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The past, present, and future of traumatic spinal cord injury therapies: a review

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This review provides a concise outline of the advances made in the care of patients and to the quality of life after a traumatic spinal cord injury (SCI) over the last century. Despite these improvements reversal of the neurological injury is not yet possible. Instead, current treatment is limited to providing symptomatic relief, avoiding secondary insults and preventing additional sequelae. However, with an ever-advancing technology and deeper understanding of the damaged spinal cord, this appears increasingly conceivable. A brief synopsis of the most prominent challenges facing both clinicians and research scientists in developing functional treatments for a progressively complex injury are presented. Moreover, the multiple mechanisms by which damage propagates many months after the original injury requires a multifaceted approach to ameliorate the human spinal cord. We discuss potential methods to protect the spinal cord from damage, and to manipulate the inherent inhibition of the spinal cord to regeneration and repair. Although acute and chronic SCI share common final pathways resulting in cell death and neurological deficits, the underlying putative mechanisms of chronic SCI and the treatments are not covered in this review.

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Introduction

Acquiring a spinal cord injury (SCI) was often viewed as a death sentence a century ago during World War One, when Harvey Cushing reported that 80% of soldiers who had an SCI died within two weeks due to major trauma and neurological sequelae such as immobility, incontinence, and autonomic disturbance.[1] It was not until 1934, when the first specialist SCI unit opened in Richmond, UK, for war veterans, signifying a move toward specialists managing and rehabilitating patients with SCIs in order to improve poor patient outcomes in Britain. Both Guttmann[2] and Munro[3] led the way in improving the care for patients by integrating different medical specialities and taking a holistic approach to their patients' care.[4] In particular, Guttmann[2] involved them in social activities and sport, which lead to the founding of the Paralympics. The advent of antibiotics,[5] assisted ventilation,[6] cardiovascular monitoring,[7] superior traction techniques,[8] and surgical instrumentation for spine stabilization,[9] in addition to improved imaging of both bone and soft-tissue,[10] lead to vast improvements in both mortality and morbidity after SCI.[3] The recognition of iatrogenic mechanical injury during the extrication process from inadequate spine immobilization was instrumental in establishing standardized training and improving equipment.[11] These, together with substantial developments in the management of a whole range of sequelae including neurogenic uropathy, pressure ulcers, spasticity, neuropathic pain, impotence, thrombosis, and suicidal ideations, further improved quality of life (QoL) for patients.[12] Technological advancements gave patients the freedom of enhanced mobility, communication, and ability to gain more independence.[13] Legislation has also played a large part in protecting care, improving occupational opportunities, and defending the entitlement to home modifications for SCI patients.[14]

In addition to the advancements made to the care of patients, the pathophysiology of SCI, as well as the potential mechanisms for repair, are much better understood.

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Initially, the brain was thought to undergo neurogenesis, the generation of new neurones, only during embryogenesis and early childhood. This dogma existed until the early 1960s as scientists and clinicians assumed that poor outcomes, minimal recovery following neurological injury, and no histological evidence of mitosis inferred the brain was mitostatic.[15] In 1962, radiolabelled thymidine, which incorporates itself into newly synthesized DNA, was used to identify dividing cells in mice and rats in vivo.[16] These experiments highlighted specific areas of the nervous system undergoing neurogenesis, in particular the adjacent areas of the ventricular system, the amygdala, and the central canal of the spinal cord.[16,17] It was not until the successful isolation and culture of these cells, capable of mitosis and differentiation,[18] that scientists could characterize these cells in vitro.[19] In the last two decades, these stem cells have been characterized in vivo using exquisite techniques such as fate mapping of the sub-ependymal layer and mouse models where expression of individual genes can be controlled via external stimuli.[20,21] These highly organized locules of stem cells exist in a small proportion of the central nervous system (CNS), which remain in an undifferentiated state and provide a stream of neurones to those lost in the olfactory bulb, together with other disputed functions in the spinal cord.[22] It is thought that these inherent adult stem cells could replace neurones and glial cells damaged in a neurological insult.[23]

The present challenges of SCI

Costs and commercial interest. Spinal cord injury results in a huge cost to healthcare and society; in 2010, it was calculated that a complete SCI to a 25-year-old would cost approximately $3 million in healthcare,[24] and $10 million when combined with the loss in earnings.[25] Despite SCI being one of the most costly and debilitating conditions, there remains limited commercial interest in developing innovative therapies. This is, in part, due to the proposed multiple mechanisms that drive a complex cascade of delayed injury,[26] a low incidence of approximately 130,000 injuries each year worldwide,[27] and a limited time window within the acute phase of an injury where there is potential to improve outcome.[28] This is offset against the cost of developing a new drug, which, on average, requires $2.6 billion.[29] Many postulate that it will require a multitude of different treatment methods in order to influence spinal cord function, thus reducing the likelihood of developing a highly effective and profitable drug.[27]

A challenging patient population. Several national databases and international studies demonstrate an increase in the mean age at injury, from 28 years in the 1970s to 42 years in 2014.[30] This is potentially due to the ageing population and the increasing number of SCI's resulting from falls, which has doubled since the 1970s and is now the second leading cause of SCI.[30,31] This increase in age of SCI patients presents a challenge to clinicians and scientists, as their life expectancy,[24] predisposition to develop complications[27] and neurological regenerative potential[32-34] are increasingly poor.

Secondary injury. Although an SCI patient suffers from neurological symptoms, which may or may not improve, it is clinically apparent that a cascade of events perpetuates many months after the original injury, causing further damage to the previously adjacent poorly functioning but intact tissue. The initial injury, commonly a compressive or contusive mechanism, causes direct cell death, permeabilization of cells, damage to the local vasculature and extravasation of blood, and proteins into the cerebrospinal fluid (CSF) exposing the susceptible spinal cord.[35,36] The epicentre of direct damage creates a hostile environment, which propagates away from the site of injury via three main domains.

Ischaemic environment. The first is the hypoxic and ischaemic environment via both systemic and local mechanisms. Systemic hypoxia can result from the paralysis of ventilatory muscles and systemic hypotension from haemorrhagic or neurogenic shock.[37] Direct external compression and oedema increases intrathecal pressure, in addition to localized microvascular and endothelial damage,[38] and impairment of autoregulation due to direct macrovascular injury.[27] The release of intracellular ions and glutamate into a previously stringently controlled extracellular environment causes neurones to become excitotoxic, thus increasing the metabolic requirements and worsening the deficit between the perfusion of the tissue and the demand for oxygen.[39] This increasingly ischaemic environment is only exacerbated by haemorrhage into predominantly grey matter, restricting perfusion of the tissue, both within and around the lesion.[40]

Induced apoptosis. In addition to this necrotic environment, marginal cells also undergo apoptosis, in particular oligodendrocytes which support a plethora of adjacent neurones.[41] The process of apoptosis requires energy and protein synthesis, thus worsening oxygen demand and inducing further apoptosis via cell-to-cell signalling in previously spared tissue.[42]

Immune activation. The third domain of damage is via inflammation and toxicity of the surrounding tissues. The necrotic products from the primary injury and ongoing cell damage, which include ATP, DNA, and intracellular ions, activate the recruitment of neutrophils and microglia. The injured spinal cord cells and resident microglia secrete cytokines within minutes.[43] Neutrophils are the first inflammatory cells to localize to the site of injury and begin releasing enzymes and reactive oxygen species (ROS) to assist in the breakdown of potential foreign material, cellular debris, and non-functional extracellular matrixes.[44] An abundance of pro-inflammatory cytokines orchestrate this destructive process which eventually settles when systemic macrophages (M2) are recruited.[45]

This inflammatory cascade is initially beneficial in clearing non-functional and toxic debris. However, prolonged parenchymal inflammation results in continued damage beyond that of the removal of debris. The continued presence and recruitment of systemic macrophages and lymphocytes were thought to be responsible, assuming that all inflammation within the CNS was detrimental.[46] This was based upon the CNS harbouring specialized immune cells, being protected from the systemic immune system,[47] and when systemic immune cells are recruited, they are implicated in further damage in neurological pathologies (i.e. MS).[48] However, more recently there is growing evidence to suggest that CD4+ lymphocytes, and systemically recruited macrophages that appear akin to local microglia, help to decrease the initial and necessary inflammatory response.[45,49] This could explain why large systemic doses of corticosteroids did not demonstrate ubiquitous and clear superiority in the acute phases of a traumatic SCI.[50,51] However, the challenge that faces scientists with any immunomodulation is the multifaceted nature of cells, cytokines, and signalling cascades and the context in which these all occur.

The glial scar: friend or foe? One of the other important and local responses is the activation and proliferation of astrocytes, microglia, and macrophages which embed high quantities of chondroitin sulphate proteoglycans (CSPGs) within an extracellular matrix to form a glial scar, approximately two weeks after the initial injury.[52] The dense glial scar compartmentalizes and attenuates the spread of any further toxicity via the adhesive properties of the CSPGs, thus increasing the focal concentration of chemokines and enhancing the attraction of immune cells to the contained area.[53] This, in addition to increasing the concentration of trophic factors released by local cells, including astrocytes, demonstrates its beneficial immunomodulatory function in the acute phase of injury.[54] A disputed property of scar tissue is its ability to occupy the vacant space left from the damage and provides a scaffold on which revascularization can occur.[55] However, after the acute phase, the glial scar inhibits axonal growth and neurogenesis, both in vivo and in vitro.[56,57] Modulation of CSPG production only after the acute phase provided functional benefit in mice,[58] highlighting the important initial function of the glial scar which becomes a barrier to regeneration.[59] However, the observations from animal SCI models often differ with each other and in comparison to human trials, due disparities in the models of injury to the spinal cord,[60] the timeframe of events after SCI,[61] and endogenous cell behaviour.[34,62] Furthermore, a range of neurotrophic growth factors have been used to minimize scarring and promote axonal sprouting following SCI.[63] Iron chelation and adenosine monophosphate have also been shown to reduce oxidative damage and subsequently diminish glial scars following SCI, but often induces an anaemia.[63,64] Another pharmacological method to reduce the glycosaminoglycan (GAG) chains expressed on such damaged cells is to use chondroitinase ABC, which degrades GAG chains and has been shown to promote regeneration to both ascending and descending tracts in the mouse spinal cord.[65] However, poor efficacy of single injections of chondroitinase and its thermal instability at human body temperature would require repeated intrathecal injections and the associated infection risk.[66]

CNS inhibition of axon regeneration. The response to injury of the CNS differs to the PNS, in particular axon regeneration after injury, is known to be inhibited, particularly in the white matter.[67] There are three main groups of inhibitory proteins that are thought to be responsible for this inconsistency: inhibitors within the glial scar, myelin associated inhibitors, and guidance type growth inhibitors, which guide axons throughout embryogenesis.[68] All of these appear to affect the Rho/Nogo pathway, which enables the formation of microtubules that are critical to developing motile growth cones within axons for sprouting and developing new connections.[69] Inhibition of the Rho pathway has demonstrated improved murine recovery of limb function in most drugs modulating this pathway.[70] However, the human phase 2b trial for a successful Rho kinase inhibitor in the mouse, Cethrin, has been abandoned due to negligible clinical effect, again demonstrating unknown distinctions in human SCI to that of the mouse.

Stem cell therapies

Many hypothesize that replacing cells damaged beyond repair will enable the restoration of function. The development of embryonic stem (ES) cells and induced pluripotent stem (iPS) cells is expected to revolutionize medical treatment of diseases which are otherwise incurable.[71] Since the development of ES and iPS cells, many animal cell transplant experiments have indicated that, despite the marginal and limited functional recovery from various mechanical insults, there are safety concerns regarding the risk of forming teratomas,[72] propagating neuropathic pain,[73] and worsening disability immediately after cell transplantation,[74] together with graft versus host disease and risks associated with any adjuvant immunosuppressive treatment.[32,75] The debate as to which stem cell type is most suitable for regenerative therapies is highly controversial due to ethical implications, diverse potential consequences together with the limited scientific validation of each cell type; only a handful of phase 1 clinical trials have been completed with neural human embryonically-derived cells.[75-77] However, recent advances in endogenous stem cell therapies, iPS cell transplantation, and alternative pharmacological techniques may provide robust alternative treatments for SCI. Moreover, direct transplantation of

cells into the spinal cord may not be necessary, with intravenous transfusion of stem cell products to avoid aseptic meningitis and further trauma adjacent to the SCI is a validated and effective method in animals.[78]

Induced pluripotent stem cells. Induced pluripotent stem cells have advantages over ES cells in that they avoid the destruction of blastocysts and complications arising from host versus graft disease, although the risk of teratomas still remain.[79] Recently, human-derived iPS cells have been transplanted into mice resulting in "significant recovery of motor deficits" after SCI.[80] They demonstrate the ability of transplanted cells to migrate a considerable distance from the injection site (> 3 mm), differentiate into all neural cell types, and successfully form synapses with both exogenous and endogenous neurones.[80] iPS cells are a viable treatment approach, although comprehensive and controlled comparisons need to be made between the efficacy of ES and iPS cell transplantation in animal models.[23] Furthermore, to date there are no published human trials using iPS cells to treat SCI, and currently the US Food and Drug Administration (FDA) has only approved the use of embryonically derived neural cells.[81] Despite this lack in translation from laboratory to bedside, iPS cell technology is constantly evolving with the generation of iPS cells without viruses and instead with minicircle DNA, which is akin to a plasmid but much smaller and only containing the human gene of interest.[82,83] High expression can be achieved for a suitable time period in which many iPS cells can be generated and transplanted without the long-term consequences of genetic upregulation.[83] Nonetheless, the clinical safety profile and further in vitro characterization will need to be examined before use in human subjects.

Induced neural stem cells. Recently, human fibroblasts were directly programmed into so-called induced neural stem cells (iNSC) using a single factor, Sox2, which did not generate tumours in vivo.[84] This technique enables scientists to avoid the insertion of multiple genes, each with a risk of disrupting the cell genome and a varied expression of each gene.[83] Moreover, the effects of a single gene up-regulation can be studied in more depth about the behaviour, morphology, gene interaction, protein expression, and ability of the genetically modified cell.[84] However, these iNSC's take two weeks in culture to exhibit characteristic bipolar NSC morphology, in addition to the time to generate a fibroblast culture, which could be an important drawback to achieving rapid autologous transplantation. For any exogenous stem cell therapy, scientists debate when cells should be selected for transplantation as laboratories use many different methods and criteria for transplantation. Furthermore, neural stem (NS) cell cultures are notoriously heterogeneous and poorly defined as no agreed neural stem cell markers exist for bona fide stem cells to differentiate them from surrounding progeny, making any comparison of such studies difficult.[85]

Cell transplantation verses recruitment of endogenous stem/progenitor cells. Despite new advances in cell-based therapies, there are important side effects to transplantation that need to be considered. In recent phase 1 clinical trials, it appeared that five out of seven patients suffered from meningitis post transplantation,[76] in addition to a high incidence of evolving neuropathic pain and induced spasticity post-injection. Current problems in transplantation provide more support for the recruitment and proliferation of endogenous stem/progenitor cells within the spinal cord.[76] Recent studies describe the phenomena that ependymal cells have multi-potent stem cell characteristics,[86,87] and are responsible for some regeneration within the spinal cord.[15,88] Experiments suggest endogenous neural stem cells are suppressed under SCI conditions in mice, as a small increase in the endogenous stem cell population and improvement in functional recovery is observed after injecting adult neural stem/progenitor cells.[32,89] Moreover, CNS cells have been known to up-regulate stem cell markers after injury,[90] and contribute to the generation of glial scar tissue after CNS injury.[91] Therefore, by understanding the inherent properties and regenerative potential of this endogenous neural stem/progenitor cell niche, it could inform us about the efficacy of these endogenous stem cells in SCI therapies. Despite a large number of studies of the mouse spinal cord, only one limited study examines the human spinal cord stem cell niche.[34,76] The characteristics of any allograft should be compared directly with endogenous stem cells already present as manipulation of these endogenous stem cells is arguably safer.[34]

Many studies comment that an effective cell-based therapy would be difficult to envisage for a chronic SCI due to the fibrosis and degeneration of afferent axons.[15] Furthermore, any transplanted cell into a SCI behaves differently and its neurogenic and proliferative potential are thought to be inhibited by in situ cells via cell-to-cell signalling from cell surface proteoglycans, inducing gliogenic cues.[32] It is essential to understand how these neural stem/progenitor cells respond to insults and subsequently develop pharmacological strategies to modulate these cells in vivo and produce functional progeny for the regeneration of tissue. Specific growth factors are used to culture neural stem cells and have been used in vivo to increase the endogenous stem cell population.[87,92]

Bio-scaffolds

Strategies applied soon after SCIs limit, but do not prevent, further tissue loss from the primary injury. Therefore, the repair of such damage requires a conduit by which neurones are directed across and bridge the breach.[93] Biodegradable polymer scaffolds composed of

collagen, chitosan, agarose, and fibronectin have been tested in animals.[94] An ultra-structure matrix of polylactic-co-glycolic acid (PGA), used in absorbable sutures and coated in a polymer of lysine for cells to attach to, demonstrated that axons could bridge such a gap,[95] reduce glial cysts and scarring, and improve recovery.[96] Subsequently, it has gained approval for an investigative medicinal device and phase 1 human trials have begun.[97]

Avoiding malnutrition

Furthermore, there is increasing evidence in mouse models and human case-controlled studies that high levels of protein intake and avoidance of hypoalbuminaemia in the early stages of SCI can improve functional recovery.[98,99] Approximately 40% to 66% of SCI centre admissions are either at risk of or already malnourished, which is higher than that of other hospital admissions.[100,101] UK and USA centres have demonstrated that malnutrition in SCI is associated with increased mortality and length of stay.[102,103] However, there are many examples where it is not possible to prevent hypoalbuminaemia, and nitrogen balance is unreliable in estimating metabolic demands in peri-trauma patients.[104]

Surgical decompression

The surgical treatment of SCI has been largely targeted at achieving spinal stability and where there is ongoing compression of the spinal cord; there is currently controversial and low-quality evidence supporting decompression within 24 hours of injury.[105] This evidence is currently based on animal studies, retrospective analyses of human SCI databases, and much smaller cohort prospective studies only. There is a significant proportion of acute SCI patients (77%) in previous feasibility studies who are not eligible for acute decompressive surgery due to the necessity of transport to a spinal centre, appropriate imaging, suitable cardiorespiratory stability, and the requirement of other lifesaving procedures.[106] This is further compounded by trauma patients often being confused, sedated and in significant pain which makes an acute neurological assessment challenging. Furthermore, an early neurological examination within four hours of injury, is not representative of prognosis or neurological loss as American Spinal Injury Association Impairment Scale (AIS) grade conversion and motor score improvements are higher.[107] Some work has already begun on using neurophysiological, MRI tractography, and blood biomarkers as predictive adjuncts to the initial neurological assessment.[108]

The STASCIS study[109] compared early decompression (< 24 hours) with late decompression (> 24 hours, but < seven days). This was limited because the early intervention group were five years' younger than the late decompression group, and there was a variation in the administration of steroids with no uniform benefit of early surgery across all patients who improved after injury (54%). The benefit was only demonstrated in a subset of these patients who had a severe cord injury, with an AIS of A-C, and improved by 2 or 3 grades. There was no correction for age and the timing of surgery was at the discretion of the attending spinal surgeon, which inherently introduces bias. This study has since been pooled into a larger analysis (n = 1,066), which demonstrated an improvement of a total of four Medical Research Council (MRC) motor points across all myotomes below the level of injury at one year follow-up.[110] However, the results from an international randomized trial, SCI-POEM, are keenly anticipated,[111] and further work examining the physiological and neurological outcomes associated with targeted spinal cord perfusion pressure,[112] duroplasty and decompression are continuing to gain more evidence.[113] There is a problematic clinical balance between the upfront risks of acute spinal surgery, in often multiple-injured patients, who are increasingly older, and have poorer physiological reserves with a real risk of worsening the perfusion of the spinal cord in comparison to the hypothesized benefit of reducing the time the spinal cord is compressed.

Stimulation adjuncts to spinal rehabilitation

Neuropathic pain control for SCI patients is frequently problematic as 80% suffer from neuropathic pain with a third refractory to pharmacotherapy.[114] Despite the advent of epidural spinal cord stimulators, due to the disruption of the rexed laminae or the continuity of the dorsal columns which are utilized to augment the small unmyelinated nerve fibres via a gate control mechanism, only 20% to 30% of SCI patients have a persistent therapy response.[115] It is proposed that both abnormal inputs to the nociceptive pathways in the spinal cord as well as a reorganisation of cortical circuitry result in pain becoming most prevalent at one year after injury. Therefore, experimental attempts are being made at mediodorsal thalamic nucleus stimulation to modulate nociception.[116] Furthermore, sub-threshold, high frequency (10 kHz), or burst stimulation, which ameliorates pain locally without ascending orthodromic activation of the dorsal columns and subsequent electrical paraesthesia, has been shown to have a higher and improved pain augmentation rate. However, the evidence for its use in neuropathic pain after SCI has not been demonstrated in randomized controlled trials (RCTs).[117]

Epidural electrical stimulation (EES) was incidentally found to improve motor function in patients suffering from MS, with an original premise to reduce neuropathic pain.[118] The mechanisms by which the stimulation parameters can enable stepping and standing, akin to central pattern generators of locomotion, remain elusive.[119] However, central to most hypotheses is the utility of proprioceptive signals, which are the only input

providing feedback of movement to an isolated spinal cord below the SCI. It is often proposed that spinal interneurons are able to form and reconnect these central pattern generators within the grey matter. Prospective clinical studies demonstrate phasic and closed loop stimulation when matched with locomotor training can greatly improve the coordination of motor groups and are currently being examined in in phase 1 RCTs to demonstrate efficacy over that of task-targeted physical therapy.[120121] Transcutaneous spinal cord or trans-spinal stimulation is an alternative to EES and avoids the invasive risks of epidural stimulation placement and maintenance. However, it differs in its generation of weak rhythmic activation of lower limb antagonist muscles via multiple spinal levels, and has been shown to increase sprouting and neuroplasticity in both animals and humans.[122,123] However, the electrode location, current intensity, and stimulation parameters are yet to be optimized in very early clinical trials.[124]

Vagal nerve stimulation (VNS) has a newly established evidence base for the rehabilitation of ischaemic stroke patients, nine months to ten years after their ictus, with paired stimulation and rehabilitative physiotherapy resulting in a two- to three-times improvement in motor scores across both functional and clinical assessments.[125] It is hoped that these observed improvements are translated to spinal cord injury patients with a human RCT pending,[126] and VNS stimulation paired with physiotherapy exercises enhancing motor recovery in animal models of traumatic cervical SCI.[127]

Neuropathic bladder and bowel

The QoL of SCI patients often is greatly influenced by their degree of incontinence. The constant burden to carry the necessary paraphernalia and be within a short distance of suitable facilities often frustrates SCI patients and can limit their activities.[128] The primary long-term treatment for neurogenic bladder in SCI is to lower bladder pressure. After the acute flaccid paralysis stage, akin to an upper motor neuron pathology, both the detrusor and external sphincter muscles become hypertonic and hyper-reflexic, generating a high bladder pressure.[128] Standard therapy starts with clean intermittent catheterization matched to a fluid schedule and anticholinergics. In more complex cases, intravesical botulinum A toxin injections and surgical procedures modulating bladder outlet resistance may be warranted.[129]

Sacral anterior root stimulation with sacral root denervation has been used to replace the overactive bladder reflex arc via an externalised stimulator where different anterior sacral roots (S2-5) are stimulated to enhance urinary voiding, defaecation (55%), and, at best, producing a non-functional erection or vaginal lubrication.[130] Although it improves bladder pressures, bladder capacity, ureterorenal reflux, urinary continence (78%), and subsequent UTIs, it irreversibly abolishes genital sensation and perianal sensation, as well as any reflex erections and ejaculations. Furthermore, the procedure itself has inherent risks, totalling over 20%, including infection, CSF leak, defects of the receiver coil, or cable requiring arthroplasty, as well as overdistention of the bladder or neurogenic failure where intermittent catheterization is required indefinitely.[130] Hence, this procedure is destructive and renders future, reversible neuromodulation therapies unfeasible.[131]

The most common pharmacological agents either inhibit the muscarinic and nicotinic receptors responsible for detrusor contraction and external sphincter contraction, respectively, or increase the sympathetic relaxation of the detrusor muscle via α1 and β3 receptors. As these receptors are also expressed in the brain, cardiovascular, and gastrointestinal systems, as well as the eye, they commonly produce systemic side-effects, including sedation, prolonged QT, constipation, and blurred vision. There is cumulative evidence that SCI patients' bladders undergo a change in chemosensitive C nerve fibres to become mechanosensitive, and innervate types 2 and 3 muscarinic receptors causing non-voiding local contractions within the bladder.[132] Intravesical instillation of vanilloid and nociceptin solutions, which target transient receptor potential (TRP) V1 channels on C nerve fibres, improves the micturition reflex in SCI patients.[133] Currently, work is ongoing to develop antagonists to the TRP receptors without the associated suprapubic pain and initial worsening of lower urinary tract symtpoms (LUTS).[134]

Sacral nerve stimulation, which modulates the afferent/ascending fibres within the S3 foraminal nerve root(s) for SCI patients with overactive bladders or faecal incontinence, is not effective when there is complete cord injury, but there are small clinical studies demonstrating improvements in bladder capacity with incomplete SCI (Frankel grade B),[135,136] and within early recovery from the injury (12 weeks).[137] However, the longevity of improvement with stimulation may decrease after six months after implantation and hence long term studies for SCI patients are important.[138]

Pudendal nerve (PN) mechanical stimulation, elicited by a penile squeeze[139] or cutaneous electrical stimulation of perigential skin, inhibits bladder contractions and has been shown in humans with SCI to be feasible.[140] The attraction of PN stimulation is evidence that low frequency stimulation (5 to 10 Hz) promotes reflex bladder inhibition,[129] while high frequency (20 to 50 Hz) produces robust bladder contractions in SCI patients.[141] There are also ongoing trials, examining the effect of EES on bladder capacity and voiding efficiency, which are yet to produce results.

Role of an exoskeletons and body weight-supported treadmills

Exoskeletons and body weight-supported treadmills enable patients with an incomplete SCI to maintain muscles used when walking and to retrain the coordination of the lower limbs. It is thought that this high-fidelity, task-orientated environment can improve the speed and stamina of walking over that of standard physical therapy.[142] It is widely accepted that the use of an exoskeleton bears the greatest benefits to those after their acute recovery rather than over 1 year after injury.[143] However, on a recent metanalysis of randomized studies, the walking speed is not significantly increased to overground physical therapy although the difference in distance walked was not conclusive.[144] It goes without saying that the cost of acquiring the equipment, maintaining it, and the need for a qualified assistant to fit the device is often beyond that of personal purchase. Furthermore, for spastic paraplegia patients' exoskeletons provide inferior improvements in comparison to physical therapy despite no association with age or spinal level of injury.[143] It is debated whether exoskeletons should be used in patients with complete SCI as the experience to be able to walk, when it cannot yet be provided long-term in the community, can be psychologically damaging despite reports of improvement in pain, bowel motility, overactive bladder, and muscle spasticity.[145] There are small additional risks of pressure ulcers, falls, and lower limb fractures, depending on the patients neurological status, exoskeleton configuration and environment.[146]

Neuropsychological effects of virtual reality

Virtual reality (VR) for neurorehabilitation patients is a rapidly evolving area. The largest RCTs to date examined stroke patients, where there was no superiority in motor function, despite the increase in time spent engaging with the VR activities, but it reduced the contact time with clinical therapists.[147,148] Moreover, for traumatic SCI, there are much smaller pilot RCTs, which correlate with the aforementioned findings with objective motor improvements similar to that of conventional physical therapy.[149–151] However, there is greater evidence of psychological improvements in motivation, neuropathic pain, balance, and planning for a range of mobility tasks.[152] It is recognized that after a SCI, the patients' perception of their poorly functioning limbs decreases over time. This is intimately linked to their perception of pain, which, when manipulated with VR illusions and multisensory stimulation, provides analgesia.[153]

Prophylaxis of autonomic dysreflexia

The treatment of autonomic dysreflexia (AD) has remained unchanged for many decades with the important principles of prompt recognition, identification and removal of noxious stimuli while monitoring and treating persistent hypertension. However, prevention of AD could be optimised as not all noxious stimuli can be eliminated promptly (urinary tract infection, ulcers, fractures, fissure, progressive syrinx, pregnancy). The SCI disrupts the bulbospinal descending tracts, which normally inhibit spinal sympathetic reflexes. Moreover, neuroplastic changes driven by nerve growth factor are thought to increase sensory inputs to the reflex, observed at four to six weeks after SCI.[154] Intraspinal sprouting of propriospinal neurones from unmyelinated pelvic C fibres further exaggerates this unmodulated reflex.[155] CD11d integrin, which was thought to ameliorate the damaging inflammatory effects within the grey matter of the spinal cord in animal models, failed to moderate the development of allodynia, nor AD after SCI.[156] However, intermittent low doses of gabapentin reduce the frequency and severity of AD in rats,[157] and so some centres use this prior to a simulating procedure, such as a urodynamic study. However, from this observation, it was thought that gabapentin at high doses for many weeks after SCI may moderate the occurrence of AD which bizarrely resulted in an increased AD burden.[158] Currently, one can only avoid AD or treat the hypertensive effects of the AD and not supress the underlying abnormal reflex. Further work is needed to ascertain pathophysiology in the development of AD.[159–161]

Conclusion

It is evident that in the near future a whole variety of advanced and costly treatments may exist for SCI, but the side-effect profile, efficacy, efficiency and standardized protocols are yet to be determined. Many publications have reported differences in the rodent and human spinal cord in both motor & sensory systems, immune systems, the temporal nature of secondary injury and stem cell characteristics.[158,162] The impact of this upon translational experimental therapies remains to be seen.[160] As with any experimental spinal cord intervention, there are many risks and potential disabling long-term consequences for patients which require caution. The ability to manipulate these complex mechanisms, by which further damage propagates and regeneration is resisted, is difficult and probably requires a multitude of adjuvant therapies at different stages of the injury. Many advances have been made in the understanding of the pathological processes after traumatic SCI, and equally there are increasingly innovative techniques which have potential to ameliorate both the structure and function of the injured human spinal cord.

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References

1. **Guttmann L**. Rehabilitation of spinal cord injuries. *Br J Phys Med*. 1946;9:162.
2. **Schültke E**. Ludwig Guttmann: emerging concept of rehabilitation after spinal cord injury. *J Hist Neurosci*. 2001;10(3):300–307.

3. **Donovan WH**. Spinal cord injury-past, present, and future. *J Spinal Cord Med.* 2007;30(2):85–100.
4. **Silver JR**. History of the treatment of spinal injuries. *Postgrad Med J.* 2005;81(952):108–114.
5. **Jacobs GB**, **Berg RA**. The treatment of acute spinal cord injuries in a war zone. *J Neurosurg.* 1971;34(2 Pt 1):164–167.
6. **Viroslav J**, **Rosenblatt R**, **Tomazevic SM**. Respiratory management, survival, and quality of life for high-level traumatic tetraplegics. *Respir Care Clin N Am.* 1996;2(2):313–322.
7. **Piepmeier JM**, **Lehmann KB**, **Lane JG**. Cardiovascular instability following acute cervical spinal cord trauma. *Cent Nerv Syst Trauma.* 1985;2(3):153–160.
8. **Nickel VL**, **Perry J**, **Garrett A**, **Heppenstall MT halo**. A spinal skeletal traction fixation device. *Clin Orthop Relat Res.* 1989;4–11.
9. **Katznelson AM**. Stabilisation of the spine in traumatic paraplegia. *Paraplegia.* 1969;7(1):33–37.
10. **Perovitch M**. The application of magnetic resonance in spinal cord disorders. *Paraplegia.* 1987;25(5):373–380.
11. **Ersson A**, **Lundberg M**, **Wramby C-O**, **Svensson H**. Extrication of entrapped victims from motor vehicle accidents: the crew concept. *Eur J Emerg Med.* 1999;6(4):341–347.
12. **Juknis N**, **Cooper JM**, **Volshteyn O**. The changing landscape of spinal cord injury. *Handb Clin Neurol.* 2012;109:149–166.
13. **Sisto SA**, **Forrest GF**, **Faghri PD**. Technology for mobility and quality of life in spinal cord injury. *IEEE Eng Med Biol Mag.* 2008;27(2):56–68.
14. **Geiger BF**. Establishing a disability-inclusive agenda for sustainable development in 2015 and beyond. *Glob Health Promot.* 2015;22(1):64–69.
15. **Barnabé-Heider F**, **Göritz C**, **Sabelström H**, **et al**. Origin of new glial cells in intact and injured adult spinal cord. *Cell Stem Cell.* 2010;7(4):470–482.
16. **ALTMAN J**. Are new neurons formed in the brains of adult mammals. *Science.* 1962;135(3509):1127–1128.
17. **Adrian EK**, **Walker BE**. Incorporation of thymidine-H3 by cells in normal and injured mouse spinal cord. *J Neuropathol Exp Neurol.* 1962;21:597–609.
18. **Temple S**. Division and differentiation of isolated CNS blast cells in microculture. *Nature.* 1989;340(6233):471–473.
19. **Reynolds BA**, **Weiss S**. Generation of neurons and astrocytes from isolated cells of the adult mammalian central nervous system. *Science.* 1992;255(5052):1707–1710.
20. **Doetsch F**. A niche for adult neural stem cells. *Curr Opin Genet Dev.* 2003;13(5):543–550.
21. **Ma DK**, **Bonaguidi MA**, **Ming G-L**, **Song H**. Adult neural stem cells in the mammalian central nervous system. *Cell Res.* 2009;19(6):672–682.
22. **Doetsch F**, **Caillé I**, **Lim DA**, **García-Verdugo JM**, **Alvarez-Buylla A**. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell.* 1999;97(6):703–716.
23. **Benchoua A**, **Onteniente B**. Intracerebral transplantation for neurological disorders. Lessons from developmental, experimental, and clinical studies. *Front Cell Neurosci.* 2011;6:2.
24. **National Spinal Cord Injury Statistical Center**. Spinal cord injury facts and figures at a glance. *J Spinal Cord Med.* 2010;33(4):439–440.
25. **Fehlings MG**, **Nguyen DH**. Immunoglobulin G: a potential treatment to attenuate neuroinflammation following spinal cord injury. *J Clin Immunol.* 2010;30 Suppl 1:S109-12.
26. **Dumont RJ**, **Okonkwo DO**, **Verma S**, **et al**. Acute spinal cord injury, part I: pathophysiologic mechanisms. *Clin Neuropharmacol.* 2001;24(5):254–264.
27. **Thuret S**, **Moon LDF**, **Gage FH**. Therapeutic interventions after spinal cord injury. *Nat Rev Neurosci.* 2006;7(8):628–643.
28. **Kwon BK**, **Okon E**, **Hillyer J**, **et al**. A systematic review of non-invasive pharmacologic neuroprotective treatments for acute spinal cord injury. *J Neurotrauma.* 2011;28(8):1545–1588.
29. **Avorn J**. The $2.6 billion pill — methodologic and policy considerations. *N Engl J Med.* 2015;372(20):1877–1879.
30. **Singh A**, **Tetreault L**, **Kalsi-Ryan S**, **Nouri A**, **Fehlings MG**. Global prevalence and incidence of traumatic spinal cord injury. *Clin Epidemiol.* 2014;6:309–331.
31. **Devivo MJ**. Epidemiology of traumatic spinal cord injury: trends and future implications. *Spinal Cord.* 2012;50(5):365–372.
32. **Barnabé-Heider F**, **Frisén J**. Stem cells for spinal cord repair. *Cell Stem Cell.* 2008;3(1):16–24.
33. **Roozbehi A**, **Joghataei MT**, **Bakhtiyari M**, **Mohammadi J**, **Rad P**, **Delaviz H**, **et al**. Age-associated changes on axonal regeneration and functional outcome after spinal cord injury in rats. *Acta Med Iran.* 2015;53(5):281–286.
34. **Dromard C**, **Guillon H**, **Rigau V**, **et al**. Adult human spinal cord harbors neural precursor cells that generate neurons and glial cells in vitro. *J Neurosci Res.* 2008;86(9):1916–1926.
35. **Choo AM**, **Liu J**, **Lam CK**, **Dvorak M**, **Tetzlaff W**, **Oxland TR**, **et al**. Contusion, dislocation, and distraction: primary hemorrhage and membrane permeability in distinct mechanisms of spinal cord injury. *J Neurosurg Spine.* 2007;6(3):255–266.
36. **Popovich PG**, **Horner PJ**, **Mullin BB**, **Stokes BT**. A quantitative spatial analysis of the blood-spinal cord barrier. I. Permeability changes after experimental spinal contusion injury. *Exp Neurol.* 1996;142(2):258–275.
37. **Guha A**, **Tator CH**. Acute cardiovascular effects of experimental spinal cord injury. *J Trauma.* 1988;28(4):481–490.
38. **Benton RL**, **Maddie MA**, **Worth CA**, **Mahoney ET**, **Hagg T**, **Whittemore SR**, **et al**. Transcriptomic screening of microvascular endothelial cells implicates novel molecular regulators of vascular dysfunction after spinal cord injury. *J Cereb Blood Flow Metab.* 2008;28(11):1771–1785.
39. **Li S**, **Mealing GA**, **Morley P**, **Stys PK**. Novel injury mechanism in anoxia and trauma of spinal cord white matter: glutamate release via reverse Na+-dependent glutamate transport. *J Neurosci.* 1999;19(14):RC16.
40. **Tator CH**, **Fehlings MG**. Review of the secondary injury theory of acute spinal cord trauma with emphasis on vascular mechanisms. *J Neurosurg.* 1991;75(1):15–26.
41. **Ackery A**, **Robins S**, **Fehlings MG**. Inhibition of Fas-mediated apoptosis through administration of soluble Fas receptor improves functional outcome and reduces posttraumatic axonal degeneration after acute spinal cord injury. *J Neurotrauma.* 2006;23(5):604–616.
42. **Beattie MS**. Inflammation and apoptosis: linked therapeutic targets in spinal cord injury. *Trends Mol Med.* 2004;10(12):580–583.
43. **Pineau I**, **Lacroix S**. Proinflammatory cytokine synthesis in the injured mouse spinal cord: multiphasic expression pattern and identification of the cell types involved. *J Comp Neurol.* 2007;500(2):267–285.
44. **Donnelly DJ**, **Popovich PG**. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. *Exp Neurol.* 2008;209(2):378–388.
45. **Shechter R**, **London A**, **Varol C**, **et al**. Infiltrating blood-derived macrophages are vital cells playing an anti-inflammatory role in recovery from spinal cord injury in mice. *PLoS Med.* 2009;6(7):e1000113.
46. **Crowe MJ**, **Bresnahan JC**, **Shuman SL**, **Masters JN**, **Beattie MS**. Apoptosis and delayed degeneration after spinal cord injury in rats and monkeys. *Nat Med.* 1997;3(1):73–76.
47. **Shirai M**, **Izumi H**, **Yamagami T**. Experimental transplantation models of mouse sarcoma 180 in ICR mice for evaluation of anti-tumor drugs. *J Vet Med Sci.* 1991;53(4):707–713.
48. **Hemmer B**, **Kerschensteiner M**, **Korn T**. Role of the innate and adaptive immune responses in the course of multiple sclerosis. *Lancet Neurol.* 2015;14(4):406–419.
49. **Moalem G**, **Leibowitz-Amit R**, **Yoles E**, **Mor F**, **Cohen IR**, **Schwartz M**, **et al**. Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med.* 1999;5(1):49–55.
50. **Hurlbert RJ**. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine (Phila Pa 1976).* 2001;26(24 Suppl):S39-46.
51. **Rozet I**. Methylprednisolone in acute spinal cord injury: is there any other ethical choice. *J Neurosurg Anesthesiol.* 2008;20(2):137–139.
52. **Jones LL**, **Margolis RU**, **Tuszynski MH**. The chondroitin sulfate proteoglycans neurocan, brevican, phosphacan, and versican are differentially regulated following spinal cord injury. *Exp Neurol.* 2003;182(2):399–411.
53. **Faulkner JR**, **Herrmann JE**, **Woo MJ**, **Tansey KE**, **Doan NB**, **Sofroniew MV**, **et al**. Reactive astrocytes protect tissue and preserve function after spinal cord injury. *J Neurosci.* 2004;24(9):2143–2155.
54. **Schwartz JP**, **Nishiyama N**. Neurotrophic factor gene expression in astrocytes during development and following injury. *Brain Res Bull.* 1994;35(5–6):403–407.
55. **Parri R**, **Crunelli V**. An astrocyte bridge from synapse to blood flow. *Nat Neurosci.* 2003;6(1):5–6.
56. **McKeon RJ**, **Schreiber RC**, **Rudge JS**, **Silver J**. Reduction of neurite outgrowth in a model of glial scarring following CNS injury is correlated with the expression of inhibitory molecules on reactive astrocytes. *J Neurosci.* 1991;11(11):3398–3411.
57. **Tan AM**, **Colletti M**, **Rorai AT**, **Skene JHP**, **Levine JM**. Antibodies against the NG2 proteoglycan promote the regeneration of sensory axons within the dorsal columns of the spinal cord. *J Neurosci.* 2006;26(18):4729–4739.
58. **Rolls A**, **Shechter R**, **London A**, **et al**. Two faces of chondroitin sulfate proteoglycan in spinal cord repair: a role in microglia/macrophage activation. *PLoS Med.* 2008;5(8):e171.
59. **Fawcett JW**. Overcoming inhibition in the damaged spinal cord. *J Neurotrauma.* 2006;23(3–4):371–383.

60. **Robins SL**, **Fehlings MG**. Models of experimental spinal cord injury: Translational relevance and impact. *Drug Discov Today Dis Models*. 2008;5(1):5–11.
61. **Fleming JC**, **Norenberg MD**, **Ramsay DA**, **et al**. The cellular inflammatory response in human spinal cords after injury. *Brain*. 2006;129(Pt 12):3249–3269.
62. **Sroga JM**, **Jones TB**, **Kigerl KA**, **McGaughy VM**, **Popovich PG**. Rats and mice exhibit distinct inflammatory reactions after spinal cord injury. *J Comp Neurol*. 2003;462(2):223–240.
63. **Jaerve A**, **Schiwy N**, **Schmitz C**, **Mueller HW**. Differential effect of aging on axon sprouting and regenerative growth in spinal cord injury. *Exp Neurol*. 2011;231(2):284–294.
64. **Rathore KI**, **Kerr BJ**, **Redensek A**, **et al**. Ceruloplasmin Protects Injured Spinal Cord from Iron-Mediated Oxidative Damage. *J Neurosci*. 2008;28(48):12736–12747.
65. **Bradbury EJ**, **Moon LDF**, **Popat RJ**, **et al**. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature*. 2002;416(6881):636–640.
66. **Bradbury EJ**, **Carter LM**. Manipulating the glial scar: chondroitinase ABC as a therapy for spinal cord injury. *Brain Res Bull*. 2011;84(4–5):306–316.
67. **Rezajooi K**, **Pavlides M**, **Winterbottom J**, **et al**. NG2 proteoglycan expression in the peripheral nervous system: upregulation following injury and comparison with CNS lesions. *Mol Cell Neurosci*. 2004;25(4):572–584.
68. **Forgione N**, **Fehlings MG**. Rho-ROCK inhibition in the treatment of spinal cord injury. *World Neurosurg*. 2014;82(3–4):e535-9.
69. **McKerracher L**, **Higuchi H**. Targeting Rho to stimulate repair after spinal cord injury. *J Neurotrauma*. 2006;23(3–4):309–317.
70. **Watzlawick R**, **Sena ES**, **Dirnagl U**, **et al**. Effect and reporting bias of RhoA/ROCK-blockade intervention on locomotor recovery after spinal cord injury: a systematic review and meta-analysis. *JAMA Neurol*. 2014;71(1):91–99.
71. **Takahashi K**, **Yamanaka S**. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663–676.
72. **Masuda S**. Rlsk of teratoma formation after transplantation of induced pluripotent stem cells. *Chest*. 2012;141(4):1120–1121.
73. **Kishk NA**, **Gabr H**, **Hamdy S**, **et al**. Case control series of intrathecal autologous bone marrow mesenchymal stem cell therapy for chronic spinal cord injury. *Neurorehabil Neural Repair*. 2010;24(8):702–708.
74. **Dobkin BH**, **Curt A**, **Guest J**. Cellular transplants in China: observational study from the largest human experiment in chronic spinal cord injury. *Neurorehabil Neural Repair*. 2006;20(1):5–13.
75. **Thompson FJ**, **Reier PJ**, **Uthman B**, **et al**. Neurophysiological assessment of the feasibility and safety of neural tissue transplantation in patients with syringomyelia. *J Neurotrauma*. 2001;18(9):931–945.
76. **Dobkin BH**. Recommendations for publishing case studies of cell transplantation for spinal cord injury. *Neurorehabil Neural Repair*. 2010;24(8):687–691.
77. **Huang H**, **Wang H**, **Chen L**, **et al**. Influence factors for functional improvement after olfactory ensheathing cell transplantation for chronic spinal cord injury. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2006;20(4):434–438.
78. **Jia X**, **Huang G**, **Wang S**, **et al**. Extracellular vesicles derived from mesenchymal stem cells containing microRNA-381 protect against spinal cord injury in a rat model via the BRD4/WNT5A axis. *Bone Joint Res*. 2021;10(5):328–339.
79. **Kanno H**. Regenerative therapy for neuronal diseases with transplantation of somatic stem cells. *World J Stem Cells*. 2013;5(4):163–171.
80. **Nori S**, **Okada Y**, **Yasuda A**, **et al**. Grafted human-induced pluripotent stem-cell–derived neurospheres promote motor functional recovery after spinal cord injury in mice. *Proc Natl Acad Sci U S A*. 2011;108(40):16825–16830.
81. **Ronaghi M**, **Erceg S**, **Moreno-Manzano V**, **Stojkovic M**. Challenges of stem cell therapy for spinal cord injury: human embryonic stem cells, endogenous neural stem cells, or induced pluripotent stem cells? *Stem Cells*. 2010;28(1):93–99.
82. **Chen Z-Y**, **He C-Y**, **Ehrhardt A**, **Kay MA**. Minicircle DNA vectors devoid of bacterial DNA result in persistent and high-level transgene expression in vivo. *Mol Ther*. 2003;8(3):495–500.
83. **Jia F**, **Wilson KD**, **Sun N**, **et al**. A nonviral minicircle vector for deriving human iPS cells. *Nat Methods*. 2010;7(3):197–199.
84. **Ring KL**, **Tong LM**, **Balestra ME**, **et al**. Direct reprogramming of mouse and human fibroblasts into multipotent neural stem cells with a single factor. *Cell Stem Cell*. 2012;11(1):100–109.
85. **Jensen JB**, **Parmar M**. Strengths and limitations of the neurosphere culture system. *Mol Neurobiol*. 2006;34(3):153–161.
86. **Doetsch F**, **García-Verdugo JM**, **Alvarez-Buylla A**. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. *J Neurosci*. 1997;17(13):5046–5061.
87. **Deleyrolle L**, **Marchal-Victorion S**, **Dromard C**, **et al**. Exogenous and fibroblast growth factor 2/epidermal growth factor–regulated endogenous cytokines regulate neural precursor cell growth and differentiation. *Stem Cells*. 2006;24(3):748–762.
88. **Verma P**, **Garcia-Alias G**, **Fawcett JW**. Spinal cord repair: bridging the divide. *Neurorehabil Neural Repair*. 2008;22(5):429–437.
89. **Hofstetter CP**, **Holmström NAV**, **Lilja JA**, **et al**. Allodynia limits the usefulness of intraspinal neural stem cell grafts; directed differentiation improves outcome. *Nat Neurosci*. 2005;8(3):346–353.
90. **Matsumura S**, **Takagi K**, **Okuda-Ashitaka E**, **et al**. Characterization of nestin expression in the spinal cord of GFP transgenic mice after peripheral nerve injury. *Neuroscience*. 2010;170(3):942–953.
91. **Frisén J**, **Johansson CB**, **Török C**, **Risling M**, **Lendahl U**. Rapid, widespread, and longlasting induction of nestin contributes to the generation of glial scar tissue after CNS injury. *J Cell Biol*. 1995;131(2):453–464.
92. **Ulloa F**, **Briscoe J**. Morphogens and the control of cell proliferation and patterning in the spinal cord. *Cell Cycle*. 2007;6(21):2640–2649.
93. **Raspa A**, **Pugliese R**, **Maleki M**, **Gelain F**. Recent therapeutic approaches for spinal cord injury. *Biotechnol Bioeng*. 2016;113(2):253–259.
94. **Tabesh H**, **Amoabediny G**, **Nik NS**, **et al**. The role of biodegradable engineered scaffolds seeded with Schwann cells for spinal cord regeneration. *Neurochem Int*. 2009;54(2):73–83.
95. **Pawar K**, **Cummings BJ**, **Thomas A**, **et al**. Biomaterial bridges enable regeneration and re-entry of corticospinal tract axons into the caudal spinal cord after SCI: association with recovery of forelimb function. *Biomaterials*. 2015;65:1–12.
96. **Teng YD**, **Lavik EB**, **Qu X**, **et al**. Functional recovery following traumatic spinal cord injury mediated by a unique polymer scaffold seeded with neural stem cells. *Proc Natl Acad Sci USA*. 2002;99(5):3024–3029.
97. **Ropper AE**, **Hlubek R**, **Danielson J**, **et al**. First Human Implantation of A Polymer Scaffold for Traumatic Spinal Cord Injury: A Clinical Pilot Study for Safety and Feasibility. In: *83rd AANS Annual Scientific Meeting*. Washington, DC: . (date last accessed May 2015).
98. **Jin GX**, **Li L**, **Cui SQ**, **Duan JZ**, **Wang H**. Persistent hypoalbuminemia is a predictor of outcome in cervical spinal cord injury. *Spine J*. 2014;14(9):1902–1908.
99. **Chen X**, **Liu Z**, **Sun T**, **Ren J**, **Wang X**. Relationship between nutritional status and mortality during the first 2 weeks following treatment for cervical spinal cord injury. *J Spinal Cord Med*. 2014;37(1):72–78.
100. **Wong S**, **Derry F**, **Jamous A**, **Hirani SP**, **Grimble G**, **Forbes A**, **et al**. The prevalence of malnutrition in spinal cord injuries patients: a UK multicentre study. *Br J Nutr*. 2012;108(5):918–923.
101. **Dionyssiotis Y**. Malnutrition in spinal cord injury: more than nutritional deficiency. *J Clin Med Res*. 2012;4(4):227–236.
102. **Wong S**, **Derry F**, **Jamous A**, **Hirani SP**, **Forbes A**. Is undernutrition risk associated with an adverse clinical outcome in spinal cord-injured patients admitted to a spinal centre. *Eur J Clin Nutr*. 2014;68(1):125–130.
103. **Frisbie JH**. Anemia and hypoalbuminemia of chronic spinal cord injury: prevalence and prognostic significance. *Spinal Cord*. 2010;48(7):566–569.
104. **Rodriguez DJ**, **Clevenger FW**, **Osler TM**, **Demarest GB**, **Fry DE**. Obligatory negative nitrogen balance following spinal cord injury. *JPEN J Parenter Enteral Nutr*. 1991;15(3):319–322.
105. **La Rosa G**, **Conti A**, **Cardali S**, **Cacciola F**, **Tomasello F**. Does early decompression improve neurological outcome of spinal cord injured patients? Appraisal of the literature using a meta-analytical approach. *Spinal Cord*. 2004;42(9):503–512.
106. **Tator CH**, **Fehlings MG**, **Thorpe K**, **Taylor W**. Current use and timing of spinal surgery for management of acute spinal cord injury in North America: results of a retrospective multicenter study. *J Neurosurg*. 1999;91(1 Suppl):12–18.
107. **Evaniew N**, **Sharifi B**, **Waheed Z**, **et al**. The influence of neurological examination timing within hours after acute traumatic spinal cord injuries: an observational study. *Spinal Cord*. 2020;58(2):247–254.
108. **Dhall SS**, **Haefeli J**, **Talbott JF**, **et al**. Motor Evoked Potentials Correlate With Magnetic Resonance Imaging and Early Recovery After Acute Spinal Cord Injury. *Neurosurgery*. 2018;82(6):870–876.
109. **Fehlings MG**, **Vaccaro A**, **Wilson JR**, **et al**. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS. *PLoS One*. 2012;7(2):e32037.
110. **Badhiwala JH**, **Wilson JR**, **Witiw CD**, **et al**. The influence of timing of surgical decompression for acute spinal cord injury: a pooled analysis of individual patient data. *Lancet Neurol*. 2021;20(2):117–126.
111. **van Middendorp JJ**, **Barbagallo G**, **Schuetz M**, **Hosman AJF**. Design and rationale of a Prospective, Observational European Multicenter study on the efficacy of acute surgical decompression after traumatic Spinal Cord Injury: the SCI-POEM study. *Spinal Cord*. 2012;50(9):686–694.

112. **Squair JW**, **Bélanger LM**, **Tsang A**, **et al**. Spinal cord perfusion pressure predicts neurologic recovery in acute spinal cord injury. *Neurology*. 2017;89(16):1660–1667.
113. **Phang I**, **Werndle MC**, **Saadoun S**, **et al**. Expansion duroplasty improves intraspinal pressure, spinal cord perfusion pressure, and vascular pressure reactivity index in patients with traumatic spinal cord injury: injured spinal cord pressure evaluation study. *J Neurotrauma*. 2015;32(12):865–874.
114. **Widerström-Noga E**. Neuropathic pain and spinal cord injury: phenotypes and pharmacological management. *Drugs*. 2017;77(9):967–984.
115. **Huang Q**, **Duan W**, **Sivanesan E**, **et al**. Spinal cord stimulation for pain treatment after spinal cord injury. *Neurosci Bull*. 2019;35(3):527–539.
116. **Whitt JL**, **Masri R**, **Pulimood NS**, **Keller A**. Pathological activity in mediodorsal thalamus of rats with spinal cord injury pain. *J Neurosci*. 2013;33(9):3915–3926.
117. **Dombovy-Johnson ML**, **Hunt CL**, **Morrow MM**, **Lamer TJ**, **Pittelkow TP**. Current evidence lacking to guide clinical practice for spinal cord stimulation in the treatment of neuropathic pain in spinal cord injury: a review of the literature and a proposal for future study. *Pain Pract*. 2020;20(3):325–335.
118. **Cook AW**. Electrical wtimulation in multiple wclerosis. *Hosp Pract*. 1976;11(4):51–58.
119. **Harkema S**, **Gerasimenko Y**, **Hodes J**, **et al**. Effect of epidural stimulation of the lumbosacral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. *Lancet*. 2011;377(9781):1938–1947.
120. Locomotor and Bladder Function in Individuals With Acute Spinal Cord Injury. https://ClinicalTrials.gov/show/NCT04879862 (date last accessed 8 March 2022).
121. STIMO: Epidural Electrical Simulation (EES) With Robot-assisted Rehabilitation in Patients With Spinal Cord Injury. https://ClinicalTrials.gov/show/NCT02936453 (date last accessed 8 March 2022).
122. **Ahmed Z**, **Wieraszko A**. Trans-spinal direct current enhances corticospinal output and stimulation-evoked release of glutamate analog, D-2,3-^{3}H-aspartic acid. *J Appl Physiol (1985)*. 2012;112(9):1576–1592.
123. **Murray LM**, **Knikou M**. Repeated cathodal transspinal pulse and direct current stimulation modulate cortical and corticospinal excitability differently in healthy humans. *Exp Brain Res*. 2019;237(7):1841–1852.
124. **Taylor C**, **McHugh C**, **Mockler D**, **Minogue C**, **Reilly RB**, **Fleming N**, **et al**. Transcutaneous spinal cord stimulation and motor responses in individuals with spinal cord injury: a methodological review. *PLOS ONE*. 2021;16(11):e0260166.
125. **Dawson J**, **Liu CY**, **Francisco GE**, **et al**. Vagus nerve stimulation paired with rehabilitation for upper limb motor function after ischaemic stroke (VNS-REHAB): a randomised, blinded, pivotal, device trial. *Lancet*. 2021;397(10284):1545–1553.
126. Targeted Plasticity Therapy for Upper Limb Rehabilitation in Spinal Cord Injuries. https://ClinicalTrials.gov/show/NCT04288245 (date last accessed 8 March 2022).
127. **Darrow MJ**, **Torres M**, **Sosa MJ**, **et al**. Vagus nerve stimulation paired with rehabilitative training enhances motor recovery after bilateral spinal cord injury to cervical forelimb motor pools. *Neurorehabil Neural Repair*. 2020;34(3):200–209.
128. **Hicken BL**, **Putzke JD**, **Richards JS**. Bladder management and quality of life after spinal cord injury. *Am J Phys Med Rehabil*. 2001;80(12):916–922.
129. **Kirkham AP**, **Shah NC**, **Knight SL**, **Shah PJ**, **Craggs MD**. The acute effects of continuous and conditional neuromodulation on the bladder in spinal cord injury. *Spinal Cord*. 2001;39(8):420–428.
130. **Kutzenberger J**. Surgical therapy of neurogenic detrusor overactivity (hyperreflexia) in paraplegic patients by sacral deafferentation and implant driven micturition by sacral anterior root stimulation: methods, indications, results, complications, and future prospects. *Acta Neurochir Suppl*. 2007;97(Pt 1):333–339.
131. **Bauchet L**, **Segnarbieux F**, **Martinazzo G**, **Frerebeau P**, **Ohanna F**. Neurosurgical treatment of hyperactive bladder in spinal cord injury patients. *Neurochirurgie*. 2001;47(1):13–24.
132. **Dorsher PT**, **McIntosh PM**. Neurogenic bladder. *Adv Urol*. 2012;2012:816274.
133. **Lazzeri M**, **Calò G**, **Spinelli M**, **et al**. Urodynamic effects of intravesical nociceptin/orphanin FQ in neurogenic detrusor overactivity: a randomized, placebo-controlled, double-blind study. *Urology*. 2003;61(5):946–950.
134. **Vanneste M**, **Segal A**, **Voets T**, **Everaerts W**. Transient receptor potential channels in sensory mechanisms of the lower urinary tract. *Nat Rev Urol*. 2021;18(3):139–159.
135. **Chartier-Kastler EJ**, **Denys P**, **Chancellor MB**, **Haertig A**, **Bussel B**, **Richard F**, **et al**. Urodynamic monitoring during percutaneous sacral nerve neurostimulation in patients with neurogenic detrusor hyperreflexia. *Neurourol Urodyn*. 2001;20(1):61–71.
136. **Chartier-Kastler EJ**, **Ruud Bosch JL**, **Perrigot M**, **Chancellor MB**, **Richard F**, **Denys P**, **et al**. Long-term results of sacral nerve stimulation (S3) for the treatment of neurogenic refractory urge incontinence related to detrusor hyperreflexia. *J Urol*. 2000;164(5):1476–1480.
137. **Redshaw JD**, **Lenherr SM**, **Elliott SP**, **et al**. Protocol for a randomized clinical trial investigating early sacral nerve stimulation as an adjunct to standard neurogenic bladder management following acute spinal cord injury. *BMC Urol*. 2018;18(1):72.
138. **Leo CA**, **Thomas GP**, **Bradshaw E**, **et al**. Long-term outcome of sacral nerve stimulation for faecal incontinence. *Colorectal Dis*. 2020;22(12):2191–2198.
139. **Kondo A**, **Otani T**, **Takita T**. Suppression of bladder instability by penile squeeze. *Br J Urol*. 1982;54(4):360–362.
140. **Dalmose AL**, **Rijkhoff NJM**, **Kirkeby HJ**, **Nohr M**, **Sinkjaer T**, **Djurhuus JC**, **et al**. Conditional stimulation of the dorsal penile/clitoral nerve may increase cystometric capacity in patients with spinal cord injury. *Neurourol Urodyn*. 2003;22(2):130–137.
141. **Yoo PB**, **Klein SM**, **Grafstein NH**, **et al**. Pudendal nerve stimulation evokes reflex bladder contractions in persons with chronic spinal cord injury. *Neurourol Urodyn*. 2007;26(7):1020–1023.
142. **Chang S-H**, **Afzal T**, **Berliner J**, **Francisco GE**, **TIRR SCI Clinical Exoskeleton Group**. Exoskeleton-assisted gait training to improve gait in individuals with spinal cord injury: a pilot randomized study. *Pilot Feasibility Stud*. 2018;4:62.
143. **Grasmücke D**, **Zieriacks A**, **Jansen O**, **et al**. Against the odds: what to expect in rehabilitation of chronic spinal cord injury with a neurologically controlled Hybrid Assistive Limb exoskeleton. A subgroup analysis of 55 patients according to age and lesion level. *Neurosurg Focus*. 2017;42(5):E15.
144. **Mehrholz J**, **Harvey LA**, **Thomas S**, **Elsner B**. Is body-weight-supported treadmill training or robotic-assisted gait training superior to overground gait training and other forms of physiotherapy in people with spinal cord injury? A systematic review. *Spinal Cord*. 2017;55(8):722–729.
145. **Kressler J**, **Thomas CK**, **Field-Fote EC**, **et al**. Understanding therapeutic benefits of overground bionic ambulation: exploratory case series in persons with chronic, complete spinal cord injury. *Arch Phys Med Rehabil*. 2014;95(10):1878–1887.
146. **Miller LE**, **Zimmermann AK**, **Herbert WG**. Clinical effectiveness and safety of powered exoskeleton-assisted walking in patients with spinal cord injury: systematic review with meta-analysis. *Med Devices (Auckl)*. 2016;9:455–466.
147. **Saposnik G**, **Cohen LG**, **Mamdani M**, **et al**. Efficacy and safety of non-immersive virtual reality exercising in stroke rehabilitation (EVREST): a randomised, multicentre, single-blind, controlled trial. *Lancet Neurol*. 2016;15(10):1019–1027.
148. **Gauthier LV**, **Nichols-Larsen DS**, **Uswatte G**, **et al**. Video game rehabilitation for outpatient stroke (VIGoROUS): A multi-site randomized controlled trial of in-home, self-managed, upper-extremity therapy. *EClinicalMedicine*. 2022;43:101239.
149. **Dimbwadyo-Terrer I**, **Trincado-Alonso F**, **de Los Reyes-Guzmán A**, **et al**. Upper limb rehabilitation after spinal cord injury: a treatment based on a data glove and an immersive virtual reality environment. *Disabil Rehabil Assist Technol*. 2016;11(6):462–467.
150. **Dimbwadyo-Terrer I**, **Gil-Agudo A**, **Segura-Fragoso A**, **et al**. Effectiveness of the virtual reality system Toyra on upper limb function in people with tetraplegia: a pilot randomized clinical trial. *Biomed Res Int*. 2016;2016:6397828.
151. **Prasad S**, **Aikat R**, **Labani S**, **Khanna N**. Efficacy of virtual reality in upper limb rehabilitation in patients with spinal cord injury: a pilot randomized controlled trial. *Asian Spine J*. 2018;12(5):927–934.
152. **Villiger M**, **Liviero J**, **Awai L**, **et al**. Home-based virtual reality-augmented training improves lower limb muscle strength, balance, and functional mobility following chronic incomplete spinal cord injury. *Front Neurol*. 2017;8:635.
153. **Pozeg P**, **Palluel E**, **Ronchi R**, **et al**. Virtual reality improves embodiment and neuropathic pain caused by spinal cord injury. *Neurology*. 2017;89(18):1894–1903.
154. **Cameron AA**, **Smith GM**, **Randall DC**, **Brown DR**, **Rabchevsky AG**. Genetic manipulation of intraspinal plasticity after spinal cord injury alters the severity of autonomic dysreflexia. *J Neurosci*. 2006;26(11):2923–2932.
155. **Hou S**, **Duale H**, **Rabchevsky AG**. Intraspinal sprouting of unmyelinated pelvic afferents after complete spinal cord injury is correlated with autonomic dysreflexia induced by visceral pain. *Neuroscience*. 2009;159(1):369–379.
156. **Hurtado A**, **Marcillo A**, **Frydel B**, **Bunge MB**, **Bramlett HM**, **Dietrich WD**, **et al**. Anti-CD11d monoclonal antibody treatment for rat spinal cord compression injury. *Exp Neurol*. 2012;233(2):606–611.
157. **Rabchevsky AG**, **Patel SP**, **Duale H**, **Lyttle TS**, **O'Dell CR**, **Kitzman PH**, **et al**. Gabapentin for spasticity and autonomic dysreflexia after severe spinal cord injury. *Spinal Cord*. 2011;49(1):99–105.
158. **Eldahan KC**, **Williams HC**, **Cox DH**, **Gollihue JL**, **Patel SP**, **Rabchevsky AG**, **et al**. Paradoxical effects of continuous high dose gabapentin treatment on autonomic dysreflexia after complete spinal cord injury. *Exp Neurol*. 2020;323:113083.

159. **Sanai N**, **Tramontin AD**, **Quiñones-Hinojosa A**, **et al**. Unique astrocyte ribbon in adult human brain contains neural stem cells but lacks chain migration. *Nature*. 2004;427(6976):740–744.

160. **Rakic P**. Neuroscience: immigration denied. *Nature*. 2004;427(6976):685–686.

161. **Meletis K**, **Barnabé-Heider F**, **Carlén M**, **et al**. Spinal cord injury reveals multilineage differentiation of ependymal cells. *PLoS Biol*. 2008;6(7):e182.

162. **Macas J**, **Nern C**, **Plate KH**, **Momma S**. Increased Generation of Neuronal Progenitors after Ischemic Injury in the Aged Adult Human Forebrain. *J Neurosci*. 2006;26(50):13114–13119.

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