Functional Electrical Stimulation for foot drop in Multiple Sclerosis: A Systematic Review and Meta-Analysis of the impact on gait speed.

Authors: Miller L, MPhil[1, 2], McFadyen A, PhD[3] , Lord AC, MSc[1], Hunter R, BSc[1], Paul L, PhD[4], Rafferty D[2], Bowers R[5], Mattison P[1]

Affiliations: 1MS service, NHS Ayrshire and Arran, Scotland ,UK ; 2 School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK; 3 AKM Statistics, Glasgow, UK; 4 School of Medicine, Glasgow University, Glasgow, UK; 5 Department of Biomedical Engineering, Strathclyde University, Glasgow, UK

Corresponding author: L Miller, Douglas Grant Rehabilitation Centre, Ayrshire Central Hospital, Irvine, UK,KA12 8SS. Tel:01294 323057 email: linda.renfrew@aapct.scot.nhs.uk

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Conflicts of Interests

There are no conflicts of interest to declare

Abstract

Objective: To review the efficacy of functional electrical stimulation (FES) used for foot drop in people with multiple sclerosis (pwMS) on gait speed in short and long walking performance tests.

Data sources: Five databases (Cochrane Library, CINAHL, Embase, MEDLINE, Pubmed) and reference lists were searched.

Study selection: Studies of both observational and experimental design where gait speed data in pwMS could be extracted were included.

Data extraction: Data were independently extracted and recorded. Methodological quality was assessed using the Effective Public Health Practice Project (EPHPP) tool.

Data synthesis: Nineteen studies (described in 20 articles) recruiting 490 pwMS were identified and rated moderate or weak, with none gaining a strong rating. All studies rated weak for blinding. Initial and ongoing orthotic and therapeutic effects were assessed with regards to the impact of FES on gait speed in short and long walking tests. Meta-analyses of the short walk tests revealed a

significant initial orthotic effect (t = 2.14, p = 0.016) with a mean increase in gait speed of 0.05 meters per second (m/s) and ongoing orthotic effect (t = 2.81, p = 0.003) with a mean increase of 0.08m/s. There were no initial or ongoing effect on gait speed in long walk tests and no therapeutic effect on gait speed in either short or long walk tests.

Conclusions: FES used for foot drop has a positive initial and ongoing effect on gait speed in short walking tests. Further fully-powered randomized controlled trials comparing FES with alternative treatments are required.

Key words: Review, Multiple Sclerosis, electric stimulation, gait disorders/neurologic, walking

Abbreviations:

AFO Ankle Foot Orthosis

EPHPP Effective Public Health Practice Project

FES Functional Electrical Stimulation

m/s meters per second

MS Multiple Sclerosis

NICE National Institute for Health and Care Excellence

ODFS Odstock Dropped Foot stimulator

pwMS people with Multiple Sclerosis

RCT Randomized Controlled trial

UK United Kingdom

USA United States of America

10MWT 10 meter walk test

6MWT 6 meter walkway test

25ftWT 25 foot walk test

2minWT 2 minute walk test

3minWT 3 minute walk test

4minWT 4 minute walk test

5minSSWS 5 minute self selected walk speed

6minWT 6 minute walk test

Introduction

Multiple Sclerosis (MS), a chronic autoimmune demyelinating central nervous system disease, is the leading cause of disability in young adults in Western Europe and North America[1-4]. In 2010, there were an estimated 130,000 cases of MS in the UK, with an incidence of 11.52 per 100,000 in women and 4.84 per 100,000 in men[4].

MS is a progressive disease with accumulation of irreversible neurological deficits, and is characterised by visual, brainstem, cerebellar, cognitive, motor and sensory symptoms[1, 2]. Ambulatory impairment is the main contributor to disability within the first 10 years[5] with around 75% of people with MS reporting limitations in walking[6]. Timed walking tests provide a quantitative measure of walking performance, which have demonstrated good reliability in pwMS[7] and are strongly associated with self-reported walking ability[6]. Habitual walking performance, described as the number of steps taken in an individual's own environment (accelerometry) is predicted by gait speed as measured by a range of walking speed performance tests, making it a valid outcome in interventional studies[8]. Walking capacity tests encompass measures of both short (e.g. 10 meter walk test (10MWT)) and longer (e.g. 6 minute walk test (6minWT)) timed measures of walking[9]. Short and long walking tests have been found to indicate distinct aspects of walking. Short walk tests are accurate descriptors of walking capacity and longer walking tests are recommended in interventional studies[9].

The inability to maintain active ankle dorsiflexion during the swing phase of the gait cycle results in foot drop, impacting on the energy cost and speed of walking[6], instability and falls[10]. FES is an assistive technology used for foot drop in MS and other

neurological conditions. FES was initially developed for use during gait in 1960 by Liberson et al.[11] who demonstrated immediate benefits on walking in hemiplegic patients. Previous studies have reported effects of FES on gait in people with MS (pwMS) with reference to walking speed and energy cost[12,13]. The effects of FES are commonly described in terms of orthotic effects and therapeutic effects. An orthotic effect, most frequently reported, refers to the difference in performance between walking with and without FES. An initial orthotic effect is the immediate change seen with FES on the first day of its use[12]. An ongoing orthotic effect is the change in walking with and without FES at a follow up point following a period of regular use[12]. The therapeutic effect describes the impact of regular use of FES on walking performance over time and is the difference in walking performance without FES prior to application compared to a follow up assessment without the device[12].

There are a number of commercially available FES devices for clinical application. They all apply electrical stimulation to the common peroneal nerve, activating ankle dorsiflexion during the swing phase of gait and assisting foot clearance. Stimulation is synchronised with the gait cycle using a variety of mechanisms employed by the devices including tilt sensors, heel switches, and wired and wireless technology. Stimulation can be applied externally via surface electrodes or internally via implantable electrodes. Recent research suggests that implantable devices are as effective as surface stimulation alternatives for pwMS[13], although there are additional risks such as device failure and neuropraxia[13].

A recent narrative review[14] described the impact of FES in MS on the speed, kinematic profile and energy cost of walking and with regards to patient satisfaction and perceived benefits of FES. The review found FES to have beneficial orthotic and training effects

on measures of gait, however not all improvements were statistically or clinically significant. Although the majority of patient reported data demonstrated positive benefits with FES, there was often no correlation with objective measures of gait. The authors highlighted areas for further research including comparisons with usual care, e.g. an Ankle-Foot Orthosis (AFO), in addition to measuring longer term effects and identifying predictors of FES response. A previous systematic review in chronic stroke found orthotic effects of FES on the speed and physiological cost of walking[15]. One review undertaking meta-analysis noted significant orthotic effect on the 10mWT[16] and another noted a therapeutic effect on the 6minWT[17] using FES for foot drop in stroke. There are clear differences however between stroke and MS, an autoimmune neurodegenerative disease, with regards to their pathology and demographic profile that may impact on the effectiveness of FES. There is a growing body of evidence for FES for foot drop in MS, therefore there is a need for a systematic review to explore the efficacy of the intervention. Thus, the aim was to systematically review the evidence to date for the orthotic and therapeutic effects of surface and implantable FES used for foot drop in pwMS, with regards to its impact on gait speed in both short and long walking performance tests.

Materials and methods

A literature search was conducted on 27th September 2016 by two authors (AS, RH) using a protocol developed a priori.

Due to the limited number of known controlled trials in this field of study the review was purposefully inclusive, including empirical research and studies of both observational and experimental design evaluating FES as an intervention. Opinion pieces, narrative reviews, conference and poster abstracts, and studies not in the English language were excluded. No restrictions were place on publication date.

Studies on adult participants (>18 years) with a diagnosis of MS were included. Studies investigating a mixed neurological sample were included where data for pwMS could be extracted separately.

Studies included all types of FES devices for foot drop. Studies investigating other interventions in addition to FES were included where the other intervention was a comparator group. Studies reporting on device development were excluded.

To be eligible for inclusion studies had to report on a minimum of one measure of gait speed using either short or long walking tests with and without the device, at a minimum of one time point. Gait speed is described in meters per second (m/s) and measured by walking over a short distance (e.g.10 meters, 25 feet) or a longer distance (e.g. 2 or 6 Minute Walk)

Search strategy

The following databases were searched: CINAHL via EBSCO, Embase and Medline via OVID, the Cochrane library and PubMed that included in-process citations. Individual search strategies were conducted in each database using the key search terms,

Medical Subject Headings and Boolean operators shown in Table 1 and applying the previously agreed eligibility criteria. A hand search of the reference lists of relevant articles was undertaken.

The search results were exported from the individual database to a specialised referencing software package (REFWORKS) and duplicates were removed. Articles were screened by title (AS) and the abstracts were reviewed by two authors (AS, RH). In the case of disagreement over inclusion at abstract review stage, consensus was reached by consulting a third reviewer (LR). The full text of articles that met inclusion/exclusion criteria were read and assessed for eligibility.

[Insert table 1 here]

Quality assessment

There is no 'gold standard' critical appraisal tool recommended in rehabilitation research, however a systematic review of available critical appraisal tools recommends tools should be selected based on the purpose of the review[18]. The Effective Public Health Practice Project (EPHPP) tool[19] was selected following consideration of the research question and recommendations from previous systematic reviews[20, 21]. The EPHPP tool provides a checklist with a summary score that allows for inclusion of a range of different study designs within the review. The EPHPP tool has demonstrated good reliability and validity[20].

The articles for review were initially identified as either observational or experimental in design using the Scottish Intercollegiate Guidelines Network algorithm for study design (Figure 1). A pilot quality check was undertaken on one article by all 4 assessors

(LR, LP, AS, RH) to ensure consistency. Subsequently 2 reviewers reviewed each article and where there were discrepancies an agreement was reached via discussion.

Data extraction and analysis

One reviewer (LR) extracted data from the articles on participants (e.g. age, gender, MS type), methods (e.g. study design) interventions (FES type, description of control intervention) and outcomes (e.g. assessment time points and outcome measures) and results using an a priori developed data extraction form. A second reviewer (AS) checked the data extracted. Authors were contacted where further clarification was required around data.

Data, where available, were subjected to meta-analysis as per Everitt[22]. Data from all 3 short walking tests (10MWT, 25 foot walk test (25ftWT), 6 meter walkway test (6MWT)) were combined and presented as the primary outcome measure. Data from all the longer walking tests (2 minute walk test (2minWT), 3 minute walk test (3minWT), 4 minute walk test (4minWT), 6minWT, 5 minute self-selected walk test (5minSSWS)) were combined and presented as the secondary outcome measure. Justification for combining data from the longer walking tests was based on previous evidence that noted a strong association between the 2minWT and 6minWT in pwMS[23]. Initial and continued orthotic and therapeutic effects of FES were analysed. Given the differences in protocol timings in each study included in the meta-analysis calculations and the lack of randomness, a heuristic approach was taken as no Odds Ratios were reported. This approach has been previously used in other clinical areas[24]. All calculations are from baseline

data given the differences in times between study protocols and, where only sample size, means and standard deviations were reported, 95% confidence intervals were estimated with the assumption of approximate Normal distributions. The estimates of the 95% confidence intervals of the mean of each outcome variable from each paper and for the pooled samples are presented. For ongoing orthotic and therapeutic effects, data from studies reporting on the time frame ranging from 2-20 weeks were included for analysis. There is currently no evidence to suggest when a therapeutic effect may occur following FES application, therefore a pragmatic approach was taken that combined the minimum and median time frames reported in the papers selected for review.

Results

Literature search

The electronic literature search yielded a total of 125 articles, 8 from CINAHL, 67 from MEDLINE (OVID and EBSO), 29 from Embase, 7 from Cochrane Library and 14 from PubMed databases. A hand search of reference lists yielded an additional 11 articles. Once duplicates were removed this yielded 90 articles for screening. The remaining 23 full text articles were reviewed (AS, RH) and a further 3 were excluded. The remaining 20 articles, reporting on 19 studies involving 490 pwMS met the inclusion criteria and were included in the quality review and meta-analysis. Results are presented in the PRISMA flowchart (Figure 2).

Study and participant characteristics

168 The characteristics of the studies and subjects are presented in Table 2. Eleven articles in the review used experimental designs,
169 including 1 randomized controlled trial (RCT)[25], 1 randomized crossover trial[26] and 8 non RCTs generating data in 9 articles[27-35].
170 Nine articles presented data from 8 observational studies, including 1 case control[36] and 8 interrupted time series
171 designs[12,13,37,38,40-42]. All studies recruited participants from hospitals or MS clinics and most recruited pwMS only[13, 25-29, 31-40,42].
172 Three studies recruited participants with different neurological diagnoses, where MS data could be extracted separately[12,30,41]. The
173 20 articles recruited a total of 447 participants. Sample numbers in the majority of studies were generally small and ranged from 2[42]
174 to 39[13], however one retrospective observational study presented data from 153 participants[40]. Most studies reported either a mix
175 of MS type or did not report MS type. Two studies recruited participants with secondary progressive MS only[25, 26]. There were
176 similarities in the age, sex, time since diagnosis and disability level of the participants recruited across the studies. The mean age
177 of participants ranged from 46.5[13] to 56[35] years and time since diagnoses ranged from 8.6[35] up to 17.7[25] years. Between 25 to 77 %
178 of participants recruited in the studies were female. Disability was only reported in 6 studies and ranged from Extended Disability
179 Status Score 3.5[32] to 5.9[26] . Walking aid use was frequently reported throughout the studies, indicating that participants had
180 significant walking impairment.

181 The detail given about inclusion and exclusion criteria varied. Some observational studies reported minimal detail[12,31,37,41,42] other
182 than the inclusion of MS participants deemed suitable for FES while others[12,25,28,30,37,41] did not indicate whether participants had
183 used FES prior to inclusion. Some studies recruited pwMS already using FES[13,29,31,36,38,39,42] while others indicated previous FES

use as an exclusion[26,27,34]. Some studies excluded potential participants unable to walk a minimum of 10 meters[27, 29, 30,] whereas others included only those able to walk longer distances, up to 6 minutes[33,36,38,39,41]. Only 4 studies reported exclusion of potential participants with unstable disease or recent relapse[27,33,38,39]. Most studies gave no indication of exclusions related to medication. Only 1 study excluded participants taking medication for fatigue or mobility[33]; however another[27] actively recruited participants on a stable dose of fampridine, a drug licensed for treating walking impairment in MS.

Interventions

Almost half of the studies investigated the single channel Odstock Dropped Foot Stimulator® (ODFS)[a] [25,28,29,31,32,35,36,39]. Four articles included data from dual channel ODFS (for bilateral foot drop or foot drop plus gluteal stimulation) in addition to single channel ODFS[12,26,37,40]. Three studies evaluated the Walkaide® system[b] [27,30,34], one study compared the ODFS with Walkaide® [38] and one study investigated the impact of the Ness L300® device[c] [33]. Two studies evaluated implantable FES, one study with the STIMuSTEP[a] [13] and another with ActiGait®[d] [42]. The only RCT [25] compared single channel ODFS with an exercise programme. A randomized crossover trial[13] compared single channel ODFS followed by dual channel ODFS (anterior tibialis and guteal stimulation) with weekly physiotherapy. A non-randomized controlled trial compared single channel ODFS with an AFO[29].

[Insert Table 2 here]

Outcome measures and effects

Details of the outcome measures used in each of the studies are presented in Table 3. All articles presented data on outcome measures that assessed gait speed. Seventeen studies measured gait speed over short distances, with most tests indicating participants walked at a fast pace. The majority of studies used the 10 metre Walk Test (10MWT)[12,13,25,27,28-30,32,37,40,41,42] however 3 studies presented data on the 25 foot Walk Test (25ftWT)[27,34,35] and two studies reported gait speed over a 6 metre walkway (6MWT)[31,33] as part of 3D gait analysis.

Walking speed over longer distances was less frequently reported. The range of walking tests used include: 6minWT[27,28], 5minSSWS[36,38,39], 4minWT[30], 3minWT[13,25] and 2minWT[32]. Data from the 6minWT and 3minWT are reported as the total distance walked in the specified time, which was converted to walking speed for the purpose of analysis. All other tests are reported in m/s. Some articles reported on other aspects of gait, which are described in Table 2, however any further analyses on these measures are out of the scope of this review and will not be discussed further.

With regards to the short walking tests, all except 2 of the articles[29,35] measuring this outcome reported on the initial orthotic effect of FES. Nine studies reported a statistically significant increase in walking speed following initial application of FES, with effects ranging from 5 to 18.3%[12,26,28,30-32,34,40,41]. In contrast, 4 studies found no difference with FES[25,27,33,37] and 2 small studies investigating 2[42] and 5[29] participants reported mixed results.

Thirteen articles reported on ongoing orthotic effects[12,13,25,26,29,30,32,33,35,37,40-42] from 4 weeks [29,35] up to a mean of 10.8 years[12] post application. All of the studies except 2[33,35] evaluating ongoing orthotic effects reported a statistically significant increase in walking speed.

The therapeutic effect of FES on gait in short walking performance tests was reported in 11 articles[12,13,25,26,30,32,33,37,40-42] at a number of time points from 6 weeks[25] to a mean of 10.8 years[12] of FES application. One study reported a statistically significant therapeutic effect at 12 weeks[30]. The majority of articles found no therapeutic effect with small or no improvements in walking speed[25,26,32,33,37,40]. Four of the studies noted a reduction in unassisted walking speed at 12[42] and 18 weeks[41], and this was significant in 2 studies at 3[13] and a mean of 5.1 years[12].

Effects of FES on gait in long walking performance tests were reported less frequently. There were mixed results with reports of initial positive orthotic effects in the 2minWT[28,32], 3minWT[41]and 4minWT[31] but not the 6minWT[27,28]. Positive ongoing orthotic effects were found from 6 weeks to 11 months[13,25,30,32,42]. Two studies reported in 3 articles[36,38,39] used the same protocol for the 5minSSWS and evaluated the impact of FES on established users of more than 6 months. Both studies noted significant ongoing orthotic effects, except in participants already walking at baseline speeds of >0.8m/s[39].

The therapeutic effect of FES on longer walking tests was investigated in only 5 studies. There were mixed results with positive effects being noted at 12 weeks[30,32] and 11 months[30], but not at 12[42] and 18 weeks[13,25].

[Insert Table 3 here]

Methodological quality

The methodological quality of the studies is detailed in Table 4. The global rating for methodological quality was moderate for 12 articles[12,13,25,26,28,30, 32,34,35,37,40,41] while the remaining 8 articles received a global rating of weak[27,29,31,33-36,42]. None of the 20 articles gained an overall strong rating largely due to difficulty blinding participants and assessors with FES. All of the studies scored weak on blinding thus indicating performance and detection bias. Twelve articles rated strong for data collection methods[12,13,25,26,28-30,32,34,36,37,40]. One study rated strong for selection bias[25], one study rated weak[29] and all the others rated moderate. Study design was rated moderate for all of the studies excluding 2 that were rated weak [29,42]. For fifteen articles the confounders variable was not applicable[12,13,28-3,40,42] as there were no comparator control groups.

[Insert Table 4 here]

Analysis of overall effect

Eleven studies recruiting 353 participants were included in the meta-analysis for the initial orthotic effect of FES on gait speed for short walking speed tests (Table 5). Eight articles with a total of 255 participants were included for meta-analysis of ongoing orthotic effects (Table 5). Meta-analyses revealed evidence of a significant initial ($t = 2.14$, $p = 0.016$) and ongoing orthotic effect of up to 20 weeks ($t = 2.81$, $p = 0.003$) using FES for foot drop on gait speed in short walking performance tests in pwMS. Walking speed

increased by 0.05 meters per second (m/s) (7.1%) for the initial orthotic effect and 0.08m/s (11.3%) and for the ongoing orthotic effect.

Six studies recruiting 244 participants were included in the meta-analysis for the therapeutic effect of FES on gait speed (Table 5). Analyses of the pooled data found no change in gait speed in the short walking performance tests and thus no therapeutic effect (t=0.03, p=0.487) with FES.

Five studies recruiting 89 participants were included in the meta-analysis for the initial orthotic effect on gait speed in long walking performance tests (Table 6). Eighty one participants were included for analyses of the ongoing orthotic effect of FES. There was a small non-significant increase in walking speed of 0.02m/s (3.3%) for the initial orthotic (t=0.57, p=0.286) and a small non-significant increase of 0.04m/s (6.2%) for ongoing continued orthotic effect (of up to 20 weeks) (t=0.94, p=0.174) with FES (Table 6).

Only 3 studies recruiting 61 participants included data that was used to evaluate the therapeutic effect (up to 20 weeks) of FES on gait speed in long walking performance tests. There was a 10.3% increase in walking speed noted, however this was non-significant (t=1.34, p=0.091) (table 6).

[Insert Tables 5 &6 here]

Discussion

This systematic review aimed to appraise the efficacy of FES for foot drop in pwMS on gait speed in short and long walking performance tests. A systematic and inclusive approach was undertaken for study selection, with independent assessment of quality and data extraction. In this review of 20 articles (19 studies) analysis of pooled data found a statistically significant initial ($t=2.14$, $p=0.016$) and ongoing ($t=2.81$, $p=0.003$) orthotic effect of FES on gait speed in short walking performance tests, increasing gait speed by 0.05 and 0.08m/s, respectively. No therapeutic effect was found. A change of 0.05m/s in walking speed is considered to be clinically significant, with a change of 0.1m/s indicating a substantial clinical change[43]. Therefore this review identified effects of FES on walking that are meaningful to pwMS. FES produced small non-significant initial and ongoing orthotic and therapeutic effects on gait speed in long walking performance tests.

Contradictory results however were found across the studies. The majority of studies reported statistically significant ongoing orthotic effects for the short walk tests, however 2 studies did not. One of these studies recruited participants with lower disability scores[33]. Both studies recruited participants with baseline walking speeds of >0.8m/s (1.2m/s[33] and 0.83m/s[35]). Miller et al.[39] had previously found FES to have no orthotic effect in pwMS walking at gait speeds of >0.8m/s. These results therefore shed some doubt on the use of FES in pwMS with lower levels of disability and faster baseline walking speeds. Further investigation of FES in pwMS walking at faster gait speeds is required.

The majority of the studies evaluating therapeutic effects of FES on short walking tests reported no significant difference, however 3 studies reported a negative therapeutic effect[13,26,42]. One of these studies recruited participants with secondary progressive MS,

where deterioration in walking speed is expected over time. The other 2 articles investigated implantable FES. Hausmann et al.[42], a study of only 2 participants, reported a negative therapeutic effect in 1 participant. Taylor et al.[13] reported therapeutic effects over a longer time frame (3 years) and although there was no detail given regarding MS type of recruited participants, the time since diagnosis (mean of 17.3 years) is indicative of participants presenting with secondary progressive MS. The results from these studies suggest that the potential therapeutic effect of FES may be limited in progressive MS patients, however further investigation is warranted.

The National Institute for Health and Care Excellence (NICE) guidelines for FES for foot drop of central neurological origin[44] found evidence to support the use of FES, however studies included in the NICE review were undertaken in stroke and not MS. There has not been a systematic review specifically evaluating FES in MS although a recent narrative synthesis found positive orthotic, but not therapeutic effects of FES on walking performance. This review recommended that FES be used to complement treatments for walking limitation in MS and had potential to optimize functional outcomes[14]. The results from this systematic review supports and further strengthens the recommendations of the NICE guidelines and the previous narrative review, by adding further evidence in terms of the positive impact of FES in MS.

There have been 3 previous reviews of FES in stroke. A narrative synthesis[14] reported positive orthotic effects of FES on gait speed in chronic stroke, although there was less conclusive evidence of a therapeutic effect. Kottink et al.[16] reviewed 8 studies and reported an increase in gait speed of 0.13 m/s (0.07–0.2, 38%) with FES, that is larger than found in this review for short walk tests

(0.08m/s (-0.01-0.1, 11%)). Pereira et al.[17] reviewed 7 RCTs and found a small but significant therapeutic effect with FES (0.379 m/s ± 0.152; 95% CI, 0.081 to 0.677; *P* = .013) in the 6minWT in chronic stroke. This increase again is more than that found in the current review for short walk tests (0m/s (-0.06-0.1, no change)); however it may be that potential therapeutic effects of FES may be limited by the neurodegenerative nature of MS in comparison to a more acute condition such as stroke and this requires further investigation.

Participants in the studies reviewed had mean Extended Disability Status Scores ranging from 3.5 (moderate disability in one functional system and more than minimal disability in several others, no impairment to walking) to 6 (requires a walking aid (cane, crutch, etc) to walk about 100 meters with or without resting). This sample is representative of pwMS with walking limitations for whom we would expect a benefit from FES application. Participants in the lower Extended Disability Status Score range (3.5) who have less obvious walking difficulties however may present with fatigable foot drop. Decreased ankle dorsiflexion at initial contact has been found to worsen with fatigue[45] in pwMS. None of the studies in this review explicitly reported on recruitment of participants presenting with fatigable foot drop. There is limited evidence that FES may not be beneficial for pwMS with less disability, walking at faster speeds[39] however further investigation is warranted. .

The majority of the articles did not report on MS type which may limit the external validity of the findings of this review, however 2 studies specifically recruited people with secondary progressive MS[12, 25]. The time since diagnosis was reported in all but 4 of the articles and ranged between 9.79 to 17.7 years, which may be more indicative of secondary progressive MS.

Most studies reviewed give little detail around the inclusion and exclusion criteria used and where detail was given there was no consistent approach taken. The use of medications and the effect of relapse and progression of disease may influence outcomes and response to FES therefore the failure of most studies to report these variables may call the validity of results of the studies into question.

There were only two randomized study designs in this review, indicating a high probability of selection bias and poor internal validity. All studies scored weak for blinding signifying performance and detection bias to be significant factors. It is impossible to blind physical treatments such as FES to participants and it is extremely difficult to blind assessors. There were no attempts to separate FES application and outcome assessment in any of the studies, suggesting performance bias. The EPHPP tool considers both blinding and confounders in its scrutiny therefore both factors impact on the overall quality ratings.

Limitations

The primary limitation of this review was the low methodological quality of the studies included. The conclusions of this review must therefore be treated with some caution until further high quality RCTs are undertaken. Although the EPHPP quality assessment tool has demonstrated acceptable levels of test re-test reliability and content and construct validity[19], it was developed to evaluate public health nursing and therefore may not have been the most appropriate tool for this review. Selection of this tool however was

320 based on the recommendations of previous systematic reviews[19,20] and supports an inclusive approach which allowed the same
321 checklist and summary score to be used across all the studies.

322 This review was limited by the inclusion of English language papers and did not include unpublished studies or studies published in
323 grey literature which may limit its applicability. There remains a debate around publication bias and the usefulness of including
324 unpublished trials[46], however it is likely that any unpublished studies would be of poor quality and lack robust peer review [46,47].

325 For the purpose of the meta-analyses data from a range of short and longer walking tests were combined. Although there is
326 evidence to support the comparability of the longer walking tests[23], there are also differences in the pace of the walking tests used
327 which may have influenced the results. A recent MS outcome measures taskforce document has also suggested that the 2minWT
328 should not be used in research due to the limited availability of psychometric data[48].

329 A pragmatic approach was taken which combined data across a range of assessment points (up to 20 weeks) in order to inform
330 continued orthotic and therapeutic effects. There is no evidence to suggest when optimal orthotic or therapeutic effects are likely to
331 occur and whether they remain stable over time. Using this approach therefore may have led to ambiguity with the results.

332 Fewer participants were included in the meta-analyses for the ongoing orthotic (n=81) and therapeutic (n=61) effects of FES on gait
333 speed on long walking performance tests, therefore there are limitations with regards to the strength of these findings. As no raw

data was available within group analysis was not viable and the between group analysis may not have detected subtle effects that may have occurred.

FES is considered a device that should be used long term for orthotic purposes and in a progressive condition like MS this may account for many years. Despite this, only one interventional study[26] reported on effects beyond 24 weeks, therefore the results of this review are only applicable over the short to moderate term.

Implications for further research

Given the low methodology quality of the studies reviewed, future research should focus on adequately powered randomized trial design with a control or comparator treatment arm, such as exercise or AFO. Improved consistency in reporting of methodology, as recommended by the CONSORT guidelines[49] is also recommended. Consistent reporting of demographics including MS type, disability level and baseline walking speed would allow for sub-group analysis. Future studies should include long term follow up and investigate initial and ongoing orthotic and therapeutic effects of FES in order to understand its full potential as a treatment for foot drop in MS.

This current review found a wide variation in the walking tests used between studies both in terms of distance, pace (fastest and preferred) and methods of collection (mean of three, warm up then final test). Researchers should agree on the most valid, reliable and clinically significant measures of gait speed using short and long walking performance tests to allow a more consistent

approach in future FES research. This review is limited to the impact of FES on gait speed in short and long walking performance tests. Some of the articles reported measures of patient experience and quality of life and future studies should consider a mixed methodological approach as recommended by the NICE guidelines [44].

Conclusion

This review found evidence of initial and ongoing orthotic effects of FES for foot drop in MS on gait speed in short walking tests which were clinically meaningful, but did not find evidence of orthotic or therapeutic effects of FES on long walking tests. However due to the poor methodological quality of studies undertaken to date, caution must be applied in making recommendations to clinical practice. There is limited evidence of the comparative effectiveness of FES with other treatments. Future research should focus on adequately powered randomized trial design with a control or comparator treatment arm, using valid and reliable measures of gait speed that can detect clinically meaningful effects.

Suppliers

a. Odstock Medical Limited, Salisbury, UK
b. Innovative Neurotronics Inc., Austin, TX, USA
c. Bioness Inc., Valencia, CA, USA

364 d. Otto Bock Health Care, Duderstadt, Germany

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366 **References**

367 1. Compston A, Coles A. Multiple sclerosis. Lancet 2008;372:1502-1517.

368 2. Noseworthy JH, Lucchinetti C, Rodriguez M, et al. Multiple sclerosis. N Engl J Med 2000;343:938-952.

369 3. Murray TJ. Diagnosis and treatment of multiple sclerosis. BMJ 2006; Mar (Clin Res ed) 332(7540):525-7.

370 4. Mackenzie IS, Morant SV, Bloomfield GA, et al. Incidence and prevalence of multiple sclerosis in the UK 1990-2010:a descriptive
371 study in the general practice research database. J Neurol Neurosurg Psychiatry 2014;85:76-84.

372 5. Confavreux C, Vukusic S. Natural history of multiple sclerosis: a unifying concept. Brain 2006;129:606-616.

373 6. Hobart J, Blight A, Goodman A, et al. Timed 25-foot walk: direct evidence that improving 20% or greater is clinically meaningful
374 in MS. Neurology 2013;80:1509-17.

375 7. Nilsagard Y, Lundholm C, Gunnarsson LG, et al. Clinical relevance using timed walk tests and 'timed up and go' testing in
376 persons with multiple sclerosis. Physiother Res Int 2007;12:105–114.

8. Gijbels D, Alders G, Van Hoof E, et al. Predicting habitual walking performance in multiple sclerosis: relevance of capacity and self-report measures. Mult Scler 2010;16:618–626.

9. Gijbels D, Dalgas U, Romberg A et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. MSJ 2012;18(3):364–371.

10. Gunn H, Creanor S, Haas B, et al. Frequency, characteristics and consequences of falls in multiple sclerosis: findings from a cohort study. Arch Phys Med Rehabil 2014; 95(3): 538-545.

11. Liberson WT, Holmquest HJ, Scot D, et al. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. Arch Phys Med Rehabil 1961; 42: 101–5.

12. Taylor P, Humphries L, Swain I. The long-term cost-effectiveness of the use of functional electrical stimulation for the correction of dropped foot due to upper motor neuron lesion. J Rehabil Med 2013;45(2):154-160.

13. Taylor PN, Wilkinson-Hart IA, Khan MS, et al. The correction of dropped foot due to multiple sclerosis using the STIMuSTEP implanted dropped foot stimulator. Int J MS Care In-Press [serial online] 2016. Available from: http://dx.doi.org/10.7224/1537-2073.2015-038

14. Dapul G, Bethoux F. Functional electrical stimulation for foot drop in multiple sclerosis. US Neurology 2015:10-18.

391 15. Roche A, Laighin GO, Coote S. Surface-applied functional electrical stimulation for orthotic and therapeutic treatment of drop
392 foot after stroke: a systematic review. Phys Ther Rev 2009;14(2):63-80.

393 16. Kottink AIR, Oostendorp LJM, Buurke JH et al. The orthotic effect of functional electrical stimulation on the improvements of
394 walking in stroke patients with a dropped foot: a systematic review. Artif Organs 2004;28(6):577-86.

395 17. Pereira S, Mehta S, McIntyre A, et al. Functional electrical stimulation for improving gait in persons with chronic stroke. Top
396 Stroke Rehabil 2012;19(6):491-8.

397 18. Katrak P, Bialocerkowski A, Massy-Westropp, et al. A Systematic review of the content of critical appraisal tools. BMC Medical
398 Research Methodol 2004 Sep 16;4: 22.

399 19. Thomas BH, Ciliska M, Dobbins M, et al. A process for systematically reviewing the literature: providing the research evidence.
400 Worldviews Evid.-Based Nurs 2004;1:176-184.

401 20. Deeks JJ, Dinnes J, D'Amico R, et al. Evaluating non-randomised intervention studies. Health Technol. Assess 2003;7:iii- x,
402 173.

403 21. Sanderson S, Tatt DI, Higgans JPT. Tools for assessing quality and susceptibility to bias in observational studies in
404 epidemiology: a systematic review and annotated bibliography. Int J. Epidemiol 2007;36:666-676.

22. Everitt, B.S. Cambridge of statistics in the medical sciences. Cambridge UK: Cambridge University Press 1995.

23. Gijbels D, Eijnde BO, Feys P. Comparison of the 2- and 6-minute walk test in multiple sclerosis. Mult Scler 2011;17(10):1269-72.

24. Tomlinson A, Khanal S, Ramaesh K, et al. Tear Film Osmolarity: Determination of a referent for dry eye diagnosis. Invest Ophthalmol. Vis Sci 2006;47(10).

25. Barrett CL, Mann GE, Taylor PN, et al. A randomized trial to investigate the effects of functional electrical stimulation and therapeutic exercise on walking performance for people with multiple sclerosis. Mult Scler 2009;15:493-504.

26. Taylor P, Barrett C, Mann G, et al. A feasibility study to investigate the effect of functional electrical stimulation and physiotherapy exercise on the quality of gait of people with multiple sclerosis. Neuromodulation 2014;17:75-84.

27. Mayer L, Warring T, Agrella S, et al. Effects of electrical stimulation on gait function and quality of life for people with multiple sclerosis taking dalfampridine. Int J MS Care 2015;17:35-41.

28. Scott SM, Van der Linden ML, Hooper JE, et al. Quantification of gait kinematics and walking ability of people with multiple sclerosis who are new users of functional electrical stimulation. J Rehabil Med 2013;45:364-69.

418 29. Sheffler LR, Norgan Bailey S, Chae J. Spatiotemporal and kinematic effect of peroneal nerve stimulation versus an ankle- foot
419 orthosis: A case series. Am J Phys Med Rehabil 2009a;1:604-11.

420 30. Stein R, Everaert DG, Thompson AK, et al. Long term therapeutic and orthotic effect of a foot drop stimulator on walking
421 performance in progressive and non-progressive neurological disorders. Neurorehabil Neural Repair 2010; 24:152-167.

422 31. Van der Linden M, Scott S, Hooper J, et al. Gait kinematics of people with multiple sclerosis and the acute application of
423 functional electrical stimulation. Gait Posture 2014a; 39: 1092–1096.

424 32. Van der Linden M, Hooper J, Cowan P, et al. Habitual functional electrical stimulation therapy improves gait kinematics and
425 walking performance, but not patient-reported functional outcomes, of people with multiple sclerosis who present with foot-drop.
426 PLOS ONE 2014(b); 9: 1-9.

427 33. Barr C, Patritti B, Bowes R, et al. Orthotic and therapeutic effect of functional electrical stimulation on fatigue induced gait
428 patterns in people with multiple sclerosis. Disabil Rehabil Assist Technol 2016;12(52):1-1331.

429 34. Downing A, Van Ryn D, Fecko A, et al. Effect of a 2 week trial of functional electrical stimulation on gait function and quality of
430 life in people with multiple sclerosis. Int J MS Care 2014;16(3):146-152.

431 35. Sheffler L, Hennessey M, Knutson J, et al. Neuroprosthetic Effect of peroneal nerve stimulation in multiple sclerosis: a
432 Preliminary Study. Arch Phys Med Rehabil 2009b;90:362-365.

433 36. Paul L, Rafferty D, Young S, et al. The effect of functional electrical stimulation on the physiological cost of gait in people with
434 multiple sclerosis. Mult Scler 2008;14:954-61.

435 37. Barrett C, Taylor P. The effects of the Odstock drop foot stimulator on perceived quality of life for people with stroke and
436 multiple sclerosis. Neuromodulation 2010;13:58-64.

437 38. Miller L, Rafferty D, Paul L et al. A comparison of the orthotic effect of the Odstock dropped foot stimulator and the Walkaide
438 functional electrical stimulation systems on energy cost and speed of walking in multiple sclerosis. Disabil Rehabil Assist Technol,
439 2015;10(6):482-85.

440 39. Miller L, Rafferty D, Paul L et al. The impact of walking speed on the effects of functional electrical stimulation for foot drop in
441 people with multiple sclerosis. Disabil Rehabil Assist Technol 2016;11(6):478-83.

442 40. Street T, Taylor P, Swain I. The effectiveness of functional electrical stimulation on walking speed, functional walking category
443 and clinically meaningful changes for people with multiple sclerosis. Arch Phys Med Rehabil 2015;96(4):667-672.

444 41. Taylor P, Burridge J, Dunkerly A, et al. Clinical use of the Odstock dropped foot stimulator: it's effect on the speed and effort of
445 walking. Arch Phys Med Rehabil 1999;80:1577-1583.

446 42. Hausmann J, Sweeney-Reed C, Sobieray U, et al. Functional electrical stimulation through direct 4-channel nerve stimulation to
447 improve gait in multiple sclerosis: a feasibility study. J Neuroeng Rehabil 2015;12(100):1-9.

448 43. Pereira S, Mody SH, Woodman RC, et al. Meaningful change and responsiveness in common physical performance measures
449 in older adults: meaningful change and performance. J Am Geriatr Soc 2006;54:743-749.

450 44. National Institute for Health and Care Excellence (NICE). Functional electrical stimulation for foot drop of central neurological
451 origin; interventional procedure guidance. United Kingdom [IPG278] 2009. .

452 45. McLoughlin JV, Barr CJ, Patritti B et al. Fatigue induced changes to kinematic and kinetic gait parameters following six minutes
453 of walking in people with multiple sclerosis. Disabil Rehabil. 2016;38:535-543.

454 46. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. West Sussex: John Wiley & Sons Ltd; 2008.

455 47. Egger M, Ju¨ni P, Bartlett C, et al. How important are comprehensive literature searches and the assessment of trial quality in
456 systematic reviews? Empirical study. Health Technology Assessment 2003;7:1.

48. Potter K, Allen D, Bennett S, et al. Multiple sclerosis outcome measures taskforce [serial online]. Available from: URL: http://www.neuropt.org/docs/ms-edge-documents/final-ms-edge-document.pdf?sfvrsn=4

49. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–732.

Figure and table legends

Table1: Search strategy for databases

Table 2: Summary of study design, sample information, outcome measures, assessment points and potential sources of bias of selected studies. (key: N=numbers of participants, NR=not reported, pwMS=people with MS, SPMS=secondary progressive MS, PP=primary progressive, RR=relapsing remitting, DF=dorsiflexion, PF=plantarflexion, EDSS=Extended Disability Status Scale, HAI=Hauser Ambulation index, L/L=lower limb, HSP=Hereditary Spastic Paraplegia, FAP=Functional Ambulation Profile, MSWS-12=Multiple Sclerosis Walking Scale-12, MSIS-29=Multiple Sclerosis Impact Scale-29, PIADS=Psychological Impact of Assistive Device Scale,SF-36= short form-36, FWC=Functional Walking Category, PCI=Physiological Cost Index, ROGA=Rivermead Observational Gait Analysis, s=seconds, m=meters, ft=feet, wks=weeks, min=minute, mths=months, meds=medications)

Table 3: Summary of outcome measures used, effects measured (initial, ongoing and therapeutic) and results for gait speed in short walking performance tests (10 meter walk test (10MWT), 25 foot walk test (25ftWT), 6 meter walk test (6MWT)) and long walking performance tests (6 minute walk test (6minWT), 5 minute self-selected walking speed (5minSSWS), 4 minute walk test (4minWT), 3 minute walk test (3minWT) and 2 minute walk test (2minWT)). (Key: ↑ increase, ↓decrease, sig=statistically significant, º=not statistically significant, NR=not reported, m=meters, s=seconds, m/s=meters per second, wks=weeks, mths=months).

Table 4: Methodological quality assessment using the Effective Public Health Practice Project (EPHPP) tool

Table 5: Initial and ongoing orthotic and therapeutic effects for combined short walking performance tests (*ft/s converted to m/s where required, + no FES OFF data reported)

Table 6: Initial and ongoing orthotic and therapeutic effects for combined long walking performance tests

Figure 1: SIGN algorithm for classifying study design

Figure 2: PRISMA flowchart demonstrating identification process for systematic review