the dura mater due to its high permeability at regions of the injured spinal cord tissue. A phase-I/IIa multicenter trial of VX-210 in patients with cervical or thoracic SCI showed a significant improvement of 1.8 ± 5.1 points in the ASIA motor score for thoracic injury and 18.6 ± 19.3 points for cervical injury (164). In addition, 31 and 6% of patients showed an improvement in ASIA C or D classification of cervical or thoracic injury, respectively. The largest and most significant improvement was observed at 12 months in the treatment of patients with cervical injury using 3 mg Cethrin (27.3 points) (165). It is worth noting that RhoA impedance and subsequent functional enhancement are also reported when non-steroidal anti-inflammatory drugs, such as ibuprofen, are used for therapy, indicating that targeting COX may be a potential therapeutic option in treating SCI (166).

Anti-Nogo-A antibody (ATI-355). ATI-355 is one type of monoclonal antibody against Nogo-A and can significantly inhibit the adult CNS myelin component (167). It can markedly impede neurite growth and plasticity in adult CNS, enhance axon growth and regeneration, and stabilize neuronal circuits (168). Blocking myelin protein Nogo-A function or its signaling pathway is an emerging strategy to suppress the release of neurite growth inhibitory factor of the adult central CNS and improve the axonal regeneration micro-environment

and plasticity following SCI (168). Anti-Nogo-A antibody treatment following SCI can significantly enhance axonal regeneration at the injured tissue area, and improve compensatory sprouting and functional recovery (165,169). Similar therapeutic effects are found in a SCI macaque monkey model (170). A study evaluated the potential therapeutic effects of acute, as well as 1 or 2 weeks delayed intrathecal anti-Nogo-A antibody infusions, on corticospinal tract (CST) axon regeneration and motor function recovery following thoracic SCI in experimental rat models (165). Lesioned CST fibers regenerated over several mm following acute or 1 week-delayed treatments, but not when the antibody treatment was started following a delay of 2 weeks. Notably, Anti-Nogo-A antibodies administration can significantly neutralize inhibitory effects on neurite growth of purified or recombinant Nogo-A, oligodendrocytes and CNS myelin *in vitro* (171). A phase-I human clinical trial with humanized anti-Nogo antibody in patients with SCI has been completed in Europe and the United States (172).

Neuroimmunophilin ligands. Cyclosporin A and FK-506 are neuroimmunophilin ligands, which exhibit neuroprotective activity in experimental models, including those of ischemia, trauma and neurodegenerative CNS disorders (173-176). These drugs are commonly used as immunosuppressants and are capable of crossing the BBB (173,176). GP-1046 is a novel neuroimmunophilin ligand, which was initially synthesized by Gold *et al* (177) but was then replaced with NIL-A, which binds with FK506 binding protein (FKBP)-12 in neuronal tissues. NIL-A is currently in phase-II clinical trials for the treatment of SCI (177). Vertex Pharmaceuticals has conducted a preclinical trial on the neurophilin ligand, V10367, which can significantly bind to the FK-506 binding protein, FKBP-12 (178). Results and opinions on the clinical use of neuroimmunophilin ligands to enhance neuronal outgrowth are conflicting; therefore, additional studies are needed for further validation (178).

Neurotrophic factors. There are different ways to administer neurotrophic factors to the injured spinal cord. Direct injection, continuous injection and growth factor-saturated gel are typically used, although these methods are not that efficient (179). However, collagenases are currently used, which involve collagen-based drug therapy as an improved method for the effective delivery of neurotrophic factors (180). An alternative approach that can overcome these shortcomings is *ex vivo* therapy. This involves removing cells (including Schwann cells and fibroblasts) from the host, genetically modifying them *in vitro* to synthesize specific neurotrophic factors, expanding the cells in culture and re-transplanting them into the host (180,181). The technique provides a significant long-term, localized, high-dose growth factor upon delivery. Gene therapies are currently being pursued by Selective Genetics, Cell Genesys, Biovex, Oxford Biomedica and Amsterdam Molecular Therapeutics (182). *Ex vivo* therapies are not very effective in promoting distal axonal growth after the initial axonal growth, although only a few studies have been conducted so far (183,184). The adverse effects, complications and potential risks of gene therapy must be carefully considered before implementation. However, Proneuron Biotechnologies

provides autotherapy of the larger arteries, where the cells of the patient are removed, activated and returned to stimulate nerve regeneration (185). Some preclinical studies show that macrophages or cytokines can be injected to promote inflammatory responses and functional outcomes (186,187). Efforts should be made to determine the potentially destructive role of macrophages in removing cell debris, promoting tissue blood flow, reconstruction, restoring phagocytic capacity and inducing cellular proliferation around the injured spinal cord by releasing factors to stimulate scar formation (30). This technology is currently in phase-I clinical trials.

Chondroitinase ABC (ChABC) enzyme. Following SCI, axons of the CNS in adult mammals cannot regenerate correctly, resulting in permanent paralysis. Glial reaction occurs at the injured area, forming a glial scar (188). The glial response leads to the recruitment of microglia, oligodendrocyte precursors, meningeal cells, astrocytes and stem cells, as well as oligodendrocytes and myelin fragments (189,190). The majority of these cells release molecules and inhibit axon regeneration, which leads to regeneration failure (177,178). The glial scar also contains chondroitin sulfate proteoglycan (CSPG), a recovery inhibitor (191). However, the natural bacterial enzyme ChABC can degrade the inhibitory carbohydrate side chains on CSPG. Indeed, ChABC administration following SCI can promote corticospinal cord and sensory axon regeneration, and enhance functional outcomes (192). These growth-promoting effects of ChABC are due to the elimination of perineuronal nets, increased germination of spare axons and the formation of new synaptic connections under the injured sites (180). ChABC may enhance axonal regeneration in the severed axon on the bridge (192). The potential therapeutic effects of ChABC administration have been identified in rodent models of SCI, nigrostriatal injury and stroke, and cats with SCI (193-195). In a study in male Wistar rats, using a combination of low-level laser therapy (LLLT) as an anti-inflammatory agent and ChABC as a CSPG digesting factor after inducing SCI by clip compression, the combination of LLLT and ChABC produced beneficial effects in the form of reductions in cavity size, increased myelination and number of axons around the cavity, and reduced glycogen synthase kinase-3 β , CSPG and aquaporin 4 expression compared with LLLT and ChABC alone, resulting in greater functional recovery in the combination group (196). ChABC treatment in rats can restore postsynaptic activity under injury, which is significant for the electrical stimulation of corticospinal neurons and enhances the functional recovery of motor and proprioceptive behavior (197).

After 4 weeks of acute SCI, ChABC combined with rehabilitation therapy can also promote functional recovery (198). In a recent study on dogs with severe chronic SCI, intracerebral injection of ChABC demonstrates impressive results (199) and the authors suggest that human trials be commenced. The effect of ChABC has been evaluated in rhesus monkeys that had undergone C7-spinal cord hemisection (200,201). At 4 weeks after hemisection, multiple-intraparenchymal ChABC injections were administered below the lesion area, targeting spinal cord circuits, which regulate hand functions (202,203). Compared with the vehicle injection control group, the hand function of the monkeys treated with ChABC

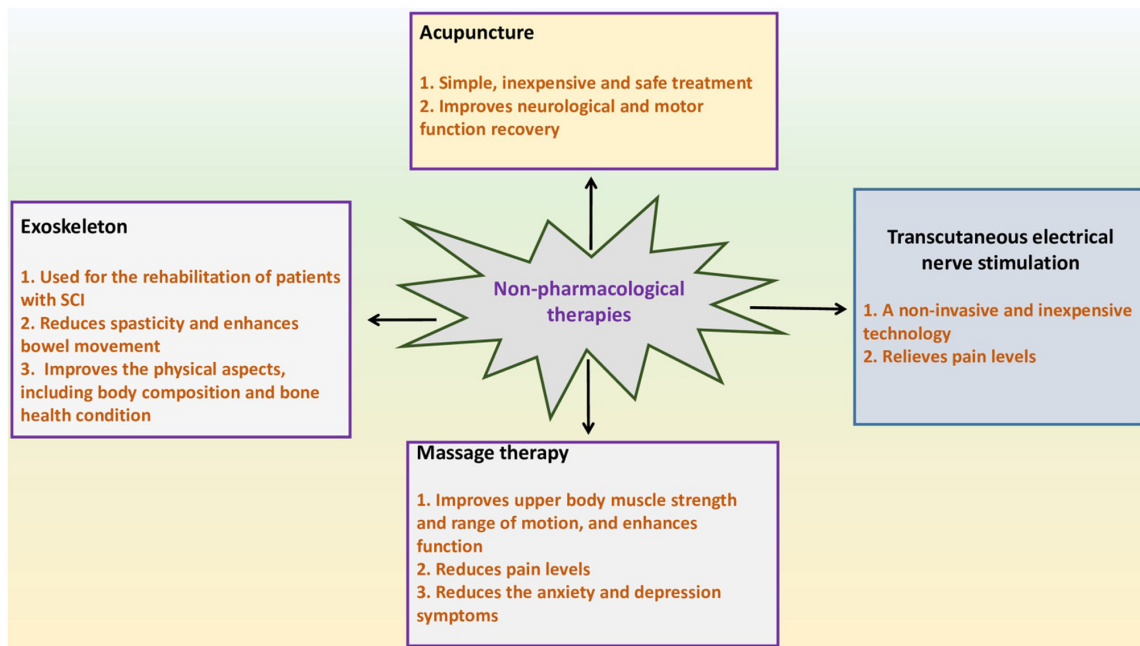


Figure 3. Non-pharmacological therapies for the treatment of SCI. SCI, spinal cord injury.

was significantly improved. In addition, ChABC can substantially increase the regeneration of corticospinal axons and synapses formed by corticospinal terminals in the gray matter caudal to the lesion (202). No harmful effects were identified. This method may be helpful for the clinical treatment of SCI. Although no human trial has been carried out thus far, the results of animal studies are promising and point to the potential benefits of ChABC in SCI treatment.

4. Non-pharmacological therapies for SCI (Fig. 3)

Acupuncture (ACP). Previous studies show that recovery of motor and sensory function following SCI is the most crucial and challenging step in rehabilitation (194,195). In addition, axonal regeneration and functional recovery following SCI are limited and challenging, especially in patients with SCI, whose paralysis duration can last a year or more. ACP is a simple, inexpensive and safe treatment, which is widely used for improving the recovery of motor and sensory function in patients with SCI (204). ACP can not only improve motor function but also promote nerve recovery (205,206). Electroacupuncture can inhibit the proliferation of astrocytes, downregulate the levels of platelet-derived growth factor and enhance motor neurons in the hind limbs of rats by inhibiting neuronal apoptosis and regulating the expression of related genes (207,208). ACP can significantly enhance the recovery of the function of motor neurons in the anterior horn of rats with SCI by augmenting the activity of acetylcholinesterase, which can upregulate the activity of neurotrophic factor mRNA (208). A study investigating the benefits of ACP therapy in neurological recovery following SCI reported that ACP therapy can substantially improve neurological and motor function recovery (204). The study also indicated that studies involving acute cases of SCI and those using different ACP treatments can achieve more significant therapeutic results in treating SCI.

Massage therapy (MT). Another study evaluated the beneficial effects of massage and exercise therapy on C5-C7 SCI (209). MT can improve upper body muscle strength and range of motion, and enhance function (209). Previous studies suggested that MT increases the range of activity and reduces the level of pain in patients with lower back pain, such as dancers (202,210). MT also reduces stiffness, pain and fatigue in patients with fibromyalgia (209,211). Furthermore, MT can reduce the symptoms of anxiety and depression in patients with SCI (212). Notably, MT reduces self-reported anxiety and depression, decreases the levels of stress hormones (cortisol and noradrenaline) and increases serotonin levels in adults (210). Exercise programs can enhance muscle strength, the range of motion and function and reduce depression and anxiety in patients with SCI (213). Patients with SCI who receive MT twice a week for 5 weeks demonstrate a significant enhancement in muscle strength, as well as in fine motor (wrist) range, compared with those in an exercise group (210). It was previously reported that an improvement in muscle strength and range of motion could significantly reduce depression and anxiety in patients with SCI (201). A study that evaluated the psychological aspects of patients show that MT can significantly mitigate depression and anxiety (209). Depression is common in patients with SCI and negatively affects their quality of life (214). Therefore, these findings indicate that patients with SCI may benefit from MT. A detailed investigation is required to evaluate MT for other SCI issues, such as spasticity and pain. Additionally, further studies are required to assess the potential effect of MT in the lower extremities of patients with SCI, especially those with affected C5-C7 vertebrae, in improving circulation and reducing muscle atrophy.

Transcutaneous electrical nerve stimulation (TENS). Electrotherapy is a non-invasive and inexpensive technique. Thus, a number of physical therapists recommend it to treat patients with SCI (215). TENS is generally used to relieve pain

during electrotherapy (211). Increasing evidence reveals that TENS is a safe treatment intervention with fewer side effects for most patients compared with other existing therapies (204). Several clinical investigations report that TENS has clear benefits in the management of SCI; however, there are controversies regarding treatment conditions and the appropriate parameters that should be adhered to during therapy using TENS (216,217). Some randomized controlled trials have explored the pain relief that can potentially be achieved using TENS and investigated its potential benefits in patients with SCI (218,219). A randomized clinical trial reported that TENS could significantly relieve pain in patients with SCI (220). Based on the visual analog scale, present pain intensity-T, pain rating index-S, pain rating index-A, present pain intensity and number of words chosen outcomes, a study indicated that 12 weeks of TENS could relieve pain in patients with SCI (220). Notably, the pain levels were significantly reduced in the TENS-treated patients with SCI (219,221). These results also indicate that TENS induces substantial effects in patients with SCI. A total of 33 patients with SCI were enrolled and were randomly assigned to the TENS and control groups (222). Patients in the TENS groups received 30 min of TENS, while those in the control group were assigned 30 min of sham TENS, once a day for 10 days. Hagen and Rekand (223) demonstrated that TENS could efficaciously relieve the pain of patients with SCI. In conclusion, TENS can be a useful approach to treat patients with SCI.

Electric exoskeleton (EXO). EXO using robotic suits is widely used for the rehabilitation of patients with SCI (224). EXO provides an alternative opportunity for patients with SCI to experience standing and walking at a low metabolic cost (224). EXO-supported walking can considerably reduce spasticity and enhance bowel movement (225). A frequency of 2-3 times or more per week for 1-2 h can be beneficial to the rehabilitation of patients with SCI (224). Using EXO-supported walking to enhance physical activity level may be attractive for patients with SCI (224). Before the development of EXO, mobility options beyond a wheelchair were few for the majority of patients with SCI lacking leg movement (226). Robotic EXOs have become increasingly popular, and it is now possible to use them for personal purposes in families and communities (227). However, it is required for users to set realistic expectations. Robotic EXOs may allow individuals with SCI with diverse levels of injury to safely and functionally walk for personal mobility or exercise (226). In addition to the potential cardiovascular benefits, physical activities and proper standing may minimize the risk of contracture, osteoporosis, cramps, pressure sores and edema in patients with SCI, especially when used early after injury (228). There is evidence that the use of EXOs affects other health aspects (229). Karelis *et al* (230) reported that after 6 weeks of EXO training the BMD of the tibia increased by 14.5%, which may have clinical significance, and the BMD of subcutaneous and muscular adipose tissue decreased by 5%. EXO can significantly improve the physical aspects, including body composition and bone health condition (231). Similar to the way the amount of physical labor depends on individual factors, individual factors may also affect the degree of influence of exoskeleton on bone health (232). The effects on bone health can also be affected

by different factors. For example, individuals who use EXO without the physical support of others may experience a significant effect on bone health compared with those who require physical support, because the ground reaction force of walking with the help of SCI exoskeletons is similar to healthy walking (233).

5. Conclusions

The pathophysiological processes following SCI are highly complex and the extent of our knowledge concerning these processes is limited. This is evident from the slow advancement of currently available neuroprotective methods compared with rapid trauma revitalization and other clinical interventions. Emerging studies continue to be added to the existing literature, comprising studies on inflammation, dysregulation, lipid peroxidation and apoptosis, which may be considered while developing suitable pharmacological therapies. Although drugs such as methylprednisolone, GM-1ganglioside and sodium channel blockers have undergone several clinical trials, other pharmacological agents and therapies have been reported to be efficacious in animal models of SCI. Additionally, some drugs show potential as candidates that can be further pursued as viable treatment options in the management of SCIs. Thus, this review considered and discussed various factors that are involved in the etiology, detection and management of SCIs, with a focus on the availability and use of current pharmacological and non-pharmacological therapies for this debilitating condition.

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Authors' contributions

YZ and AAM wrote the paper. YY, QL, JX and SY participated in literature collection and producing the figures. CW participated in literature collection and edited the manuscript. YW and JW conceived the study and wrote the manuscript. All authors reviewed and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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