



Database of Knowledge Translation Tools

Intervention Summary

1. Exercise Interventions for Fatigue Management in Multiple Sclerosis

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2. Intervention Description and Dose Recommendations

Purpose and Introduction to the intervention:

- Different types of exercise may impact fatigue in MS, but aerobic and progressive resistance training have the most evidence to support their use.
 - Primary fatigue: impacted by cardiovascular, immunologic and neuroendocrine changes
 - Secondary fatigue: impacted by conditioning, decreased sleep disturbances, and depression (Safari, van der Linden & Mercer 2017).
- Overview of systematic reviews and guidelines:
 - Exercise interventions: *moderate favorable effect* compared to no exercise (Safari et al 2017).
 - Recommendations:
 - Use exercise that includes aerobic, balance, yoga and stretching exercises to treat MS-related fatigue (NICE guidelines, 2014)
 - Mindfulness-based training and moderate progressive resistance training might also be considered (NICE guidelines, 2014)
 - Physical activity is recommended for MS patients (Norwegian MS-guide, 2016):
 - Consult a PT to select exercise type and adjustments.
 - Morning exercise might have a positive effect on fatigue and cognitive function during the day (Nasjonalt kompetansetjeneste for Multipel sklerose 2016).

Recommended dose: *Considering intervention heterogeneity and the amount of evidence, firm recommendations of exercise interventions for MS related fatigue cannot be made. Exercise interventions that progress over time and involve trained facilitators seem to contribute to fatigue reduction. This summary provides recommendations based on published recommendations and doses that resulted in positive outcomes in research.*

Initial recommended dose: Aerobic training

- **Frequency:** 2x/wk for at least 8 weeks, patient should continue after completion of PT
- **Intensity:** Moderate intensity
 - 40-77% of age predicted HR (heart rate calculator <https://www.ntnu.edu/cerg/hrmax>)
 - Borg scale and increase of work load (RPE ranged from 11-17 in studies)
- **Time during the session:** 60 minutes: 5-10 minutes for stretching and warming up/cool down
30-40 minutes aerobic conditioning training.
- **Total time (duration) of the intervention in the research:** 40-60 minutes
- **Type of intervention:** Aerobic exercise on treadmill, ergometry bicycle, aquatic exercise training

Resistance training, Initial recommended dose: aligns with some MS research studies and the American College of Sports Medicine (2009) recommendations

- **Frequency:** 2x/wk
- **Intensity:**
 - 10 – 12 repetition maximum (maximum load that can be completed in 10 – 12 reps)

- Weight should be increased when 2 sets of 12 repetitions can be completed
- **Time during the session:**
 - Time required to complete repetitions and sets
 - 2 minute rest period provided between sets
- **Total time (duration) of the intervention in the research:** at least 10 weeks
- **Type of intervention:** Lower extremity strength training
 - Muscle groups often included hip extensors and flexors, knee extensors and flexors, plantarflexors
- **Recommended progression of intervention:** Weight should be increased when 2 sets of 12 repetitions can be completed
- **Considerations for dose recommendation:** Several doses of aerobic exercise were studied. The study with the largest effect included treadmill walking performed at 3x/wk at an intensity of 40 to 75% of predicted heart rate, however, further details about intensity were not provided. Other studies that demonstrated large effects included frequencies of 1x/wk and 2x/wk. The ideal frequency, intensity, time, and duration have not been determined in the research.

3. Considerations for Clinical Use

Knowledge Expert group recommendation for application to regional health authority:

- Discuss and select exercise options with your patients, keeping in mind that aerobic and resistance training have demonstrated the best effects
 - Consider patient preferences for exercise
 - If aerobic or resistance training is selected, *deliver it at a dose that has demonstrated positive results (see dose recommendations below)*
 - Patients should be encouraged to continue exercise after the programme ends
 - This intervention could potentially be delivered as a component of a group exercise program with mixed diagnoses

Considerations:

- NICE guidelines (2014): Recommends a programme of aerobic and moderate progressive resistance activity combined with cognitive behavioural techniques for patients with moderately impaired mobility and EDSS score ≥ 4 .
- Consider how to embed exercise a part of an everyday lifestyle (Moss-Morris & Norton 2017)
- Mixed training, aerobic and resistive training, shows greatest effects, but the quality of the evidence is low. (Heine et al 2015)

4. Appropriate Patients for the Intervention (characteristics in studies)

Diagnosis: Multiple sclerosis, predominantly Relapsing Remitting type of MS have been studied.

Acuity level: EDSS <6, predominantly women, mean age 48, ranging from 18-65 years

Current level of function: Predominantly individuals able to walk with or without an aid 100 m.

5. Recommended Outcome Measures

- Assessment of fatigue severity and/or impact
 - Fatigue Impact Scale ([see measure description online](#))
 - Modified Fatigue Impact Scale ([see measure description online](#))
 - Fatigue Severity Scale ([see measure description online](#))
 - Chalder Fatigue Scale ([see test](#))
 - Fatigue scale for motor and cognitive functions (FSMC) ([see test](#))
 - Patient Reported Outcomes Measurement Information System (PROMIS)-fatigue ([see measure description online](#))

*There is limited evidence for the psychometric properties of the FSS and MFIS (Safari et al 2017).

6. Overview of the Literature

Brief overview of the theoretical basis for intervention:

- Physical activity is associated with positive effects in several MS symptoms (Casey, Coote, Hayes & Gallagher 2018)
- Aerobic exercise may improve fitness, normalization of hormonal functions and changes in neuroinflammatory and neuroprotective biomarkers (Moss-Morris & Norton 2017)

Meta-analyses on effects of exercise intervention studies:

Safari, van der Linden & Mercer (2017):

- Exercise versus control: (Effect Size; 95% CI)
 - Heine et al 2015: *Small to moderate effect* (-0.35; CI: -0.13, -0.57)
 - Asano and Finlayson 2014: *Moderate to large effect* (-0.57; CI: 0.10, -1.04)
- Exercise versus no exercise: (Effect Size; 95% CI)
 - Heine et al (2015): *Small to moderate effect* (-0.58; -0.34, -0.81)
 - Pilutti et al (2013): *Small to moderate effect* (-0.45; 0.22, -0.68)
 - Cramer et al (2014): *Small to moderate effect* (-0.52; -0.02, -1.02)
 - Motle and Gosney (2008): *Small to moderate effect* (-0.19; -0.01, -0.39)
- Type of exercise: *Authors stated evidence quality was low. More than one body of literature is required to link interventions to fatigue reduction.* (Effect Size; 95% CI)
 - Mixed training (Heine et al 2015): *Moderate to large effect* (-0.73; -1.23, -0.23; p<0.01)
 - Other training (Heine et al 2015): *Moderate to large effect* (-0.54; -0.79, -0.29; p<0.01)
 - Endurance exercise (Heine et al 2015): *Small to moderate effect* (-0.43; -0.69, -0.17; p=0.004)
 - Muscle power training (Heine et al 2015): *No effect* (0.03; -1.02, -0.33)
 - Task oriented training (Heine et al 2015): *Small to moderate effect* (-0.34; -1.02, -0.33; p>0.05)

Systematic review:

Asano, Berg, Johnson, Turpin & Finlayson 2015:

- 17 studies assessed exercise interventions (n = 7 to 36; age = 30 – 55; primarily women and relapsing-remitting MS)
 - Duration varied from a single session 1-7 sessions/wk for up to 12 weeks
 - Time per session varied from 5-60 minutes
- Small (.2) to large (1.70) effect sizes, largest effect sizes were found with the interventions:
 - Vestibular rehabilitation 2xwk, 60min sessions, x 6 wks (*Large effect size* = 1.70, Hebert et al)
 - Home-based self-managed graded exercise program 45-60 minutes, 7 sessions in 2 weeks, home exercise x 6 weeks (*Large effect size* = 1.01, Navipour et al)
 - Progressive resistance training
 - 45 min, 2xwk, 10 weeks (*Moderate-Large effect size* = .79, Dodd et al)
 - 2xwk, 12 wks (*Moderate-Large effect size* = .73, Dalgas et al)
 - 30 min, 2xwk, 8 wks (*Small effect size* = .31, White et al)
 - 45-60 min, 3xwk, 12 wks (*Large effect size* = .88, Hayes et al)
 - 2xwk, 8 wks (*Moderate-Large effect size* = .72, Cakt et al)
- Active control interventions demonstrated *no to large effects* (effect size -.003 to .79)
- Groups receiving no intervention (i.e control groups that didn't receive an intervention) demonstrated *large negative to small positive effects* (effect size -1.62 to .30)

Single study designed for fatigue

Heine et al, 2017:

- Intervention:

- Frequency: 3 x week, 16 weeks; First 12 sessions in OP clinic, 36 sessions at home with minimal supervision
- Intensity: Six interval cycles: 3 min at 40%, 1 min at 60% and 1 min at 80% of peak power
- Time: 30 minutes
- Type: Aerobic interval training on cycle ergometer,
- Results:
 - Adherence:
 - 74 ± 25% completed sessions
 - 71 ± 25% of prescribed workload
 - average intensity of 14.0 ± 2.1 on the 6–20 Borg scale of perceived exertion.
 - significantly lower in the second 8-week period (66 ± 30% completed session; 62 ± 31% of prescribed workload) in comparison to the first 8-week period (86 ± 14% completed session; 79 ± 25% of prescribed workload)
 - perceived exertion was significantly higher (13.5 ± 2.0 vs 14.8 ± 2.4; $p < 0.05$) during the second 8 weeks of training
 - Results:
 - Primary outcome measure Checklist Individual Strength – Fatigue subscale: Statistically significant changes from pre to post intervention (wk 16) in comparison to control group; No long-term differences noted.
 - Although statistically significant, authors stated the change did not meet the 8 point cut-off for clinical relevance. However, we are not sure how the authors determine this cut-off and a psychometric study that determined it was not cited.

7. Documentation Tips:

Components to include in documentation: Dose of intervention provided, minutes at target intensity, recommendations to progress during the next session

8. Links to other relevant resources:

Websites:

- Applying Evidence with Confidence Website, <https://www.appeco.net/>
- Heart rate calculator, <https://www.ntnu.edu/cerg/hrmax>

9. References:

Full reference list to be posted online

Heine M, Verschuren O, Hoogervorst ELJ, van Munster E, Hacking HGA, Visser-Meily A, Twisk JWR, Beckerman H, de Groot V, Kwakkel G, TREFAMS -ACE study. Multiple Sclerosis Journal 2017, Vol.23(11)1517-1526.

- *Sample:* RCT. N=89. 73% female. Age 45.8 EDSS:<4. Predominantly RR type of MS, 16 participants diagnosed with PP and 8 with SP.

*Heine et al 2015: Exercise vs no exercise: 27 studies. 1325 participants
Endurance. 26 studies and 1299 participants.
Muscle power: 4 studies and 207 participants*