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Background: Spasticity is a common secondary complication of spinal cord injury (SCI), which can severely impact functional independence and quality of life. 4-Aminopyridine (4-AP) is a potassium channel blocker that has been studied as an intervention for spasticity in individuals with SCI. **Objective:** To conduct a systematic review of the available evidence regarding the effectiveness of 4-AP for the management of spasticity in individuals with SCI. **Methods:** A comprehensive literature search was conducted on five electronic databases for articles published in English up to January 2017. Studies were included if (1) the sample size was three or more subjects, (2) the population was ≥50% SCI, (3) the subjects were ≥18 years old, (4) the treatment was 4-AP via any route, and (5) spasticity was assessed before and after the intervention. Subject characteristics, study design, intervention protocol, assessment methods, side effects, adverse events, and outcomes were extracted from selected studies. Randomized controlled trials (RCTs) were evaluated for methodological quality using the Physiotherapy Evidence Database (PEDro) tool. Levels of evidence were assigned using a modified Sackett scale. **Results:** Nine studies met inclusion criteria with a pooled sample size of 591 subjects. Six studies were RCTs (PEDro = 6-10, Level 1 evidence) and three studies were pre-post tests (Level 4 evidence). There was a wide range in duration, severity, and level of SCI across subjects. Oral 4-AP was investigated in five studies; one study reported significant improvements on the Ashworth Scale (AS), while the remaining four studies found no improvement. Three studies found no significant improvements on the Spasm Frequency Scale. Intravenous 4-AP was investigated in three studies; no significant improvements were found on the AS or in the Reflex Score. Intrathecal 4-AP was investigated in one study, which did not find significant improvements on the AS. **Conclusion:** There is weak evidence supporting the effectiveness of 4-AP in reducing spasticity post SCI. Future research should utilize contemporary measures of spasticity and address methodological limitations such as small sample sizes. **Key words:** *4-aminopyridine, spasticity, spinal cord injury*

The organic compound 4-aminopyridine (4-AP) is marketed as *Apyra* in the United States and *Fampyra* in Canada and Europe; however, it is known by two other names under the United States Adopted Names Council (dalfampridine) and current International Nonproprietary Name list (fampridine).[1] The molecule has been used as a drug, exerting its effects by blocking potassium channels thereby promoting the conduction of action potentials along demyelinated axons in individuals with multiple sclerosis.[1] Furthermore, 4-AP improves synaptic transmission by enhancement of presynaptic calcium currents, secondary to potassium channel blockade.[2] As of February 10, 2012, 10 mg of 4-AP taken every 12 hours has been approved for use only in treating walking impairment in adults with multiple sclerosis.[1] This approval was predominately based on two phase III clinical trials demonstrating efficacy for its use.[3,4]

Given the proposed mechanism of action, 4-AP may be useful in treating impairments in other neurological populations such as spinal cord injury (SCI). Primary mechanical insults and secondary biochemical insults, such as oxidative stress, cause damage to axons and myelin in SCI.[5,6] The variation in configuration, combination, and repair of both types of damage contribute to the heterogeneity of acute, subacute, and chronic SCI. Upper motor neuron lesions from SCI may contribute to the development of spasticity, a

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disordered sensorimotor control presenting as intermittent or sustained involuntary muscle activation.[7] The significant effects of post-SCI spasticity on quality of life have prompted the emergence of both pharmacological (eg, intrathecal baclofen) and nonpharmacological (eg, neurostimulation) agents to decrease tone, generally or locally, and improve function.[8] Several trials have independently found 4-AP to have promising but mixed results in reducing spasticity post SCI.[9,10] Additional studies have also reported beneficial effects on bowel and bladder function and reduced neurogenic pain.[11-13]

Studies have shown that only a subset of patients with multiple sclerosis respond to 4-AP.[4] The cost incurred to an individual taking 4-AP is substantial, as it is not currently covered by Medicare in Canada, and the risk for adverse events at high-dose concentrations is not without consideration. As a result of its effect on neural membranes, 4-AP can induce seizures in persons with a lowered threshold for seizure activity.[2] With each of these considerations, it is important that clinicians are certain that the drug is appropriate for a patient, such that the benefits of prescribing the medication outweigh the risks. In a population for which this drug has not been approved, these concerns take on greater importance, particularly when 4-AP is prescribed off label to address impairments. Despite the individual trials undertaken to date, no study has evaluated all of the available evidence on the role of 4-AP in improving spasticity post SCI. As such, we aimed to undertake a systematic review to examine the effectiveness of 4-AP on spasticity in this select population.

Methods

The current review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[14]

Search strategy

A comprehensive literature search was conducted on five electronic databases (PubMed, Scopus, Embase, CINAHL, PsycINFO) for articles published up to and including January 2017. The following combination of key terms was used as a search strategy for each database to identify relevant articles: (spinal cord injur*) AND (spasticity) AND (aminopyridine). Filters were applied in each database to restrict searches to articles published in English and with only human subjects. Retrieved articles were then reviewed to identify additional articles that may not have been discovered in the initial search.

Study selection

Articles were included for review if they met all of the following a priori inclusion criteria:

- sample had three or more subjects,
- 50% or more of the sample sustained an SCI,
- subjects were 18 years old or older,
- subjects received 4-AP or placebo via any route, and
- spasticity was assessed before and after the intervention with a formal outcome measure.

Articles were excluded if information on subject characteristics, intervention protocols, or outcomes could not be adequately extracted.

Study appraisal

Two independent reviewers assessed the selected articles for methodological quality (J.W., J.H.), and discrepancies were resolved by a third reviewer (A.McI.). Randomized controlled trials (RCTs) were evaluated using the Physiotherapy Evidence Database (PEDro) tool (**Table 1**).[15] The PEDro tool consists of 11 items, each answered with "yes" (score = 1) or "no" (score = 0). The first item is not used in calculating the final score, such that the tool yields a maximum score of 10. Descriptive assessment of PEDro scores categorized them as poor (<4), fair (4-5), good (6-8), or excellent (9-10).[16]

Data synthesis

Data were extracted precisely from the studies without assumptions or simplifications. Extracted data included subject characteristics (ie, age, gender, injury duration, injury severity, injury level), sample size, study design, intervention protocols, assessment methods, side effects, adverse events, and spasticity-related outcomes.

Table 1. Physiotherapy Evidence Database (PEDro) tool

Item	Description
1	Eligibility criteria were specified.
2	Subjects were randomly allocated.
3	Allocation was concealed.
4	Groups were similar at baseline regarding the most important prognostic factors.
5	All subjects were blinded.
6	All therapists who administered therapy were blinded.
7	All assessors who measured at least one key outcome were blinded.
8	Measures of at least one key outcome were obtained from >85% of the subjects initially allocated to groups.
9	All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome were analyzed by intention-to-treat.
10	Results of between-group statistical comparisons were reported for at least one key outcome.
11	Study provided both point measures and measures of variability for at least one key outcome.

Table 2. Modified Sackett scale

Level of evidence	Study design
1	RCT with PEDro score >6
2	RCT with PEDro score <6, prospective controlled trial
3	Case-control study
4	Pre-post test, post test, case series
5	Observational study, case report, clinical consensus

Note: PEDro = Physiotherapy Evidence Database; RCT = randomized controlled trial.

Data were collated and organized into tables that included the aforementioned categories. All studies were assigned levels of evidence using a modified Sackett scale, which simplified the original 10-level scale into five levels (**Table 2**).[16]

Outcome measures

Three outcome measures were used to evaluate spasticity: Ashworth Scale/Modified Ashworth Scale, Spasm Frequency Scale, and Reflex Score.

Ashworth Scale (AS)/Modified Ashworth Scale (MAS). The AS/MAS is a measure of spasticity based on subjective clinical assessments of muscle tone during passive range of motion.[17,18] Each muscle is rated on a 0 to 4 scale, with 0 indicating no increase in muscle tone and 4 indicating rigidity in flexion/extension. The MAS includes an additional item (1+) to indicate resistance through less than half of the range of motion.

Spasm Frequency Scale (SFS). The SFS measures the number of sustained flexor and extensor muscle spasms per hour. All spasms are rated on a 0 to 4 scale, with 0 indicating no spasms and 4 indicating >10 spasms per hour.[19]

Reflex Score (RS). The RS measures the briskness of deep tendon reflexes and accompanying clonus at the knee and ankle of both legs. Each reflex is rated on a 0 to 4 scale, with 0 indicating no detectable response and 4 indicating very brisk response with accompanying clonus.[20]

Safety and tolerability

The safety and tolerability of a medication depend on its reported side effects and adverse events. A side effect is considered to be "any unintended effect of a pharmaceutical product occurring at a dose normally used in [humans], which is related to the pharmacological properties of the drug."[21(p42)] An adverse event is considered to be "any untoward medical occurrence that may appear during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment."[21(p40)]

Results

Study characteristics

For this systematic review, 9 of 131 studies met inclusion criteria (**Figure 1**). Studies

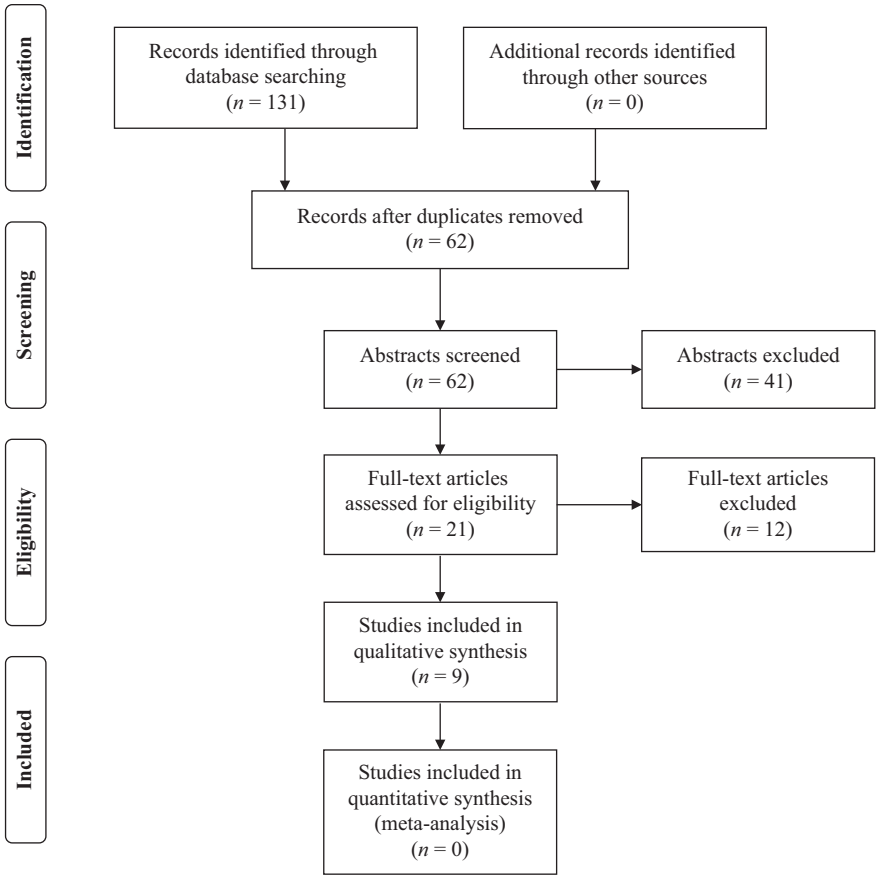

Figure 1. Study selection flow process.

were published between 1993 and 2014. Five studies[2,9,10,22,23] were conducted in the United States, and four studies[11-13,24] were conducted in Canada. Six studies[2,9-11,23,24] were RCTs and assigned Level 1b evidence, with PEDro scores ranging from 6 (*good*) to 10 (*excellent*). Three studies[12,13,22] were pre-post tests and assigned Level 4 evidence. One RCT[10] reported on two separate trials.

Subject characteristics

The total pooled sample size of all included studies was 591, with sample sizes in each study ranging from 3 to 212 (**Table 3**). The duration of injury ranged from 1 to 49 years. One study[10] did not report the duration of injury, only that subjects were injured for more than 1.5 years. The severity of injury was measured using the American Spinal Injury Association Impairment Scale (AIS) in seven studies[2,9,10,13,22-24] and the Frankel scale in two older studies,[11,12] with grades ranging from A to D. One study[23] did not report the specific severity scores, only that injuries were either incomplete or complete. Four studies[9,10,13,24] only included subjects with incomplete injuries. The level of injury ranged from cervical to lumbar. Two studies[2,22] only included subjects with paraplegia and one study[13] only included subjects with tetraplegia. One study[10] did not report the level of their subjects' injuries. Only one study[10] required that subjects have clinically significant levels of spasticity (AS >2) for inclusion.

Study design

4-AP was administered orally in five studies,[9,10,13,23,24] intravenously in three studies,[2,11,12] and intrathecally in one study[22] (**Table 4**). Intrathecal 4-AP was infused at 5 µg/h for a period of 5 hours.[22] The study was a pre-post test

Table 3. Study and subject characteristics

Study	Country	Design Evidence (PEDro)	Sample size	Gender	Age[a]	Duration[a]	Severity	Level
Oral								
Cardenas et al[10]	USA	RCT Level 1 (8)	I_1: 114 C_1: 98 I_2: 103 C_2: 100	M_1: 185 F_1: 27 M_2: 172 F_2: 31	I_1: 41.6 yr (12.1) C_1: 40.1 yr (13.1) I_2: 41.3 (11.8) C_2: 40.5 (12.3)	>1.5	Incomplete	NR
Cardenas et al[9]	USA	RCT Level 1 (7)	I_1: 30 I_2: 30 C: 31	M: 72 F: 19	I_1: 44 (23-66) I_2: 42 (21-67) C: 38 (19-61)	I_1: 8.3 (1-30) I_2: 10.8 (1-35) C: 8.3 (1-37)	Incomplete	Para: 18 Tetra: 73
Potter et al[23]	Canada	RCT Level 1 (10)	29	M: 28 F: 1	40.6 (10.0)	12.7 (8.8)	Incomplete	Para:10 Tetra: 19
Potter et al[13]	Canada	Pre-Post Level 4	3	M: 2 F: 1	42 (2.65)	6.8 (8.0)	Incomplete	Tetra
Segal et al[22]	USA	RCT Level 1 (7)	I_1: 6 I_2: 10 C: 5	NR	I_1: 51.8 (14.5) I_2: 49.0 (8.7) C: 49.2 (4.9)	I_1: 18.9 (15.8) I_2: 18.6 (11.5) C: 18.3 (16.1)	Incomplete=12 Complete=9	Para: 3 Tetra: 8
Intravenous								
Donovan et al[2]	USA	RCT Level 1 (9)	12	M: 11 F: 1	46.9 (12.6)	10.9 (9.1)	Incomplete=7 Complete=5	Para
Hansebout et al[11]	Canada	RCT Level 1 (6)	8	M: 5 F: 3	39.4 (13.9)	6.25 (3.0)	Incomplete=2 Complete=6	Para: 5 Tetra: 3
Hayes et al[12]	Canada	Pre-Post Level 4	6	M: 3 F: 3	29.8 (8.5)	4.9 (5.2)	Incomplete=5 Complete=1	Para: 2 Tetra: 4
Intrathecal								
Halter et al[21]	USA	Pre-Post Level 4	6	M:5 F:1	47.8 (15.3)	9.0 (9.3)	Incomplete=5 Complete=1	Para

Note: C = control group; F = female; I = intervention group; M = male; NR = not reported; Para = paraplegia; PEDro = Physiotherapy Evidence Database tool; RCT = randomized control trial; Tetra = tetraplegia.
[a]Age and Duration are reported in years as mean (*SD*), median (range), or range.

and did not report criteria regarding the use of concomitant medications. Intravenous 4-AP was infused up to a maximum dosage of 15 to 30 mg over a period of 2 to 4 hours. Two studies[2,11] were RCTs and one study[12] was a pre-post test. Both RCTs were crossover trials, in which all subjects received both 4-AP and placebo. In all three studies, subjects were prohibited from taking concomitant antispasmodic medications during the trial.

Oral 4-AP was provided in sustained-release (SR) tablets in three studies[9,10,24] and immediate-release (IR) tablets in two studies.[13,23] The target dosage ranged from a total of 20 to 80 mg daily. The duration of intervention ranged from 2 to 16 weeks. Three studies[9,10,23] incorporated 2-week titration periods, before and after attaining the target dosage, into the total intervention period. Four studies[9,10,23,24] were RCTs and one study[13] was a pre-post test. The control groups in two RCTs[9,10] received placebo, while the control group in one RCT[23] received low-dose 4-AP. One RCT[24] was a crossover trial, in which all subjects received both 4-AP and placebo. Two RCTs[9,23] had two unique intervention groups. In three studies,[13,23,24] subjects were prohibited from taking concomitant antispasmodic medications during the trial. In

Table 4. Study protocols, outcome measures, and results

Study	Intervention protocol	Control protocol	Outcome measure(s)	Results[a]
Oral				
Cardenas et al[10]	4-AP SR, 25 mg bid, 16 wks	Placebo, bid, 16 wks	Ashworth Scale Spasm Frequency Scale	ns ns
Cardenas et al[9]	4-AP SR, 8 wks I_1: 25 mg, bid I_2: 40 mg, bid	Placebo, bid, 8 wks	Ashworth Scale Spasm Frequency Scale	ns ns
Potter et al[23]	4-AP SR, 2 wks W_1: 12.5 mg bid W_2: 17.5 mg bid	Placebo, bid, 2 wks (crossover)	Modified Ashworth Scale Spasm Frequency Scale	* ns
Potter et al[13]	4-AP IR, 10 mg bid/tid, 16 wks	NA	Modified Ashworth Scale	NR
Segal et al[22]	4-AP IR, 30 mg qd, 12 wks I_1: blinded I_2: unblinded	4-AP IR, 6 mg qd, 12 wks	Modified Ashworth Scale	ns
Intravenous				
Donovan et al[2]	4-AP, 15-30 mg, 2 hrs	Placebo (crossover)	Ashworth Scale Reflex Score	ns ns
Hansebout et al[11]	4-AP, 18-30 mg, 2 hrs	Placebo (crossover)	Reflex Score	NR
Hayes et al[12]	4-AP, 24-25 mg, 2-4 hrs	NA	Reflex Score	NR
Intrathecal				
Halter et al[21]	4-AP, 2 μg, 4-5 hrs	NA	Ashworth Scale	NR

Note: 4-AP = 4-aminopyridine; bid = twice a day; I = intervention group; IR = immediate release; NA = not applicable; qd = once a day; SR = sustained release; tid = three times a day; W = week.
[a]* = statistically significant; ns = not significant; NR = significance not reported.

two studies,[9,10] the majority of subjects were taking concomitant antispasmodic medications during the trial, as long as they were taken consistently and had been doing so for more than 3 weeks. One study[10] stratified group allocation by concomitant medication use and accounted for the effects during statistical analysis.

Outcomes

Spasticity was a primary outcome measure in four studies[2,9,10,24] and a secondary outcome measure in five studies[11-13,22,23] (**Table 4**).

Ashworth Scale (AS)/Modified Ashworth Scale (MAS). The AS/MAS was used in seven studies.[2,9,10,13,22-24] Halter et al[22] reported that two subjects (33%) showed increases in AS score after intrathecal 4-AP. In one study of intravenous 4-AP, Donovan et al[2] reported mean changes in the intervention and control groups for AS score on the right side (+0.34 vs +0.34) and left side (+0.50 vs +0.50) post intervention, but the differences were not significant within or between groups ($p > .05$).

In a small pre-post test of oral 4-AP IR, Potter et al[13] reported that two subjects (66%) showed reductions in MAS score post intervention. In a trial of oral 4-AP SR, Potter et al[24] found that a greater proportion of the intervention group showed greater reduction in MAS scores than the control group post intervention, although the difference was not significant (15% vs 4%; $p = .180$). Analysis of mean MAS scores, however, revealed a statistically significant ($p < .05$) and clinically meaningful ($\Delta = \pm 1$) reduction that was only attributable to 4-AP. In a trial of oral 4-AP IR, Segal et al[23] reported that all subjects

showed a significant reduction in MAS score post intervention (2.6 ± 1.5 to 1.9 ± 1.7; $p = .04$); however, there were no significant differences between intervention and control.

In a phase II trial of oral 4-AP SR, Cardenas et al[9] reported that the intervention groups showed lower mean AS scores than the control group post intervention, for both 25 mg bid (1.0 vs 1.2; $p = .04$) and 40 mg bid (1.1 vs 1.2; $p = .23$). While these differences were not significant ($p > .025$), post hoc analysis of subjects with baseline AS >1 revealed that the 25 mg bid intervention group showed significantly greater reduction in AS scores than the control group ($p = .02$). As such, for two phase III trials, Cardenas et al[10] selected subjects with clinically significant levels of spasticity at baseline (AS >2). The intervention groups had greater reductions in mean AS scores compared to the control groups in both trials, but these differences were not significant ($p > .05$).

Spasm Frequency Scale (SFS). The SFS was used in three studies,[9,10,24] all of which examined oral 4-AP. Potter et al[24] found that a greater proportion of the control group showed reduction in SFS score than the intervention group post intervention, although the difference was not significant (23% vs 12%; $p = .317$). Cardenas et al[9] reported no significant differences in SFS scores within or between the intervention and control groups post intervention ($p > .025$). In two trials, Cardenas et al[10] found reductions in overall SFS scores in the intervention and control groups. The intervention group showed significantly greater reduction in mean upper extremity (UE), but not lower extremity (LE), SFS score than the control group after one of the two trials (0.13 ± 0.05 vs 0.02 ± 0.05; $p = .044$).

Reflex Score (RS). The RS was used in three studies,[2,11,12] all of which examined intravenous 4-AP. Hansebout et al[11] reported that four subjects (50%) showed reductions in RS post intervention, while Hayes et al[12] reported that two subjects (33%) showed reductions in RS. Donovan et al[2] reported mean changes in the intervention and control groups for RS score on the left side (+0.25) and right side (+0.17) respectively post intervention, but the differences were not significant within or between groups ($p < .05$).

Safety and tolerability

In earlier studies of oral 4-AP,[13,23,24] there was inconsistent reporting of side effects and adverse events. Potter et al[24] reported that subjects ($n = 29$) experienced side effects of dizziness (17%), pneumonia (3%), and urinary tract infection (3%) with 4-AP SR (12.5-17.5 mg bid), while no adverse events were experienced. Segal et al[23] noted that dizziness and abdominal distress were common though transient side effects of 4-AP IR (30 mg qd), but did not specify the respective rates. Potter et al[13] did not report any information regarding side effects or adverse events of 4-AP IR (10 mg bid/tid).

The more recent trials of oral 4-AP SR by Cardenas et al[9,10] did not distinguish between side effects and adverse events, referring to all such occurrences by the latter term. Cardenas et al[9] performed statistical analyses comparing the rate of adverse events in the placebo group ($n = 31$) to those in the low-dose 4-AP SR (25 mg bid; $n = 30$) and high-dose 4-AP SR (40 mg bid; $n = 30$) groups. In the low-dose group, there were significantly higher rates of generalized pain (37% vs 13%) and abdominal pain (23% vs 3%) than the placebo group, respectively. In the high-dose group, there were significantly higher rates of insomnia (43% vs 10%), dizziness (40% vs 6%), paresthesia (27% vs 3%), abdominal pain (23% vs 3%), anxiety (23% vs 3%), and nervousness (23% vs 0%) than the placebo group, respectively. The rate of dropouts due to adverse events was significantly higher in the high-dose group (37%) than in the low-dose (10%) and placebo (7%) groups.

In two separate trials, Cardenas et al[10] compared 4-AP SR (25 mg bid; $n_1 = 114$, $n_2 = 103$) to placebo ($n_1 = 98$, $n_2 = 100$). The rate of adverse events was greater with 4-AP than placebo in both the first (43.0% vs 24.5%) and second (48.5% vs 25.0%) trials. The most common of these events in all subjects who received 4-AP were urinary tract infection (25.8%), hypertonia (21.7%), and dizziness (14.7%), while the least common were urinary incontinence (4.6%), peripheral edema (4.6%), and pharyngitis (2.8%). The rate of discontinuation due to adverse events was greater with 4-AP than placebo in both the first (16.7% vs

3.1%) and second (15.5% vs 3.0%) trials. The most common reasons for discontinuation in all subjects who received 4-AP were dizziness (5.1%) and hypertonia (2.8%). Only one death was reported between the two trials, which occurred in a subject receiving placebo due to a preexisting medical condition.

In the three studies of intravenous 4-AP,[2,11,12] there were no serious adverse events, but localized pain at the site of infusion was common. Hansebout et al[11] reported that five of eight subjects (62.5%) experienced such pain, and Hayes et al[12] found it in all six subjects (100%). Donovan et al[2] noted that 9 of 12 subjects (75%) experienced localized pain only during 4-AP infusion. In the one study[22] of intrathecal 4-AP, there were no serious adverse events, but four of six subjects (66.7%) each experienced one minor side effect (ie, pain, spasm, headache, and dysesthesia).

Discussion

For the last 25 years, multiple reports regarding the effects of 4-AP on spasticity in SCI have emerged. A total of five small studies,[11-13,23,24] utilizing intravenous or compounded 4-AP oral tablets, have reported varying improvements in spasticity secondary to SCI. Spasticity assessments were all secondary endpoints with the exception of one study[24] that collected the MAS as a co-primary endpoint. When efficacy was reported in a subset of subjects, the percentage of subjects experiencing improvement was consistent with larger scale, later studies[9,10] (≥30%). Two other small studies utilizing intravenous[2] or intrathecal[22] 4-AP reported no significant reduction in spasticity secondary to SCI.

Given the uncertainty of 4-AP's effectiveness in managing SCI-related spasticity, and thus the potential for additional study, Acorda Therapeutics conducted a phase II clinical trial (n = 91) of a 4-AP SR matrix tablet (*Fampridine-SR*) for 25 mg bid and 40 mg bid dosage arms compared to placebo.[9] Cardenas et al[9] reported that the phase II trial showed a nonsignificant but strong trend in reduction of mean AS score in the group receiving the lower of two dose levels compared to controls. Since a large proportion of subjects had little or no spasticity at baseline, a post hoc subgroup analysis performed on those receiving 25 mg with baseline AS score >1 (n = 14) revealed statistical significance for improved AS over controls (n = 16; p = .04). For a similar subgroup with AS ≥2, the magnitude of AS reduction was greater than that of the subgroup with AS >1. Despite this larger magnitude, the effect in the second subgroup did not reach significance (p > .025) when compared to controls.

Two parallel phase III trials (n_1 = 213, n_2 = 203) treated subjects with 25 mg bid or placebo, with change from baseline AS score as a co-primary endpoint.[10] Cardenas et al[10] reported small, nonsignificant differences in the change from baseline AS score in favor of the intervention over placebo for both phase III studies. A similar trend was also observed for the secondary endpoint (ie, SFS). However, nominal significance was achieved for the SFS UE subscale in the second phase III study.

It has been noted that higher rates of side effects at higher doses of 4-AP may have contributed to the failure of the phase II and phase III clinical trials to reveal significant improvement in spasticity secondary to SCI.[5,25] Discontinuation of intervention in these trials was more than five- to six-fold greater in treated subjects than controls. The frequency of adverse events considered possibly or probably related to intervention was almost double in treated subjects compared to controls. Such observations may be the rationale for future clinical trials using derivatives of 4-AP such as 4-aminopyridine-3-methanol (4-AP-3-MeOH) that have shown a 10-fold increased potency in restoring axonal conduction with less side effects in animal studies.[5,6,25,26] Consistent efficacy trends and known off-label use of 4-AP in subjects with SCI suggest a need for further study,[27] whether future clinical trials be focused on 4-AP or a derivative with fewer side effects.

Different dimensions of spasticity are likely represented by different efficacy measurements as assessed by subject self-reports (ie, SFS is correlated with clonus and/or activities of daily living [ADLs] interference) and clinical examination (ie, AS/MAS reflects single-joint resistance to movement). Subject perception of changes in multiple ADLs throughout the day as compared to a single weekly clinical assessment may account for the stronger trend in SFS over AS seen in both phase III trials.

Differences between results of UE and LE SFS may reflect the differences noted by the subject when performing repetitive UE ADLs (eg, grasping, lifting, pushing, turning) compared to less repetitive LE ADLs (eg, transfers that move the LE). UE ADLs are likely more prevalent during the majority of the day for all subjects regardless of neurological level of injury. SFS for performance of UE and LE ADLs that require coordinated movement and are common across subjects may help to elucidate consistent functional improvements resulting from 4-AP administration.

Outcome measures have evolved since the phase II and III trials were conducted. Additional validated spasticity and functional measures specific to SCI, such as the Spinal Cord Assessment Tool for Spastic Reflexes (SCATS), Spinal Cord Injury Spasticity Evaluation Tool (SCI-SET), Spinal Cord Independence Measure (SCIM), Graded Redefined Assessment of Strength, Sensibility and Prehension (GRASSP), and Spinal Cord Ability Ruler (SCAR), are now available to improve the measurement of spasticity and related outcomes. As well, uncontrolled adjunctive interventions such as ongoing clinical therapies including extension to home-based practices, self-initiated activities, and individual activity levels may have impacted spasticity outcomes.

Limitations

The conclusions of the current review are limited by the small number of studies that met inclusion criteria. Seven studies[2,11-13,22-24] with small sample sizes reported that adequate power was not achieved. Five studies[11-13,22,23] did not assess spasticity as a primary outcome. Four studies[11-13,22] did not perform statistical analysis and only reported rates of improvement. There was considerable variation between the studies in terms of route, dose, and/or duration of 4-AP administration. All of these factors complicated the synthesis and interpretation of findings in the context of a systematic review.

It should also be noted that the current review only included peer-reviewed studies that were published in English. Studies published in other languages and other formats (eg, conference abstracts, grey literature) were not included. These factors rendered the review susceptible to publication bias and may have contributed to the limited number of included studies. Additionally, a meta-analysis was not performed due to insufficient raw data available in most of the studies.

Conclusion

There is a lack of significant evidence supporting the efficacy of 4-AP via oral, intravenous, or intrathecal administration to warrant its routine use in managing SCI-related spasticity. Factors such as different outcome measures used and higher rates of side effects at higher doses may have contributed to the obfuscation of a clear effect. Future phase III trials should utilize contemporary outcome measures validated for spasticity in SCI and should ensure that 4-AP is administered in safe and tolerable doses. Additional analyses should be conducted to account for the use of adjunctive interventions and the heterogeneity of SCI subjects.

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