Developing Novel Therapies for Degenerative Cervical Myelopathy [AO Spine RECODE-DCM Research Priority Number 7]: Opportunities From Restorative Neurobiology

Aref-Ali Gharooni, MBChB, MSc (Dist)1, Brian K. Kwon, MD, PhD, FRCSC2, Michael G. Fehlings, MD, PhD, FRCSC, FACS3, Timothy F. Boerger, PhD4, Ricardo Rodrigues-Pinto, MD, PhD, FEBOT5,6, Paul Aarne Koljonen, MBBS(HK), FRCSED(Ortho), FHKOS, FHKAM(Orthopaedic Surgery)7, Shekar N. Kurpad, MD, PhD4, James S. Harrop, MD, MSHQS, FACS8, Bizhan Aarabi, MD9, Vafa Rahimi-Movaghar, MD10, Jefferson R. Wilson, MD, PhD, FRCSC3, Benjamin M. Davies, MRCS, BSc, MPhil1, Mark R. N. Kotter, MD, MPhil, PhD1, and James D. Guest, MD, PhD, FACS11

Abstract

Study design: Narrative review.

Objectives: To provide an overview of contemporary therapies for the James Lind Alliance priority setting partnership for degenerative cervical myelopathy (DCM) question: ‘Can novel therapies, including stem-cell, gene, pharmacological and neuroprotective therapies, be identified to improve the health and wellbeing of people living with DCM and slow down disease progression?’

Methods: A review of the literature was conducted to outline the pathophysiology of DCM and present contemporary therapies that may hold therapeutic value in 3 broad categories of neuroprotection, neuroregeneration, and neuromodulation.

Results: Chronic spinal cord compression leads to ischaemia, neuroinflammation, demyelination, and neuronal loss. Surgical intervention may halt progression and improve symptoms, though the majority do not make a full recovery leading to lifelong disability. Neuroprotective agents disrupt deleterious secondary injury pathways, and one agent, Riluzole, has undergone Phase-III investigation in DCM. Although it did not show efficacy on the primary outcome modified Japanese Orthopaedic Association
scale, it showed promising results in pain reduction. Regenerative approaches are in the early stage, with one agent, Ibudilast, currently in a phase-III investigation. Neuromodulation approaches aim to therapeutically alter the state of spinal cord excitation by electrical stimulation with a variety of approaches. Case studies using electrical neuromuscular and spinal cord stimulation have shown positive therapeutic utility.

**Conclusion:** There is limited research into interventions in the 3 broad areas of neuroprotection, neuroregeneration, and neuromodulation for DCM. Contemporary and novel therapies for DCM are now a top priority, and whilst research in these areas is limited in DCM, it is hoped that this review will encourage research into this priority.

**Keywords**
degenerative cervical myelopathy, neuroprotection, neuromodulation, neuroregeneration, inflammation, demyelination, electrical stimulation, spinal cord stimulation, neuromuscular electrical stimulation, functional electrical stimulation

**Introduction**

Individuals diagnosed with Degenerative Cervical Myelopathy (DCM) may require surgical and/or non-surgical interventions depending on the severity of the disease and clinical manifestations. Surgical intervention in the form of decompressive surgery with or without fusion is the mainstay of treatment for moderate to severe disease as assessed by modified Japanese Orthopaedic Association (mJOA) scale.\(^1^,\(^2\) The optimal management of mild DCM, early in its course, is unknown, as studies have not pointed towards a significant benefit for prophylactic surgical intervention.\(^3^,\(^4\) However, this opens a window for the possible application of non-surgical interventions such as disease modifying therapeutics physical therapy, cervical traction, collars and spinal injection.\(^4^,\(^5\)

Despite the success of surgical decompression in halting neurological decline and providing some recovery, myelopathy symptoms may reoccur,\(^6\) and full recovery is rarely seen, with estimates suggesting less than 5% make a full recovery,\(^7^,\(^8\) with lower limb and sphincter function demonstrating the slowest recovery responses.\(^9\) Ongoing myelopathy may affect domains such as mobility, weakness, manual dexterity, pain and bladder/bowel dysfunction demonstrating the slowest recovery responses.\(^9\) Ongoing myelopathy may affect domains such as mobility, weakness, manual dexterity, pain and bladder/bowel dysfunction demonstrating the slowest recovery responses.\(^9\) Ongoing myelopathy may affect domains such as mobility, weakness, manual dexterity, pain and bladder/bowel dysfunction demonstrating the slowest recovery responses.\(^9\) Ongoing myelopathy may affect domains such as mobility, weakness, manual dexterity, pain and bladder/bowel dysfunction demonstrating the slowest recovery responses.\(^9\)

This uncertainty was highlighted in the recent James Lind Alliance\(^12\) (JLA) priority setting partnership, with one of the top priorities and questions agreed upon being, ‘Can novel therapies, including stem-cell, gene, pharmacological and neuroprotective therapies, be identified to improve the health and wellbeing of people living with DCM and slow down disease progression?’. The objective of this narrative review is to provide an overview of potential contemporary therapies that may enhance recovery in DCM. We will briefly outline the pathophysiology of DCM and then present contemporary therapies in 3 main areas, namely, neuroprotection, neuroregeneration and neuromodulation, which may in the future have a therapeutic role in DCM.

**Pathophysiology of DCM**

Degenerative cervical myelopathy is an umbrella term encompassing a number of degenerative processes and responses in the cervical spine, which leads to progressive chronic spinal cord compression.\(^14^,\(^15\) Osseous, ligamentous, and intervertebral disc tissue undergo degenerative changes as part of normal ageing and/or repetitive stress leading to structural changes such as spondyloses, hypertrophy/ossification/calcification of ligaments (e.g. Ossification of the posterior longitudinal ligament) and disc herniation/prolapse.\(^1^,\(^16\) Whilst these changes lead to static compression and direct injury to the spinal cord, they are compounded by the mobility of the cervical spine, causing further compression due to physiological or pathological (i.e. spondyloolisthesis) movements.\(^1^,\(^16\) Mechanical compression leads to direct primary injury but also initiates a complex sequence of secondary injury processes in the spinal cord.\(^17\) These include macro- and microvascular compromise causing hypoxia and ischaemia\(^18^,\(^19\) and neuroinflammation.\(^17^,\(^20\) The consequence of these processes include loss of neurons, oligodendrocytes,\(^20\) demyelination\(^21\) and axonal degeneration.\(^17\)

Demyelination can act as a functional conduction block on axons contributing to the sensorimotor deficits seen in DCM. Post-mortem studies have found extensive thin myelinated fibres in the spinal cord white matter suggestive of focal demyelination and remyelination.\(^22\) Studies have also found an association between reduced myelin content on myelin water imaging on MRI and impaired somatosensory evoked potential in DCM, which demonstrates the impact of demyelination seen on long tract axonal function in DCM.\(^23\) Therefore, strategies to mitigate demyelination and stimulate endogenous mechanisms of myelin repair may provide a viable therapeutic strategy.

The neuroinflammatory cascade resulting from chronic compression is of interest as it can be both protective and damaging. An increase in activated microglia and macrophages has been observed at the site of chronic spinal cord
compression and are a source of pro-inflammatory cytokines and can lead to further cell death by necrosis and apoptosis.24 Alternatively, immune cells can also exhibit neuroprotective effects such as releasing neuroprotective cytokines and growth factors.25 This has created interest in immunomodulatory strategies to alter this balance as a therapeutic strategy.

**Neuroprotection**

Neuroprotective agents prevent further cell death and dysfunction by altering secondary injury pathways. A notable example is Riluzole, a benzothiazole sodium channel-blocker developed in the mid-20th century as a muscle relaxant,26 with later indications as an anticonvulsant27 and neuroprotective agent to prolong survival in ALS.28 In the context of DCM, animal studies have shown Riluzole can mitigate secondary injury mechanisms related to sodium channels and glutamate excitotoxicity thus resulting in functional improvements.29-31 These promising findings have led to a Phase III randomized placebo-controlled trial (CSM-PROTECT) to assess the efficacy of Riluzole as an adjunct to surgical decompression in chronic cervical myelopathy to promote neurologic recovery.32 The study was recently published and reported no significant difference in the primary endpoint of mJOA at 6-month follow-up. However, Riluzole was associated with potentially promising reduction in neck pain at 6- and 12-month follow-up compared to placebo.33 As pain is a major patient priority, further investigations may be warranted into which subgroups would benefit most. Inflammatory pathways are implicated in the deleterious effects of chronic cord compression and recent work in humans and animal models has implicated microRNA21 (miR21) as a key mediator of the inflammatory/ischemic cell injury in DCM. A prospective cohort study of patients with DCM has identified a positive correlation between miR21, initial symptom severity and poor treatment outcomes, the findings of which were further corroborated in mouse models of DCM. This work suggests the possibility of miR21 as a possible biomarker of disease risk in DCM and a potential therapeutic target for intervention.34

Anti-inflammatory agents such as corticosteroids are also candidates for potential clinical translation as a neuroprotective adjunct to surgery and have been extensively studied in traumatic SCI.35-37 In a rodent study of DCM, Methylprednisolone, an agent used in acute-onset traumatic spinal cord injury,38 was used as a perioperative adjunct to surgical decompression.39 Significant improvement was found in the group treated by methylprednisolone when compared to the control 2-weeks post decompression in forepaw function. However, by 5-weeks, no significant difference was apparent between the groups.39 Few human clinical studies have been conducted, though one retrospective study of thoracic myelopathy used intraoperative methylprednisolone found better neurological recovery at 2 weeks, though no significant difference in neurological outcomes between methylprednisolone and control group at long-term follow-up.40 The use of corticosteroids perioperatively in anterior cervical spine surgery has however shown benefit in reducing post-operative complications with significant reduction in airway oedema, pain, hospital stay and improved swallowing in Phase-III randomized controlled trials.41,42 This surgical approach is used in the surgical management of DCM and future studies should look into the potential functional benefits of corticosteroids in these patients.

The perioperative period is a key time point in which neuroprotective agents should be considered due to ischaemia-reperfusion injury, but also due to axonal plasticity, which is thought to emerge after decompression.43 Whilst no neuroprotective agent has shown efficacy in Phase 3 clinical trials, improved understanding of the pathophysiology of DCM may provide an avenue for the development of more targeted neuroprotective therapies. Of note, neck and arm pain represent potentially important targets if intervention in DCM, as suggested by the recent CSM-Protect trial.33 However, this will require the design of trials which use more sensitive outcomes to detect changes in neck and arm pain.

**Regenerative Medicine**

People with DCM often develop and then suffer from lifelong disability, with less than 5% making a full recovery even despite surgical decompression.7,8 This occurs due to failure to recognize the clinical deterioration, delayed medical intervention, the limited regenerative capacity of the spinal cord, loss of local cellular structures and disruption of the spinal cord architecture. Replacing lost tissue and enhancing intrinsic recovery capacity is an area of interest in spinal cord injuries as a means to enhance recovery. Attempts are being made to achieve this through a number of different approaches, including pharmacological and cell-based therapies.44-48

One potential beneficiary pharmacological agent is Ibudilast, which is currently licensed in Japan for the treatment of asthma and post-stroke dizziness.49 The mechanisms by which it exerts its effects for the aforementioned indications have been attributed to its anti-inflammatory, bronchodilatory and vasodilatory effects.50-55 More recently, it has been found to exhibit central anti-inflammatory, neuroprotective and neurotrophic/regenerative effects by its inhibition of phosphodiesterase-4 (PDE-4 and -10) and macrophage migration inhibition factor, leading to attenuation of activated glial cells and enhancement of neurotrophic factors.49,50,56,57 This has generated interest in its application in a number of neurological conditions. These include early-stage clinical trials in progressive Multiple Sclerosis,58,59 ALS,60 alcoholism,61,62 drug addiction63,64 and pain.65,66 The combination of anti-inflammatory, neuroprotective and neuro-regenerative properties has led to interest for its use in DCM and is the basis for RECEDE-Myelopathy (NCT04631471), a phase 3, double-blind, randomized controlled trial assessing the
efficacy of Ibudilast as an adjuvant treatment to decompressive surgery for DCM on mJOA score and neck pain.

Cell-based therapies have also gained considerable attention over the last few decades. Stem cells possess the ability to differentiate into a variety of cell types creating the possibility of a potential therapeutic tool to repair and/or replace damaged tissue. Challenges for cell-based therapies include the cell type first surviving the transplantation, then migrating appropriately to the site of therapeutic action, differentiating into the correct lineage and finally to behave physiologically in the manner intended. Currently, the most widely applied clinical use of this therapy is haematopoietic stem cell transplantation with research dating back to the 1950s and indicated for conditions such as lymphoma, leukemia and anaplastic anaemia with curative potential. Whilst there has been little research for its application in DCM; specifically, there is ongoing research to develop stem cell therapies for traumatic spinal cord injury sharing pathophysiological features. Several mechanisms by which stem cells can promote recovery in spinal cord injuries can be applicable to DCM. These include replacement of lost tissue (ie neurons, glial precursors/oligodendrocytes), integration into host neuronal circuits, release of neurotrophic factors, anti-apoptotic, anti-inflammatory and immunomodulatory effects. Trials in SCI are typically underpowered for efficacy and lack controls as they are early-stage open-label trials. In addition, there is considerable heterogeneity between cell-based interventions such as type of cell utilized, source of stem cell (i.e embryonic stem cells, adult stem cells and induced pluripotent stem cells; autologous vs allogeneic), processing (i.e lab purification, amplification, good manufacturing practice adherence and quality control) and delivery of stem cells (i.e Intravenous, intrathecal, direct intraspinal and impregnated tissue engineered materials) highlighting uncertainty in optimal intervention parameters. Further, adjuncts to enhance cell-based therapies are undergoing investigation to overcome some of the challenges faced such as poor cell survival, migration and integration. These include co-administration of growth factors, cell delivery and structural support with biomaterials/scaffolds, guidance of migration and differentiation by electric fields, degradation of glial scar and self-assembling peptides to improve extracellular matrix environment.

One of the inciting factors for DCM is cervical spondylosis and disc degeneration. Cell-based, growth-factor based and small molecule-based therapies aiming to repair or regenerate the degenerate intervertebral disc may offer an opportunity to halt DCM progression or even reverse its symptoms. This may be particularly important in patients with mild DCM symptoms and in asymptomatic patients with imaging evidence of cord compression. Several human clinical trials using stem cells (autologous or allogeneic; bone marrow and adipose-derived mesenchymal, notochordal and chondrocyte-like nucleus pulposus cells) for intervertebral disc degeneration have been or are currently being undertaken. While most studies report significant reduction in pain, increase in disc height, improved patient mobility and quality of life concerns have been raised due to the poor design of some studies and their low number of patients and lack appropriate controls.

Due to the nature of DCM, the majority of patients are in an older age category (>55 years), which presents a unique challenge. The central nervous system undergoes structural and functional changes as part of the normal ageing process. This includes reduced neuroplasticity, which could contribute to post-decompression recovery, and strategies to enhance endogenous regenerative processes may be confounded by aging. Regenerative therapies provide prospects for new treatments in DCM; however, it is currently a very young field of research. Research in this field aiming to overcome some of the current challenges and specific to its role in DCM are warranted.

Gene therapy offers the prospect for sustained and localized production of therapeutics that is particularly attractive for ‘biologics’ that are otherwise complex to deliver. One therapy has been studied extensively for possible direct tissue application in SCI with a lead strategy aimed at neuroplasticity using an enzyme, chondroitinase, that remodels the basal lamina of neuronal nets to enhance neuroplasticity. In spinal muscular atrophy, a gene therapy (Zolgensma) that restores a critical functional protein (SMN protein, important in motor neurone survival) to motor neurons has been approved for clinical use. Gene therapies such as myostatin inhibition are also under development for muscular dystrophy, which aims to improve muscle function. Whilst gene therapy is in its early stages of development for many conditions, it offers the prospects for sustained production of therapeutic molecules which remains to be explored in DCM.

Neuromodulation

Neuromodulation is broadly defined by the International Neuromodulation Society as ‘the alteration of nerve activity through targeted delivery of a stimulus, such as electrical stimulation or chemical agents, to specific neurological sites in the body’. Electrical neuromodulation is used in the treatment of conditions and symptoms including but not limited to chronic pain, movement disorders, epilepsy, psychiatric disorders, stroke, traumatic brain injury, sensory deficits and pain. A variety of devices have been developed to deliver stimulation to the target of interest, with some being invasive such as deep brain stimulation and spinal cord stimulation (SCS) and others noninvasive such as transcranial Direct Current Stimulation (tDCS), repetitive Transcranial Magnetic Stimulation (rTMS) and peripheral surface electrode Neuromuscular Electrical Stimulation (NMES) or Functional Electrical Stimulation (FES). The mechanism of action of these devices in modulating the nervous system and
pathways and is not fully understood, but here we will briefly explore their application in related conditions.

Spinal cord stimulation has become an established therapeutic tool in the management of chronic neuropathic and ischaemic pain syndromes, including Failed Back Surgery Syndrome (FBSS). Complex Regional Pain Syndrome Type 1 and chronic leg ischaemia. Though the exact mechanism of its analgesic effects is elusive, early proposals included the gate control theory of pain, but more recent biochemical hypotheses propose SCS works by enhancing GABAergic systems of dorsal horn cells by stimulating their dendrites. There is limited evidence for the use of SCS for pain in DCM but one case study of a cervical spinal cord stimulator placed (C3-C6) for significant post-operative pain following posterior decompression, resulting in a significant reduction in pain. Of note, the efficacy of SCS for SCI-induced pain appears to be more limited when compared to the aforementioned indications, such as FBSS, which may be due to the significant damage to underlying neural circuits required for the analgesic effects of SCS.

Although the use in spinal cord–mediated pain has been limited, epidural SCS has shown to be capable in restoring motor and autonomic function in a small number of chronic complete SCI patients. It is thought that epidural SCS increases the excitability of the spared spinal cord circuitry within the injury site, leading to enhancement of transmission and volitional control. Whether this strategy could be used for paralysis due to severe DCM remains to be investigated.

Transcranial Magnetic Stimulation (TMS) allows painless, noninvasive, cortical stimulation by means of electromagnetic induction from a coil positioned over the scalp. It serves as a useful electrophysiological diagnostic tool by measuring parameters such as central motor conduction time (CMCT), a sensitive measure to detect myelopathy. Repeated stimulation in the form of rTMS has gained interest as a method of neuromodulation to induce changes in brain activity lasting beyond the duration of stimulation suggestive of neuroplastic changes. The clinical sphere, it has gained FDA approval as a treatment for major depressive disorder, obsessive-compulsive disorder and migraine, with ongoing research in a number of other psychiatric and neurological conditions. Early clinical studies in SCI have found potential application of rTMS in the management of SCI-related pain, spasticity, motor function and autonomic function, albeit the outcomes across studies were not consistent. This may be attributed to the heterogeneity in rTMS protocols used, and ongoing research is warranted to further optimize existing protocols and to investigate their potential application in DCM.

Transcranial direct current stimulation modulates neural activity non-invasively by surface electrodes, which are placed over the scalp with low-intensity currents are passed across them. In contrast to TMS, tcDCS does not induce action potentials but modulates the resting membrane potentials to alter excitability. There is ongoing research investigating its role in a number of psychiatric and neurological conditions. A recent meta-analysis found tcDCS improves upper-limb motor performance in healthy adults. Its utility in chronic incomplete cervical SCI has been investigated in early-stage studies and noted significant improvement in hand grasp, which were synergistic when combined with physical training.

Neuromuscular electrical stimulation, also known as FES, is a well-established tool in which surface electrodes are placed over muscles and peripheral nerves to deliver electrical stimulation and achieve muscle contraction. It is used routinely for motor retraining in conditions such as SCI and stroke to restore motor functions such as standing or grasping. Whilst the artificial stimulus leading to muscle contraction can lead to muscle strengthening, effects have also been demonstrated in the central nervous system with modulation of spinal reflex, corticospinal excitability and neurophysiological changes in the cortex. It is proposed that the underlying mechanism stems not only from the propagation of action potentials leading to muscle contraction but also antidromic propagation of action potential across motor axons and sensory afferents, which traverse to the central nervous system. Despite extensive research for its use for injuries to the CNS such as SCI, only case reports have been published for its use in DCM, which have demonstrated significant improvement in upper limb function and gait. Whilst these case reports are encouraging, it presents low level of evidence and further research is necessary, especially as NMES is a safe and less expensive intervention.

An exciting new clinical trial in SCI is the Up-LIFT study (NCT04697472) that employs transcutaneous spinal stimulation over the injury region. In an open-label study, this method of stimulation was shown to increase arm and hand function in subjects with chronic cervical SCI. Given the similarities between chronic DCM and SCI, an effect of this methodology might be observed.

Implementation Strategies

A broad overview of contemporary interventions which may have therapeutic utility in DCM is presented in the 3 broad categories of neuroprotection, neuromodulation and neuroregeneration. Whilst specific interventions within these groups may overlap between these broad categories (i.e interventions with regenerative and neuroprotective properties), these categories also provide useful reference for when interventions could be given in the natural course of the disease. Mild DCM may benefit from neuroprotective agents to slow neurological deterioration. In moderate to severe cases, patients may have received surgical decompression and restorative therapies with
Figure 1. Graph illustrating simplified natural history of degenerative cervical myelopathy with progressive deterioration of neurological function including slow change phase and rapid functional decline phase with red line. Timepoints in natural history which neuroprotective and neurorestorative intervention can be of therapeutic value in slowing neurological decline and regaining neurological function are highlighted. Paler lines indicate differing natural history which may be experienced by people with degenerative cervical myelopathy, including continuous slow decline with no rapid phase, rapid decline with no slow phase, and after intervention those with no significant improvement in neurology or deterioration.

Figure 2. Timeline of potential application of contemporary interventions (neuroprotection, neuromodulation and neuroregeneration) according to natural history and severity of degenerative cervical myelopathy. In mild-moderate degenerative cervical myelopathy, neuroprotective strategies may prevent/slow down progression by interfering in pathological process. In severe degenerative cervical myelopathy, it is likely that the spinal cord is too damaged for there to be significant improvement gained from neuroprotective strategies. In moderate-severe cases, surgery will remove the focus of compression. At this stage, neuromodulatory strategies may enhance plasticity implicated in the recovery process and neuroregenerative strategies can be considered after the spine has been decompressed if significant neurological damage is present. Graphics produced with support of Myelopathy.org.
neuromodulation or neuroregenerative strategies could be beneficial. The effects of these categories of intervention on the natural history of DCM are presented in Figures 1 and 2. Combinations of interventions may also enhance recovery as they can work on different aspects of the pathological and regenerative process to reduce neurological injury and enhance recovery. Combinatorial strategies have been gaining traction in SCI research and are useful to consider in DCM.

The interventions presented are at different stages of development and readiness for clinical testing in adequately powered efficacy studies. Some interventions are quite mature and are currently undergoing phase-III trials (e.g. Ibudilast) or completed efficacy trials (e.g. Riluzole), whilst others are undergoing early stage pre-clinical investigation (e.g. miR21 regulators). Neuroprotective and neuroregenerative trials typically follow the more typical drug development process, whilst neuromodulatory interventions are devices, and are technologically mature and developed, though ongoing research into optimal intervention protocols and utilization in DCM are required. DCM and chronic cervical SCI have considerable pathophysiological overlap, and potential benefit of an intervention in one can be used to gauge potential efficacy in the other, though careful consideration of severity of cord injury and pathophysiological/restorative targets of interventions are required. An example is acute intermittent hypoxia, which has demonstrated efficacy as an adjunct to rehabilitation in improving gait function in subacute incomplete SCI, which may show similar benefit in DCM.

Figure 3 demonstrates technological development and readiness of potential interventions for DCM.

**Conclusion**

Therapeutic research in DCM over the last few decades has predominantly focused on the role and timing of surgical decompression. Surgery has shown improved outcomes for DCM patients; however, the majority do not make a full recovery and have a subsequent lifelong disability. The impetus for this article was the newly formed JLA priority setting partnership for DCM, which has determined the research priority and question of whether novel therapies can improve health and wellbeing in people with DCM. We present contemporary therapies in the broad domains of neuroprotection, neuroregeneration and neuromodulation, which may have potential therapeutic utility in DCM. As research in this area has been limited, it is hoped that this review will encourage research into this priority.
Acknowledgements

Further details on this priority, including how it was prioritized, why it was prioritized, and ongoing research activity can be found at aospine.org/recode/novel-therapies We would like to thank Myelopathy.org for their time and support in the development of graphics utilized within this article.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The research priorities were organized and funded by AO Spine through the AO Spine Knowledge Forum Spinal Cord Injury, a focused group of international Spinal Cord Injury experts. AO Spine is a clinical division of the AO Foundation, which is an independent medically guided not-for-profit organization. Study support was provided directly through the AO Spine Research Department. MRNK is supported by the National Institute for Health Research (NIHR) Brain Injury MedTech Co-operative based at Cambridge University Hospitals NHS Foundation Trust and University of Cambridge, and BMD a NIHR Clinical Doctoral Research Fellowship. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

ORCID iDs

Aref-Ali Gharooni https://orcid.org/0000-0002-6705-1115
Michael G. Fehlings https://orcid.org/0000-0002-5722-6364
Timothy F. Boerger https://orcid.org/0000-0003-1587-3704
Ricardo Rodrigues-Pinto https://orcid.org/0000-0002-6903-348X
Paul Aarne Koljonen https://orcid.org/0000-0002-9250-653X
Jefferson R. Wilson https://orcid.org/0000-0001-5965-0305
Benjamin M. Davies https://orcid.org/0000-0003-0591-5069
James D Guest https://orcid.org/0000-0003-0931-0286

References

1. Davies BM, Mowforth OD, Smith EK, Kotter MR. Degenerative cervical myelopathy. BMJ. 2018;360:k186.
2. Fehlings MG, Tetreault LA, Riew KD, et al. A clinical practice guideline for the management of patients with degenerative cervical myelopathy: recommendations for patients with mild, moderate, and severe disease and nonmyelopathic patients with evidence of cord compression. Global Spine J. 2017;7(3 suppl):70s-83s.
3. Kadaňka Z, Bednářík J, Novotný O, Urbánek I, Dušek L. Cervical spondylotic myelopathy: conservative versus surgical treatment after 10 years. Eur Spine J. 2011;20(9):1533-1538.
4. Rhee J, Tetreault LA, Chapman JR, et al. Nonoperative versus operative management for the treatment degenerative cervical myelopathy: an updated systematic review. Global Spine J. 2017;7(3 suppl):35S-41S.
5. Ghobrial GM, Harrop JS. Surgery vs conservative care for cervical spondylotic myelopathy: nonoperative operative management. Neurosurgery. 2015;62(Suppl 1):62-65.
6. Gharooni A-A, Grodzinski B, Davies BM, Kotter MRN. How common is repeat surgery and multi-level treatment in degenerative cervical myelopathy? Findings from a patient perspective survey. J Clin Neurosci. 2020;77:181-184.
7. Fehlings MG, Ibrahim A, Tetreault L, et al. A global perspective on the outcomes of surgical decompression in patients with cervical spondylotic myelopathy: results from the prospective multicenter AOSpine international study on 479 patients. Spine. 1976;40(17):1322-1328.
8. Davies B, Mowforth O, Sadler I, et al. Recovery priorities in degenerative cervical myelopathy: a cross-sectional survey of an international, online community of patients. BMJ Open. 2019;9(10):e031486.
9. Cheung WY, Arvinte D, Wong YW, Luk KDK, Cheung KMC. Neurological recovery after surgical decompression in patients with cervical spondylotic myelopathy - a prospective study. Int Orthop. 2008;32(2):273-278.
10. Lebl DR, Hughes A, Cammisa FP Jr., O’Leary PF. Cervical spondylotic myelopathy: pathophysiology, clinical presentation, and treatment. JSS J. 2011;7(2):170-178.
11. Oh T, Lafage R, Lafage V, et al. Comparing quality of life in cervical spondylotic myelopathy with other chronic debilitating diseases using the short form survey 36-health survey. World Neurosurg. 2017;106:699-706.
12. Alliance JL. Degenerative Cervical Myelopathy Top 10 Research Priorities; 2020. https://www.jla.nihr.ac.uk/priority-setting-partnerships/Degenerative-Cervical-Myelopathy/top-10-priorities.htm (Accessed 01/08/2020).
13. Nouri A, Tetreault L, Singh A, Karadimas SK, Fehlings MG. Degenerative Cervical myelopathy: epidemiology, genetics, and pathogenesis. Spine. 2015;40(12):E675-E693.
14. Tetreault L, Goldstein CL, Arnold P, et al. Degenerative cervical myelopathy: a spectrum of related disorders affecting the aging. Neurosurgery. 2015;77(suppl 1):S51-S67.
15. Yamaguchi S, Mitsahara T, Abiko M, Takeda M, Kurisu K. Epidemiology and overview of the clinical spectrum of degenerative cervical myelopathy. Neurosurg Clin. 2018;29(1):1-12.
16. Baptiste DC, Fehlings MG. Pathophysiology of cervical myelopathy. Spine J. 2006;6(6 suppl):190s-197s.
17. Akter F, Yu X, Qin X, et al. The pathophysiology of degenerative cervical myelopathy and the physiology of recovery following decompression. Front Neurosci. 2020;14(138):138.
18. Gooding MR, Wilson CB, Hoff JT. Experimental cervical myelopathy: autoradiographic studies of spinal cord blood flow patterns. Surg Neurol. 1976;5(4):233-239.
19. Gooding MR, Wilson CB, Hoff JT. Experimental cervical myelopathy. J Neurosurg. 1975;43(1):9-17.
20. Yu WR, Liu T, Kiehl TR, Fehlings MG. Human neuropathological and animal model evidence supporting a role for Fas-mediated apoptosis and inflammation in cervical spondylotic myelopathy. Brain. 2011;134(Pt 5):1277-1292.
21. Uchida K, Nakajima H, Watanabe S, et al. Apoptosis of neurons and oligodendrocytes in the spinal cord of spinal hyperostotic mouse (twy/twy): possible pathomechanism of human cervical compressive myelopathy. *Eur Spine J.* 2012;21(3):490-497.
22. Ito T, Oyamagi K, Takahashi H, Takahashi HE, Ikuta F. Cervical spondylotic myelopathy. Clinicopathologic study on the progression pattern and thin myelinated fibers of the lesions of seven patients examined during complete autopsy. *Spine.* 1976;21(7):827-833.
23. Liu H, MacMillian EL, Jutzeler CR, et al. Assessing structure and function of myelin in cervical spondylotic myelopathy: evidence of demyelination. *Neurology.* 2017;89(6):602-610.
24. Kalsi-Ryan S, Karadimas SK, Fehlings MG. Cervical spondylotic myelopathy: the clinical phenomenon and the current pathobiology of an increasingly prevalent and devastating disorder. *Neuroscientist.* 2013;19(4):409-421.
25. 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.
26. Domino EF, Unna KR, Kerwin J. Pharmacological properties of Benzazoles I. Relationship between structure and paralyzing action. *J Pharmacol Exp Therapeut.* 1952;105(4):486-497.
27. Mizoule J, Meldrum B, Mazadier M, et al. 2-Amino-6-trifluoromethoxy benzothiazole, a possible antagonist of excitatory amino acid neurotransmission–I. Anticonvulsant properties. *Neuropharmacology.* 1985;24(8):767-773.
28. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev.* 2012;3:CD001447.
29. Schwartz G, Fehlings MG. Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole. *J Neurosurg.* 2001;94(2 suppl):245-256.
30. Ates O, Cayli SR, Gurses I, et al. Comparative neuroprotective effect of sodium channel blockers after experimental spinal cord injury. *J Clin Neurosci.* 2007;14(7):658-665.
31. Tetreault LA, Zhu MP, Wilson JR, Karadimas SK, Fehlings MG. The impact of riluzole on neurobehavioral outcomes in preclinical models of traumatic and nontraumatic spinal cord injury: results from a systematic review of the literature. *Global Spine J.* 2020;10(2):216-229.
32. Fehlings MG, Wilson JR, Karadimas SK, Arnold PM, Kopjar B. Clinical evaluation of a neuroprotective drug in patients with cervical spondylotic myelopathy undergoing surgical treatment: design and rationale for the CSM-protect trial. *Spine.* 2013;38(22S):S68-875.
33. Fehlings MG, Badhiwala JH, Ahn H, et al. Safety and efficacy of riluzole in patients undergoing decompressive surgery for degenerative cervical myelopathy (CSM-Protect): a multicentre, double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet Neurol.* 2021;20(2):98-106.
34. Laliberte AM, Karadimas SK, Vidal PM, Satkunendranjagah K, Fehlings MG. Mir21 modulates inflammation and sensorimotor deficits in cervical myelopathy: data from humans and animal models. *Brain Communications.* 2021.
35. Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. *J Am Med Assoc.* 1984;251(1):45-52.
36. Fehlings MG, Wilson JR, Harrop JS, et al. Efficacy and safety of methylprednisolone sodium succinate in acute spinal cord injury: a systematic review. *Global Spine J.* 2017;7(3 suppl):1165-1375.
37. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. *N Engl J Med.* 1990;322(20):1405-1411.
38. Fehlings MG, Wilson JR, Tetreault LA, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. *Global Spine J.* 2017;7(3 suppl):203s-211s.
39. Vidal PM, Uindreaj A, Badner A, Hong J, Fehlings MG. Methylprednisolone treatment enhances early recovery following surgical decompression for degenerative cervical myelopathy without compromise to the systemic immune system. *J Neuroinflammation.* 2018;15(1):222.
40. Huo X, Zhou J, Liu S, Guo X, Xue Y. Clinical efficacy of single intraoperative 500 mg methylprednisolone management therapy for thoracic myelopathy caused by ossification of the ligamentum flavum. *BMC Musculoskelet Disord.* 2020;21(1):177.
41. Jayamohan SB, Kenning TJ, Petronis KA, Feustel PJ, Drazin D, DiRisio DJ. Effect of steroid use in anterior cervical discectomy and fusion: a randomized controlled trial. *J Neurosurg Spine.* 2015;23(2):137-143.
42. Cui S, Daffner SD, France JC, Emery SE. The effects of perioperative corticosteroids on dysphagia following surgical procedures involving the anterior cervical spine: a prospective, randomized, controlled, double-blind clinical trial. *J Bone Joint Surg Am.* 2019;101(22):2007-2014.
43. Dhillon RS, Parker J, Syed YA, et al. Axonal plasticity underpins the functional recovery following surgical decompression in a rat model of cervical spondylotic myelopathy. *Acta Neuropathol Commun.* 2016;4(1):89.
44. Gao L, Peng Y, Xu W, et al. Progress in stem cell therapy for spinal cord injury. *Stem Cell Int.* 2020:2020:2853650.
45. Ashammakhi N, Kim H-J, Ehsanipour A, et al. Regenerative therapies for spinal cord injury. *Tissue Eng Part B Rev.* 2019;25(6):471-491.
46. Courtine G, Sofroniew MV. Spinal cord repair: advances in biology and technology. *Nat Med.* 2017;34(21):2950-2963.
47. Santamaría AJ, Benavides FD, DiFede DL, et al. Clinical and neurophysiological changes after targeted intrathecal injections of bone marrow stem cells in a C3 tetraplegic subject. *J Neurotrauma.* 2019;36(3):500-516.
48. Rovan P, Gibbons JA, He L, et al. Ibudilast in healthy volunteers: safety, tolerability and pharmacokinetics with single and multiple doses. *Br J Clin Pharmacol.* 2008;66(6):792-801.
50. Mizuno T, Kurotani T, Komatsu Y, et al. Neuroprotective role of phosphodiesterase inhibitor ibudilast on neuronal cell death induced by activated microglia. *Neuropsychopharmacology*. 2004;46(3):404-411.

51. Wakita H, Tomimoto H, Akiyama I, et al. Ibudilast, a phosphodiesterase inhibitor, protects against white matter damage under chronic cerebral hyperperfusion in the rat. *Brain Res.* 2003;992(1):53-59.

52. Rolan P, Hutchinson M, Johnson K. Ibudilast: a review of its pharmacology, efficacy and safety in respiratory and neurological disease. *Expert Opin Pharmacother.* 2009;10(17):2897-2904.

53. Soukiasian J, Audouin A, Sargent C. Immunosuppressive and anti-inflammatory effects of cyclic AMP phosphodiesterase (PDE) type 4 inhibitors. *Immunopharmacology*. 2000;47(2):127-162.

54. Li H, Zuo J, Wang T. Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. *Front Pharmacol.* 2018;9(1048):1048.

55. Fukuyama H, Kimura J, Yarnaguchi S, et al. Pharmacological effects of ibudilast on cerebral circulation: a PET study. *N Engl J Med.* 2013;369(14):1399-1408.

56. Johnson KW, Matsuda K, Iwaki Y. Ibudilast for the treatment of drug addiction and other neurological conditions. *Clin Invest.* 2014;4:269-279.

57. Xu L, Li Y, Sun H, et al. Current developments of macrophage migration inhibition factor (MIF) inhibitors. *Drug Discov Today.* 2013;18(11):592-600.

58. Fox RJ, Coffey CS, Conwit R, et al. Phase 2 trial of ibudilast in patients with schizophrenia. *J Clin Psychopharmacol.* 2003;23(6):586-589.

59. Naismith RT, Bernel RA, Coffey CS, et al. Effects of ibudilast on MRI measures in the phase 2 SPRINT-MS study. *Neurology.* 2020;96:e491-e500. doi:10.1212/WNL.0000000000013114.

60. Oskarsson B, Dojillo J, Makky M, Matsuda K. COMBAT-ALS Phase 2b/3 Trial of MN-166 (Ibudilast) in ALS: study design and trial update (5149). *Neurology.* 2020;94(15 suppl):5149.

61. Ray LA, Bujarski S, Shoptaw S, Roche DJ, Heinzlerling K, Miotti K. Development of the neuroimmune modulator ibudilast for the treatment of alcoholism: a randomized, placebo-controlled, human laboratory trial. *Neuropsychopharmacology.* 2017;42(9):1776-1788.

62. Burnette EM, Baskerville WA, Grodin EN, Ray LA. Ibudilast for alcohol use disorder: study protocol for a phase II randomized clinical trial. *Trials.* 2020;21:779.

63. Heinzlerling KG, Briones M, Thomas AD, et al. Randomized, placebo-controlled trial of targeting neuroinflammation with ibudilast to treat methamphetamine use disorder. *J Neuroimmune Pharmacol.* 2020;15(2):238-248.

64. Metz VE, Jones JD, Manubay J, et al. Effects of ibudilast on the subjective, reinforcing, and analgesic effects of oxycodone in recently detoxified adults with opioid dependence. *Neuropsychopharmacology.* 2017;42(9):1825-1832.

65. Ledebor A, Hutchinson MR, Watkins LR, Johnson KW. Ibudilast (AV-411). A new class therapeutic candidate for neuropathic pain and opioid withdrawal syndromes. *Expert Opin Invest Drugs.* 2007;16(7):935-950.

66. Kwok YH, Swift JE, Gazerani P, Rolan P. A double-blind, randomized, placebo-controlled pilot trial to determine the efficacy and safety of ibudilast, a potential glial attenuator, in chronic migraine. *J Pain Res.* 2016;9:899-907.

67. Zakrzewski W, Dobrzyński M, Szymonowicz M, Rybak Z. Stem cells: past, present, and future. *Stem Cell Res Ther.* 2019;10(1):68.

68. Rowland JW, Hawryluk GWJ, Kwon B, Fehlings MG. Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. *Neurosurg Focus.* 2008;25(5):E2.

69. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354(17):1813-1826.

70. Thomas ED, Lochtche HL Jr., Cannon JH, Sahler OD, Ferrebee JW. Supralethal whole body irradiation and isologous marrow transplantation in man. *J Clin Invest.* 1959;38(10 Pt 1-2):1709-1716.

71. Ahuja CS, Mothe A, Khazaei M, et al. The leading edge: emerging neuroprotective and neuroregenerative cell-based therapies for spinal cord injury. *Stem Cells Transl Med.* 2020;9(12):1509-1530.

72. Riley J, Glass J, Feldman EL, et al. Intraspinal stem cell transplantation in amyotrophic lateral sclerosis: a phase I trial, cerebral microinjection, and final surgical safety outcomes. *Neurosurgery.* 2014;74(1):77-87.

73. Manley NC, Priest CA, Denham J, Wirth ED 3rd, Lebkowski JS. Human embryonic stem cell-derived oligodendrocyte progenitor cells: preclinical efficacy and safety in cervical spinal cord injury. *Stem Cells Transl Med.* 2017;6(10):1917-1929.

74. Zhao J, Sun W, Cho HM, et al. Integration and long distance axonal regeneration in the central nervous system from transplanted primitive neural stem cells. *J Biol Chem.* 2013;288(1):164-168.

75. Lu P. Chapter 1 - Stem cell transplantation for spinal cord injury repair. In: SB Dunnett, A Björklund, eds *Progress in Brain Research.* Elsevier; 2017; 231; 1-32.

76. Pandamooz S, Salehi MS, Zibaii MI, Ahmadiani A, Nabiiuni M, Dargahi L. Epidermal neural crest stem cell-derived glia enhance neurotrophic elements in an ex vivo model of spinal cord injury. *J Cell Biochem.* 2018;119(4):3486-3496.

77. Lu P, Jones LL, Snyder EV, Tusznyski MH. Neural stem cells constitutively secrete neurotrophic factors and promote extensive host axonal growth after spinal cord injury. *Exp Neurol.* 2003;181(2):115-129.

78. Li Z, Gao G-H, Wang G-S, Guan C-X, Yue L. In *Brain Res*. 2017;1663:282-289.

79. Nicola Fd C, Marques MR, Odorey F, et al. Neuroprotective effect of stem cells from human exfoliated deciduous teeth transplanted after traumatic spinal cord injury involves inhibition of early neuronal apoptosis. *Brain Res.* 2017;1663:95-105.
81. Cheng Z, Zhu W, Cao K, et al. Anti-inflammatory mechanism of neural stem cell transplantation in spinal cord injury. *Int J Mol Sci*. 2016;17(9):1380.

82. Cheng Z, Bosco DB, Sun L, et al. Neural stem cell-conditioned medium suppresses inflammation and promotes spinal cord injury recovery. *Cell Transplant*. 2017;26(3):469-482.

83. Cofano F, Boido M, Monticelli M, et al. Mesenchymal stem cells for spinal cord injury: current options, limitations, and future of cell therapy. *Int J Mol Sci*. 2019;20(11):2698.

84. Willison AG, Smith S, Davies BM, Kotter MRN, Barnett SC. A scoping review of trials for cell-based therapies in human spinal cord injury. *Spinal Cord*. 2020;58(8):844-856.

85. Assinck P, Duncan GJ, Hilton BJ, Plemel JR, Tetzlaff W. Cell transplantation therapy for spinal cord injury. *Nat Neurosci*. 2017;20(5):637-647.

86. Zweckberger K, Ahuja CS, Liu Y, Wang J, Fehlings MG. Self-assembling peptides optimize the post-traumatic milieu and synergistically enhance the effects of neural stem cell therapy after cervical spinal cord injury. *Acta Biomater*. 2016;42:77-89.

87. Binch ALA, Fitzgerald JC, Growney EA, Barry F. Cell-based strategies for IVD repair: clinical progress and translational obstacles. *Nat Rev Rheumatol*. 2021.

88. Bae HW, Amirdeifan K, Coric D, et al. A phase II study demonstrating efficacy and safety of mesenchymal precursor cells in low back pain due to disc degeneration. *Spine J*. 2014;14(11):S31-S32.

89. Noriega DC, Ardura F, Hernández-Ramajo R, et al. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: a randomized controlled trial. *Transplantation*. 2017;101(8):1945-1951.

90. Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up. *Int Orthop*. 2017;41(10):2097-2103.

91. Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, Silva FJ. Intra-discal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. *J Transl Med*. 2016;14(1):253.

92. Burke SN, Barnes CA. Neural plasticity in the ageing brain. *Nat Rev Neurosci*. 2006;7(1):30-40.

93. Rosenzweig ES, Salegio EA, Liang JJ, et al. Chondroitinase improves anatomical and functional outcomes after primate spinal cord injury. *Nat Neurosci*. 2019;22(8):1269-1275.

94. James ND, Shea J, Muir EM, Verhaagen J, Schneider BL, Bradbury EJ. Chondroitinase gene therapy improves upper limb function following cervical contusion injury. *Exp Neurol*. 2015;271:131-135.

95. Al-Zaiedy SA, Kolb SJ, Lowes L, et al. AVXS-101 (Onasemnogene Abeparvovec) for SMA1: comparative study with a prospective natural history cohort. *J Neuromuscul Dis*. 2019;6(3):307-317.

96. Hagg A, Kharoud S, Goodchild G, et al. TMEPAI/PMEPA1 Is a positive regulator of skeletal muscle mass. *Front Physiol*. 2020;11(1420):560225.

97. International Neuromodulation Society. https://www.neuromodulation.com/. https://www.neuromodulation.com/. Accessed 23/01/2021.

98. Hofmeister M, Memedovich A, Brown S, et al. Effectiveness of neurostimulation technologies for the management of chronic pain: a systematic review. *Neuromodulation*. 2020;23(2):150-157.

99. Fishman MA, Antony A, Esposito M, Deer T, Levy R. The evolution of neuromodulation in the treatment of chronic pain: forward-looking perspectives. *Pain Med*. 2019;20(suppl 1):S58-S68.

100. Dallapiazza R, McKisic MS, Shah B, Elias WJ. Neuromodulation for movement disorders. *Neurosur Clin N Am*. 2014;25(1):47-58.

101. Bledsoe IO, Viser AC, San Luciano M. Treatment of dystonia: medications, neurotoxins, neuromodulation, and rehabilitation. *Neurotherapeutics*. 2020.

102. Pereira EA, Green AL, Nandi D, Aziz TZ. Deep brain stimulation: indications and evidence. *Expert Rev Med Devices*. 2007;4(5):591-603.

103. Sisterson ND, Kokkinos V. Neuromodulation of epilepsy networks. *Neurosur Clin*. 2020;31(3):459-470.

104. Kwon C-S, Ripa V, Al-Awar O, Panov F, Ghatan S, Jetté N. Epilepsy and neuromodulation—randomized controlled trials. *Brain Sci*. 2018;8(4):69.

105. Ishii R, Nishida K, Youssef NA, Jann K, Takahashi S. Editorial: neuromodulation in basic, translational and clinical research in psychiatry. *Front Hum Neurosci*. 2019;13(438):438.

106. Sonmez AI, Camsari DD, Nandakumar AL, et al. Accelerated TMS for depression: a systematic review and meta-analysis. *Psychiatry Res*. 2019;273:770-781.

107. Chiang C-F, Lin M-T, Hsiao M-Y, Yeh Y-C, Liang Y-C, Wang T-G. Comparative efficacy of noninvasive neurostimulation therapies for acute and subacute poststroke dysphagia: a systematic review and network meta-analysis. *Arch Phys Med Rehabil*. 2019;100(4):739-750.

108. Dukelow S, Kirton A. Enhancing stroke recovery across the life span with noninvasive neurostimulation. *J Clin Neurophysiol*. 2020;37(2):150-163.

109. Buhagiar F, Fitzgerald M, Bell J, Allanson F, Petchell C. Neuromodulation for mild traumatic brain injury rehabilitation: a systematic review. *Front Hum Neurosci*. 2020;14(554):598208.

110. Demirtas-Tatlidede A, Vahabzadeh-Hagh AM, Bernabeu M, Tormos JM, Pascual-Leone A. Noninvasive brain stimulation in traumatic brain injury. *J Head Trauma Rehabil*. 2012;27(4):274-292.

111. Gall C, Schmidt S, Schmittkowsky MP, et al. Alternating current stimulation for vision restoration after optic nerve damage: a randomized clinical trial. *PLoS One*. 2016;11(6):e0156134.

112. Hoare DJ, Adjamian P, Sereda M. Electrical stimulation of the ear, head, cranial nerve, or cortex for the treatment of tinnitus: a scoping review. *Neural Plast*. 2016;2016:5130503.

113. Kumar K, Taylor RS, Jacques L, et al. The effects of spinal cord stimulation in neuropathic pain are sustained: a 24-month
follow-up of the prospective randomized controlled multicenter trial of the effectiveness of spinal cord stimulation. Neurosurgery. 2008;63(4):762-770. discussion 770.

114. Kapural L, Peterson E, Provenzano DA, Staats P. Clinical evidence for spinal cord stimulation for failed back surgery syndrome (FBSS): systematic review. Spine. 1976;42(Suppl 14):S61-S66.

115. Taylor RS, Buyten J-P, Buchser E. Spinal cord stimulation for complex regional pain syndrome: a systematic review of the clinical and cost-effectiveness literature and assessment of prognostic factors. Eur J Pain. 2006;10(2):91.

116. Moore DM, McCrory C. Spinal cord stimulation. BJA Education. 2016;16(8):258-263.

117. Ubbink DT, Vermeulen H. Spinal cord stimulation for non-reconstructable chronic critical leg ischaemia. Cochrane Database Syst Rev. 2003;3:CD004001.

118. Jensen MP, Brownstone RM. Mechanisms of spinal cord stimulation for the treatment of pain: still in the dark after 50 years. Eur J Pain. 2019;23(4):652-659.

119. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971-978.

120. Lawson McLean A, Kalff R, Reichart R. Spinal cord stimulation for acute pain following surgery for cervical myelopathy: a novel treatment strategy. Pain Pract. 2019;19(3):310-315.

121. Huang Q, Duan W, Sivanesan E, et al. Spinal cord stimulation for pain treatment after spinal cord injury. Neurosurg. 2019; 35(3):527-539.

122. Chari A, Hentall ID, Papadopoulos MC, Pereira EA. Surgical neurostimulation for spinal cord injury. Brain Sci. 2017;7(2):18.

123. Harkema S, Gerasimenko Y, Hodes J, et al. Effect of epidural stimulation of the lumbar spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia: a case study. Lancet. 2011;377(9781):1938-1947.

124. Gill ML, Grahm PJ, Calvert JS, et al. Neuromodulation of lumbar spinal networks enables independent stepping after complete paraplegia. Nat Med. 2018;24(11):1677-1682.

125. Grahm PJ, Lavrov IA, Sayenko DG, et al. Enabling task-specific volitional motor functions via spinal cord neuromodulation in a human with paraplegia. Mayo Clin Proc. 2017;92(4):544-554.

126. Angeli CA, Edgerton VR, Gerasimenko YP, Harkema SJ. Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. Brain. 2014;137(5):1394-1409.

127. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. Lancet. 1985;325(8437):1106-1107.

128. Chen R, Cros D, Curra A, et al. The clinical diagnostic utility of transcranial magnetic stimulation: report of an IFCN committee. Clin Neurophysiol. 2008;119(3):504-532.

129. Deftereos SN, Kechagias E, Ioakeimidou C, Georgonikou D. Transcranial magnetic stimulation but not MRI predicts long-term clinical status in cervical spondylosis: a case series. Spinal Cord. 2015;53(1):S16-S18.

130. Gharooni A-A, Khan M, Yang X, Anwar F, Davies B, Kotter M. Therapeutic repetitive transcranial magnetic stimulation (rTMS) for neurological dysfunction in degenerative cervical myelopathy: an unexplored opportunity? Findings from a systematic review. J Clin Neurosci. 2021;90:76-81.

131. Klomjai W, Katz R, Lackmy-Vallee A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Annals of Physical and Rehabilitation Medicine. 2015; 58(4):208-213.

132. McClintock SM, Reti IM, Carpenter LL, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the treatment of depression. J Clin Psychiatry. 2018;79(1):16cs10905.

133. FDA. FDA Permits Marketing of Transcranial Magnetic Stimulation for Treatment of Obsessive Compulsive Disorder. https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-transcranial-magnetic-stimulation-treatment-obessive-compulsive-disorder. Accessed 23/01/2021.

134. Trevizol AP, Shiozawa P, Cook IA, et al. Transcranial magnetic stimulation for obsessive-compulsive disorder: an updated systematic review and meta-analysis. J Ect. 2016;32(4):262-266.

135. Lan L, Zhang X, Li X, Rong X, Peng Y. The efficacy of transcranial magnetic stimulation on migraine: a meta-analysis of randomized controlled trials. J Headache Pain. 2017;18(1):86.

136. Lefaucheur J-P, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol. 2020;131(2):474-528.

137. Yilmaz B, Kesikburun S, Yasar E, Tan AK. The effect of repetitive transcranial magnetic stimulation on refractory neuropathic pain in spinal cord injury. J Spinal Cord Med. 2014;37(4):397-400.

138. Defrin R, Grunhaus L, Zamir D, Zeitig G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. Arch Phys Med Rehabil. 2007;88(12):1574-1580.

139. Kang BS, Shin HI, Bang MS. Effect of repetitive transcranial magnetic stimulation over the hand motor cortical area on central pain after spinal cord injury. Arch Phys Med Rehabil. 2009;90(10):1766-1771.

140. Gharooni A-A, Nair KPS, Hawkins D, Scivill I, Hind D, Harirhan R. Intermittent theta-burst stimulation for upper-limb dysfunction and spasticity in spinal cord injury: a single-blind randomized feasibility study. Spinal Cord. 2018;56(8):762-768.

141. Nardone R, Langthaler PB, Orioli A, et al. Effects of intermittent theta burst stimulation on spasticity after spinal cord injury. Restor Neurol Neurosci. 2017;35:287-294.

142. Alexeeva N, Balan C. Efficacy of QuadroPulse rTMS for improving motor function after spinal cord injury: three case studies. J Spinal Cord Med. 2016;39(1):50-57.

143. Gudmundsdottir A, Rothwell J, Vidal J, Kramar H. Non-invasive brain stimulation to promote motor and functional recovery following spinal cord injury. Neuroregeneration Research. 2017;12(12):1933-1938.

144. Kuppuswamy A, Balasubramaniam AV, Maksimovic R, et al. Action of 5 Hz repetitive transcranial magnetic stimulation on sensory, motor and autonomic function in human spinal cord injury. Clin Neurophysiol. 2011;122(12):2452-2461.
145. Niu T, Bennett CJ, Keller TL, Leiter JC, Lu DC. A proof-of-concept study of transcutaneous magnetic spinal cord stimulation for neurogenic bladder. Sci Rep. 2018;8(1):12549.

146. Vasquez N, Balasubramaniam V, Kuppuswamy A, et al. The interaction of cortico-spinal pathways and sacral sphincter reflexes in subjects with incomplete spinal cord injury: a pilot study. Neurourol Urodyn. 2015;34(4):349-355.

147. Fregni F, El-Hagrassy MM, Pacheco-Barrios K, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation (tDCS) in neurological and psychiatric disorders. Int J Neuropsychopharmacol; 2020.

148. Patel R, Ashcroft J, Patel A, et al. The impact of transcranial direct current stimulation on upper-limb motor performance in healthy adults: a systematic review and meta-analysis. Front Neurosci. 2019;13(1213):1213.

149. Cortes M, Medeiros AH, Gandhi A, et al. Improved grasp function with transcranial direct current stimulation in chronic spinal cord injury. NeuroRehabilitation. 2017;41:51-59.

150. Yozbatiran N, Keser Z, Davis M, et al. Transcranial direct current stimulation (tDCS) of the primary motor cortex and robot-assisted arm training in chronic incomplete cervical spinal cord injury: a proof of concept sham-randomized clinical study. NeuroRehabilitation. 2016;39(3):401-411.

151. Potter-Baker KA, Janini DP, Lin Y-L, et al. Transcranial direct current stimulation (tDCS) paired with massed practice training to promote adaptive plasticity and motor recovery in chronic incomplete tetraplegia: a pilot study. J Spinal Cord Med. 2018;41(5):503-517.

152. Howlett OA, Lannin NA, Ada L, McKinstry C. Functional electrical stimulation improves activity after stroke: a systematic review with meta-analysis. Arch Phys Med Rehabil. 2015;96(5):934-943.

153. Marquez-Chin C, Popovic MR. Functional electrical stimulation therapy for restoration of motor function after spinal cord injury and stroke: a review. Biomed Eng Online. 2020;19(1):34.

154. Milosevic M, Marquez-Chin C, Masani K, et al. Why brain-controlled neuroprosthetics matter: mechanisms underlying electrical stimulation of muscles and nerves in rehabilitation. Biomed Eng Online. 2020;19(1):81.

155. Nagai MK, Marquez-Chin C, Popovic MR. Why is functional electrical stimulation therapy capable of restoring motor function following severe injury to the central nervous system? In: MH Tuszynski, ed. Translational Neuroscience: Fundamental Approaches for Neurological Disorders. Boston, MA: Springer US; 2016; 479-498.

156. Popovic MR, Zivanovic V, Valiante TA. Restoration of upper limb function in an individual with cervical spondylotic myelopathy using functional electrical stimulation therapy: a case study. Front Neurol. 2016;7(81):81.

157. Pastor D. Use of electrical stimulation and exercise to increase muscle strength in a patient after surgery for cervical spondylotic myelopathy. Physiother Theory Pract. 2010;26(2):134-142.

158. Inanici F, Brighton LN, Samejima S, Hofstetter CP, Moritz CT. Transcutaneous spinal cord stimulation restores hand and arm function after spinal cord injury. IEEE Trans Neural Syst Rehabil Eng. 2021.

159. Griffin JM, Bradke F. Therapeutic repair for spinal cord injury: combinatorial approaches to address a multifaceted problem. EMBO Mol Med. 2020;12(3):e11505.

160. Navarrete-Opazo A, Alcayaga J, Sepúlveda O, Rojas E, Astudillo C. Repetitive intermittent hypoxia and locomotor training enhances walking function in incomplete spinal cord injury subjects: a randomized, triple-blind, placebo-controlled clinical trial. J Neurotrauma. 2017;34(9):1803-1812.