NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of electrical stimulation to improve muscle strength in non-neurological chronic conditions

Muscle weakness can be caused by chronic conditions that do not affect nerves directly (non-neurological), such as chronic obstructive pulmonary disease, chronic heart failure and chronic kidney disease. In this procedure, small electrical impulses are delivered to weakened muscles, usually in the arms or legs, using electrodes placed on the skin. The aim is to contract the muscles, making them stronger.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in August 2019.

Procedure name

- Electrical stimulation to improve muscle strength in non-neurological chronic conditions

Professional societies

- British Society of Rehabilitation Medicine
- Chartered Society of Physiotherapists
- Institute of Physics and Engineering in Medicine
- Royal College of Physicians
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Physicians of Edinburgh
- Society for Research in Rehabilitation

Description of the procedure

Indications and current treatment

Non-neurological chronic conditions such as chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) or chronic kidney disease (CKD) can cause impaired muscle function and weakness.

Rehabilitation is described in NICE's guidance on rehabilitation after critical illness, chronic obstructive pulmonary disease and chronic heart failure. Current management for muscle weakness or dysfunction caused by non-neurological chronic conditions includes lifestyle change, medication (including oxygen therapy), rehabilitation (such as pulmonary rehabilitation or cardiac rehabilitation) and treating the underlying conditions.

What the procedure involves

Electrical stimulation produces muscle contractions that aim to mimic exercise training. Small electrical impulses are applied to nerves supplying groups of muscles typically in either the arms or legs, using self-adhesive electrodes applied to the skin and connected to an electrical stimulator. This causes the muscles supplied by the nerve to contract and relax. A typical programme consists of 30 to 60 minutes of stimulation.

Outcome measures

The **6-minute walk test** determines the submaximal exercise capacity. It consists of a 6-minute free walk, as fast as possible, across a flat surface of 30 m length scaled at each meter. The total distance walked is recorded at 6 minutes.

The **Beck Depression Inventory** is a 21-item, multiple choice, self-administered inventory. Scores 1 to 10 are considered normal, while a score over 40 indicates extreme depression.

The **Borg dyspnoea scale** is a self-administered measure for dyspnoea and ranges from 0 (no breathlessness) to 10 (maximum breathlessness).

The **Medical Research Council dyspnoea scale** is a self-administered questionnaire for grading the effect of breathlessness on daily activities. It consists of 5 statements: grade 1 indicates mild disabling COPD (only get breathless with strenuous exercise) while grade 5 presents severely disability (too breathless to leave the house).

The **Minnesota Living with Heart Failure Questionnaire** is a self-administered questionnaire to determine whether a treatment for heart failure is effective for improving a patient's quality of life by reducing the adverse effects of heart failure.

The **Short Form-8 Health Survey** is an abbreviated version of an original 36-item health survey. The 8 domains include general health, physical functioning, role physical, bodily pain, vitality, social functioning, mental health, and role emotional. Higher scores indicate better health.

The **St George's Respiratory Questionnaire** (SGRQ) is self-administered and includes 50 items in 3 components: symptoms, activity and impact on daily life. The scores range from 0 to 100, with 0 indicating no impairment and a higher score representing worse health-related quality of life.

Efficacy summary

COPD, chronic respiratory disease, CHF or thoracic cancer

Muscle strength and mass

In a systematic review and meta-analysis of 18 studies of 933 patients with advanced disease (COPD, chronic respiratory disease, chronic heart failure or thoracic cancer), compared with control groups, the electrical stimulation groups showed a statistically significantly improvement in quadriceps muscle strength (standardised mean difference [SMD]=0.53 Nm, 95% confidence interval [CI] 0.19 to 0.87, p=0.002, I^2=72%; 12 studies of 781 patients)[1]. For quadriceps muscle mass, the electrical stimulation groups improved muscle mass compared with the control groups measured using anthropometry (SMD=0.69 cm^3, 95% CI -0.05 to 1.42, p=0.89, I^2=0%; 2 studies of 31 patients), using DEXA (SMD=0.09 cm^3, 95% CI -0.20 to 0.38, p=0.89, I^2=0%; 4 studies of 179 patients), using ultrasound (SMD=0.82 cm^3, 95% CI 0.26 to 1.39, p=0.0045; 1 study of 52 patients) and using computed tomography (SMD=1.01 cm^3, 95% CI 0.42 to 1.60, p=0.00081, I^2=0%; 2 studies of 52 patients)[1].

Pulmonary function

In the systematic review and meta-analysis of 18 studies of 933 patients, the electrical stimulation groups showed improved peak oxygen uptake compared with the control groups (mean difference [MD]=45 mL/min, 95% CI 7.3 to 97.0, p=0.092, I^2=0%; 4 studies of 109 patients)[1].

Walking distance

In the systematic review and meta-analysis of 18 studies of 933 patients, compared with the control groups, the electrical stimulation groups showed increased walking distance measured using the 6-minute walking test (6MWT, MD=35 m, 95% CI 13.52 to 56.05, p=0.0013, I^2=60%; 8 studies of 317 patients), using the incremental shuttle walk test (MD=9 m, 95% CI -34.87 to 52.31, p=0.69, I^2=83%; 3 studies of 434 patients) and using the endurance shuttle walk test (MD=65 m, 95% CI -17.79 to 146.05, p=0.12, I^2=30%; 4 studies of 452 patients)[1].

Chronic heart failure

Muscle strength and circumference

In a systematic review and meta-analysis of 13 studies of 435 patients with heart failure, for electrical stimulation compared with no-exercise controls, there was a statistically significant improvement in muscle strength of 30.74 Nm (95% CI 3.67 to 57.81, p=0.03, I^2=0%; 2 studies)[2]. In a randomised controlled trial of 91 patients with chronic heart failure, statistically significant increases in quadricipital muscles strength and circumference were reported in both the electrical stimulation plus exercise group (baseline 23.7 kg ± 11.4 kg compared with end of trial 29.9 kg ± 14.1 kg, p<0.01; baseline 44.7 cm ± 5.5 cm compared with end of trial 46.0 cm ± 5.6 cm, p<0.01; respectively) and in the exercise-only group (baseline 23.4 kg ± 10.5 kg compared with end of trial 30.5 kg ± 13.6 kg, p<0.01; baseline 43.0 cm ± 4.4 cm compared with end of trial 43.8 cm ± 4.4 cm, p<0.01)[3].

Pulmonary function

In the systematic review and meta-analysis of 13 studies of 435 patients, compared with the aerobic exercise groups, the electrical stimulation groups showed a statistically significant low peak VO_2 of -0.44 ml/kg/min (95% CI -0.68 to -0.20, p=0.0004, I^2=0%; 6 studies of 217 patients)[2], and compared with no-exercise controls the electrical stimulation groups showed statistically significantly improved peak VO_2 by 1.85 ml/kg/min (95% CI 0.46 to 3.23, p=0.009, I^2=97%; 3 studies of 76 patients)[2]. In the randomised controlled trial of 91 patients, both groups showed statistically significant improvements in ventilatory threshold (VT) VO_2 (electrical stimulation plus exercise: baseline 12.6 ml/kg/min ± 3.6 ml/kg/min compared with end of trial 13.3 ml/kg/min ± 4.3 ml/kg/min, p=0.03; exercise: baseline 12.2 ml/kg/min ± 3.3 ml/kg/min compared with end of trial 13.5 ± 3.3 ml/kg/min, p=0.005), and peak VO_2 (electrical stimulation plus exercise: baseline 17.5 ml/kg/min ± 5 ml/kg/min compared with end of trial 19.8 ml/kg/min ± 6.7 ml/kg/min, p=0.004; exercise: baseline 16.1 ml/kg/min ± 4.9 ml/kg/min compared with end of trial 18.4 ml/kg/min ± 4.9 ml/kg/min, p=0.006). Improvements in these measures were not statistically different between groups (p>0.05), even if the age groups were compared separately[3].

Walking distance

In the systematic review and meta-analysis of 13 studies of 435 patients, there was a non-statistically significant improvement in the 6MWT distance in the electrical stimulation group compared with the aerobic exercise groups (weighted mean difference [WMD]=0.72 m, 95% CI −23.74 to 25.18, p=0.95, I^2=42%; 5

studies of 168 patients), and a statistically significantly increase compared with no-exercise controls (WMD=63.54 m, 95% CI 35.81 to 91.27, I^2=53%, p<0.00001; 6 studies of 156 patients)[2]. In the randomised controlled trial of 91 patients, both groups showed statistically significant improvements in the 6MWT distance (electrical stimulation plus exercise: baseline 441 ± 89 m compared with end of trial 513 ± 101 m, p<0.001; exercise: baseline 448 ± 118 m compared with end of trial 515 ± 106 m, p=0.003). No statistically significant difference was found between groups (p>0.05), even if the age groups were compared separately[3].

Health-related quality of life (HRQOL)

In the systematic review and meta-analysis of 13 studies of 435 patients, the total score of the Minnesota questionnaire was improved in the electrical stimulation groups compared with the aerobic exercise groups (WMD=2.21 points, 95% CI -4.58 to 8.99, p=0.52, I^2=0%; 2 studies of 76 patients), and statistically significantly enhanced HRQOL compared with no-exercise controls (SMD=0.89 points, 95% CI 0.55 to 1.24, p<0.00001, I^2=0%; 5 studies)[2]. In the randomised controlled trial of 91 patients, there was a statistically significant improvement in the Minnesota questionnaire total score in the electrical stimulation plus exercise group (baseline 41 ± 22 points compared with end of trial 24 ± 15 points, p<0.01) and in the exercise group (baseline 37 ± 17 points compared with end of trial 25 ± 15 points, p<0.05), without any statistically significant differences between groups (p>0.05)[3].

Depressive symptoms

In the systematic review and meta-analysis of 13 studies of 435 patients, depressive symptoms were statistically significantly improved in patients who had electrical stimulation compared to no-exercise controls (WMD=-3.86 points, 95% CI -6.46 to -1.25, p=0.004, I^2=0%; 2 studies) using the Beck Depression Inventory[2].

Chronic obstructive pulmonary disease

Muscle strength and force

In a systematic review and meta-analysis of 16 studies of 267 patients with COPD, peripheral muscle force statistically significantly improved in patients who had electrical stimulation compared with usual care (SMD=0.34, 95% CI 0.02 to 0.65, p=0.037, I^2=0%; 6 studies of 159 patients), and non-statistically significantly increased in patients who had electrical stimulation plus exercise compared with exercise only (SMD=0.47, 95% CI -0.10 to 1.04, p=0.10, I^2=39%; 4 studies of 84

patients)[5]. In a meta-analysis of 9 studies of 276 patients with stable, moderate-to-severe COPD, compared with the control groups, electrical stimulation statistically significantly enhanced quadriceps muscle strength (SMD=1.12, 95% CI 0.64 to 1.59, p<0.00001, I^2=54%; 6 studies of 207 patients)[6].

Peripheral muscle endurance

In the systematic review and meta-analysis of 16 studies of 267 patients, compared with usual care, electrical stimulation statistically significantly improved peripheral muscle endurance (SMD=1.36, 95% CI 0.59 to 2.12, p=0.00052, I^2=0%; 2 studies of 35 patients)[5].

Pulmonary function

In the systematic review and meta-analysis of 16 studies of 267 patients, electrical stimulation increased VO_2 peak compared with usual care (MD=0.10 L/min, 95% CI 0.00 to 0.19, p=0.040, I^2=0%; 4 studies of 73 patients)[5]. In a randomised controlled trial of 51 patients with stable COPD the VO_2 peak increased by 0.5 mL/kg/min (95% CI -0.3 to 10.5, p=0.22) in patients who had electrical stimulation plus pulmonary rehabilitation (PR) and statistically significantly improved by 1.1 mL/kg/min (95% CI 0.2 to 1.9, p=0.04) in patients who had PR alone. Comparing electrical stimulation plus PR with PR alone, the difference between means was -0.5 mL/kg/min (95% CI -1.8 to 0.7, p=0.37)[7].

In the systematic review and meta-analysis of 16 studies of 267 patients, compared with usual care, electrical stimulation improved dyspnoea on completion of an exercise test assessed using the Borg score (MD=-1.03 units, 95% CI -2.13 to 0.06, p=0.064, I^2=59%; 3 studies of 55 patients)[5]. In the randomised controlled trial of 51 patients, the improvement in the modified Medical Research Council dyspnoea scale was statistically significant in the electrical stimulation plus PR group (MD=-0.4 points, 95% CI -0.6 to -0.1, p<0.01) but not for the PR alone group (MD=-0.2 points, 95% CI -0.5 to 0.1, p=0.27)[7]. Comparing electrical stimulation plus PR with PR alone, the difference between means was −0.2 points (95% CI -0.6 to 0.2, p=0.38)[7].

Walking distance

In the systematic review and meta-analysis of 16 studies of 267 patients, the 6MWT distance statistically significantly improved in the electrical stimulation groups compared with usual care (MD=39.26 m, 95% CI 16.31 to 62.22, p=0.00080, I^2=0%; 2 studies of 72 patients), and in the electrical stimulation plus exercise groups compared with the exercise only groups (MD=25.87 m, 95% CI 1.06 to 50.69, p=0.041, I^2=8%; 6 studies of 138 patients)[5]. In a meta-analysis of 9 studies of 276 patients, compared with control groups, the electrical stimulation

groups showed a statistically significant increase in exercise distance travelled for the 6MWT and SWT (WMD=51.53 m, 95% CI 20.13 to 82.93, $I^2_{overall}$ =90%, $I^2_{subgroup\ differences}$=0, p=0.001; 7 studies of 235 patients)[6]. In the randomised controlled trial of 51 patients, the 6MWT distance increased by 17.5 m (95% CI 1.8 to 33.2, p=0.54) in patients having electrical stimulation plus PR and statistically significantly increased by 21.33 m (95% CI 4.6 to 38.1, p=0.02) in patients who had PR alone[7], with the minimum clinically important difference being 25 m. Comparing electrical stimulation plus PR with PR alone, the difference between means was -3.9 m (95% CI -26.3 to 18.6, p=0.73)[7].

Exercise endurance

In the systematic review and meta-analysis of 16 studies of 267 patients, the electrical stimulation groups showed statistically significantly increased exercise endurance compared with usual care (MD=3.62 minutes, 95% CI 2.33 to 4.91, p<0.00001, I^2=32%; 3 studies of 55 patients)[5]. In the meta-analysis of 9 studies of 276 patients, the electrical stimulation groups showed statistically significantly enhanced exercise endurance for the constant-work test and the shuttle walk test compared with controls (SMD=1.11 minutes, 95% CI 0.14 to 2.08, $I^2_{overall}$ =85%, $I^2_{subgroup\ differences}$=81.6%, p=0.02; 5 studies of 163 patients)[6].

Days to first transfer out of bed

In the systematic review and meta-analysis of 16 studies of 267 patients, compared with exercise alone, patients having electrical stimulation plus exercise statistically significantly decreased the number of days between randomisation and when they first transferred out of bed (MD=4.98 days, 95% CI -8.55 to -1.41, p=0.0063, I^2=60%; 2 studies of 44 patients)[5].

Health-related quality of life (HRQOL)

In the systematic review and meta-analysis of 16 studies of 267 patients, the electrical stimulation groups showed improved HRQOL compared with usual care (MD=4.12 points, 95% CI -12.60 to 4.35, p=0.34, I^2=74%; 2 studies of 72 patients) using the St George's Respiratory Questionnaire (SGRQ), and the electrical stimulation plus exercise groups showed improved HRQOL compared with exercise alone (SMD=0.56 points, 95% CI -1.27 to 0.15, p=0.12, I^2=55%; 4 studies of 95 patients)[5]. In the meta-analysis of 9 studies of 276 patients, electrical stimulation did not improve HRQOL using SGRQ compared with the control groups (WMD=-0.07 points, 95% CI -2.44 to 2.30, p=0.95, I^2=56%; 4 studies of 180 patients)[6]. In the randomised controlled trial of 51 patients, the change in the total score of SGRQ was statistically significant in the electrical stimulation plus PR group (MD=5%, 95% CI -9 to -1, p=0.03) but not for the PR group (MD=-4%, 95% CI -10.1 to 2.6, p=0.23). The change between groups was

-1% (95% CI -8.1 to 5.7, p=0.72), with the minimum clinically important difference being -4%[7].

Chronic kidney disease (CKD)

Muscle strength

In a randomised controlled trial of 44 patients with CKD on haemodialysis, patients in the high frequency and intensity electrical stimulation group showed a statistically significant increase in right peripheral muscle strength (155.35 ± 65.32 Nm initial compared with 161.60 ± 68.73 Nm final; p=0.01) and in left peripheral muscle strength (156.60 ± 66.51 Nm initial compared with 164.10 ± 69.76 Nm final; p=0.02)[8]. Patients who had low frequency and intensity electrical stimulation reported a statistically significant improvement in right peripheral muscle strength (109.40 ± 32.08 Nm initial compared with 112.65 ± 38.44 Nm final, p=0.50) but not left peripheral muscle strength (113.65 ± 37.79 Nm initial compared with 116.15 ± 43.01 Nm final, p=0.61). For the between-group comparison, there was a statistically significant difference in the left peripheral muscle strength (p=0.50) but not the right peripheral muscle strength (p=0.79)[8].

In a randomised controlled trial of 51 patients with CKD on haemodialysis, at 10 weeks, comparing modelled mean changes, adjusted for baseline value, age and sex, low frequency electrical stimulation was superior to control in isometric leg strength (94 Nm, 95% CI 35.6 to 152.3, p=0.002) but not for cycling (p>0.05)[9].

In a randomised controlled trial of 40 patients with CKD on haemodialysis, patients in the electrical stimulation group showed statistically significantly increased muscular strength in maximum 1-repetition test (p<0.001) compared with patients in the control group[10].

In a randomised controlled trial of 26 patients with CKD on haemodialysis, compared with the control group, the electrical stimulation group showed a statistically significant increase in the knee extensor strength (right: 22.3 ± 12.8 Nm compared with -10.8 ± 22.3 Nm, p<0.001; left: 26.1 ± 29.7 Nm compared with -8.3 ± 18.7 Nm, p=0.001), and in the cross-sectional area (CSA) at 3 positions of the quadriceps muscle, 25%, 50% and 75% of the segment length from the greater trochanter to the inferior border of the lateral epicondyle of the femur (25% right: electrical stimulation 1.7 ± 2.0 cm^2 compared with control -0.4 ± 1.8 cm^2, p=0.05; 25% left: electrical stimulation 1.3 ± 1.1 cm^2 compared with control -0.6 ± 1.8 cm^2, p=0.01; 50% right: electrical stimulation 2.0 ± 2.2 cm^2 compared with control -0.7 ± 1.9 cm^2, p=0.004; 50% left: electrical stimulation 2.7 ± 2.1 cm^2 compared with control -0.7 ± 1.6 cm^2, p=0.001; 75% right: electrical stimulation 1.8 ± 2.2 cm^2 compared with control -0.7 ± 1.5 cm^2, p=0.003; 75%

left: electrical stimulation 2.1 ± 1.9 cm^2 compared with control -0.4 ± 1.5 cm^2, p=0.003)[11].

Pulmonary function

In the randomised controlled trial of 51 patients, comparing modelled mean changes, adjusted for baseline value, age and sex, low frequency electrical stimulation was superior to control in VO_2 peak (2.0 $ml.kg^{-1}$per min^{-1}, 95% CI 0.3 to 3.7, p=0.02) and $VO_{2\ AT}$ (1.8 $ml.kg^{-1}$per min^{-1}, 95% CI 1.0 to 2.6, p<0.001) but not for cycling (p>0.05) at 10 weeks[9]. In the randomised controlled trial of 40 patients, compared with the control group, patients who had electrical stimulation had a statistically significantly increased maximum inspiratory pressure (p=0.02), maximum expiratory pressure (p<0.0001) and respiratory frequency (p<0.001)[10].

Walking distance

In the randomised controlled trial of 44 patients, the 6MWT distance statistically significantly increased in both groups: high frequency and intensity electrical stimulation (435.55 ± 95.81 m initial compared with 457.25 ± 90.64 m final; p=0.02) and low frequency and intensity electrical stimulation (403.80 ± 90.56 m initial compared with 428.90 ± 87.42 final; p=0.007). There was no statistically significant difference between groups in the 6MWT distance (p=0.32) after the intervention[8]. In the randomised controlled trial of 42 patients, the 6MWT distance statistically significantly improved in the electrical stimulation group (before 350.40 m ± 97.53 m compared with after 373.20 m ± 112.94 m, p=0.03) and increased in the control group (before 330.00 m ± 68.77 m compared with after 327.20 m ± 53.93 m, p=0.71). The between-group comparison showed a statistically significant improvement in distance (p=0.03) after the stimulation[10].

Health-related quality of life

In the randomised controlled trial of 26 patients, both electrical stimulation and control groups exhibited no statistically significant changes in the scores of the Short Form-8 health survey after the intervention, but the improvements in physical functioning (baseline 43.8 ± 10.7 compared with final 50.3 ± 4.4, p=0.08) and vitality (baseline 49.0 ± 6.8 compared with final 53.1 ± 5.5, p=0.09) in the electrical stimulation group were close to the statistical significance level[11].

Safety summary

COPD, chronic respiratory disease, CHF or thoracic cancer

Muscle discomfort following the stimulation during the initial few days was reported in 4% (19/518) of patients allocated to electrical stimulation (in 4

studies) in the systematic review and meta-analysis of 18 studies of 933 patients[1].

Persistent erythema, which was considered possibly related to use of adhesive electrodes, was reported in 2 patients (1 study of 52 patients) in the systematic review and meta-analysis of 18 studies of 933 patients[1].

Chronic heart failure

Electromagnetic interference was provoked in 2 patients with heart failure who had implantable cardioverter defibrillators (case report of 2 patients) in a systematic review of 4 studies of 43 patients[4]. Electromagnet interference happened when electrical stimulation was applied to abdominal muscles, and resulted in implantable cardioverter defibrillator discharge due to misinterpreting electrical signals as cardiac signals in the ventricular fibrillation zone[4].

Electrode allergy was reported in 16 sessions of electrical stimulation in the randomised controlled trial of 91 patients[3].

Variculae were reported following 3 sessions of electrical stimulation in the randomised controlled trial of 91 patients[3].

Pain was reported, with a mean score of 3.8 on a scale of 1 to 10, in the randomised controlled trial of 91 patients[3].

Paraesthesia was reported following 3 sessions of electrical stimulation in the randomised controlled trial of 91 patients[3].

Chronic kidney disease

Muscle discomfort was reported in 2 patients (1 in the high frequency and intensity electrical stimulation group and 1 in the low frequency and intensity group) during the intervention in the randomised controlled trial of 44 patients, and the intensity was not increased on that day[8].

Muscle pain was reported in 1 patient in the low frequency and intensity electrical stimulation group in the randomised controlled trial of 44 patients, resulting in 1 training session not taking place[8]. Muscle pain was reported in 3 patients after the stimulation in the randomised controlled trial of 26 patients, but pain spontaneously healed within a few days[11].

Leg cramps were observed in 1 patient during the stimulation in the randomised controlled trial of 26 patients, but this event rapidly faded without treatment[11].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts listed the following anecdotal adverse events: intolerance to the sensation caused by stimulation, and skin reactions to the electrodes used. They considered that the following were theoretical adverse events: interference with pacemaker or defibrillator function, worsening epilepsy, and inappropriate stimulation of other areas of the body such as the heart.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to electrical stimulation to improve muscle strength in non-neurological chronic conditions. The following databases were searched, covering the period from their start to 5 August 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with non-neurological chronic conditions, e.g. chronic heart failure, chronic kidney disease and chronic obstructive pulmonary disease, who are experiencing muscle weakness or dysfunction.
Intervention/test	Electrical stimulation, e.g. functional electrical stimulation, neuromuscular electrical stimulation, and electrical muscle stimulation.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 2,253 patients from 5 systematic reviews and/or meta-analyses[1, 2, 4-6] and 6 randomised controlled trials[3, 7-11].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on electrical stimulation to improve muscle strength in non-neurological chronic conditions

Study 1 Jones S (2016) – Electrical stimulation for COPD, chronic respiratory disease, CHF or thoracic cancer

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Publication years for the included studies: 2001 to 2016
Study population and number	n=**933 patients (18 studies) with 4 different conditions:** - COPD: 13 studies (403 patients) - Chronic respiratory disease: 1 study (389 patients) - CHF: 2 studies (76 patients) - Thoracic cancer: 2 studies (65 patients)
Age and sex	Mean 53 to 71 years; 54% (505/933) male
Patient selection criteria	Inclusion criteria: randomised controlled trials in adults with advanced chronic respiratory disease, chronic heart failure, cancer, or HIV/AIDS comparing a programme of neuromuscular electrical stimulation as a sole or adjunct intervention to no treatment, placebo electrical stimulation, or an active control. There was no language restriction. Exclusion criteria: locomotor or neurological conditions that would affect ability to exercise, or features that could restrict the use of neuromuscular electrical stimulation, such as an implantable cardiac pacemaker.
Technique	All programmes targeted the quadriceps either alone or with additional muscle groups including the hamstrings, calves, glutei and deltoids. Stimulation parameters and programme characteristics varied considerably among studies, with median (range) values of: stimulation frequency 50 (15 to 75) Hz, pulse duration 400 (200 to 700) μs, target duty cycle 33 (13 to 75) %, session length 30 (18 to 240) minutes, session frequency 5 (2 to 7) times each week, and programme duration 6 (4 to 11) weeks.
Follow-up	**Programme duration: median 6 (range 4 to 11) weeks.**
Conflict of interest/source of funding	The National Institute for Health Research (NIHR) is the largest single funder of the Cochrane PaPaS Group.

Analysis

Study design issues: This Cochrane review updated a previously published review in the Cochrane Database of Systematic Reviews Issue 1, 2013 on neuromuscular electrical stimulation for muscle weakness in adults with advanced disease. The primary objective was to evaluate the effectiveness of neuromuscular electrical stimulation on quadriceps muscle strength in adults with advanced disease. The secondary objectives were to examine the safety and acceptability of neuromuscular electrical stimulation, and its effect on peripheral muscle function (strength or endurance), muscle mass, exercise capacity, breathlessness and health-related quality of life.

Two authors independently extracted data from the published reports, assessed the risk of bias for included studies using the Cochrane Collaboration's Risk of Bias tool, and assessed the quality of evidence using GRADE (study limitations, consistency of effect, imprecision, indirectness and publication bias).

Study population issues: Of the 18 included studies in this update, there were 7 new studies since the previous version. Most studies were conducted in a single centre in a small group of participants (fewer than 50 per study arm in 16

studies). Some studies targeted patients with predetermined body mass index, muscle weakness, or level of breathlessness, whilst others had broad inclusion criteria.

Electrical stimulation interventions were offered at home after an initial period of teaching, with the exception of five studies with interventions offered following a period of acute critical illness, which were offered to inpatients. Electrical stimulation was offered alone in all but 7 studies, where electrical stimulation was offered as part of a more comprehensive rehabilitation programme.

The quality of the evidence was from moderate to very low across the different outcomes. The main limiting factor, which was the reason for downgrading quality in some outcomes, was the inconsistency of results across studies and imprecision regarding estimates of effect, especially on the secondary outcomes.

Where reported, rates of adherence with the recommended programme were generally high, with mean values of 95%, 97%, and 100%, and a median of 80%. One study described participants as “compliant”, and another as “excellent”. In the only “pragmatic” study, 61% of participants reported daily adherence to the home-based component of a programme utilising electrical stimulation alongside other interventions. Four studies noted that participants with COPD were able to commence or continue to use electrical stimulation during an acute exacerbation of disease.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **933 (18 studies; COPD, 13 studies of 403 patients; chronic respiratory disease, 1 study of 389 patients; CHF, 2 studies of 76 patients; thoracic cancer, 2 studies of 65 patients)**

Electrical stimulation compared with controls

Variables	**Studies, n**	**Patients, n**	**SMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**	**GRADE**
Quadriceps muscle strength, Nm	12	781	0.53	0.19 to 0.87	0.002	72%	0.00002	low
Muscle mass	8	314						Very low
Anthropometry, cm^3	2	31	0.69	-0.05 to 1.42	0.068	0%	0.89	
DEXA, cm^3	4	179	0.09	-0.20 to 0.38	0.55	0%	0.89	
Ultrasound, cm^3	1	52	0.82	0.26 to 1.39	0.0045	-	-	
Computed tomography, cm^3	2	52	1.01	0.42 to 1.60	0. 00081	0%	0.50	
Variables	**Studies, n**	**Patients, n**	**MD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**	**GRADE**
Exercise performance – walking distance	13	788						Very low
6MWT, m	8	317	34.78	13.52 to 56.05	0.0013	60%	0.01	

Safety

No serious adverse events were reported in 18 studies of 933 patients**.**

Adverse events:

Muscle discomfort during the initial few days: 3.7% (19/518) across 4 studies.

Persistent erythema: <1% (n=2) in 1 study of 52 patients, which was considered possibly related to use of adhesive electrodes.

For both serious adverse events and adverse events, the quality of the evidence was judged to be moderate due to the small overall sample size and limitations in reporting of safety data collection.

ISWT, m	3	434	8.72	-34.87 to 52.31	0.69	83%	0.003	
ESWT, m	4	452	64.13	-17.79 to 146.05	0.12	30%	0.23	
Exercise performance - Peak oxygen uptake, mL/min	4	109	44.8	7.3 to 97.0	0.092	0%	0.86	Low

Hamstring muscle strength increased following electrical stimulation in 2 studies of 60 patients, with statistically significant differences favouring electrical stimulation compared to control groups (exact data were not shown).

Peripheral muscle strength was increased following electrical stimulation, as compared to the control condition, in 1 study of 24 patients, but not in another of 30 patients (exact data were not shown).

A statistically significant improvement in quadriceps endurance following electrical stimulation, as compared to the control condition, was reported in 3 studies of 79 patients (exact data were not shown).

The quality of the evidence for these outcomes was judged to be low.

Breathlessness:

- Self-reported breathlessness during daily life significantly improved following electrical stimulation in 2 studies that used quality of life questionnaires containing 'dyspnoea' or 'dyspnoea in daily tasks' (exact data were not shown)
- Following electrical stimulation compared with control in 2 studies, no differences were found in disability scores due to breathlessness using the medical research council breathlessness scale (exact data were not shown).
- Breathlessness at an equivalent workload during a walking test was significantly reduced following electrical stimulation in 1 study (exact data were not shown).

Health-related quality of life:

- One study reported a significant between-group difference, favouring electrical stimulation, in quality of life as assessed by the Chronic Respiratory Questionnaire, which arose primarily from an effect in the "dyspnoea" domain (exact data were not shown).
- One study reported a significant between-group difference in the SGRQ favouring electrical stimulation, which arose from the "activity" domain (exact data were not shown).
- One study reported a significant between-group difference in the "dyspnoea in daily tasks" domain of the Maugeri Foundation Respiratory Failure Questionnaire in favour of electrical stimulation, but the total score was not significantly different between groups (exact data were not shown).

Abbreviations used: 6MWT, 6-minute walk test; CI, confidence interval; DEXA: dual energy X-ray absorptiometry; ESWT, endurance shuttle walk test; ISWT, incremental shuttle walk test; SGRQ, St George's respiratory disease questionnaire.

Study 2 Neto MG (2016) – Electrical stimulation for CHF

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Publication years for the included studies: 2001 to 2013
Study population and number	n=**435 (13 studies)** Patients with heart failure (HF, New York Heart Association classes II to IV)
Age and sex	Mean 50 years to 65 years; gender not reported
Patient selection criteria	Inclusion criteria: articles were randomised controlled trials that reported the effects of any type of neuromuscular electrical stimulation in patients with heart failure. Exclusion criteria: the studies that enrolled patients with respiratory disease were excluded.
Technique	Electrical stimulation was performed with patients with heart failure. The duration of electrical stimulation programmes ranged from 2 to 12 weeks, and the length of the sessions was from 30 to 120 minutes. The frequency of sessions ranged from 5 to 7 times per week. The intensity of electrical stimulation was adjusted for 25% to 30% of a preceding maximal voluntary contraction in 2 studies and in the other studies was adjusted to obtain visible muscle contraction.
Follow-up	**Programmes duration: 2 to 12 weeks**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: This systematic review with meta-analysis examined the effects of electrical stimulation on physiologic and functional measurements in patients with heart failure. The primary aim investigated the effects of electrical stimulation in exercise capacity and quality of life patients with HF, and the secondary aim analysed the effects of electrical stimulation on endothelial function and depressive symptoms. The search and selection of studies were performed following the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria.

The main outcome measures of interest were peak oxygen uptake (peak VO2), distance walked in a 6-minute walk test (6MWT), quadriceps muscle strength, health-related quality of life (HRQOL) and depressive symptoms (Beck Depression Inventory). Two comparisons were made: i) electrical stimulation compared with control (non-exercise) group, and ii) electrical stimulation compared with exercise group.

Two authors independently extracted data from the published reported, assessed the risk of bias for included studies using the Cochrane Collaboration's Risk of Bias tool, and assessed the quality of evidence using the 11-item PEDro scale (1 item relating to external validity was not used, resulting in a range of method score from 0 to 10).

Study population issues: The sample sizes were from 10 to 46 participants. Of the 13 studies included in the meta-analysis, 1 study had a score of 7, 3 had a score of 6, 4 had a score of 5, 3 had a score of 4, 1 had a score of 3, and 1 had a score of 2. Details of the generation and concealment of the random allocation sequence were poorly reported. Only 3 studies presented objective evidence of the random allocation characteristics and 1 study stated that the authors blinded those involved in the assessments.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **435 (13 studies)**

Electrical stimulation compared with aerobic exercise

	Studies, n	Patients, n	WMD	95% CI	P	I^2	P for heterogeneity
Peak VO_2, $mL \cdot kg^{-1} \cdot min^{-1}$	6	217	-0.44	-0.68 to -0.20	0.0004	0%	0.85
6WMT, m	5	168	0.72	-23.74 to 25.18	0.95	42%	0.14
HRQOL, point	2	76	2.21	-4.58 to 8.99	0.52	0%	0.54

Considering the total time of stimulation (≤30 hours or >30 hours), the results were similar for peak VO2 and 6MWT (data were not shown).

Electrical stimulation compared with no exercise

	Studies, n	Patients, n	WMD	95% CI	P	I^2	P for heterogeneity
Peak VO_2, $mL \cdot kg^{-1} \cdot min^{-1}$	3	76	1.85	0.46 to 3.23	0.009	97%	0.06
6WMT, m	6	156	63.54	35.81 to 91.27	<0.00001	53%	0.06
HRQOL, point	5	Not reported	0.89[a]	0.55 to 1.24	<0.00001	0%	0.63

[a]Because of the different instruments used in the measurement of quality of life, a meta-analysis with standardised mean difference was used.

Electrical stimulation compared with no exercise – subgroup analysis

	Studies, n	Patients, n	SMD	95% CI	P	I^2	P for heterogeneity
Peak VO_2, $mL \cdot kg^{-1} \cdot min^{-1}$	3	76	3.49	0.26 to 6.72	0.03	94%	<0.00001
Peak VO_2 <30 hours, $mL \cdot kg^{-1} \cdot min^{-1}$	1	24	0.76	-0.12 to 1.64	0.09	-	-
Peak VO_2 ≥30 hours, $mL \cdot kg^{-1} \cdot min^{-1}$	2	52	4.98	3.75 to 6.21	<0.00001	92%	0.30
	Studies, n	**Patients, n**	**WMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**
6WMT, m	6	156	63.54	35.81 to 91.27	<0.00001	53%	0.06
6WMT <30 hours, m	3	84	41.63	18.18 to 65.09	0.0005	0%	0.86
6WMT ≥30 hours, m	3	72	85.66	41.21 to 130.12	0.0002	62%	0.07

Electrical stimulation compared with no exercise

	Studies, n	Patients, n	WMD	95% CI	P	I^2	P for heterogeneity
Quadriceps muscle strength, Nm	2	Not reported	30.74	3.67 to 57.81	0.03	0%	0.82
Endothelial function, %	2	Not reported	2.67	0.86 to 4.49	0.004	31%	0.23
Depressive symptoms, point	2	Not reported	-3.86	-6.46 to -1.25	0.004	0%	0.82

Abbreviations used: CI, confidence interval; HRQOL, health-related quality of life; peak VO_2, peak oxygen uptake; SWD, standardised mean difference; WMD, weighted mean difference; 6MWT, 6-minute walk test.

Study 3 Iliou MC (2017) – Electrical stimulation for CHF

Details

Study type	**Randomised controlled trial**
Country	France (8 centres)
Recruitment period	2011 to 2014
Study population and number	n=**91 (electrical stimulation plus exercise 50 compared with exercise 41)** Patients with chronic heart failure
Age and sex	Electrical stimulation plus exercise: mean 57.6 years; 76% (38/50) male Exercise: mean 59.2 years; 78% (32/41) male
Patient selection criteria	Inclusion criteria: patients were included if they were 18 to 80 years, had stable CHF diagnosed since more than 3 months, whatever their aetiology of heart failure, with NYHA functional class II to IIIb, left ventricular ejection fraction <40%, and in whom the cardiopulmonary exercise test was feasible. Exclusion criteria: recent acute heart failure or inotropic intravenous agents used (<10 days), recent coronary angioplasty (<10 days), recent cardiac surgery (<1 month), severe respiratory failure (forced expiratory volume (FEV) <1000 ml), pregnancy, pacemakers (cardiac stimulation dependence or unknown) or automatic implantable defibrillator, obesity (body mass index (BMI)>35), known and documented peripheral myopathy, inability to achieve the exercise test and/or exercise training, contra-indications for CR,4 or previous treatment by functional electrical stimulation.
Technique	Exercise: 20±5 physical training sessions, during 4 to 8 weeks. Electrical stimulation plus exercise: Patients had 20±3 low frequency quadricipital electrical stimulation after aerobic training and/or additional physical activities. Electrical stimulation consisted of stimulating both quadriceps, using a COMPEX 2 device (Compex Medical, Ecublens, Switzerland) delivering a low frequency 10Hz biphasic current, with a pulse duration of 200 ms. The stimulus was alternatively 'on' for 20 s and 'off' for 40 s. The negative electrode (10x5 cm) was positioned on the thighs approximately 1 to 3 cm below the inguinal fold and the positive electrode (5x5 cm) was positioned on the vastus medialis and vastus lateralis muscles. The mean tolerated amplitude was 48.2 mA.
Follow-up	**Programme duration: 4 to 8 weeks**
Conflict of interest/source of funding	This work was sponsored by French Society of Cardiology with grants from Bourgogne and Ile de France Associations of Cardiology (Federation Franc¸aise de Cardiologie). Equipment was provided free of charge by the manufacturer (Compex Medical, Ecublens, Switzerland).

Analysis

Follow-up issues: Among the 94 patients included in the study, 3 dropped out very early before the beginning of the allocated treatment for personal reasons. Thus 91 patients completed the study and they were evaluated at the beginning and at the end of the cardiac rehabilitation programme.

Study design issues: This large, prospective multicentre study determined whether electrical muscle stimulation had an additive effect on maximal and submaximal exercise capacities, muscular function and quality of life in patients with chronic heart failure who were able to perform a conventional exercise training programme.

Patients were randomised using a special computer programme (RandoWeb). The patients were randomised into 2 groups: exercise group or electrical stimulation plus exercise group. The randomisation was performed in each centre according to their age (≤60 or >60 years). Each patient underwent an exercise capacities evaluation (the symptom limited cardiopulmonary exercise test [CPET] and 6MWT) , a muscular evaluation (isometric maximal voluntary muscle strength using the maximal resistance [RM]), and biological measurements (Natraemia, kalaemia, creatinine, haemoglobin, brain natriuretic peptide [BNP], muscular enzymes, creatine kinase [CK], lactate dehydrogenase [LDH], aldolase and myoglobin), and quality of life (the Minnesota questionnaire). All CPET data were re-analysed in a blinded way and adjudicated by a central core laboratory by 3 external reviewers.

Study population issues: Both groups were similar, without any statistically significant differences for clinical characteristics, cardiovascular drugs, exercise tests and muscular data. The population was mostly represented by males, relatively young, predominantly in class II, and particularly well treated. The number of patients treated with statins was not different between the 2 groups: 56% in the electrical stimulation plus exercise group and 58% in the exercise group. For the exercise sessions, both groups performed a mean of 20.1±3.4 sessions (21.2±2.6 in electrical stimulation plus exercise group compared with 20.5±4.2 in exercise group). For the electrical stimulation sessions, patients underwent 20±3.8 sessions, and 96% of patients had ≥15 sessions.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **91 (electrical stimulation plus exercise 50 compared with exercise 41)**

Comparison of cardiopulmonary exercise testing and 6MWT by treatment group

Variables	Electrical stimulation plus exercise			Exercise		
	Baseline	End of trial	P	Baseline	End of trial	p
Rest heart rate, bpm	69.5±11.6	67.8±10.8	ns	71.9±16	68.3±12.5	ns
VT VO_2, ml/kg/min	12.6±3.6	13.3±4.3	0.03	12.2±3.3	13.5±3.3	0.005
Peak exercise						
Heart rate, bpm	118±25	124±23	ns	113±23	119±20	ns
Workload, watt	85±26	105±29	<0.001	79±24	100±33	<0.001
VO_2, ml/kg/min	17.5±5	19.8±6.7	0.004	16.1±4.9	18.4±4.9	0.006
RER	1.14±0.1	1.17±0.1	0.08	1.11±0.1	1.16±0.1	0.01
Test duration, min	7.5±2.6	9.1±2.7	0.001	7.1±2.5	8.7±2.8	<0.001
6MWT, m	441±89	513±101	<0.001	448±118	515±106	0.003

Improvement in peak VO2, VO2 at VT1 and 6MWT distance was not statistically different between the 2 groups, even if the age groups were compared separately (p>0.05).

Changes in peak oxygen uptake:

- Electrical stimulation plus exercise: baseline compared with end of trial, p<0.05
- Exercise: baseline compared with end of trial, p<0.05
- Age group ≤60: electrical stimulation plus exercise compared with exercise alone, p>0.05
- Age group >60: electrical stimulation plus exercise compared with exercise alone, p>0.05

Exact data were not reported.

Patients were considered as responders if their mean gain in peak VO2 was ≥12%, corresponding to the median of the sample. Univariate analysis found that age, baseline heart rate, baseline peak VO2, and Minnesota score were significantly associated with the response to the CR programme, but the randomisation group (electrical stimulation plus exercise or exercise) was not associated with the response.

Comparison of muscular data by treatment group

Variables	Electrical stimulation plus exercise	Exercise

Safety

Adverse events during electrical stimulation:

Adverse events	No. of sessions
Electrode allergy	16
Paraesthesia	3
Variculae	3

Mean pain score: 3.8 (on a pain scale of 1 to 10)

	Baseline	End of trial	P	Baseline	End of trial	P
Quadricipital strength, kg	23.7±11.4	29.9±14.1	<0.01	23.4±10.5	30.5±13.6	<0.01
Quadricipital circumference, cm	44.7±5.5	46.0±5.6	<0.01	43.0±4.4	43.8±4.4	<0.01
CK, UI/l	101.4±81	99.6±68	ns	103.1±83	138.1±54	0.02
LDH, UI/l	255.3±125	257.4±132	ns	239.1±100	257.0±108	ns
Aldolase, UI/l	4.5±1.8	4.1±1.4	ns	4.7±1.7	4.8±3.2	ns
Myoglobin, µg/l	52.3±26	53.4±44	ns	52.0±36	84.5±16.9	ns

Comparison of quality of life by treatment group

Variables	Electrical stimulation plus exercise			Exercise		
	Baseline	End of trial	P	Baseline	End of trial	P
Quality of life	41±22	24±15	<0.01	37±17	25±15	<0.05

Statistically significant differences in the quality of life did not find between the 2 groups.

A visible contraction was obtained in 91% of patients during electrical stimulation.

Abbreviations used: CK, creatine kinase; EMS, electrical muscle stimulation; LDH, lactate dehydrogenase; ns, not statistically significant; RER, respiratory exchange ratio; SD, standard deviation; VO_2, oxygen uptake; VT, ventilatory threshold.

Study 4 Cenik F (2016) – Electrical stimulation for CHF

Details

Study type	**Systematic review**
Country	Not reported for individual studies
Recruitment period	Publication years for the included studies: 2003 to 2016
Study population and number	n=**43 (4 studies)** Patients with heart failure having implantable cardioverter defibrillators
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: original articles/safety studies, pilot studies, case reports, and reviews concerning the topic neuromuscular electrical stimulation in ICD patients were included. Language was restricted to English and German. Exclusion criteria: full text not available in English or German, and reporting an intervention using transcutaneous electrical nerve stimulation (TENS, for treatment of pain) or other currents for analgesia, but no neuromuscular electrical stimulation.
Technique	Neuromuscular electrical stimulation was applied to quadriceps, gastrocnemius, thigh, and/or abdominal muscles. Multiple stimulation devices were used, with varied stimulation parameters.
Follow-up	**Not reported for individual studies**
Conflict of interest/source of funding	Open access funding provided by Medical University of Vienna.

Analysis

Study design issues: This systematic review summarised the updated knowledge from the scientific literature concerning neuromuscular electrical stimulation of thighs in patients with implantable cardioverter defibrillators. Two researchers independently performed the systematic literature search, which was supervised by 2 senior researchers. There was no information relating to data extraction, quality assessment, data analysis and synthesis, etc.

Study population issues: There was variation in the implanted devices and stimulation parameters across studies.

Author	Study design	Implanted device	Stimulation parameters
Kamiya et al. 2016	Safety (pilot) study (n=27)	Left pectoral implanted ICD with dual-chamber lead system: - Medtronic Concerto® - 5x Medtronic Consulta® - 19x Medtronic Protecta® - 2x Boston Scientific Cognis 100-D®	50 Hz, biphasic, 20 min, burst, 2.5 kHz, 5 s stim. +5 s interval, highest tolerable intensity (thigh: 25 to 60 mA; calf: 15 to 40 mA)
Crevenna et al. 2004	Safety study (n=6)	Subpectoral implanted ICD: - Medtronic 7223 CX® - Medtronic 7231® - Medtronic 7275® - Intermedics 101-10® - Guidant 1900® - Ventritex V-190HV3®	- 4 patients: 63.3 Hz, 3.5 s on +4.5 s off, biphasic, 55 to 100 mA - 2 patients: 15 Hz, 2 s on +4 s off, biphasic, 500 ms pulse width
Crevenna et al. 2003	Safety study (n=8)	Subpectoral ICDs: - ELA 9201® - St. Jude V-230 HV®	- IG50: dir. cur., 128 mA, 200 Hz, 400 µs stim. + serial duration of 50 ms

		- Medtronic 7229 CX® - Guidant 1850® - Medtronic 7223 CX® - Guidant 1831® - Ventritex Contour MD® - ELA Defender IV®	- FM: 3.33 to 33.3 Hz, 400 µs alternated by tetanizing impulse effects - HF-TENS: 100 Hz, 200 µs stim. - LF-TENS: 2 Hz, 200 µs stim. - E200: 200 ms rise +270 ms pulse dur., 0.44 Hz. - aS: 400 µs pulse dur. +6.5 s thresh. dur., 66.7 Hz - aS1: 400 µs pulse dur. +3.6 s thresh. dur., 66.7 Hz - FIB: 60 ms impulse with an interval of 200 ms. - Home treatment devices. - biphasic, 500 µs impulse, 15 Hz, 2 s pulse dur. - biphasic, 250 µs impulse, 8/15/30 and 50 Hz, 1 s rise time, steady impulse over 8 s, 1 s fall time.
Wayar et al. 2003	Case report (n=2)	- 1st patient: pectoral ICD (Ventak® Mini III [Guidant Inc., St. Paul, Minnesota, USA]) - 2nd patient: pectoral ICD (Ventak® AV [Guidant Inc., St. Paul, Minnesota, USA])	55 to 75 Hz, biphasic, 7.3 to 10 mA, 5 to 11 V

Key efficacy and safety findings

Safety
Number of patients analysed: **43 (4 studies)** **Electromagnetic interference:** - A case report of 2 patients: **EMI was provoked in 2 patients** when applied electrical stimulation to abdominal muscles, resulting in ICD discharge due to misinterpreting electrical signals as cardiac signals in the ventricular fibrillation zone. - A case series of 8 patients: **EMI of ventricular sensing was reported in 3 patients,** caused by stimulating trapezoid muscles during FM in 1 patient and during LF-TENS in 2 patients. During thigh stimulation with FIB, **EMI was seen in 2 patient**s and intermittent ventricular under-sensing due to post-sense blanking occurred in 1 of these patients. EMI did not fulfil ICD detection criteria of a tachyarrhythmic ventricular episode in any of the patients under study. - A case series of 6 patients: **EMI did not occur** when applied electrical stimulation to thigh muscles, because of an individual risk was excluded prior to start of the electrical stimulation therapy. - A case series of 27 patients: **EMI did not happen** when applied electrical stimulation to quadriceps and gastrocnemius muscles.
Abbreviations used: EMI, electromagnetic interference; FIB, 60-minute triangular impulse, 200-minute interval, FM, frequency modulation, ICDs, implantable cardioverter defibrillators; LF-TENS, low-frequency transcutaneous electrical nerve stimulation.

Study 5 Hill K (2018) – Electrical stimulation for COPD

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Publication years for the included studies: 2002 to 2017
Study population and number	**n=267 (16 studies; electrical stimulation 150 compared with controls 117)** Patients with chronic obstructive pulmonary disease
Age and sex	Mean 56 to 76 years; 67% (179/267) male
Patient selection criteria	Inclusion criteria: randomised controlled trials that recruited adults with COPD if they had compared outcomes between a group that received electrical stimulation and a group that received usual care or compared outcomes between a group that received electrical stimulation plus conventional exercise training and a group that participated in conventional exercise training alone. Exclusion criteria: randomised cross-over trials were excluded
Technique	Neuromuscular electrical stimulation was applied to bilateral quadriceps and/or other muscles, including hamstrings, calf muscles, and gluteals. In terms of intensity, when described, most studies reported that stimulation was set to the maximum current that was perceived to be tolerable. Regarding frequency, 9 studies stimulated using 50 Hz, and Other studies reported using frequencies that ranged between 8 Hz and 45 Hz (1 study), 10 Hz and 50 Hz (1 study), 5 Hz and 35 Hz (1 study), 8 Hz and 35 Hz (1 study), or 35 Hz (3 studies). For duration, most studies stimulated once or twice a day for 30 to 60minutes on 4 to 7 days per week for 4 to 8 weeks.
Follow-up	**Programme duration: 4 to 8 weeks**
Conflict of interest/source of funding	This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group.

Analysis

Study design issues: This Cochrane review determine the effects of neuromuscular electrical stimulation, applied in isolation or concurrently with conventional exercise training to 1 or more peripheral muscles in people with COPD. The primary outcomes were peripheral muscle force, peripheral muscle endurance/fatigability, thigh muscle size, and serious adverse events, and the secondary outcomes were exercise capacity, functional performance, symptoms of dyspnoea and fatigue and health-related quality of life.

Two authors independently extracted data from the published reported, assessed the risk of bias for included studies using the Cochrane Collaboration's Risk of Bias tool, and assessed the quality of evidence using GRADE (study limitations, consistency of effect, imprecision, indirectness and publication bias). Data were double-checked for quality assurance.

Study population issues: Nineteen studies met the criteria for inclusion, and of which, 16 were included in the meta-analyses as 3 provided no data that could be used in any meta-analyses. The intervention was undertaken: i) at home by 5 studies, ii) with supervision as well as in the home by 1 study, iii) at a pulmonary rehabilitation or outpatient centre by 3 studies, iv) on a hospital ward then at home following discharge by 1 study, v) at an inpatient rehabilitation facility by 2 studies, vi) in a high dependency unity by 1 study, and vii) in the ICU by 2 studies. One study did not state the location for the intervention, but it was likely that this study provided the intervention in the home.

The lower limb muscles stimulated were: i) bilateral quadriceps by 8 studies, ii) bilateral quadriceps and the hamstrings by 2 studies, iii) bilateral quadriceps, hamstrings and calf muscles by 1 study, iv) bilateral quadriceps and calf muscles by 2 studies, or v) bilateral quadriceps and gluteals by 1 study.

Studies included in this review were undertaken at single centres and recruited modest sample sizes (fewer than 30 per group). Using the GRADE approach, the quality of the evidence for most outcomes was low or very low. This was mainly because of the risk of bias, imprecision and inconsistent findings across studies.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **267 (16 studies; electrical stimulation 150 compared with controls 117)** **Peripheral muscle force:** - Electrical stimulation compared with usual care (6 studies of 159 patients): SMD=0.34, 95% CI 0.02 to 0.65, p=0.037, I^2=0% (p=0.98) – GRADE: low-quality evidence - Electrical stimulation plus exercise compared with exercise only (4 studies of 84 patients): SMD=0.47, 95% CI -0.10 to 1.04, p=0.10, I^2=39% (p=0.18) – GRADE: very low-quality evidence In real terms, using data available in 1 study that reported changes in quadriceps force in kg, an SMD of 0.34 was equivalent to a difference in force of 3.1 kg (from a baseline mean force of 23.1 kg). **Peripheral muscle endurance/fatigability:** - Electrical stimulation compared with usual care (2 studies of 35 patients): SMD=1.36, 95% CI, 0.59 to 2.12, p=0.00052, I^2=0% (p=0.83) – GRADE: low-quality evidence - Comparison of 2 Electrical stimulation programmes (1 study as an abstract): the gains in endurance may have been greater following an electrical stimulation training programme designed to increase endurance (i.e. low-frequency, high-duty cycle) when compared with an electrical stimulation training protocol designed to increase strength (i.e. high-frequency, low-duty cycle) (exact data were not shown) **Thigh muscle size:** - Electrical stimulation compared with usual care (4 studies of 124 patients): SMD=0.25, 95% CI, -0.11 to 0.61, p=0.17, I^2=0% (p=0.86) – GRADE: low-quality evidence - Electrical stimulation plus conventional exercise training compared with conventional exercise training alone (1 studies): no difference in measures of thigh circumference (exact data were not shown). **Exercise capacity – 6MWT distance, m:** - Electrical stimulation compared with usual care (2 studies of 72 patients): MD=39.26, 95% CI, 16.31 to 62.22, p=0.00080, I^2=0% (p=0.33) - GRADE: low-quality evidence - Electrical stimulation plus exercise compared with exercise only (6 studies of 138 patients): MD=25.87, 95% CI, 1.06 to 50.69, p=0.041, I^2=8% (p=0.37) - GRADE: very low-quality evidence **Exercise capacity – ISWD, m**: - 1 study: a significant between-group increase in favour of electrical stimulation (exact data were not shown)	**Serious adverse events: mortality** Electrical stimulation compared with usual care (5 studies of 131 patients: RD=-0.02, 95% CI, -0.08 to 0.05, p=0.62, I^2=0% (p=0.99). Electrical stimulation plus exercise compared with exercise only (7 studies of 183 patients): RD=0.00, 95% CI, -0.05 to 0.05, p=1.0, I^2=0% (p=1.00). **Minor adverse events**: Electrical stimulation compared with usual care (5 studies of 139 patients): RD=0.00, 95% CI, -0.07 to 0.07, p=0.98, I^2=0% (p=0.44) - GRADE: low-quality evidence. Electrical stimulation plus exercise compared with exercise only (6 studies of 144 patients): RD=0.00, 95% CI, -0.05 to 0.05, p=1.0, I^2=0% (p=1.00) - GRADE: low-quality evidence.

Exercise capacity – VO_2 peak, L/min: - Electrical stimulation compared with usual care (4 studies of 73 patients): MD=0.10, 95% CI, 0.00 to 0.19, p=0.040, I^2=0% (p=0.92) **Exercise capacity – Peak power, W:** - Electrical stimulation compared with usual care (2 studies of 33 patients): MD=5.77, 95% CI, -6.00 to 17.53, p=0.34, I^2=0% (p=0.71) **Exercise capacity – endurance time, min** - Electrical stimulation compared with usual care (3 studies of 55 patients): MD=3.62, 95% CI, 2.33 to 4.91, p<0.00001, I^2=32% (p=0.23) **Functional performance – days to first transfer out of bed:** - Electrical stimulation plus exercise compared with exercise only (2 studies of 44 patients): MD=-4.98, 95% CI, -8.55 to -1.41, p=0.0063, I^2=60% (p=0.11) - GRADE: very low-quality evidence **Symptoms of dyspnoea at end exercise, units**: - Electrical stimulation compared with usual care (3 studies of 55 patients) MD=-1.03, 95% CI, -2.13 to 0.06, p=0.064, I^2=59% (p=0.09) - GRADE: very low-quality evidence - Electrical stimulation plus exercise compared with exercise only (2 studies of 44 patients): MD=-0.44, 95% CI, -2.27 to 1.38, p=0.63, I^2=69% (p=0.07) - GRADE: very low-quality evidence **Symptoms of leg fatigue at end exercise, units**: - Electrical stimulation compared with usual care (3 studies of 55 patients): MD=-1.12, 95% CI, -1.81 to -0.43, p=0.0015, I^2=31% (p=0.23) - Electrical stimulation plus exercise compared with exercise only (1 study): no differences between groups (exact data were not shown) **Health-related quality of life, points**: - Electrical stimulation compared with usual care, using SGRQ (2 studies of 72 patients): MD= -4.2, 95% CI, -12.60 to 4.35, p=0.34, I^2=74% (p=0.05) - GRADE: very low-quality evidence - Electrical stimulation compared with usual care, using CRDQ (1 study): no between-group difference (exact data were not shown) - Electrical stimulation plus exercise compared with exercise only (4 studies of 95 patients): SMD=-0.56, 95% CI, -1.27 to 0.15, p=0.12, I^2=55% (p=0.08) – GRADE: very low-quality evidence	
Abbreviations used: CI, confidence interval; ISWD, incremental shuttle walk distance; MD, mean difference; RD, risk difference; SGRQ, Saint George's Respiratory Questionnaire, SMD, standardised mean difference; 6MWT, 6-minute walk test.	

Study 6 Chen RC (2016) – Electrical stimulation for COPD

Details

Study type	**Meta-analysis**
Country	Not reported for individual studies
Recruitment period	Publication years for the included studies: 2002 to 2016
Study population and number	n=**276 (9 studies; electrical stimulation 139 compared with controls 137)** Patients with stable, moderate-to-severe COPD
Age and sex	Mean 56 years to 70 years; 61% (168/276) male
Patient selection criteria	Inclusion criteria: RCTs investigated the role of neuromuscular electrical stimulation in patients with moderate-to-severe COPD, predefined programme of electrical stimulation applied to the lower limbs, unstimulated or other treatment (e.g. sham stimulation) defined as the control group, and primary outcome quadricep strength and exercise capacity, defined as moving distance and endurance time. The secondary outcome was St George's Respiratory Questionnaire (SGRO) score. The criteria complied with PICO principles. Exclusion criteria: abstracts published merely in academic conferences or website materials were excluded.
Technique	Neuromuscular electrical stimulation was applied to the quadriceps and to accessory respiratory muscles. Stimulation-pulse duration was 250 to 400 μs, and stimulation frequency ranged from 8 to 120 Hz. Intensities ranged from 10 to 100 mA and were gradually increased throughout the entire stimulation according to the patient's individual tolerance.
Follow-up	**Programme duration: 4 to 10 weeks**
Conflict of interest/source of funding	No conflicts of interest.

Analysis

Study design issues: This meta-analysis investigated the efficacy of electrical stimulation in patients with moderate-to-severe COPD. The primary outcomes were quadricep strength and exercise capacity, and the secondary outcome was health-related quality of life using the SGRO. This study was written in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines. For articles reported in more than 2 publications, only the full version was used for meta-analysis.

Two investigators independently extracted and assessed eligibility and quality of the papers, and a third investigator was consulted in case of disagreement to reach a final consensus. Freedom from bias was evaluated for each study in accordance with the basis of methodological domains: adequacy of random-sequence generation and allocation concealment, attrition bias, reporting bias and other biases, with a value of 'high', 'low' or 'unclear' being assigned to each study. The methodological quality of the included trials was scored independently using the GRADE system, with 4 levels – high, moderate, low and very low. Any divergences were resolved by a third investigator to enhance the reliability of the grade.

Outcomes were assigned to categories according to comparable features and representation. Quadricep strength was measured using various methods, including isokinetic quadricep peak torque, maximum voluntary contraction, and author-defined sore. Exercise capacity was primarily 6MWT, shuttle walk test (SWT), and constant-work test (CWT); exercise distance and endurance time were pooled from these tests.

Study population issues: Inadequate description of data on the randomisation protocol or blinding strategy was reported in most of the RCTs, except for 2, which may have led to "unclear risk of bias". The outcomes for quadriceps muscle strength, exercise distance, exercise endurance time and SGRQ were assessed as high-quality evidence.

There was a variation in the control groups, consisting of sham electrical stimulation, usual care, ALM, strength training and conventional pulmonary rehabilitation. In addition, the authors stated that the subgroup analysis with small sample size led to insufficient evidence; the diversity of measurement could have led to heterogeneity correspondingly; and electrical stimulation with different parameter settings or programmes might lead to different physiological effects and outcomes.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **276 (9 studies; electrical stimulation 139 compared with controls 137)**

Effects of electrical stimulation compared to controls

	Studies, n	**Patients, n**	**SMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**
Quadriceps muscle strength,	6	207	1.12	0.64 to 1.59	<0.00001	54%	0.06
Exercise capacity							
	Studies, n	**Patients, n**	**SMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**
CWT endurance time, min	3	116	1.78	1.16 to 2.40	<0.00001	35%	0.22
SWT endurance time, min	2	47	0.28	-0.82 to 1.38	0.62	70%	0.07
	Studies, n	**Patients, n**	**WMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**
6MWT distance, m	4	170	37.27	31.82 to 42.73	<0.00001	0	0.54
SWT distance, m	3	65	68.06	-50.70 to 186.83	0.26	96%	<0.00001
Health-related quality of life							
	Studies, n	**Patients, n**	**WMD**	**95% CI**	**P**	**I^2**	**P for heterogeneity**
SGRO scores, points	4	180	-0.07	-2.44 to 2.30	0.95	56%	0.08

There was a benefit of electrical stimulation in improving exercise capacity, evaluated as longer exercise distance travelled for 6MWT and SWT (WMD=51.53 m, 95% CI 20.13 to 82.93, $I^2_{overall}$ =90%, $I^2_{subgroup\ differences}$=0, p=0.001) in 7 studies of 235 patients, exceeding the MCID ranging of 25 to 33 m for 6MWT distance, or longer exercise endurance time for CWT and SWT (SMD=1.11 min, 95% CI 0.14 to 2.08, $I^2_{overall}$ =85%, $I^2_{subgroup\ differences}$=81.6%, p=0.02) in 5 studies of 163 patients.

Abbreviations used: CI, confidence interval; CWT, constant-work test; SWT, shuttle walk test; SWD, standardised mean difference; WMD, weighted mean difference; 6MWT, 6-minute walk test.

Study 7 Bonnevie T (2018) – Electrical stimulation for COPD

Details

Study type	**Randomised controlled trial**
Country	France (3 centres)
Recruitment period	2010 to 2013
Study population and number	n=**51 (electrical stimulation plus pulmonary rehabilitation 27 compared with pulmonary rehabilitation 24)** Patients with stable, severe to very severe COPD
Age and sex	Mean 59 years; 86% (52/59) male
Patient selection criteria	Inclusion criteria: i) aged ≥18 years; ii) forced expiratory volume in 1 second <60% predicted with a total lung capacity >80% predicted; iii) baseline modified Medical Research Council dyspnoea scale ≥1; iv) motivated to participate in PR; and v) optimised medical therapy. Exclusion criteria: i) body mass index <18 or >35kg/m^2; ii) pregnancy or potential pregnancy; iii) peripheral neuropathy; iv) contraindication to cardiopulmonary exercise testing (CPET); v) progressive cancer; vi) cardiac pacemaker; vii) implanted cardiodefibrillator; and viii) refusal to consent.
Technique	In addition to the comprehensive pulmonary rehabilitation (outpatient or home-based), the electrical stimulation plus pulmonary rehabilitation group underwent bilateral electrical stimulation of the quadriceps muscle (Mi-Thera-Pro device) at home, with 30 minutes of stimulation, 5 times per week during the 8 weeks of the programme. Three self-adhesive surface electrodes were placed on each thigh to deliver a biphasic symmetric current with a pulse duration of 400 milliseconds. After a 2-minute continuous warmup at 6 Hz, the intensity was individually adjusted to just under the pain threshold. The stimulation then alternated between contractions and active rest phases for 25 minutes. The frequencies used were 35 Hz for the contractions and 4 Hz for the active rest phases, with a duty cycle of 0.5 and 1.5 seconds, respectively. The session was completed with a 3-minute recovery period at 3 Hz.
Follow-up	**Programme duration: 8 weeks**
Conflict of interest/source of funding	This study was reported by the French “Ministère des Solidarités et de la Santé”. It was not involved in the design of the study, collection, analysis and interpretation of the data; and in the writing of the manuscript.

Analysis

Follow-up issues: Of the 73 patients, 22 discontinued the study but only 1 dropout was related to the intervention (leg discomfort).

Study design issues: This prospective, multicentre, randomised controlled trial assessed the additional effect of a home-based electrical stimulation programme as an add-on to pulmonary rehabilitation (PR), on functional capacity in patients with chronic COPD. The primary outcome was change in functional capacity evaluated by the difference in distance walked during the 6MWT between the pre- and post-evaluations. and the secondary outcomes were peak oxygen consumption (VO_2 peak), maximal workload during CPET, dyspnoea, and health related quality of life including SGRQ sub scores (symptom, activity and impact) and a total score.

Patients were randomly assigned to receive either electrical stimulation plus PR or PR alone by an individual unrelated to the study (concealed allocation). The randomisation was generated by blocks of 6 patients by a statistician using a computer-generated sequence. Randomisation was stratified by centre and centralised so that investigators were not involved in the procedure. Patients were not blinded to the treatment allocation. In the electrical stimulation plus PR group, each patient was taught to use the device by a trained physiotherapist, and then carried out autonomously at home while intensity was increased as tolerated.

Patients were evaluated before and after the intervention, including pulmonary function tests, evaluation of exercise capacity using the 6MWT and CPET, and health related QoL using the St George’s Respiratory Questionnaire. Dyspnoea

was assessed using the modified Medical Research Council scale. The BMI, airflow obstruction, dyspnoea, and exercise capacity index were noted. Muscle strength, which might had been more sensitive to the electrical stimulation intervention than the 6MWT, was not evaluated.

Study population issues: Of the 51 patients, 28% (14/51) were long-term oxygen users, median (25^{th} to 75^{th} percentile) BMI was 23.5 kg/m^2 (20.2 to 27 kg/m^2), and median (25^{th} to 75^{th} percentile) forced expiratory volume in 1 second was 1L (0.8 to 1.4 L). In terms of the stages of COPD, the numbers of patients were 5 at GOLD II, 26 at GOLD III, and 20 at GOLD IV. Baseline characteristics were similar between groups except for VO_2 peak, which was statistically significantly lower in the electrical stimulation plus PR group (p=0.05).

There was no difference in the number of sessions performed between the PR and electrical stimulation plus PR groups (median number of sessions [25^{th} to 75^{th} percentile], 24 [18 to 25] and 24 [21.3 to 26.8], respectively; p=0.27). The median duration of each session was 31 minutes (30 to 35.5 minutes) for the PR group and the mean (±SD) duration of each session was 35±8.1 minutes for the electrical stimulation plus PR group (p=0.16). Patients in the electrical stimulation plus PR group performed a mean (±SD) of 32.9±12.7 sessions of electrical stimulation (e.g. 82% of the prescribed sessions) at a median intensity of 65 mA (41.5 to 87 mA).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **51 (electrical stimulation plus PR 27 compared with PR 24)**

Baseline evaluation

Variable	Electrical stimulation plus PR (n=27)	PR (n=24)	P	Total population (n=51)
6MWT, m	425 (375 to 500)	452.1±80.3	0.43	450 (385 to 495)
Peak VO_2, mL/kg/min	14.2±2.1	16 (13.5 to 17.6)	0.05	14.8 (13.1 to 16.5)
Wmax, W	59.3±16.2	68.8±19.4	0.10	60 (50 to 70)
mMRC scale	2 (2 to 3)	2 (1.3 to 2)	0.06	2 (2 to 2)
BODE	4 (3 to 5)	3.5 (3 to 4.8)	0.18	4 (3 to 5)
SGRO				
Symptoms, %	34.2±20	31.6±21	0.87	32±20.3
Activity, %	72.2±11.3	67.2±18.8	0.64	73 (60.5 to 79)
Impact, %	40±16.4	33.5 (18.5 to 40.3)	0.12	37 (25 to 44.5)
Total, %	47 (38 to 55)	43.6±15.5	0.22	46.3±13.9

Values are mean±SD, median (25^{th} to 75^{th} percentile), or as otherwise indicated.

Effectiveness of PR programme (n=51)

Outcome	Pre	Post	MD	95% CI	P
6MWT, m	450 (385 to 495)	462 (400 to 520)	19.3	8.2 to 30.4	<0.01
Peak VO_2, mL/kg/min	14.8 (13.1 to 16.5)	15.4 (13.5 to 17.8)	0.7	0.1 to 1.3	0.02
Wmax, W	60 (50 to 70)	67.5 (58.8 to 80)	6.6	3.6 to 9.6	<0.01
mMRC scale	2 (2 to 2)	2 (1 to 2)	-0.3	-0.5 to -0.1	<0.01
BODE	4 (3 to 5)	4 (3 to 5)	-0.1	-0.4 to 0.2	0.58
SGRO					

Symptoms, %	32±20.3	25.6±16	-3	(-7 to 1)	0.21
Activity, %	73 (60.5 to 79)	66 (60 to 79.3)	-1.8	-6.5 to 2.8	0.62
Impact, %	37 (25 to 44.5)	31.9±19.4	-5.1	-9.3 to -0.9	0.02
Total, %	46.3±13.9	40.9±14.7	-4.4	-7.8 to -1.1	0.01

Values are mean±SD, median (25th to 75th percentile), or as otherwise indicated.

Changes after intervention

	Electrical stimulation plus PR			**PR**			**Comparison of changes between groups after intervention**		
Outcome	**MD**	**95% CI**	**P**	**MD**	**95% CI**	**P**	**Difference between means (electrical stimulation plus PR compared with PR)**	**95% CI**	**P**
6MWT, m	17.5	1.8 to 33.2	0.54	21.33	4.6 to 38.1	0.02	-3.9	-26.3 to 18.6	0.73
Peak VO_2, mL/kg/min	0.5	-0.3 to 10.5	0.22	1.1	0.2 to 1.9	0.04	-0.5	-1.8 to 0.7	0.37
Wmax, W	5.9	1.3 to -0.1	0.01	7.4	3.4 to 11.4	<0.01	-1.5	-7.6 to 4.6	0.41
mMRC scale	-0.4	-0.6 to -0.1	<0.01	-0.2	-0.5 to 0.1	0.27	-0.2	-0.6 to 0.2	0.07
BODE	-0.3	-0.8 to 0.1	0.13	0.2	-0.3 to 0.7	0.42	-0.5	-1.1 to 0.1	0.07
SGRO									
Symptoms, %	-1.7	-6.6 to 3.2	0.49	-4.7	-11.8 to 2.5	0.21	3	-5.1 to 11.1	0.39
Activity, %	-0.2	-4.8 to 4.4	0.93	-4.1	-13.6 to 5.4	0.57	3.9	-5.5 to 13.3	0.54
Impact, %	-6.2	-11.9 to -0.5	0.03	-3.6	-10.4 to 3.2	0.19	-2.7	-11.2 to 5.9	0.54
Total, %	-5	-9 to -1	0.03	-3.7	-10.1 to 2.6	0.23	-1.2	-8.1 to 5.7	0.72

Abbreviations used: BODE, BMI, airflow obstruction, dyspnoea, and exercise capacity index; CI, confidence interval; CPET, contraindication to cardiopulmonary exercise testing; MD, mean difference; mMRC, modified Medical Research Council; PR, pulmonary rehabilitation; Wmax, maximal workload achieved during CPET;

Study 8 Brüggemann AK (2017) – Electrical stimulation for CKD

Details

Study type	**Randomised controlled trial**
Country	Brazil (single centre)
Recruitment period	2015 to 2016
Study population and number	n=**40 (high frequency and intensity electrical stimulation 20 compared with low frequency and intensity electrical stimulation 20)** Patients with chronic kidney disease (CKD) on haemodialysis
Age and sex	High frequency and intensity electrical stimulation: mean 52.65 years; 75% (15/20) male Low frequency and intensity electrical stimulation: mean 60.50 years; 55% (11/20) male
Patient selection criteria	Inclusion criteria: patients with CKD undergoing HD regularly for at least 6 months; aged 20 to 85 years; in stable clinical condition and under medical supervision; absence of uncontrolled hypertension, recent ischemic heart disease (≤3 mo), unstable angina, or severe cardiac arrhythmias; absence of disease (respiratory, orthopaedic, and/or neurological), which might limit the assessment protocol and training; did not perform any form of physical exercise or exercised more than 6 months ago. Exclusion criteria: inability to perform any of the study assessments (lack of understanding or cooperation); clinical deterioration during the research period; clinical complications due to cardiorespiratory and/or musculoskeletal reasons during the research period.
Technique	Isometric strength training on quadriceps muscle was performed with electrical stimulation for 1 hour, 3 times a week. The intervention was performed in the first 2 hours of haemodialysis. Stimulation was applied using portable dual-channel muscle stimulator (Fesmed IV), with self-adhesive surface electrodes placed on the vastus lateralis muscle and on the vastus medialis muscle. High frequency and intensity electrical stimulation: frequency of 50 Hz, pulse width of 400 μs, rise time and fall time of 2 second, on/off stimulation, initially with a 1:2 relation in the first weeks, to be increased to a 1:1 relation in the second week, and a medium intensity of 72.90 mA. Low frequency and intensity electrical stimulation: frequency of 5 Hz, an on/off stimulation time of 1:3, a pulse duration of 100 μs and a medium intensity of 13.85 mA.
Follow-up	**Programme duration: 4 weeks.**
Conflict of interest/source of funding	This study was supported by Coordination of Improvement of Higher Level Personnel (CAPES).

Analysis

Follow-up issues: A total of 51 patients were eligible for the study: 26 were randomised for high frequency and intensity electrical stimulation and 25 for low frequency and intensity electrical stimulation. Of these, 6 patients were excluded from the high frequency and intensity group and 5 from low frequency and intensity group. The rationale for exclusion were hospitalisation (n=4), absence (n=1), transplant (n=2), allergic reaction to electrodes (n=1), and not reassessed (n=3). Thus, 40 patients were included in the analysis, and they were assessed on the first working day after haemodialysis and after 12 training sessions.

Study design issues: This randomised, double-blind, controlled trial evaluated the effects of electrical stimulation of high and low frequency and intensity, performed during haemodialysis, on physical function and inflammation markers in patients with CKD. The hypothesis was that high frequency and intensity training would bring more benefits to this population. The primary outcomes were peripheral muscle strength and submaximal exercise capacity, and the secondary outcomes included biochemical markers of muscle trophism (insulin growth factor 1 [IGF-1]) and inflammation-induced changes (the proinflammatory [TNF-α] and anti-inflammatory [interleukin 10, IL-10] cytokines).

Patients were blind to group allocation. Randomisation was stratified according to sex, using a block size of 4, and performed using opaque sealed envelopes after the assessments. The training programme was implemented by 1 physiotherapist, while all assessments were performed by the same examiner blinded for the patients' group allocation.

Study population issues: In the baseline assessment, anthropometric and pulmonary variables 6MWTD, Kt/V, creatinine level, IGF-1 level, IL-10 level, and TNF-α level showed no statistically significant differences between the groups; however, statistically significant differences were found in GFR, initial right muscle strength and initial left muscle strength between the groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **40 (high frequency and intensity electrical stimulation 20 compared with high frequency and intensity electrical stimulation 20)**

Comparisons between the groups before and after the electrical stimulation protocol

Characteristics	**High frequency and intensity**		**Low frequency and intensity**		**P**
	mean±SD	**95% CI**	**mean±SD**	**95% CI**	
Initial right peripheral muscle strength, Nm	155.35±65.32	124.78 to 185.92	109.40±32.08	94.38 to 124.42	0.008
Final right peripheral muscle strength, Nm	161.60±68.73	129.43 to 193.77	112.65±38.44	94.66 to 130.64	0.79
P	0.01		0.50		NA
Initial left peripheral muscle strength, Nm	156.60±66.51	125.47 to 187.73	113.65±37.79	95.96 to 131.34	0.01
Final left peripheral muscle strength, Nm	164.10±69.76	131.45 to 196.75	116.15±43.01	96.02 to 136.28	0.50
P	0.02		0.61		NA
Initial 6MWT distance, m	435.55±95.81	390.71 to 480.39	403.80±90.56	361.41 to 446.19	0.28
Final 6MWT distance, m	457.25±90.64	414.83 to 499.67	428.90±87.42	387.99 to 469.81	0.32
P	0.02		0.007		NA
Initial IGF-1 level, pg/Ml*	389.64±201.66	254.16 to 525.12	252.38±156.35	140.53 to 364.23	0.10
Final IGF-1 level, pg/mL*	406.59±162.27	297.57 to 515.61	336.97±207.34	188.65 to 485.30	0.40
P	0.65		0.03		NA
Initial IL-10 level, pg/mL**	7.26±1.81	5.87 to 8.66	6.27±1.92	4.78 to 7.75	0.27
Final IL-10 level, pg/mL**	6.32±1.54	5.13 to 7.51	5.81±1.46	4.69 to 6.93	0.48
P	0.03		0.22		NA
Initial TNF-α level, pg/mL**	6.74±1.75	5.58 to 7.94	7.27±1.60	6.16 to 8.13	0.15
Final TNF-α level, pg/mL**	6.30±0.86	5.77 to 6.99	7.07±1.60	6.00 to 8.16	0.32

Safety

Adverse events

Muscle discomfort: 1 patient in each group reported muscle discomfort during the intervention, and the intensity was not increased on that day.

Muscle pain: 1 patient in the low frequency and intensity electrical stimulation group did not perform 1 training session because of muscle pain.

P	0.79		0.50		NA
Initial intensity, mA	23.70±10.23	18.91 to 28.49	37±12.40	31.20 to 42.80	0.002
Final intensity, mA	96.60±37.21	79.18 to 114.02	48.45±14.29	41.76 to 55.14	>0.001
P	>0.001		0.001		NA

* 11 patients were analysed in the high frequency and intensity electrical stimulation group and 10 in the low frequency and intensity electrical stimulation group.

** 10 patients for each group were analysed.

Correlations between muscle strength and 6MWT, and between muscle strength and age

Characteristic	High frequency and intensity			Low frequency and intensity		
	P	r	r^2	P	r	r^2
Initial right muscle strength and 6MWT distance	>0.001	0.78	0.60	0.004	0.61	0.38
Initial left muscle strength and 6MWT distance	0.001	0.68	0.46	0.001	0.69	0.48
Final right muscle strength and 6MWT distance	>0.001	0.80	0.64	0.06	0.41	0.17
Final left muscle strength and 6MWT distance	>0.001	0.74	0.55	0.06	0.43	0.18
Initial right muscle strength and age	0.001	-0.67	0.46	0.39	-0.19	0.04
Initial left muscle strength and age	>0.001	-0.96	0.51	0.40	-0.19	0.03
Final right muscle strength and age	>0.001	-0.98	0.46	0.22	-0.26	0.07
Final left muscle strength and age	<0.001	-0.96	0.48	0.26	-0.26	0.06

Abbreviations used: CI, confidence interval; NA, not applicable; r, Pearson correlation coefficient; r^2, coefficient of determination.

Study 9 McGregor 2018 – Electrical stimulation for CKD

Details

Study type	**Randomised controlled trial**
Country	UK (A tertiary centre and satellite units)
Recruitment period	2014 to 2015
Study population and number	**n=51 (low frequency electrical muscle stimulation 17, cycling 16, and usual care 18)** Patients with chronic kidney failure on haemodialysis
Age and sex	Low frequency electrical muscle stimulation: mean 51.5 years; 82% (14/17) male Cycling: mean 52.1 years; 81% (13/16) male Usual care: mean 54.3 years; 61% (11/18) male
Patient selection criteria	Inclusion criteria: age >18 years, dialysis three times weekly for 3±4 hours, dialysis vintage of >3 months, urea reduction rate of >65%, and ability to complete dynamic exercise testing and training. Exclusion criteria: active malignant disease, ischemic cardiac event (<3 months), significant valvular heart disease or dysrhythmia, planned kidney transplant during the study, and life expectancy of <6 months.
Technique	Exercise was performed for up to 1 hour 3 times per week. Cycling workload was set at 40±60% oxygen uptake (VO_2) reserve, and low frequency electrical muscle stimulation, delivered using a stimulator (NT2010 Biomedical Research Ltd) at maximum tolerable intensity (and patients, initially under supervision, were encouraged to increase the current amplitude to achieve a level of stimulation sufficient to evoke an increase in HR, BP, respiratory rate and body temperature).
Follow-up	**Programme duration: 10 weeks**
Conflict of interest/source of funding	This study was funded by West Midlands Comprehensive Local Research Network. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Analysis

Follow-up issues: Patients were assessed at weeks 0 and 10. Of the 64 randomised patients, 4 were unable to commence exercise due to new medical problems and 9 were excluded from the final analysis because of becoming medically unfit during the study (n=4), declining follow-up (n=2), or reporting intolerance to the intervention (n=3, 1 was unable to tolerate cycling and 2 low frequency electrical muscle stimulation). Therefore, the overall trial retention rate was 79.7% (n=51).

Study design issues: This pilot randomised controlled trial compared the feasibility of low frequency electrical muscle stimulation and dynamic cycle training during haemodialysis and investigated the effects of intra-dialytic low frequency electrical muscle stimulation and cycle training, compared to usual care, on exercise capacity and cardiovascular structure and function. The primary outcome was the assessment of feasibility, no power calculation was conducted. The secondary outcomes were cardio-respiratory reserve, isometric muscle strength, cardiac structure and function, arterial stiffness and endothelial function.

Permuted block randomization (block sizes 3 and 6) was stratified by sex and age (55 years) and performed independently by the trial statistician. Post study measures were conducted on a non-dialysis day by experienced outcome assessors blinded to group allocation. Regarding stimulation, 2 weeks of familiarization allowed participants to become accustomed to the sensation of low frequency electrical muscle stimulation and progress to at least 30 minutes of stimulation.

Study population issues: There were no statistically significant differences between groups at baseline in terms of demographics, clinical parameters and exercise capacity. During the trial, there were no significant changes in medication.

Regarding adherence to exercise, in total, 91.0% ± 0.1% of sessions were completed in the low frequency electrical muscle stimulation group and 93.0% ± 0.1% in the cycling group. Mean exercise time and intensity achieved by week 10 was 56.3±6.7 mins and 63.8±20.7 watts (equivalent to 63.8% VO_2peak from CPET) for cycling and 60.0±0.1 mins and 119.7±13.0 mA for low frequency electrical muscle stimulation.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **51 (low frequency electrical muscle stimulation [LF-EMS] 17, cycling 16, and usual care 18)**

Exercise capacity, cardiac and vascular measures at 10 weeks adjusted for baseline values, age and sex.

Variables	Lease squares estimates at week 10, mean (95% CI)						
	LF-EMS (n=17)	Cycling (n=16)	Usual care (n=18)	P (between 3 groups)	P (cycling compared with LF-EMS)	P (LF-EMS compared with usual care)	P (cycling compared with usual care)
Exercise capacity							
HR rest ($b.min^{-1}$)	83.85 (78.90 to 88.81)	77.09 (72.00 to 82.18)	80.90 (76.49 to 85.32)	0.1	0.04	0.4	0.2
HR peak ($b.min^{-1}$)	135.44 (127.46 to 143.42)	126.65 (118.84 to 134.45)	123.44 (116.69 to 130.20)	0.06	0.09	0.02	0.5
$VO_{2\ AT}$ ($ml.kg^{-1}.min^{-1}$)	12.30 (11.67 to 12.92)	12.66 (12.03 to 13.29)	10.50 (9.94 to 11.05)	<0.001	0.4	<0.001	<0.001
VO_2 peak ($ml.kg^{-1}.min^{-1}$)	18.94 (17.62 to 20.26)	19.88 (18.55 to 21.21)	16.93 (15.69 to 18.17)	0.004	0.3	0.02	0.02
RER at $VO_{2\ AT}$	0.95 (0.92 to 0.97)	0.96 (0.94 to 0.99)	0.93 (0.91 to 0.96)	0.2	0.4	0.4	0.4
Max. load (Watts)	105.08 (98.09 to 112.07)	109.89 (102.82 to 116.97)	88.87 (82.10 to 95.64)	<0.001	0.3	0.001	0.001
Leg strength (Newtons)	517.28 (471.65 to 562.92)	488.45 (442.82 to 534.09)	423.32 (382.28 to 464.37)	0.007	0.3	0.002	0.002
Cardiac							
LVMI (g/m^2)	114.95 (87.00 to 142.90)	138.99 (110.98 to 167.00)	111.60 (88.09 to 135.11)	0.2	0.2	0.8	0.1
LVEDVI (ml/m^2)	44.33 (38.31 to 50.34)	50.37 (45.61 to 55.12)	47.84 (43.33 to 52.35)	0.2	0.09	0.3	0.4
LEVSVI (ml/m^2)	21.12 (17.45 to 24.78)	23.14 (20.32 to 25.95)	21.97 (19.43 to 24.52)	0.6	0.3	0.7	0.5
LVEF (%)	50.15 (44.37 to 55.94)	54.10 (49.78 to 58.41)	53.59 (49.57 to 57.61)	0.5	0.2	0.3	0.9
E/A ratio	1.16 (0.91 to 1.41)	1.05 (0.81 to 1.29)	1.04 (0.82 to 1.26)	0.7	0.5	0.5	0.9
Mean E/e'	8.90 (6.65 to 11.16)	12.06 (9.95 to 14.17)	8.52 (6.31 to 10.72)	0.04	0.05	0.8	0.03
LA diameter (cm)	3.82 (3.45 to 4.18)	4.06 (3.69 to 4.44)	3.93 (3.61 to 4.24)	0.6	0.3	0.6	0.6
Vascular							
SBP rest (mm/Hg)	130.19 (117.93 to 142.45)	136.88 (124.54 to 149.23)	126.26 (115.51 to 137.00)	0.4	0.4	0.6	0.2
DBP rest (mm/Hg)	69.89 (62.18 to 77.59)	70.48 (62.73 to 78.23)	71.20 (64.41 to 78.00)	0.9	0.9	0.8	0.8
PWV	8.17 (7.40 to 8.94)	7.94 (7.19 to 8.70)	8.45 (7.76 to 9.14)	0.6	0.6	0.6	0.3
FMD delta (cm)	0.03 (0.02 to 0.03)	0.02 (0.02 to 0.03)	0.03 (0.02 to 0.04)	0.08	0.1	0.6	0.03
FMD delta (%)	6.96 (5.51 to 8.40)	5.29 (3.90 to 6.69)	7.54 (6.26 to 8.82)	0.05	0.08	0.5	0.02

Abbreviations used: AT, anaerobic threshold; DBP, diastolic blood pressure; E/A ratio, ratio of peak early (E) to late (A) mitral inflow velocity; E/e', ratio of peak early mitral inflow velocity to peak early diastolic mitral annulus tissue velocity; FMD, flow mediated dilatation; HR, heart rate; LF-EMS, low-frequency electrical muscle stimulation; LV, left ventricular; LVMI, LV mass index; LVEDVI, LV end diastolic volume index; LVESI, LV end systolic volume index; LVEF, LV ejection fraction; LA, left atrium; PWV, pulse wave velocity; RER, respiratory exchange ratio; SBP, systolic blood pressure; VO_2, oxygen uptake.

Study 10 Roxo 2016 – Electrical stimulation for CKD

Details

Study type	**Randomised controlled trial**
Country	Brazil (single centre)
Recruitment period	Not reported
Study population and number	n=**40 (electrical stimulation 20 compared with control 20)** Patients with chronic kidney disease on haemodialysis
Age and sex	Electrical stimulation: mean 46.40 years; 47.1% male Control: mean 54.65 years; 52.9% male
Patient selection criteria	Inclusion criteria: patients aged 18 or older, haemodynamically stable and on haemodialysis for more than 6 months. Exclusion criteria: patients who required any emergency or elective surgery during the study; those who presented acute heart or lung disease, skin rashes, metallic implants, tumours, infections, diabetes mellitus or hypoesthesia in the region that the neuromuscular electrical stimulation would be applied; those who practiced physical activities 3 times a week or more; and those who presented physical or cognitive changes that would not enable the completion and collecting of results in the proposed tests.
Technique	Neuromuscular electrical stimulation (Neurodyn II, Ibramed, Amparo, Brazil) was applied on the quadriceps muscle bilaterally during haemodialysis for 24 sessions (8 weeks). Each session was performed 3 times a week for 30 minutes, with pulse width within 350 microseconds, frequency of 50 Hz for 2 seconds if bearable, and resting for 10 seconds, and the intensity of the electrical current determined by the tolerance of each patients.
Follow-up	**Programme duration: 2 months**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: 42 patients participated in the study, of whom, 2 were lost to follow-up: 1 in the control group did not complete all evaluation exams and 1 in the treatment group had to undergo abdominal surgery for hernia correction. Thus, 40 patients were included in the analysis, and they were assessed before the haemodialysis session and after 2 months (24 sessions across 8 weeks). No adverse events during or after the sessions were observed.

Study design issues: This randomised clinical study evaluated the effects of neuromuscular electrical stimulation on the pulmonary function and functional capacity of patients with CKD undergoing haemodialysis, conducted at the dialysis unit. The sample size of 40 was determined using a confidence interval of 95% and 5% error for infinite sample. Patients were randomised into 2 groups by means of opaque, sealed envelopes: group control and treatment, and the tests included pulmonary function test forced vital capacity (FVC), volume expired in 1 second (FEV_1), FEV_1/FVC, forced expiratory $flow_{25/75\%}$, ($FEF_{25/75\%}$), peak expiratory flow (PEF), maximum respiratory pressures (maximum inspiratory pressure [MIP], maximum expiratory pressure [MEP]), peak flow, 1-repetition-maximum test (1RM) and 6MWT.

Study population issues: The baseline characteristics of the patients were not statistically significantly different between groups in relation to age, height and duration of haemodialysis. The aetiology of CKD in group treatment was chronic glomerulonephritis in 12 patients, hypertensive nephrosclerosis in 7 and an unknown aetiology in 1. In the control group aetiology was chronic glomerulonephritis in 11 patients, hypertensive nephrosclerosis in 7, and cystic kidney disease in 2.

Key efficacy and safety findings

Efficacy

IP overview: Electrical stimulation to improve muscle strength in non-neurological chronic conditions

Number of patients analysed: **40 (electrical stimulation 20 compared with control 20)**

Laboratory results and weight, mean±SD

Variables	Before			After		
	Electrical stimulation	Control	P	Electrical stimulation	Control	P
Kt/V	1.40±0.17	1.38±0.21	0.56	1.40±0.15	1.48±0.16	0.15
Creatine, mg/L	11.28±2.88	9.95±1.79	0.08	12.24±3.35	9.95±1.97	0.01
Albumin, g/Dl	3.53±0.37	3.58±0.40	0.65	3.78±0.30	3.67±0.41	0.36
Hg, g/Dl	10.53±1.62	11.86±1.59	0.01	10.49±1.17	11.60±1.47	0.01
Urea, mg/Dl	151.18±31.57	137.80±27.28	0.16	146.66±35.80	132.78±29.56	0.18
Weight, kg	59.75±12.33	60.83±10.48	0.76	60.40±12.24	61.88±9.58	0.22

Pulmonary function, mean±SD

Variables	Electrical stimulation			Control			Comparison between groups
	Before	After	P	Before	After	P	P
MIP, cmH_2O	49.80±12.94	58.90±18.39	0.01	57.00±19.84	53.80±21.26	0.41	0.02
MEP, cmH_2O	68.60±17.87	83.00±12.57	<0.001	64.20±17.24	69.80±23.52	0.11	<0.0001
Peak expiratory flow, L/min	299.00±69.50	296.00±82.10	0.72	304.00±84.25	293.00±70.79	0.15	-
IRM, kg	1.65±0.84	3.03±1.25	<0.001	2.00±0.74	1.70±0.76	<0.001	<0.001

There was no statistically significant difference in the comparison of pulmonary function test (PFP) between groups. The baseline evaluation mean (±SD) value of FEV_1 in control group was 1.95±0.52 and decreased to a mean 1.82±0,47 after 2 months, and so the comparison between them showed the same significance for FEV_1 (p = 0.00), with the highest averages for treatment.

Functional capacity, mean±SD

Variables	Electrical stimulation			Control			Comparison between groups
	Before	After	P	Before	After	P	P
SBP, mmHG	8.20±10.33	4.30±7.52	0.15	5.50±8.25	12.00±9.51	0.02	<0.001
DBP, mmHG	1.80±8.55	4.10±7.77	0.19	3.00±7.32	5.50±7.59	0.17	-
HR, bpm	14.20±12.89	15.30±10.81	0.73	27.40±9.66	34.30±8.48	0.05	-
F, ipm	6.90±4.38	3.85±5.47	0.05	7.40±3.69	9.30±4.21	0.05	<0.001
SpO_2, %	-0.50±1.10	0.70±1.68	0.02	-0.70±0.97	-0.35±0.93	0.09	-
Borg	3.75±2.63	4.35±2.81	0.46	3.50±2.89	4.90±2.40	0.06	-
6MWT distance, m	350.40±97.53	373.20±112.94	0.02	330.00±68.77	327.20±53.93	0.71	0.03

Abbreviations used: Borg, scale of effort perception; DBP, diastolic blood pressure; f, respiratory rate; Hg, haemoglobin; HR, heart rate; Kt/V, rate of removal of urea (clearance); MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SpO_2, oxygen saturation; 1RM, 1-repetition-maximum test; 6MWT, 6-minute walking test.

Study 11 Suzuki (2018) – Electrical stimulation for CKD

Details

Study type	**Randomised controlled trial**
Country	Japan (single centre)
Recruitment period	2013 to 2015
Study population and number	**n=26 (electrical stimulation 13 compared with control 13)** Patients with chronic kidney disease on haemodialysis
Age and sex	Electrical stimulation: mean 66.2 years; 92.3% male Control: mean 65.1 years; 92.3% male
Patient selection criteria	Inclusion criteria: age of 20 years or more, dialysis duration for a minimum of 2 months with adequate dialysis delivery, and stable medical condition. Exclusion criteria: severe or symptomatic cardiovascular disease, orthopaedic complaints interfering with physical function test, severe dementia, and implanted medical devices contraindicating magnetic resonance imaging scans.
Technique	Electrical muscle stimulation using a handheld muscle stimulator (Auto Tens Pro, Homer Ion Co. Ltd., Tokyo, Japan) was conducted 3 times per week for 8 weeks for the lower extremities at a frequency of 20 Hz with a pulse width of 250 μs, each duty cycle included a 5 s stimulation period with a 2 s pause for a period of 20 min using a monophasic, exponential climbing pulse. The intensity was adjusted the highest level attainable according to individual tolerance (maximum intensity of the thigh and lower leg ranged from 110.0 to 257.5 and from 30.6 to 104.0 mA, respectively).
Follow-up	**Programme duration: 8 weeks**
Conflict of interest/source of funding	This study received no external funding and no conflicts of interest.

Analysis

Follow-up issues: A total of 29 eligible patients were randomly assigned to either the electrical stimulation group or the control group. In the electrical stimulation group, 86.7% (13/15) of patient completed electrical stimulation training as 1 was hospitalised before intervention and 1 dropped out due to discomfort of the web electrode bands. In the control group, 92.9% (13/14) completed the protocol as 1 withdrew consent. Thus, the final analysis included 13 patients in each group. Patients were assessed within 7 days prior to the 8-week-intervention period and within 5 days after the completion of the intervention.

Study design issues: This prospective, open label, randomised controlled trial quantified the effects of electrical muscle stimulation during haemodialysis in terms of changes in muscle strength and size, physical function, quality of life and biochemical parameters. The primary and secondary outcomes were improvement of quadriceps muscle strength and size, respectively. Measurement of isometric knee extensor strength using the handheld dynamometer, evaluation of the quadriceps cross-sectional areas using magnetic resonance imaging, the timed up & go test for physical function assessment, the Japanese version of the short form-8 health survey, and blood test were performed before and after the intervention period. Measurements were performed by assessors blinded to the intervention.

Patients were randomly assigned to either the electrical muscle stimulation group or the control (no training) group by simple random allocation (drawing lots). The expected improvement in the strength of the quadriceps femoris muscles in the electrical stimulation group was 35 N with a standard deviation of 40. To ensure a 2-sided test at $\alpha=0.05$ and power of 0.80, the sample size requirement for each group was calculated as 13. A sample size of 40 was calculated to account for dropouts and exclusions. The open-label trial was stopped after recruiting 29 patients as each group had met the required number of 13.

Study population issues: There were no statistically significant differences in baseline characteristics between the 2 groups. Patients had conventional haemodialysis or predilutional on-line hemodiafiltration 3 times a week, 3 to 4.5 hours per session. The composition of the dialysis bath and the hemodiafiltration infuscate was the same throughout the study period.

The mean weekly frequency of the electrical stimulation training was 2.95±0.08. For baseline values of all parameters concerning dry weight, blood pressure, muscle strength and size, physical function, quality of life, and biomedical parameters, there were no statistically significant differences between the 2 groups. In addition, dry weight, blood pressure, and serum albumin showed no statistically significant changes and absolute changes following intervention in both groups.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **26 (electrical stimulation 13 compared with control 13)**

Muscle strength, muscle size and physical function before and after the 8-week intervention period

Variables	Electrical stimulation group			Control group			Absolute change within the group		
	Baseline	Final	P	Baseline	Final	P	Electrical stimulation	Control	P
Muscle strength, N									
Knee extension R	302.7±62.3	325.0±68.6	0.004	292.8±70.9	282.0±62.7	0.28	22.3±12.8 (7.4±3.2)	-10.8±22.3 (-3.1±5.9)	<0.001
Knee extension L	286.2±61.1	312.2±65.8	0.004	276.9±62.7	268.6±55.9	0.27	26.1±29.7 (9.6±10.5)	-8.3±18.7 (-2.5±5.3)	<0.001
Muscle size (quadriceps CSA), cm^2									
25% quadriceps R	40.5±8.6	42.2±9.3	0.01	39.2±4.5	38.8±5.2	>0.99	1.7±2.0 (4.0±4.7)	-0.4±1.8 (-1.1±4.6)	0.05
25% quadriceps L	40.4±8.9	41.7±9.2	0.004	39.2±4.1	38.6±4.3	0.66	1.3±1.1 (3.1±2.8)	-0.6±1.8 (-1.5±4.4)	0.01
50% quadriceps R	49.3±10.4	51.3±11.0	0.03	50.7±7.1	50.0±6.7	>0.99	2.0±2.2 (4.0±4.7)	-0.7±1.9 (-1.3±3.6)	0.004
50% quadriceps L	48.9±11.3	51.6±12.5	0.01	49.8±6.9	49.0±6.3	0.35	2.7±2.1 (5.3±3.9)	-0.7±1.6 (-1.3±3.3)	0.001
75% quadriceps R	37.0±8.3	37.5±8.2	0.02	35.8±6.2	35.0±65.4	0.16	1.8±2.2 (5.4±6.6)	-0.7±1.5 (-1.6±4.5)	0.003
75% quadriceps L	35.4±7.6	37.5±9.1	0.01	34.6±6.5	34.2±6.3	0.59	2.1±1.9 (5.4±4.5)	-0.4±1.5 (-1.1±4.7)	0.003
Physical function									

Safety

Adverse events:

Leg cramps: n=1 during electrical stimulation but rapidly faded without treatment

Muscle pain: n=3 after the electrical stimulation but healed within a few days

Timed up & go, s	9.3±3.1	8.5±3.1	0.004	8.4±0.9	8.6±1.3	0.55	-0.8±0.6 (-9.1±5.6)	0.2±0.5 (2.5±5.2)	<0.001

Numbers shown in parentheses reflect mean percentage change from baseline values.

Quality of life before and after the 8-week intervention period

Variables	Electrical stimulation group			Control group			Absolute change within the group		
	Baseline	Final	P	Baseline	Final	P	Electrical stimulation	Control	P
SF-8									
GH	51.8±5.6	53.5±4.2	0.86	50.8±6.7	48.2±6.5	>0.99	1.7±5.7 (4.1±13.3)	-2.5±8.3 (-3.8±16.1)	0.45
PF	43.8±10.7	50.3±4.7	0.08	44.6±7.6	47.2±9.8	>0.99	6.5±9.5 (21.6±32.6)	2.6±13.0 (9.9±34.7)	>0.99
RP	48.0±10.2	53.6±1.8	0.20	49.4±6.4	52.5±4.0	0.29	5.6±9.2 (17.7±31.4)	3.1±6.5 (7.8±15.4)	>0.99
BP	55.4±8.0	56.0±6.8	>0.99	54.2±10.2	52.2±11.8	>0.99	0.6±8.5 (2.7±16.7)	-2.0±15.0 (-0.2±29.4)	>0.99
VT	49.0±6.8	53.1±5.5	0.09	49.7±6.8	51.4±6.4	>0.99	4.0±4.8 (9.1±10.1)	1.7±7.5 (4.6±16.2)	0.98
SF	47.1±13.0	53.8±4.9	0.20	53.8±4.9	52.4±7.5	>0.99	6.7±10.7 (24±38.9)	-1.4±9.3 (-1.4±19.7)	0.15
MH	55.3±5.7	56.5±1.7	>0.99	56.5±1.7	55.5±13.6	>0.99	1.1±6.1 (3.5±16.3)	-0.9± 4.2 (-1.5±7.5)	>0.99
RE	53.3±3.3	53.7±1.7	0.95	52.8±3.6	50.9±10.0	>0.99	0.4±1.6 (1.1±3.8)	-1.9±10.8 (-3.0±20.7)	>0.99
PCS	45.6±8.7	50.8±3.2	0.12	45.5±5.8	47.2±7.0	>0.99	5.2±7.2 (15.0±21.1)	1.7±9.0 (5.3±20.4)	>0.99
MCS	53.5±5.9	54.5±1.8	>0.99	55.7±2.3	53.6±3.9	0.47	1.0±6.2 (3.4±16.5)	-2.1±4.6 (-3.6±8.3)	0.81

Numbers shown in parentheses reflect mean percentage change from baseline values.

Spearman's rank correlation coefficients between absolute change of muscle size and that of muscle strength, physical function and quality of life

Variables	Overall (n=26)		Electrical stimulation (n=13)		Control (n=13)	
	r	P	r	P	r	P
Muscle strength, N						
Knee extension R	0.70	<0.001	-0.08	0.81	0.46	0.11
Knee extension L	0.76	<0.001	0.26	0.40	0.36	0.23
Physical function						
Timed up & go, s	-0.63	0.001	0.19	0.54	-0.17	0.59
Quality of life (SF-8)						
GH	0.20	0.34	0.03	0.92	0.06	0.84
PF	0.15	0.47	-0.07	0.83	0.17	0.57
RP	0.12	0.56	-0.03	0.91	0.15	0.64

BP	0.20	0.33	0.42	0.16	0.12	0.69
VT	0.01	0.96	-0.20	0.52	-0.11	0.71
SF	0.25	0.22	-0.14	0.65	0.19	0.54
MH	0.07	0.75	-0.26	0.39	0.27	0.37
RE	0.20	0.32	0.39	0.19	0.16	0.61
PCS	0.14	0.50	0.30	0.32	-0.07	0.82
MCS	0.24	0.24	-0.02	0.94	0.45	0.13

Biochemical parameters before and after the 8-week intervention period

Variables	**Electrical stimulation group**			**Control group**			**Absolute change within the group**		
	Baseline	**Final**	**P**	**Baseline**	**Final**	**P**	**Electrical stimulation**	**Control**	**P**
ANP, pg/mL	95.0±90.8	125.0±115.6	0.14	96.4±42.0	91.1±51.5	>0.99	30.0±45.9 (48.5±78.5)	-5.3±64.2 (8.8±73.5)	0.24
BNP, pg/mL	180.2±198.3	227.1±282.7	0.52	161.1±128.6	178.5±189.5	>0.99	47.0±134.7 (62.4±123.5)	17.4±127.8 (21.3±66.5)	>0.99
CK, U/L	98.8±79.2	118.8±90.9	0.98	106.5±60.7	102.3±38.5	>0.99	20.0±51.6 (27.0±59.6)	-4.2±41.5 (4.9±28.0)	>0.99
CRP, µg/mL	2.0±2.9	2.0±3.2	>0.99	2.2±2.8	3.0±3.5	0.66	0.1±1.9 (25.4±79.1)	0.8±2.6 (129.7±283.3)	>0.99
Fibrinogen, mg/dL	348.2±68.3	336.0±64.5	>0.99	303.2±69.3	305.5±72.0	>0.99	-12.2±50.3 (-2.5±14.0)	2.2±32.6 (1.0±11.0)	0.91
Glucose, mg/dL	115.3±35.7	134.0±31.9	0.21	142.6±64.3	153.0±92.5	>0.99	18.7±31.0 (21.0±28.9)	10.4±42.7 (4.8±23.0)	0.06
HbA1c, %	5.5±0.6	5.6±0.9	>0.99	6.2±1.6	6.0±1.3	0.92	0.01±0.6 (-0.04±10.6)	-0.2±0.6 (-2.2±9.7)	>0.99
Insulin, µIU/mL	13.6±12.7	17.2±11.4	0.52	16.7±15.7	12.0±15.3	0.19	3.5±8.5 (100.6±196.4)	-4.7±8.4 (-16.2±58.8)	0.06
HDL, mg/dL	44.8±13.2	45.5±11.7	0.92	47.2±13.8	46.6±8.7	>0.99	0.7±5.6 (2.8±10.9)	-0.6±9.4 (2.8±18.7)	>0.99
LDL, mg/dL	88.3±30.5	82.9±22.7	>0.99	89.7±25.2	95.3±24.0	>0.99	-5.4±21.7 (-2.0±20.7)	5.6±21.0 (10.1±30.4)	>0.99
T-Cho, mg/dL	159.5±35.4	154.1±29.7	>0.99	161.0±35.3	169.6±30.8	0.93	-5.4±22.1 (-2.0±11.9)	8.6±23.0 (7.3±16.7)	>0.99
TG, mg/dL	126.9±94.2	122.8±88.0	>0.99	122.8±113.2	127.4±128.1	>0.99	-4.2±36.6 (7.7±36.4)	4.6±51.9 (13.5±39.1)	>0.99
IGF-1, ng/mL	136.7±44.9	121.9±44.9	0.04	137.9±59.7	125.6±56.1	0.62	-14.8±18.1 (-11.6±12.3)	-12.3±27.2 (-8.4±22.9)	>0.99
DHEAS, µg/dL	173.0±128.5	175.8±130.8	>0.99	147.0±95.1	150.9±94.7	>0.99	2.8±44.8 (5.1±24.4)	3.9±17.1 (6.3±18.8)	>0.99
Homocysteine, nmol/mL	67.7±101.1	54.5±63.2	>0.99	36.9±17.3	38.7±22.3	>0.99	-13.2±44.0 (-5.6±23.8)	1.7±16.5 (7.0±42.1)	>0.99

Adiponectin, µg/mL	21.6±15.7	21.9±15.8	>0.99	17.8±7.7	17.8±7.0	>0.99	0.3±3.8 (2.4±14.5)	0.02±3.3 (4.7±26.9)	>0.99

Numbers shown in parentheses reflect mean percentage change from baseline values.

Abbreviations used: BP, bodily pain; CSA, cross-sectional area; GH, general health perception; L, left; MCS, mental component summary; MH, mental health; PCS, physical component summary; PF, physical functioning; R, right; RE, role emotional; RP, role physical; SF, social functioning; SF-8, the short form-8 health survey; VT, vitality.

Validity and generalisability of the studies

- The study design for the 11 studies in table 2 were randomised controlled trials, systematic reviews and/or meta-analysis.
- Although studies 1 and 6 were Cochrane systemic review and meta-analysis, the quality of the evidence, assessed using GRADE, was from moderate to very low across the different outcomes.
- Several publications[1, 2, 5, 6], which focused on different efficacy outcomes, included the same population; there was likely to be some sample overlap.
- Patient populations were heterogenous, including patients with non-neurological chronic conditions such as COPD, CHF, CKD and thoracic disease.
- Regarding dropouts, where reported, the numbers ranged from 2 to 22 (the proportions ranged from 3% to 30%) and intention-to-treat analysis was not used[3, 7-11]. Of these dropouts, 3 were related to the electrical stimulation (discomfort and allergic reaction)[8, 9, 11] and 2 were unable to tolerate the stimulation[9].
- The programme duration was no longer than 12 weeks, with most being 4 to 8 weeks.
- There was variation among the studies in the device used, targeted muscles, stimulation parameters and programme characteristics.

Existing assessments of this procedure

The scientific statement from the American Heart Association (AHA) and the Heart Failure Society of America (HFSA) on heart failure management in skilled nursing facilities was published in 2015. The efficacy of neuromuscular electrical stimulation was based on 1 meta-analysis, 2 randomised controlled trials, 1 non-randomised comparative study and 1 review. AHA and HFSA recommended that, for patients with advanced heart failure severity and unable to participate in traditional rehabilitation in a meaningful way, neuromuscular electrical stimulation could be considered provided it was consistent with their goals and cognitive and physical function. This recommendation was classified as ‘Class IIa; level of evidence B’, indicating recommendation in favour of treatment or procedure being useful/effective.

The official statement of ATS and ERS: updated on limb muscle dysfunction in chronic obstructive pulmonary disease (COPD) was published in 2014. The efficacy of neuromuscular electrical stimulation for limb muscle function in chronic obstructive pulmonary disease derived from 7 randomised controlled trials. ATS and ERS concluded that neuromuscular electrical stimulation was emerging as a useful training modality in patients severely impaired by COPD and during exacerbations.

The joint statement of the American Thoracic Society (ATS) and the European Respiratory Society (ERS) statement on pulmonary rehabilitation was published in 2006. The efficacy of neuromuscular electrical stimulation for treating patients with extreme muscle weakness caused by severe chronic respiratory disease was based on 3 randomised controlled trials. ATS and ERS recommended that neuromuscular electrical stimulation might be an adjunctive therapy for patients with severe chronic respiratory disease who were bed-bound or suffering from extreme skeletal muscle weakness.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

NICE guidelines

- Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline 115 (2018). Available from https://www.nice.org.uk/guidance/ng115
- Chronic heart failure in adults: diagnosis and management. NICE guideline 106 (2018). Available from https://www.nice.org.uk/guidance/NG106
- Chronic kidney disease in adults: assessment and management. NICE clinical guideline 182 (2014). Available from https://www.nice.org.uk/guidance/cg182
- Rehabilitation after critical illness in adults. NICE clinical guideline 83 (2009). Available from https://www.nice.org.uk/guidance/cg83

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The

advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three professional expert questionnaires for electrical stimulation to improve muscle strength in non-neurological chronic conditions were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 5 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submissions. These were considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials

- Neuromuscular electrical stimulation (NMES) as an adjunct to pulmonary rehabilitation in patients with COPD. ISRCTN40579508. RCT. Estimated study completion date: March 2022. Estimated enrolment: 108 patients. Harefield hospital, United Kingdom.

- Building Strength Through Rehabilitation for Heart Failure Patients (BISTRO-STUDY) NCT03615469. Active. RCT. Estimated study completion date: December 2019. Estimated enrolment: 60 patients. Indiana University, United States.

- Clinical trial of neuromuscular electrical stimulation of the lower extremities in acute exacerbated patients with chronic obstructive pulmonary disease. ChiCTR-IPR-16009845. RCT. Estimated enrolment: 60 patients. Shandong, China.

References

1. Jones S, Man WDC, Gao W et al. (2016) Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease (Review). Cochrane database of systematic reviews Issue 10. Art. No.: CD009419
2. Neto MG, Oliveira FA, dos Reis HFC et al. (2016) Effects of neuromuscular electrical stimulation on physiologic and functional measurements in patients with heart failure. Journal of cardiopulmonary rehabilitation and prevention 36: 157-166
3. Iliou MC, Vergès-Patois B, Pavy B et al. (2017) Effects of combined exercise training and electromyostimulaiton treatmetns in chronic heart failure: a prospective multicentre study. European journal of preventive cardiology 24(12): 1274-1282
4. Cenik F, Schoberwalter D, Keilani M et al. (2016) Neuromuscular electrical stimulation of the thighs in cardiac patients with implantable cardioverter defibrillators. Wien Klin Wochenschr 128: 802-808
5. Hill K, Cavalheri V, Mathur S et al. (2018) Neuromuscular electrostimulation for adutls with chronic obstructive pulmonary disease (Review). Cochrane database of systematic reviews Issue 5. Art. No.: CD010821
6. Chen RC, Li XY, Guan BP et al. (2016) Effectiveness of neuromuscular electrical stimulation for the rehabilitation of moderate-to-severe COPD: a meta-analysis. International journal of COPD 11: 2965-2975
7. Bonnevie T, Gravier FE, Debeaumont D et al. (2018) Home-based neuromuscular electrical stimulation as an add-on to pulmonary rehabilitation does not provide further benefits in patient with chronic obstructive pulmonary disease: a multicentre randomised trial. Archives of physical medicine and rehabilitation 99: 1462-1470
8. Brüggemann AK, Mello CL, Pont TD et al. (2017) Effects of neuromuscular electrical stimulation during haemodialysis on peripheral muscle strength and exercise capacity: a randomised clinical trial. Archives of physical medicine and rehabilitation 98: 822-831
9. McGregor G, Ennis S, Powell R et al. (2018) Feasibility and effects of intra-dialytic low-frequency electrical muscle stimulation and cycle training: A pilot randomized controlled trial. PLoS ONE 13(7): e0200354
10. Roxo RS, Xavier VB, Miorin LA et al. (2016) Impact of neuromuscular electrical stimulation on functional capacity of patients with chronic kidney disease on haemodialysis. J Bras Nefrol 38(3): 344-350

11. Suzuki T, Ikeda M, Minami M et al. (2018) Beneficial effect of intradialytic electrical muscle stimulation in haemodialysis patients: a randomised controlled trial. Artificial organs 42: 899-910

12. Jurgens CY, Goodlin S, Dolansky M et al. (2015) Heart failure management in skilled nursing facilities: a scientific statement from the American Heart Association and the Heart Failure Society of America. Circ Heart Fail 8:655-687

13. Maltais F, Decramer M, Casaburi R et al. (2014) An official American Thoracic Society/European Respiratory Society statement: update on limb muscle dysfunction in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 189(9) e15-e62

14. Nici L, Donner C, Wouters E et al. (2006) American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. Am J Respir Crit Care Med 173: 1390-1413

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	05/08/2019	Issue 8 of 12, August 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	05/08/2019	Issue 8 of 12, August 2019
HTA database (CRD website)	05/08/2019	n/a
MEDLINE & MEDLINE In-Process (Ovid)	05/08/2019	1946 to August 02, 2019
MEDLINE ePubs ahead of print (Ovid)	05/08/2019	August 02, 2019
EMBASE (Ovid)	05/08/2019	1974 to 2019 August 02
BLIC	05/08/2019	n/a

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Chronic Disease/ (256029)
2 ((underlying or exist* or chronic or long term or long-term) adj4 (condition* or illness* or disease* or disorder* or sickness or afflict*)).tw. (366653)
3 Heart Failure/ (111745)

4 ((chronic* or congest*) adj4 (heart* or cardiac* or myocardial*) adj4 (fail* or disease* or disorder* or decompensat*)).tw. (57200)
5 exp Pulmonary Disease, Chronic Obstructive/ (52241)
6 (chronic adj4 obstruct* adj4 (pulmonar* or lung* or airway*) adj4 (disease* or disorder*)).tw. (42328)
7 (chronic adj4 (airflow* or airway*) adj4 obstruct*).tw. (2782)
8 (COPD or COAD).tw. (36322)
9 Emphysema/ (6973)
10 emphysem*.tw. (22968)
11 Bronchitis, Chronic/ (1722)
12 exp Renal Insufficiency, Chronic/ (108671)
13 (chronic* adj4 (kidn* or renal*) adj4 (disease* or failure* or insuffic*)).tw. (65606)
14 or/1-13 (808868)
15 Muscle Weakness/ (7812)
16 Muscle Strength/ (17850)
17 (musc* adj4 (weak* or atroph* or defic* or degener* or impair* or declin* or deteriorat* or strength* or strong* or improv*)).tw. (75095)
18 or/15-17 (88095)
19 Electric Stimulation Therapy/ (19882)
20 Electric Stimulation/ (112431)
21 (electric* adj4 stimulat* adj4 (therap* or treat* or interven* or proced*)).tw. (2579)
22 ((neuromusc* or function*) adj4 electric* adj4 stimulat*).tw. (3377)
23 (Peripher* adj4 nerve* adj4 stimulat*).tw. (2141)
24 Transcutaneous Electric Nerve Stimulation/ (4465)
25 (transcutaneous* adj4 (electric* or nerve*) adj4 stimulat*).tw. (3110)
26 electrotherap*.tw. (1170)
27 (analgesic adj4 cutan* adj4 (electrostimulat* or electro-stimulat* or (electric* adj4 stimulat*))).tw. (3)
28 TENS.tw. (9768)
29 (transdermal adj4 (electrostimulat* or electro-stimulat* or (electric* adj4 stimulat*))).tw. (23)
30 (PNS or NMES or FES).tw. (13964)
31 electroanalges*.tw. (179)
32 (percutan* adj4 neuromodulat*).tw. (44)
33 or/19-32 (157636)
34 14 and 18 and 33 (191)
35 (Microstim adj4 2V2).tw. (0)
36 (H200 and Bioness).tw. (0)
37 WalkAide*.tw. (4)
38 MyndMove*.tw. (0)
39 Tensmed.tw. (0)

40 OmniStim.tw. (1)
41 or/34-40 (196)
42 animals/ not humans/ (4572154)
43 41 not 42 (172)
44 limit 43 to english language (159)

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chronic heart failure			
Sbruzzi G, Ribeiro RA, Schaan BD et al. (2010) Functional electrical stimulation in the treatment of patients with chronic heart failure: a meta-analysis of randomised controlled trials. European journal of cardiovascular prevention & rehabilitation 17(3): 254-260	Meta-analysis n=224 (7 studies)	FES increased the peak VO_2 and the distance of the 6MWT as compared with the control group. FES provided similar gain for the distance of the 6MWT and muscle strength when compared with CA, and a small gain for the peak $V0_2$, of little clinical significance. These findings showed that FES might be an alternative to CA for patients with CHF and for those who were unable to perform this kind of exercise.	All selected studies in the meta-analysis were included in Neto et al. (2016) in table 2.
Banerjee P, Caulfield B, Crowe L et al. (2009) Prolonged electrical muscle stimulation exercise improves strength, peak VO_2 and exercise capacity in patients with stable chronic heart failure. Journal of cardiac failure 15(4): 319-326	Randomised, controlled crossover trial n=10 (mean 66 years, 90% male) programme duration: 18 weeks.	Electrical muscle stimulation can be used in sedentary adults with stable chronic heart failure to improve physical fitness and functional capacity. It may provide a viable alternative for patients unable to undertake some conventional forms of exercise.	This study was included in Neto et al. (2016) in table 2.
Chaplin EJL, Houchen L, Greening NJ et al. (2013) Neuromuscular stimulation of quadriceps in patients hospitalised during an exacerbation of COPD: a comparison of low (35 Hz) and high (50 Hz) frequencies. Physiother Res Int 18: 148-156	Randomised controlled trial n=20 (low frequency n=10 [mean 65 years, 50% male] compared with high frequency n=10 [mean 71 years, 50% male])	neuromuscular electrical stimulation is a feasible intervention to improve muscle strength in a cohort of patients admitted with an exacerbation of COPD. The response appears to be independent of the frequency used and both were well-tolerated.	Studies with a larger sample size and/or better design was included in table 2.

de Araújo CJ, Gonçalves FS, Bittencourt HS et al. (2012) Effects of neuromuscular electrostimulation in patients with heart failure admitted to ward. Journal of cardiothoracic surgery 7: 124	Randomised controlled trial n=20 (stimulation 10 compared with control 10)	The neuromuscular electrostimulation group showed greater improvement in the walked distance in the six-minute walking test in patients admitted to ward for compensation of heart failure.	This study was included in Neto et al. (2016) in table 2.
Deley G, Kervio G, Verges B et al. (2005) Comparison of low-frequency electrical myostimulation and conventional aerobic exercise training in patients with chronic heart failure. European journal of cardiovascular prevention & rehabilitation 12(3): 226-233	Randomised controlled trial n=24 (mean 56.7 years; 93% male) Programme duration: 5 weeks	In patients with moderate to severe CHF, 5 weeks of electrical stimulation and conventional exercise training produce similar improvements to exercise capacity and muscle performance.	This study was included in Neto et al. (2016) in table 2.
Eicher JC, Dobsak P, Berteau O et al. (2004) Rehabilitation in chronic congestive heart failure: comparison of bicycle training and muscle electrical stimulation. Scripta medica (BRNO) 77: 261-270	Randomised controlled trial n=24 (12 in the electrical stimulation group compared with 12 in the classical bicycle training group)	The results showed that an improvement of exercise capacities could be achieved either by classical training method or by electrical stimulation.	This study was included in Neto et al. (2016) in table 2.
Ennis S, McGregor G, Hamborg T et al. (2017) Randomised feasibility trial into the effects of low-frequency electrical muscle stimulation in advanced heart failure patients. BMJ open 7:e016148	Randomised controlled trial n=60 (mean 67 years; 70% male) Programme duration: 8 weeks	The results showed that 12 (20%) of the 60 patients (4 LF-EMS and 8 sham) withdrew. Forty-one patients (68.3%), adhered to the protocol for at least 70% of the sessions. The physiological measures indicated no significant differences between groups in 6MWT distance (p=0.13) and quality of life (p=0.55) although both outcomes improved more with LF-EMS.	Studies with a larger sample size were included in table 2.
Greening NJ, Williams JEA, Hussain SF et al. (2014) An early rehabilitation intervention to enhance	Randomised controlled trial n=389 (early rehabilitation 196 [mean	Early rehabilitation during hospital admission for chronic respiratory disease did not reduce the risk of	This study was included in Jones et al. (2016) in table 2.

recovery during hospital admission for an exacerbation of chronic respiratory disease: randomised controlled trial. BMJ 349:g4315	71 years, 45% male] compared with usual care 193 [mean 71 years, 44% male]) Follow-up: 1 year	subsequent readmission or enhance recovery of physical function following the event over 12 months. Mortality at 12 months was higher in the intervention group. The results suggest that beyond current standard physiotherapy practice, progressive exercise rehabilitation should not be started during the early stages of the acute illness.	
Groehs RV, Antunes-Correa LM, Nobre TS et al. (2016) Muscle electrical stimulation improves neurovascular control and exercise tolerance in hospitalised advanced heart failure patients. European journal of preventive cardiology 23(15): 1599-1608	Randomised controlled trial n=30 (FES, mean 54 years, 93% male; control, mean 49 years, 87% male) Programme duration: 8 to 10 days	Functional electrical stimulation (FES) significantly decreased muscle sympathetic nerve activity and increased muscle blood flow and muscle strength. No changes were found in the control group. Walking distance and quality of life increased in both groups. However, these changes were greater in the FES group.	Studies with a larger sample size were included in table 2.
Harris S, LeMaitre JP, Mackenzie G et al. (2003) A randomised study of home-based electrical stimulation of the legs and conventional bicycle exercise training for patients with chronic heart failure. European heart journal 24: 871-878	Randomised controlled trial n=46 (FES group, mean 63 years, 77.3% male; bicycle group, mean 61.8 years, 87.5% male) Programme duration: 6 weeks	Functional electrical stimulation (FES) produces beneficial changes in muscle performance and exercise capacity in patients with CHF. Within this study, the benefits were similar to those in the bicycle training. FES could be offered to patients with HF as an alternative to bicycle training as part of a home-based rehabilitation programme.	This study was included in Neto et al. (2016) in table 2.
Karavidas A, Driva M, Parissis JT et al. (2013) Functional electrical stimulation of peripheral muscles improves endothelial function and clinical and emotional status in heart failure patients with preserved	Randomised controlled trial n=30 (mean 69 years; 40% male) Programme duration: 6 weeks	As in heart failure and reduced left ventricular ejection fraction, FES also improves exercise capacity, quality of life, emotional status, and endothelial function in heart failure patients with preserved ejection	This study was included in Neto et al. (2016) in table 2.

left ventricular ejection fraction. American heart jouronal 166(4): 760-767		fraction. Given the lack of effective evidence-based therapies in these patients, FES warrants further investigation.	
Kucio C, Niesporek J, Kucio E et al. (2016) Evaluation of the effects of neuromuscular electrical stimulation of the lower limbs combined with pulmonary rehabilitation on exercise tolerance in patients with chronic obstructive pulmonary disease. Journal of human kinetics 54: 75-82	Randomised controlled trial n=28 (electrical stimulation plus PR n=15 [mean 68 years, 64% male] compared with PR n=13 [mean 61 years, 50% male]) Programme duration: 3 weeks	In the electrical stimulation plus PR group, an increase in exercise tolerance manifested by a longer distance walked in the 6MWT was observed in comparison to the pulmonary rehabilitation group. No effects of electrical stimulation combined with RP on selected spirometric and gasometric parameters in patients with COPD were observed in comparison with traditional PR. The acquired results suggest that electrical stimulation of the lower limbs may be applied as an additional form of PR in patients with COPD.	Studies with a larger sample size were included in table 2.
LeMaitre JP, Harris S, Hanna J et al. (2006) Maximum oxygen uptake corrected for skeletal muscle mass accurately predicts functional improvements following exercise training n chronic heart failure. The European journal of heart failure 8: 243-248	Randomised controlled trial n=36 (FES group, mean 63.9 years, 71% male; bike group, mean 60.7 years, 79% male) Programme duration: 6 weeks.	In moderate stable chronic heart failure, exercise training using bicycle ergometer or FES results in favourable qualitative rather than quantitative changes in skeletal muscle. Correction of maximum oxygen uptake for skeletal muscle mass rather than total body mass is a more sensitive measure of changes associated with exercise training.	Studies with a larger sample size were included in table 2.
Lopez LL, Santiago MG, Galindo MD et al. (2018) Efficacy of combined electrostimulation in patients with acute exacerbation of COPD: randomised clinical trial.	Randomised controlled trial n=39 (functional electrostimulation n=14, electrostimulation with calisthenics exercises n=13, and control group n=12)	An electrostimulation treatment improves the exercise capacity, functionality and fatigue in hospitalised AECOPD patients.	Studies with a larger sample size were included in table 2.

Med Clin (Barc) 151(8): 323-328			
Nuhr MJ, Pette D, Berger R, et al. (2004) Beneficial effects of chronic low-frequency stimulation of thigh muscles in patients with advanced chronic heart failure. European heart journal (25): 136-143	Randomised controlled trial n=34 (mean 53 years; 85% male) Programme duration: 10 weeks	The results suggested that CLFS was a suitable treatment to counteract detrimental changes in skeletal muscle and to increase exercise capacity in patients with severe CHF.	This study was included in Neto et al. (2016) and Jones et al. (2016) in table 2
Quittan M, Wiesinger GF, Sturm B et al. (2001) Improvement of thigh muscles by neuromuscular electrical stimulation in patients with refractory heart failure. American journal of physical medicine & rehabilitation 80: 206-224	Randomised controlled trial n=42 (stimulation group, mean 59 years, 71% male; control group, mean 57 years, 56% male) programme duration: 8 weeks.	The results showed an increase of muscle strength by mean 22.7 for knee extensor and by 35.4 for knee flexor muscles. The control group remained unchanged or decreased by -8.4 in extensor strength. Cross-sectional area increased in the stimulation group by 15.5 and in the control group by 1.7.	This study was included in Neto et al. (2016) and Jones et al. (2016) in table 2
Schardong J, Kuinchtner GC, Sbruzzi G et al. (2017) Functinal electrical stimulation improves muscle strength and endurance in patients after cardiac surgery: a randomised controlled trial. Brazilian journal of physical therapy 21(4): 268-273	Randomised controlled trial n=20 (FES group, mean 60 years, 70% male; placebo group, mean 63.5 years; 70% male) programme duration: 8 weeks	The findings showed that FES improved lower limb muscle strength and endurance in patients after cardiac surgery. Larger trials are needed to confirm our findings.	Studies with a larger sample size were included in table 2.
Soska V, Dobsak P, Pohanka M et al. (2014) Exercise training combined with electromyostimulation in the rehabilitation of patients with chronic heart failure: a randomised trial. Biomed rap med fac 158(1): 98-106	Randomised controlled trial n=71 (mean 59 years; 79% male) programme duration: 12 weeks	No significant difference was found between electromyostimulation and aerobic training and nor did their combination have any significant additional improvement.	Studies with a larger sample size was included in table 2.
Vivodtzev I, Decorte N, Wuyam B et al. (2013) Benefits of neuromuscular electrical stimulation prior to endurance training in patients with	Randomised controlled trial n=14 (electrical stimulation 7 compared with control 7)	Neuromuscular electrical stimulation training performed prior to endurance training is useful for strengthening peripheral muscles, which in turn may	Studies with a larger sample size was included in table 2.

cystic fibrosis and severe pulmonary dysfunction. CHEST 143 (2): 485-493	programme duration: 14 weeks	augment gains in body weight and quality of life, further reductions in ventilation requirements during exercise, and retard insulin resistance in patients with CF with severe pulmonary obstruction.	
Coquart JB, Grosbois JM, Olivier C et al. (2016) Home-based neuromuscular electrical stimulation improves exercise tolerance and health-related quality of life in patients with COPD. International journal of COPD 11: 1189-1197	Non-randomised comparative study n=188 (electrical stimulation 71 [mean 66 years; 76% male] compared with UEPEs 117 [mean 63 years; 32% male]) Programme duration: 6 to 8 weeks	Home-based PR including self-monitored electrical stimulation seems feasible and effective for severely disabled COPD patients with severe exercise intolerance.	Studies with a larger sample size and/or better design was included in table 2.
Karavidas A, Parissis JT, Matzaraki V et al. (2010) Funcitonal electrical stimulation is more effective in severe symptomatic heart failure patients and improves their adherence to rehabilitation programmes. Journal of cardiac failure 16(3): 244-249	Non-randomised comparative study n=31 (mean 62 years; 81% male) Programme duration: 6 weeks	Functional electrical stimulation might exert a grater beneficial effect on clinical and neurohormonal status of NYHA III-IV patients in comparison to NYHA II patients. This effect may have important clinical relevance leading to increased adherence of severe CHF patients to exercise rehabilitation programmes.	Studies with a larger sample size were included in table 2.
Kaymaz D, Ergun P, Demirci E et al. (2015) Comparison of the effects of neuromuscular electrical stimulation and endurance training in patients with severe chronic obstructive pulmonary disease. Tuberk Toraks 63(1): 1-7	Non-randomised comparative study n=50 (electrical stimulation 23 [mean 63 years] compared with endurance training 27 [mean 63 years]) Programme duration: 8 to 10 weeks	Neuromuscular electrical stimulation can be used as an effective treatment strategy in PR programs for peripheral muscle training in patients with severe COPD.	Studies with a larger sample size and/or better design was included in table 2.
Sbruzzi G, Schaan BD'A, Pimentel GL et al. (2011) Effects of low frequency functional electrical stimulation with 15 and 50 Hz on	Non-randomised comparative study n=22 (mean 61.6 years; 100% male)	The IMPT generated by acute 50 Hz application of FES was higher than the one generated by 15 Hz, but it was lower than MVC in controls	Studies with a larger sample size were included in table 2.

muscle strength in heart failure patients. Disability and rehabilitation 33(6): 486-493		and patients with heart failure. Thus, the higher the frequency, the greater the motor recruiting, producing increased muscle strength.	
Crevenna R, Mayr W, Keilani M et al. (2003) Safety of a combined strength and endurance training using neuromuscular electrical stimulation of thighs muscles in patients with heart failure and bipolar sensing cardiac pacemakers. Wien Klin Wochenschr 115: 710-714	Case series n=7 (mean 60 years; 86% male)	Neuromuscular electrical stimulation treatment of thigh muscles using a combined electrical stimulation protocol to enhance strength and endurance capacity appears to be safe in patients with heart failure and implanted pacemakers with bipolar sensing, as far as the described electrode configuration and parameter range is applied.	Studies with a larger sample size were included in table 2.
Crevenna R, Wolzt M, Fialka-Moser V et al. (2004) Long-term transcutaneous neuromuscular electrical stimulation in patients with bipolar sensing implantable cardioverter defibrillators: a pilot safety study. Artificial organs 28: 99-102	Case series n=6 (mean 68 years; 100% male)	Long-term electrical stimulation of thigh muscles seems to be safe in patient with implantable cardioverter defibrillators, providing that an individual risk is excluded before.	This study was included in Cenik et al. (2016) in table 2.
Dobšák P, Nováková M, Siegelová J et al. (2006) Low-frequency electrical stimulation increases muscle strength and improves blood supply in patients with chronic heart failure. Circ J 70: 75-82	Case series N=15 (mean 56.5 years; 93% male) Programme duration: 6 weeks	Six weeks of LFES significantly increased F_{max} (from 224.5±96.8 N to 340.0±99.4 N; $p<0.001$), and PT_{max} (from 94.5±41.5 Nm to 135.3±28.8 Nm; $p<0.01$). BFV in the femoral artery increased after 6 weeks from 35.7±15.4 cm/s to 48.2±18.1 cm/s ($p<0.05$); BFV values at rest before and after 6 weeks of LFES did not differ significantly.	Studies with a larger sample size were included in table 2.
Crevenna R, Stiz G, Pleiner J et al. (2003) Electromagnetic interference by	Case series	Electromagnetic interference (EMI) occurred during stimulation of the neck	This study was included in Cenik et al. (2016) in table 2

transcutaneous neuromuscular electrical stimulation in patients with bipolar sensing implantable cardioverter defibrillators: a pilot safety study. PACE 26(2): 626-629	n=8 (mean 58 years; 75% male)	(n=2) and thigh (n=2). EMI by electrical stimulation with atrial sensing was seen in 2 of 4 patients with dual chamber ICDs. The safety of peripheral electrical stimulation has to be individually tested as EMI can also occur in ICD patients with bipolar sensing.	
Maillefert JF, Eicher JC, Walker P et al. (1999) Effects of low-frequency electrical stimulation f quadriceps and calf muscles in patients with chronic heart failure. Journal of cardiopulmonary rehabilitation 18(4): 277-282	Case series n=14 (mean 56.4 years) Programme duration: 5 weeks	The results suggested that low-frequency muscular electrical stimulation was well tolerated, induced an increased exercise capacity in patients with chronic heart failure, without an undesirable increase in cardiac output.	Studies with a larger sample size were included in table 2.
Quittan M, Sochor A, Wiesinger GF et al. (1999) Strength improvement of knee extensor muscles in patients with chronic heart failure by neuromuscular electrical stimulation. Artificial organs 23(5): 432-435	Case series n=7 (mean 56 years) Programme duration: 5 weeks	The results demonstrated that electrical stimulation of skeletal muscles in patients with severe chronic heart failure was a promising method for strength training in this group of patients.	Studies with a larger sample size were included in table 2.
Deley G, Kervio G, Verges B et al. (2008) Neuromuscular adaptations to low-frequency stimulation training in a patient with chronic heart failure. American journal of physical medicine and rehabilitation 87: 502-509	Case report n=1 (54 years; male) Programme duration: 5 weeks	An increase in maximal strength (10.5%) was accompanied by increased twitch torque (13.9%) and showing of muscle contractile properties (half-relaxation time, time to peak torque, and maximal rate of relaxation increased by 7.1, 31.1 and 16.6%, respective) with changes in muscle activation.	Studies with a larger sample size were included in table 2.
Arena R, Pinkstaff S, Wheeler E et al. (2010) Neuromuscular electrical stimulation and inspiratory muscle training as potential adjunctive rehabilitation	Review	The addition of electrical stimulation and inspiratory muscle training may serve a role as adjunctive rehabilitation options in the population with HF,	The mainly cited papers relating to electrical stimulation and heart failure were included in Neto et al. (2016).

options for patients with heart failure. Journal of cardiopulmonary rehabilitation and prevention: JCRP 30(4): 209-223		particularly in those patients who present with a greater degree of functional impairment at baseline. Future research is required to better elucidate their clinical value.	
Arena R, Cahalin LP, Borghi-Silva A et al. (2014) Improving functional capacity in heart failure: the need for a multifaceted approach. Current opinion in cardiology: bi-monthly review of the world literature 29: 467-474	Review	The use of electrical stimulation should not be viewed as a replacement for traditional aerobic and resistance training programmes. Rather, there were 2 scenarios in which the use of electrical stimulation might warrant particular consideration: first, in heart failure patients presenting with advanced disease severity who had difficulty participating in traditional aerobic and resistance training exercises secondary to a severely compromised functional capacity and second, to augment the training stimulus in heart failure patients currently participating in an aerobic or resistance training programme.	The mainly cited papers relating to electrical stimulation and heart failure were included in Neto et al. (2016).
Arena R, Lavie CJ, Borghi-Silva A et al. (2015) Exercise training in group 2 pulmonary hypertension: which intensity and what modality. Progress in cardiovascular diseases	Review	The benefits of electrical stimulation appeared to be enhanced in heart failure patients with advanced disease severity, so it could be a useful tool in this population.	The mainly cited papers relating to electrical stimulation and heart failure were included in Neto et al. (2016).
Banerjee P (2010) Electrical muscle stimulation for chronic heart failure: an alternative tool for exercise training? Curr Heart Fail Rep 7: 52-58	Review	Evidence indicated that electrical stimulation produced similar benefits to conventional exercise in improving exercise capacity, making electrical stimulation an alternative to aerobic exercise training in those that could not	The mainly cited papers relating to electrical stimulation and heart failure were included in Jones et al. (2016) in table 2.

		undertake conventional exercise. The improvement seen in leg muscle strength promised also to improve mobility in patients with chronic heart failure.	
Saitoh M, dos Santos MR, Anker M et al. (2016) Neuromuscular electrical stimulation for muscle wasting in heart failure patients. International journal of cardiology 225: 200-205	Review	Neuromuscular electrical stimulation seemed to be a safe and effective modality to prevent muscle wasting in patients with HF who were unable or unwilling to engage in conventional aerobic and/or resistance exercise, either as 'target' therapy or as a 'bridge' therapy to conventional exercise.	The mainly cited papers were included in table 2.
Chronic obstructive pulmonary disease			
Roig M and Reid WD (2009) Electrical stimulation and peripheral muscle function in COPD: a systematic review. Respiratory Medicine 103: 485-498	Systematic review n=5 studies	The modest effect sizes after electrical stimulation, small n, and small number of studies provide weak evidence for the effectiveness of electrical stimulation to improve lower limb muscle function in COPD patients. Further study should elucidate the optimal parameters for electrical stimulation protocols and selection criteria for responders and non-responders	All cited 5 papers were included in Jones et al. (2016) in table 2.
Pan L, Guo YZ, Liu XC et al. (2014) Lack of efficacy of neuromuscular electrical stimulation of the lower limbs in chronic obstructive pulmonary disease patients: a meta-analysis. Respirology 19(1): 22-29	Meta-analysis n=156 (8 studies; mean 58.5 years to 70 years; 74% male) Programme duration: 4 to 6 weeks	Evidence to support the benefits of electrical stimulation to COPD patients is currently inadequate. Larger-scale studies are needed to investigate the efficacy of electrical stimulation.	Most selected studies in the meta-analysis were included in Hill et al. (2018) and Chen et al. (2016) in table 2.
Akar O, Günay E, Ulasli SS et al. (2015) Efficacy of neuromuscular electrical stimulation in patients with COPD followed in intensive	Randomised controlled trial N=30 (mean 67 years, 50% male)	Neuromuscular electrical stimulation alone and neuromuscular electrical stimulation with active extremity	This study was included in Jones et al. (2016) in table 2.

care unit. The clinical respiratory journal: the official journal of the Nordic respiratory 11(6): 743-750	Programme duration: 4 weeks	exercise training seemed more superior than active extremity muscle training alone to prevent and strengthen lower extremity muscled function of patient with COPD acute exacerbation and respiratory failure, in earlier period, in ICUs. Additionally, neuromuscular electrical stimulation with or without exercise training combinations and exercise training alone did not differ duration of weaning and discharge from ICU.	
Bourjeily-Habr G, Rochester CL, Palermo F et al. (2002) Randomised controlled trial of transcutaneous electrical muscle stimulation of the lower extremities in patients with chronic obstructive pulmonary disease. Thorax 57(12): 1045-1049	Randomised controlled trial n=18 (stimulation group, mean 58.5 years; control group, mean 61.5 years; 56% male) Programme duration: 6 weeks	Transcutaneous electrical muscle stimulation of peripheral muscles can be a useful adjunct to the comprehensive pulmonary rehabilitation of patients with COPD.	This study was included in Jones et al. (2016) in table 2
Maddocks M, Nolan CM, Man WDC et al. (2016) Neuromuscular electrical stimulation to improve exercise capacity in patients with severe COPD: a randomised double-blind, placebo-controlled trial. Lancet respir MED 4:27-36	Randomised controlled trial n=52 (mean years: 86% male) Programme duration: 6 weeks	Neuromuscular electrical stimulation improves functional exercise capacity in patients with severe COPD by enhancing quadriceps muscle mass and function. These data supported the use of neuromuscular electrical stimulation in the management of patients unable to engage with conventional pulmonary rehabilitation.	This study was included in Jones et al. (2016) in table 2.
Nápolis LM, Corso SD, Neder JA et al. (2011) Neuromuscular electrical stimulation improves exercise tolerance in chronic obstructive pulmonary disease patients with	Randomised controlled trial n=30 (mean 63.7 years: 86% male)	high-frequency neuromuscular electrical stimulation improved the exercise capacity of COPD patients with better-preserved fat-free mass because they tolerated higher training	This study was included in Jones et al. (2016) in table 2

better preserved fat-free mass. Clinical science 66(3): 401-406	Programme duration: 6 weeks	stimulus levels. These data suggest that early training with high-frequency neuromuscular electrical stimulation before tissue wasting begins might enhance exercise tolerance in patients with less advanced COPD.	
Neder JA, Sword D, Ward SA et al. (2002) Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). Thorax 57: 333-337	Randomised controlled trial n=15 (stimulation group, 66.6 years; control group, 65.0 years; 60% male) Programme duration: 6 weeks	For severely disabled COPD patients with incapacitating dyspnoea, short term electrical stimulation of selected lower limb muscles involved in ambulation can improve muscle strength and endurance, whole body exercise tolerance, and breathlessness during activities of daily living.	This study was included in Jones et al. (2016) in table 2
Sillen MJH, Franssen FME, Vaes AW et al. (2014) Metabolic load during strength training or NMES in individuals with COPD: results from the DICES trial. BMC pulmonary medicine 14: 146	Randomised controlled trial n=24 (mean 66 years; 58% male) Programme duration: 8 weeks	The metabolic load and symptom scores for dyspnoea, fatigue and muscle pain remain acceptable low over time with increasing training loads during HF-NMES, LF-NMES or strength training. For this reason, these interventions are recommended in severely dyspnoeic patients with COPD for improving their muscle function and exercise performance.	Studies with a larger sample size were included in table 2.
Tasdemir F, Inal-Ince D, Ergun P et al. (2015) Neuromuscular electrical stimulation as an adjunct to endurance and resistance training during pulmonary rehabilitation in stable chronic obstructive pulmonary disease. Exert Rev. Respir. Med. 9(4): 493-502	Randomised controlled trial N=27 (electrical stimulation plus cPR 13 [mean 62.1 years; 85% male] compared with sham plus cPR 14 [mean 62.9 years; 93% male]) Programme duration: 10 weeks	The increase in exercise capacity is less important when neuromuscular electrical stimulation is used as an adjunct to the comprehensive pulmonary rehabilitation programme.	Studies with a larger sample size were included in table 2.

Vieira PJC, Chiappa AM, Cipriano G Jr et al. (2014) Neuromuscular electrical stimulation improves clinical and physiological function in COPD patients. Respiratory medicine 108: 609-620	Randomised controlled trial n=20 (mean 56.4 years, 100% male) Programme duration: 8 weeks	Eight weeks of electrical stimulation promotes reduction of the perceived sensation of dyspnoea during exercise in patients with COPD. This finding is accompanied by improvements in FEV1, exercise tolerance and quality of life, and DH.	Studies with a larger sample size were included in table 2.
Vivodtzev I, Debigaré R, Gagnon P et al. (2012) Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD. Chest 141: 716-725	Randomised controlled trial n=20 (electrical stimulation, mean 70 years; sham, mean 68 years; 65% male) Programme duration: 6 weeks	In patients with severe COPD, electrical stimulation improved muscle CSA. This was associated with a more favourable muscle anabolic to catabolic balance. Improvement in walking distance after electrical stimulation training was associated with gains in muscle strength, reduced ventilation during walking, and the ability to tolerate higher stimulation intensity.	This study was included in Jones et al. (2016) in table 2
Vivodtzev I, Pépin JL, Vottero G et al. (2006) Improvement in quadriceps strength and dyspnea in daily tasks after 1 month of electrical stimulation in severely deconditioned and malnourished COPD. Chest, 129(6): 1540-1548	Randomised controlled trial n=17 (stimulation group, 59 years; control group, 68 years; 65% male) Programme duration: 4 weeks	The combination of electrostimulation (ES) and usual rehabilitation (UR) was associated with greater improvement in quadriceps strength and dyspnoea during the performance of daily tasks than UR alone in severely disabled COPD patients with low BMI. In this population, ES has been revealed as a useful procedure, complementing the usual pulmonary rehabilitation	This study was included in Jones et al. (2016) in table 2
Zanotti E, Felicetti G, Maini M et al. (2003) Peripheral muscle strength training in bed-bound patients with COPD receiving mechanical ventilation: effect of electrical stimulation. Chest 124: 292-296	Randomised controlled trial n=24 (stimulation group, 66.2 years; control group, 64.5 years; 71% male)	In bed-bound patients with COPD receiving mechanical ventilation, with marked peripheral muscle hypotonia and atrophy, application of electrical stimulation in addition to classical active limb mobilisation significantly improved	This study was included in Jones et al. (2013) in table 2

	Programme duration: 4 weeks	muscle strength and decreased the number of days needed to transfer from bed to chair.	
Azevedo D, Medeiros W, de Freitas F et al. (2016) High oxygen extraction and slow recovery of muscle deoxygenation kinetics after neuromuscular electrical stimulation in COPD patients. Eur J Appl Physiol 116: 1899-1910	Non-randomised comparative study n=26 (13 patients with COPD compared with 13 healthy people)	COPD patients exhibited a slower muscle deoxygenation recovery time after the electrical stimulation. The absence of desaturation, low torque and work, high μO_2EF and high values for recovery time corrected by muscle mass and work suggest that intrinsic muscle dysfunction has an impact on muscle recovery capacity.	Studies with a larger sample size and/or better design were included in table 2.
Latimer LE, Constantin D, Greening NJ et al. (2019) Impact of transcutaneous neuromuscular electrical stimulation or resistance exercise on skeletal muscle mRNA expression in COPD. International journal of chronic obstructive pulmonary disease 14: 1355-1364	Non-randomised comparative study n=26 (electrical stimulation 13 [mean 64 years, 54% male] compared with voluntary RE 13 [mean 64 years, 62% male])	Compared with electrical stimulation, RE had a broader impact on mRNA abundance and, therefore, appears to be the superior intervention for maximizing transcriptional responses in the quadriceps of patients with COPD. However, if voluntary RE is not feasible in a clinical setting, electrical stimulation by modifying expression of genes known to impact upon muscle mass and strength may have a positive influence on muscle function.	Studies with a larger sample size and/or better design were included in table 2.
Vivodtzev I, Rivard B, Gagnon P et al. (2014) Tolerance and physiological correlates of neuromuscular electrical stimulation in COPD: a pilot study. PLoS one 9(5): e94850	Case series n=20 (mean 65 years; 70% male) programme duration: 8 days	Mean ΔInt was 12±10 mA. FEV_1, fat-free-mass, quadriceps strength, aerobic capacity and leg discomfort during the last electrical stimulation session positively correlated with ΔInt ($r=0.42$ to 0.64, all $p\leq0.06$) while post/pre electrical stimulation IL-6 ratio negatively	Studies with a larger sample size and/or better design were included in table 2.

		correlated with ΔInt (r=20.57, p=0.001). FEV_1, leg discomfort during last electrical stimulation session and post/pre IL-6 ratio to electrical stimulation were independent factors of variance in ΔInt (r2=0.72, p=0.001).	
Giavedoni S, Deans A, McCaughey P et al. (2012) Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. Respiratory medicine 106: 1429-1434	Case series n=11 (mean 72.2 years; 45% male) Programme duration: 14 days	Mean quadriceps muscle strength decreased in control legs (DQMVC -2.9±5.3 N, p=ns) but increased in the stimulated legs (DQMVC 19.2±6.1 N, p<0.01). The difference in DQMVC between groups was statistically significant (p<0.05). The effect of electrical stimulation was directly related to the stimulation intensity (ΣmA) applied throughout the 14 sessions (r=0.76, p<0.01). All patients tolerated electrical stimulation without any side effects.	Studies with a larger sample size were included in table 2.
Palanova P, Mrkvicova V, Nedbalkova M et al. (2018) Home-based training using neuromuscular electrical stimulation in patients on continuous ambulatory peritoneal dialysis: a pilot study. Artificial organs 43: 796-805	Case series n=14 (mean 61.9 years; 43% male) programme duration: 20 weeks	The results demonstrated that an improvement of exercise capacity and quality of life could be achieved by home-based electrical stimulation in patients with continuous ambulatory peritoneal dialysis.	Studies with a larger sample size and/or better design were included in table 2.
Borges VM, de Oliveira LRC, Peixoto E et al. (2009) Moto physiotherapy in intensive care adult patients. Rev Bra Ter Intensiva 21(4): 446-452	Review	evidence compared the use of electrical stimulation associated with physical therapy in patients with COPD, showing increased muscle strength and shorter time for these patients' bed to chair transference as compared with those only receiving physiotherapy.	The only cited paper relating to electrical stimulation and COPD was included in Hill et al. (2018) and Jones et al. (2016) in table 2.

De Brandt J, Spruit MA, Hansen D et al. (2018) Changes in lower limb muscle function and muscle mass following exercise-based interventions in patients with chronic obstructive pulmonary disease: a review of the English-language literature. Chronic respiratory disease 15(2): 182-219	Review	Evidence showed that electrical stimulation improved muscle strength, muscle endurance, muscle mass after the intervention. Evidence also presented the superiority of electrical stimulation over other training modalities.	The cited articles for electrical stimulation and COPD were included in Hill et al. (2018) and Jones et al. (2016) in table 2.
Dourado VZ and Godoy I (2004) Muscle reconditioning in COPD: main interventions and new tendencies. Revista Brasileira de Medicina do Esporte 10(4): 335-338	Review	The electrical stimulation was useful for the skeletal muscle reconditioning in patients with COPD.	The only cited RCT for electrical stimulation and COPD was included in Jones et al. (2016) in table 2.
Jackson AS and Hopkinson N (2009) Skeletal muscle in chronic obstructive pulmonary disease. Clinical pulmonary medicine 16(2): 61-67	Review	Evidence suggested that electrical stimulation seemed to be a promising intervention for those patients unable to benefit from rehabilitation or as an adjunct to rehabilitation, but further research is required with larger patient numbers to establish the optimum intensity and duration of training.	The mainly cited papers were included in Hill et al. (2018) and Jones et al. (2016) in table 2.
Sillen MJH, Wouters EFM, Franssen FME et al. (2009) Resistance training and neuromuscular electrical stimulation during acute exacerbations of chronic obstructive pulmonary disease. International journal of respiratory care: 14-16	Review	Neuromuscular electrical stimulation could enhance the management of acute exacerbations of COPD. Further research is required to investigate whether the electrical stimulation has to be combined with other non-pharmacological interventions.	The cited articles for electrical stimulation and COPD were included in Hill et al. (2018) and Jones et al. (2016) in table 2.
Spruit MA and Wouters EFM (2007) New modalities of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease. Sports medicine 37(6): 501-518	Review plus case report (n=2)	Neuromuscular electrical stimulation has been shown to improve skeletal muscle function and sometimes also exercise capacity but the translation to an improved health-related	The mainly cited articles for electrical stimulation and COPD were included in Hill et al. (2018) and Jones et al. (2016) in table 2.

		quality of life is currently lacking.	
Vivodtzev I, Lacasse Y and Maltais F (2008) Neuromuscular electrical stimulation of the lower limbs in patients with chronic obstructive pulmonary disease. Journal of cardiopulmonary rehabilitation and prevention 28: 79-91	Review	Evidence suggested that electrical stimulation might be more appropriate in severely deconditioned (with low body mass index and/or fat-free mass index) and bed-ridden patients. However, appropriately powered clinical trials using controlled and randomised study designs are needed to better characterise its actual benefits.	The cited articles for electrical stimulation and COPD were included in Hill et al. (2018) and Jones et al. (2016) in table 2.
Wijkstra PJ and Wempe JB (2011) Series "novelties in pulmonary rehabilitation" Eur respir j 38: 1468-1474	Review	There was not enough evidence to start electrical stimulation routinely in patients with COPD and further studies should focus on the optimal parameters of electrical stimulation and investigate which type of patient will have the most benefit from electrical stimulation.	The mainly cited papers relating to electrical stimulation were included in Jones et al. (2016) in table 2.
Chronic kidney disease			
Schardong J, Dipp T, Bozzeto CB et al. (2017) Effects of intradialytic neuromuscular electrical stimulation on strength and muscle arthitecture in patients with chronic kidney failure: randomised clinical trial. Artificial organs 41(11): 1049-1058	Randomised controlled trial n=21 (electrical stimulation 11 compared with 10 control) Programme duration: 8 weeks	The results suggested that electrical stimulation increased muscle strength and had a protective effect against muscle atrophy of the lower limbs of patients with chronic kidney failure on haemodialysis.	Studies with a larger sample size were included in table 2.
Combined conditions and others			
Sillen MJ, Speksnijder CM, Eterman RMA et al. (2009) Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD. Chest 136(1): 44-61	Systematic review N=14 studies	In terms of the methodological quality, PEDro scores for the 14 identified trials were generally moderate to good. Many studies reported significant improvements in muscle strength, exercise capacity, and/or health	All selected studies in the systematic review were included in Neto et al. (2016) and Jones et al (2016) in table 2.

		status. neuromuscular electrical stimulation looks promising as a means of rehabilitating patient with CHF and COPD.	
Gong H, Jiang Q, Shen D et al. (2018) Neuromuscular electrical stimulation improves exercise capacity in adult patients with chronic lung disease: a meta-analysis of English studies. Journal of thoracic disease 10(12): 6722-6732	Systematic review and meta-analysis n=368 (11 studies)	This systemic review and meta-analysis provided evidence supporting the beneficial role of neuromuscular electrical stimulation in improving exercise capacity in patients with chronic respiratory disease.	The mainly selected studies in the meta-analysis were include in Jones S (2016) in table 2.
Meesen RLJ, Dendale P, Cuypers K et al. (2010) Neuromuscular electrical stimulation as a possible means to prevent muscle tissue wasting in artificially ventilated and sedated patients in the intensive care unit: a pilot study. Neuromodulation 13: 315-321	Randomised controlled trial n=19 (ES 7 [mean 65 years, 43% male] compared with control 12 [mean 67 years; 75% male])	The intervention resulted in a significant reduction of muscle atrophy in the stimulated as compared with the non-stimulated limb ($p<0.05$), without making any impact on cardiovascular, respiratory and hemodynamic characteristics.	Studies with a larger sample size were included in table 2.
Simó VE, Jiménez AJ, Oliveira JC et al. (2015) Efficacy of neuromuscular electrostimulation intervention to improve physical function in haemodialysis patients. Int Uro Nephrol 47: 1709-1717	Randomised controlled trial n=38 (stimulation 23 [mean 67.9 years, 58% male] compared with control 15 [mean 72.5 years, 51% male]) programme duration: 12 weeks	Intradialytic electrical stimulation of both quadriceps improved muscular strength, functional capacity and quality of life in patients on haemodialysis. With the obtained results, electrical stimulation constitutes a novel therapeutic alternative to improve the deteriorated physical condition and quality of life of these patients.	Studies with a larger sample size were included in table 2.
Heizig D, Maffiuletti NA and Eser P (2015) The application of neuromuscular electrical stimulation training in various non-neurologic patient populations: a narrative review. PM&R 7(11): 1167-1178	Review	Effectiveness of neuromuscular electrical stimulation in improving muscle force and muscle function as well as exercise capacity in deconditioned patients could be enhanced by appropriate choice of stimulation parameters	The mainly cited papers relating to electrical stimulation and chronic conditions (e.g. COPD, CHF and CKD) were included in table 2.

		according to specific training goals and tailored to patients' diseases.	
Sachs S and Weinberg RL (2009) Pulmonary rehabilitation for dyspnoea in the palliative-care setting. Current opinion in supportive and palliative care 3(2): 112-119	Review	Evidence showed that the effects of electrical stimulation in patients with COPD and heart failure. Electrical stimulation could be adapted to the palliative-case setting to benefit potential patients.	The mainly cited papers relating to electrical stimulation and chronic conditions (COPD and HF) were included in Jones et al. (2016) and Hill et al. (2018) in table 2.