CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

In a 30 year old woman with RRMS who ambulates without an assistive device, is aerobic exercise or dalfampridine more effective for improving gait speed?

AUTHOR

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CLINICAL SCENARIO

Limitations in impacts one's independence and overall health. Since MS attacks the myelin sheath and disrupts the nervous system, many patients experience difficulty walking as one of their symptoms.

Dalfampridine, the "walking pill," is prescribed widely to patients with MS to combat walking difficulties. While positive effects on gait speed have been noted, there are also a variety of possible negative side effects of dalfampridine, including dizziness, difficulty with balance, and a worsening of symptoms.

Physical therapists encourage patients with MS to exercise regularly to improve their cardiovascular health and mobility, improve community participation, and decrease fatigue.

It is important to understand whether aerobic exercise or dalfampridine is more effective in improving gait speed in patients with RRMS. If exercise is equally effective or more effective, then it may be a safer intervention for patients.

SUMMARY OF SEARCH

[Best evidence appraised and key findings]

- No studies were found which directly compared dalfampridine to aerobic exercise. Therefore, the search was modified to include studies that examined the impact of dalfampridine or aerobic exercise on gait speed in patients with MS. 10 studies were found that met the inclusion/exclusion criteria, including 3 randomized controlled trials, 1 pooled analysis of two phase 3 randomized controlled trials, 5 single group pre-post interventions (4 of which were pilot studies), and 1 retrospective chart review. Three studies were further reviewed based on the quality of evidence with reference to the PICO question.
- 10mg of dalfampridine, taken 2x/day over a 14-week period, resulted in a statistically significant improvement for 35% of participants receiving the intervention. These dalfampridine responders ambulated .64m/s at baseline on the Timed 25 Foot Walk and improved by .16m/s. The other 65% of participants taking dalfampridine showed no significant improvement in gait speed.
- Three aerobic treadmill training sessions per week for 4 weeks resulted in an improvement of .08m/s on the 10m walk test in participants with MS who ambulated .64m/s at baseline.
- 1 aerobic training session and 3 strength training sessions per week for 6 months resulted in an improvement of .27m/s in participants with MS who ambulated 2.0m/s at baseline.
- Both dalfampridine and aerobic exercise may lead to improvements in gait speed, but superiority of one over the other is unclear. The preferred intervention may depend upon baseline characteristics and one's neuropathology.

CLINICAL BOTTOM LINE

Dalfampridine may lead to a significant and clinically meaningful improvement in gait speed. However, only about 1/3 of patients with MS significantly improve gait speed after taking dalfampridine. On the other hand, a larger percentage of patients with MS may benefit from aerobic exercise, and the reviewed studies suggest that 1 to 3 sessions of aerobic exercise per week for at least 4 weeks may lead to a significant increase in gait speed. Aerobic exercise may benefit a greater percentage of patients with MS than dalfampridine, and seems to be the more effective intervention in patients who are non-responders to dalfampridine. There is not enough evidence to suggest whether aerobic exercise or dalfampridine is a superior intervention in a person who is a dalfampridine responder.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
Multiple sclerosis (MS) Relapsing Remitting Multiple Sclerosis (RRMS)	Aerobic exercise Aerobic activity Cardiovascular exercise	Dalfampridine Ampyra Fampridine 4-aminopyridine	Gait speed

Final search strategy:

1.) (MS [MeSH] OR RRMS [MeSH]) OR Multiple Sclerosis [MeSH]
2.) (Aerobic OR cardiovascular) AND (exercise OR activity)
3.) dalfampridine OR ampyra OR fampridine OR 4-aminopyridine
4.) gait speed
5.) #1 AND #2 AND #3 AND #4 (*no results found*)
6.) #1 AND #2 AND #4
7.) #1 AND #3 AND #4

Databases and Sites Searched	**Number of results**	**Limits applied, revised number of results (if applicable)**
PubMed	**11**	**None applied**
CINAHL	**1**	**None applied**
Pedro	**0**	**Not applicable**
Cochrane	**1**	**None applied**
Web of Science	**24**	**9 (Further limited search to Multiple Sclerosis, as MS included studies on Metabolic Scope)**

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
-studies published in English -peer reviewed journals -studies including an aerobic exercise intervention and/or treatment with dalfampridine -studied a population of adults (over 18) diagnosed with multiple sclerosis -measured gait speed before and after the intervention -studies that examined effects of aerobic activity and/or dalfampridine on gait speed over at least 3 weeks
Exclusion Criteria
-Case studies or case series

-Conference proceedings

-Letters to the editor

-Dissertations

RESULTS OF SEARCH

A total of 10 relevant studies were located and categorized as shown in the following table using the PEDro quality assessment rating scale for RCTs and the Downs and Black Checklist for measuring study quality.

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
Salem Y, Scott AH, Karpatkin H, Concert G, Haller L, Kaminsky E, Weisbrot R, Spatz E. (2011)[1]	15/29 D&B	2b	Pilot- Single group Pre-Post Intervention
Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, Izadi H. (2007)[2]	18/29 D&B	2b	Pilot- Single group Pre-Post Intervention
Magnin E, Sagawa Y Jr, Chamard L, Berger E, Moulin T, Decavel P. (2015)[3]	16/29 D&B	2b	Pilot- Single group Pre-Post Intervention
Lo AC, Ruiz JA, Koenig CM, Anderson BM, Olson KM, Triche EW. (2015)[4]	18/29 D&B	2b	Single group Pre-Post Intervention
Rabadi MH, Kreymborg K, Vincent AS. (2013)[5]	17/29 D&B	2b	Retrospective Chart Review
Hobart J, Blight AR, Goodman A, Lynn F, Putzki, N (2016)[6]	7/10 PEDro	2b	Pooled analysis of two Phase 3 Randomized Controlled Trials
Wonneberger M, Schmidt S (2015)[7]	14/29 D&B	2b/c	Pilot- Single group Pre-Post Intervention
Romberg A, Virtanen A, Ruutiainen J, Aunola S, Karppi SL, Vaara M, Surakka J, Pohjolainen T, Seppanen A (2004)[8]	6/10 PEDro	1b	Randomized Controlled Trial
Hupperts R, Lycke J, Short C, Gasperini C, McNeill M, Medori R, Tofil-Kaluza A, Hovendon, M, Mehta LR, Elkins J (2016)[9]	7/10 PEDro	1b	Randomized Controlled Trial
Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, Marinucci LN, Blight AR (2009)[10]	10/10 PEDro	1b	Randomized Controlled Trial

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **Goodman (2009)**[10] **–** this well-conducted RCT specifically examined the impact of dalfampridine on walking speed, as measured by the timed 25-foot walk test. They compared patients receiving the intervention with controls receiving a placebo, and had a large number of subjects (228), with fewer than 10% discontinuing the intervention.
- **Newman (2007)**[2]**-** this pilot single group pre-post intervention specifically examined the benefits of only aerobic treadmill training as an intervention on gait speed in patients with MS (as measured by comfortable walking speed). Though the study included a small sample size of 19 and lacked a control group, it was well-designed with participants receiving 12 sessions of supervised treadmill training for up to 12 sessions. Comparatively, some other studies consisted of aerobic training in addition to flexibility and strength training, or unsupervised training with far less reported compliance.
- **Romberg (2004)**[8]**-** this RCT had a larger sample size of 95 participants over a time period of 6 months. One limitation and possible confounder was that patients concurrently received strength training along with aerobic exercise training. However, this was a unique study that included aquatic aerobic activity and/or a subject's chosen aerobic activity as a part of training. It also included an extensive follow-up time period. I also chose to include this study since several others primarily looked at treadmill aerobic training, which may more easily transfer to gait speed.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: a pilot study by Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, & Izadi H (2007)[2]

Aim/Objective of the Study/Systematic Review:
The authors investigated: 1.) Whether 4 weeks of treadmill training could reduce the effort of walking for patients with MS (mild to moderate disability) 2.) The effects of treadmill training on gait parameters, endurance, and fatigue.
Study Design [e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant] Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.
Pilot single group pre-post intervention (assessors were blinded). Outcomes were measured at baseline and after the 4 week intervention. There were no opportunities for allocation concealment since all subjects participated in the same intervention.
Setting [e.g., locations such as hospital, community; rural; metropolitan; country]
The setting was not specified, other than being conducted in a "single-centre" (p. 113) with the training in a physiotherapy gymnasium. The assessments appear to have been conducted in an academic institutional lab.
Participants [N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up] Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.
A convenience sample of 19 total participants were recruited in a non-consecutive manner from a regional neurological rehabilitation center, community physiotherapists, and the local MS Society. They all had a confirmed diagnosis of MS (for an average of 17.3 years), the ability to walk 10m (all but two used an

assistive device), and the ability to walk safely on a treadmill without the support of a therapist or a body weight support harness.

Three participants dropped out (reasons unrelated to training or MS). The 16 who completed treatment were between the ages of 30-65 (mean age 53.6). 13/16 participants were females, 3/16 were males. All participants participated in the intervention.

None of the participants reported using a treadmill in the past two years, but 7 participants reported exercising weekly: 2 in a MS exercise class, 2 swam only, and 2 both swam and visited the gym. No participants reported a change in exercise routine or receiving any therapy during the time of the study.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

There was no control group. All participants participated in the intervention.

Experimental

- Each participant received 12 sessions of treadmill training over four weeks, supervised by a physiotherapist in a physiotherapy gymnasium.
- Participants exercised for up to 30 minutes, and were "encouraged" to exercise an intensity above 55% of age-predicted maximum heart rate (APMHR), and prohibited to exercise above 85%.
- Participants could take rest breaks as needed. After three rest breaks, the training session was terminated.
- The initial treadmill speed was set to the participant's comfortable walking speed (CWS) as measured at baseline, but could be increased by the participant once able to walk 30 minutes continuously.
- Over the course of the program, participants spent a mean of 310 minutes walking on the treadmill (out of a possible total of 360 minutes). 180 minutes, or 58.5% of the possible time was spent at 55-85% APMHR.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Multiple outcome measures were administered at baseline and then after one month/12 sessions of treadmill training. The assessors were blinded, but it was unclear whether those assessors were physiotherapists. For the purpose of this CAT, only outcome measures related to gait speed will be discussed. The 10m walk test was administered over a straight track and 2 minute walk test was administered around a shuttle corridor track. Distances walked were recorded in meters and used to calculate gait speed. Participants were permitted to use an assistive device if needed.

The 2 minute walk test has no established cut-off scores. However, one study recorded an average distance of 173m walked for patients with mild MS and 104m for patients with moderate MS.[11]

A previous study compared gait speed as measured by the 10 meter walk test to function with the following findings:[12]
0.0-0.4 m/s = household walker
0.4-0.8= limited community ambulator
>.8 = community ambulator

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

The authors noted significant results among multiple speed, endurance, and physiologic measures. For the purpose of this CAT, only results related to gait speed will be discussed.

- Significant improvement in speed and endurance:
  10m walk time decreased by 1.7 seconds, from an average of 15.6 seconds (SD 5.6) to 13.9 seconds (SD 5.3), p=.016
- 2 min walk distance increased by 6.1 meters, from an average of 88.2 meters (SD 32.2) to 94.3 meters (SD 32.2), p=.020

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The authors concluded that aerobic treadmill training for one month can improve self-selected walking speed in ambulatory patients with MS, therefore increasing potential for improved independence and functional mobility.

The authors also suggested that treadmill training decreased the subject's required energy for walking, based on their increased gait speed and their lower resting metabolism (another measure recorded in the study).

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

The generalizability of the results of the study is likely affected by selection bias. Since a convenience sample was utilized, subjects were not necessarily representative of the entire target MS population. Further, this subgroup had a diagnosis of MS for an average of 17 years. It's possible that individuals may respond differently to treadmill training based on their age and/or disease progression.

The internal validity of the results may have been affected by confounding bias. Though the authors mentioned that 7 participants reported exercising weekly and did not change their routines during the study, the authors did not further discuss the possible influence that this could have had on their findings. They also did not note whether these participants experienced a greater or smaller improvement than the other participants.

Further, the authors did not describe why three patients were lost to follow-up, other than stating that it wasn't a result of the MS or a result of the training.

The lack of a control group also makes it difficult to confirm that the intervention itself lead to an improved outcome. The subjects were not blinded, and it's possible that they were expecting to improve with the intervention, leading to a placebo effect. On the other hand, assessors were blinded, eliminating chances of an expectation bias.

A power analysis to justify the sample size was not reported. It is not known if the study was powered to detect a clinically meaningful result. Though the results were significant, the effect size seemed too small to be clinically meaningful. (See "Interpretation of Results" for further information)

For the reasons noted above, I calculated the overall Downs and Black score as 18/29 as a measurement of methodological quality. While this was a high-quality pilot study, further research with a more representative sample and a blinded intervention and control group could strengthen the validity of the author's conclusions.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

According to the results, the effect size of the treadmill training on the timed 10m walk test was 1.7 seconds. This equates to an average improvement from .64m/s to .72m/s, with an improvement of .08m/s (self-calculated). According to Rehab Measures, the MCID for most populations is greater than .1m/s.[13] According to a previous gait speed study, average speeds prior to and after the intervention both suggest limited community ambulation.[12]

The effect size in the 2min walk test was 6.1m. The MDC for patients with MS is 19.21 meters,[11] which suggests that the increase reported could have been due to an error in measurement. Further, this equates to an improvement from .74 m/s to .79 m/s in gait speed (self-calculated), which does not seem to translate to significant change in household or community participation.

While the authors reported statistically significant improvements in walking speed based on both assessments, those assessments do not seem to translate to a meaningful functional change for the subjects.

Another concern was that this intervention was specifically looking at the impact of aerobic exercise. However only 58.5% of the total time was spent exercising in the 55-85% parameters for aerobic exercise. Further, we only know that participants exercised *up to* 30 minutes. It's possible that some participants exercised for a much shorter time period. It is possible that the study would have yielded different results if all participants exercised within the aerobic range for a consistent timeframe. On the other hand, only selecting participants with this capability may have drastically limited the sample size for this study.

Finally, it is important to note that only measures of gait speed were examined in this study. It is possible that when combined with the results of the other assessments, the treadmill training produced meaningful changes in endurance. However, those changes do not appear to be found when looking at walking speed alone.

(2) Description and appraisal of Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial by Goodman AD, Brown TR, Krupp LB, et al (2009)[10]

Aim/Objective of the Study/Systematic Review:

The authors' objective was to produce additional evidence supporting both the benefit and safety of sustained-release fampridine for ambulation and leg strength in patients with MS.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

This was a randomized, double-blinded controlled trial. Participants were screened at baseline, and subsequently randomly assigned to the experimental or control group during visit 2. They returned for examinations 2 weeks later for visit 3, then every 4 weeks for visits 4, 5, and 6. This concluded the 14-week treatment period, which was followed by a 4 week period without treatment. During the no-treatment period, participants received follow-up assessments every two weeks for visits 7 and 8.

To ensure allocation concealment, a computer-generated randomization schedule, pre-numbered treatment kits, and distribution contractors were used. The computer-generated randomization ensured a ratio of 3:1 assignment between the control and experimental group.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

This study took place over 33 sites in the USA and Canada. The individual settings were not specified, but appear to have been conducted in an academic institutional medical center and lab.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

The authors did not clarify how the participants were recruited. Participants were 18-70 years of age (mean age: 51.4 years) with a diagnosis of MS for an average of 13.1 years. Key inclusion criteria included the ability to complete the timed 25-foot walk (T25FW) twice with an average speed of 8-45 seconds. EDSS scores ranged from 2.5-6.5, with an average score of 5.8.

301 participants were randomized into two groups: 229 were assigned to the fampridine group, and 72 were assigned to the placebo group. Of the 229 assigned to the fampridine group, 224 were analysed. 3 discontinued due to adverse events unrelated to treatment, and 1 withdrew consent before data was collected. 72/72 participants were analysed from the placebo group. Data was analysed based on an intention-to-treat analysis.

The age, race, disease duration, and EDSS scores were similar for both groups. Both groups demonstrated a similar distribution of MS types, and about half of each group had secondary progressive MS. All baseline outcome measure averages were also similar. There were more females than males in both groups, with males comprising 40% of the placebo and 29% of the fampridine group, and females comprising 60% of the placebo and 71% of the fampridine group. There were no apparent differences between groups at baseline that may have confounded the results.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

For the initial two weeks, all participants received placebo medication, with instructions to take one tablet every 12 hours. For the next twelve weeks, the control group continued taking the placebo medication with the same instructions. Since the participants were blinded, they did not know if they were receiving the placebo medication or fampridine. After fourteen weeks, all participants went through a 4-week period of no treatment.

Experimental

As noted above, the experimental group received placebo medication for the first two weeks, with instructions to take one tablet every twelve hours. For the next twelve weeks, the experimental group received fampridine tablets (10mg each), with instructions to take one tablet every twelve hours. Since they were also blinded, they did not know if they were receiving the placebo medication or fampridine. After fourteen weeks, the experimental group also went through a 4-week period of no treatment.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Multiple outcome measures were reviewed. For the purpose of this CAT, only outcome measures related to gait speed will be discussed.

Primary

- The primary outcome measure was walking speed, based on the average of two trials of T25FW.
- Participants were instructed to walk a marked 25-foot distance in an unobstructed hallway.
- Participants were allowed to use a walking device, but usage had to be consistent across assessments.
- A maximum of 3 minutes is permitted to complete each trial, and up to 5 minutes of rest is provided between trials.
- The median T25FW time has previously been recorded as 4.4s for individuals with MS, as compared to 3.7s in healthy adults without MS.[14]
- A trained evaluator who was typically a physical therapist conducted all functional outcome measures. The same evaluator conducted functional outcome measures across visits when possible. This evaluator was unaware of the patient's other assessment data.

Secondary

- The 12-item multiple sclerosis walking scale (MSWS-12), a self-reporting tool, was used at visits 2-8.
- Participants rated each item on a scale of 1-5, 1 meaning no limitation and 5 meaning extreme limitation. The maximum score is 60, which represents extreme limitation for every item. The minimum score is 12, which represents minimal limitation for each item.
- A previous study reported the average score for healthy controls as 2.2, and the average for patients with MS as 29.2.[15]

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

T25FW
78/224 participants (35%) in the experimental group demonstrated significant improvement and were categorized as timed walk responders, versus 146/224 who did not ($p<.0001$). 6/72 participants (8%) in the placebo group demonstrated significant improvement ($p<.0001$). The authors' results were originally reported in percentage of improvement and feet per second, which have been changed to meters per second for the purpose of this CAT.

The timed walk responders in the experimental group improved walking speed by an average of 25.2% (95% CI [21.5, 28.8]) throughout the 14 week treatment period. Their baseline walking speed was .64m/s (SD .21),[16] which improved to .80m/s (self-calculated based on reported baseline speed and effect size). The effect size was an increase in speed of .16 m/s (95% CI [.12, .19]).[16]

On the other hand, the non-responders in the experimental group improved an average of 7.5% (95% CI [5.0, 10.0]). Their baseline walking speed was .61m/s (SD .24)[16], which improved to .66m/s (self-calculated based on reported baseline speed and effect size). The reported effect size was an increase of .05m/s (95% CI [.03,.06])[16].

The placebo group demonstrated a 4.7% improvement (95% CI [1.0, 8.4]). Their baseline walking speed was .64 m/s (SD .21),[16] which improved to .67 m/s (self-calculated based on reported baseline speed and effect size). The reported effect size was an increase of .03 m/s (95% CI [.01,.05]).[16]

The timed walk responders in the experimental group showed a significantly greater average walking speed than the non-responders and placebo group at all visits during the treatment period ($p<.001$). The non-responders in the experimental group demonstrated a statistically significant improvement in walking speed compared to the placebo group only at visit 3 ($p<.001$).

At visits 7 and 8 during the 4-week follow-up period of no treatment, there was no significant difference between the groups.

MSWS-12
Timed walk responders in the experimental group reported an average change of -6.84 (95% CI [9.65,-4.02], $p = .0002$), suggesting an improved self-perception of walking ability. The non-responders of the experimental group and the placebo group reported an average change of .5 (95% CI [-1.48, 1.57], $p = .0002$).

Safety
58/72, or 81% of the control group and 191/228, or 84% of the experimental group reported an adverse event. The authors concluded that 26% of the adverse events in the control group and 27% of the adverse events in the experimental group might be due to treatment-related effects.

Most of the adverse events reported were considered to be mild or moderate for both groups, with the most commonly reported events being falls and urinary tract infections. Of those, 0 in the placebo group and 16/228, or 7% of those in the fampridine group reported serious adverse events.

Compliance
Overall, the participants reported 97% compliance with medications.

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The authors concluded that some patients with MS demonstrate a clinically meaningful and statistically significant improvement in walking after taking fampridine. The authors further suggested that of those in the experimental group, the fampridine responders may have improved due to their individual neuropathology. Since the improvement reversed during the four week period that treatment was removed, they also determined that the treatment effects of fampridine were reversible.

With regard to safety, the authors noted that the reported adverse events were somewhat typical for patients with MS, and they concluded that fampridine was a relatively safe treatment intervention for patients with MS.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

A power analysis was conducted to justify the sample size for each group. The authors determined that 180 participants in the experimental group and 60 participants in the control group would provide sufficient power of 90% to detect clinically meaningful outcomes. They surpassed this number in their recruitment and analysis of participants.

The generalizability of the results of the study may have been affected by selection bias. It is not clear how patients were recruited, and if a convenience sample was utilized, subjects were not necessarily representative of the entire target MS population. However, the authors included participants in each group with all four disease types, and it is possible that the results may apply to the general population with MS. The placebo and experimental groups were also similar at baseline, and there were no confounding variables found in this study.

The authors chose an effective assessment tool to measure gait speed. The MS Society recommends the T25FW test as a valuable functional outcome measure for gait speed with strong validity and reliability.[17] Since this was a double-blinded study with trained evaluators and staff, there authors also minimized the chance of measurement and intervention bias.

For the reasons noted above, this article was calculated as a 10/10 on the PEDro scale.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

Based on the results of this study, dalfampridine (referred to as fampridine in this study) appears to be an effective and relatively safe drug for improving walking speed in patients with MS. However, it only benefits a fraction of the population with MS.

The timed walk responders in the experimental group demonstrated a 25% increase in walking speed, suggesting a significant level of improvement. A 20% increase in walking speed or greater on the T25FW indicates substantial improvement in gait speed.[6,18] Further, this group improved from an average gait speed of .64m/s to an average gait speed of .80m/s. According to gait speed calculations for the 10m walk test, .64m/s classifies one as a limited community ambulator, while greater than .80 m/s indicates community ambulation.[12] Though the 10m walk test and T25FW are different measures, they both assess one's ability to travel a similar distance since 25 feet is equivalent to 7.62 meters. An individual who demonstrates this growth in gait speed is likely to benefit from improved community participation.

An improvement of 6.84 on the MSWS-12 suggests that the subjects demonstrated a significant self-perceived improvement as well. Since the total test is out of 60 points, 6.84 represents an 11% reduction in perceived limitation of walking ability. This was significantly greater than the reduction of 0.5 experienced by the placebo group and non-responders in the experimental group. It appears that after receiving fampridine, responders were able to walk faster and also perceived a much greater improvement in their walking ability while performing functional daily activities. Despite receiving the same drug, non-responders demonstrated a marginal change in perceived ability and walking speed that may have been due to the placebo effect or measurement error.

In summary, dalfampridine can effectively improve gait speed in some patients with MS. However, it does not seem to be a sufficient treatment for all patients since it only benefited 35% of the population assessed.

(3) Description and appraisal of Effects of a 6-month exercise program on patients with multiple sclerosis: A randomized study by Romberg, Virtanen, and Ruutiainen (2004).[8]

Aim/Objective of the Study/Systematic Review:

The authors sought to examine the impact of a progressive 6 month exercise program on ambulation and function in patients with mild to moderate MS.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

This was a single-blinded randomized controlled trial. After screening all subjects, they were stratified by gender and randomly assigned to the experimental or control group. The evaluators were not blinded, and there was no apparent allocation concealment. Outcomes were measured at baseline and six months later.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

This took place across two centers. The individual settings were not specified, but appear to have been conducted at the Masku Neurological Rehabilitation Centre in Finland.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

This was a convenience sample of patients on a waiting list for inpatient rehabilitation at the Masku Neurological Rehabilitation Centre in Finland. The participants' ages ranged between 30 and 55 years (mean

age: 43.9), had a history of MS symptoms for an average of 9.7 years, and their EDSS scores were between 1.0 and 5.5, indicating that all participants could walk at least 100m without an assistive device or rest. They were excluded from the study if were already regularly exercising at least 5 times per week for 30 or more minutes at a time. 276 patients were screened, and 114 were included in the study. 45/56 remained in the exercise group throughout the study, and 46/58 remained in the control group throughout the study. Using an intention-to-treat analysis, 95 participants were included in the final evaluation analysis. Of the 95 included in the analysis, 61 were female and 24 were male. None of the dropouts were intervention-related, and 5/9 dropouts in the exercise group reported work-related reasons.

The groups were comparable at baseline in age, gender distribution, height, and years after first symptoms and diagnosis of MS. The control group showed a slightly higher EDSS (2.5 on average vs. 2.0), and a greater average weight (by 6kg), and greater average BMI (26.0 compared with 24.2). A greater percentage of the control group also was using disease modifying drugs (54% versus 40%).

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

Participants in the control group were told not to change their physical activity habits over the next six months. They were contacted by phone 3 times throughout the 6 month period before reporting for follow-up.

Experimental

Weeks 1-3:
Setting: Inpatient rehabilitation center
Structure: Participants were supervised by trained PTs for 5 strength training sessions and 5 aerobic exercise sessions during this time.
Strength Exercise: Participants completed 10 exercises in a circuit, with 2 sets of 10-15 repetitions. 4 of the exercises targeted upper extremities, 4 targeted lower extremities, and 2 targeted the trunk.
Aerobic Exercise: Participants participated in aquatic exercise 1 day per week.

Weeks 4-26:
Setting: Home
Structure: A trained PT taught the home exercise program, consisting of 3 weekly strength training sessions and one aerobic exercise session, to each participant 1-on-1. The patients were called (though it is unclear who called them) at weeks 5, 8, 14, and 20 to check in and answer questions, as well as to encourage the patients to continue with the program. Otherwise, they performed their exercise program independently.
Strength Exercise: Participants continued to perform most of the same exercises, but were provided with a Theraband and instructed to perform 2 sets of 10-12 repetitions. At week 9, the duration was increased gradually to 12-15 repetitions. At week 15, the intensity was increased by instructing patients to use more challenging Therabands. When the intensity was increased, the number of repetitions was decreased back to 10-12. Further, participants performed 2 of the 10 exercises standing to simulate walking.
Aerobic Exercise: Participants were told that they could continue with aquatic exercise or choose a different form of aerobic activity. The authors did not report the number of minutes that participants were told to exercise per session.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

An independent examiner who was not blinded to group assignment conducted all functional outcome measures at baseline and after 6 months. For the purpose of this CAT, only outcome measures related to gait speed will be discussed.

Primary

- The 7.62m walk/Timed 25 foot walk (T25FW) and 500 meter walk (500 MWT) were performed at the beginning and end of the study to measure gait speed and endurance.
- The study did not indicate where these assessments were performed, though they may have been conducted at the Masku Neurological Rehabilitation Centre in Finland.
- Participants were instructed to walk as quickly as possible, and their performance was calculated using the mean of both trials for each test. In the T25FW, participants were provided with a 2m path to increase their speed just before the start of the test, as well as 2m to decelerate after the end of the timed test.

- The median T25FW time has previously been recorded as 4.4s for individuals with MS, as compared to 3.7s in healthy adults without MS.[14]

Secondary

- The participants also kept a diary to separately track compliance with aerobic and strength sessions.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

T25FW
The baseline mean for participants in the experimental group was 3.8s (SD .9), which equates to 2.00m/s. They demonstrated an average 12% decrease in time for the T25FW (95% CI [16 ,7], p<.001), improving their time by an average of .44s (95% CI [-.63, -.27], p=.04) with a final time of 3.36s, or 2.27m/s. Therefore, the improvement in speed from baseline was .27 m/s. The authors reported an effect size of .50 (medium), and also noted that 22% of participants in this group improved by more than 20%.

The baseline mean for participants in the control group was 4.0s (SD 1.1), which equates to 1.91m/s. They demonstrated an average 6% decrease in time (95% CI [11,2], p =.002), improving their time by an average of .25s (95% CI [-.43, -.08), p=.04) with a final time of 3.75s, or 2.03m/s. Therefore, their average change in speed was .12m/s. The authors reported this effect size as .19 (negligible).

500 MWT
The baseline mean for participants in the experimental group was 5.50 min (SD 1.2), or 1.52m/s. The participants in the experimental group demonstrated an average 6% decrease in time for the 500 MWT. (95% CI [10,2], p<.001). The effect size was reported as .26 (small) by the authors. The actual difference in 500 MWT means from baseline to six months was -.33 min (95% CI [-.53,-.12], p=.008). Therefore, the final average time was 5.17 min, and the average speed was 1.61m/s. The difference in means from baseline to six months was .09m/s.

The baseline mean for participants in the control group was 5.63 min (SD 1.4). The participants in the control group did not demonstrate a change in average time for the 500 MWT (mean change = 0, 95% CI [-3,4], p=.99. The effect size was reported as .02 (negligible) by the authors. The actual difference in 500 MWT means was -.02 (95% CI [-.23,19], p=.008).

Exercise adherence:
Mean exercise adherence was 93+/- 46% for all exercise, 59+/=31% for strength training, and 185+/-144 for aerobic exercise.
24% reported participating in less than 1/3 of the strength training sessions
9% reported participating in less than 1/3 of the aerobic exercise sessions

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

The authors concluded that exercise was a safe intervention to improve gait speed in patients with MS who have mild to moderate disability. They further concluded that 22% of participants in the exercise group improved enough to indicate meaningful, functional change in gait speed and therefore improved participation.

The authors acknowledged the wide variance in reported compliance, and suggested that compliance might have been stronger with more frequent phone calls and contacts.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

There was no allocation concealment in this study. There may have been measurement bias since the individual assigned to assess gait speed was aware of the group assignments. The authors noted this potential bias as well.

The groups were slightly different at baseline, with the control group having a slightly greater average disability level and BMI. Further, a greater percentage of the control group was receiving disease-modifying therapy. Some of these differences between groups may have affected the results, though the authors noted that height, weight, and BMI did not influence gait speed.

The data from the exercise journals may also have been skewed, since the participants self-reported the

amount they exercised. If this was the case, then the data may point to the benefits of exercise prescription while falling short of demonstrating the recommended exercise dosage with its benefits.

A power analysis was conducted to justify the sample size, and it was determined that at least 62 participants were needed to detect a difference of 20% or more on the T25FW. Further, the authors noted that an intention-to-treat analysis was used, as the participants' inconsistent program compliance might reflect what would happen in clinical practice. However, data was only analysed for 83% (95/114) of the participants recruited. This increase in dropout rate may have been influenced by the duration of the study.

For the reasons noted above, the article was calculated as a 6/10 on the PEDro scale. The validity could have been improved with more similar characteristics between groups at baseline, blinding of assessors, and allocation concealment.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

The results of this study suggests that a progressive exercise program of 3 strength exercise sessions and 1 aerobic exercise session each week may increase gait speed in patients with Multiple Sclerosis who have minimal disability.

However, the extent to which gait speed improves may not be clinically meaningful for all patients. In this study, only 22% of the participants in the experimental group demonstrated over a 20% change in speed. The overall average improvement of 12%, though significant, does not represent consistent clinically meaningful change. Additionally, the experimental group only decreased their time on the 500 MWT by 6%, suggesting that gait speed and endurance did not improve as much over longer distances.

Further, this group of participants was functioning at a high level based on EDSS scores and initial gait speeds. Their baseline T25FW time of 3.8 seconds, or 2.0m/s, was more than sufficient for community ambulation.[12] The participants in this study do not appear to mirror the general population with MS. While an average increase of .27m/s would be a very meaningful improvement for a person with limited community participation and slower gait speed, this increase is likely not as meaningful to a person who already ambulates at a speed comparable to healthy adults. A recent study reported an average time of 3.7 seconds for healthy controls in the T25FW, and an average of 4.4 seconds for patients with mild to moderate MS,[14] further suggesting that these participants' initial gait speeds were more typical of a healthy adult than one with MS.

The authors did not report on the degree to which exercise compliance correlated with improvement in gait speed, though one might expect to find a relationship between the two. Overall, subjects on average exceeded expectations for aerobic exercise and did not consistently meet expectations for strength training. Given the structure of the study and the wide variance of compliance, it is not possible to determine whether the strength training, aerobic training, or combination of the two was more influential in this study. Furthermore, the dosage of aerobic exercise in this intervention is also unclear. Though participants were told to exercise one time per week, the authors did not clarify the duration or intensity level of each session.

EVIDENCE SYNTHESIS AND IMPLICATIONS

The reviewed studies support both exercise and dalfampridine as relatively safe and effective interventions for improving gait speed in patients with MS. The impact of these interventions may vary depending upon the baseline characteristics of the population.

Both exercise interventions reported statistically significant improvements in gait speed.[2,8] Based on the two studies, the recommended dosage for aerobic exercise is unclear and may vary depending on the patient's initial gait speed and level of disability. Newman et al demonstrated that up to 30 minutes of aerobic treadmill training 3 times per week for 4 weeks lead to an average improvement of .08m/s in the 10 meter walk test.[2] According to the results of Romberg et al, one weekly aerobic exercise session combined with 3 weekly strength training sessions for 6 months improved gait speed by an average of .27m/s in the Timed 25 Foot Walk.[8] However, it is important to note that Romberg et al included participants with a significantly greater average gait speed at baseline than the participants in the study conducted by Newman et al (2.0m/s compared with .64 m/s, respectively).[2,8] Also, the participants from Romberg et al received treatment for 6 months, while the participants from Newman et al only received 4 weeks of treatment. This disparity in treatment length also makes it difficult to compare the two interventions.

Taken together, these studies suggest that aerobic exercise can help to improve gait speed, though the patient's baseline abilities and length of treatment may also influence the extent of improvement. While the frequency of exercise varied between the two studies, improvements in gait speed occurred with as few as 1

to 3 aerobic exercise sessions per week.[2,8] However, the improvements in gait speed and function were not large enough to be clinically meaningful for all of the participants. This suggests that exercise parameters may need to be adjusted according to the patient's baseline abilities and goals.

Goodman et al demonstrated that dalfampridine (10mg every 12 hours) was a safe and highly effective gait speed intervention for 35% of the population with MS, resulting in an improvement of .16m/s for dalfampridine responders.[10] However, non-responders failed to show a significant improvement in gait speed, suggesting that this intervention is not sufficient for many patients with MS.[10]

None of the reviewed studies directly compared dalfampridine with aerobic exercise. Given the differences between populations, it is difficult to directly compare the improvement in gait speed for dalfampridine and aerobic exercise. The combination of aerobic training and strength training demonstrated the greatest increase in gait speed (.27m/s), but this population also had a faster gait speed at baseline than the populations in the other two studies.[8] Aerobic treadmill training 3 times per week lead to an improvement of .08m/s,[2] compared to the fampridine-responders who improved by .16m/s.[10] The participants in these two studies were also similar in gait speed at baseline, both with average speeds of .64m/s. From this comparison, it appears that dalfampridine may produce greater improvements than aerobic exercise in patients who are dalfampridine-responders. However, these gait speeds were calculated from both the T25FW and 10 meter walk test, which may skew the comparison. Further, since the two interventions were not compared within the same study, the same population, or the same test, one cannot effectively conclude whether dalfampridine or aerobic exercise is a superior intervention for a dalfampridine responder.

Collectively, these results suggest that both dalfampridine and aerobic exercise may improve the gait speed of a 30 year old woman with RRMS who ambulates without an assistive device. If she is a dalfampridine responder, then it is unclear from the evidence reviewed whether her gait speed would improve more with dalfampridine or aerobic exercise. If she is not a dalfampridine responder, then she is likely to show a greater improvement with aerobic exercise than dalfampridine. The intensity, frequency, and duration may need to be adjusted according to the patient's baseline abilities and goal.

It is important to also note that all three studies examined populations 10 to 20 years older than the patient identified in the PICO question. Therefore, it is unclear if the results identified in this study would also apply to this patient.

None of the reviewed studies directly compared or examined a combination of the two interventions of interest. It is possible that a combination of the two may lead to greater improvements than dalfampridine or aerobic exercise alone. Further studies could directly compare dalfampridine and aerobic exercise interventions within the same population, determine the most effective dosage of aerobic exercise for improving gait speed, and examine the combined impact of dalfampridine and aerobic exercise.

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