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Review Article

Pharmacological Treatment of Degenerative Cervical Myelopathy: A Critical Review of Current Evidence

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Degenerative cervical myelopathy (DCM) is the leading cause of spinal cord dysfunction in adults, representing substantial morbidity and significant financial and resource burdens. Typically, patients with progressive DCM will eventually receive surgical treatment. Nonetheless, despite advancements in pharmacotherapeutics, evidence for pharmacological therapy remains limited. Health professionals from various fields would find interest in pharmacological agents that could benefit patients with mild DCM or enhance surgical outcomes. This review aims to consolidate all clinical and experimental evidence on the pharmacological treatment of DCM. We conducted a comprehensive narrative review that presents all pharmacological agents that have been investigated for DCM treatment in both humans and animal models. Riluzole exhibits effectiveness solely in rat models, but not in treating mild DCM in humans. Cerebrolysin emerges as a potential neuroprotective agent for myelopathy in animals but had contradictory results in clinical trials. Limaprost alfadex demonstrates motor function improvement in animal models and exhibits promising outcomes in a small clinical trial. Glucocorticoids not only fail to provide clinical benefits but may also lead to adverse events. Cilostazol, anti-Fas ligand antibody, and Jingshu Keli display promise in animal studies, while erythropoietin, granulocyte colony-stimulating factor and limaprost alfadex exhibit potential in both animal and human research. Existing evidence mainly rests on weak clinical data and animal experimentation. Current pharmacological efforts target ion channels, stem cell differentiation, inflammatory, vascular, and apoptotic pathways. The inherent nature and pathogenesis of DCM offer substantial prospects for developing neurodegenerative or neuroprotective therapies capable of altering disease progression, potentially delaying surgical intervention, and optimizing outcomes for those undergoing surgical decompression.

Keywords: Intervertebral disc degeneration, Cervical cord, Erythropoietin, limaprost-alfadex, Glucocorticoids, Riluzole

INTRODUCTION

Globally, degenerative cervical myelopathy (DCM) is the leading cause of spinal dysfunction in adults over the age of 55.[1] Given an increasingly aging population, and a growing awareness about the condition,[2] global health care systems should anticipate a rise in patients presenting with DCM.[3] Therefore, DCM leads to various significant problems not only for the patients but also from the perspective of healthcare, society, and economy, affecting the quality of life of many patients, many of whom are still in the workforce.[4]

Although the natural history of DCM in individual patients is variable and unpredictable, it is usually characterized by progression of the associated symptoms.[5,6] However, the disease may demonstrate long quiescent periods, especially in patients with mild DCM.[7] Thus, pharmacological management could be implemented in patients with mild and stable myelopathy or with paraclinical findings associated with the development or worsening of myelopathy to delay or halt the progression of the symptoms.[5,8] Indeed, optimizing the pharmacologic management of DCM could also be attractive for elderly or high-risk surgical patients or patients who do wish to undergo surgery.[9] As a principle, surgery should ideally become the last resort, whereas currently, it is often considered the main treatment.

Surgical decompression remains the gold standard in the management of moderate to severe cases of DCM that have not responded to conservative management, with the aim of relieving symptoms and preventing further injury.[10] Nevertheless, despite appropriate surgical intervention, some patients may be left with permanent neurological disability due to preoperative irreversible injury to the spinal cord.[11,12] Additionally, some patients may experience postoperative worsening due to neuroinflammation and reperfusion injury, leading to suboptimal recovery after decompression surgery.[13] Therefore, the development of pharmacotherapy that could complement surgical decompression for DCM and optimize outcomes holds significant clinical importance.

However, despite such clinical potential, the evidence for nonsurgical management or adjuvant pharmacological therapy in DCM remains scarce. Nonetheless, this topic has piqued the interest of researchers from various fields, physicians from different specialties, and a large patient population. The objective of this study is to provide a detailed review of the current evidence regarding the pharmacological therapy of DCM. To our knowledge, this is the only review that comprehensively presents all pharmacological agents investigated for the treatment of DCM in both humans and animals.

METHODS

This narrative review was conducted by searching PubMed, Embase, Scopus, and Cochrane databases from inception to April 2022. The following keywords were used in various combinations: cervical spondylotic myelopathy, CSM, degenerative cervical myelopathy, DCM, spinal cord compression, neuroprotective, regenerative, neuroregenerative, reparative, neuroreparative, drugs, pharmaceutical, substance, medication, nonsteroidal, and steroids. English-language full-text studies were included if they involved a pharmacological component in the management of DCM in humans or animals. We chose the following exclusion criteria: publications that were not peer-reviewed, *in vitro* studies, articles that were not original studies (e.g., case reports, published congress abstracts, reviews), studies that did not report neurological/functional outcomes, and studies on medications or dietary supplements that were not clearly defined (e.g., active ingredients and their dose). Two authors (MG and MVA) screened all studies independently and in duplicate by title and abstract. Studies meeting all inclusion criteria were subsequently screened by their full-text in a similar fashion. The reference lists of the included articles were cross-referenced to identify additional articles. Data were extracted from the included studies in duplicate (JJL and MG) using a standardized charting template, which included the following information: author/year, study design, aim, population, drug/dosage/administration, outcomes, potential biases/limitations, and level of evidence (using Levels of Evidence for Therapeutic Studies from the Centre for Evidence-Based Medicine). For animal studies, the extracted data included animal model and pathology findings in addition to the aforementioned details. Studies were subsequently aggregated into their respective pharmacological agents, and were screened for dosages, adverse events, significant improvement in Japanese Orthopaedic Association (JOA) score, level of evidence (Table 1)/sample size, and strength of evidence.[14]

RESULTS

1. Riluzole

Moon et al.[15] demonstrated that riluzole administration (8 mg/kg intraperitoneal once a day [QD]) significantly improved gait performance and sensory symptoms in a rat model of DCM induced by a titanium screw-based chronic compres-

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Table 1. Levels of evidence for therapeutic studies from the center for evidence-based medicine (http://www.cebm.net)

Level	Type of evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual cohort study (including low quality RCT, e.g., < 80% follow-up)
2C	"Outcomes" research; ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual case-control study
4	Case series and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

RCT, randomized controlled trials.

sion device ($p < 0.05$). Karadimas et al.[16] examined the effects of postoperative riluzole administration in a rodent model of DCM. Rats with DCM demonstrated a transient postoperative neurological deterioration similar to what is observed in some patients, suggesting that ischemia-reperfusion injury may occur after decompression surgery. Riluzole administration demonstrated a decrease in oxidative stress and postoperative decline of gait parameters after decompression surgery in the DCM rat model. Riluzole-treated rats displayed a significantly lower proportion of 8-oxoG DNA-positive cells (indicating oxidative damage) *in vitro* ($p < 0.05$).

Rajasekaran et al.[17] conducted a clinical trial to evaluate the effectiveness of riluzole administration in patients with mild forms of DCM. Thirty patients with modified JOA (mJOA) scores ≥13 were recruited for this double-blinded, placebo-controlled randomized controlled trial. The study group was administered riluzole (50 mg orally twice a day [PO BID]) for a period of one month while the placebo group was administrated vitamin B complex tablets. The patients were assessed with a new magnetic resonance imaging (MRI) and diffusion tensor imaging and clinical scores. There was no significant change in the clinical outcome scores and diffusion tensor indices of patients treated with riluzole as a standalone pharmacotherapeutic agent after one month. The strength of evidence[14] of this study was considered moderate.

The most significant clinical trial investigating the efficacy of perioperative riluzole administration is the CSM-PROTECT trial.[18] This international, double-blinded, randomized phase 3 clinical trial was conducted by 16 university-affiliated centers in Canada and the United States. Patients aged 18 to 80 years with moderate to severe DCM as characterized by mJOA scores of 8 to 14 were included in this trial. A total of 290 patients were randomized. Patients randomized to the study group were administered riluzole (50 mg PO BID) 14 days preoperatively and 28 days postoperatively. The primary endpoint was change in mJOA score from baseline to 6 months in the intention-to-treat population, defined as all patients who have undergone randomization and surgical decompression. There was no significant difference between the riluzole and placebo groups in mJOA scores at 6 months of follow-up ($p = 0.14$). Therefore, adjuvant treatment with riluzole in the perioperative setting did not improve functional recovery beyond decompression surgery alone for patients with moderate to severe DCM in this study.[18] The strength of evidence of this study was considered moderate.

2. Cerebrolysin

Allam et al.[19] conducted a prospective randomized control trial to evaluate the effect of cerebrolysin as a treatment modality for DCM. A group of 192 patients with moderate to severe DCM who refused surgery were subdivided blindly into 2 equal groups. The study group received 5 weekly parenteral injection of cerebrolysin (5 mL) for a total duration of 4 weeks while the control group received a placebo injection. Both groups also received a single daily dose of celecoxib during the treatment (200 mg PO daily). The JOA score was recorded at 1, 3, and 6 months. Over the 6-month study period, the mean JOA score of patients in the group that received the cerebrolysin injection improved from 11.5 ± 1.2 to 13.9 ± 1.3 while the mean JOA score of the placebo group increased from 11.3 ± 1.2 to 11.8 ± 1.23 with statistically significant differences when comparing the mean JOA recovery rate between the 2 groups at 1, 3, and 6 months ($p < 0.0001$). Also, no reported cases of neurologic deterioration over 6 months of follow-up were recorded in the cerebrolysin group. The strength of evidence of this study was considered high.

A prospective randomized control trial was conducted recently to determine the value of perioperative cerebrolysin administration.[20] Sixty patients who underwent surgical decompression for DCM were divided into 2 groups. One group was administered a daily preparation of cerebrolysin for 21 days postoperatively while the second group was administered a placebo. The mJOA score, visual analogue scale (VAS) and an assessment of hand power and sensation were used to assess each group. The trial failed to identify any significant difference in

postoperative mJOA and VAS scores between the 2 groups but demonstrated an improved hand function in the cerebrolysin group at 1 year ($p = 0.03$). In addition, the group outlined that only 2 minor adverse effects were reported in the group that was administered their preparation of cerebrolysin. The strength of evidence of this study was considered moderate.

3. Limaprost Alfadex

A study by Kurokawa et al.[11] demonstrated that limaprost alfadex improved the motor function in a rodent model of cervical myelopathy. An expandable polymer was implanted under the C5–6 laminae of rats to develop compression-induced cervical myelopathy. Twice daily limaprost administration (300 μg/kg PO BID at a concentration of 60 μg/mL) resulted in a significant increase in forced locomotion capability, measured via forelimb stride length, in the treated rats when compared with the control group ($p < 0.05$).

A clinical trial was conducted by Sugawara et al.[21] to investigate the potential benefits of limaprost alfadex in patients with DCM. A group of 21 patients with mild DCM managed nonoperatively were treated with an oral dose of 15 μg of limaprost alfadex daily for 3 months. The treatment resulted in an improvement in mJOA scores and grip and release count at 1 month that were maintained at 3 months ($p = 0.017$ and $p = 0.001$, respectively). The mean mJOA score improved by 1.30 points and the mean grip and release improved from 17.8 to 22.6 over the 3-month period. However, there was no control group in this trial. A phase 3 prospective randomized double-blinded clinical trial on the efficacy of oral limaprost administration following surgery for cervical myelopathy is currently being conducted by the Seoul National University Hospital (ClinicalTrials.gov Identifier: NCT02125981). The strength of evidence of this study was considered moderate.

4. Glucocorticoids

Vidal et al.[22] conducted a study to assess the efficacy of perioperative methylprednisolone in enhancing neurological recovery and to evaluate its effect on the inflammatory response following decompression in an animal model of DCM. DCM was induced in a C57BL/6 mice model using an aromatic polyether material implanted underneath the C5–6 laminae to cause progressive compression of the spinal cord due to focal ossification. Decompressive surgery was conducted 12 weeks post-initial implantation. The mice in the trial group received one dose of methylprednisolone half an hour before surgical decompression and at 2 weeks after the decompression. This study demonstrated that methylprednisolone improved locomotor recovery without affecting the composition of circulating white blood cells ($p < 0.05$). Histological assessment of the spinal cords showed significant neuronal preservation ($p < 0.05$).

Human trials have examined the role of glucocorticoids as an adjunct to decompressive surgery. Blume et al.[23] conducted a retrospective cohort study of patients undergoing posterior decompression and instrumentation of the cervical spine for DCM to investigate the effect of intraoperative dexamethasone. A 40-mg dose of intravenous (IV) dexamethasone was administered intraoperatively at the discretion of the senior surgeon. A total of 49 patients were recruited for the study and 25 patients received an intraoperative dose of dexamethasone. Patients were assessed pre- and postoperatively using the Neck Disability Index (NDI) and the mJOA score and there was no significant difference in the baseline scores between the 2 groups prior to surgery. No significant differences were observed between the 2 groups in terms of NDI and mJOA scores at follow-up. Furthermore, a significantly higher rate of wound infections was detected in the group that received intraoperative dexamethasone ($p = 0.021$). The strength of evidence of this study was considered moderate.

Lastly, a randomized controlled trial by Jeyamohan et al.[24] aimed at comparing the effectiveness of intraoperative dexamethasone administration (0.2 mg/kg IV intraoperatively) on the incidence of postoperative swallowing and airway compromise also examined the effects on functional outcomes (including mJOA scores) and fusion rates. Patients who underwent multilevel anterior cervical discectomy and fusion (ACDF) were randomly assigned to receive intraoperative and postoperative doses of dexamethasone or normal saline and a placebo. The authors demonstrated that intraoperative administration of dexamethasone did not lead to a significant difference in mJOA scores. Moreover, dexamethasone administration significantly delayed fusion rates at 6 months ($p = 0.048$) without affecting the long-term fusion rates at 12 months ($p = 0.57$). The strength of evidence of this study was considered moderate.

5. Erythropoietin

A recent study by Tanaka et al.[25] demonstrated that erythropoietin (EPO) improved the motor function in a rodent model of cervical myelopathy. An expandable polymer was implanted under the C5–6 laminae of rats to develop compression-induced cervical myelopathy. EPO administration started 8 weeks after the insertion of the polymer and motor function was assessed after surgery. Motor neurons and apoptotic cell death were eval-

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uated with immunohistochemistry. Results from this study demonstrated that rats treated with high-dose EPO maintained better motor function in strength ($p < 0.0001$). EPO also suppressed neuronal apoptotic cells and significantly prevented the loss of motor neurons ($p < 0.0001$).

A second study by Eryilmaz and Farooque[26] investigated the therapeutic effects of the combination of EPO and methylprednisolone in the prevention of ischemia-reperfusion injury following decompression in patients with DCM. This randomized controlled study included 110 patients who underwent surgical decompression for DCM. The treatment group received 30 mg/kg of methylprednisolone and 3,000 U/kg of EPO intravenously 30 minutes prior to the start of their spinal decompression surgery while the control group only received 30 mg/kg of methylprednisolone without EPO. This study reported a statistically significant ($p < 0.001$) increase in quality of life parameters, i.e., all dimensions of the World Health Organization Quality of Life assessment instrument (WHOQOL-100), in the group of patients who had also received EPO. Additionally, the JOA score improved significantly in the EPO group after surgery compared to the control group ($p = 0.025$). The EPO group had a preoperative JOA score of 10.25 ± 1.72 (control: 10.31 ± 2.05) and increased to 18.43 ± 2.81 (control: 15.06 ± 2.93) 3 months postoperatively. A significant decrease in the levels of interleukin (IL)-1β and IL-8 3 months after the treatment was also noted in the EPO group ($p = 0.028$ and $p = 0.026$, respectively). The strength of evidence of this study was considered high.

These recent findings suggest that EPO may prove beneficial in the management of DCM. Nonetheless, EPO's therapeutic applications may be limited by its hematological adverse effects, such as red blood cell proliferation, high blood pressure, and prothrombotic properties. As a result, EPO derivatives that retain cytoprotective and neuroprotective effects with minimal erythropoietic activity have been developed.[27-29]

6. Cilostazol

Yamamoto et al.[30] investigated the neuroprotective effects of cilostazol on cervical myelopathy using a rat model of chronic cervical cord compression. Cord compression was induced using a chronic compression device of thin polyurethane sheets that gradually expanded over 48–72 hours by absorbing water after being surgically implanted under the C5–6 laminae. Cilostazol was orally administered (30 mg/kg PO) to the treatment group prior to the implantation of the device and continuing for the total trial period of 25 weeks, while the control group was administered vehicle solution under the same protocol. Results demonstrated that cilostazol preserved forepaw grip strength and forced running capability 25 weeks postimplantation of the device ($p < 0.05$). In addition, histopathological examination of the cervical spinal cords demonstrated that the drug helped preserve anterior horn motor neurons in the C5–6 spinal cord segments ($p < 0.05$).

7. Jingshu Keli

Using a rat model of cervical myelopathy, Yan et al.[31] demonstrated that rats fed Jingshu Keli (JSKL) 4.8 g/kg daily from day 7 to day 28 postoperatively recovered better gait performance than the control group ($p < 0.001$). Moreover, the active ingredients in JSKL, ginsenoside Rb1 (GRb1), and notoginsenoside R1 (NGR1), decreased neuronal excitability through modulation of K+ (Kir) channels by reducing the frequency of action potentials and hyperpolarizing the resting membrane potential ($p < 0.05$). This led to decreased levels of mechanical and thermal pain at 21 days in the JSKL group ($p < 0.001$ and $p < 0.05$, respectively). Although this study was conducted in a small group of rats ($n = 40$), further studies should elaborate on traditional Chinese herbs and other alternative medicines that can be beneficial in animal studies, and ultimately in humans.

8. Granulocyte Colony-Stimulating Factor

Yoshizumi et al.[32] conducted a study on a rat spinal cord compression model. They administered granulocyte colony-stimulating factor (G-CSF) 15 mg/kg daily for 5 days subcutaneously to the treatment group and normal saline to the control group and found that the control group had significantly less motor neurons after treatment compared to the G-CSF group ($p < 0.001$). Moreover, measured using TUNEL (terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling) staining, G-CSF significantly decreased the number of apoptotic cells at 8 weeks ($p < 0.05$).

In a phase I and IIa prospective clinical trial, Sakuma et al.[33] observed improved muscle function ($p < 0.01$), touch ($p < 0.05$), and pain sensation ($p < 0.05$) in a cohort of 15 patients with worsening symptoms of compressive cervical myelopathy. These patients were administered G-CSF 10 μg/kg once daily for 5 consecutive days. Mean JOA recovery rates at 1 and 6 months after administration were $49.9\% \pm 15.1\%$ and $59.1\% \pm 16.3\%$, respectively, where recovery rates were defined as (postoperative score–preoperative score/full score–preoperative score) × 100 (%). White blood cell count increased to more than 22,700 cells/mm^3 after G-CSF therapy. No serious adverse events occurred during or after treatment. However, these results should be inter-

preted with caution as this was an open-label trial without a control group. The strength of evidence of this study was considered very low.

The restorative function of G-CSF holds great promise as it promotes neural tissue repair and it reduces cell death, hence an ideal candidate for DCM patients. Use of G-CSF in the clinical setting is still in the early stages of research. Rigorous prospective trials are needed to assess the safety profile, efficacy, and optimal dosing regimens of G-CSF in humans.

9. Anti-Fas Ligand Antibody

Yu et al.[12] performed a postmortem human tissue study to investigate the pathology and apoptotic mechanisms in human DCM and the therapeutic potential of anti-Fas ligand antibody in a mouse model. In the postmortem samples of patients with DCM, they showed increased Fas-mediated apoptosis of neurons and oligodendrocytes and an increase in inflammatory cells. To demonstrate the therapeutic potential of an anti-Fas ligand antibody, they administered anti-Fas ligand antibody (MFL3) at 50 mg intraperitoneally twice weekly for 4 weeks in Twy/Twy (tiptoe-walking-yoshimura) mice. Treatment decreased neural inflammation mediated by macrophages and activated microglia, glial scar formation and caspase-9 activation. Furthermore, the treatment promoted dramatic functional neurological recovery.

The antiapoptotic property of an anti-Fas ligand antibody represents a viable therapeutic direction in DCM patients. Although these results seem promising in attenuating proinflammatory pathways and neural degeneration in DCM, the recommended posology of anti-fas ligand antibody remains unknown as administration in DCM patients has yet to be conducted.

Characteristics of the included studies evaluating the pharmacological agents in humans and animals can be found in Tables 2 and 3, respectively.

DISCUSSION

Herein, we present the first comprehensive review of pharmacological agents for the management of mild DCM. Several findings were reported, including the following: (1) riluzole is not effective for treating mild DCM in humans, but only in rat models; (2) cerebrolysin shows potential as a neuroprotective agent for myelopathy, but its effectiveness in DCM patients should be further investigated; (3) limaprost alfadex has demonstrated motor function improvement in animal models and has promising results in a small clinical trial; (4) glucocorticoids not only failed to offer clinical benefits, but may have also led to adverse events; (5) cilostazol, anti-Fas ligand antibody, and Jingshu Keli have shown promise in animal studies, while EPO, G-CSF, and limaprost alfadex, in both animal and human studies. Overall, only weak clinical evidence and animal studies are available. Thus, these results have yet to be validated in large scale studies that provide a high level of evidence.

Research on the pharmacological management of patients with DCM might have multiple relevant clinical applications. Most patients present a progressive deterioration or a stepwise decline in their neurological function that may be characterized by significant periods of symptom stability.[34] Also, previous reports have suggested similar results between patients with mild DCM treated conservatively and in those treated with surgical decompression.[35] Moreover, the AO Spine North America and Cervical Spine Research Society guidelines suggest offering either surgical intervention or a supervised trial of structured rehabilitation for patients with mild DCM, with surgery recommended in cases of neurological deterioration or lack of improvement.[8] In addition, symptomatic radiculopathy, presence of MRI cervical cord hyperintensity, prolonged motor evoked potentials and somatosensory evoked potentials, and electromyographic findings of anterior horn cell lesions have been associated with development of myelopathy in asymptomatic patients.[5] Furthermore, circumferential cord compression on axial MRI, a deformity of the spinal cord due to compression with an acute-angled lateral corner (one or both sides), abnormally increased range of preoperative neck and head motion, lower segmental lordotic angle, segmental instability, and reduced diameter of the cerebrospinal fluid column have been correlated with further worsening of myelopathy.[5] Thus, neuroprotective substances that prevent the progression of the disease or promote neuro-regeneration might be a reasonable alternative in the future for the aforementioned categories of patients (i.e., patients with findings associated with the development or worsening of myelopathy or patients with mild and stable myelopathy). However, it is important to stress that pharmacological treatment is far yet from being a main treatment for DCM, especially for patients with moderate or severe DCM, where surgical intervention is recommended based on moderate quality evidence and a strong recommendation.[8]

Furthermore, surgical management remains indicated in patients with moderate to severe forms of DCM.[8] However, some patients may present neurological deterioration after surgical decompression. Up to 11.6% of patients who undergo decompression for DCM may experience deterioration of their neuro-

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Table 2. Summary of studies investigating the pharmacological treatment of DCM in humans

Study	Study design	Aim	Study population (# in groups)	Drug, dosages, and administration	Outcome(s)	Potential biases/ limitations	Level of evidence
Rajasekaran et al.,[17] 2016	Double-blinded, placebo-controlled randomized controlled trial	To evaluate the effectiveness of Riluzole as a pharmacotherapeutic treatment option for early cervical myelopathy	Intervention: 15 patients received Riluzole Control: 15 patients received vitamin B	Riluzole 50 mg PO BID for 1 month	Clinical scores: modified JOA, Nurick grading, SF-12, Neck Disability Index; diffusion tensor imaging datametrics: apparent-diffusion coefficient, fractional anisotrophy, volume ratio, anisotrophy, Eigen vectors No significant change in modified JOA scores or other clinical scores between groups, diffusion tensor imaging datametrics did not show statistically significant changes	Small sample size; Lack of standardized data for dosing and duration of Riluzole treatment	1B
Fehlings et al.,[18] 2021	Multicentre, double-blind, placebo-controlled, randomized, phase 3 trial	To investigate whether riluzole enhances outcomes in patients undergoing decompression surgery for DCM	Intervention: 141 patients undergoing decompression for DCM received riluzole Control: 149 patients undergoing decompression surgery for DCM received a placebo	Riluzole 50 mg PO BID for 14 days preoperatively and then for 28 days postoperatively	No significant change in modified JOA score at 6 months ($p = 0.14$). Increased serious adverse events in the riluzole group compared to the control group ($n = 43$ vs. $n = 34$, respectively). Most common adverse events were neck or arm or shoulder pain, arm paraesthesia, dysphagia, and worsening of myelopathy	Heterogeneity of spinal cord injury etiology in DCM; insensitivity and interpretation of statistical significance in the outcome instruments (i.e., modified JOA scale and Nurick grade); poor generalizability of findings to other populations; < 80% 1-year follow-up	2B (< 80% follow-up)
Allam et al.,[19] 2018	Prospective randomized study	To evaluate the effect of cerebrolysin as a conservative modality on DCM patients	Intervention: 96 patients received cerebrolysin Control: 96 patients received placebo IM injection Both groups received celecoxib 200 mg as a single, after-meal daily dose for 4 weeks	Cerebrolysin 5 mL IM QD for 5 days/week for 4 weeks	At 1 month, myelopathy improved in 92% of patients in group I and 52% in group II. At 6 months, the improvement was seen in 87% of patients in group I and 33% in group II. The mean JOA recovery rate was significantly higher in group I compared to group II at all time points (1, 3, and 6 months) ($p < 0.0001$)	Treatment was not uniquely cerebrolysin, rather a combination of cerebrolysin and celecoxib; lack of blinding of the drug provider and the main investigator	1B
Sharma et al.,[20] 2022	Prospective randomized controlled trial	To analyze the role of cerebrolysin in patients with DCM managed with surgery	Intervention: 30 patients received cerebrolysin Control: 30 patients received a placebo	Cerebrolysin 5 mL IV QD diluted in 100 mL 0.9% NaCl over 30 minutes for 21 days postoperatively	Both groups showed significant improvement in mJOA and VAS scores at 3 weeks, 3 months, 6 months, and 1 year postoperatively ($p < 0.01$), but no significant difference between the groups. The cerebrolysin group showed significant improvement in hand function at 1 year compared to the placebo ($p = 0.03$)	Small sample size, single-center study, long duration of IV therapy, social determinants influencing the sex ratio	2B

(*Continued*)

Table 2. Summary of studies investigating the pharmacological treatment of DCM in humans (Continued)

Study	Study design	Aim	Study population (# in groups)	Drug, dosages, and administration	Outcome(s)	Potential biases/ limitations	Level of evidence
Sugawara et al.,[21] 2009	Prospective study	To examine the effect of oral administration of limaprost alfadex on myelopathy symptoms in patients with mild cervical spinal canal stenosis	21 Patients with mild spondylotic cervical spinal canal stenosis without any improvements after oral administration of NSAID drugs, muscle relaxant, and/or vitamin B12 for at least 2 months before referral Control group NS	Limaprost alfadex 15 μg PO QD	JOA score significantly improved from 14.0 to 15.0 at 1 month ($p=0.022$) and 15.2 at 3 months ($p=0.009$) Grip and release count significantly improved from 17.8 to 21.4 at 1 month ($p=0.017$) and 22.6 at 3 months ($p=0.001$) Finger escape sign grade improved in most patients ($p<0.05$) Stabilometry area with eyes closed and Romberg rate significantly improved at 1 and 3 months ($p<0.05$)	Observational study – no study group, short follow-up	2B
Blume et al.,[23] 2018	Retrospective study	To investigate the effect of intraoperative dexamethasone on wound healing, complications, and clinical outcome in patients with posterior surgery for DCM	Intervention: 25 patients underwent posterior instrumentation – decompression and received dexamethasone Control: 24 patients also underwent posterior instrumentation – decompression, but did not receive dexamethasone	Dexamethasone 40 mg IV intraoperatively	No significant differences between groups in pre- and postoperative findings, complications, neurologic symptoms, and follow-up (NDI and modified JOA score). There was a higher rate of wound healing complications in the dexamethasone group ($p=0.021$)	Retrospective design, small sample size, different lengths of follow-up, exclusion of ventral decompressive surgical cases, selection bias in dexamethasone administration	2B
Jeyamohan et al.,[24] 2015	Prospective, randomized, double-blinded, controlled trial	To determine if perioperative dexamethasone use improves perioperative dysphagia and airway edema	Intervention: 56 patients underwent multilevel anterior cervical reconstruction and received dexamethasone Control group: 56 patients also underwent multilevel anterior cervical reconstruction, but received saline	Dexamethasone 0.2 mg/kg IV intraoperatively Postoperative doses: D examethasone 0.06 mg/kg IV Q6H for the first 24 hours	No significant differences in the myelopathy scores, axial pain scores, extremity pain scores, ODI, or SF-12 scores (either mental or physical summary component) 6, 12, and 24 months. Severity of dysphagia in the postoperative period up to 1 month was significantly lower in the steroid group ($p=0.027$). Airway difficulty and need for intubation trended toward significance in the placebo group ($p=0.057$). Fusion rates at 6 months were significantly lower in the steroid group, but lost significance at 12 months ($p=0.048$ and $p=0.57$, respectively)	Nonstandardized dexamethasone-dosing schedule; subjectivity of functional outcome swallowing scale score; steroid treatment deviations; inherent bias towards steroid treatment; short follow-up; < 80% 1-year follow-up	2B (< 80% follow-up)

(*Continued*)

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Table 2. Summary of studies investigating the pharmacological treatment of DCM in humans (Continued)

Study	Study design	Aim	Study population (# in groups)	Drug, dosages, and administration	Outcome(s)	Potential biases/ limitations	Level of evidence
Eryilmaz et al.,[26] 2021	Prospective randomized controlled trial	To investigate the therapeutic effects of combined erythropoietin and methylprednisolone therapy on ischemia-reperfusion injury to the spinal cord and its effects on interleukin-1 beta (IL-1β), IL-1 receptor antagonist (IL-1RA), and IL-8 (IL-8) levels	Intervention: 55 patients received both methylprednisolone and erythropoietin Control: 55 patients received only methylprednisolone	Methylprednisolone: 30 mg/kg IV 30 minutes preoperatively spinal cord decompression Erythropoietin: 3,000 U/kg IV 30 minutes preoperatively spinal cord decompression	Three months after treatment, the observation group showed a significant improvement in JOA scores ($p = 0.025$) and 40-point rating method scores ($p = 0.019$) compared to the control group. Three months after treatment, the observation group had higher S-100β levels ($p = 0.041$), lower neuron-specific enolase levels ($p = 0.032$), lower IL-1β levels ($p = 0.026$), higher IL-1RA levels ($p = 0.021$), and lower IL-8 levels ($p = 0.028$) compared to the control group. The observation group had higher scores in all dimensions of the World Health Organization Quality of Life assessment instrument (WHOQOL-100), indicating better quality of life compared to the control group ($p < 0.001$ for all dimensions)	No comparator group that did not receive methylprednisolone; no justification of sample size or selection of dosages; short follow-up	1B
Sakuma et al.,[33] 2011	Prospective clinical trial (Phase I and IIa)	To evaluate the safety and efficacy of neuroprotective therapy using G-CSF for patients with worsening symptoms of compression myelopathy	15 Patients with worsening symptoms of compression myelopathy Intervention: 5 patients received the 5 μg dose (followed by decompression surgery) and 10 patients received the 10 μg dose (followed by decompression surgery in 9 patients) Control group: NA (open-label study design)	G-CSF 5 μg/kg IV QD or 10 μg/kg IV QD for 5 consecutive days	G-CSF administration suppressed the progression of myelopathy in all 15 patients. Muscle ($p < 0.01$), touch ($p < 0.05$), and pain ($p < 0.05$) improvement were observed in all patients receiving G-CSF 10 μg/kg QD at 6 months. Mean JOA recovery rates at 1 and 6 months after administration in the 10 μg group were 49.9% ± 15.1% and 59.1% ± 16.3%, respectively. White blood cell count increased to more than 22,700 cells/mm^3 after G-CSF therapy. No serious adverse events occurred during or after treatment	Absence of a control group; open-label design	4

DCM, degenerative cervical myelopathy; PO, orally; BID, twice a day; JOA, Japanese Orthopaedic Association; IM, intramuscular; QD, once a day; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; NS, not specified; mJOA, modified JOA; VAS, visual analogue scale; Q6H, every 6 hours; ODI, Oswestry Disability Index; SF-12, 12-item Short Form health survey; G-CSF, granulocyte colony-stimulating factor.

Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Moon et al.,[15] 2014	Experimental animal research	To examine the effects of riluzole on neurobehavioral outcomes, neuropathic pain, and tissue preservation in a rat model of chronic cervical spinal cord compression (DCM)	Sham group (n = 6), control group (n = 18), riluzole group (n = 17)	Female Sprague-Dawley rats that underwent C6–7 laminectomy and implantation of the rod of a chronic compression device into the C2 and the T2 spinous processes A threaded screw with an extradural plate fixed to the tip was advanced through the chronic compression device rod. The screw was then advanced very precisely by 0.2 mm	Riluzole 8 mg/kg intraperitoneal QD or control solution (30% 2-hydroxypropyl-β-cyclodextrin) was initiated 1 week postoperatively and continued for 7 weeks	Control group showed increased sensitivity of mechanical allodynia (via von Frey filament testing) compared to the sham group at weeks 2–8 ($p = 0.003$ for week 2, $p < 0.001$ for weeks 3–8) Riluzole group had decreased sensitivity compared to the control group at weeks 2, 6, 7, and 8 ($p = 0.012$, $p = 0.025$, $p = 0.039$, $p < 0.001$, respectively) Control group demonstrated decreased latency of thermal hyperalgesia (via tail flick test) compared to the sham group ($p = 0.007$) Riluzole group showed increased latency compared to the control group ($p = 0.006$) Gait assessed using CatWalk system: Riluzole group had increased swing phase duration in forelimbs and hindlimbs compared to the control group ($p < 0.05$). Riluzole group showed increased paw intensity in forelimbs and hindlimbs compared to the control group ($p < 0.05$). Riluzole group exhibited increased hindlimb swing speed compared to the control group ($p < 0.05$)	Immunohistochemical analysis revealed decreased phosphorylated NR1 and NR2B positive cells in the dorsal horns of the riluzole group compared to the control group ($p < 0.001$) Riluzole administration reduced microglia activation in the dorsal horns compared to the control group ($p = 0.001$). Riluzole treatment led to decreased scar tissue area and increased preserved gray matter area compared to the control group ($p < 0.05$)	The experimental design did not allow for investigation of the potential effects on the induction of thermal hyperalgesia after the gradual spinal cord compression The quantification of the immunofluorescence involves certain limitations The results only allowed to make an associative inference regarding the relationship between pNR1 expression and pNR2B expression changes in the microglia phenotype

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Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals (Continued)

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Karadimas et al.,[16] 2015	Experimental animal research & retrospective review of pospective clinical trial (AOSpine North America CSM study)	Investigate the role of ischemia-reperfusion injury and the use of riluzole in improving DCM outcomes	Animal model: Five groups of rats (sham, control, riluzole alone, decompression alone, riluzole+ decompression) Clinical trial: 278 DCM patients	Female Sprague-Dawley rats in which a piece of aromatic polyether was inserted underneath the C6 lamina This aromatic polyether serves as a scaffold for the precipitation of inorganic salts, leading to controlled, progressively increased pressure on the cervical spinal cord	Riluzole 8 mg/kg intraperitoneal QD started at 4 weeks after material implantation. Surgical decompression took place 6 weeks after material implantation, and riluzole administration continued until 2 weeks after decompression	Animal study: Rats in the decompression group showed significant declines in forelimb stride length and manual dexterity 1 week after surgery Riluzole-treated rats did not exhibit significant declines in gait parameters in the first week after decompression surgery. Riluzole treatment significantly improved forelimb stride length, forepaw initial contact, and regularity index parameters compared to the decompression-only group ($p < 0.05$) Riluzole administration reduced the proportion of preserved neurons expressing oxidative DNA damage in the rat spinal cord ($p < 0.05$). Riluzole-treated rats displayed a significantly lower proportion of 8-oxoG DNA-positive cells (indicating oxidative damage) *in vitro* ($p < 0.05$). Riluzole reduced depolarization of the mitochondrial membrane potential *in vitro* ($p < 0.05$) Rats receiving combined decompression surgery and riluzole treatment showed significantly improved forelimb stride length compared to decompression surgery alone ($p < 0.05$). Combined treatment significantly improved coordination between forelimbs and hindlimbs compared to the control, riluzole, and decompression groups ($p < 0.05$). Rats treated with the combination approach had superior motor neuron preservation in the cervical spinal cord compared to decompression alone ($p < 0.05$) Riluzole or decompression alone significantly decreased below-level neuropathic pain in DCM rats ($p < 0.05$). Combination of decompression surgery and riluzole administration led to significantly lower microglial activation in the lumbar dorsal horns compared to either treatment alone ($p < 0.05$)	Immunohistochemistry for choline acetyltransferase, neuronal nuclei, protein kinase C–γ, glial fibrillary acidic protein, Iba-1; Double immunofluorescence for 8-oxoG DNA and neuronal nuclei; JC-1 staining for mitochondrial membrane potential	Small sample size of each group One of the authors was the Chairman of AOSpine North America, a not-for-profit foundation, which served as the sponsor of the study

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Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals (Continued)

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Kuroka-wa et al.,[11] 2011	Experimental animal research	To explore the possibility of limaprost alfadex for DCM	Group A: Sham operation without permanent cord compression (receiving distilled water 5 mL/kg BID (n = 6)) Group B: Sham operation (receiving 300 μg/kg limaprost BID (n = 6)) Group C: Cord compression (receiving the vehicle (n = 15)) Group D: Cord compression, receiving the drug (n = 15)	Male Wistar rats, in which a sheet of expandable urethane-compound polymer was inserted in the C5 and C6 sublaminal space	Limaprost alfadex 300 μg/kg PO BID at a concentration of 60 μg/mL	Rats with chronic spinal cord compression demonstrated latent and progressive deterioration in forced locomotion capability 6 to 11 weeks after the induction of compression. Specifically, forelimb stride length decreased significantly ($p < 0.05$) in the decompression group compared to baseline values Rats with the compression treated with limaprost alfadex retained the ability to perform the forced exercise. Notably, the limaprost alfadex treatment group showed no significant decrease in forelimb stride length, indicating preserved forced locomotion capability compared to the decompression-only group ($p < 0.05$)	Spinal cord harvested for motor neuron counts	Small sample size of each group Limaprost alfadex provided by Ono Pharmaceutical Co., Osaka, Japan
Vidal et al.,[22] 2018	Experimental animal research	To assess the efficacy of perioperative methylpred-nisolone in enhancing neurological recovery and evaluate its effect on the inflammatory response following de-compression for DCM	Intervention: 18 mice received decompression with methyl-prednisolone treatment (30 mg/kg) Control: 18 mice received compression with saline treatment	C57BL/6 mice with induced DCM (polyether material implanted underneath C5–6 laminae)	Methylprednisolone 30 mg/kg IV. One dose given 30 minutes before decompression and another dose at 2 weeks postdecompression	Improved locomotor recovery and reduced motor complications following methylprednisolone treatment ($p < 0.05$) (measured using CatWalk system). Preservation of neurons in the spinal cord with methylprednisolone treatment compared to the control group ($p < 0.05$). Modest reduction in parenchymal inflammation with methylprednisolone treatment	Cervical spinal cord homogenates analyzed for cytokines (interleukin [IL]-1α, IL-1β, TNF-α, IL-4, IL-10, IL-6) using Luminex assay Immunohistochemistry used for glial (Iba1, glial fibrillary acidic protein) and neuro-nal (neuronal nuclei, oligodendrocyte transcription factor 2) cell markers	Composition of peripheral white blood cells between humans and mice is different. Thus, the inflammatory response after surgical decompression may differ between mice and humans DCM patients may have other comorbidities, including cardiovascular disease and diabetes, which are not present in the animal model. Therefore, the potential clinical translation of this work to DCM patients will need to control for the relevant side-effects of steroids

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Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals (Continued)

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Tanaka et al.,[25] 2019	Experimental animal research	To evaluate the effect of human recombinant EPO on a rat model of spinal cord compression-induced cervical myelopathy	Sham group (n = 12), Vehicle group (compression+ normal saline; n = 12), low-dose EPO group (compression+ EPO low dose; n = 12), and high-dose EPO group (compression+ EPO high dose; n = 12)	Male Wistar rat model of spinal cord compression-induced cervical myelopathy (expandable polymer implanted underneath C5–6 laminae)	Human recombinant EPO administered subcutaneously: low-dose EPO group received 500 IU/kg QD; high-dose EPO group received 5,000 IU/kg QD of human recombinant EPO. Administration started at 8 weeks postoperatively and continued until 16 weeks	High-dose EPO significantly maintained motor function in the compression groups. Strength improved in the high-dose EPO group throughout the period of EPO administration from 9 to 16 weeks postoperatively ($p < 0.0001$). EPO significantly prevented the loss of motor neurons and decreased neuronal apoptotic cells ($p < 0.0001$). The number of synaptophysin-positive axons was significantly higher in the high-dose group compared to the vehicle group at 10 and 16 weeks postoperatively ($p < 0.005$). High-dose EPO significantly lowered EPO-receptor-positive anterior horn cells ($p < 0.005$). EPO significantly decreased TUNEL-positive cells and Caspase-3-positive cells compared to the vehicle group ($p < 0.0001$ and $p < 0.001$, respectively). High-dose EPO significantly reduced APP-positive cells in the white matter ($p < 0.05$)	H&E, neuronal nuclei, choline acetyltransferase, glial fibrillary acidic protein, allophycocyanin, EPO receptor, 5-HT, growth associated protein 43, synaptophysin, and amyloid precursor protein staining were performed to assess motor neurons, glial cells, and axonal markers. TUNEL and Caspase-3 staining were used to investigate apoptotic cell death	Clinically there are several known side-effects EPO that make the continuous administration of EPO over a long period seem unrealistic
Yamamoto et al.,[30] 2014	Experimental animal research	To investigate the neuroprotective effect of cilostazol on DCM	40 male Wistar rats (group A: sham operation+ vehicle, n = 7; group B: sham operation+ cilostazol, n = 7; group C: compression+ vehicle, n = 13; group D: compression+ cilostazol, n = 13)	Male Wistar rat model of chronic spinal cord compression-induced cervical myelopathy (expandable polymer implanted underneath C5–6 laminae)	Cilostazol 30 mg/kg PO QD for 25 weeks	Preservation of forepaw grip strength: group D had significantly higher grip strength compared to group C at 7 weeks and thereafter ($p < 0.05$); Preservation of forced running capability: group D showed no decrease in locomotion, while group C exhibited progressive deterioration starting at 18 weeks ($p < 0.05$); Preservation of anterior horn motor neurons: group D had a significantly lower loss of motor neurons (7.1%) compared to group C (34.4%) ($p < 0.05$); Decreased number of TUNEL-positive apoptotic cells: group D (compression+Cilostazol) showed significantly lower numbers of apoptotic cells in both gray and white matter compared to group C (compression+vehicle)	Histopathological examination of cervical spinal cords	The results s uggested that the acute effects of surgery were more significant than the inflation of the polymer sheet, which was to occur only in the compression groups after surgery This study was supported by a grant-in-aid and the provision of cilostazol from Otsuka Pharmaceutical Co. The expandable polymer was provided courtesy of Sanyo Chemical Industries, Ltd.

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Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals (Continued)

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Yan et al.,[31] 2019	Experimental animal research	To investigate the effects of Jingshu Keli on DCM	Behavioral tests: 40 rats for gait analysis, divided into 5 groups (control, model (underwent DCM modeling surgery), and 3 Jingshu Keli treatment groups (1.2 g/kg, 2.4 g/kg, and 4.8 g/kg)) Cultured brainstem neurons: obtained from newborn Sprague-Dawley rats	Sprague-Dawley rats with DCM induced by compression. A plastic monofilament fishing line was passed cranially from the C6–7 to the C4–5 interlaminar space and was secured on the dorsal aspect of the laminae at C5 and C6	Jingshu Keli 1.2 g/kg or 2.4 g/kg or 4.8 g/kg PO QD starting from day 7 postoperatively and continued until day 28	Gait Performance (28th day): Jingshu Keli 4.8 g/kg group showed a significant improvement in gait compared to the model group ($p<0.001$) Mechanical Pain (14th and 21st day): Jingshu Keli 2.4 g/kg and 4.8 g/kg groups showed a significant increase in paw withdrawal threshold compared to the model group ($p<0.01$ on day 14, $p<0.001$ on day 21) Thermal Pain (14th and 21st day): Jingshu Keli 4.8 g/kg group showed a significant increase in paw withdrawal threshold compared to the model group ($p<0.05$ on day 14, $p<0.01$ on day 21) Neuronal Excitability: Jingshu Keli, GRb1, and NGR1 significantly reduced the frequency of action potentials by 38.5%, 27.2%, and 25.9%, respectively, and hyperpolarized the resting membrane potential by 15.0%, 13.8%, and 12.1%, respectively. The effects were mediated through modulation of Kir channels ($p<0.05$)	In cell culture, brainstem neurons were prepared from newborn Sprague-Dawley rats. Whole cell patch clamp recordings were used to study the action potentials and K+ currents (KV and Kir) in the cultured cells. Fluorescence immunostaining was conducted to study the Kir3.1 protein in the cells	Small sample size of each group Whether the phosphorylation of Kir3.1 is the reason or result for JSKL promotion on Kir currents remains debatable, uncommon animal DCM model
Yoshizumi et al.,[32] 2016	Experimental animal research	To explore the potential of G-CSF as a pharmacologic treatment for DCM	36 Rats were divided into 3 groups: group A (sham operation+ normal saline), group B (cord compression+ normal saline), and group C (cord compression+ G-CSF)	Wistar rats in which a sheet of expandable urethane-compound polymer was implanted between the C5–6 laminae. The volume of the sheet expands by absorbing tissue water, reaches 230% of the original volume, and remains constant	G-CSF 15 mg/kg QD or normal saline administered subcutaneously 5 days a week	In the prevention experiment, G-CSF preserved motor functions throughout 26 weeks, significantly decreased the number of apoptotic cells at 8 weeks ($p<0.05$) In the treatment experiment, G-CSF administration from 8 weeks after surgery temporarily restored motor function to a level equal to the sham group Motor neuron count: group B (compression+normal saline) had significantly fewer motor neurons compared to groups A (sham+normal saline) and C (compression+G-CSF) ($p<0.001$)	Cervical spinal cords were examined histopathologically using H&E staining. TUNEL staining was performed to assess apoptotic cell death at 8 weeks after surgery	Small sample size of each group, Recombinant human G-CSF was provided by Chugai Pharmaceutical Co., Ltd., Tokyo, Japan Clinically there are several known side-effects which make the continued administration of G-CSF for CSM over long periods seem unrealistic

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Table 3. Summary of studies investigating the pharmacological treatment of DCM in animals (Continued)

Study	Study design	Aim	Study population (# in groups)	Animal model	Drug, dosages, and administration	Outcome(s)	Pathology	Potential biases/ limitations
Yu et al.,[12] 2011	Experimental animal research & postmortem tissue study	To investigate the pathology and apoptotic mechanisms in human DCM and the therapeutic potential of anti-Fas ligand antibody in a mouse model	Human DCM group: 6 patients (61–89 years old) with DCM, 6 patients with motor weakness, sensory disturbances, and spinal cord compression Control group: 4 patients (56–85 years old) without central nervous system conditions 12 Twy/Twy mice	Twy/Twy mice (NPPS gene mutation) which develop extradural calcified deposits at C2–3, spinal cord compression and progressive spinal cord dysfunction	Anti-Fas ligand antibody (MFL3) 50 mg intraperitoneally twice weekly for 4 weeks in Twy/ Twy mice	Human DCM: Severe anterior horn atrophy, neuronal loss, axonal loss, myelin pallor, and gliosis observed in compressed epicentre. Decreased motor neurons (MAP2-positive) and axonal density (NF200-positive) in compressed region. Increased Fas-positive neurons, Fas ligand-positive neurons, and apoptotic cells (TUNEL-positive) in compressed region compared to controls ($p = 0.002$, $p = 0.001$, and $p < 0.05$, respectively) Twy/Twy Mice: Reduced number of Iba1-positive macrophages and reactive microglia in compressed epicentre with anti-Fas ligand antibody treatment. Decreased Iba1-protein expression with anti-Fas ligand antibody treatment compared to saline control ($p = 0.003$). Prevention of worsening of inter-limb coordination and locomotor function	Autopsies performed within 1-30 hours postmortem. Morphological assessment with H&E, Luxol fast blue, and immuno-histochemistry (Fas, Fas ligand, MAP2, CD68, Iba1, TUNEL) in human DCM. Luxol fast blue and H&E staining used to identify atrophy, neuronal loss, axonal loss, and myelin pallor	Small sample size of each group Lack of randomized control group, potential biases from postmortem interval and tissue storage, limited general-izability to other populations, lack of long-term follow-up

DCM, degenerative cervical myelopathy; QD, once a day; TNF, tumor necrosis factor; PO, orally; BID, twice a day; EPO, erythropoietin; TUNEL, terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate-biotin nick end labeling; H&E, haematoxylin and eosin; GRb1, ginsenoside Rb1; NGR1, notoginsenoside R1; G-CSF, granulocyte colony-stimulating factor; Twy/Twy, tiptoe-walking-yoshimura.

logical function in the immediate postoperative period.[36] In addition, data from the recent AO Spine North America CSM study demonstrated that 9.3% of patients exhibited postoperative functional decline and that 44% of operated patients were left with significant neurological deficits 6 months after surgery.[16] Therefore, adjunct medical therapy that could improve or optimize the outcomes of patients undergoing surgical decompression would be valuable.

The pathophysiology of DCM is complex and diverse. Multiple mechanisms are thought to be responsible for the neuronal loss, axonal degeneration and myelin impairment seen in DCM.[37] Mechanical compression of the spinal cord can lead to inflammation, ischemia and apoptosis resulting in spinal cord dysfunction.[38] In addition, histological and immunohistochemical studies in rodents have demonstrated that immediate neurological decline after decompression may be initiated by an ischemia-reperfusion injury and immune reaction in the spinal cord.[16,22] Rapidly released cytokines perpetuate the inflammatory response after decompression.[13] Furthermore, rat spinal cords demonstrate an increase in oxidative stress after decompression. Fig. 1 summarizes the common mechanisms of action of the abovementioned medications.

Riluzole (2-amino-6(trifluoromethoxy)benzothiazole; Rilutek, Sanofi-Aventis Inc., Paris, France) is a sodium channel/glutamate blocker from the benzothiazide group that is the first and only drug approved for the management of amyotrophic lateral sclerosis (ALS) in the United States. Studies have suggested a key role of sodium and glutamate mediated cellular injury in models of spinal cord compression.[39] Therefore, it was hypothesized that riluzole could slow the neurodegeneration process of motor neurons via sodium channels and by decreasing glutamate mediated excitotoxicity.[15,40] Cerebrolysin is a mixture of peptides derived from enzymatic lysis of porcine brains products. Its pharmacodynamics are similar to endogenous neurotrophic factors, and it can readily cross the blood-brain barrier.[41] Cerebrolysin has demonstrated its neuroprotective potential through its action on cellular structural integrity and neurogenesis and has been studied in patients with neurological disorders such as dementia, stroke, and traumatic brain injury.[42-45] Limaprost alfadex is an oral prostaglandin E1 analog that

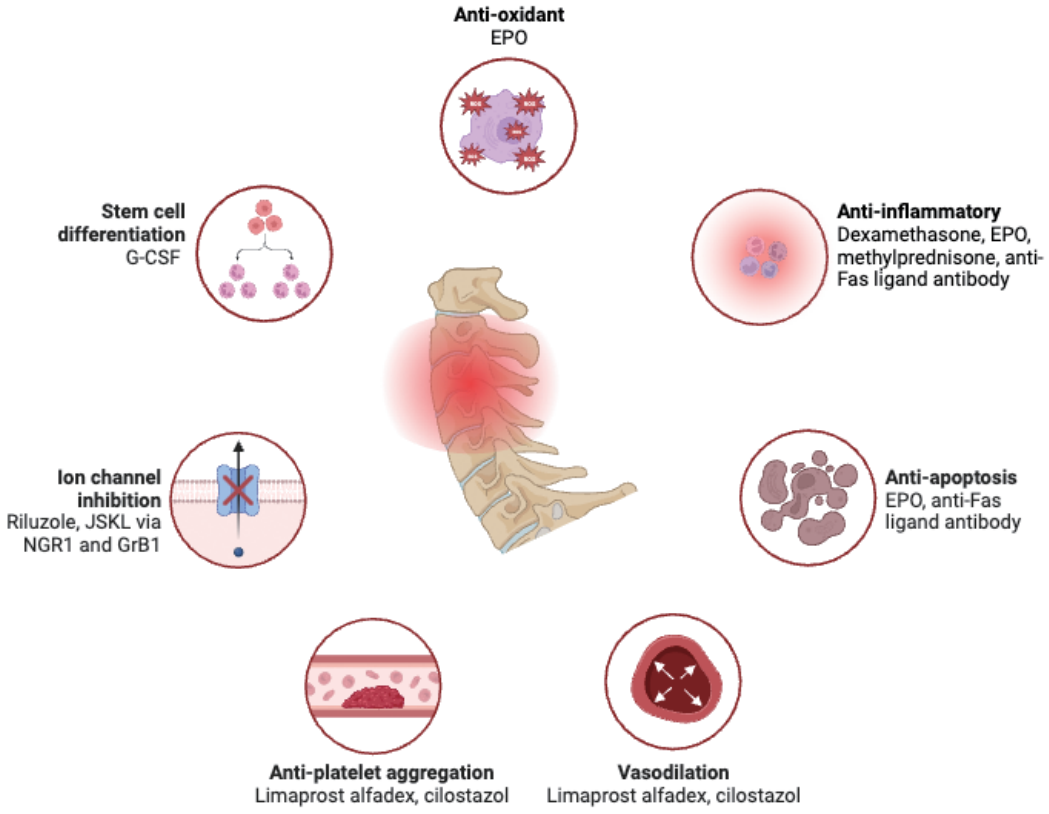

Fig. 1. Target mechanisms of current pharmacological agents used for the treatment of degenerative cervical myelopathy. EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; JSKL, Jingshu Keli; NGR1, notoginsenoside R1; GrB1, ginsenoside Rb1.

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has vasodilatory and antithrombotic properties. Its use was approved for the treatment of lower extremity ischemic symptoms and neurogenic claudication secondary to lumbar spinal stenosis.[46] Glucocorticoids are a potent class of anti-inflammatory and immunosuppressive drugs. Their action on the glucocorticoid receptor mediates multiple pathways that suppress the inflammatory response. Steroids are commonly used in the management of metastatic spinal cord compression.[47,48] Therefore, it was hypothesized that steroids could help mitigate the potential postsurgical inflammatory response and spinal cord reperfusion injury following decompressive surgery in patients with DCM.[22,23] EPO is a glycoprotein cytokine secreted mainly by the kidney in response to hypoxia that stimulates erythropoiesis. In addition, EPO protects tissue from ischemia and reperfusion injury, has antiapoptotic effects and improves regeneration after injury.[49] In the past 2 decades, several studies have demonstrated its neuroprotective benefits in cerebral infarction, brain trauma, and acute spinal cord injuries. In hypoxic conditions, endogenous EPO is secreted by astrocytes in response to low oxygen partial pressure and may act on neurons as an important paracrine neuroprotective mediator of ischemic preconditioning. Locally produced EPO may also protect the neural tissue by promoting angiogenesis.[50,51]

Cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl) butoxy]-3,4-dihydro-2-(1H)-quinolinone) is a potent phosphodiesterase inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator. Its use has been approved in the U.S. Food and Drug Administration and in many Asian countries for the management of intermittent claudication.[52,53] Moreover, nerve conduction velocity and blood flow were significantly higher with the administration of cilostazol to a canine model with cauda equina compression.[54] In addition, cilostazol has demonstrated its neuroprotective effect by reducing the size of ischemic brain infarction in a rat model of cerebral ischemia through inhibition of apoptotic and oxidative cell death.[55] JSKL is a traditional Chinese herbal formula. Previous research demonstrated that some active ingredients of the formula could alleviate pain through the modulation of ion channels. Its active components, NGR1, and GRb1, can suppress voltage-gated K+ channels[56] and activate chloride channels,[57] respectively. G-CSF is a cytokine that promotes differentiation of cells in the neutrophil lineage. It mobilizes bone marrow cells to the peripheral circulation. It has shown to restore damaged spinal cord tissue and it has recovered neural function in rats[32,58] and mice.[59] Fas, also known as Fas antigen or CD95, is a cell surface protein involved in cell death. When it binds to its ligand, FasL, caspases are activated to promote apoptosis. Elevated expression of Fas was associated with neural apoptosis and release of proinflammatory cytokines in a rat model.[60]

Some studies on the pharmacotherapy of DCM did not evaluate any neurologic/functional outcome, but some findings which might be worthy of further investigation. To characterize the effect of glucocorticoids on the postsurgical systemic inflammatory response, Demura et al.[61] investigated the relationship between perioperative steroid administration and IL-6 serum levels in patients with cervical myelopathy treated by laminoplasty. The study concluded that preoperative administration of dexamethasone attenuates the systemic inflammatory reaction to surgery, as demonstrated by decreased postoperative IL-6 levels. Neurotrophic factors play an important role in cell survival and have an antiapoptotic activity on neurons.[62-64] Uchida et al.[65,66] have conducted studies on the applications of neurotrophins in the treatment of DCM. Most of their research was completed using a Twy mouse; a naturally existing mutant rodent that develops spontaneous calcification at the C1–2 vertebral level, which mimics significant compression of the spinal cord between C2 and C3 segments with aging. The above research team successfully achieved adenovirus vector (Adv) mediated transfer of the brain-derived neurotrophic factor (BDNF) to the spinal accessory motor neurons between C1 and C3. They also demonstrated that the number of anterior horn neurons was significantly higher in the Adv-BDNF-transfected mice compared to the control.[67] Two years later, the same team repeated their adenovirus-mediated retrograde transfer with the neurotrophin-3 gene. Once again, mice transfected with the Adv-NT-3 gene showed enhanced survival of anterior horn neurons in the Twy mice chronic cord compression model.[65] Further immunohistochemical studies in 2012 revealed that there was a significant decrease in apoptosis and an increased presence of neurons and oligodendrocytes in the spinal cords of the Adv-BDNF transfected mice.[66]

Several other substances have been investigated in relevant conditions and it may be reasonable to investigate their use regarding DCM. Through a rodent model of compressive thoracic myelopathy, Holly et al.[68] demonstrated that rats fed a diet rich in docosahexaenoic acid and curcumin (DHA-Cur) maintained significantly higher tissue concentrations of spinal cord BDNF both at the level of compression and in the region of lumbar enlargement than those that did not receive dietary treatment. An animal model of DCM underwent either a diet rich in DHA and curcumin or a standard Western diet.[68] The omega-3 fatty acid DHA has demonstrated therapeutic poten-

tial secondary to its effects in decreasing inflammation and providing building material to plasma membranes and to its effects on overall neuronal function.[69] Curcumin is a naturally occurring chemical compound found in turmeric, which has anti-inflammatory and antioxidant properties.[70,71] Together, they might have beneficial effects on neuronal function. Gait analysis revealed significantly improved function in the DHA-Cur group. Moreover, levels of syntaxin-3 were elevated, and levels of lipid peroxidation (4-HNE) were decreased in the DHA-Cur group, suggesting the neural repair potential of this dietary regimen in DCM.

It has been suggested that autophagy promotes neuronal survival under hypoxic conditions.[72] The expression levels of p62, ubiquitinated proteins, and LC3 in mice models of spinal cord compression were examined by Tanabe et al.[72] and p62 was expressed in neurons, axons, astrocytes, and oligodendrocytes under hypoxic stress. These results suggested according to the authors that autophagy induction can be another potential therapeutic target for patients with spinal cord compression or DCM that has not been further investigated so far.

The most common mechanisms implicated in the pathobiology of DCM encompass apoptosis, inflammation, and vascular changes.[70] Considering the vascular nature of DCM, one study[73] examined if renin-angiotensin system inhibitors or other antihypertensors were associated with preoperative functional status and imaging markers of spinal cord compression. In their retrospective study of 266 patients, 37 patients were taking angiotensin-II receptor blockers, 44 were taking angiotensin-converting enzyme inhibitors, and 61 were taking other medications. Patients with hypertension presented with poor preoperative neurological status measured using mJOA and Nurick scores ($p < 0.01$). Moreover, patients with hypertension who were treated with renin-angiotensin system inhibitors (specifically, angiotensin-II receptor blockers) had decreased T2-weighted signal intensity change compared to the untreated patients without hypertension ($p = 0.04$).

Ossification of the posterior longitudinal ligament (OPLL) is a disease that can lead to DCM. Recent studies have demonstrated that the use of H_2-receptor antagonists, that are primarily used in the treatment of gastroesophageal reflux disease, may also be effective in treating heterotopic ossification.[74,75] The therapeutic potential of famotidine was evaluated with a mice model for OPLL.[76] The results of this study showed that administration of famotidine suppressed the progression of the ossification and reduced mortality when administered early in the development of the ossification. Furthermore, Liu et al.[77] examined the suppression by famotidine of osteogenic differentiation in mesenchymal stem cells in patients with OPLL. Patients with DCM and OPLL were treated with famotidine and their ligamentum flavum was later collected during cervical spine surgery. Famotidine at a dose of 100 nM for 3 weeks strongly suppressed mRNA production of multiple osteogenic markers by the mesenchymal stem cells.

While the discussed treatments have potential benefit in the treatment of DCM, they are associated with side-effects and adverse events that should be thoroughly considered. For instance, Riluzole may cause dizziness, gastrointestinal disturbances, hepatotoxicity, and asthenia in ALS.[78] Moreover, its administration requires careful monitoring since it can induce hypersensitivity reactions.[79] Limaprost, an oral prostaglandin E1 analog, has been associated with gastrointestinal disturbances, flushing, and vertigo.[80] Its vasodilatory effects requires careful monitoring in patients with underlying cardiovascular conditions. The use of glucocorticoids, notably dexamethasone in the context of DCM, is accompanied by immunosuppression, delayed wound healing, blood glucose elevations, and a decrease in bone mineral density.[81-83] Its administration significantly delayed fusion rates at 6 months in a randomized controlled trial of patients undergoing ACDF.[24] While EPO exhibits antiapoptotic effects, its administration increases the risk of hypertension, thrombosis, hyperviscosity, and anaphylactic reactions.[84] Although Cilostazol has demonstrated neuroprotective effects in animal models, its systemic vasodilatory mechanisms can lead to serious adverse events, including headaches, palpitations, and diarrhea.[85] Its antithrombotic properties increase bleeding risks, which can be a concern in the perioperative setting of a patient with DCM. The adverse events reported in the included human studies are outlined in Table 4. Overall, the risk-benefit ratio of the pharmacological interventions is a complex interplay of their therapeutic benefits against their side-effects profiles. While animal models provide valuable insight into the neuroprotective properties of these drugs, the translation of these findings to human subjects requires rigorous clinical trials to ascertain their efficacy and safety profiles. Moreover, the majority of findings in human subjects stem from clinical trials with short follow-up or small sample size. To properly inform clinical decisions for the pharmacological treatment of DCM, larger clinical trials with diverse populations are warranted.

The balance of evidence surrounding riluzole's efficacy remains uncertain. While preclinical studies, such as those by Moon et al.[15] and Karadimas et al.[16] have shown neurological

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Table 4. Posology, adverse events, JOA score improvement, and level of evidence of the pharmacological agents trialed in humans

Study	Dose	Adverse events	Significant difference improvement in JOA score	Level of evidence[§]/ sample size	Strength of evidence[¶]
EPO (Eryilmaz et al.[26])	EPO: 3,000 U/kg IV 30 minutes preoperatively spinal cord decompression Methylprednisolone: 30 mg/kg IV 30 minutes preoperatively spinal cord decompression	NS	Yes	1B[†]/n = 110	High
Limaprost alfadex (Sugawara et al.[21])	15 μg PO QD for 3 months	Vertigo, disequilibrium, lightheadedness	Yes	2B/n = 21	Moderate
Riluzole (Rajasekaran et al.[17]/ Fehlings et al.[18] [CSM-Protect])	50 mg PO BID for 1 month	NS	No*	1B[†]/n = 30	Moderate
	50 mg PO BID for 14 days preoperatively and then for 28 days postoperatively	Neck or arm or shoulder pain, arm paraesthesia, dysphagia, and worsening of myelopathy	No*	2B/n = 290	Moderate
Cerebrolysin (Allam et al.[19]/ Sharma et al.[20])	5 mL IM QD for 5 days/week for 4 weeks	Headache, dizziness, rash	Yes	1B/n = 192	High
	5 mL IV QD diluted in 100 mL 0.9% NaCl over 30 minutes for 21 days postoperatively	Headache & dizziness	No	2B[‡]/n = 60	Moderate
G-CSF (Sakuma et al.[33])	5 μg/kg IV QD or 10 μg/kg IV QD for 5 consecutive days	Surgical site infection	Yes**	4/n = 15	Very low
Glucocorticoids (Blume et al.[23]/ Jeyamohan et al.[24])	40 mg IV intraoperatively	Wound healing complications	No*	2B/n = 49	Moderate
	0.2 mg/kg IV intraoperatively Postoperative doses: dexamethasone 0.06 mg/kg IV Q6H for the first 24 hours	Delayed fusion rates at 6 months	No*	2B/n = 112	Moderate

JOA, Japanese Orthopaedic Association; EPO, erythropoietin; NS, not specified; PO, orally; QD, once a day; BID, twice a day; IM, intramuscular; IV, intravenous; Q6H, every 6 hours 6. *Modified JOA score used instead of JOA score. **No p-value reported. [†]No mention of loss to follow-up. [‡]Pilot study. [§]From the Centre for Evidence-Based Medicine, http://www.cebm.net. (see Table 1). [¶]Definition of levels of evidence (LoE) and overall strength of evidence (SoE). Global Spine J 2015;5:262.

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improvements in rodent models, these findings have not been consistently replicated in human trials. Most notably, the CSM-PROTECT[18] trial and the double-blinded, placebo-controlled randomized controlled trial by Rajasekaran et al.[17] did not demonstrate clinical neurological improvement following administration of riluzole. Thus, its clinical applicability remains uncertain, requiring further investigation.

The optimal clinical use of cerebrolysin in the context of DCM remains controversial. Allam et al.[19] demonstrated significant improvement in JOA scores over a 6-month period for the nonoperative management of DCM. However, Sharma et al.[20] did not find significant differences in perioperative JOA and VAS scores. There was improvement in hand function at one year. Considering the conflicting results in these randomized controlled trials, careful consideration must be taken whether cerebolysin is administered in a perioperative or nonoperative context. Future studies should elaborate on the optimal conditions of its administration in DCM patients.

Consistent findings across human studies indicate either improvement or worsening of functional outcomes with each medication. However, studies using glucocorticoids for the management of neurological symptoms presented conflicting results.[23,24,26] Two[23,24] of these studies were used in the perioperative setting and observed no significant difference in myelopathy neurological symptoms scores between groups administered with the glucocorticoid (dexamethasone). However, the third study used a glucocorticoid (methylprednisolone) in combination with EPO preoperatively and found a significant improvement in JOA score and 40-point rating scale compared to the control group. Thus, the effects of the glucocorticoid could be masked by the EPO in this study. Glucocorticoids suggest improvement in locomotor recovery postdecompression surgery in animal models.[22] However, such neurological benefits lack applicability in the clinical setting, as demonstrated by a retrospective cohort study[23] and a randomized controlled trial.[24] Glucocorticoids delayed fusion rates at 6 months and increased surgical wound infection rates. Considering the systemic side-effects associated with glucocorticoids and its inability to provide neurological improvement to DCM patients, caution is advised, especially in patients managed operatively.

Limaprost alfadex improved motor function in rodent models[11] and in a phase 3 randomized double-blinded clinical trial.[21] The results from the latter study should be interpreted with caution considering the small sample size and the absence of control group. The current evidence supports continued investigation (a phase 3 double-blind randomized control trial is currently underway [ClinicalTrials.gov Identifier: NCT02125981]).

EPO has demonstrated neuroprotective effects in both animal and human studies. Clinical trials showed improved quality of life outcomes and JOA scores when combined with methylprednisolone following decompression surgery in DCM patients. The combination with methylprednisolone is a confounding factor, however, regarding the efficiency of EPO per se.

Cilostazol has shown significant preservation of motor function and neural tissue integrity in preclinical studies. These findings suggest that this pharmacological agent holds promise for DCM in animal models. To our knowledge, there are no clinical trials in human subjects that evaluate its efficacy, thus lacking in clinical applicability. Similarly, JSKL exhibits neuroprotective and analgesic effects in animal models, but lacks evidence in humans. Anti-Fas ligand antibody also lacks trials in humans. Only a postmortem[12] and a preclinical mouse study[60] of anti-Fas ligand antibody demonstrated a reduction in inflammation and an improvement in neurological recovery.

G-CSF restored damaged spinal cord tissue and recovered neural function in rats[32,58] and mice.[59] It was demonstrated in a phase I and IIa[33] clinical trial that G-CSF improved motor and sensory outcomes in patients with worsening symptoms of compressive cervical myelopathy. However, this was an open-label trial without a control group and a small sample size (cohort of 15 patients).

Of the treatment regimens that demonstrated significant improvement in mJOA score, administration of EPO with methylprednisolone was supported by level 1B (individual randomized controlled trial with narrow confidence interval) and high strength of evidence, limaprost alfadex by level 2B (cohort study with small sample size) and moderate strength of evidence. G-CSF was supported by level 4 (case series) and very low strength of evidence. Regarding cerebrolysin, one study demonstrated significant improvement in mJOA (level 1B [individual randomized controlled trial with narrow confidence interval] and high strength of evidence), and another did not demonstrate functional improvement (level 2B [randomized controlled trial with a small sample size] and moderate strength of evidence). The pharmacological agents that did not demonstrate improvement in mJOA score were supported by either level 1B (riluzole) or 2B (riluzole, cerebrolysin, glucocorticoids) studies with moderate strength of evidence. Fig. 2 graphically represents the level of evidence pyramid, with EPO combined with methylprednisolone demonstrating the highest level of evidence with functional improvement, followed by limaprost alfadex and cerebrolysin.

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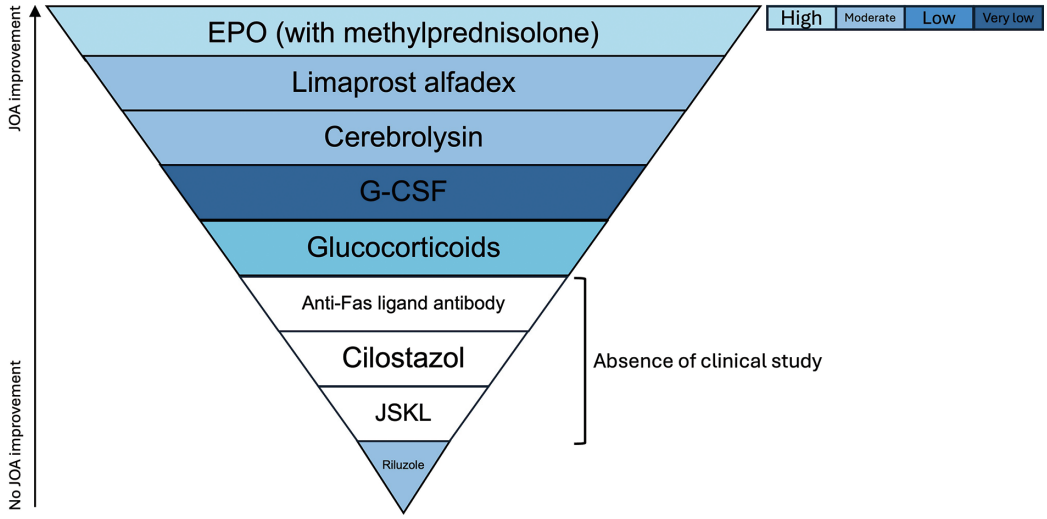

Fig. 2. Strength of evidence and reported functional improvement of human and animal studies. EPO, erythropoietin; G-CSF, granulocyte colony-stimulating factor; JSKL, Jingshu Keli; JOA, Japanese Orthopaedic Association.

The level of evidence of the included studies was classified according to the Levels of Evidence for Therapeutic Studies from the Centre for Evidence-Based Medicine (https://sebm.net). The appraisal is outlined in Table 4 with the criteria for levels of evidence in Table 1. We summarized the level and strength of evidence and the functional outcome improvement of the discussed pharmacological agents in Fig. 2.

LIMITATIONS AND FUTURE DIRECTION

Despite the promise of the pharmacological treatment options for DCM, several limitations hinder the widespread adoption of these treatments. First, half of the studies investigating therapeutic drugs for the treatment of DCM are in animal models. Although this is a pivotal step before pursuing clinical trials in humans, the current studies in humans only include small sample sizes and/or short follow-up, which compromised the reliability of the results. While animal models provide a setting for preliminary experimentation of new pharmacological agents, the results from these studies present several clinical drawbacks. Pharmacokinetics differ between humans and animals, making it more challenging to evaluate potential side-effects in animal studies. Moreover, the pathophysiology of DCM differs between humans and animals, including variations in the composition of peripheral leucocytes.[22] Additionally, the presence of comorbidities can confound results in human trials, considerations for which are generally less extensive in animal studies. The generalizability of lower quality evidence presents an obstacle in translating scientific findings into clinical practice. That said, these results should be interpreted with caution due to the potential presence of significant intrinsic bias within each study. Also, the variation in study settings is significant; some studies present results in the perioperative setting, while others do not take surgery into consideration. By aggregating these studies, we aimed to provide a comprehensive overview of the available evidence for clinicians to appraise and tailor to their practice. In addition, these studies in humans often lack control groups or standardized comparators. Second, the studies investigating the pharmacological treatment of DCM have different endpoints since the medication is initiated at different periods (e.g., preoperative, postoperative, etc.) and different kinds of evaluation. Third, the safety profiles of the available drugs and their interactions are not fully elucidated. As demonstrated in preclinical studies, intrinsic patient characteristics can alter the therapeutic mechanism of a given medication. Lastly, the lack of standardized treatment protocols and guidelines for the medical management of DCM impedes evidence-based practices. Addressing these limitations will be critical to translating experimental findings to clinical practice for patients with DCM.

Our review highlights the heterogeneity in clinical outcomes observed in DCM studies. Future trials should aim to standardize clinical endpoints and incorporate patient-reported outcomes to facilitate a comprehensive evaluation of these interventions. Considering the extensive array of potential drugs available for the management of DCM, maintaining consistent outcomes will enable more robust comparisons among the drugs. Also, considering the potential variations in how these drugs interact with DCM patients, there is a need for rigorous pharmacoki-

netic and pharmacodynamic studies to understand the interplay of genetic predispositions and drug response. Only after the efficacy and safety profiles of these drugs have been established in large trials should standardized treatment protocols and guidelines be developed through consensus among experts and evidence-based practice.

Current guidelines[8] recommend the surgical management of patients with moderate (mJOA 12–14) to severe (mJOA ≤11) DCM, while there is controversy surrounding the management of patients with mild DCM (mJOA 15–17). Considering that the pathophysiology of DCM is so diverse, several treatment modalities have been conceived. That said, other than standard pain management and physical rehabilitation, no standardized guidelines on the nonoperative management of DCM exist. The discussed pharmacological agents were evaluated either in the perioperative or the nonoperative setting. In the nonoperative setting, limaprost alfadex (15 μg PO QD for 3 months; level 2B and moderate strength of evidence) and cerebrolysin (5 mL intramuscularly QD for 5 days/wk for 4 weeks; level 1B and high strength of evidence) could be recommended. EPO combined with methylprednisolone (3,000 U/kg IV EPO and 30 mg/kg IV of methylprednisolone 30 minutes preoperatively decompression; level 1B and high strength of evidence) could be recommended in the perioperative setting, while its effects in the nonoperative setting have not been studied.

For patients with mild DCM, it would be of interest to know whether pharmacologic treatment delays or prevents the need for surgery. Furthermore, it is important to elaborate on the postoperative effects of these drugs on patients. Exploring whether the pharmacologic treatment under investigation delays the clinical manifestations of DCM in patients with concordant radiologic or neurophysiologic findings is of significant interest.

CONCLUSION

This article presents a comprehensive review of the current status of evidence regarding the pharmacological management of DCM. Efforts aim at addressing inflammatory, vascular, and apoptotic pathways. EPO (combined with methylprednisolone), limaprost alfadex and G-CSF report neurological improvements in patients with DCM. Studies administering riluzole or cerebolysin present conflicting results. Glucocorticoids should be avoided as they increase infection rates and delay fusion. Anti-Fas ligand antibody, cilostazol, and JSKL have demonstrated promising results only in animal models. Further translational research ought to be conducted under multidisciplinary collaborations utilizing molecules that have demonstrated therapeutic potential in animal models. Additionally, robustly designed clinical studies are imperative to thoroughly explore the clinical outcomes associated with the aforementioned medications.

NOTES

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"With profound grief and sorrow, we regret to inform you that our co-author and friend Dr. Georgios Klironomos passed away unexpectedly on August 24, 2023, at the young age of 48 years. Before I present a short professional biography of Dr. Klironomos, I want to highlight that Dr. Klironomos was not just an outstanding neurosurgeon, but a real gem as a person with a kind personality and a smile that always touched our hearts. He had been a dear friend and a mentor, eager to help and listen, and a role model to many of us as a father, a husband, and a great doctor-neurosurgeon. He was born in a small village in a small country, i.e., Talanta in Greece, but made it to some of the best institutions and hospitals worldwide. Despite his exceptional career, he would always tell me that nothing else can be important without the happiness and love of our families.

It is not an exaggeration to claim that everyone loved and admired George. He was very charismatic but also a very simple person at the same time. Surely his lovely daughter and wife are deeply sad, but I am sure that they are also greatly proud of George. Personally, I can not yet accept the reality when it comes to George's passing. I wish I could hear his voice again greeting me in a typical Greek manner befitting close friends.

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Dr. Klironomos was an Assistant Professor of neurosurgery at the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell in Hempstead, NY, and an attending Neurosurgeon at Northwell Health, NY, mainly at the South Shore University Hospital, with a subspecialization in neuro-oncology, skull base, and cerebrovascular neurosurgery. He was awarded as the top neurological surgeon in Long Island, New York for 2023. Before that, he was a Clinical Assistant Professor in Neurosurgery at the University of Pittsburgh. Moreover, he received extensive fellowship training at a high level in cerebrovascular and skull base neurosurgery at North Shore/Lenox Hill University Hospital in New York and in neurooncology and skull base (incl. endoscopic) neurosurgery at Toronto Western Hospital of the University of Toronto in Canada. Additionally, he also had other positions throughout his career, including research roles, and participated in many publications in major journals. He had a Ph.D. and an M.Sc. degree from the University of Patras, Greece, where he also completed his undergraduate studies in medicine with the 2nd highest grade among his class.

The whole team would like to honor George for his contribution to neurosurgery and medicine and offer our sincere condolences to his family."

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