General discussion
The TREFAMS-CBT trial was an integral part of the TREFAMS-ACE programme, which consisted of three high-quality RCTs designed to investigate the effectiveness of Aerobic Training, Cognitive Behavioural Therapy and Energy Conservation Management on MS-related fatigue and societal participation in patients with MS-related fatigue. The main objective of this PhD thesis was to gain insight into the effectiveness and underlying mechanisms of Cognitive Behavioural Therapy (CBT) in the treatment of fatigue and societal participation in patients with MS. In the following sections, the findings of each part of this PhD thesis will be discussed in relation to recent literature, methodological considerations will be reviewed, and final conclusions and suggestions for future research provided.

Part 1. Cardiopulmonary exercise testing in patients with MS

Unravelling the mechanisms underlying each therapeutic approach was an important goal of the TREFAMS-ACE trials. Component factors of these mechanisms may include biomarkers in blood and saliva, physiological parameters and psychosocial variables. One important physiological parameter is aerobic capacity, due to its relation to MS-related fatigue.\(^1\,^2\) The gold standard measure of aerobic capacity is CPET.\(^1\,^3\,^4\) However, the use of CPET in patients with MS is controversial, since patients with MS often have compromised physical abilities, suffer from relapses, and because of the relationship between MS and autonomous dysregulation. All of these factors complicate the use of CPET in patients with MS. Therefore, a secondary goal of this PhD thesis was to assess the feasibility, safety, responsiveness and reliability of CPET in patients with MS. A better understanding of aerobic capacity in patients with MS may also be important for CBT, because graded activity (a component of CBT) has been shown to improve aerobic capacity.\(^5\)

Performing CPET in patients provides better insights into aerobic exercise capacity. A key outcome of CPET is maximal oxygen uptake (VO\(_{2\text{max}}\)), as it reflects the individual’s maximal aerobic capacity. In Chapter 2 we evaluated whether CPET is a feasible and safe measurement instrument in patients with MS. The results showed that CPET is feasible and safe when correct precautions are taken. One major limitation addressed in Chapter 2 was the failure of most published articles to report in accordance with ATS/ACCP quality guidelines. The first step in optimizing CPET protocols for patients with MS is detailed and standardized reporting according to the ATS/ACCP quality guidelines.\(^6\)
Due to the limitations inherent to MS, it is open to question whether the peak aerobic capacity measured with CPET in patients with MS is a valid measure of maximal aerobic capacity. Indeed, a recent study\(^7\) showed that the validity of CPET is related to the level of disability. CPET appeared to be a valid measure of cardiorespiratory capacity in patients with a low to mild level of disability (Expanded Disability Status Scale scores [EDSS] of ≤4.0). Validity was determined based on the following criteria: an oxygen consumption (VO\(_2\)) plateau was reached; a maximal heart rate within 90% of the age-predicted maximal heart rate was achieved; a respiratory exchange ratio of 1.10 or greater was achieved; and the participants perceived their exertion to be 18 or higher on the Borg Scale of Perceived Exertion (range scores of 6–20). However, in patients with moderate levels of MS severity (EDSS>4.0), CPET outcomes are related to the severity of MS, i.e. the results in patients in this category are likely to be limited due to MS symptoms such as muscle weakness or spasms. This leads to the inevitable conclusion that CPET is less valid in patients with higher EDSS scores. Therefore, due to physical limitations common in MS, not all CPET modalities are suitable for all patients. For example, CPET on a treadmill might not be feasible in patients with balance problems. In order to ensure safety, the physical abilities of patients with MS need to be taken into account when performing CPET. However, the influence of the CPET modality on VO\(_{2\max}\) also needs to be taken into account. For example, VO\(_{2\max}\) during arm cranking is about 70% of that in the leg cycling exercise, due to the smaller muscle mass and lower achievable maximum work rate.\(^8,9\) This implies that CPET modalities, protocols and physiological measurements need to be adjusted for the MS population: in other words, MS-specific modalities and protocols (continuous vs. multistage progressive).\(^4\) To interpret CPET results, reference values are needed for the same CPET modalities and protocols. Notwithstanding the progress that can still be made in the field of CPET for patients with MS, it can be concluded that CPET is safe and feasible in this patient group when the appropriate test modality is used.

In Chapter 3 we showed that CPET can be used reliably to assess physical fitness in individuals and in groups. However, the smallest detectable change in individuals with MS was relatively large (a change of at least 0.37 L/min [~21%] is required to show a statistically significant improvement or deterioration). Therefore, caution is warranted in the use of CPET when attempting to measure change over time in individuals. Nevertheless, CPET can be reliably used to measure change over time at the group level. The change required for CPET to be responsive at the group level needs to be
determined based on group size (smallest real change/$\sqrt{n}$). The results of Chapter 3 also lead to different advice in relation to research and clinical practice, respectively. CPET can be used in research to determine the effectiveness of interventions at a group level. In clinical practice, using CPET to interpret the effectiveness of interventions at the individual level is more challenging, as responsiveness is low (measurement error is too great). CPET is therefore not recommended for individual patient monitoring in clinical practice. To ensure that real individual changes are reached, the standard error of measurement needs to be determined to calculate the smallest real change.

Panel 9.1  Cardiopulmonary exercise testing in patients with MS: implications for clinical practice and future research

Taken together, these findings support the following recommendations for clinical practice and research:

- CPET is feasible in patients with MS when the physical abilities of the patient are taken into account when determining the CPET modality
- CPET is safe in patients with MS when the recommended precautions and safety measures are used
- CPET can be used reliably to assess physical fitness in individuals and in groups
- CPET is a responsive measure to assess change over time in groups
- CPET is a less suitable measure to assess change over time in individuals, and is therefore not recommended for individual patient monitoring in clinical practice
- Future research will benefit from a description of the employed CPET protocol standardized according to ATS/ACCP guidelines
- Reference values for multiple CPET modalities and protocols need to be made available
- In patients with more severe disabilities, alternative testing modalities and outcomes (besides $VO_{\text{max}}$) should be further explored

Part 2. MS-related fatigue and participation

In the general population, the prevalence of fatigue ranges from 7% to 45%, whereas fatigue is reported in about 80% of patients with MS. Literature has shown that fatigue is one of the most frequent reasons for seeking medical care. MS-related fatigue interferes with many aspects of a person’s life, including home life and/or the workplace (societal participation). One common assumption is that societal participation will improve as MS-related fatigue is alleviated.

Although fatigue questionnaires are increasingly used in research and clinical practice, the measurement of MS-related fatigue remains complicated due to the complex nature of the symptom. MS-related fatigue was measured in participants of the TREFAMS-ACE trials using the CIS20r fatigue subscale. This tool is increasingly applied...
to measure fatigue in patients with chronic fatigue syndrome, rheumatoid arthritis, and cancer patients.\textsuperscript{21-24} The CIS20r20 focuses on the previous two weeks, and is considered reliable and valid for measuring fatigue in a clinical setting in patients with MS.\textsuperscript{25,26} The total CIS20r consists of 4 subscales: fatigue, concentration, motivation and physical activities. To ensure that the changes found in the TREFAMS-ACE trials were not only significant but also beneficial for the patient, a change of at least 8 points was considered clinically relevant.\textsuperscript{27,28} Unfortunately, no clear explanation for the 8-point cut-off score is found in literature. It is important to keep in mind that a statistically significant change does not necessarily translate to a relevant patient treatment experience.\textsuperscript{11} One aspect that CIS20r fatigue does not consider is the difference in diurnal fatigue patterns in patients with MS. In Chapter 4, a low correlation was found between conventional fatigue questionnaires and the real-time fatigue scores, with none of the fatigue questionnaires specifically addressing diurnal variation. This effect could work both ways: diurnal assessment of fatigue is not a valid measure for MS-related fatigue or, alternatively, conventional fatigue questionnaires do not actually assess the day-to-day fatigue experience. Future studies on this topic are therefore recommended to further unravel why these fatigue measures show a low correlation and whether fatigue patterns in patients with MS are comparable to fatigue patterns in healthy individuals. Furthermore, it would be interesting to study whether expanding conventional questionnaires with questions related to diurnal patterns can provide additional insights into MS-related fatigue.

In Chapter 5, the relation between appraisal, coping and societal participation was studied. The measurement of societal participation in patients with MS can be challenging. The terms participation, social participation and societal participation are used interchangeably. In this PhD thesis the term ‘societal participation’ was mainly used and the Impact on Participation and Autonomy (IPA) questionnaire was included as a primary outcome to measure societal participation.\textsuperscript{29} The latent construct ‘societal participation’ was developed by combining the outcomes of all subscales into one score. The mediated relationship assumed and studied was that appraisal is related to coping styles and that these coping styles influence societal participation. The results showed that societal participation was related to a better score on the latent construct appraisal: a positive patient view of their own ability to deal with a situation (appraisal) is related to better societal participation. Remarkably, this relationship was not mediated by coping styles. Appraisal was related to coping styles, but coping styles were not related to societal participation. Since this study was performed on cross-sectional data, no
causal conclusions could be drawn from the results. Future research on longitudinal
data is required to further clarify this interesting observation. A robust relation between
appraisal and societal participation (Chapter 5) is also found in literature. A recent review
of systematic reviews concluded that working on appraisal can have positive effects
on participation over the long-term.30 Interventions that target self-esteem, appraisal
and societal participation include, among others, educational programs,31 cognitive
behavioural therapy,32 and psychodynamic psychotherapy.33

Panel 9.2  MS-related fatigue and participation: implications for clinical practice and proposals
for future research

Implications for clinical practice:
• MS patients show diverse diurnal patterns of fatigue. Although still unexplained, the
  underlying mechanisms of fatigue may differ depending on the pattern
• When targeting societal participation, consider the role of appraisal: i.e. work on increasing
  self-efficacy and disease acceptance, and decreasing helplessness

Proposals for future research:
• Unravel the relationship between real-time assessment of fatigue and the use of
  conventional fatigue questionnaires
• Study whether the relationship between appraisal and societal participation is causal, and
  study the possibility that coping styles influence appraisal, which in turn, influences societal
  participation
• Determine whether expanding the fatigue questionnaire with questions about diurnal
  patterns can provide new insights into MS-related fatigue

Part 3. Cognitive Behavioural Therapy for MS-related fatigue

To put the results of the third part of this PhD thesis into perspective, the results of
the TREFAMS-CBT trial (Chapter 7) were added to the meta-analysis as presented
in Chapter 6 and displayed in Figure 9.1 and Figure 9.2. All five trials seem to show a
different pattern. Most comparable with the TREFAMS-CBT trial is the study by van
Kessel et al.38 This study did not provide one-year follow-up data. Combining the results
of these five studies34-38 led to a standardized mean difference (SMD) of -0.53 [95% CI
-0.89, -0.17], implying a moderate positive effect of CBT for MS-related fatigue post-
treatment (i.e. short-term). The study by Moss-Morris et al. (2012) showed the largest
treatment effects.35 However, these results might be biased since it was a pilot study that
included a small number of patients. The TREFAMS-CBT was the second largest study in
terms of short-term results (Figure 9.1A). Furthermore, the quality of the trial was high,
Figure 9.1  A. Post-treatment effectiveness of CBT and control conditions on fatigue in patients with MS; B. Long-term effectiveness of CBT and control conditions on fatigue in patients with MS (+ = low risk; - = high risk).
since the recruitment target was met, we used concealed computer-generated random treatment allocation, assessors were blinded to patient allocation, blinded statistical analyses were performed, and study attrition was low. One explanation for the large post-treatment effects found in the TREFAMS-CBT trial might be that CBT treatment was tailored to patient needs.

At one-year follow-up, the TREFAMS-CBT trial showed the smallest effect (Figure 9.1 B). The total standardized mean difference of -0.25 [95% CI -0.45, -0.06] indicated a small long-term effect size, which leads to the conclusion that long-term effects of CBT for MS-related fatigue are not yet proven. One difficulty with longitudinal measurement is that changes between pre- and post-test can be biased due to a patient’s change in internal standards (recalibration), values (reprioritization) or meaning (reconceptualization) regarding MS-related fatigue.39,40 These changes are defined in literature as response shift. Future analyses of the TREFAMS-ACE programme should consider the influence of response shift as a possible explanation of the diminishing effects.40,41 The lack of long-term results is not unique for MS-related fatigue, long-term effects of CBT are also limited in patients with depression and anxiety,42 and panic disorders.43 In contrast, in fatigued cancer survivors the results of CBT were maintained at 2-year follow-up.44,45 The CBT in these trials and in the TREFAMS-CBT trial was developed by the same researchers. The major difference was that the number of sessions varied in the trial performed in fatigued cancer survivors,45 varying based on the number of modules that appeared to
be appropriate for the patient (determined using intake questionnaires, comparable to the TREFAMS-CBT trial) and whether the treatment goal was reached. The number of sessions varied between 5 and 26 sessions over a 6-month period. In addition, the patients were offered a maximum of two sessions during the 6-month follow-up period. These extra sessions might have helped to sustain the positive long-term results. Future CBT studies on MS-related fatigue should take a lesson from cancer CBT studies and adapt their protocols sensibly in order to try to improve long-term effects.

The effects of CBT on societal participation were measured with the IPA. This questionnaire consists of five subscales: autonomy indoors, family role, autonomy outdoors, social life and relationships, and work and education. On these separate subscales no significant effects of CBT compared to the MS nurse control condition were found (except for a single significant result on IPA work and education at T26), suggesting that CBT does not influence societal participation. A note of caution regarding the interpretation of the IPA is due here, as the IPA might not be the most valid tool when measuring societal participation. Nevertheless, the secondary societal participation measures, Short Form-36 (SF36) and Rehabilitation Activity Profile (RAP), also failed to show significant between-group differences, with the exception of SF36 physical role functioning at 8 weeks. Although the measurement of societal participation remains ambiguous, the conclusion in the present thesis is that the use of CBT for MS-related fatigue does not influence participation as measured with IPA, SF36 and RAP.46

The results of the TREFAMS-CBT trial presented in part 3 show that MS-related fatigue can be alleviated with CBT, but little is known about the process of change during and after CBT. In Chapter 8, factors that are related to the process of change during CBT are unravelled, providing insights that might contribute to the optimization of CBT. The results presented in Chapter 8 suggest that the following factors mediate the positive effect of CBT on MS-related fatigue: more positive fatigue perceptions, increase in physical activity level, improvement of physical functioning, reduced daytime sleepiness, and decreased feelings of helplessness. The idea underlying CBT is that fatigue should not determine a patient's daily life. The insight that fatigue should no longer determine daily life empowers patients regarding their fatigue and assists in explaining why helplessness acts as a mediator. Building on this, greater feelings of control over fatigue might help patients to increase their physical activity and physical functioning. A patient's focus shifts from fatigue to their own physical and mental abilities. In line with this, patients were asked not to sleep during daytime, which probably contributed to a decrease in daytime sleepiness. Patients were allowed to rest during the day.
Since the TREFAMS-CBT treatment effects were not maintained, understanding the factors that relate to the process of change after cessation of treatment might help an improved CBT achieve better long-term effects. An innovative approach described in Chapter 8 was the study of mediators related to the process of change after CBT. The results showed that the following factors mediate the effect of CBT on MS-related fatigue after cessation of treatment: decrease in physical activity level, a decrease in concentration and an increase in daytime sleepiness. Focusing during CBT on the maintenance of new behaviours and cognitions related to physical activity, concentration and daytime sleepiness is likely to improve long-term results. Furthermore, focusing on these factors during, for example, booster sessions after cessation of treatment might also help maintain the positive short-term effects.

Methodological considerations

The TREFAMS-ACE study stands out for its extensive follow-up period (one-year). Data on long-term follow-up is especially valuable when examining behavioural treatments that are designed to achieve long-term results. Although it is obvious that behavioural treatments also need to be assessed over the long-term, this is not yet common practice. Another valuable aspect of the TREFAMS-CBT trial was that the CBT therapists were certified psychologists who received three days of training in CBT for MS-related fatigue. To ensure compliance with the protocol, during the study the psychologists received patient-specific supervision every other week from an experienced CBT psychologist.

The TREFAMS-CBT trial is the first study of MS-related fatigue in which the treatment was tailored to the patients’ needs. Similarly, a trial performed by van Gielissen et al. also showed a positive effect of CBT on fatigue,44,45 thus supporting a patient-specific approach. A difficulty when working with severely fatigued patients was the challenge of patient recruitment. CBT treatment was demanding of severely fatigued patients, and twelve visits to the outpatient clinic over 16 weeks itself was itself tough for the patients, which might explain the extra time required to complete patient recruitment. In clinical practice this factor might result in decreased treatment adherence, and a possible solution might be to provide online sessions, as performed by Moss-Morris (2012).35 Although this study was only a pilot, the authors concluded that internet-based CBT appears to be a clinically and cost-effective treatment for MS-related fatigue.35
The TREFAMS-ACE research programme focused on severe primary MS-related fatigue. The advantage of this focus was that secondary factors that may contribute to MS-related fatigue were excluded. The content of CBT was therefore designed purely to influence fatigue and the results can be generalized to any population with primary MS-related fatigue. A secondary factor that can influence fatigue is depression. Depression and fatigue frequently go hand in hand. One drawback of excluding secondary fatigue is that the results cannot be generalized to patients that experience both fatigue and depressive symptoms.

To indicate whether certain modules of the CBT provided patient benefit, questionnaires with cut-off scores were used as indicators by psychologists at the start of treatment. These questionnaires focused specifically on treatment modules. Unfortunately, these questionnaires were not included in follow-up measurements due to the amount of time and effort already demanded of patients. The questionnaires that were used for follow-up measures were therefore more generic, although it would be preferable to use the module-specific measures to assess changes over time.

To conclude this general discussion, a patient’s perspective on the TREFAMS-CBT can be found in Panel 9.3.

Panel 9.3  A patient’s experience of the TREFAMS-CBT trial

A participant (in the TREFAMS-CBT trial) described the effect of CBT as follows:

‘I was more than happy with CBT! This therapy forced me to take a closer look at my life. This led to insights I could share with my family, which led to a better understanding of my situation. By planning my weekly activities, it appeared that I even had spare time. I still use the weekly to-do lists, I exercise weekly, and the most effective part of treatment was the sleep/wake cycle! That has given me my life back. The consequences of therapy exceeded my expectations: I no longer sleep during daytime and I have more energy than before! I told my MS nurse that every patient with MS should receive this therapy.’

PhD thesis conclusions

- CPET is a feasible approach to measurement of physical fitness in patients with MS, provided that the modality is tailored to individual physical abilities. Furthermore, CPET is safe when the recommended precautions and safety measures are implemented. At an individual level, CPET is a reliable measure to assess physical fitness, but it is not sufficiently responsive to changes over time. At a group level, CPET is a reliable measure to assess changes over time.
Fatigue in patients with MS shows varying diurnal patterns and conventional fatigue questionnaires correlate poorly with real-time fatigue scores. More research is required to study whether expanding the fatigue questionnaires to include questions on diurnal patterns can provide new insights into MS-related fatigue.

A robust relation between appraisal and societal participation was shown. Remarkably, it appeared that this relationship was not mediated by coping styles: appraisal is related to coping styles, but coping styles were not related to societal participation.

CBT delivered according to the TREFAMS-CBT protocol is an effective treatment for decreasing MS-related fatigue in the short-term. Future research is necessary to develop effective ways to maintain these effects long-term.

During CBT, improved fatigue perceptions, increased physical activities, less sleepiness, less helplessness, and improved physical functioning appear to mediate the effect of CBT. After treatment, the changes in fatigue levels were mediated by reduced physical activities, reduced concentration, and increased sleepiness.
References


