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.

Keywords: Spinal cord injury, Stem cells, Secondary injury, Glial scar, future therapies, stimulation, neuromodulation, Neuropathic bladder, Bioscaffold, neuropsychology, autonomic dysreflexia

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. 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 and Munro led the way in improving the care for patients by integrating different medical specialities and taking a holistic approach to their patients’ care. In particular, Guttmann involved them in social activities and sport, which lead to the founding of the Paralympics. The advent of antibiotics, assisted ventilation, cardiovascular monitoring, superior traction techniques, and surgical instrumentation for spine stabilization, in addition to improved imaging of both bone and soft-tissue, lead to vast improvements in both mortality and morbidity after SCI. The recognition of iatrogenic mechanical injury during the extrication process from inadequate spine immobilization was instrumental in establishing standardized training and improving equipment. 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. Technological advancements gave patients the freedom of enhanced mobility, communication, and ability to gain more independence. Legislation has also played a large part in protecting care, improving occupational opportunities, and defending the entitlement to home modifications for SCI patients.

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.
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.\textsuperscript{15} In 1962, radiolabelled thymidine, which incorporates itself into newly synthesized DNA, was used to identify dividing cells in mice and rats in vivo.\textsuperscript{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.\textsuperscript{16,17} It was not until the successful isolation and culture of these cells, capable of mitosis and differentiation,\textsuperscript{18} that scientists could characterize these cells in vitro.\textsuperscript{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.\textsuperscript{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 brain.\textsuperscript{15} It is thought that these inherent adult stem cells could replace neurones and glial cells damaged in a neurological insult.\textsuperscript{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,\textsuperscript{24} and $10 million when combined with the loss in earnings.\textsuperscript{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,\textsuperscript{26} low incidence of approximately 130,000 injuries each year worldwide,\textsuperscript{27} and a limited time window within the acute phase of an injury where there is potential to improve outcome.\textsuperscript{28} This is offset against the cost of developing a new drug, which, on average, requires $2.6 billion.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{30,31} This increase in age of SCI patients presents a challenge to clinicians and scientists, as their life expectancy,\textsuperscript{24} predisposition to develop complications\textsuperscript{27} and neurological regenerative potential\textsuperscript{12-36} 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.\textsuperscript{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.\textsuperscript{37} Direct external compression and oedema increases intrathecal pressure, in addition to localized microvascular and endothelial damage,\textsuperscript{38} and impairment of autoregulation due to direct macrovascular injury.\textsuperscript{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.\textsuperscript{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.\textsuperscript{40}

**Induced apoptosis.** In addition to this necrotic environment, marginal cells also undergo apoptosis, in particular oligodendrocytes which support a plethora of adjacent neurones.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{44} An abundance of pro-inflammatory cytokines orchestrate this destructive process which eventually settles when systemic macrophages (M2) are recruited.\textsuperscript{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. However, after the acute phase, the glial age and provides a scaffold on which revascularization can occur.55 This was based upon the CNS harbouring specialized immune cells, being protected from the systemic immune system, and when systemic immune cells are recruited, they are implicated in further damage in neurological pathologies (i.e. MS). 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 local responses is the activation and proliferation of astrocytes, microglia, and macrophages which embed high quantities of chondroitin sulfate 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, the timeframe of events after SCI, 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.43 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.46

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, propagating neuropathic pain, and worsening disability immediately after cell transplantation, 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.\textsuperscript{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.\textsuperscript{79} Recently, human-derived iPS cells have been transplanted into mice resulting in “significant recovery of motor deficits” after SCI.\textsuperscript{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.\textsuperscript{81} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{83} Moreover, the effects of a single gene up-regulation can be studied in more depth about neural stem/progenitor cells respond to insults and subsequent gliogenic cues.\textsuperscript{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.\textsuperscript{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.\textsuperscript{93} Biodegradable polymer scaffolds composed of
collagen, chitosan, agarose, and fibronectin have been tested in animals.\(^9^\) 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,\(^9^5\) reduce glial cysts and scarring, and improve recovery.\(^9^6\) Subsequently, it has gained approval for an investigative medicinal device and phase 1 human trials have begun.\(^9^7\)

**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.\(^9^8,9^9\) 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.\(^1^0^0,1^0^1\) UK and USA centres have demonstrated that malnutrition in SCI is associated with increased mortality and length of stay.\(^1^0^2,1^0^3\) 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.\(^1^0^4\)

**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.\(^1^0^5\) 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.\(^1^0^6\) 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.\(^1^0^7\) Some work has already begun on using neurophysiological, MRI tractography, and blood biomarkers as predictive adjuncts to the initial neurological assessment.\(^1^0^8\)

The STACIS study\(^1^0^9\) 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.\(^1^1^0\) However, the results from an international randomized trial, SCI-POEM, are keenly anticipated,\(^1^1^1\) and further work examining the physiological and neurological outcomes associated with targeted spinal cord perfusion pressure,\(^1^1^2\) duroplasty and decompression are continuing to gain more evidence.\(^1^1^3\) 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.\(^1^1^4\) 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.\(^1^1^5\) 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.\(^1^1^6\) 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).\(^1^1^7\)

Epidural electrical stimulation (EES) was incidentally found to improve motor function in patients suffering from MS, with an original premise to reduce neuropathic pain.\(^1^1^8\) The mechanisms by which the stimulation parameters can enable stepping and standing, akin to central pattern generators of locomotion, remain elusive.\(^1^1^9\) However, central to most hypotheses is the utility of proprioceptive signals, which are the only input.
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. 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. 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.

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. Although it improves bladder pressures, bladder capacity, uretero-renal 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. Hence, this procedure is destructive and renders future, reversible neuromodulation therapies unfeasible.

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 fibre nerves to become mechano-sensitive, and innervate types 2 and 3 muscarinic receptors causing non-voiding local contractions within the bladder. 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. Currently, work is ongoing to develop antagonists to the TRP receptors without the associated suprapubic pain and initial worsening of lower urinary tract symptoms (LUTS).

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), and within early recovery from the injury (12 weeks). However, the longevity of improvement with stimulation may decrease after six months after implantation and hence long term studies for SCI patients are important.

Pudendal nerve (PN) mechanical stimulation, elicited by a penile squeeze or cutaneous electrical stimulation of perigential skin, inhibits bladder contractions and has been shown in humans with SCI to be feasible. The attraction of PN stimulation is evidence that low frequency stimulation (5 to 10 Hz) promotes reflex bladder inhibition, while high frequency (20 to 50 Hz) produces robust bladder contractions in SCI patients. 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.  

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. However, on a recent metaanalysis of randomized studies, the walking speed is not significantly increased to overground physical therapy although the difference in distance walked was not conclusive. It goes without saying physical therapy, although the difference in distance walked was not conclusive. 

Despite reports of the benefits of exoskeletons in improving motor outcomes, there is no association with age or spinal level of injury. However, for spastic paraplegia patients' exoskeletons provide inferior improvements in comparison to physical therapy despite no association with age or spinal level of injury. 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. There are small additional risks of pressure ulcers, falls, and lower limb fractures, depending on the patients neurological status, exoskeleton configuration and environment. 

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. 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. However, there is greater evidence of psychological improvements in motivation, neuropathic pain, balance, and planning for a range of mobility tasks. 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.

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. Intraspinal sprouting of propriospinal neurones from unmyelinated pelvic C fibres further exaggerates this unmodulated reflex.  

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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. The impact of this upon translational experimental therapies remains to be seen. 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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