CRITICALLY APPRAISED TOPIC

FOCUSED CLINICAL QUESTION

Is functional electrical stimulation (FES) or a standard orthotic (i.e. AFO) more effective in improving gait speed and endurance in a 45-year-old female with relapse-remitting multiple sclerosis and unilateral foot drop who uses a unilateral assistive device (EDSS score 6.0) and has been diagnosed for 7 years?

AUTHOR

Prepared by	Spencer Edgerton	**Date**	12/4/2018
Email address	spencer_edgerton@med.unc.edu		

CLINICAL SCENARIO

A 45-year-old female presents to her follow-up appointment at a MS clinic rehabilitation department. She is complaining of increased fatigue and episodes of foot dragging on her right side, which tends to occur more in the afternoon after she has been walking throughout the day. She has had relapse-remitting MS for 7 years, with no clinical exacerbations in the last 3 months and currently receives infusions of rituximab. She ambulates with a single point walking pole in her left hand and has recently noted that she feels that she has started to walk slower. When her gait speed is measured, it has decreased to 0.72m/s from 0.85m/s, measured 1 month prior. She is not currently taking any medication for fatigue or mobility (i.e. dalfampridine). The patient has expressed increased interest in interventions for her "exertional foot drop" on the right that seems to be impairing her walking ability and concerning her due to fear of falling. She has heard that functional electrical stimulation has been increasingly used for foot drop in MS and wonders if that would be a good option for her to increase her walking speed and decrease the feeling of reduced endurance that she has been experiencing later in the day or on longer walking trips. The PICO question above was formed to investigate the effects of FES on gait speed and endurance compared to AFOs, the standard of care to treat foot drop in MS.[1]

SUMMARY OF SEARCH

[Best evidence appraised and key findings]

- 8 studies were identified that met all inclusion/exclusion criteria. Due to lack of results specific to MS, 2 studies were included that only included participants with stroke. A systematic review of RCTs,[2] and a long-term RCT follow-up.[3] Six studies included only persons with MS (pwMS). One was a systematic review of experimental and observational studies,[4] and 4 were of quasi-experimental design lacking a control or comparison group. Of these 4, only 1 study compared FES with AFO in a randomized cross-over design comparison.[5] The other study comparing FES and AFO in MS was a case series of only 4 patients.[6]
- The systematic review and randomized cross-over trial mentioned immediately above were chosen for this CAT due to relevance to the clinical scenario, applicability to population of interest, and inclusion of interventions for comparison.
- These 2 studies indicate that FES is effective in producing clinically meaningful increases in gait speed resulting from initial and ongoing orthotic effects, but not a therapeutic effect in MS. Compared to use of an AFO, patients with MS may report significantly less exertion while using FES, and walk for longer duration and distance, although the latter two outcomes were not statistically significant. Energy and efficiency of use as measured metabolically was comparable between FES and AFO use among pwMS.

CLINICAL BOTTOM LINE

Both FES and AFO can be effective treatments for foot drop in MS in order to increase gait speed. There is not enough evidence to recommend FES over AFO, rather patient clinical characteristics and personal preference should be considered in clinical decision making. More high-quality research with larger samples, focusing on thorough patient characteristic reporting to allow subgroup analysis, use of consistent walking measures, especially longer walking tests to assess endurance, and longitudinal follow-up after prolonged device use is needed to make more meaningful conclusions. Additionally, future research should focus on comparison of FES with other treatments and identifying patients that are most likely to benefit from its use.

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

The above information should fit onto the first page of your CAT

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
"Multiple sclerosis" MS "Autoimmune demyelinating disease"	"functional electrical stimulation" FES stimulat* neuromuscular stimulation "peroneal nerve stimulation" electric*	orthotic orthosis orthosis AFO "ankle foot orthosis"	"gait speed" "gait velocity" "walking speed" "walking velocity" "walking endurance" "walking distance" endurance "energy expenditure" distance gait walk* ambulat*

Final search strategy (history):

Show your final search strategy (full history) from PubMed. Indicate which "line" you chose as the final search strategy.

Search	Query	Items found
#64	Search (#2 AND #4)	81
#63	Search (#1 AND #4)	56
#65	Search (#1 AND #4) Filters: Randomized Controlled Trial	12
#64	Search (#1 AND #4) Filters: Systematic Reviews	4
#53	Search (#3 AND #4 AND (#5 OR #6))	76
#54	Search (#3 AND #4 AND (#5 OR #6)) Filters: Systematic Reviews	9
#55	Search (#3 AND #4 AND (#5 OR #6)) Filters: Systematic Reviews; Randomized Controlled Trial	17
#46	Search (#1 AND #4 AND gait)	44
#17	**Search (#2 AND (#3 OR #4) AND (#5 OR #6))**	**71**
#16	Search (#1 AND (#3 OR #4) AND (#5 OR #6))	35
#14	Search (#2 AND #3 AND #4 AND #5 AND #6)	5
#7	Search (#1 AND #3 AND #4 AND #5 AND #6)	4
#6	Search ("walking endurance" OR walking distance OR endurance)	43295
#5	Search ("gait speed" OR "gait velocity" OR "walking speed" OR "walking velocity")	10178
#4	Search (orthoses OR orthosis OR orthotic OR "ankle-foot orthosis")	15069

#3	Search ("functional electrical stimulation" OR neuromuscular stimulation OR "peroneal nerve stimulation")	13377
#2	Search ("multiple sclerosis" OR MS OR "autoimmune demyelinating disease")	371087
#1	Search "multiple sclerosis"[MH]	53448

In the table below, show how many results you got from your search from each database you searched.

Databases and Sites Searched	Number of results	Limits applied, revised number of results (if applicable)
PubMed	**71**	**No limits applied; Using Boolean term "OR" for the interventions and the outcomes yielded most results**
CINAHL	**27**	**No limits applied; Searching ((#3 OR #4) AND (#5 OR #6)) yielded 40 results**
PEDro	**18**	**18: "Multiple sclerosis, ankle foot"** **10: "Multiple sclerosis, functional electrical stimulation"** **8: "Ankle foot orthosis, functional electrical stimulation"**

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
- Studies evaluating the orthotic and/or therapeutic effects of FES and/or orthoses which enlisted ambulatory adult subjects (>18 yo) with a diagnosis of MS or foot drop due to central nervous system/upper motor neuron pathology - At least one outcome measure related to gait speed or distance (i.e. T25FWT, 10MWT, 2MWT, 6MWT) - All varieties of FES products used for drop foot
Exclusion Criteria
- Studies that did not include gait speed or endurance measures for after intervention for foot drop - Not published in English

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

For each article being considered for inclusion in the CAT, score for methodological quality on an appropriate scale, categorize the level of evidence, indicate whether the relevance of the study PICO to your PICO is high/mod/low, and note the study design (e.g., RCT, systematic review, case study).

Author (Year)	Risk of bias (quality score)*	Level of Evidence**	Relevance	Study design
Prenton (2016)[2]	**8/11 - AMSTAR**	**1a**	**Moderate**	**Systematic review of RCTs**
Bethoux (2015)[3]	**5/11 – PEDro** ***Funded by manufacturers of FES**	**2b**	**Low**	**Long-term follow-up to Unblinded parallel-group RCT**
Miller (2017)[4]	**6/11 - AMSTAR**	**3a**	**High**	**Systematic review and Meta-analysis of observational and experimental studies**
Sheffler (2009)[6]	**Downs and Black (D&B):** **Reporting (R) = 8/11** **Ext. Validity (EV) = 0/3** **Int. Validity - bias (IV-b)= 3/7** **Int. Validity – confounding (IV-c)= 2/6** **Power (P)= 0/2** **TOTAL = 13/29**	**4**	**High**	**Small case series**
Sheffler (2008)[1]	**D&B:** **R = 7/11** **EV = 0/3** **IV-b = 2/7** **IV-c = 3/6** **P = 0/2** **TOTAL = 12/29**	**4**	**Moderate**	**Cross-sectional, quasi-experimental**
Miller (2016)[7]	**D&B:** **R = 10/11** **EV = 0/3** **IV-b = 5/7** **IV-c = 3/6** **P = 0/2** **TOTAL = 18/29**	**4**	**High**	**Cross-sectional quasi-experimental**
Khurana (2017)[5]	**D&B:** **R = 10/11** **EV = 0/3**	**4**	**High**	**Crossover counterbalanced, quasi-experimental**

	IV-b = 3/7 **IV-c = 3/6** **P = 0/2** **TOTAL = 16/29**			
Downing (2014)[8]	**D&B:** **R = 8/11** **EV = 1/3** **IV-b = 3/7** **IV-c = 2/6** **P = 0/2** **TOTAL = 14/29** ***funded by the manufacturers of FES**	**4**	**High**	**Cohort quasi-experimental, repeat measures**

*Indicate tool name and score

**Use Portney & Watkins Table 16.1 (2009); if downgraded, indicate reason why

BEST EVIDENCE

The following 2 studies were identified as the 'best' evidence and selected for critical appraisal. Rationale for selecting these studies were:

- **Miller (2017):**[4]

  This systematic review and meta-analysis included a total of 19 studies, including both RCTs and non-RCT, experimental and observational studies, where gait speed data could be extracted. The participants all had a diagnosis of MS, and outcomes included in the meta-analysis were orthotic and therapeutic effects of FES as measured by gait speed at short, medium, and long-term periods (up to 20 weeks in meta-analysis). As several different outcome measures were used across studies for short and long-distance walking, there was conversion to m/s for each tool for meta-analysis. Although the inclusion of lower quality studies decreases the validity of the results, this review is more relevant to pwMS and the intervention and outcomes of interest. The broadening of inclusion criteria by the researchers reflects the overall lack of RCTs for this intervention in MS.

- **Khurana (2017):**[5]

  This study enrolled a group of 20 adults (32–74 yo) with MS (EDSS 4.0–6.0) to explore the effects of both FES and AFO on walking. This study refers to itself several times as a "randomized crossover controlled trial", which the researchers did randomize individuals to perform tests with either FES or AFO first (this order was reversed for each individual in a repeat measure taken 1-4 weeks later). I have classified this study as a cross-over counterbalanced quasi-experimental study because I feel that it lacks a true control. While perceived exertion, energy, and efficiency were the primary outcomes measured as RPE, kcal/kg/min, and mL/kg/m respectively, they did include distance and speed as secondary outcomes. This was also the only experimental study in the search results, the other being a case series of only 4 patients,[6] that actually compared FES and AFO in pwMS.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of Functional Electrical Stimulation for Foot Drop in Multiple Sclerosis: A Systematic Review and Meta-Analysis of the Effect on Gait Speed by Miller et al. (2017)[4]

Aim/Objective of the Study/Systematic Review:

This systematic review aims to synthesize evidence to assess the effects of functional electrical stimulation (FES) on gait speed in persons with multiple sclerosis (pwMS) with foot drop. The meta-analysis aimed to assess and compare the immediate and ongoing orthotic effects and therapeutic effects (performed with no FES) of FES in pwMS during both short and long walking performance tests.

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 is a systematic review and meta-analysis that includes experimental (RCTs and non-RCTs) and observational studies in which gait speed was an outcome measure in pwMS using FES for foot drop.

Search Strategy:

- Two authors independently performed a systematic literature search according to an a priori protocol
- The search was performed on September 27, 2016 through the following databases: CINAHL via EBSCO, Embase and MEDLINE via OVID, Cochrane Library, and PubMed
- Common search terms included: "multiple sclerosis", "functional electrical stimulation", gait, walk, foot drop, "neuromuscular electrical stimulation", stimulat*, electric*, peroneal nerve stimulat*. These were used in a combination of MeSH terms and with Boolean operators to advance the search.
- One author screened article titles, 2 authors reviewed abstracts independently, and disagreement was settled by consulting a third reviewer.
- Full text articles meeting selection criteria were assessed for eligibility

Selection Criteria: No restrictions placed on publication date. Authors noted that the selection of included studies was "purposefully inclusive" due to the "limited number of known controlled trials in this field of study"(p.1436)

- Inclusion:
  - Studies that reported on at least 1 outcome of gait speed with and without FES device in short or long walking performance tests
  - Participants >18 years old with multiple sclerosis
  - Studies that included other neurological diagnoses were included only if data for pwMS could be extracted separately.
  - All types of FES devices were included (surface and implantable)
  - Studies that compared FES to another intervention (i.e. exercise)
- Exclusion:
  - Opinion pieces, narrative reviews, conference and poster abstracts
  - Studies not in English

Quality Assessment:

- The review used the Effective Public Health Practice Project (EPHPP) tool to appraise the selected studies given inclusion of a variety of study designs.
- 2 reviewers appraised each articles and discrepancies were resolved with discussion

Data Extraction and Analysis:

- Data from studies was extracted by one reviewer and checked by another. Where data required clarification, study authors were contacted.
- For meta-analysis, data for short walking tests (10mWT, 25-ft walk test, and 6-meter walk test) were combined as the primary outcome measure, while data from the long walking tests (2-,3-,4-,6-minute walk test, and 5-min self-selected walk test) were combined to represent the secondary outcome measure. Both were extracted, combined, and expressed in units of meters/second (m/s)
- A "heuristic approach"(p.1437) was used in calculations for the meta-analysis due to variability in included study protocols
- 95% confidence intervals were estimated in studies that did not report them based on assumption of approximate normative distributions.

- Studies that reported data at time frames from 2 to 20 weeks were included in the meta-analysis for ongoing orthotic and therapeutic effects. This range represents the minimum and the median time frames, respectively, in the included articles.

Heterogeneity:

- The analysis does not include, nor mention, a test for heterogeneity

Setting

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

Not specified. Most likely performed at a university given affiliation of researchers with Galsgow Caledonian University, Glasgow, UK.

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 review included 20 articles reporting on 19 studies with a total of 490 pwMS

11 articles used an experimental design:

- 1 RCT
- 1 randomized crossover trial
- 8 non-RCTs (9 articles)

9 articles with observational design:

- 1 case-control
- 8 interrupted time series

Participants were recruited from hospitals or MS clinics, and most studies had small sample sizes ranging from 2 to 39 participants. One retrospective study included data from 153 participants.

Subject characteristics:

- Mean age range: 46.5 to 56 years
- Mean time since diagnosis range: 8.6 – 17.7 years
- Sex: 25% to 77% of participants in studies were women
- Mean EDSS score range: 3.5 – 5.9
- Type of MS: two studies only recruited participants with secondary progressive MS, whereas others included a mix or did not report MS type.
- There is considerable variability among the inclusion/exclusion criteria in the individual studies. Some recruited only participants that had previous experience with FES, while this was exclusion criteria in others. One study actively recruited pwMS taking fampridine, while another excluded participants taking medication for fatigue or mobility. There were a wide range of baseline walking ability requirements ranging from ability to walk 10m to ability to walk for 6 minutes.

Intervention Investigated

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

Control

Most studies did not include a proper control and were quasi-experimental or observational in design.

The one RCT included compared a FES treatment group to an exercise program group

Experimental

The Odstock Dropped Foot Stimulator (ODFS) was the most commonly used FES device, in 15 studies. Four studies also included dual-channel ODFSs used for bilateral foot drop or foot drop plus gluteal stimulation.

3 studies used the Walkaide FES device, one comparing it to the ODFS

1 study used the Bioness L300 FES device

2 studies evaluated implantable FES devices

One non-RCT (a small case series)[6] compared the ODFS to the use of an AFO

In general, studies assessed the efficacy of FES on gait speed in pwMS as measured immediately after device application (initial orthotic effects) and/or after a period of gradual increased use or unlimited use (ongoing orthotic effect). A small number of studies assessed therapeutic effects of FES use on short and long walking tests (performance without the FES device after a period of regular use).

Outcome Measures

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

All of the articles included in the review included an outcome measure for gait speed.

Short distances:

- 10 meter walk test (10MWT): used in most (12) studies in review. A valid and reliable measure of gait speed in m/s, with MCID of 0.05m/s.[4,9]
- 25-ft walk test: 3 studies. Reliable and valid measure recommended for use in pwMS. A 20% change in time is considered to be clinically meaningful in MS, and healthy matched controls perform in 3.7s.[10]
- 6-meter walk test: 2 studies; this measure was used as part of studies performing a 3-dimensional gait analysis on subjects. Gait speed in m/s was extrapolated by this review.

Longer distances: (less common)

- 2-, 3-, 4-, and 6-minute walk tests
- 5-minute self-selected walk speed
- The distances for long walk tests, typically reported as distance in meters, were converted to speed (m/s) for meta-analysis

*All measures were converted to gait speed in m/s for purposes of meta-analysis. Other aspects of gait that studies measured were not analysed or discussed in this review.

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. You may summarize results in a table but you must explain the results with some narrative.]

Results of the meta-analysis of this review, indicating the overall effect of FES on gait speed in pwMS is organized by primary and secondary outcomes, short and long walking tests, respectively. Under each, the initial orthotic, ongoing orthotic, and therapeutic effect observed through the pooled data were calculated as averages and displayed below:

Average Overall Effects of FES for Gait Speed on Short Walking Performance Tests (m/s)								
Initial Orthotic		N = 353	Ongoing Orthotic		N = 255	Therapeutic		N = 244
No FES	FES	p-value	No FES	FES	p-value	No FES (baseline)	FES	p-value
0.69 ± 0.03	0.74 ± 0.03	0.016*	0.74 ± 0.04	0.82 ± 0.04	0.003*	0.74 ± 0.04	0.74 ± 0.04	0.487

11 studies with 353 participants were used to calculate the initial orthotic effect of FES on gait speed in short walking tests, while 8 articles with 255 participants were included for ongoing orthotic effects up to 20 weeks. Gait speed increased significantly for both, 0.05m/s and 0.08 m/s, or 7.1% and 11.3%, respectively.

6 studies with 244 participants reported on therapeutic effects on gait speed after FES use, indicating no overall change from baseline.

Average Overall Effects of FES for Gait Speed on Long Walking Performance Tests (m/s)								
Initial Orthotic		N = 89	Ongoing Orthotic		N = 81	Therapeutic		N = 61
No FES	FES	p-value	No FES	FES	p-value	No FES (baseline)	FES	p-value
0.61 ± 0.05	0.63 ± 0.05	0.286	0.64 ± 0.07	0.68 ± 0.05	0.174	0.58 ± 0.06	0.64 ± 0.07	0.091

5 studies with 89 participants demonstrated an overall small nonsignificant (p=0.286) increase in gait speed (0.02 m/s; 3.3%) for initial orthotic effect. This was increased in the 81 participants for ongoing orthotic effect (0.04 m/s; 6.2%) but still not statistically significant (p=0.174).

Just 3 studies with 61 participants were included in the calculation for therapeutic effect of FES on long walking tests. There was a nonsignificant (p=0.091) increase in gait speed of 0.06 m/s (10.3%).

Original Authors' Conclusions

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

The authors conclude that the studies included in the analysis demonstrate a statistically significant initial and ongoing orthotic effect, as measured by gait speed, for pwMS using FES, but that there is no therapeutic effect seen in short walking tests. They also conclude that FES produced small but nonsignificant increases in gait speed on longer walking tests. Additionally, they draw conclusions on the lack of therapeutic effects after FES use, pointing to inclusion of studies that recruited participants with secondary progressive MS, small sample sizes, and the neurodegenerative nature of MS as compared to chronic stroke. Therefore, they suggest that FES may have limited therapeutic potential in persons with progressive MS subtypes. Overall, they conclude that the use of FES in MS provides initial and ongoing orthotic effects realized through increases in gait speed, but not therapeutic effects.

Critical Appraisal

Validity

[Summarize the internal and external validity of the study. Highlight key strengths and weaknesses. Comment on the overall evidence quality provided by this study.]

This article scored a 6/11 on the AMSTAR tool, and classifies as Level 3a evidence.

The strength of this review is reflected in its systematic search strategy that is well disclosed with use of multiple evidence-based databases and search terms. The search was carried out by multiple researchers and consensus was met through use of established inclusion criteria. The study also used a Scottish Intercollegiate Guidelines Network algorithm for classifying included study designs. This review reports search strategy and methods consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. By including a larger number of studies, this review includes a large sample (n=490) that may be more representative of the general population of pwMS (external validity) that would be appropriate for consideration of FES as intervention.

The inclusive nature of this review, while it affords a larger participant sample, is a major weakness in its internal validity. There are a variety of study designs, of which only one was an RCT, including experimental and observational. Of the included studies, 12 were of moderate methodological quality while 8 were weak. 75% of the studies did not include any comparator control group. Additionally, there are numerous different FES devices used, including implanted devices, and a wide range of walking outcome measures that were used to extract data for the meta-analysis. In order to perform the meta-analysis for intervention effect on gait speed, all short and long walking measures were converted to gait speed in m/s. This "heuristic approach" may lead to inclusion of data that has been affected by confounding variables and lends the reader to interpret results of overall effects of the intervention with caution, especially with the lack of a heterogeneity calculation in the review. The researchers also chose the cutoff of 20 weeks for the

interpretation of an ongoing orthotic effect and therapeutic effects, with no evidence to indicate when such an effect may actually occur and if it is maintained. Finally, the meta-analysis for orthotic and therapeutic effects on long walking tests included data from a significantly smaller number of studies, and thus participants, with some inconsistent results among studies. This should lead to caution when interpreting these results and overall effects.

Additionally, the authors acknowledge that there may be publication bias as studies were limited to the English language and did not include a search of gray literature.

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.]

This review uses a wide variety of studies, implementing a variety of FES devices over different time periods, to assess the effects of FES on gait speed in pwMS with foot drop. Overall, the results support the use of FES in producing significant increases in gait speed in short walking measures while using the chosen device (orthotic effects). Therapeutic effects are not supported by evidence in the use of FES for a prolonged period of time (up to 20 weeks). Additionally, none of the long walking outcomes (initial/ongoing orthotic, therapeutic effects) demonstrated a statistically significant increase in gait speed with use of FES. As the meta-analysis for the short walking tests was able to include more studies, and the increases in gait speed with orthotic effect was at least the MCID of 0.05m/s, one can be fairly confident that the result is actually due to FES intervention and clinically meaningful. Conversely, the relative shortage of long walking test use in the reviewed studies limited the sample included in this part of the meta-analysis, such that statistical and meaningful benefits may not have been detected or may be misleading.

Applicability of Study Results

[Describe the relevance and applicability of the study to your clinical question and scenario. Consider the practicality and feasibility of the intervention in your discussion of the evidence applicability.]

This review and meta-analysis is highly relevant to the clinical question posed in this CAT as it specifically focuses on the intervention in question, FES, and one of the outcomes of interest, gait speed. The majority of studies included in this review capture the demographic and health characteristics of the patient presented in the clinical scenario of this CAT, however, there is an overall need for better baseline characteristic reporting in the literature, potentially allowing subgroup analyses. Also, this review solely assessed gait speed as the only outcome of interest, neglecting other potential gait outcomes that may be clinically relevant. It is also not possible to tell from this review whether subjects ambulated with assistive devices and how this was affected by treatment with FES, if at all, and vice versa.

The overall lack of high-quality studies investigating FES for foot drop in MS is highlighted by this study, particularly in regards to the use of long walking tests that could assist in determining effects of FES treatment on walking endurance.

(2) Description and appraisal of Perceived Exertion Is Lower When Using a Functional Electrical Stimulation Neuroprosthesis Compared With an Ankle-Foot Orthosis in Persons With Multiple Sclerosis by Khurana SR, Beranger AG, and Felix ER (2017)[5]

Aim/Objective of the Study/Systematic Review:

The aim of this study is to compare the energy cost, efficiency, and perceived exertion of walking with FES and an AFO in patients with MS and foot drop. The authors hypothesized that FES would require less energy, be more metabolically efficient, and yield lower reports of exertion while walking.

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 is a cross-over counterbalanced quasi-experimental study.

Eligibility Criteria:

- Inclusion:
  - Aged 18-75 with diagnosis of MS
  - EDSS $\leq$6.5
  - Unilateral or bilateral foot drop
  - Able to walk with or without assistive device, but without human assistance, for minimum of 3 minutes
- Exclusion:
  - Disease exacerbation within 3 months
  - Unable to walk without risk of fall
  - Less than 10 degrees passive excursion of ankle or presence of contracture at ankle

Experiment Design:

- This study consisted of 2 separate visits set 1 to 4 weeks apart. At each visit participants were assessed under 2 conditions: walking with FES and walking with an AFO. Participants were randomly assigned to which device was used first at visit 1, allocated by the researcher drawing a device name from an envelope. A break of at least 1 hour was taken between walking trials. This order was then reversed on visit 2 for each participant.
- On visit 1 participant characteristics were gathered including: weight, age, sex, race, concomitant medications, MS subtype, history of symptom onset and diagnosis, and history of falls in past 3 months.
- Participants also completed the self-reported Kurtzke EDSS, Fatigue Severity Scale, and Falls Efficacy Scale on visit 1 before beginning the first trial.

Devices:

- In AFO trials participants either used an AFO that they owned (n=6) or an off the shelf polyethylene posterior leaf spring AFO (n=14) fitted to the participants leg and foot.
- In FES walking trials, a physical therapist positioned the device (WalkAide) correctly and then manually delivered the stimulation via a tethered device at the right phase of the gait cycle.

Data Analysis:

- Outcomes were compared 2 ways:
- Repeated measures analysis of variance (rm-ANOVA) using device and visit number as within-participant independent variables. Additional rm-ANOVA using device and device order as within-participant variables
- Categorical analysis:
- Comparison, using chi-squared analyses, of number of participants who consistently performed better with AFO vs. FES for each outcome variable
- Analysis also included exploring potential associations between participant characteristics and differences in performance with each device

Setting

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

Not specified, but presumed to be at a hospital or university research facility in Miami based upon study author affiliations.

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.

- 22 patients were initially enrolled
- 1 did not complete any walk trails, and 1 withdrew due to temporary paresthesias with FES (data not discussed or presented)
- 20 patients then completed the study and were included in the analysis
- Participants were recruited from the primary author's MS clinics over a 10-month period as approved by the University of Miami Institutional Review Board

- Results below are presented as mean (range)
- Average age of participants, years: 54.6 (32-74)
- EDSS: 5.5 (4.0 – 6.0)
- Fatigue Severity Scale: 5.4 (1.8 – 7.0)
- Falls Efficacy Scale: 46.5 (13 – 91)
- 11 females
- MS subtypes: 14 relapse-remitting, 2 primary progressive, 4 secondary progressive
- Time since diagnosis, years: 8.8 (0.17 – 22)
- 6 patients had their own AFO previously, which was used in the study
- 2 patients owned and used a FES device previously

Intervention Investigated

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

Control

There was no true control in this experiment

Experimental

Participants underwent measures during walking trials with FES and AFO on each of 2 visits.

Walking trials were completed on a smooth oval track with distance markers in a thermoneutral environment. Instructions were to "walk at a comfortable pace for as long as possible, with a 3-minute minimum and a 10-minute maximum."(p.134) Heart rate, VO2, and pulmonary ventilation were measured using a chest strap, Hans-Rudolf Softmask, and portable metabolic monitor device. Metabolic data was collected over a 5-minute pre-trial period of rest, during the walking trial, and a 5-minute post-trial rest.

Borg RPE scores for during the trial were reported by participants immediately after the trial

Outcome Measures

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

Primary Outcomes:

- Borg RPE score: a self-report measure of exertion during physical activity, reported on a scale of 6 to 20, where higher numbers represent more exertion. The Borg rating has been shown to be associated with heart rate during activity. MCID = 1 unit, based on study cited by the authors which is based on data from chronic lung disease patients.[11]
- Caloric expenditure ("energy") – "computed as the weight-corrected product of measured VO2 and a standard caloric constant (6 kcal/L O2consumed) and expressed as kcal/kg per minute" (p. 136)
- Metabolic efficiency ("efficiency") – "computed as the quotient of VO2and the distance ambulated in meters after correction for individual body weight (in mL/kg per meter)." (p. 136)
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Secondary Outcomes:

- Time, distance and speed during walking trials (speed was calculated as a function of the time and distance of walking)
- Heart rate elevation, VO2, and pulmonary ventilation (VE) during walking compared with resting baseline – "calculated by subtracting peak values during the walk (corresponding with the time of peak absolute VO2value) from the average values obtained during the 5-minute pre – walk rest period." (p. 136)

Other Self-report Measures included in Analysis:

- EDSS
- Fatigue Severity Scale (FSS): contains 9 items and is scored from 1 to 7, with higher scores indicating more severe fatigue.
- Falls Efficacy Scale: Measures fear of falling, where higher scores (out of 100) indicate fear of falling

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. Use a table to summarize results if possible.]

- FES had lower Borg RPE scores than AFO across sessions:
  - Within-Subjects Difference Mean **(FES – AFO)** = -1.63 (95% CI: -2.76 to -0.49)
- 13/20 participants reported lower RPE with FES for both visits
- 1/20 reported lower RPE with AFO for both visits
- 1/20 reported RPE was equal with AFO and FES
- 5/20 reported different results for different visits
- The difference between number of participants with consistently lower RPE scores for FES vs. consistently lower with AFO was statistically significant ($x^2 = 15.82$; $P < 0.01$)
- No significant differences were found in energy or efficiency for device with quantitative or categorical analysis (rm-ANOVA: P=0.42 and P=0.10, respectively; and x^2: P=1.0 and P=0.74)
- Mean Duration showed a trend towards significantly increased time walked while using FES:
  - Within-Subjects Difference Mean = 36.25s (-2.26 to 74.76), P=0.06
- Mean Distance and speed were higher in FES but not significant:
  - Within Subjects Difference Mean - Distance: 28.57m (-11.79 to 68.92), P=0.16
  - Within Subjects Difference Mean - Speed: 0.03m/s (-0.03 to 0.08), P=0.29
- Visit number: Distance and speed were affected by visit number such that there was a mean increase in distance of 42.30 m (95% CI, 9.19 – 75.41 m), and mean increase in speed was 0.06 m/s (95% CI, 0.01 – 0.10 m/s), but this did not depend on device order.
- RPE and Demographic and Health Factors:
  - Analysing the percent difference scores for RPE with AFO and FES with participant characteristics revealed higher Falls Efficacy Scale scores (Spearman p = 0.48, P=0.03) and longer time since diagnosis (Spearman p = 0.51, P=0.02) were significantly associated with lower RPE while walking with FES

Original Authors' Conclusions

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

The authors concluded that the use of FES was effective in leading to statistically and clinically significant less perceived effort (RPE) compared to the AFO, and that this effect was not dependent on device order as more patients consistently reported lower RPE scores for the FES across trials and visits. They conclude that the association of the Falls Efficacy Scale and time since diagnosis may suggest that patients with a longer diagnosis and higher fear of falling may benefit from FES more than AFO for improving activity levels secondary to fatigue and foot drop. They warrant caution with interpreting results in light of study limitations, suggesting need for future longitudinal trials to compare effects of these different devices.

Critical Appraisal

Validity

[Summarize the internal and external validity of the study. Highlight key strengths and weaknesses. Comment on the overall evidence quality provided by this study.]

This study scores a 16/29 on the Downs & Black quality rating tool, and classifies as Level 4 evidence.

Strengths of the study exist in its design of randomized cross-over method and use of rest breaks in between trials that serve to limit confounding effects of device order and fatigue, respectively. This is also the only identified experimental trial that directly compares the use of FES and AFO for foot drop in pwMS.

There are several weaknesses noted in this study. The interventions did not allow blinding of participants or assessors. The use of a physical therapist to manually stimulate the FES device during walking trials may have led to error and bias in participant performance with the device. Patient characteristics were not controlled or reported thoroughly, leading to caution in interpretation of results and lack of internal validity. For example, 6 participants had previous AFOs and used these in the trials, and 2 participants had previously prescribed FES devices. There is no reporting on baseline patient characteristics such as bilateral/unilateral foot drop, use of assistive device, or baseline gait speed and RPE without FES or AFO, all of which could be potential confounders in trial performance with devices in the study. There is also no indication whether participants used assistive devices in walking trials. One participant did not complete any trials, while another withdrew due to adverse effects of the FES but was not discussed further and no data was reported for this participant.

The small convenience sample, recruited from the primary author's clinic, yields low power and limited external validity to the study. There is no mention that the researchers performed a power analysis.

In general, while the internal validity of the study was strengthened by the randomized cross-over design, the lack of standardization in walking times, device use prior to the study, and poor reporting on baseline characteristics limit the internal validity of the study results. Furthermore, the sampling bias warrants caution in generalizing the study results.

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.]

Despite the weaknesses discussed above, this study demonstrates that FES may lead to a reduction in perceived exertion while walking compared to with an AFO for persons with MS. This was observed in a significant 65% of the participants on both visits, indicating a true result that was not due to device order or visit number. Only one of the participants consistently reported less exertion with the AFO across both visits. Interestingly, this difference was not reflected in the data on the other primary outcomes for energy and efficiency or secondary outcomes. The results do suggest that participants tended to walk for longer duration and further distance with the FES device compared to the AFO, and although not significant they trend towards favouring FES for increased ambulatory ability. However, due to the lack of standardized walking trial times, the clinical significance of these differences is unable to be determined. The results of the study offer information regarding the patient experience of walking with different devices for foot drop, indicating that FES may "feel" easier to patients. This is clinically relevant as we should consider this dimension in recommending treatment options for patients with MS. This study also found an association that indicates that pwMS that have a higher fear of falling or longer disease duration may see additional potential in the use of FES for walking and reducing exertion levels compared to AFO use. In regards to gait speed, the devices resulted in similar gait speed outcomes (expressed an average and a function of distance and time). The participant gait speeds are relatively low, even with device use, but the reason for this cannot be determined as there is no trial performed with no device and lack of participants' baseline disability (i.e. unilateral/bilateral footdrop, assistive device use). It would be ideal if the study had included baseline measures of participants performing the walking trial without a device to compare the effectiveness of each intervention on outcomes, including distance, speed, and duration. Furthermore, as speed was calculated as a function of distance and time and reported as an average, the device effect on speed is not a primary focus and should be interpreted with caution. Also, these results should be interpreted within the limitations of the study and the design, which only included repeated measures at two points in time. Differences in treatment effects may be more pronounced after a period of prolonged use for either intervention, as which occurs in clinical practice, not captured in this study design.

Applicability of Study Results

[Describe the relevance and applicability of the study to your clinical question and scenario. Consider the practicality and feasibility of the intervention in your discussion of the evidence applicability.]

This study was chosen for its high relevance to the clinical question posed by this topic as it includes both the intervention in question, FES, and the comparison intervention, AFO. It is the only experimental study, to my knowledge, that directly compares the use of FES vs. AFO for foot drop in MS. The results indicate that FES should be considered as an effective treatment option for drop foot in MS, and may lead to decreased reports of exertion when walking as compared to an AFO. That said, the efficiency and energy associated with its use appear to offer no advantage based on the study results. This places particular emphasis on patient appropriateness for treatment options and personal preference. The measurement and analysis of additional participant data would have increased the usefulness of this study's results. It would appear that the participants had slow walking speeds as a group with either device with mean gait speeds of 0.57m/s and 0.55 m/s with FES and AFO, respectively. It is not possible to tell what participant's baseline walking speeds were from the study, and these values with device must be interpreted with caution as they used average speeds as a function of time and distance which was not standardized in the walking trials. Overall the results trend towards more favourable values with FES use; however, nonsignificant in all but the RPE outcome. The fact that most participants walked the full 10-minute maximum allotted in trials with the FES, may indicate an increase in walking endurance. Things to consider in clinical application in addition to patient characteristics (i.e. ipsilateral quadriceps strength, spasticity, available ankle excursion) and preference, are the affordability and ease of use of each treatment. These variables are not discussed in this study, but are important factors in clinical decision making. The small sample size includes individuals with similar gender, EDSS, and time since diagnosis and appears representative of the patient in the clinical scenario for the CAT, albeit small.

SYNTHESIS AND CLINICAL IMPLICATIONS

[Synthesize the results, quality/validity, and applicability of the two studies reviewed for the CAT. Future implications for research should be addressed briefly. Limit: 1 page.]

Walking difficulty is among the most common impairments associated with multiple sclerosis, often secondary to foot drop.[4] Physical therapists are directly involved in targeted interventions for foot drop that are intended to increase walking ability and functional mobility and decrease fall risk. Several outcome measures are available and recommended for assessing walking ability in MS, many focusing on gait speed and endurance. The review and meta-analysis by Miller et al., which specifically focuses on the outcome of gait speed with use of FES in pwMS, provides support that FES results in statistically and clinically significant initial and ongoing orthotic effects, but not therapeutic effects.[4] The meta-analysis used extracted data from all included studies such that walking performance outcome measures for both short and long distances were all converted to the same unit, meters/second. This method warrants caution in interpretation of results, especially as included studies were highly variable in design, outcomes used, and typically of low quality, but overall provides significant evidence that FES can increase gait speed in pwMS, especially on short walking measures. Furthermore, mean increases were at or above a clinically significant change of 0.05m/s.[4] The lack of therapeutic effects may point to the neurodegenerative disease nature of MS and the inclusion of participants with long disease duration, possibly indicating that they belong to progressive subtypes.[4] The inclusivity of this review highlights the overall paucity of high quality studies and RCTs investigating the use of FES in MS. In fact, only one of the studies was an RCT, comparing FES to exercise, also finding no training effect for FES.[12] This study, however, did find evidence that exercise training in secondary progressive MS produced a significantly greater increase in gait speed compared to FES which only resulted in orthotic effects, indicating need for studies that assess combined therapeutic interventions.[12] The majority of experimental studies lack a control or a comparator group. Overall this study supports FES as an option for the treatment of foot drop in a patient similar to that included in the clinical scenario of this CAT as most study samples capture the age, sex, EDSS score, and time of diagnosis. Importantly though, the authors in this review point to the need for stronger designed studies and "further research, including comparisons with usual care (eg, an ankle-foot orthosis) in addition to measuring longer-term effects and identifying predictors of FES response."[4,(p.1436)] At the time of this review the Khurana et al. study was not published, yet it does just that: compares the use of FES and AFO among subjects with MS.

The study by Khurana et al. strengthens the body of evidence that supports the use of FES for foot drop in pwMS, however, the study is also hampered by methodological weaknesses. The small convenience sample detracts from the study's power and external validity, while the inclusion of participants with previous familiarity with interventions may have affected performance, lowered internal validity, and warrant caution upon interpreting results. That said, a large portion, 65%, of participants consistently reported less exertion while using the FES, while only 1 out of 20 reported this with the AFO, a result likely due to true differences in treatment itself.[5] While not specifically aligned to the outcomes posed by the clinical question, this is valuable information as it measures the patient's perspective of effort/exertion, comparing the use of the two interventions that this CAT aims to address in the same population. It can be concluded that patients may perceive FES as requiring less effort compared to AFO, but that the other primary outcomes in this study, energy and efficiency were not statistically different. Another result that the authors discuss that is applicable to the clinical question of this CAT, was that participants tended to walk for longer times when wearing the FES compared to the AFO.[5] As speed was reported as an average, and walking trials were not standardized (could have been 3 minutes or 10 minutes), the data may not represent differences in walking speed within the same time walked. It may be inferred that since individuals tended to walk for longer times and distances with the FES, and report significantly less exertion, this reflects an increase in walking endurance, however, this association was not formally explored in the analysis and deserves further research. Ideally this study would have also included baseline walking data with no device as a control such that treatment effects could be compared to these values. It is impossible to tell from the data whether participants performed trials with assistive devices, had unilateral/bilateral foot drop, or if previous experience with the devices showed trends of favoring walking trials with the same device. More detailed reporting of participant baseline characteristics may have allowed for subgroup analysis that could reveal clinically relevant information when choosing treatment options, especially between two interventions that both seem to work.

The Miller et al. and Khurana et al. articles support the use of FES for pwMS, however, there is a lack of high-quality studies which compare this intervention to other treatment options, let alone AFOs. This led to inclusion of studies in stroke and a small case series in the search performed for this CAT. The low-quality evidence gathered by Miller et al. points to the need for high-quality research that has consistent use of standardized measures of gait speed and endurance, particularly longer walking tests which would allow more reliable analysis and may reveal treatment effects on deterioration of gait with fatigue in MS.[13] While the Khurana study attempts to answer this call, comparing FES to AFO, it does so with significant design limitations and only at two isolated applications. Future research with longitudinal design, such that interventions can be assessed after a period of continued use, as it would occur in clinical practice, is also needed. Applying available evidence to the patient scenario, it appears that there is evidence that both interventions may be effective in increasing gait speed, and that FES may permit longer walking with less perceived exertion. There is very little evidence adequately comparing FES to AFO in pwMS and outcomes of gait speed and endurance, but comparable outcomes have been observed in stroke.[2,3] This would lead the clinician to base decisions on patient preference and/or other clinical factors that may guide treatment such

as assistive device use, gross lower extremity strength, and treatment burden (including cost). For example, there is some evidence to support that FES may not be beneficial in persons with baseline gait speed >0.8 m/s.[7] Additionally, the pros and cons of treatment must always be considered. For example, AFOs may limit mobility and encourage disuse atrophy, an obviously undesirable result in a neurodegenerative disease when preservation of remaining function is a priority.[4] These factors need further exploration in research that reports on patient traits and explores associations with treatment responses for pwMS.

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