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**Summary and
general discussion**

This thesis focuses on studying three key topics in fatigue management in patients with multiple sclerosis. First, we investigated the measurement properties of outcomes to assess fatigue. Second, we explored the heterogeneity in diurnal patterns of daily physical activity in patients with MS. Third, we investigated the impact of fatigue on observed daily physical activity. Finally, we studied the effectiveness of multidisciplinary treatment of fatigue when compared to MS nurse consultation. In the present chapter the main findings are summarised, discussed in perspective of the current knowledge regarding fatigue in MS. Finally, clinical implications and recommendations for future research on fatigue in MS are provided.

Measurement properties of fatigue questionnaires

Summary

In preparation for our randomized controlled trial on the effect of an individually tailored, multidisciplinary outpatient rehabilitation programme on chronic fatigue in MS presented in **chapter 7**, we have selected three questionnaires for outcome measurement. Based on the available evidence¹ and existing guidelines² at that time we have chosen for the CIS20R, FSS, and the MFIS. In **chapter 2** of this thesis reliability, agreement, measurement error and concurrent validity of these three fatigue questionnaires were determined and compared in the same sample of patients with MS. Forty-three ambulatory patients with MS completed the questionnaires twice with a one week interval. Test-retest reliability was determined using the Intraclass correlation coefficient for agreement ($ICC_{\text{agreement}}$). $ICC_{\text{agreement}}$ was good for the FSS, MFIS and CIS20R, respectively 0.76, 0.85 and 0.81. Following the Bland and Altman method for agreement, no systematic differences between the two assessments of all questionnaires were found. Measurement error expressed by the smallest detectable change (SDC) was 13.1 for the FSS, 16.2 for the MFIS and 24.8 for the CIS20R, resulting in an minimal detectable change (MDC) of 20.7% for the FSS, 19.2% for the MFIS and 17.7% for the CIS20R, respectively. Concurrent validity was moderate. Pearson's correlation coefficients ranged from 0.66 for FSS when compared to MFIS, 0.54 for MFIS when compared to CIS20R and 0.42 for CIS20R when compared to FSS. These results suggest that in ambulatory patients with MS the CIS20R, FSS, and MFIS are reliable estimates of fatigue, and may be adequate to detect change of fatigue over time in group evaluations. In addition the fatigue questionnaires do not seem very responsive for change in individual patients with MS. The moderate mutual associations suggest that the three questionnaires largely quantify different aspects of perceived fatigue in patients with MS.

To assist clinicians and researchers in selecting a fatigue questionnaire for clinical care or research, **chapter 3** of this thesis presents a systematic review of studies investigating clinimetric properties of self-report fatigue questionnaires validated in patients with multiple sclerosis, Parkinson's disease and stroke. A critical appraisal tool, the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN)³ was used, containing standards for systematically evaluating the methodological quality of studies on the measurement properties of health measurement instruments. A qualitative data synthesis was performed to rate the measurement properties for each questionnaire. Thirty-eight studies were included, evaluating 31 different questionnaires. Moderate evidence was found for adequate internal consistency and structural validity of the multidimensional Fatigue Scale for Motor and Cognitive functions (FSMC) and adequate reliability and structural validity of the Unidimensional Fatigue Impact Scale (U-FIS) in patients with MS. The Functional Assessment of Chronic Illness Therapy Fatigue subscale (FACIT-F) and Fatigue Severity Scale (FSS) showed promise for the unidimensional assessment of fatigue in patients with PD, and the Profile Of Mood States Fatigue subscale (POMS-F) for stroke. No multidimensional fatigue questionnaires were adequately validated in patients with PD or stroke. These results however, should be considered with caution, as the level of evidence supporting the overall quality of most measurement properties was limited. In addition, studies investigating measurement error, responsiveness and interpretability were lacking.

Discussion

In order to measure fatigue accurately, measurements that adequately reflect the level of fatigue are required. However, a limitation of most systematic reviews evaluating measurement properties of fatigue questionnaires is the lack of a uniform definition and standards for the assessment of the methodological quality of the included studies. As a consequence, absence of proper determination of the methodological quality can be a source of bias if results of high quality studies differ from the results of low quality studies.

To overcome different sources of bias the COSMIN group developed a critical appraisal tool (a checklist),³ which consists of 114 items, grouped in twelve domains. Nine of these domains contain standards for measurement properties (i.e. internal consistency, reliability, measurement error, content validity, structural validity, hypotheses testing, cross-cultural validity, criterion validity and responsiveness). One domain contains standards for studies

on interpretability. In addition, two domains contain requirements for studies in which Item Response Theory (IRT) methods are applied, and requirements for the generalizability of the results, respectively.³

Using the COSMIN checklist,³ the results of the systematic review presented in **chapter 3** show that robust evidence regarding the overall quality of most measurement properties of instruments was limited, due to paucity or even absence of studies performed on the different COSMIN domains. Newly published evidence may alter the current found synthesis, which in turn would result in different recommendations for appropriate outcome measurement. The systematic review presented in **chapter 3** has identified the gaps in current research regarding the measurement properties: measurement error, responsiveness and interpretability. In order to provide more solid recommendations for clinical usefulness, new developed measurements on fatigue should obey the standards of COSMIN checklist,³ whereas current outcome measures on fatigue can be evaluated for their psychometric properties.

A more fundamental consideration regarding the development of fatigue self-report questionnaires regards the problem of poor description of the concepts underlying the items of self-report in questionnaires about fatigue. As long as the exact etiology of fatigue in MS remains unknown and consensus on defining fatigue and its many dimensions is lacking this problem will continue to exist. Future studies should aim to investigate the complex interaction between underlying disease process,⁴⁻⁶ psychological^{7,8} and physical characteristics⁶ as well as patients' environmental factors from a translational perspective.^{9,10} In order to develop the theoretical construct of self-report fatigue questionnaires it is highly relevant that such studies do repeated systematic measurements to longitudinally assess the interrelatedness of these different levels of interaction.

Clinical implications

Pending a widely accepted theoretical construct of self-report fatigue questionnaires and considering the methodological issues related to appropriate outcome measurement, the question can be raised as to how currently available self-report fatigue questionnaires should be used in clinical practice.

First and foremost, clinicians that use self-report questionnaires to monitor changes in fatigue perception should be aware of the limitations of these instruments. Outcome measures that are used to evaluate treatment effects in clinical practice should be able to reliably identify

clinically relevant changes at an individual level. This suggests that the demands with regard to reliability and responsiveness are high, in comparison with outcome measures that are used for research purposes at the group level. In this context, the results as presented in **chapter 2** have several implications. The reported good test-retest reliability, but rather high measurement error for the FSS, MFIS and CIS20R imply that the scales are useful for use in clinical trials, but may be less appropriate for detecting clinically meaningful changes in perceived levels of fatigue in individuals.

In choosing a self-report fatigue questionnaire, clinicians or researchers have to consider that each questionnaire is characterized by its own unique underlying construct, measurement properties and practical feasibility. In our study presented in **chapter 2** we found moderate associations, albeit significant, between the FSS, MFIS and CIS20R, which suggests that the three questionnaires largely measure different aspects of perceived fatigue. The systematic review presented in **chapter 3** confirmed this finding. For now, researchers or clinicians assessing fatigue should carefully consider whether a questionnaire reflects the most relevant aspects of fatigue of their interest.

In most self-report questionnaires, these relevant aspects are reflected in different (sub) domains. For example, the MFIS assesses the impact of fatigue on the domains physical, cognitive and psychosocial functioning, whether the CIS20R assesses the four domains subjective experience of fatigue, reduction in motivation, reduction in activity and reduction in concentration. The FSS¹¹ provides a total score which does not discriminate between the various dimensions it assesses (e.g. lack of motivation, impact on physical functioning). Acknowledging that each fatigue questionnaire measures different aspects of fatigue, simultaneous use of different questionnaires in research is recommended. Nevertheless, this approach does not overcome the problem of poor conceptualization of the theoretical constructs of different fatigue questionnaires.

Furthermore, a comprehensive evaluation of fatigue should be accompanied by the assessment of secondary related factors, such as pain and muscle spasms, and concomitant conditions such as viral infections, urinary infections, pregnancy, alcohol or substance abuse and depression that may also contribute to feelings of fatigue.

Measurement properties of activity monitoring

Summary

Accumulating evidence suggests that patients with MS are less physically active than non-diseased people. The observed reduction in the daily activities of patients with MS is often attributed to underlying impairments, such as muscle weakness, spasticity, ataxia, and fatigue. The study in **chapter 4** evaluated the reliability, agreement and measurement error of home-based 24-hour monitoring of mobility-related activities assessed with a portable activity monitor in 43 ambulatory patients with MS. Mobility related activities were expressed by dynamic activity which on itself is subdivided into: number of transitions; number of walking periods; and time spent on walking, whereas static activity was subdivided into: time spent on sitting; standing; and lying. Test-retest reliability expressed by the ICC_{agreement} was 0.72 for dynamic activity, 0.74 for number of transitions, 0.77 for walking, 0.71 for static activity, 0.67 for sitting, 0.62 for standing, and 0.55 for lying. Bland and Altman analysis indicated no systematic differences between the first and second assessment for both dynamic and static activities. Measurement error expressed by the SDC was 1.23 for dynamic activity, 66 for number of transitions, 0.99 for walking, 1.52 for static activity, 4.68 for lying, 3.95 for sitting, and 3.34 for standing. The results show that with 24-hour monitoring, a reproducible estimate of physical activity in the home and community setting can be obtained in ambulatory patients with MS. No previous data on measurement error of the AM used have been published in patients with MS, making it difficult to interpret and compare the calculated SDCs.

Discussion

A central, still neglected issue in the assessment of physical activity is to gather objective information regarding the real quantity and type of daily activities performed in the patient's own home environment. Advances in technology have fostered the development of objective methods allowing more continuous monitoring of daily physical activity in patients' natural environment using actigraphy and/or accelerometer. Our study on activity monitoring (AM) presented in **chapter 4** shows that with a relatively short monitoring period of 24 hours, a sufficiently reliable estimate of daily activity can be obtained for group evaluation of ambulatory patients with MS, with a high degree of detail about the types of activity, e.g. walking, making transitions, sitting and lying. However, the used concept for measuring physical activity, namely

classification of postures and motions, does not provide information on what participants were doing while performing daily activities such as sitting and standing and with that may provide an underestimation of upper body activities. A more elaborate, preferably wireless AM setup with accelerometers on the arms could provide such information. Moreover, it enables assessment of non-ambulatory, wheelchair-bound patients with MS as well and would provide relevant physical activity information on, for example, wheelchair propulsion activity. On the other hand, there is a growing interest in the use of commercially available devices as an objective measure of the actually performed physical activity. Researchers and clinicians have an increasing number of options for measuring physical activity, such as Fitbit, Jawbone and Nike Fuelband.¹² In making appropriate decisions for measuring physical activity as an outcome measure within cross-sectional, prospective and clinical trials as well as rehabilitation settings one should be aware of the measurement properties of the device being used in conjunction with the purpose of the study or rehabilitation program.

Clinical implications

Clinical measures of physical capacity commonly used in patients with multiple sclerosis, such as a 6-Minute Walk test and a Timed 25-Foot Walk Test do not reflect daily activities performed in the patient's own home environment. Therefore, both clinicians and researchers have increasingly directed their attention towards understanding activity behaviour in patients' customary environment. Technological developments increasingly allow objective measurement of this physical activity in daily life and may provide additional information for the clinician on patients' behavioural responses to MS and its symptoms, such as perceived fatigue. For example, Skerret et al.¹³ reported a relationship between feelings of fatigue and engaging in excessive rest on the one hand, and extreme activity when feeling fit followed by a collapse, all-or-nothing behaviour, on the other hand.

To fully understand physical behaviour in persons with MS physical activity should preferably be studied in conjunction with facilitators and barriers to engagement in physical activity. In this context, Beckerman et al.¹⁴ suggested the use of a helpful model for better understanding physical activity behaviour in MS research; the Physical Activity for People With a Disability (PAD) model.¹⁵ Figure 9.1 shows the PAD model, which is based on the International Classification of Functioning, Disability and Health (ICF) framework.¹⁶

In the PAD-model, physical activity behaviour and its determinants are integrated into the ICF framework. The factors determining physical activity are mainly based on those used

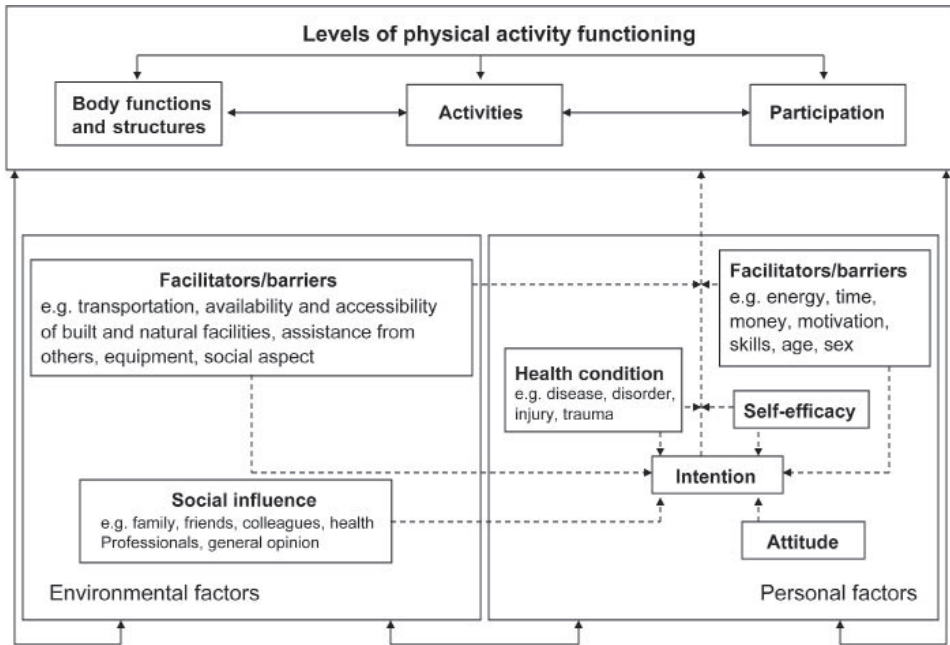


Figure 9.1 The PAD model.

The dashed arrows in the PAD model represent the pathway through which these factors determine physical activity, although not all possible pathways and relations are shown in the model. Most of the dashed arrows also work in the opposite direction and, as shown in the general framework, all components of the integrated model more or less interact with each other.

in the Attitude, Social influence and self-Efficacy (ASE) model^{17,18} and can be divided in personal and environmental factors. Environmental factors include the social influence of family members, friends and health professionals, as well as environmental facilitators and barriers, such as transportation, availability and accessibility of built and natural facilities, assistance from others, equipment, social aspect. Personal factors include demographic factors; health-related factors; and cognitive and behavioural factors, such as knowledge of the effects of physical activity on health, attitude toward physical activity, self efficacy, perceived benefits and barriers, motivation to adhere, and past physical activity behaviour. Understanding modifiable factors that are related to physical inactivity is important for developing effective programs that promote physical activity for patients with MS.

Fatigue and daily physical activity

Summary

Reduced physical activity is an important consequence of Multiple Sclerosis. However, little is known about the real quantity and type of daily activities that people with MS perform in their own home environment. The study in **chapter 5** compared the amount and pattern of physical activities performed over a 24 hour period in the own community environment of 43 ambulatory patients with MS and 26 age and gender matched healthy individuals. Physical activity recorded with an ambulatory activity monitor was classified into dynamic activity (subdivided in number of transitions, walking periods, time spent on walking) and static activity (subdivided in time spent on sitting, standing and lying) parameters. For statistical analyses the 24 hours registration period was divided into 4 daily periods, namely: morning from 6.00 to 12.00 hours, afternoon from 12.00 to 18.00 hours, evening from 18.00 to 24.00 hours, and night from 24.00 to 06.00 hours. Multi-level analyses showed that MS patients on average spent 0.27 times lower amount of time on dynamic activity compared with a group of healthy controls ($p < 0.001$). Similarly, patients with MS spent significant less time on walking and had fewer walking periods ($p < 0.001$), whereas no significant between group differences were found for the number of transitions ($p = 0.875$). Patients with MS spent more time on overall static activity ($p = 0.003$), and less time on its subgroup classification standing ($p = 0.011$). No significant between group differences were found for the subgroup classifications of static activity lying ($p = 0.244$) and sitting ($p = 0.317$). Comparing the free living activity patterns for different parts of the day for the time dependent variables showed that patients with MS started with lower physical activity levels already in the morning ($p < 0.001$), and this difference persisted in afternoon ($p = 0.002$), and evening ($p = 0.032$). Across the parameters dynamic activity and the subgroup classifications time spent on walking, and number of walking periods the activity patterns are quite similar.

The study presented in **chapter 6** aimed to determine the relationship between the actual amount of home-based physical activity measured for 24 hour with an Activity Monitor (AM) and perceived fatigue as assessed with three self-report fatigue questionnaires, viz. the CIS20R, the FSS and the MFIS. Forty-three ambulatory patients with MS were recruited.

Linear regression analysis was applied to explore the relationship between physical activity and perceived fatigue. In addition, potential confounding factors of this relationship, such as age, disability status, disease duration, disease sub-type, depression and anxiety were

introduced in a multivariate regression model. No significant associations between physical activity measured with AM and fatigue scores were found, except for the MFIS sub-scale 'physical activity' ($\beta=-0.044$; $SE=0.020$). The association between physical activity and the FSS score was distorted by age, MS type, anxiety and depression and the association between physical activity and the MFIS score by age and depression. The inverse association between MFIS sub-scale 'physical activity' and the actual amount of physical activity measured with AM was significantly strengthened by adjusting the regression model for age ($\beta=-0.052$; $SE=0.019$), disease duration ($\beta=-0.044$; $SE=0.020$), sub type of MS ($\beta=-0.048$; $SE=0.020$), anxiety ($\beta=-0.070$; $SE=0.023$) and depression ($\beta=-0.083$; $SE=0.023$). These results suggest that there is no or at best a weak association between severity of perceived fatigue and physical activity. In addition, depending on the fatigue questionnaire used, patient characteristics such as age, type of MS, depression and anxiety are factors that may affect this relationship.

Discussion

Extensive evidence¹⁹⁻²² indicates that patients with MS do not engage in sufficient amounts of physical activity for health benefits, and physical activity further declines over time in this disease. By means of an activity monitor we confirmed in **chapter 5** that ambulatory patients with MS show a significant overall lower amount of daily physical activity as compared with healthy controls. However, we were not only interested in the amount of activity performed, acknowledging this parameter is only one aspect of physical activity behaviour. Moreover, detailed information of activities performed and distribution of these activities over the day may provide information about the nature of the reduced physical activity levels and will lead to a better understanding of the consequences of MS. For that reason we studied physical activity day patterns for specific movements and postures in **chapter 5**. We hypothesized that patients with MS are less active in the morning due to a slower start as a result of coping with neurological deficits and to anticipate on limited energy levels by reducing activities to prevent depletion of energy. Moreover, we assumed that patients with MS would show earlier decrement in free living physical activity in the evening due to higher fatigue perception in the late afternoon or evening, when compared to activity profiles of healthy subjects. We found that patients with MS compared to healthy subjects started with lower physical activity levels already in the morning, and that this difference persisted in the afternoon, and the evening. This approach of assessment of daily physical activity gave us also insight in time spent on, and distribution over the day of sedentary activities,²³ such as time spent sitting, which has been independently associated with morbidity and mortality in the general

population.^{24,25} Recently Bussmann et al.²⁶ stressed that the amount of performed physical activity is just one of the dimensions of physical behaviour. For example, MS rehabilitation interventions (e.g., energy conservation management)²⁷ do not usually focus on the total amount of activity, but on issues such as balancing daily activity patterns, frequency and intensity of activities, and distribution of activity and rest.

The observed reduction in daily activity in patients with MS is often held against underlying impairments such as, muscle weakness, spasticity, ataxia and fatigue.^{4,28,29} Both fatigue and reduced physical activity are important consequences of Multiple Sclerosis (MS) and their mutual relation is poorly understood. In the literature, it has been hypothesized that being less active due to fatigue can lead to a vicious circle in which impaired fitness due to a reduction in physical activity in turn may result in increased feelings of fatigue.^{14,30} In **chapter 6**, we studied the relationship between fatigue and amount of activity performed during 24 hours and found that in MS there is no or at best a weak association between severity of perceived fatigue and daily physical activity. This finding questions the existence of a vicious circle of inactivity mediated only by fatigue and challenges the assumption that patients who are reporting more fatigue will automatically show less physical activity, i.e. a downward directed spiral between inactivity and fatigue. However, due to the cross-sectional study design we were unable to draw firm conclusions about the causality of this relationship. The use of longitudinal designs would help to better understand whether perceived fatigue actually induces a reduction in physical activity or vice-versa. In addition, such designs could take into account diurnal variations of physical activity and fatigue.

Acknowledging that this relationship is complex, our second objective of the study presented in **chapter 6** was to investigate if the associations between recorded physical activity and measures of fatigue were confounded by factors such as age, EDSS, sub type of MS, anxiety, and depression. We found that depending on the fatigue questionnaire used, e.g. FSS, MFIS and CIS20R, patient characteristics such as age, type of MS, depression and anxiety are factors that may affect this relationship. Remarkably, our a priori hypothesis that the association between actual levels of physical activity and measures of fatigue were significantly distorted by disability status as expressed by the EDSS was not confirmed. An explanation of this finding may be that disability status does not directly affect physical activity, but does so through self-efficacy, which in turn partly determines physical activity.¹⁹ In addition, Motl¹⁹ and Sekkrett¹³ suggested that patients' personal interpretations and responses to their symptoms are important in understanding their levels physical activity and fatigue, rather than the disability status itself.

In **chapter 3** we concluded that different questionnaires such as FSS, MFIS and CIS20R, have different properties reflecting different underlying constructs of fatigue. This conclusion is demonstrated in the results of **chapter 6**, viz. that depending on the fatigue questionnaire used patient characteristics such as age, type of MS, depression and anxiety are factors that may affect this relationship. Apparently, all dimensions of fatigue assessed with the MFIS i.e. perceived impact of fatigue on physical, cognitive and psychosocial functioning, and the CIS20R, i.e. subjective experience of fatigue; reduction in motivation; reduction in activity and reduction in concentration all provide their unique contribution to the description of patients' fatigue, and are consequently differently related to the fatigue-physical activity association.

Above findings further emphasize that there is an urgent need for consensus regarding a uniform definition of fatigue including its dimensions. Based on this consensus a worldwide core set of measures is needed allowing better comparison between published trials and prediction models.

Clinical implications

The absence of a vicious circle of inactivity mediated only by fatigue, may suggest that central fatigue in MS is a perceptual problem in which patients will rather compensate or even overcompensate their daily tasks than yield to feelings of fatigue. Based on this line of thought, patients with MS may benefit from cognitive behavioural therapy for the treatment of fatigue, in which patients learn to restructure their living habits, including strategies to balance between activity and rest.²⁷ The acquisition of such helpful coping strategies might additionally enhance efficacy of other therapies, such as aerobic training.³¹ In addition, the findings in the present study confirm that fatigue management in MS should comprise identification and treatment of other factors that are expected to contribute to fatigue, such as depression and anxiety.

Management of fatigue

Summary

Chapter 7 describes the effects of the “Treatment of Fatigue” (ToF) trial. This programme was focussed on the treatment of chronic fatigue in MS. The rationale of this programme obeyed the recommendations of the Multiple Sclerosis Council for Clinical Practice Guidelines

(MSCCPG), suggesting that chronic fatigue should be distinguished from acute fatigue, and requires different management approaches. Descriptive modifiers postulated by the MSCCPG were used to differentiate between acute and chronic fatigue. A single-blinded, randomized controlled trial (RCT) was conducted to investigate the effect of an individually tailored, multidisciplinary outpatient rehabilitation programme (MDR) on chronic fatigue in MS compared to mono disciplinary consultation by an MS nurse. Forty-eight ambulatory MS patients suffering from chronic fatigue according to the MSCCPG definition were randomized to MDR or to MS–nurse consultation. Perceived fatigue was assessed by the CIS20R. Secondary outcomes included two other self-report questionnaires for fatigue viz. the MFIS and the FSS, as well as the Functional Independence Measure (FIM), the Disability and Impact Profile (DIP), the Multiple Sclerosis Impact Scale (MSIS-29) and the Impact on Participation and Autonomy (IPA) instrument. Treatment effects were tested by calculating changes scores from baseline to 12 weeks and from 12 to 24 weeks. Non-parametric analysis of change scores of the primary outcome measure CIS20R overall score showed no significant differences between groups at 12 weeks ($p=0.39$) and 24 weeks follow-up ($p=0.14$), nor for subscales at 12 and 24 weeks ($0.19 \leq p \leq 0.88$). No significant within-group effects were found for both groups with respect to the primary ($0.57 \leq p \leq 0.97$) and secondary ($0.11 \leq p \leq 0.92$) outcome measures from baseline to 12 or from 12 to 24 weeks. The results show that multidisciplinary rehabilitation was not more effective in terms of reducing self-reported fatigue in MS patients compared to MS-nurse consultation. Moreover, the results of the present trial suggest that chronic fatigue in patients with MS is highly invariant over time, irrespective of type or number of disciplines involved.

Discussion

The poor understanding of the etiology underlying fatigue, the diverse consequences of fatigue, and the lack of adequate methods for measuring the impact of fatigue result in the current challenge of developing, testing, and prescribing effective interventions in patients with MS experiencing disabling fatigue.^{32,33} Both the causes and consequences of MS fatigue are considered to be associated with several factors or mechanisms.^{7,34,35} Considering this multidimensionality, fatigue in MS should be managed in a multidisciplinary way. This multidisciplinary approach should particularly be directed at identifying all contributing factors to fatigue, and other non-MS causes should be excluded and/or treated appropriately. In addition, evidence for effective strategies to reduce chronic persisting fatigue, i.e. pharmacological or non-pharmacological or combinations, is lacking.

Multidisciplinary diagnostics

An important methodological consideration regarding studies evaluating interventions that aim to reduce fatigue in MS is to establish well-defined eligibility criteria of the population under study. For example, the review of Asano³³ revealed that 50% of the included studies did not screen for fatigue as a eligibility criterion. This means that studies aimed at reducing fatigue have included MS patients without fatigue, and consequently introduced bias. Hence, based on current knowledge and in order to get homogeneous study samples, studies should stratify for origin of fatigue, i.e. acute fatigue or chronic fatigue. Proper demarcation may provide a better understanding of underlying mechanisms and in turn help to distinguish between treatable and untreatable causes of fatigue in MS.

Finally, for adequate referral to disciplines and subsequent determination of intervention goals the screening process should incorporate identification of the most important daily problems related to fatigue as perceived by the patient. For example, it seems obvious that patients following all-or-nothing behaviour probably benefit more from behaviour change interventions than from an exercise intervention. In our RCT presented in **chapter 7** the referral pathway by the multidisciplinary team was an integral part of the intervention. Although all members of the team were experts in the treatment of MS, we are unable to confirm that this procedure led to an optimal deployment of disciplines. Current literature^{33,36} and guidelines³⁷ do not provide recommendations for this screening and referral process. So, the optimal diagnostic process and subsequent referral to disciplines remain to be precisely determined.

Above described inclusion trajectory was applied in the TOF trial as presented in **chapter 7**. This RCT was designed to evaluate interventions in chronic fatigued patients with MS. First of all patients had to suffer from fatigue, and perceive this fatigue for more than 6 weeks (chronic fatigue). Furthermore people were screened, for factors secondary to MS, such as pain and muscle spasms, and concomitant conditions such as viral infections, urinary infections, pregnancy, alcohol or substance abuse, depression and anxiety that may contribute to feelings of fatigue (secondary fatigue). Finally, the most important daily problems related to fatigue as perceived by the patient were identified, for example dividing time between rest and activity, improving or maintaining physical condition and coping with MS symptoms. A multidisciplinary team discussed the results of the fatigue screening and a tailored pathway of referral was determined for each individual patient. Following this procedure we found that multidisciplinary outpatient rehabilitation was not more effective

than nurse consultation at reducing the impact of chronic fatigue for people with MS. In fact, chronic fatigue in patients with MS was quite invariant over time, irrespective of the interventions applied.

Multidisciplinary treatment

Our finding that chronic fatigue in patients with MS was quite invariant over time, irrespective of the interventions applied, challenges the use of interventions such as aerobic training, behavioural approaches or energy conservation management to treat chronic fatigue.

In current clinical practice, both pharmacological (e.g., Amantadine, Modafinil, Pemoline) and non-pharmacological (e.g., exercise, energy or fatigue self-management education, and cognitive behavioural therapy) interventions are used individually or in combination, reflecting a multi-disciplinary approach.^{33,36,38} Recent reviews^{33,36} show that evidence supporting the efficacy of pharmacological interventions in MS-related fatigue is still ambiguous and insufficient. Remarkably, the literature and current guidelines^{33,36-38} do recommend pharmacological options such as amantadine, minopyridines, modafinil. However, pharmacological interventions are beyond the focus of the present thesis.

Recently, Kahn and colleagues³⁶ suggested that non-pharmacological interventions appear to have a stronger and more significant favourable effect on reducing the impact or severity of fatigue when compared to commonly prescribed pharmacological agents.³⁶ For non-pharmacological interventions, both aerobic training and behaviour change interventions demonstrate some degree of effectiveness for managing MS fatigue.³⁶ However, these results are to a large extent, based on evidence found in studies that did not screen for fatigue as an eligibility criterion. Moreover, most studies did not distinguish between different types (i.e. primary, chronic or secondary-contributing) of fatigue at inclusion or in their management approaches. Research in the field of fatigue suffers from major shortcomings, such as: (1) the small number of randomized controlled trials; (2) small number of studies evaluating fatigue as the primary outcome; (3) small sample sizes; (4) the lack for control for amount of attention; (5) and lack of follow-up post intervention.

More robust, high quality RCTs are needed in different populations (acute or chronic) of fatigued patients with MS.

The number of RCTs evaluating multidisciplinary rehabilitation for fatigue are even more scarce. In line with our finding, Kos and colleagues³⁸ failed to find a difference in effects

between a multidisciplinary fatigue management programme and a placebo intervention programme. In contrast with our results, both groups in the study of Kos showed similar statistically significant changes in fatigue over time on the MFIS. Interestingly, Kos et al.³⁸ did not distinguish between acute or chronic fatigue, but patients were selected largely based on the severity of impact of fatigue over the previous month as assessed with the Guy's Neurological Disability scale. An explanation of the different finding might be that our inclusion procedure was aimed at a more demarcated study sample of MS patients suffering from chronic fatigue, whose chronic fatigue was hardly influenced by our rehabilitation intervention. This in turn may support the idea that acute and chronic fatigue should be managed differently, with an initial focus on identifying and treating all factors that can contribute to the acute feelings of fatigue, and subsequently addressing the chronic aspects. In addition, in both clinical practice and research, attention should be paid to the idea of perpetuation which might be useful in explaining why acute fatigue in MS can become chronic.³⁹ Perpetuation refers to a situation where factors such as specific cognitive and behavioural responses to fatigue and the physiological changes that may accompany these responses maintain the fatigue symptoms over time once fatigue has developed. Examples of these perpetuating factors are catastrophizing about the symptoms, symptom focusing and avoidance of physical activity.³⁹ Catastrophizing about fatigue may be an important target for cognitive-behavioural interventions during which dysfunctional fatigue-related thoughts can be challenged.⁴⁰ Also depression and sleep disturbances seem important perpetuating factors in chronic fatigue.³⁹

Clinical implications

On the basis of our study and available evidence in the literature^{33,36-38} it is recommended that the management of MS-related fatigue should preferably start with a comprehensive evaluation to determine if fatigue is perceived as a problem by the patient and if it is acute or chronic in nature.² Next, particular attention should be devoted to identification and specific treatment of factors secondary to MS, such as pain and muscle spasms, and concomitant conditions such as depression, anxiety, viral infections, urinary infections, pregnancy, alcohol or substance abuse that may contribute to feelings of fatigue. Neurologic sequelae and concomitant factors can be addressed with drugs and/or psychological support and/or physical and occupational therapy.⁴¹

For fatigue that is persistent and characterised as primary and chronic in nature it is more difficult to provide recommendations for therapy. Perchance, patients with MS suffering

from chronic fatigue may benefit from cognitive-behavioural interventions that address dysfunctional fatigue-related thoughts. In addition, in case of no dysfunctional fatigue-related thoughts there is the consideration that self-selected diurnal distribution of activity may already be an optimal energy management strategy of patients with MS related fatigue.

Future research directions

The pathophysiological mechanism underlying fatigue in MS is probably multifactorial. Pathophysiological mechanisms that have been proposed include dysregulation of the immune system, neuro-endocrine/ neurotransmitter dysregulation, and dysfunction of the CNS.¹⁴ Better understanding and conceptualization of these mechanisms could be used to move the field of MS fatigue research forward, emphasizing clinical utility and potential routes of future research. Resulting in more insight in which mechanisms actually be part of the cause of the different modalities of fatigue. Based on this conceptualization international consensus about the definition and concepts of MS related fatigue should be composed, followed by determination of a comprehensive evaluation tool of these concepts of fatigue.

In addition, future RCTs should investigate the effects of interventions that are especially aimed at patients experiencing fatigue. To date, of the trials focusing on reducing fatigue in patients with MS, that did screen for fatigue as an eligibility criterion, patients have been included based on the impact of fatigue as measured with self-report scales like the MFIS and FSS. One may question if this inclusion method leads to a clear definition of chronic fatigue and factors secondary to MS that may contribute to feelings of fatigue. When it comes to including participants in trials, a combination of using descriptive modifiers and screening for factors contributing to fatigue may help to discriminate acute, intermittent fatigue from chronic persistent fatigue. Proper demarcation may in turn help distinguish between treatable and untreatable causes of fatigue in MS.

An example of such trials is the TREFAMS research programme⁴² which aims to: (1) assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and improving societal participation in patients with MS; and (2) study the neurobiological mechanisms of action that underlie treatment effects and MS-related fatigue in general. The study is ongoing and includes, only patients that report MS-related fatigue and uses the CIS20R as the primary measure of outcome. Moreover, participants are screened for factors that may contribute to feelings of fatigue such as infections, pregnancy, primary

sleep disorders and depression. The trial-specific interventions are Aerobic Training, Cognitive Behavioural Therapy, and Energy Conservation Management. In order to study neurobiological mechanisms of action, pro- and anti-inflammatory cytokines in serum, salivary cortisol, physical fitness, physical activity, coping, self-efficacy, illness cognitions and other determinants are longitudinally measured.

Pending a better conceptualisation of fatigue, studies on anchor-based responsiveness and the minimally important change score of self-report fatigue questionnaires are needed to establish whether an instrument can detect clinically meaningful changes in assessment of fatigue in patients with MS. The same is relevant for assessment of level of activity.

The last decade there is a growing interest in lifestyle interventions focusing on physical activity as a therapeutic strategy next to supervised and prescriptive exercise training in people with MS. The paradigm shift reflects promotion of a physically active lifestyle through behavioural interventions that teach people the skills, techniques, and strategies based on established theories for modifying and self-regulating health behaviours.¹⁹ Moreover, physical behaviour should also be looked at as a multi dimensional construct, in which parameters other than total amount of physical activity should be considered in determining outcomes for research and rehabilitation. Current methods of AM are feasible methods to objectively assess physical activity and are capable of recording physical activity behaviour in more detail. Longitudinal studies in which the relation between fatigue and physical activity is assessed for longer time intervals may offer more precise insight into the real diurnal or weekly varying activity patterns of patients with MS. In addition, the covariates that may distort the longitudinal association of self-reported fatigue and physical activity need to be further investigated. Such prospective designs with intensive repeated measurements in time do justice to the time-dependent fluctuation of fatigue, mood and performance, and may help to unravel if fatigue is an antecedent or consequence of daily physical activity in patients suffering from MS.

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