British Medical Bulletin, 2024, **151**:49–68
https://doi.org/10.1093/bmb/ldae009
Advance Access Publication Date: 2 September 2024

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Invited Review

Pharmacological management of secondary chronic spinal cord injury: a systematic review

Filippo Migliorini[†,‡], Federico Cocconi[‡], Luise Schäfer[†], Francesco Simeone[‡], Madhan Jeyaraman[§], and Nicola Maffulli[¶,‖,,*]**

[†]Department of Life Sciences, Health, and Health Professions, Link Campus University, Via del Casale di S. Pio V, 44, 00165 Rome, Italy, [‡]Department of Orthopaedics and Trauma Surgery, Academic Hospital of Bolzano (SABES-ASDAA), via Lorenz Boelher 7, 39100 Bolzano, Italy, [§]Department of Orthopaedics, ACS Medical College and Hospital, Dr MGR Educational and Research Institute, Poonamallee High Rd, Velappanchavadi, Chennai 600077, Tamil Nadu, India, [¶]Department of Medicine and Psychology, University of Rome La Sapienza, via dei Marsi 78, 00185 Rome, Italy, [‖]School of Pharmacy and Bioengineering, Keele University Faculty of Medicine, Hornbeam Building, Keele ST5 5BG, UK, and [**]Queen Mary University of London, Barts and the London School of Medicine and Dentistry, Centre for Sports and Exercise Medicine, Mile End Hospital, 275 Bancroft Road, E1 4DG London, UK

[*]Correspondence address. Queen Mary University of London, Mile End Hospital, 275 Bancroft Road, London E1 4DG, England. E-mail: n.maffulli@qmul.ac.uk

Received 10 January 2024; Revised 10 July 2024; Accepted 20 August 2024

Introduction: Spinal cord injury (SCI) may bring lifelong consequences for affected patients and a high financial burden to the health care system.

Source of data: Published peer-reviewed scientific articles identified from EMBASE, Google Scholar, PubMed and Scopus.

Areas of agreement: Surgery and blood pressure management are the main targets in acute SCI to avoid secondary damage.

Areas of controversy: The management of secondary chronic SCI is challenging, with unpredictable outcomes.

Growing points: Given the lack of consensus on pharmacological therapy for acute and secondary chronic SCI, the present study analyses the currently available drugs and treatment options to manage secondary chronic SCI.

Areas timely for developing research: Different approaches exist for the pharmacological management of secondary chronic SCI. One of the most investigated drugs, 4-aminopyridine, improves central motor conduction

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and shows improvement in neurological signs. Positive results in different areas have been observed in patients receiving the anti-spastic drugs tizanidine and baclofen or Granulocyte colony-stimulating factor. Growth hormone showed only minimal or no significant effects, and the therapy of secondary chronic SCI with riluzole has been poorly researched to date.

Key words: secondary spinal cord injury, SCI, chronic, pharmacological therapy

Introduction

Spinal cord injury (SCI) is a very major destructive injury to the central nervous system, leading to lifelong consequences and a high financial burden to the health care system.[1,2] The injury can result from physical trauma or atraumatic events, such as reduced blood flow in the CNS, inflammatory processes or oncological diseases.[3,4] SCI causes major motor, sensory and autonomic dysfunctions.[5] Overall, the annual incidence of SCI ranges from 15 to 40 cases per million people.[6,7] In >70% of patients, SCI is associated with other lesions.[8] A relevant rate of complications characterizes the acute and later phases of SCI due to multiple concomitant injuries.[8,9] Therefore, expectancy and quality of life have been reduced in SCI patients.[10,11] During acute SCI, the main goals are surgical and blood pressure management to avoid secondary damage.[12–14] SCI can be classified into primary (<48 hours), delayed (48 hours to 14 days), secondary (14 days to 6 months) and chronic (> 6 months).[15,16] Chronic SCI is estimated to affect 300 000 to 1 million US population.[17,18] Given the lack of consensus on pharmacological therapy for acute and chronic SCI, the present investigation analyses the currently available drugs and treatment options to manage chronic SCI.

Methods

Eligibility criteria

The total number of clinical investigations about the pharmacological management of secondary chronic SCI was accessed. Considering the authors language abilities, papers published in English, German, Italian, French, and Spanish were eligible. Only publications with levels I to IV of evidence aligned with the Oxford Centre of Evidence-Based Medicine were considered.[19] Opinions, reviews, letters, and editorials were not eligible, as were in vitro, biomechanics, biomechanics, computational, and cadaveric investigations. Lacking quantitative data under the outcomes of interests dictated the exclusion of the study.

Search strategy

This systematic review was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the 2020 PRISMA statement.[20] The subsequent PICO algorithm was employed for the database search involved:

- P (Problem): secondary chronic SCI;
- I (Intervention): pharmacological chronic SCI management;
- C (Comparison): neuro-regenerative drug treatment, placebo;
- O (Outcomes): neurological function recovery, treatment safety, efficacy, and side effects.

In April 2024, PubMed, Web of Science, Google Scholar and Embase were explored without limitations. The medical topic headings utilized for the database search are reported in the appendix.

The list of references with the related full-text papers was evaluated by hand.

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Selection and data collection

Two authors (L.S. & F.C.) individually searched each database. A screen selection by the hand of the resulting title was conducted, and only the articles with appropriate subjects which matched the PICO algorithm were reviewed. The full texts of the abstracts deemed of interest were accessed. A third senior author (N.M.) reviewed and settled any discrepancies.

Data items

Two authors (L.S. and F.C.) individually collected data. The subsequent information was extrapolated: author and year, name of the journal and study type, duration of the follow-up, number of recruited patients, mean age, percentage of women, type of pharmacological treatment and main findings.

Assessment of the risk of bias and quality of the recommendations

The Cochrane Handbook for Systematic Reviews of Interventions was used to determine the possibility of bias.[21] Two reviewers (L.S. & F.C.) individually assessed the bias risk in the extracted studies. The revised Risk of Bias assessment tool (RoB2)[22,23] of the Cochrane tool for assessing Risk of Bias in randomized trials (RoB) has been used to review randomized controlled trials (RCTs).[24] The following biases were considered: originating from the randomization process, deriving from deviations from planned interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool was used to assess nonrandomized controlled trials (non-RCTs).[25] The assessment of potential bias in non-RCTs resulted in seven different domains. Two domains were used to detect possible confounding elements before the beginning of the study and to compare them with the nature of the patient selection. Another domain assessed bias in the classification during the intervention. The final four domains evaluated the methodological quality after implementing the intervention comparison. These domains relate to deviations from previously intended interventions, missing data, erroneous assessment of outcomes, and bias in the selection of reported outcomes. The Robvis Software (Risk-of-bias VISualization, Riskofbias.info, Bristol, UK) allowed to produce the figure of the ROBINS-I.[26]

Synthesis methods

For descriptive statistics, the IBM software version 25 c was used. For continuous variables, the arithmetic mean and standard deviation were used.

Results

Study selection

The systematic bibliography search evidenced 251 investigations about the subject of interest. Of them, 104 articles were not considered because they were identical. After screening the abstracts of the remaining 147 articles, 110 studies were excluded because the inclusion criteria were not respected. In detail, the causes that led to not being published included inadequate study design ($N = 52$), inadequate strength of results ($N = 12$), not evaluating the chronic phase of secondary SCI ($N = 41$), and language accessibility ($N = 5$). Additionally, 21 articles were not included because of lacking information on the outcomes of interest. The present review includes, therefore, 16 different investigations. Of them, 14 were RCTs, and two had a prospective study design. The results of the literature search are shown in Fig. 1.

Methodological quality assessment

The Cochrane risk of bias assessment tool (ROB2) was used to investigate the risk of bias in 87.5% (14 of 16) of the investigations included in the present review, as they were RCTs. Given the established comparability of the intervention groups at baseline, bias related to the randomization process was rated with a minimal risk of bias. Risk of bias according

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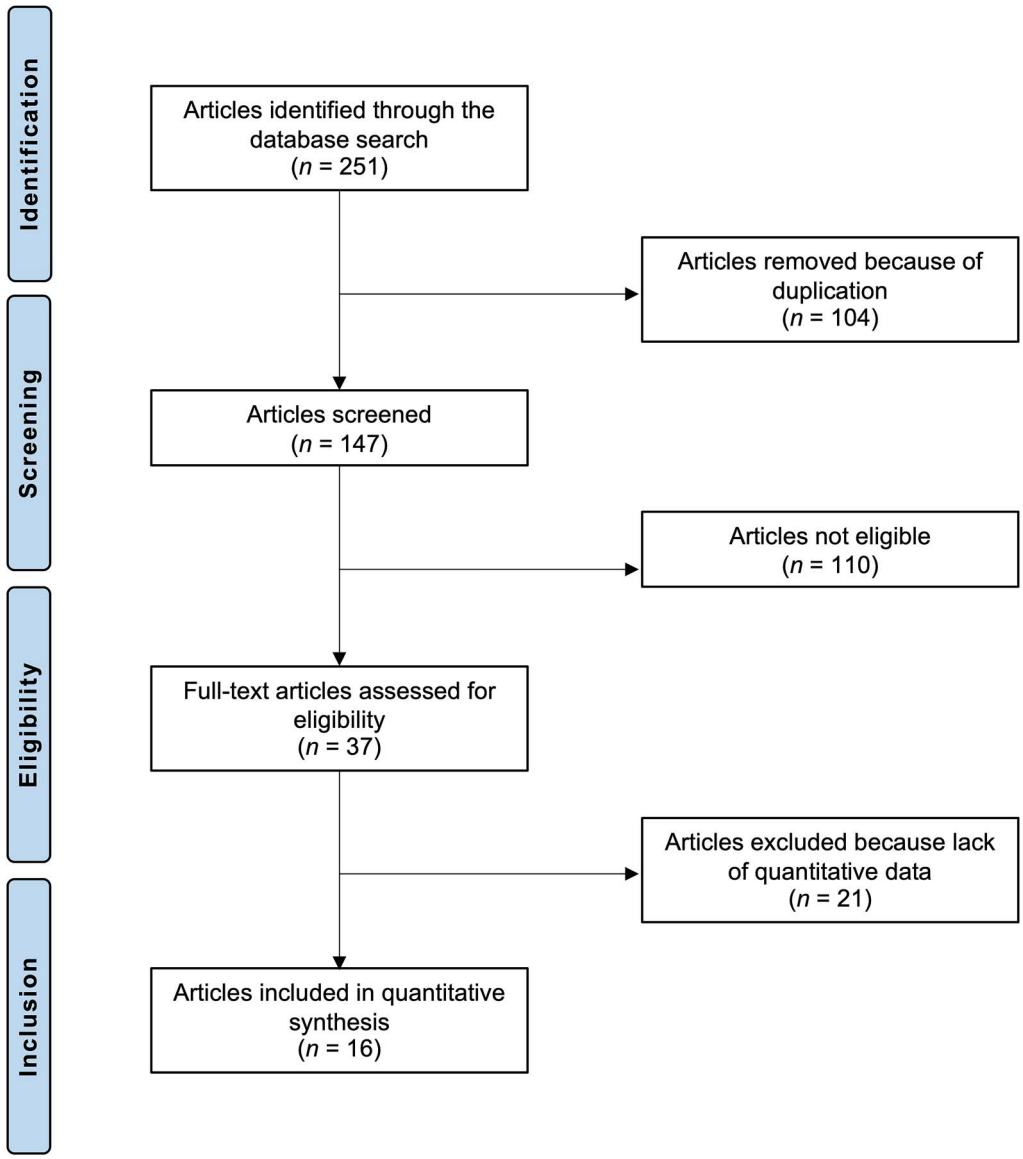


Fig. 1 PRISMA flow chart of the literature search.

to the deviations from the intended intervention, absent outcome data, the selection of the reported outcome, and the measurement of the outcome were occasionally noted with some concerns, conducting to a low to moderate overall risk of bias in these domains. Missed assessor blinding resulted in a high risk of bias in measuring the outcome in one of the articles; in all other studies, a low to moderate risk was present in this domain. In conclusion, the risk of bias graph highlighted the good quality of the methodological assessment of RCTs (Fig. 2).

The ROBINS-I risk of bias tool estimated the risk of bias of non-RCTs. 12.5% (2 of 16) of the included trials were non-RCTs. Serious or critical risks of bias were not noted. The authors reported

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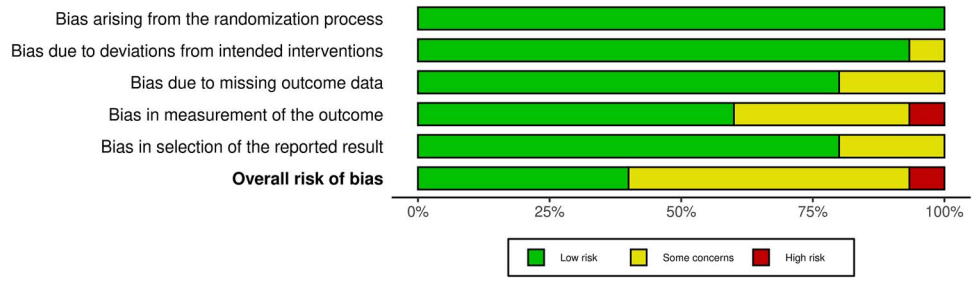


Fig. 2 Cochrane risk of bias 2.0 tool (RoB2 tool).

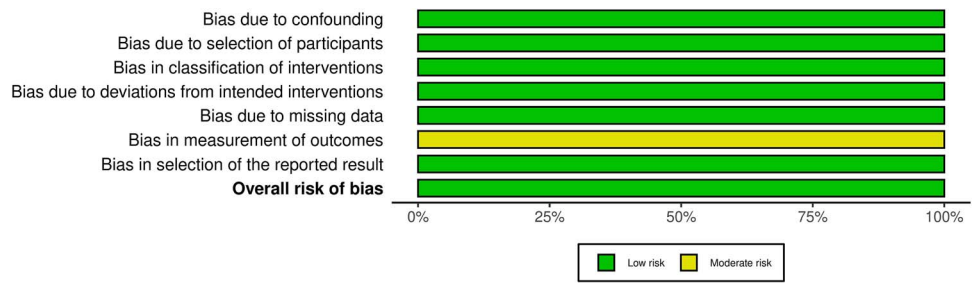


Fig. 3 The ROBINS-I of non-RCTs.

high-quality allocation concealments, resulting in comparable study groups at baseline and leading to a low risk of bias based on confounding and the participant selection process. The risk of bias in the intervention classification resulted uniformly low, as neither nondifferential misclassification nor differential misclassification was identified. A mild risk of bias was reported in both reviewed studies because of lacking assessor blinding. No concerns were raised about the selection of the reported results. The overall risk of bias was low due to the high methodological quality of the included studies (Fig. 3).

Study characteristics and results of individual studies

Data from 932 patients were collected. Of them, 16.2% were women. 94.6% (882 of 932) had an incomplete spinal cord injury with decreased motor and sensory function. The mean age of the patients was 40.3 ± 6.0 years, and the mean length of the follow-up was 7.4 ± 4.2 months.

The benefits of 4-aminopyridine (4-AP) in secondary chronic SCI therapy are reported in terms of assisted walking, sphincter control, male sexual function and reduction of chronic pain, especially in those patients with partial spinal cord lesions. Further, it is suggested that the central motor conduction is enhanced. However, some studies showed no significant effect of drug treatment with 4-AP in chronic secondary SCI patients. Tizanide and Baclofen have a positive impact on motor sensory recovery. Tizanide exerts a more substantial suppressory activity on the knee extensors and flexors muscles. Baclofen exhibits a more significant suppressory activity on the knee flexors; volitional torque was not reduced in both group. GCS-F showed significant motor, sensory, and functional improvement at the 6-month follow-up. GH is considered a potential drug for improving motor function in chronic secondary SCI. The present study could not confirm these assumptions. GH showed no statistical differences in the management of SCI in one study and only minimal improvements at one-year follow-up in another. The activity of riluzole was evaluated in only one

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trial, which included seven patients, and led to a considerable reduction in the highest point component of the ankle dorsiflexion torque of the flexion withdrawal reflex. Patient characteristics, generalities and main results of the studies included in the systematic review are reported in Table 1.

Discussion

Secondary SCI sets in a few minutes after primary SCI.[27,28] Multiple phases characterize secondary SCI: from the primary injured tissue, there is a continuous amplification of the damage, especially inflammation-induced apoptosis of surrounding cells and axotomy of living neurons.[29,30] Moreover, secondary SCI can be subdivided into three phases: acute, subacute and chronic.[31,32] Chronologically, the period from the primary injury until 48 hours is considered acute SCI, while the subacute phase continues 2 weeks after the injury.[16,33] Meanwhile, the chronic phase sets on from 2 weeks after the injury and continues for years.[34,35] Microscopically, acute secondary SCI results in neuronal excitotoxicity due to biochemical cellular dysregulation, which leads to high calcium concentration and increased intracellular reactive oxygen content and glutamate levels.[36–38] This reduces and modifies the production of nucleic acid, proteins and phospholipids, leading to neurological impairment.[36–38] Haemorrhage in the spinal cord results from lesions of blood vessels followed by a migration of different immunological elements such as neutrophils, monocytes, macrophages T- and B-lymphocytic cells to spinal tissues, which release several different inflammatory cytokines leading to neuron inflammation.[18,39,40] If this cascade of events persists, it is followed by the subacute phase, which consists of a remodelling process triggered by neuronal apoptosis, axonal demyelination, Wallerian deterioration, axonal deterioration and glial scar formation, leading to chronic SCI.[41–43] Macroscopically, the main structural alterations of the central nervous system are cystic cavitation, axonal dieback, and development of glial scar, which characterize chronic secondary SCI.[30,31]

Similarly, given the deficiency of neuronal plasticity and regenerative cells, the ability of CNS to spontaneously regenerate is dramatically limited.[44,45] On the one hand, the inflammatory cascade released after SCI positively impacts the elimination of residual cellular and myelin debris. On the other hand, the expansion of damage to the perilesional tissues is caused by pro-inflammatory cytokines and free oxygen radicals.[46,47] Cystic cavitation results from the lost volume of the injured CNS, which aims to produce a barrier to limit the local damage.[15] However, the diffuse multiple cyst lesions impair axonal regeneration by forming a physical obstacle to the inflow of substrates necessary for the neuronal healing process.[15,40] Moreover, the glial scars are caused by the local proliferation of astrocytes and secrete growth-inhibiting proteoglycan.[18,48]

The study of the pathophysiological steps present in chronic SCI is paramount to point out possible targets of pharmacological therapy aiming to limit the consequences of SCI or stimulate axonal regeneration when possible.[49,50]

One of the most investigated drugs is 4-AP,[12,51,52,53,54–56,57–58,60] a potassium channel blocker stimulating synaptic transmission and signal driver on demyelinated axons.[61,62] 4-AP is a neuroregenerative drug which mainly targets the reduction of spasticity.[63] Therefore, it is routinely used in patients with multiple sclerosis to improve their general health status and walking kinetics.[64,65] Several authors reported benefits from 4-AP therapy in chronic SCI patients in terms of assisted walking, sphincter control, male sexual function and reduction of chronic pain, especially in those patients with partial spinal cord lesions.[51,54–56,57–58] Qiao *et al.*[57] analysed the potential benefits of one administration orally (10 mg) of 4-AP on motor-evoked potentials registered from the paralytic extremities in SCI patients. After that, the motor cortex has been stimulated by transcranial magnetic waves. They highlighted that after the intake of 4-AP, chronic SCI patients showed amplification of motor-evoked potential magnitude and decreased latency and cortical stimulation limit.[57] No parallel alterations were observed in the retardation or magnitude of

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Table 1 Generalities, patient characteristics, and main results of the included studies

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
Cardenas et al., 2007[51]	Spinal Cord	USA	RCT	> 18	1	30	44.0	27.0	0	30	4-AP (Fampridine) 25 mg	Assessing the safety and potential efficacy of two different doses of 4-AP (Fampridine 25 mg b.i.d. and 40 mg b.i.d.) compared with placebo in subjects with chronic, motor-incomplete SCI.	Treatment with 4-AP (Fampridine 25 mg) was associated with significantly improved SGI in subjects with chronic motor-incomplete SCI and in subjects with baseline Ashworth scores greater than the median it was associated with significantly reduced spasticity. With appropriate patient selection and gradual dose titration, sustained release 4-AP (Fampridine) can be well tolerated. 4-AP (Fampridine) should be investigated further as a potential treatment for spasticity in patients with chronic SCI.
						30	42.0	13.0	0	30	4-AP (Fampridine) 40 mg		
						31	38.0	23.0	0	31	Placebo		
Cardenas et al., 2014 (SCI-F301)[52]	Spinal Cord	USA	RCT	> 18	5	114	41.6	12.3	0	114	4-AP (Fampridine) 25 mg	Evaluation of the efficacy and safety of 4-AP (Fampridine) 25 mg twice daily for moderate-to-severe spasticity in patients with chronic SCI.	The between-treatment difference was not significant for either the Ashworth score or the SGI and neither were the secondary end points (Penn Spasm Frequency Scale; the motor/sensory score from the International Standards for Neurological Classification of SCI; Clinician's Global Impression of Change of neurological status; and the International Index of Erectile Function (men) or the Female Sexual Function Index (women)). Fampridine was generally well tolerated; TEAEs and serious TEAEs were reported with similar frequency between treatments.

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
				98	40.1	13.3	0	98	Placebo				
Cardenas et al., 2014 (SCI-F302)[52]	Spinal Cord	USA	RCT	5	103	41.3	16.5	0	103	4-AP (Fampridine) 25 mg			
					100	41.5	14.0	0	100	Placebo			
Chu et al., 2014[81]	Arch Phys Med Rehabil	California	RCT (cross over design)	> 6		10	49.0	0.0	0	10	Tizanidine	Investigating the effects of antispastic drugs baclofen and tizanidine on reflexes and volitional tasks.	Reduced stretch reflex activity was observed after the administration of either tizanidine or baclofen. Tizanidine had a stronger inhibitory effect on knee extensors and plantar flexors whereas baclofen had a stronger inhibitory effect on the knee flexors. The effects of these drugs on strength during isometric and isokinetic tasks varied across participants, without a consistent reduction in torque output despite decreased electromyographic activity.
											Baclofen		
											Placebo		
Derakhshanrad et al., 2018[91]	J Neurosurg Spine	Iran	RCT	6	6	56	35.1	12.5	0	56	G-CSF	Investigating the efficacy of G-CSF administration for chronic incomplete traumatic SCI.	The mean improvement in ASIA motor score in the G-CSF group was significantly more than in the placebo group. The mean light touch and pinprick sensory scores, respectively, increased in both groups. Evaluation of functional improvement by the IANR-SCIFRS instrument revealed significantly more improvement in the G-CSF group. A significant difference was observed in functional improvement between the two groups as measured by SCIM-III instrument. Administration of G-CSF for incomplete chronic SCI is associated with significant motor, sensory, and functional improvement.

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
				58	37.2	17.3	0	58	Placebo				
Derakhshanrad et al., 2019[92]	J Neurosurg Spine	Iran	RCT	3.7	6	28	36.5	10.7	0	28	G-CSF	Determining the safety and efficacy of G-CSF administration for neurological and functional improvement in subacute, incomplete traumatic SCI.	After 6 months of follow-up, the AIS grade remained unchanged in the placebo group, whereas it improved in the G-CSF group. Change in ISNCSCI motor score in the G-CSF group was significantly greater than in the placebo group. Evaluation of functional improvement according to the IANR-SCIFRS instrument revealed significantly more functional improvement in the G-CSF group. A significant difference was observed between the two groups as measured by the SCIM-III instrument. Incomplete subacute traumatic SCI is associated with significant motor, sensory, and functional improvement after administration of G-CSF.
				3.9		26	31.0	7.7	0	26	Placebo		
Donovan et al., 2000[53]	Spinal Cord	USA	RCT (cross over design)	10.9		12	46.9	8.3	5	7	4-AP	Determing the efficacy of 4-AP in the treatment of SCI patients for neurologic impairment, pain and spasticity.	No significant differences were noted in the clinical and EMG parameters at the times measured. Individual changes in sensory function were reported by some patients in both the placebo and 4-AP trials, however mean values were not robust. Frequently, patients complained of unpleasant symptoms during the 4-AP infusion. The intravenous route may not be the best way to administer 4-AP as no short term benefits were observed.

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
Esclarin-Ruz et al., 2021[99]	Spinal Cord	Spain	RCT	Placebo 9.1	12	28	36.3	17.9	0	28	GH	Investigating the possibility to use exogenous GH administration for motor recovery in chronic traumatic incomplete SCI and establishing the safety and efficacy of a combined treatment of subcutaneous GH (or placebo) and rehabilitation.	Combined treatment of GH plus rehabilitation treatment is feasible and safe. GH but not placebo increases the ISNCSCI motor score. Motor-score increment was marginal after one-year combined treatment. Intensive and long-lasting rehabilitation program per se increases the functional outcome of SCI individuals (measured using SCIM III and WISCI II).
				8.2		26	36.2	15.4	0	26	Placebo		
Grijalva et al., 2010[54]	Arch Med Res	Mexico	RCT (cross over design)	> 36	12	14	29.0	28.6	14	0	4-AP	Testing the functional effect of high doses of 4-AP on patients with chronic complete SCI with cord continuity at the site of injury demonstrated by magnetic resonance imaging.	Positive changes were seen mainly in patients with cyst or atrophy of the injury site. High doses of 4-AP in the studied population produced several functional benefits not observed using lower doses. Patients with chronic complete SCI but without cord section on MRI obtained several functional benefits with high doses of 4-AP (assisted walking, sphincter control, male sexual function)
Grijalva et al., 2003[55]	Pharma-cotherapy	Mexico	RCT	91.2	12	12	34.0	16.0	0	12	Placebo 4-AP	To study the efficacy and safety of 4-AP, and to document sensorimotor changes after discontinuation of the drug in patients with long-term SCI.	Positive gains in motor function, sensation, and independence occurred more frequently in patients receiving 4-AP than those receiving placebo. Significant functional improvement was noted in those treated with 4- AP. When each evaluation scale was considered separately, significant improvement was seen only in motor function. Persistent effects of the drug were assessed at week 24 in the group that initially received 4-AP. A persistent, significant 4-AP effect was observed in evaluations of sensation and independence. The drug is safe; after starting 4-AP therapy, patients must be carefully monitored for the possible occurrence of peripheral vasospasm.

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
				79.2	13	33.0	16.0	3	10	Placebo			
Hansebout et al., 1993[56]	J Neurotrauma	Canada	RCT (cross over design)	> 18		8	39.4	37.5	2	6	4-AP	Investigating the ability of 4-AP to restore conduction of impulses in demyelinated nerve fibers.	Administration of the drug was associated with significant temporary neurologic improvement in patients with incomplete SCI. Improvements in neurologic status following drug administration included increased motor control and sensory ability below the injury, and reduction in chronic pain and spasticity. The effects persisted up to 48 h after infusion of the drug, and patients largely returned to preinfusion status by three days. Compared with the more rapid elimination of the drug, these prolonged neurologic effects appear to involve a secondary response and are probably not a direct expression of potassium channel blockade.
Martin-Rojas et al., 2020[110]	J Pers Med	Spain	RCT	> 18	12	23	35.0	17.1	0	23	Placebo GH	Studying the safety and efficacy of GH treatment in incomplete chronic traumatic SCI.	Combined treatment of GH plus rehabilitation treatment is feasible and safe. GH but not placebo slightly improves the SCI individual motor score. Moreover, intensive and long-lasting rehabilitation program per se increases the functional outcome of SCI individuals.
						23			0	23	Placebo		

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
Qiao et al., 1997[57]	J Neurotrauma	Canada	prospec-tive	> 12		19	37.2	31.6	4	15	4-AP	Testing the hypothesis that 4-AP ameliorates central motor conduction deficits in individuals with SCI.	The administration of a single oral dose of 10 mg 4-AP in SCI patients resulted in statistically significant increases in MEP amplitude and reduction in MEP latency and cortical stimulation threshold. The absence of parallel alterations in the latency or amplitude of segmental reflex measures suggests that the MEP changes are attributable to enhanced central motor conduction. Reduction in CMCT time supports this interpretation. The electrophysiological changes brought about by 4-AP, which are most likely attributable to fast, voltage-gated K+ channel blockade and overcoming of conduction deficits due to demyelination, and/or enhanced neuroneuronal transmission, appear to provide the physiological substrate for the enhanced motor function.
						13		30.8	0	0	healthy controlgroup without treatment		
Segal et al., 1999[59]	Pharmacother-apy	California	RCT	> 24	3	6	51.8	14.3	2	4	4-AP 30 mg blinded	Determining the effects of the long-term administration of 4-AP on sensorimotor function in humans with long- standing SCI.	Composite motor and sensory scores had statistically significant increases at three months. Also spasticity decrease significant. Serial biochemical profiles and electroencephalographs were unchanged from baseline, and no clinically significant drug toxicity was encountered. Each patient who received immediate-release 4-AP 30 mg/day showed a response in one or more of the outcome measures.
						5	49.2		3	2	4-AP 6 mg blinded		
						10	49.0		4	6	4-AP 30 mg cognizant		

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Table 1 Continued

Author, year	Journal	Country	Design	Time since injury (month)	Last follow up (month)	Patients (n)	Mean age (mean)	Female (%)	Complete injury (n)	In-complete injury (n)	Drug Treatment (name)	Purpose of the study	Main Findings
Segal et al., 1998[58]	J Spinal Cord Med	California	prospec-tive	> 12		9	47.0	0.0	0	9	4-AP 10 mg	Describing efforts to delineate the pharmacological effects of 4-AP on gait parameters in SCI humans who have retained some capacity to ambulate bipedally.	4-AP appears to enhance gait in a subset of humans with SCI and suggest that the pharmacological effects of 4-AP may have clinically significant application in the restoration of useful motor function.
Theiss et al., 2011[116]	J Neurophysiol	USA	RCT	> 12		7	43.7	14.3	0	7	Riluzole 50 mg	To probe the contribution of spinal neuron persistent sodium conductances to reflex hyperexcitability in human chronic SCI.	Riluzole significantly decreased the peak ankle dorsiflexion torque component of the flexion withdrawal reflex. Peak maximum voluntary torque in both dorsiflexion and plantarflexion directions was not significantly changed. Average dorsiflexion torque sustained during the 5-s isometric maximum voluntary contraction increased significantly. There was no effect on the monosynaptic plantar and dorsiflexor H-reflex responses.
											Placebo		
van der Bruggen et al., 2001[60]	J Neurol	Netherlands	RCT (cross over design)	> 18		20	44.5	5.0	0	20	4-AP	To test the efficacy of 4-AP on functional status, walking speed and vibration perception in patients with chronic, incomplete SCI.	No significant benefit was found on functional status. A statistically significant treatment effect was found on the VPT in the left fingers. Patients receiving 4-AP treatment responded less favourably than patients receiving placebo. Neither comfortable nor maximum walking speed altered significantly following 4-AP treatment.
											Placebo		

RCT: randomized controlled trial; 4-AP: 4-aminopyridine; G-CSF: granulocyte colony-stimulating factor; GH: growth hormone; SCI: spinal cord injury; SGI: Subject Global Impression; TEAEs: treatment-emergent adverse events; ASIA: American Spinal Injury Association scale; IANR-SCIFRS: International Association of Neurorestoratology-Spinal Cord Injury Functional Rating Scale; SCIM-III: Spinal Cord Independence Measure; ISNCSCI: International Standards for Neurological Classification of Spinal Cord Injury; WISCI II: The Walking Index for Spinal Cord Injury; MEP: motor evoked potentials; CMCT: central motor conduction time; VPT: vibration perception threshold

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segmental reflex measures.[57] This finding suggests that the central motor conduction is enhanced.[57,66] This may result from the blockade of the fast, voltage-gated K+ channel and the overrunning of transmission impairments from demyelination, which leads to a stimulating environment for motor function.[57,66] Moreover, Grijalva et al.[54] conducted a study on 14 patients with complete SCI who received an extended period of 4-AP to treat chronic SCI. At the last follow-up at 12 months, they reported several improvements in the neurologic condition in terms of walking ability with orthopaedic devices, control of bladder and anal sphincters, improvement of somatosensory evoked potentials and psychogenic erection.[54] Meanwhile, other authors[52,53,60] did not provide evidence of a significant effect of 4-AP medical treatment in SCI chronic patients.

Other investigated drugs are tizanidine and baclofen, which are antispastic drugs.[67] Tizanidine is an imidazoline derivative and is an alpha-2 receptor agonist.[68,69] Tizanidine acts on interspinal neurons to block the discharge of stimulating amino acids such as glutamate and aspartate.[70,71] Therefore, tizanidine stimulates the presynaptic inhibition of motor neurons with a relevant effect on spinal polysynaptic pathways.[72,73] Baclofen is a gamma-aminobutyric acid $(GABA)_B$ receptor agonist.[74] The CNS is primarily inhibited by the neurotransmitter GABA.[75] Central nervous system (CNS) has two different types of GABA receptors: $GABA_A$ and $GABA_B$.[76,77] $GABA_B$ receptors are placed on pre- and postsynaptic neurons in the CNS and peripheral nervous system.[75,78] Baclofen has an all-around effect on the spinal cord because it inhibits the transmission of monosynaptic and polysynaptic reflexes, relaxing spasticity.[79,80] One clinical trial included in the present review compared the effect of baclofen and tizanide in 10 chronic SCI patients.[81] Both drugs evidenced a positive impact on motor sensory recovery.[81] Tizanide had a more substantial inhibitory effect on knee extensors and plantar flexors, while baclofen had a more significant suppressive impact on the knee flexors; volitional torque was not reduced in both groups.[81]

Granulocyte colony-stimulating factor (G-CSF) has been used in patients with chronic SCI[82] as it is a neuroprotective agent which stimulates angiogenesis and neuronal repair and reduces inflammation and cell apoptosis.[83–85] In animals, G-CSF could reduce the extension of the injured zone and improve body function in severe SCI.[86–88] Moreover, stem cell therapy in chronic SCI may be enhanced by G-CSF.[89,90] One phase II/III clinical trial was conducted on 60 patients with chronic SCI to analyse the effects of G-CSF administration on neurological and functional improvement.[91] At the 6-month follow-up, the G-CSF group patients evidenced clinically relevant neurological progress in functional, motor and sensory activities.[91] Derakhshanrad et al.[92] conducted a stage III clinical trial on 120 chronic SCI patients to test the efficacy of G-CSF administration. At the last (6-month) follow-up, motor, sensory, and functional improvements were observed in G-CSF patients.[92]

Growth hormone (GH) is a peptide hormone synthesized and released by the somatotrophs of the anterior pituitary gland.[93,94] The hypothalamic GH-releasing hormone stimulates the release of GH.[95,96] Conversely, somatostatin has an inhibitor effect on it.[97] GH acts on the metabolic pathway of lipids, sugar and muscles and is involved in cellular growth and maturation.[98] The anabolic effect and the synthesis of body protein are stimulated by insulin-like growth factor I (IGF1), including skeletal muscle and collagen amino acids.[99,98] IGF1 GH-related effects are involved in growth, glucose uptake, and protein metabolism; meanwhile, IGF1 GH-unrelated effects involve hydrolyzation of triglycerides, glucose biosynthesis and insulin release.[100–102] GH and IGF1 can penetrate the blood-cerebrospinal fluid-brain barriers.[103,104] The GH-IGF1 pathway is central to CNS performance, myelination, neurogenesis and synaptic plasticity.[105,106] Therefore, GH has been considered a potential drug to enhance motor activities not only in the first stages of SCI.[107–109] One clinical trial phase II/III investigated the possibility of GH administration for motor recovery in 54 chronic partial SCI patients.[99] At one year follow-up, no statistical difference was observed in favour of the GH

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group.[99] Another phase II/III trial highlighted minimal improvement in chronic SCI following treatment with GH at a one-year follow-up.[110]

Riluzole is a benzothiazole anti-epileptic drug currently used to treat amyotrophic lateral sclerosis.[111,112] A sodium channel antagonist, riluzole, inhibits the constant stimulation of sodium channels, avoiding intracellular oedema.[113,114] Cytotoxicity is reduced by riluzole by suppressing the release of glutamate.[115] Theiss *et al.*[116] analysed the potential benefits of riluzole on seven chronic SCI patients. They pointed out that riluzole significantly decreased the flexion peak ankle dorsiflexion torque component of the withdrawal reflex.[116] The maximal voluntary torque in dorsiflexion and plantarflexion guiding was not considerably modified.[116]

Conclusion

There are different approaches to the pharmacological management of secondary chronic SCI. One of the most commonly investigated drugs is 4-AP, which improves central motor conduction and neurological conditions. Positive results in different areas have been observed in patients receiving the anti-spastic drugs tizanidine and baclofen or G-CSF. GH showed only minimal or no significant effects, and the therapy with secondary chronic SCI with riluzole has been poorly researched to date.

Author contributions

Filippo Migliorini (CRediT contribution not specified), Federico Cocconi (CRediT contribution not specified), Luise Schäfer (CRediT contribution not specified), Francesco Simeone (Data curation, Formal analysis, Visualization, Writing—original draft), Madhan Jeyaraman (CRediT contribution not specified), Nicola Maffulli (CRediT contribution not specified).

Conflict of interest statement

There are no conflicts of interest.

Funding

The authors did not receive support from any organization for the submitted work.

Data availability

The data underlying this article are available in the article and in its online supplementary material.

Ethical approval

This article contains no studies with human participants or animals performed by any authors.

Informed consent

For this type of study, informed consent is not required.

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