Treating fatigue in post-polio syndrome
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Chapter 9

General discussion
The burden of fatigue in people with post-polio syndrome (PPS) is high and the impact on functioning large. However, fatigue in PPS is a poorly understood symptom when it comes to its etiology, the course over time and its treatment. The general aim of this thesis was to expand the knowledge on the treatment of fatigue in PPS. To this end, we studied the severity, course, and factors related to fatigue, as well as the effectiveness of interventions aimed at reducing fatigue. In the final chapter of this thesis, the main findings of the presented studies are critically discussed and clinical implications and directions for future research are presented.

Main findings

Severity, course and factors related to fatigue

Insight into the severity, course and factors that contribute to fatigue is needed to design targeted interventions aimed at reducing fatigue in polio survivors. The longitudinal study as presented in Chapter 3, revealed that 80% of the cohort of patients with late-onset sequelae of polio (most of them fulfilling the diagnostic criteria for PPS) experienced moderate to high levels of fatigue that persisted over time. This was in line with earlier studies investigating the burden of fatigue in polio,\textsuperscript{1-5} and with a recent case-control study, which found that experienced fatigue is a frequent problem in polio survivors (93% reported fatigue against 13% in healthy controls).\textsuperscript{7} The results presented in Chapter 3 also confirmed the assumption that perceived fatigue is multifactorial and relates to biological, physical, psychological and cognitive-behavioral factors. In Chapter 8, the body of evidence for an association between cognitive-behavioral factors and fatigue in PPS was further increased by the finding that fatigue in severely fatigued patients with PPS is significantly associated with sense of control over fatigue, fatigue catastrophizing (which is a negative cognitive-affective response to anticipated or actual fatigue), acceptance of the disease and focusing on fatigue symptoms. However, even with the longitudinal design of the study described in Chapter 3 we could not determine whether relationships between the investigated factors and fatigue were causal, due to the stable character of fatigue.

Existing evidence on treatment of fatigue

Because of its multidimensional character, a variety of interventions to alleviate fatigue have been studied in PPS. Our Cochrane systematic review from 2011, which was updated and published early 2015 with searches performed until July 2014 (Chapter 4), evaluated the existing evidence on treatment for PPS, including therapies aimed at reducing fatigue. The review included thirteen studies investigating ten different interventions, both pharmacological and non-pharmacological, of which eleven reported fatigue as a primary or secondary outcome.
Our review concluded that no definite conclusions on the effectiveness of any of the studied interventions for reducing fatigue in PPS could be made. There is evidence varying from very low quality to moderate quality that intravenous immunoglobulin (IVIg, low quality evidence\textsuperscript{8,10}); modafinil (low to moderate quality evidence\textsuperscript{11,12}); pyridostigmine (low to moderate quality evidence\textsuperscript{13,14}); amantadine (very low quality evidence\textsuperscript{15}); prednisone (very low quality evidence\textsuperscript{16}); and rehabilitation in a warm or cold climate (very low quality evidence\textsuperscript{17}) are not beneficial for reducing fatigue in PPS (Table 1). Furthermore, there is inconsistency in the evidence of the effects of lamotrigine on reducing fatigue.\textsuperscript{18} In this study, a significant reduction in fatigue was found on the Fatigue Severity Scale (FSS) and the Nottingham Health Profile-Energy in the medication group compared to the control group post-treatment, but not on the Visual Analogue Scale. A high risk of bias and imprecision of the results downgraded the quality of the evidence for efficacy of lamotrigine to very low (Table 1).

**New evidence on treatment of fatigue with exercise therapy and cognitive behavioral therapy**

Exercise therapy (ET) and cognitive behavioral therapy (CBT) were found to be effective in reducing fatigue in cancer survivors, chronic fatigue syndrome and multiple sclerosis.\textsuperscript{19-24} Since these two approaches had so far not been studied adequately in PPS, a three-arm multicenter, single-blinded randomized controlled trial, with the acronym FACTS-2-PPS, was conducted to test the hypothesis that ET and CBT would be effective in reducing fatigue in severely fatigued patients with PPS as compared to usual care (Chapter 5). This study was part of the FACTS-2-NMD study program, which included two additional randomized controlled trials in neuromuscular disorders (FACTS-2-FSHD and FACTS-2-ALS) with a similar approach in interventions and outcome measures. ET aimed to improve physical capacity, and CBT aimed to change dysfunctional cognitive-behavioral factors related to fatigue. However, findings from our study did not demonstrate a beneficial effect of ET or CBT on reducing fatigue, the primary endpoint, compared with usual care (UC) (Chapter 6). Neither beneficial effects on the secondary outcomes, i.e. activities and HRQoL were found. These results were consistent with the absence of positive effects on any of the exploratory endpoints investigated, such as pain, mood disturbance, sleep disturbances, illness cognitions, coping and general self-efficacy. Also no effects on the various exploratory parameters of physical capacity (i.e. cardio-respiratory fitness, muscle strength, and functional capacity) and physical performance (actual daily physical activity level) were found.

**Contribution of the new evidence to existing knowledge**

The FACTS-2-PPS trial fulfills the selection criteria of the Cochrane review and will therefore be included in a next update of the review, which then is the first study contributing to the...
existing body of knowledge on ET (with the emphasize on aerobic exercise) and CBT for reducing fatigue in PPS. To value our study, we performed a risk of bias assessment and an assessment of the quality of the evidence according to the Cochrane Handbook for Systematic Reviews of Interventions.\textsuperscript{25} For both interventions, blinding of participants and administrators of the intervention was not possible. Although outcome assessors were blinded, the primary outcomes were self-reported and therefore this should be rated a high risk of bias, which downgrades the evidence for the efficacy of ET and CBT. The wide confidence intervals of the estimated effects of both interventions can be considered a second factor for downgrading the evidence for the efficacy. Therefore, including the FACTS-2-PPS trial in the Cochrane review will lead to the conclusion that there is low quality evidence of no beneficial effect of ET and CBT for reducing fatigue in PPS as compared to usual care (Table 1).

**Explaining lack of efficacy of exercise therapy**

Possible explanations for the lack of efficacy of ET in PPS were explored in Chapter 7, by investigating whether patients in the trial were adequately exposed to the intervention. Although we found that patients were not able to adhere to the high target intensities as prescribed in the training program (i.e., 60% of the heart rate reserve or higher), they did exercise at or little above their anaerobic threshold (AT, a measure that is often used to target training intensity in healthy subjects\textsuperscript{26} and individuals with chronic diseases\textsuperscript{27,28}), most of the training period. Therefore it is unlikely that the lack of efficacy of ET in PPS is explained by underexposure to the intervention.

In the search for other explanations for the lack of efficacy of ET to improve cardio-respiratory fitness and, therewith, reduce perceived fatigue in PPS, we evaluated the effect of ET on muscular endurance. It is known that improvement of cardiorespiratory fitness requires involvement of large muscle groups to impose an adequate stimulus for adaptations on central level.\textsuperscript{29} We therefore evaluated whether the exercise intervention did result in muscular adaptations, which, due to the reduced muscle mass of the lower extremities, did not lead to an increased cardiorespiratory fitness. However, it was shown that muscle endurance of the knee extensor muscles had not changed. A possible explanation for this finding is that the trained muscles were, apart from the reduced muscle mass, not deconditioned in most individuals. Although abnormal muscle fatigue is one of the key symptoms of PPS, and several studies have proven that muscles of patients with PPS are more fatigable than muscles of healthy subjects,\textsuperscript{30-32} our assumption that there is no deconditioning of muscles is corroborated by two recent studies in PPS. The first study found that intrinsic fatigability of the knee extensor muscles in PPS, as assessed with repeated isometric electrically evoked contractions, was not different from that found in healthy subjects.\textsuperscript{33} In line with these findings, the second study, conducted by Murray and colleagues found that muscle fatigue of four different lower extremity muscles, as mea-
sured with sustained maximum voluntary isometric contractions, was also not different from healthy subjects. Accordingly, it can be assumed that the assessed muscle groups had already adapted considerably in response to the relative higher load of performing daily life activities, and that the ET as conducted in the FACTS-2-PPS trial, which primarily focused on training of the lower extremities, could thus not further improve muscle function and subsequent cardiorespiratory fitness and experienced fatigue.

**Explaining lack of efficacy of cognitive behavioral therapy**

Possible explanations for the lack of efficacy of CBT in PPS were explored in Chapter 8, by investigating the role of cognitions related to fatigue in PPS. The hypothesis was tested that fatigue related cognitions (sense of control over fatigue; catastrophizing; acceptance of the disease; focusing on fatigue symptoms; and perceived social support) in patients with PPS were different from those experienced by patients suffering from facioscapulohumeral dystrophy (FSHD), another slowly progressive neuromuscular disorder for which CBT was proven effective as shown in the FACTS-2-FSHD-trial. If a difference was found, this might also explain the difference in efficacy of CBT between PPS and FSHD. However, the results demonstrated that fatigue-related cognitions in PPS were not significantly different from those found in FSHD. Also, no differences in the association of the assessed cognitions with fatigue were found between the two groups, except for the cognition perceived social support. However, the low absolute scores on this factor in both groups, and the lack of an association with fatigue per group, indicated that perceived social support was not a major problem in these two groups. Thus, the lack of efficacy of CBT in PPS in contrast with FSHD cannot be attributed to unique cognitive characteristics of this population. Possibly, cognitive patterns in PPS are more difficult to change due to the specific disease history usually with functional limitations from early age onwards and the long-term duration of fatigue as found in this study (on average 12.5 years). Another explanation for the lack of efficacy may be related to the possibility that alleviation of fatigue is not a priority for patients with PPS. Namely, although all patients in this study did experience severe fatigue, a number of patients did not prioritize fatigue as a treatment goal, and, therefore, the CBT intervention was not initiated. This assumption is supported by findings of a qualitative study that ran parallel to the FACTS-2-PPS trial, in which CBT therapists indicated that most patients did not experience specific distress from the fatigue, nor had they needs for support in reducing fatigue. This finding of low perceived distress from fatigue is in contrast with the results found in a study performed in 1999 on disability and health problems in 76 Dutch patients with PPS, where 78% of the subjects selected fatigue as their main problem. Possibly, in the population of ageing polio survivors patients are getting used to the persistent feeling of fatigue and therefore experience less distress.
Methodological considerations

Measuring fatigue

To investigate the prevalence, severity and natural course of fatigue, as well as to evaluate the effect of treatments aimed at reducing fatigue, various questionnaires have been used in literature in PPS, including the Fatigue Severity Scale (FSS)\(^\text{9,12,13,15,17,18,36-38}\); the Multidimensional Fatigue Inventory\(^\text{8,36,39}\); the Piper Fatigue Scale\(^\text{11}\); the Visual Analogue Scale for Fatigue\(^\text{12,15,18}\); the Hare Fatigue Symptom Scale\(^\text{13}\); and the Fatigue Impact Scale.\(^\text{11}\) Previous studies have mainly focused on assessing the reliability and construct validity of these questionnaires in PPS.\(^\text{40-42}\)

However, although the choice of a fatigue instrument should primarily be dependent on the construct to be measured, the exact conceptual properties (i.e. the content validity) of the above mentioned questionnaires are largely unknown.

Throughout this thesis we used two different instruments to measure fatigue. In the longitudinal study (Chapter 3) we used the FSS, and in the FACTS-2-PPS trial (Chapter 6) we used the subscale ‘subjective experience of fatigue’ of the Checklist Individual Strength (CIS-F). In Chapter 2 we compared the conceptual properties of these two instruments and concluded that they differ in content with regard to the International Classification of Functioning, Disability and Health (ICF) categories they represent. We suggested that the CIS-F primarily quantifies severity of fatigue, while the emphasis of the FSS is on measuring the interference of fatigue with functioning. Yet, although the linking process provided information on the ICF categories represented in the FSS and the CIS-F items, indicating that the two questionnaires differ in content, and therefore cannot be used interchangeably, it remains uncertain how relevant the items in these fatigue instruments are for PPS patients, as they were not originally developed for measuring fatigue in PPS. This also holds for other frequently used fatigue instruments in PPS.

Regarding reliability, we found that although the FSS and CIS-F lack precision to detect real changes in fatigue in individual patients, they are considered sufficient to detect changes over time at group level. Hence, it is unlikely that possible changes in fatigue in our longitudinal study and in the FACTS-2-PPS trial could not have been detected.

Sample size

People with PPS constitute a highly heterogeneous group with respect to the severity of sequelae and new or increased symptoms. For this and other reasons, in- and exclusion criteria are set to create a relatively homogenous study sample consisting of patients that are eligible for the investigated intervention. This limits the number of participants available for a study and may explain why studies in PPS often have a relatively small sample size (according to our Cochrane review, the sample sizes of included studies varied from 10 to 203). In the study in which
we investigated the reliability of the CIS-F and the FSS, almost 50 participants were included, which, according to the critical appraisal tool of COSMIN (the COnsensus-based Standards for the selection of health Measurement INstruments) group is a fair sample size for reliability studies.\textsuperscript{43} In the longitudinal study as presented in Chapter 3, in which the severity, course and factors of fatigue were investigated, 168 patients were included, which is considered good according to the quality assessment criteria list from Borghouts et al.\textsuperscript{44} In our RCT, after prolongation of the planned recruitment with one year, recruitment was stopped for logistical and financial reasons. In total, 67 patients were included, which was unfortunately below the target sample size of 81 patients, and can partly be explained by the selective inclusion criteria e.g. diagnosis of PPS, CIS-F $\geq$ 35, and ability to cycle on a cycle ergometer against a load of at least 25 Watt.

A risk of using small sample sizes in clinical trials is a lack of power or the inability to detect intervention effects of clinical importance. We are fairly confident that the relatively small sample size is not the reason for the negative result of the FACTS-2-PPS study, considering the magnitude of the estimated effects of ET and CBT. Had the pattern of change noted in the included patients continued and thus the magnitude of the estimated effects remained in the same order, thus small in relation to the 95% CI (mean difference in fatigue scores: 1.47, 95% CI = -2.84 to 5.79 for ET versus UC; and 1.87, 95% CI = -2.24 to 5.98 for CBT versus UC), the extra precision in estimates from another 14 patients would not have generated a statistically significant result for either intervention. Moreover, when a larger sample size would have led to significant differences, these differences would not be considered clinically relevant, as the lower limits of the 95% CIs are, for both interventions, well below the clinical relevant decline of 8 points on the CIS-F.\textsuperscript{32}

**Design of intervention studies**

An important but difficult issue in addition to the selection and specification of the interventions of interest, is the control condition against which these interventions are compared. Although in PPS research, there appears to be a positive trend in effects of interventions being investigated in randomized designs, in the Cochrane review we had to exclude a substantial number of randomized studies, because they did not use a control condition consisting of placebo, usual care or no treatment as the comparator. Four out of six studies that were excluded for this reason had an intervention-arm with two interventions, whereas the comparison-arm also included one of these interventions (for example coenzyme Q10 as add-on to resistance training against the effect of resistance training only). As long as the effects of these single interventions are unknown, investigating the effectiveness of combinations of these interventions does not contribute to the existing knowledge and will not be helpful for clinical decision-making.

In the FACTS-2-PPS trial (Chapter 6), usual care was chosen as the comparator. In all three allocation groups, patients received usual care, which could include the use of assistive devic-
es, orthoses, physical therapy, and/or medication. Patients were furthermore not restricted in their activities. All newly prescribed co-interventions were monitored throughout the study. We found that co-interventions varied between the groups. However, it seems unlikely that this explains the absence of positive effects of the studied interventions on reducing fatigue and improving activities or HRQoL. Although slightly more co-interventions were prescribed in the usual care only-group during the study period compared with the intervention-groups, these were almost never specifically targeted at alleviating fatigue. Moreover, we did not find a reduction in fatigue-scores, nor in the scores for activities and HRQoL within the usual care only-group.

**Generalizability**

The generalizability of the results obtained in the different studies in this thesis to the population of polio survivors is considered to be good, since the characteristics of the three different cohorts in this thesis (Chapter 2, Chapter 3, Chapter 5) were comparable to those in previous cohort-studies in polio survivors in the Netherlands\(^45\) and other Western countries.\(^46\) However, the question is to what extent the results obtained in this thesis can be generalized to the non-Western countries. Although for the Cochrane review there were no language or country restrictions, almost all included studies were conducted in Western countries. It is expected that the results obtained from these studies are not generalizable to polio survivors living in developing countries as this usually concerns a much younger population with more complex problems probably due to relative under treatment. Moreover, due to the lack of resources rehabilitation care is limited compared to the rehabilitation care in Western countries.\(^47\)

A second interesting question is to what extent the results obtained in this thesis can be generalized to other slowly progressive neuromuscular disorders. The difference in results from the FACTS-2 PPS trial and the FACTS-2 FSHD trial,\(^34\) wherein the latter found positive effects of both ET and CBT for reducing fatigue, illustrates that the results obtained in our trial cannot simply be generalized to other slowly progressive neuromuscular disorders. This finding emphasizes that disease specific features may influence treatment effects and should be carefully considered.

**Clinical implications**

Based on the results of this thesis and other studies, it can be concluded that fatigue in PPS is severe, impacts on daily functioning, and is persistent (Chapter 3,1-7). However, it is currently unknown to what extent patients with PPS feel a need for treatment of fatigue. Therefore, the first step in the approach of PPS-related fatigue concerns a comprehensive assessment of fa-
tigue. This should be aimed at identifying at the individual level, not only the severity of fatigue and the interference this fatigue has with daily functioning, but also the perceived distress from fatigue and the perceived need for treatment.

Using a combination of different scales is necessary to obtain a complete picture of the different dimensions of fatigue. Based on the results of this thesis, fatigue severity can be assessed with the CIS-F and the interference of fatigue with functioning with the FSS (Chapter 2). Care should be taken when evaluating the course of fatigue or when evaluating the effects of its treatment, since these and other questionnaires lack precision to detect real changes in fatigue in individual patients (Chapter 2). Multiple repeated measures over time might partly overcome this problem of large measurement error.

In this thesis we concluded that fatigue in PPS relates to biological, physical, psychological and cognitive-behavioral factors. The next step in the work-up of fatigue concerns the identification of factors that cause fatigue in the individual patient. Factors that commonly cause fatigue in the general population should be identified and treated including infections, endocrine-metabolic causes like thyroid dysfunction, medication side effects, sleep disturbances and psychological causes like depression. Furthermore, medical professionals should be aware of chronic ventilatory insufficiency as a cause of fatigue, especially in polio survivors who have had respiratory muscle involvement during acute polio.

An important step in the approach of PPS-related fatigue is to inform the patient about the course and etiology of fatigue. Acknowledging that fatigue is one of the most frequent complaints in PPS may contribute to acceptance. Furthermore, informing patients about the usually stable character of PPS-related fatigue, may reassure those who fear worsening of this symptom.

Concerning possible treatment options, this thesis showed that no definite conclusions on the effectiveness of interventions for reducing fatigue in PPS can be drawn. Due to the lack of good quality external clinical evidence, the role of expert opinion as well as patient preferences remain important for selecting the best available treatment options of fatigue in PPS. Results of one trial provided very low-quality evidence that lamotrigine might be effective in reducing fatigue in PPS without generating adverse events. However, the high risk of bias and imprecision of the results of that trial preclude a recommendation for prescription of this drug. Likewise, a recommendation for prescription of IVIg, modafinil, pyridostigmine, amantadine, prednisone, rehabilitation in a warm or cold climate, ET and CBT seems not justified based on the existing evidence (varying from very low quality to moderate quality) that these interventions are not beneficial for reducing fatigue in PPS.

The two follow-up studies on explanations for the lack of efficacy of ET and CBT may suggest that these interventions are only effective in subgroups of patients. Alleviating PPS-related fatigue through ET may be feasible for those patients in whom deconditioning due to physical
inactivity is demonstrated. Then, an individual selection of exercise modes that ensure that the cardiorespiratory system is sufficiently loaded may improve the aerobic (muscle) capacity, which, in turn, may reduce PPS-related fatigue. Managing PPS-related fatigue by means of a CBT approach may have a place in the management of patients who not only have dysfunctional cognitions and behavior with respect to fatigue, but who also express a need for treating fatigue, are willing and able to change cognitions and behavior and are optimistic about the change of success in therapy.\textsuperscript{54} However, as the sample size of the trial was too small to allow for subgroup analyses, we were not able to test these hypotheses and therefore no strong recommendations for prescription of ET and CBT in subgroups of patients can be given.

Besides the above mentioned treatments, which mainly focus on enhancing the physical load capacity, also interventions focusing on reducing the physical load strain should be considered, for example reducing the elevated energy cost of walking, which may also cause fatigue, by means of leg orthoses or other assistive devices. These devices have been shown to be effective in reducing walking energy cost in PPS,\textsuperscript{52,53} although their effect on experienced fatigue has not yet been reported.

Future research

Burden of fatigue

A first and important step in fatigue-related research in PPS is to further clarify the burden of fatigue for PPS-patients. This thesis, as well as earlier studies, showed that compared to healthy individuals, patients with PPS experience much higher levels of fatigue\textsuperscript{5,6} that persists over time (Chapter 3), and leads to a decline in functioning and HRQoL.\textsuperscript{54,55} Moreover patients with PPS select fatigue as a key problem.\textsuperscript{4} However, the results of the FACTS-2-PPS trial indicate that the perceived distress and need for treatment on alleviating fatigue in this population may be limited, possibly because they have spent a lifetime managing the challenges of living with functional limitations and experienced long durations of fatigue. Research on the perceived distress from fatigue, acceptance of fatigue symptoms and the felt need for treatment on alleviating fatigue is essential in order to establish to what extent future interventions in this field are needed.

Etiology of fatigue

In this thesis, the assumption of the multidimensional character of fatigue in PPS was confirmed. Although our results are based on a longitudinal study with a follow-up period of five years and a rather large cohort size (n = 168), the causality of the relationships between bio-
logical, physical, psychological and cognitive-behavioral factors and fatigue could not be determined. It may be questioned whether an attempt to discover cause-effect relationships should be a research priority in this field. The relationship between fatigue and the different factors associated are probably reciprocal, resulting in complex processes, which are difficult to disentangle. As described above, for daily clinical practice, it is recommended to investigate at the individual level (by means of an extensive multidisciplinary assessment), which factors perpetuate fatigue.

**Measuring fatigue**

Ideally, questionnaires (to measure experienced fatigue) should be tailored to the target population and the target intervention. At the start of this thesis, no PPS-specific questionnaires for measuring fatigue were available. Although the scales used in this thesis (FSS and CIS-F) were proven reliable in our population they were not specifically developed for the PPS population. Future research should investigate whether a recently developed PPS-specific questionnaire (the Neurological Fatigue Index for Post-Polio Syndrome, NFI-PP) that was based on patient experiences can be translated and cross-culturally validated in a Dutch version. An additional advantage of this recently developed scale is that it is a Rasch-derived instrument, which is preferred above the ordinal scales as used in this thesis, when performing parametric analyses. Furthermore, the responsiveness of fatigue questionnaires should be studied to determine their adequateness to detect meaningful changes in fatigue over time.

**Ongoing research on treatment of fatigue**

A world-wide multicenter RCT (NCT02176863) is currently being performed investigating the effect of different doses of intravenous immunoglobulines (IVIg) on fatigue as one of the outcome measures. This study has a target sample size of 210 patients and evaluates the effects of infusions with one or two grams immunoglobulin per kilogram body weight every four weeks during a treatment period of one year. Particularly with regard to the dosing intervals, this study differs from the three earlier performed RCTs with only one or two IVIg infusions. This new study will eventually contribute considerably to the evidence of IVIg for reducing symptoms in PPS, including PPS-related fatigue. Furthermore, the results of two completed studies and one ongoing study have to be awaited and will hopefully contribute to the existing evidence for the effectiveness of home-based exercise therapy with muscle strengthening exercises (ISRCTN00378146), coenzymeQ10 (ACTRN12612000552886) and L-carnitine combined with piracetam (NCT01549847).

**Recommendations for future research on treatment of fatigue**

Considering the negative results of a wide range of interventions aimed at alleviating fatigue
in PPS, including ET and CBT, which have been proven effective in other patient populations.\textsuperscript{20,24,34} The question arises why fatigue in PPS is so difficult to treat.

We showed that a 4-month ET intervention with the main focus on home-based aerobic training did not lead to a reduction in fatigue and improvement in activities and HRQoL. Future studies should investigate whether a targeted selection of patients with deconditioning due to physical inactivity and individualized aerobic training programs with exercise modes that ensure that the cardiorespiratory system is sufficiently loaded may lead to better treatment effects.

In the Cochrane review, we concluded that there is very low quality evidence that progressive resistance training of polio-affected thumb muscles has a beneficial effect on muscle strength, but the effects on fatigue were not investigated. In the ET intervention in the FACTS-2-PPS trial, muscle strengthening (with sessions only once a week) was not the primary aim. It is known that for improvement of muscle strength of healthy persons and patients with several chronic diseases, a training frequency of at least three times a week is required.\textsuperscript{58,59} It may be valuable to investigate whether strength training of larger muscle groups and a higher training frequency would result in increased strength and whether these changes are large enough to have beneficial effects on reducing fatigue in PPS.

Regarding CBT, future studies should investigate whether a targeted selection of patients’ with dysfunctional cognitions and behavior with respect to fatigue, and with an expressed need for treatment of fatigue, willingness and ability to change dysfunctional cognitions and behavior and optimism about the change of success in the therapy may lead to better treatment effects. To gain more insight in the modifiability of dysfunctional cognitions and behavior, these factors should be evaluated before and after the intervention period.

There is very low quality evidence that lamotrigine at a daily dose of 50 mg to 100 mg has a positive effect on activity limitations and pain after four weeks of treatment, without generating adverse events.\textsuperscript{18} However, the beneficial effects on fatigue are inconsistent.

Placebo-controlled studies with a large sample size, a long follow-up period and adequate blinding are needed to establish the efficacy of lamotrigine.

Finally, other possible interventions not evaluated in our review, such as individualized goal-oriented comprehensive rehabilitation,\textsuperscript{60,61} orthoses and assistive devices,\textsuperscript{52,53} and transcranial direct current stimulation\textsuperscript{62} should be tested in randomized controlled trials, aimed at evaluating the effectiveness on experienced fatigue, in addition to other relevant outcome measures. In future studies, monitoring and reporting of adverse effects of both pharmacological and non-pharmacological interventions should be systematically addressed and multi-center studies, whereby, in a shorter period of time larger sample sizes can be achieved are warranted.
Final remarks

It seems increasingly likely that polio will soon be eradicated. As argued by others, a logical extension of the current global commitment to polio eradication is the obligation to continue to provide support and services to those millions of children and adults in Western and non-Western countries who live with the late sequelae of polio, including PPS. However, due to the fact that there are still many unanswered questions regarding the frequency, cause, course, risk factors and therapies for PPS in general, but also more specifically regarding fatigue in PPS, providing good quality care for these individuals is a great challenge. It is obvious that the management of PPS is not easily captured in fixed protocols or clinical guidelines. Against this background, concentrating care for polio survivors in centers of excellence seems crucial in order to maintain their quality of life at the highest possible level despite the functional decline that awaits many of them.
### Table 1. Evidence on treatment of fatigue in post-polio syndrome.

<table>
<thead>
<tr>
<th>Scale</th>
<th>Illustrative comparative risk (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
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<tr>
<td></td>
<td>Assumed risk control</td>
<td>Corresponding risk Intervention versus control</td>
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<tr>
<td><strong>IVIg versus placebo</strong></td>
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<tr>
<td>MFI general fatigue (scale 4 to 20) Follow-up: ≤ 3 months</td>
<td>The mean change in fatigue in the control group was -1.0</td>
<td>The mean change in fatigue in the intervention group was 0 higher (1.05 lower to 1.05 higher)</td>
<td>130 (1 study)</td>
<td>low&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>FSS (scale 1 to 7) Follow-up: ≤ 3 months</td>
<td>The mean fatigue in the control groups was 4.7</td>
<td>The mean fatigue in the intervention groups was 0.08 higher (0.71 lower to 0.87 higher)</td>
<td>70 (2 studies)&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>low&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>FSS (scale 1 to 7) Follow-up: ≥ 3 months</td>
<td>The mean fatigue in the control groups was 5.4</td>
<td>The mean fatigue in the intervention groups was 0.5 lower (1.15 lower to 1.15 higher)</td>
<td>70 (2 studies)&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>low&lt;sup&gt;c&lt;/sup&gt;</td>
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<td><strong>Modafinil versus placebo</strong></td>
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<td>PFS (scores normalised to that at baseline, %) Follow-up: 5 weeks</td>
<td>The mean fatigue in the control group was 57</td>
<td>The mean fatigue in the intervention group was 12 higher (4.16 to 19.84 higher)</td>
<td>14 (1 study)&lt;sup&gt;11&lt;/sup&gt;</td>
<td>low&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>FSS (scale 1 to 7) Follow-up: 6 weeks</td>
<td>The mean fatigue in the control group was 4.8</td>
<td>The mean fatigue in the intervention group was 0.39 higher (0.24 lower to 1.02 higher)</td>
<td>33 (1 study)&lt;sup&gt;12&lt;/sup&gt;</td>
<td>moderate&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Scale</td>
<td>illustrative comparative risk (95% CI)</td>
<td>relative effect (95% CI)</td>
<td>no of participants (studies)</td>
<td>quality of the evidence (GRADE)</td>
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<td>VASF (0 to 10 cm)</td>
<td>the mean fatigue in the control group was 5.5</td>
<td>the mean fatigue in the intervention group was 0.01 lower (0.93 lower to 0.91 higher)</td>
<td>33 (1 study)</td>
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<td>follow-up: 6 weeks</td>
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<tr>
<td>FIS (scale 0 to 160)</td>
<td>the mean fatigue in the control group was 45.6</td>
<td>the mean fatigue in the intervention group was 3.32 lower (15.22 lower to 8.58 higher)</td>
<td>33 (1 study)</td>
<td>moderate e</td>
</tr>
<tr>
<td>follow-up: 6 weeks</td>
<td></td>
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<tr>
<td>pyridostigmine versus placebo</td>
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<tr>
<td>FSS (scale 1 to 7)</td>
<td>the mean change in fatigue in the control group was 0.31</td>
<td>the mean change in fatigue in the intervention groups was 0.06 lower (0.34 lower to 0.21 higher)</td>
<td>186 (2 studies)</td>
<td>moderate h</td>
</tr>
<tr>
<td>follow-up: 14 weeks and 6 months</td>
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<tr>
<td>HFSS (scale 0 to 4)</td>
<td>the mean change in fatigue in the control group was 0.2</td>
<td>the mean change in fatigue in the intervention group was 0.07 higher (0.17 lower to 0.31 higher)</td>
<td>115 (1 study)</td>
<td>low i</td>
</tr>
<tr>
<td>follow-up: 6 months</td>
<td></td>
<td></td>
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<tr>
<td>NHP-energy (scale 0 to 100)</td>
<td>the mean change in fatigue in the control group was 17.2</td>
<td>the mean change in fatigue in the intervention group was 1.1 higher (16.24 lower to 18.44 higher)</td>
<td>62 (1 study)</td>
<td>low i</td>
</tr>
<tr>
<td>follow-up: 14 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Scale</td>
<td>Illustrative comparative risk (95% CI)</td>
<td>Relative effect (95% CI)</td>
<td>No of participants (studies)</td>
<td>Quality of the evidence (GRADE)</td>
</tr>
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</tr>
<tr>
<td></td>
<td>Assumed risk control</td>
<td>Corresponding risk Intervention versus control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lamotrigine versus control</td>
<td></td>
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</tr>
<tr>
<td>FSS (scale 1 to 7) Follow-up: 4 weeks</td>
<td>The mean fatigue in the control group was 3.9</td>
<td>The mean fatigue in the intervention group was 1.4 lower (2.26 to 0.54 lower)</td>
<td>30 (1 study)</td>
<td>very lowk</td>
</tr>
<tr>
<td>VASF (scale 0 to 10 cm) Follow-up: 4 weeks</td>
<td>The mean fatigue in the control group was 4</td>
<td>The mean fatigue in the intervention group was 1 lower (3.3 lower to 1.3 higher)</td>
<td>30 (1 study)</td>
<td>very lowl</td>
</tr>
<tr>
<td>NHP-energy (scale 0 to 100) Follow-up: 4 weeks</td>
<td>The mean fatigue in the control group was 35.7</td>
<td>The mean fatigue in the intervention group was 33.3 lower (53.13 to 13.47 lower)</td>
<td>30 (1 study)</td>
<td>very lowm</td>
</tr>
<tr>
<td>Amantadine versus placebo</td>
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<tr>
<td>Number of patients improved Follow-up: 6 weeks</td>
<td>214 per 1000</td>
<td>546 per 1000 (174 to 1000)</td>
<td>RR 2.55 (0.81 to 7.95)</td>
<td>25 (1 study)</td>
</tr>
<tr>
<td>Prednisone versus placebo</td>
<td></td>
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</tr>
<tr>
<td>Number of patients improved or not changed Follow-up: 3 months</td>
<td>857 per 1000</td>
<td>969 per 1000 (643 to 1000)</td>
<td>RR 1.13 (0.75 to 1.7)</td>
<td>12 (1 study)</td>
</tr>
<tr>
<td>Rehabilitation in cold climate versus usual care</td>
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<tr>
<td>FSS (scale 1 to 7) Follow-up: 3 months following intervention</td>
<td>The mean fatigue in the control group was 5.6</td>
<td>The mean fatigue in the intervention group was 0.1 higher (0.47 lower to 0.67 higher)</td>
<td>53 (1 study)</td>
<td>very lowo</td>
</tr>
<tr>
<td>Scale</td>
<td>Illustrative comparative risk (95% CI)</td>
<td>Relative effect (95% CI)</td>
<td>No of participants (studies)</td>
<td>Quality of the evidence (GRADE)</td>
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<tr>
<td></td>
<td>Assumed risk control</td>
<td>Corresponding risk Intervention versus control</td>
<td></td>
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<tr>
<td><strong>Rehabilitation in warm climate versus usual care</strong></td>
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<tr>
<td>FSS (scale 1 to 7)</td>
<td>The mean fatigue in the control group was 5.6</td>
<td>The mean fatigue in the intervention group was 0.4 lower (1.02 lower to 0.22 higher)</td>
<td>57 (1 study)</td>
<td>very low</td>
</tr>
<tr>
<td>Follow-up: 3 months following intervention</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Exercise therapy versus usual care</strong></td>
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</tr>
<tr>
<td>CIS-F (scale 8 to 56)</td>
<td>The mean fatigue in the control group was 36.1</td>
<td>The mean fatigue in the intervention group was 1.10 higher (5.42 lower to 7.62 higher)</td>
<td>36 (1 study)</td>
<td>low</td>
</tr>
<tr>
<td>Follow-up: directly following intervention</td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Cognitive Behavioural Therapy versus usual care</strong></td>
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</tr>
<tr>
<td>CIS-F (scale 8 to 56)</td>
<td>The mean fatigue in the control group was 36.1</td>
<td>The mean fatigue in the intervention group was 3.20 higher (2.94 lower to 9.34 higher)</td>
<td>41 (1 study)</td>
<td>low</td>
</tr>
<tr>
<td>Follow-up: directly following intervention</td>
<td></td>
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</tr>
</tbody>
</table>

The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval.

GRADE Working Group grades of evidence

**High quality**: Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality**: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality**: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

MFI: general fatigue: Multidimensional Fatigue Inventory. Higher scores represent more fatigue.
FSS: Fatigue Severity Scale. Higher scores represent more fatigue.
PFS: Piper Fatigue Scale. Higher scores represent more fatigue.
VASF: Visual Analogue Scale for Fatigue. Higher scores represent more fatigue.
FIS: Fatigue Impact Scale. Higher scores represent more fatigue.
HFSS: Hare Fatigue Symptom Scale.
NHP-energy: Nottingham Health Profile, domain energy. Higher scores represent more fatigue.
CIS-F: Checklist Individual Strength, subscale subjective experience of fatigue. Higher scores represent more fatigue.

a Risk of bias: likely that blinding was broken due to side effects of the treatment. However, because the result was negative, it is unclear if unblinding actually did influence this result (-1). Imprecision: wide confidence interval (13%) (-1)
b Risk of bias: likely that blinding was broken in one trial due to side effects of the treatment. However, because the result was negative, it is unclear if unblinding actually did influence this result. In the other study the randomisation procedure was unclear (-1). Imprecision: wide confidence interval (26%) (-1)
c Risk of bias: likely that blinding was broken in one trial due to side effects of the treatment. However, because the result was negative, it is unclear if unblinding actually did influence this result. In the other study the randomisation procedure was unclear (-1). Imprecision: wide confidence interval (22%) (-1)
d Risk of bias: the randomisation procedure was unclear. Insufficient reporting on incomplete outcome data (-1). Imprecision: small sample size (n = 14), wide confidence interval (16%) (-1)
e Imprecision: wide confidence interval (21%) (-1)
f Imprecision: wide confidence interval (18%) (-1)
g Imprecision: wide confidence interval (15%) (-1)
h Risk of bias: in one study analysis on effectiveness of blinding provided evidence for unblinding. However, because the result was negative, it is unclear if unblinding actually did influence this result. In the other study the randomisation procedure was unclear (-1)
i Risk of bias: analysis on effectiveness of blinding provided evidence for unblinding. However, because the result was negative, it is unclear if unblinding actually did influence this result (-1). Imprecision: wide confidence interval (12%) (-1)
j Risk of bias: the randomisation procedure was unclear (-1). Imprecision: wide confidence interval (35%) (-1)
k Risk of bias: open-label study and therefore no blinding. Randomisation procedure was unclear. Insufficient reporting on incomplete outcome data. Baseline imbalance in fatigue score (-2). Imprecision: small sample size (n = 30) and wide confidence interval (29%) (-1)
l Risk of bias: open-label study and therefore no blinding. Randomisation procedure was unclear. Insufficient reporting on incomplete outcome data. Baseline imbalance in fatigue score (-2). Imprecision: small sample size (n = 30) and wide confidence interval (46%) (-1)
m Risk of bias: open-label study and therefore no blinding. Randomisation procedure was unclear. Insufficient reporting on incomplete out-
come data. Baseline imbalance in fatigue score (-2). Imprecision: small sample size (n = 30) and wide confidence interval (40%) (-1)

Risk of bias: Randomisation procedure is unclear. Likely that blinding was broken because of the side effects of the treatment. Insufficient reporting on missing outcomes (-2). Imprecision: small sample size (n = 25) (-1)

Risk of bias: sequence generation is unclear. Insufficient reporting on missing outcome data (-2). Imprecision: small sample size (n = 12) (-1)

Risk of bias: randomisation procedure was unclear. Blinding not possible. (-2). Imprecision: wide confidence interval (19%) (-1)

Risk of bias: randomisation procedure was unclear. Blinding not possible. (-2). Imprecision: wide confidence interval (21%) (-1)

Risk of bias: blinding not possible (-1). Imprecision: wide confidence interval (14%) (-1)

Risk of bias: blinding not possible (-1). Imprecision: wide confidence interval (13%) (-1)
REFERENCES


32. Sharma KR, Kent-Braun J, Mynhier MA, Weiner MW, Miller RG. Excessive muscular fatigue in


