

Patient education in persons with disease-related fatigue

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Summary

Fatigue is a very common, highly disabling symptom caused by many chronic diseases or resulting from treatment. The self-management education of persons with disease-related fatigue enables new behavior habits and to engage successfully in daily routines and social participation through managing their available energy.

The aim of this thesis has been to explore the effectiveness of self-management education in persons with diseases-related fatigue. Three Studies had been run: Study I developed the inpatient energy management education (IEME) program and integrated it into a regular inpatient rehabilitation stay. Study II showed the feasibility of a study protocol aimed to lead a large-scale randomized clinical trial and reported promising outcomes of IEME. In Study III an over-disciplinary perspective and non disease-oriented approach, permitted to highlight the positive potential of self-management on fatigue and quality of life in persons with disease-related fatigue.

The three studies and their related works and following projects have highlighted the need of major support for persons with disease-related fatigue in managing this condition. This work has underlined the potential of occupational therapy, made topical a neglected clinical field and created new evidence-based treatment opportunities in different settings.

Abbreviations

EME	Energy management education
HrQoL	Health-related Quality of Life
IEME	Inpatient energy management education
MS	Multiple sclerosis
OT	Occupational therapy / therapist
PMR	Progressive muscle relaxation
pwMS	Persons with multiple sclerosis
RAU	Rehabilitation as usual
RCT	Randomized controlled trial
SME	Self-management education
SUPSI	University of Applied Sciences and Arts of Southern Switzerland
2rLab	Rehabilitation Research Laboratory

Preface

I have become an occupational therapist in 1993 and have worked for over 20 years in different rehabilitation settings with persons after neurological events or diseases. At the end of the 90s, I have heard for the first time from evidence-based practice and it seemed to me the solution of many open questions in our daily practice. Nevertheless, to find and to understand relevant research results was difficult and I had to acquire new skills on research methodologies and statistical analysis. In this way, I have discovered the world of science, which has fascinated me for its methodological way to proceed. I started to formulate research questions in my mind, which were inspired by my daily practices and I tried to imagine how answers to them through an appropriate methodology. I was convinced that it was only a question of time that the knowledge on effective interventions would have changed our practice; however, I had to realize that it is not at all automatic and that the implementation of new practices does not depend only on the quality of the evidence.

In 2015, Prof. Luca Crivelli¹ invited Prof. Marco Barbero², and me, by a short e-mail to suggest a research project on the topic of the rehabilitation of people with multiple sclerosis (MS). At this time, I had finished my Master of Science in occupational therapy just from a few years and I was thinking, if dare the step towards research or to continue with clinical practice and education of occupational therapist students. I knew about the high prevalence of fatigue in people with MS and was aware about the disabling impact on daily and quality of life. I remembered some attempts to address the issue of fatigue during treatment constructively and the difficulties of effectively improve the problems of my patients in everyday life. I searched for literature on fatigue management and was surprised of the recently published positive evidence for interventions based on occupational therapy in this field.

I informed myself by colleagues in Switzerland about their practice in people with MS-related fatigue. It emerged that they were conscious on the importance of the issue, but that they felt stuck in practices routines of usual care. Further on, I realized that not only people with MS, but also other populations living with fatigue, had no-access to an evidence-based occupational

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therapy, that this subject was neglected in our professional community and that I wanted to dedicate my time and energy to this research topic. Since we started this adventure, the topic of fatigue-management education, continues to present us new implications and interesting questions and is far from conclude.

Chapter 1

General introduction

Before presenting the overall aim, the research questions and the methods applied in this thesis, I will contextualize fatigue as a symptom and patient education as an intervention option in a larger framework. In chapter two and three, I will present two studies, which included people with multiple sclerosis (MS) related fatigue in Switzerland. Chapter four reports the findings from a systematic and comprehensive literature review on different populations with chronic disease-related fatigue. This thesis will be concluded in chapter 5 with a general discussion on the findings and an outlook towards the future.

Fatigue – a common symptom in chronic diseases

Fatigue is a universal complaint and a nonspecific phenomenon that may be related to particular medical diagnoses, chronic disease and long-term conditions, or result from treatment (Tiesinga et al., 1996). The term “fatigue” describes difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); or difficulty with concentration, memory, and emotional stability (mental fatigue; Markowitz & Rabow, 2007).

Cancer-related fatigue has been reported to be experienced by up to 80% of patients (Abrahams et al., 2016; Hofman et al., 2007), and to be the most distressing symptom during and after treatment for cancer (National Comprehensive Cancer Network, 2018). Among neurological disorders, the prevalence of fatigue is particularly increased in patients with MS [prevalence 75-95%; (Krupp, 2006)], traumatic brain injury and stroke (Eskes et al., 2015), Parkinson’s disease [prevalence 33 -58%; (Friedman et al., 2007)], spinal cord injury (Anton et al., 2017) and in neuromuscular disorders (Finsterer & Mahjoub, 2014). Fatigue is present in persons with chronic obstructive pulmonary disease [prevalence 50-70%; (Spruit et al., 2017)] and survivors of heart failure [prevalence after three years: 50%; (Wachelder et al., 2009)]. Also patients with rheumatoid arthritis (Walter et al., 2018), and connective tissue disorders such as systemic lupus erythematosus [prevalence 90%; (Cleanthous et al., 2012)] frequently report fatigue. Other diseases in which fatigue and its management is an important issue are e.g. HIV-infection (Barroso, 1999), diabetes (Fritschi & Quinn, 2010), hepatitis (Swain, 2006) or kidney

diseases (Jhamb et al., 2008). Fatigue is also related to psychiatric disorders such as depression and often occur comorbid. Despite this overlap, the estimated prevalence of fatigue without psychiatric comorbidity is around 7% (Harvey et al., 2009).

According to the current understanding, fatigue is an extreme and persistent mental and/or physical tiredness, weakness or exhaustion (Dittner et al., 2004) and different from normal fatigue, as it is not related to performance, relieved either by rest or by sleep (Bower et al., 2014). Chaudhuri and Behan (2004) described fatigue in neurological disorders as a purely subjective symptom that is often not easily distinguishable from normal tiredness, excessive daytime sleepiness, muscle fatigability and weakness, cognitive fatigability, and depression. In oncology, cancer-related fatigue is defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that significantly interferes with usual functioning (Bower et al., 2014). Because of the many different conditions that are confronted with fatigue and its multidimensional character, a universally accepted definition of fatigue is still lacking (Finsterer & Mahjoub, 2014; Neill et al., 2006).

The pathophysiology of fatigue is thought to be a complex process caused by physical, mental, and emotional aspects, and characterized by the etiology of the specific disease. The onset and the persistence of fatigue are attributed to multiple pathogenic processes (e.g. changes in the central and peripheral nervous system, inflammatory response or changes in endocrine system), in addition to environmental, psychosocial and behavior factors. Their interplay is not yet fully understood and the relationship between factors that contribute to fatigue are complex and highly interdependent (Bower et al., 2014; Penner & Friedemann, 2017). Due to the multidimensional character of fatigue, it is not surprising that this phenomenon is a very common underlying symptom with particular relevance in the management of patients with multiple chronic conditions (Connolly et al., 2013; M. Swain, 2000).

Although the understanding of the pathophysiology of fatigue is limited, it is possible to describe it based on the current knowledge of different phenomenological elements (Kluger et al., 2013). Primary fatigue emerges independently of other comorbidities, and can be considered part of the underlying disease. In the case of MS, primary fatigue probably develops as a result of continuous focal and diffuse tissue destruction, leading to disruption of certain cortical–subcortical connections in the brain and subsequent impairment of anatomical or

functional connectivity (Penner & Friedemann, 2017). By contrast, secondary fatigue is the result of disease-related complications, e.g. pain, physical disability, musculoskeletal problems, medication side effects, sleep disorders or depression. Another possible specification of the condition is between physical (difficulty to sustain physical workload) and mental fatigue (difficulty to maintain cognitive performance). The intensity and duration of fatigue can be transient and very variable in time, with fluctuations influenced by circumstances, or constant over a certain time, influenced by the state of the body at a certain time point.

Due to the difficulties to define fatigue and its unclear pathogenesis, it is also challenging to measure and quantify fatigue. Clinicians and researchers distinguish between perceived fatigue scored using standardized questionnaires, which describe the subjective sensation, and a more objective aspect of fatigue measured in fatigability, which can be compared to norm values of the general population (Kluger et al., 2013).

In this thesis, people with MS-related fatigue were the investigated study population two times. Therefore and because it's a consensus among patients and health professionals, I will here adopt the definition of the Multiple Sclerosis Council for Clinical Practice Guidelines (1998) which have defined fatigue as "a distressing, persistent, subjective sense of tiredness or exhaustion with a lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities" (p. 2).

After the data on the prevalence of fatigue and its causes, it is now necessary to give some insights into the experiences of people living with this symptom, to better understand the impact on everyday life and its quality.

Living with disease-related fatigue

Fatigue can be a major source of disablement and is often reported by patients as being among their most severe and distressing symptom (Elbers et al., 2014; Flechtner & Bottomley, 2003; Wijesuriya et al., 2012). Different authors (Flensner et al., 2008; Friedman et al., 2007; Turpin et al., 2018) have explored in depth the experiences of persons affected by disease-related fatigue, highlighting its devastating effect. A representative example for that is reported by Corbett et al., (2016, p.8): a person aged 53, 36 months posttreatment.

“Cancer was not the worst ordeal of my life. The diagnosis, the treatment, the surgery wasn’t debilitating- didn’t stop me from doing anything. But the fatigue does...”

No sphere of life, including daily activities, work, leisure and social activities are spared from the influence of fatigue. Activity and performance levels decrease undermining life roles and its trajectory. Fatigue elicits feelings of social isolation through being unable to participate in the surrounding world and feeling like an outsider, which affects personal interactions and relationships and one’s self-concept (Olsson et al., 2005; Omisakin & Ncama, 2011). In Turpin et al., (2018, p. 82), Lisa, a women with MS, summarized this experience as following:

“You can’t trust your body any more. You can’t trust your brain. So, it’s not like you can listen to your body and go, ‘oh, I need to rest’. I mean, you can within reason, but if I’d listened to my body for the last four years, I wouldn’t have left my house”

Besides the practical implications of the reduced performance and the sense of insufficiency, there is the invisible character of fatigue. For the affected, it is difficult to recognize and to understand this symptom and then to explain it to relatives, friends or colleagues. Individuals with fatigue report that a ‘medicalized’ self-identity is unavailable to them, in contrast to those impaired due to medically- and socially- legitimated illnesses (Pertl, Quigley, and Hevey 2014). In Hersche et al., (2019, p. 271) a young man who was diagnosed with MS two years ago, shared his difficulties to explain his main symptom with peers during a focus group:

“...I do not feel like explaining anymore and then I say: “google it”

Another issue is the limited support perceived by the health system and health professionals. Fatigue is often neglected as a target for treatment, perhaps because it typically appears unrelated to the severity of the central disease process (Dittner et al., 2004). People living with fatigue report the lack of efficient treatment options, and an insufficient knowledge and understanding from physicians and health professionals about the devastating effects of fatigue on

their daily lives and quality of life. A man aged 67, 7 months post-cancer treatment, expressed his experience in Corbett et al., (2016, p. 6) as following:

“You’re left lonely. You’re left not having that support that you thought that the doctor might be able to give you.”

Although this is only a brief and incomplete summary, it clearly emerges that the experience of living with fatigue has strong implications. Viewing illness and symptoms as controllable supports active coping, whereas perceptions that symptoms are uncontrollable and chronic have been found to be associated with avoidance and denial coping (Hagger & Orbell, 2003). An effective support to manage fatigue and its related tasks and consequences might therefore be an aspect that can support wellbeing in persons living with fatigue.

Before addressing effective patient education in fatigue management, I will contextualize this approach in a bigger framework of reference, highlighting its evolution and finally linking it to the occupational therapy (OT) practice.

Patient education an intervention for managing fatigue

According to Swain (2000), the management of fatigue has to be faced through a multidimensional and transdisciplinary approach, due to the multidimensional character and the complex interplay of biological and psychosocial factors, considering pharmacological and non-pharmacological treatment options. Their main approaches are patient education together with physical therapy and exercises training. While the aim of exercises training is to reduce the perceived fatigue and to reestablish the bases for a more active life style, through an adequate and regular physical activity, patient education trains how to manage the symptom and to adapt to its consequences, through behavior changes, in order to maintain employment, social participation and quality of life over time.

Self-management education

Until the 1960s, patient education was a unidirectional communication from the doctor to the patient, from which were not expected to participate actively in diagnose and treatment decisions or to ask any questions. The professional development of patient education as a discipline and its foundation in scientific research is relatively new (Hoving et al., 2010) and evolved from a merely knowledge transfer to a systematic approach based on psychological behavior research. The development of interventions became more systematic and theory-

based frameworks such as the Precede-Proceed model (Green & Kreuter, 1991), the social learning theory (Bandura, 1977) or the transtheoretical model of change (Norcross et al., 2011; Prochaska & Velicer, 1997) guided the intervention developers and the evaluation of developed treatments. Within the framework of this new scientific discourse, patient education became more participative and the concept of self-management education got central. The patient-centered approach (Rogers, 1979) and the concept of empowerment (Castro et al., 2016) had thereby a guiding function, conceding a more active role to participants in the definition of goals and the decision-making process (Omisakin & Ncama, 2011).

In health care, self-management refers to the individual's ability to manage the symptoms, treatment, physical and psychosocial consequences and the lifestyle changes inherent in living with a chronic condition (Barlow et al., 2002). That means to be in charge of one's life and managing one's condition, instead of being managed by that condition.

Self-management education consists in learning specific health-management skills and can, according to Lorig et al., (2003), be divided into three task categories. (1) The medical and behavioral management, which focuses on symptom reduction or adherence to treatment programs. Applied to fatigue that would mean, e.g. exercise, or sleep hygiene. These interventions are often part of physiotherapy or nursing and physician intervention. (2) The emotional management related to fatigue, addresses mainly thoughts, beliefs and behaviors, approached by cognitive behavior therapy and sometimes combined with relaxation exercise (e.g., mindfulness). Mainly psychologists or other experts (e.g., specialized nurses) provide these treatments. (3) The role management concerns coping with everyday tasks and duties. In the case of disease-related fatigue, OTs would teach the use of energy management strategies, (e.g., daily activity schedules, occupational balance or workload, and environment adaptation) to support the performance of routines and roles in favor of a more satisfying everyday-life.

Independent of the focus of the education, to become effective all learned self-management skills must be consistently, habitually, and correctly performed and integrated into existing routines.

Occupational therapy

Before confronting OT and persons with multiple sclerosis (pwMS), I wish I gave a short overview about this relatively new profession, by providing the main elements of its conceptual roots and developments over time. In the last part of the introduction of the thesis, I will focus on evidence-based OT interventions in pwMS-related fatigue and the knowledge gap in this field.

Herbert James Hall, MD (1870 -1923) was a pioneer in the systematic and organized study of occupation as therapy for persons with nervous and mental disorders in the early 20th century (Reed, 2005). His primary interest was neurasthenia³, a precursor of the modern term of fatigue. Hall believed that neurasthenia was not caused by overwork, but by fault living habits that could be corrected through an ordered life schedule and selected occupations. He has identified several principles of therapy that are still used today, including graded activity and energy conservation (Reed, 2005).

Over the decades, the OT practice evolved, and was influenced by the civil right movement and rights of persons with disability, and in exchange with many different disciplines and fields (e.g. rehabilitation, medicine, ergonomics, social sciences and psychology, occupational sciences) toward a new paradigm. Nowadays, occupational therapy is defined as a client-centered health profession concerned with promoting health and well-being through occupation (American & Occupational Therapy Association, 2014). The primary goal and core business of occupational therapy is to enable people to participate in the daily activities and to promote behavior changes in everyday life patterns and its determinant factors in favor of self-determination, well-being and health. The intervention consists of a combination of procedures: recovery of performance abilities through the use of meaningful occupations, teaching of strategies to improve or maintain life-role performance, training of self-management skills, or counselling of environmental modifications.

For the OT, like for other rehabilitation professions, the methods of evidence-based rehabilitation are a big chance to consolidate current practice with high quality research and to explore new areas of intervention or procedures, based on the integration of new knowledge. The evidence base is growing rapidly, but moving these findings into practice remains a substantial challenge (Thomas & Law, 2013).

³ Before 1860, there were no medical or scientific studies about the overwhelming feeling of tiredness and exhaustion. However at the beginning of the 20 century there are already hundreds of studies on muscle tiredness and fatigue as well as on 'nervous exhaustion', 'neurasthenia' etc., which were understood as diseases of energy – 'maladies de l'énergie' (Kesseling, 2013)

Occupational therapy in person with MS-related fatigue

Multiple sclerosis is a neurodegenerative disease characterized by demyelination, axonal loss, and inflammation of the central nervous system. In Switzerland, prevalence is estimated at 110/100,000 and incidence at 4–5.5 /100,000/year, resulting in 350-400 new diagnoses every year and 8000 persons living with MS (Pugliatti et al., 2006).

In 2017, the National Institute for Health and Care Excellence guidelines (NICE) has recommended for the management of fatigue in pwMS a multidisciplinary approach that involves exercise therapy, fatigue self-management education concurrent with medication therapy (table 1).

Table 1: Multidisciplinary approach to management of fatigue in persons with MS

Physical & sports therapy	Self-management education	Drugs
Strength training Endurance training	Energy conservation Activity balance Ergonomics Activities schedules Goal setting	e.g. Amantadine

The current body of evidence for fatigue self-management education is based on several clinical trials (Mathiowetz et al. 2005; Finlayson et al. 2011; Thomas et al. 2013; Mathiowetz et al. 2007; Thomas et al. 2013; Thomas et al. 2014;) and meta-analyses (Asano and Finlayson 2014; Blikman et al. 2013; Khan and Amatya 2017; Miller and Soundy 2017). The relevant studies are randomized clinical trials (crossover or parallel-arm design) with mostly small to medium study population sizes and with medium to high quality. The data reported on fatigue impact and health-related quality of life (HrQoL) show moderate to strong evidence in favor of an occupational therapy-based intervention combined with a cognitive behavior therapy approach, performed in peer-groups in an outpatient setting. By contrast, interventions provided in an individual interaction are less promising (Kos et al. 2016; Blikman et al. 2017). Typical characteristics of the manualized intervention are stable participant-groups with one session (1.5 - 2 hours) per week for four to six weeks. Every session addresses a specific topic and builds upon on the previous one. Participants try to apply the energy conservation strategies in their ecological environment and discuss their experiences in the following group session.

Despite the good efficacy of these studies, their limited external validity has prevented the implementation of these treatment protocols in Switzerland and other European countries. The intervention programs do not fit with the structure of healthcare in Switzerland, as pwMS here usually spend three to four weeks as inpatients in specialized rehabilitation centers yearly or biennially. During the rest of the year, they receive at best physiotherapy in the meantime, but have no access to specialized OT due to time, energy and availability constraints. Until 2017, no studies had been performed in an inpatient setting and no programs had focused on treating patients in dynamic group compositions over a shorter period (three weeks), but with higher frequency, which is necessary for successful implementation in the Swiss rehabilitation context. Information is missing on how such treatment characteristics influence the reduction of fatigue impact and quality of life and on the likelihood of implementing learned strategies in pwMS daily routine.

General aim

The primary goals of this thesis have been to explore the effectiveness of self-management education and to document the factors, which support successful patient education in persons with diseases-related fatigue. The intention on the long-term perspective was to facilitate the implementation of evidence-based practices in persons with any disease-related fatigue.

Specific aims

Such goals have been pursued by implement three studies, each with specific aims, corresponding research questions, and methods.

Study I aimed to develop a group-based Inpatient Energy Management Education (IEME) program for people with MS-related fatigue established on current evidence and to evaluate the experiences of 15 participants with MS and leading OTs during a pilot program.

Study II aimed to evaluate the feasibility of a randomized controlled trial and to investigate the effect size of IEME in four different outcome dimensions.

Study III aimed to systematically synthesize the effectiveness of fatigue self-management education (SME) on fatigue and quality of life (QoL) in persons with disease-related fatigue, and to describe the intervention characteristics.

Methods

The following section gives an overview of the different methods, which we have applied in the three studies comprised in the thesis (tab. 2).

Study I was characterized by the use of a qualitative research method. In a first phase, we explored the actual literature and developed the IEME, and in phase two we collected the experiences of OTs who delivered it and pwMS participating on IEME-sessions. In Study II we used a mix method approach, collecting quantitative and qualitative data during a small randomized clinical trial. Study I and II are highly related to each other and were part of the same research project. The findings and new questions arisen from the conclusions of Study I and II have induced us to perform, in Study III, a systematic literature review to gain a new and comprehensive overview. We have identified, a pool of self-management educations and documented their effectiveness on fatigue and quality of life for persons with any disease-related fatigue, and summarized the intervention characteristics systematically.

Table 2: Overview of the method of the three studies comprised in the thesis

	Study I	Study II	Study III
Study design	Phase 1: Development based on literature research Phase 2: Pilot study, qualitative method	Feasibility study with single-blinded randomized controlled trial, mixed methods	Systematic literature review, best evidence synthesis methods
Settings / Database	3-week inpatient rehabilitation at the Rehabilitation Centre Valens	3-week inpatient rehabilitation at the Rehabilitation Centre Valens	MEDLINE, CINAHL, PsycINFO and Scopus electronic database
Participants / Sample	OTs trained in IEME (n = 3) Adults with confirmed diagnosis of MS, experience of fatigue, moderate level of disability, no cognitive impairment (n = 15)	Adults with confirmed diagnosis of MS, experience of fatigue, moderate level of disability, no cognitive impairment, no major depression (n = 47)	Randomized clinical trial investigating the effect of self-management education interventions on fatigue and HrQoL in people with assessed fatigue. 26 RCT (n = 3526)
Interventions	Training course for OTs in leading IEME-sessions 3-week IEME + care as usual for persons with MS	<i>Experimental group:</i> IEME + care as usual <i>Control group:</i> PMR +care as usual	NA
Experiences / Assessment / Data extraction	<i>Experiences addressed during focus groups</i> with IEME-participants: - IEME material, content, session structure - The group - Self-reflection and competence acquisition - Behavioral change - Needed changes with IEME-leading OTs: - Preliminary training course - IEME materials, content, session structure - Needed changes	<i>Assessment:</i> - Process quality - Treatment fidelity - Patient satisfaction - Amount of OT-treatment minutes - Estimate of treatment effect size (fatigue impact, occupational performance, HrQoL, self-efficacy)	<i>Data extraction:</i> - Study characteristics - Sample characteristics - Intervention characteristics - Intervention focus - Behavior change techniques applied - Effect on fatigue impact and HrQoL measurement (means, SD, effect size, p-value)
Sampling	Maximum variety sampling (OTs) Convenience sampling (pwMS)	Random sampling with block randomization based on computerized random number generation.	NA
Data analysis / Statistic methods	Content analysis	Description of synthesized data. T-tests for change over time within and between-groups. Cohen's d. as standardized measure of effect size	Narrative description of synthesized data. Effect on HrQoL computed with Cohen's d.

Abbreviations: IEME: Inpatient Energy Management Education, MS: multiple sclerosis, pwMS: persons with multiple sclerosis OT: Occupational therapist, PMR: Progressive muscle relaxation, HrQoL: Health related quality of life, RCT: randomized controlled trial, SD: standard deviation, NA: not applicable

Chapter 2

Development and Preliminary Evaluation of a 3-Week Inpatient Energy Management Education Program for People with Multiple Sclerosis–Related Fatigue

Hersche, R., Weise, A., Michel, G., Kesselring, J., Barbero, M., & Kool, J. (2019).

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Development and Preliminary Evaluation of a 3-Week Inpatient Energy Management Education Program for People with Multiple Sclerosis–Related Fatigue

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Marco Barbero, PhD; Jan Kool, PhD

Background: Energy conservation strategies and cognitive behavioral therapy techniques are valid parts of outpatient fatigue management education in people with multiple sclerosis (MS). In many European countries, multidisciplinary rehabilitation for people with MS is chiefly delivered in specialized rehabilitation centers, where they benefit from short intensive inpatient rehabilitation annually. However, no evidence-based and standardized fatigue management education program compatible with the inpatient setting is available.

Methods: Based on a literature search and the expertise of occupational therapists (OTs), a manualized group-based Inpatient Energy Management Education (IEME) program for use during 3-week inpatient rehabilitation that incorporates energy conservation and cognitive behavioral management approaches was developed. An IEME pilot program operated by trained OTs included 13 people with MS-related fatigue. The experiences of the IEME users and OTs were collected during focus groups to refine the program's materials and verify its feasibility in the inpatient setting.

Results: The program was feasible in an inpatient setting and met the needs of the people with MS. Targeted behaviors were taught to all participants in a clinical context. In-charge OTs were able to effect behavioral change through IEME.

Conclusions: Users evaluated the evidence-based IEME program positively. The topics, supporting materials, and self-training tasks are useful for the promotion and facilitation of behavioral change. The next step is a clinical trial to investigate the efficacy of IEME and to evaluate relevant changes in self-efficacy, fatigue impact, and quality of life after patients return home. *Int J MS Care*. 2019;21:265-274.

Multiple sclerosis (MS) is an inflammatory demyelinating and degenerative disease of the central nervous system that is considered one of the most frequent causes of disability in young adults.¹ Fatigue is a common symptom for people with MS, affecting almost 90% of this population. Furthermore, two-thirds of people with MS describe fatigue as

their most disturbing symptom.² The Multiple Sclerosis Council for Clinical Practice Guidelines declared in a multidisciplinary consensus definition that fatigue is “a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities.”^{3(p2)} Primary fatigue refers to fatigue in the absence of an apparent cause and is specific

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to MS, whereas secondary fatigue is a consequence of other concomitant conditions (eg, psychological disturbances, musculoskeletal problems, sleep disorders, or medication adverse effects) that may be related to MS as well as to other diseases.⁴ The pathophysiology of primary fatigue in MS is highly complex and, so far, not completely understood.⁵ Fatigue related to MS limits participation in everyday activities⁶ and has a major effect on quality of life, affecting productivity and employment.⁷

National Institute for Health and Care Excellence guidelines⁸ recommend a multidisciplinary approach for the management of fatigue that involves exercise therapy, self-management, and education concurrent with medication therapy. To date pharmacologic treatments do not produce desired effects, whereas rehabilitation strategies provide a better effect and are first-line treatments.⁹ Two meta-analyses^{9,10} provide moderate-to-strong evidence that fatigue management education affects the impact fatigue has on occupational performance and quality of life. These treatment protocols¹¹⁻¹⁴ are based on work by Packer et al¹⁵ and integrate both energy conservation strategies and cognitive behavioral therapy (CBT) techniques, taking place in outpatient group settings with 6 to 12 peer participants. Six sessions (± 2 hours per week, ± 12 hours total) follow a hierarchical order and support the development of activity patterns to reduce fatigue through a methodical analysis of working tasks and household and leisure activities in all relevant settings. To support the acquisition of new skills and the formulation of new behavior goals, an occupational therapist (OT) provides information and stimulates discussion and exchange between course participants through guiding questions and activity involvement. Homework assignments are used to apply energy conservation strategies and to implement behavioral change.

In Switzerland and other European countries, multidisciplinary rehabilitation for people with MS is widely used in specialized rehabilitation centers. People with MS benefit from intensive inpatient rehabilitation (2-4 weeks) annually, but there is still a lack of evidence that traditional multidisciplinary inpatient rehabilitation can significantly improve fatigue management in people with MS.¹⁶ During the rest of the year, people with MS maintain their normal lifestyle, which includes job, family life, and social and leisure activities. Some patients receive physiotherapy, but currently no specialized fatigue management is offered. Outpatient protocols are

different from typical multidisciplinary and intensive inpatient rehabilitation. Hence, there is a barrier to the transfer of knowledge. Other barriers are the lack of trained OTs, organizational constraints of rehabilitation centers, and the need for culturally appropriate translation of relevant educational materials. Centers that regularly treat people with MS have a need for a standardized and evidence-based fatigue education program compatible with an inpatient setting that maintains the principal components of the outpatient program (eg, main topics, reinforcing effect of peers, principals of patient education, empowerment, and change management).

To adapt fatigue management education from an outpatient to an inpatient setting, four conditions must be met. 1) The duration must be reduced from 6 to 3 weeks, with increased frequency. 2) It must be feasible with a dynamic group composition in that continuous enrollment and discharge of people with MS may occur on any day of the week. 3) Self-training tasks must be redesigned because patient activities are different during rehabilitation. 4) Learned lessons and target behaviors must be transferred from the clinic to the home setting.

The first aim of this study was to develop a group-based Inpatient Energy Management Education (IEME) program for people with MS-related fatigue based on current evidence. The second aim was to complete a pilot program with 10 to 15 people with MS to evaluate OT and participant experiences.

Methods

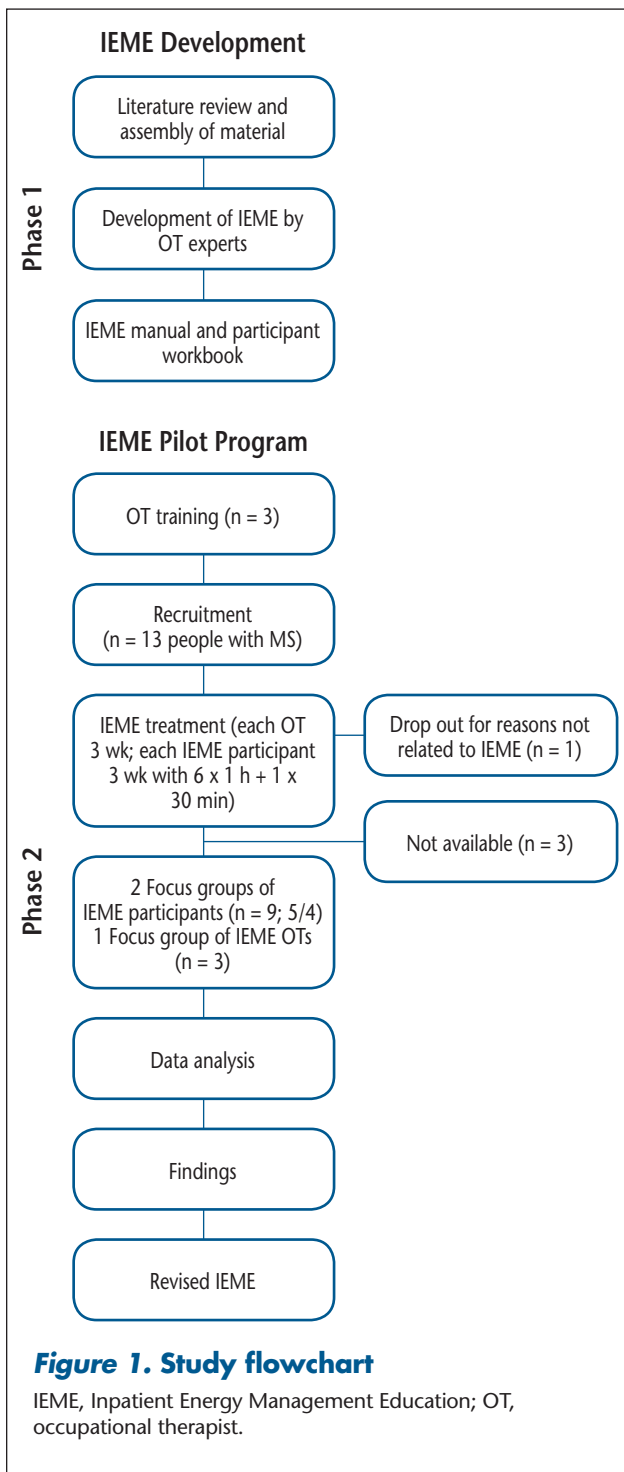
Design

A qualitative research method based on focus group discussions was used.¹⁷ The study flowchart in Figure 1 shows the development and the pilot program phase. Ethical approval was obtained from the local research ethics committee (Ethikkommission Ostschweiz). The study was prospectively registered (German Clinical Trials Register at drks.de; ID: DRKS00011634).

Phase 1: Development of the IEME Program

Literature Review and Assembly of Materials

The aims were as follows. 1) Obtain overview knowledge of clinical trials that included energy conservation strategies, CBT approaches, and fatigue management education interventions for people with MS-related fatigue. 2) Identify user evaluation studies of fatigue management education. 3) Prepare manuals of fatigue management education protocols and materials



appropriate for people with MS. We searched MEDLINE, Embase (Ovid), the Cumulative Index to Nursing and Allied Health Literature (CINAHL [EBSCO]), peer-reviewed reviews¹⁸ and meta-analyses updated to 2014,^{9,10} and clinical studies from 2014 to 2016.^{19,20} Search terms included *multiple sclerosis, fatigue management education, energy conservation, cognitive behavioral therapy, self-management, randomized clinical trials, effica-*

cy, effectiveness, and user experience. Intervention settings, topics, work materials, and intervention techniques were extracted from selected studies. Authors and experts in the field were contacted directly for more detailed information about intervention content and techniques. Actual practice guidelines,^{8,21} books,^{22,23} websites from national and international OT and MS associations,²⁴ and information booklets about fatigue management education were consulted. Two of us (R.H. and A.W.) reviewed the collected materials and classified them by strength of evidence,²⁵ topic, relevance, and affinity with the principles of patient education, empowerment, behavioral change focus, human occupation, and energy conservation.

Development of Intervention by OT Experts

Two OT experts (R.H. and A.W.) with 15 years of experience in neurorehabilitation and MS care in both inpatient and outpatient settings led the intervention development. Representative intervention protocols for energy conservation strategies^{15,26} and CBT approaches^{20,27} identified in the literature were used for development of the IEME program. Recommendations in published studies for intervention evaluation and user experience assessment²⁸⁻³⁰ were considered and included where applicable. The process during the development stage was a circular process, contaminated by the exchange of experiences and the integration of knowledge accumulated during the literature review.

IEME Manual and Participant Workbook

Integrated knowledge and materials from the literature review along with the expertise of two of us (R.H. and A.W.) were used in creating the IEME OT manual and the participant workbook. The IEME program incorporates the typical features of fatigue management education derived from previous studies, including 1) group interventions, 2) topics and content, 3) self-learning tasks between lessons, and 4) individual goal setting and the integration of recommendations. During editing of the IEME materials, didactic principles for adult education,³¹ principles of patient education,³² user-friendliness, and practical aspects were considered.

Phase 2: IEME Pilot Program

Training for OTs

After completion of the IEME manual and workbook, three OTs from the Rehabilitation Centre Valens (Valens, Switzerland) were chosen for the IEME introduction day and the pilot program. The selection was

purposefully heterogeneous (maximum variety sampling) regarding aspects such as age, work experience, educational level, and country of education. Two of us (R.H. and A.W.) taught the course together. The purpose was to transmit the underlying concepts and to provide the OTs with the opportunity to simulate activities, role-play, and increase their skills in group management and moderation. Direct OT feedback and critical reflections about content, clarity, and teaching methods were noted when training was complete. These notes were considered for development of the focus group interview guidelines for the IEME pilot program participants and the OTs.

Setting and Participants

The aim was to include 10 to 15 people with MS in a 9-week pilot program to guarantee that every OT and participant completed the education program at least once. The Rehabilitation Centre Valens is specialized in neurologic rehabilitation, and approximately 400 inpatients with MS are treated every year. People with MS who were on the waiting list for a 3-week rehabilitation at the center from March until May 2017 and who fulfilled the inclusion criteria (>18 years of age, confirmed diagnosis of MS according to the McDonald criteria,³³ Fatigue Severity Scale³⁴ score ≥ 4 , and Expanded Disability Status Scale³⁵ score ≤ 6.5) were informed by mail about the study. A few days before admission they were contacted by phone to verify additional inclusion criteria (literacy in German, agreement to attend the IEME lessons during rehabilitation) and exclusion criteria (telephone Mini-Mental Status Examination³⁶ score <21, Beck Depression Inventory–fast screening³⁷ score >4) and to answer any questions. Thirteen people with MS were recruited for the IEME pilot program. Informed consent was provided by each.

IEME and Multidisciplinary Rehabilitation

People with MS participated in six IEME lessons, each lasting 1 hour. The IEME was part of the multidisciplinary rehabilitation program in the center, which is a combination of 2- to 3-hour therapeutic interventions per day in individual and group settings. This individualized and goal-oriented program included physiotherapy (endurance and reinforcement training), occupational therapy (ability and adaptation training), speech therapy, neuropsychological training, and medical and social counseling as needed. At the end of the 9-week pilot program, 12 IEME participants completed

the program. One person dropped out after two lessons for administrative reasons unrelated to IEME (Figure 1).

Focus Groups

The methodological approach chosen for the focus groups was based on that of Krüger and Casey,¹⁷ with R.H. in the role of moderator and A.W. participating as co-moderator. The interview guideline for people with MS focused on IEME content and comprehensibility, organization, behavioral change, group as intervention format, and possible improvements; with the OTs, the IEME training day was also discussed. For the focus groups with IEME participants, two dates were purposefully chosen to grantee a maximum of experience with IEME in a sample as large as possible. All IEME participants present in the center on these 2 days (five in April and four in May) agreed to participate in the group discussions. The participants knew that R.H. and A.W. had developed the IEME. The focus group with the three IEME OTs took place at the end of the pilot program (May). At the first IEME session, people with MS and OTs were asked to take notes in their manual whenever they found something disturbing, irrelevant, or improbable. Focus group participants were asked to consider their notes before the start of the discussion. The OTs kept record sheets during the training and the IEME pilot program. The interview guidelines for the focus groups were devised to collect participant and OT suggestions for improvements of IEME. The three focus groups took place at the center in a quiet meeting room without the presence of nonparticipants or disturbances. All the group interviews were audio recorded. As co-moderator, A.W. took field notes that summarized the main arguments at the end of every discussion. R.H. and A.W. had a debriefing immediately after each focus group. The first participant group discussion lasted nearly 60 minutes, and the OT group discussion a few minutes more. The second participant group discussion lasted just longer than 50 minutes.

Data Analysis

The focus groups (two for IEME participants and one for IEME OTs) were transcribed verbatim based on the audio recordings. In addition to the transcript, the co-moderator's notes, the member check summaries, and the debriefing notes were part of the analysis process. A content analysis was performed using open and axial coding to explore and systematically organize the data into a structured format.³⁸

Results

Phase 1: IEME Development

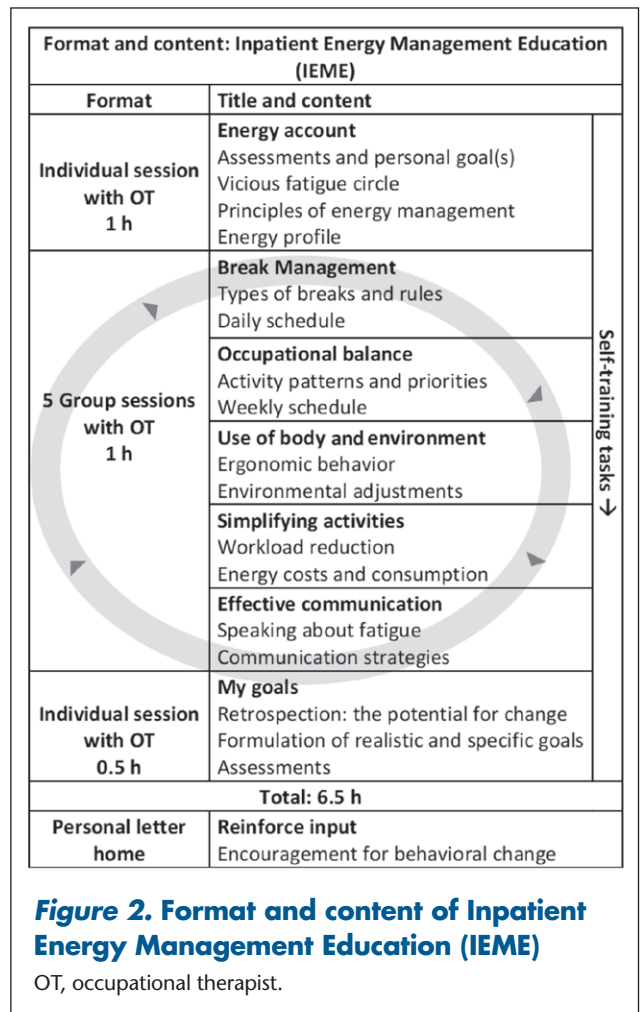
The underlying concepts of IEME are the principles of patient education³⁹ and empowerment,⁴⁰ the trans-theoretical model with its stages of change,⁴¹ self-efficacy theories,⁴² theoretical basis and specific knowledge of the OT discipline,^{21,43,44} and the techniques of behavior change.^{45,46}

Format

The complete education program is 6.5 hours in duration and is conducted by a trained OT over a 3-week period. The IEME starts on the first day after admission with an individual lesson, followed by five 1-hour IEME group sessions delivered continuously on two fixed days per week, and concludes with an individual session (0.5 hour). The order in which an individual attends the group sessions is flexible because they are self-contained units. Between each lesson, participants are instructed to complete specific self-training assignments. Six weeks after returning home, participants receive a reinforcement in the form of a letter/e-mail.

Content and Materials

The content and structure of IEME are shown in Figure 2. The IEME treatment protocol is described in the manual, which consists of an introduction with relevant information about the underlying concepts of IEME as well as a detailed description of every session. The workbook for participants accompanies the program. It includes detailed information on all the topics, all worksheets for the lessons, and for the time after hospitalization both self-training and appropriate additional information. Each IEME lesson is deliberately structured such that all stages of change can be addressed and supported. Knowledge available in the group is shared during each session, but the focus is on reflection and exchange within the group, individual analysis and formulation of goals, and the acquisition of new skills. Self-training served as practice for new behavior patterns, which depend on the need and stage of the person, deepened reflection, and knowledge of specific topics. Based on the taxonomy of behavior change techniques,⁴⁶ the IEME used primarily knowledge, social support, feedback, monitoring, behavior and outcome comparisons, goals and action planning, antecedents, self-belief, repetition, and substitution as techniques that supported behavior change in the participants.



Phase 2: Pilot Program

IEME Treatment

Between March and June 2017, every OT guided every part of the IEME program at least once. In total, they completed 24 individual and 15 group sessions. Based on the record sheets, the OTs reported high treatment fidelity, with the completion of 83% of all described tasks in the manual.

Focus Group with IEME Participants

The IEME participants in the rehabilitation program were heterogeneous regarding age, sex, MS onset, and educational level (Table 1). Four main topics emerged from discussions. 1) IEME is described as a new therapeutic experience tailored to the needs of people with MS with related fatigue. The format and content are judged as an ideal framework for dealing with symptoms of fatigue, learning about effective behavioral strategies, and increasing a sense of personal control. Participants suggested that during the session “effective communi-

Table 1. Characteristics of focus group participants

Characteristic	Value
People with MS (n = 9)	
Sex, F:M	5:4
Age, y	45/51 (32-56)
Time since MS diagnosis, y	11/8.5 (3-25)
Cohabitation, yes/no	6/3
Education	
Lower secondary level	1
Upper secondary level	4
Tertiary level	4
Occupational therapists (n = 3)	
Sex, F:M	3:0
Age, y	23, 25, 44
Time since certification, y	0, 3, 14
Nation of certification	Switzerland/Switzerland/ Netherlands
Level of certification: diploma:BSc	1:2
Occupational therapy experience, y	0, 3, 13

Note: Values are given as number or mean/median (range).
Abbreviation: MS, multiple sclerosis.

cation” and more structured guidance for role-playing would be useful. 2) The group setting, with its open exchange and peer support, was perceived as an important incentive that contributed to a more profound reflection on daily routines, reinforcing the use of energy conservation strategies. Even participants with many symptoms and educational experience found something valuable and were reassured in their approach and direction. 3) Self-reflection and competence acquisition as main goals of IEME were recognized as meaningful. The activities during the sessions and the self-training tasks allowed an in-depth individualized approach. 4) Behavioral change is the long-term goal of IEME. At the time of the focus groups, participants had positively experienced the effects of inpatient energy conservation strategies but had not experienced those in real-life situations. The confidence of the IEME participants in their capacity to transfer new knowledge and maintain behavioral change over time during their daily routine was unstable (Table 2).

Focus Group with IEME OTs

The three OTs who have been trained and have led the IEME pilot program were heterogeneous regarding age, OT practice, and experience in the care of people with MS (Table 1).

The discussion can be summarized in four main topics. 1) OT education day: The IEME-led training was

rated positively and was appropriate for all OTs. Communication skills for group discussion management should be improved. Group training for fatigue management, the principles of patient education, and the stages of behavioral change were somewhat new to the OTs but were communicated well. All the OTs wanted more time during the introduction to practice skills, for example, group moderation. 2) The IEME format: The structure of the IEME program, with its self-contained units, could be easily integrated into an inpatient setting. The content and time frame of the sessions were realistic and feasible. All relevant aspects for handling symptoms were addressed and covered by group tasks and self-training. Group cohesiveness increased despite a constant change in member composition. 3) The role of OTs: Leading IEME requires a high level of mental presence, content knowledge, flexibility, and creativity. Depending on the group constellation, open exchange and deeper reflection are more or less easy to achieve. For all the OTs, the therapy sessions were a personal and professional enrichment. 4) Improvements needed: For the OTs, the IEME does not require any significant structural or substantive change. Only for the lesson “effective communication” was a different sequence suggested, and concrete recommendations were provided. Furthermore, ideas for minor optimizations could be collected, such as a clearer distinction between training tasks to perform during rehabilitation from those more related to transfer in the home setting. The OTs identified a need to share the principles of energy management with multidisciplinary teams to ensure coherent patient communication during rehabilitation.

Discussion

The IEME program was developed based on evidence-based literature. For that reason, the course addresses similar issues and is based on the same principles as outpatient programs. Nevertheless, note that IEME takes 6.5 hours instead of ±12 hours and is performed in a different context.

We trained three OTs in IEME execution and included 12 patients with MS with related fatigue in a pilot program. The user experience was positive, and the six sessions were feasible within a 3-week inpatient rehabilitation stay. The IEME was well received, and attendance was high. For some patients, it was the first time they had received specific information about fatigue management, whereas others had previous experiences

Table 2. Findings with illustrative quotations for the nine IEME focus group participants

Main topic/subthemes	Examples
IEME: a new therapeutic experience	
Organization and structure	<p>"...for me the time was perfect, at 10:00 o'clock, then it goes 1 hour, and then I hope we have lunch." (P3)</p> <p>"Four, five, or six is a good group size. I would not make it much bigger." (P7)</p> <p>"It [self-training] was versatile and not so time-consuming. We still had 3-4 days in between, so it is feasible." (P9)</p>
Materials	<p>"It [the workbook] is very broad and valuable, I think. I will certainly pick it up again when I'm at home." (P5)</p> <p>"I can take the workbook with me and put it somewhere in the kitchen drawer ... that I know that I can take sometimes, open it ... that's a good thing, that you can orientate yourself at home." (P4)</p>
Content	<p>"The lessons are very different. A broad spectrum. All the points that are up to date have been hit." (P1)</p> <p>Contents that were spontaneously remembered during the focus groups: Bring structure into everyday life, adapt communication to others, determine energy levels through self-perception, weekly schedule, dividing up energy, goal formulation</p> <p>Session effective communication:</p> <p>"Do it [role-play] differently, I like it but maybe with more structure." (P1)</p> <p>"Well, I would rather say that you have to do it differently." (P4)</p> <p>"Talking about it (how to communicate) is not easy but still important." (P2)</p>
Appropriateness	"It is also written clearly, it is understandable. It is not a doctor's language. It is well explained." (P6)
Meeting needs	<p>"I think I'll do it [IEME] again during my next inpatient rehab, especially to hear the others ..." (P8)</p> <p>"It was very good, because I got the diagnosis 3 years ago, and in these 3 years I did not experience as much as in these lessons." (P2)</p> <p>"Fatigue is a tacit topic, but it's very up to date for me." (P3)</p>
The group setting	
Exchange	<p>"We had a deepened exchange, we could hear that it is similar for others, you are not alone in everyday life." (P6)</p> <p>"She [group member] has been very open and also, he [group member] has been honest." (P2)</p>
Peer support	<p>"...they [group member] did it in that way and now I do it that way that helped me a lot." (P9)</p> <p>"I already knew a lot, but it was still interesting because I could help others." (P1)</p>
Self-reflection and competence acquisition	
Activities during the lesson	<p>"Everything has been discussed in great detail, I was amazed how it got into the subject." (P7)</p> <p>"I realized that what I put on paper is better in my head than what I'm saying, and if I do not remember I can take out the book and I read the first row and then I say 'Ah ok' and I can try again." (P7)</p> <p>"She [group member] played really realistic [role-play]. Because it is exactly the same problem for me when I do not feel like explaining anymore and then I say: 'Google it' [fatigue]." (P2)</p>
Self-training	"I found it generally valuable to reflect again. For some [tasks] I said to myself 'Ok, I have it under control.' I do not have to work on it for much longer. For others, I started to write." (P7)
Problem analysis	<p>"I have found out more in detail where the problems are." (P8)</p> <p>"I will still look for the one-to-one interview [at the end] to work up even better, there are certain things stuck." (P6)</p>
Self-reflection	<p>"I've met people here with MS who have the chronic progressive form, and I've just relapsing, and I'm as good as you can see. She is in a wheelchair, someone cannot walk so well, he is tired, she runs weird, I walk normally, so I'm the least bad, but all of them have found a way to manage with everyday life." (P2)</p> <p>"I wonder how other people manage this for 15 years and I cannot make it 3 years, that [fatigue] annoys me so much." (P5)</p>
Self-awareness	<p>"Focus on ourselves in terms of energy and the relationship between energy and fatigue." (P7)</p> <p>"I felt that was very important because I got able to analyze myself ... and why it is the way it is and what can I do different." (P3)</p>
Behavioral change	
Barriers	<p>"There is still a big question mark for me, because after [returning home] no one is there and says 'Did you think of that? Have you done it?' I realize that it is still a difficulty for me at this moment." (P1)</p> <p>"I still find it [behavior change] difficult for me, the transfer, because here I'm in a protected context." (P4)</p>
Behavioral strategies	"I noticed it [change in energy profile] because I wrote it in my plan and I wrote my break the same day, and I really realized that it worked." (P9)

Abbreviations: IEME, Inpatient Energy Management Education; MS, multiple sclerosis; P, participant.

with energy conservation information. All the participants highly valued peer interaction, the exchange of ideas, and deep reflection based on focus group transcripts. All the developed materials and tasks were easy to understand and were considered useful for the future. The IEME, with its circular frame, was integrated without problem into the regular rehabilitation program with no drastic structural or substantive changes.

The present findings are in line with data from outpatient courses, which reported similar user experiences and opinions despite the structural and contextual differences.²⁸⁻³⁰ Thanks to the reported critical aspects from outpatient programs^{28,47} (worksheets in disorder, unclear instructions, unfocused lessons), we were able to improve IEME during the development phase. Indeed, IEME participants emphasized their satisfaction with the well-structured workbook and the goal-oriented lessons. Another important difference between IEME and outpatient courses is that participants implement energy conservation strategies in an environment in which they do not have routines. This can be an advantage because they do not need to modify their habits and are freer to verify the potential effects of energy conservation strategies. In contrast, rehabilitation has a prefixed time schedule that is artificial and dissimilar to real life. For that reason, we created two types of self-training tasks. The first type refers to the inpatient environment with specific tasks that are easy to train (eg, ergonomic postures during sitting activities); the second type stimulates the participants to reflect on useful behavioral changes in their own life situations (eg, arrangement of activity stations). They are asked to formulate concrete plans and to imagine solutions.

Although positive experiences and empowerments were perceived with IEME, a preoccupation of IEME participants was their capacity to maintain and consolidate desired changes after returning home. Participants were concerned about their self-efficacy and their ability to overcome barriers during implementation. Hence, it was important to reduce their anxiety and provide support. Bandura⁴² suggested four ways to increase self-efficacy: 1) learn how to manage stress and anxiety when performing a new task, 2) experience success in overcoming obstacles, 3) observe peers being successful, and 4) be persuaded by others that you can perform a required task. The results of the focus groups confirm that IEME participants used successful energy conservation strategies during the self-task training. They shared

their experiences at the beginning of every group session and received encouragement from peers and the OT. To reinforce the management of stress, OTs should refer repeatedly to the aim of the individual session and especially the importance of setting concrete and realistic goals. In addition, the challenge of transfer should be emphasized in the workbook, as well as the relationships among self-training, skills acquisition, and the facilitated transfer of energy conservation strategies. Visual cues in the workbook would help to identify those self-training tasks meant to facilitate the transfer of new skills and strategies into an everyday context. A digital version of the workbook with facilitated access, customizable outputs, and an energy profile application would be useful for future development (eg, assistive devices and audiobooks could reduce obstacles and increase self-efficacy). An internet platform that provides boosters and supplemental information would maintain and build a supportive community, which would support self-management and reduce concerns about implementation.^{48,49} One-to-one OT sessions after the return home would be useful for those still in a preparative stage of change, and they have been shown to be valuable.⁵⁰

This study has shown that three OTs with different experience in MS care were able to execute IEME after 1 day of education. The manual is a practical and helpful instrument and supports OTs in their complex task of managing interactions and the needs of people with MS. They suggested an increase in typical situation simulations and the practice of moderating skills during the training day. Based on that, future OT education will be for 2 days, with more time to discuss underlying concepts such as self-efficacy, the transtheoretical model, and the practice of motivational interviewing.⁵¹

This study has some limitations. All the focus group participants and OTs were aware that the facilitators of the focus groups were also the IEME developers. However, the validity of results was supported by the provocative questions included in the interview guidelines, the field notes and comments from the focus groups, the completed workbooks, and the member check at the end of each focus group. Currently, we do not have data on the long-term effectiveness of the program. Because this was a pilot, the sample size of 12 participants and three OTs was small. The chosen method allowed gathering suggestions and exploring experiences but did not allow for conclusions regarding the strength of the interven-

tion, modifying variables such as self-efficacy, or outcomes such as Modified Fatigue Impact Scale score.

The strengths of the IEME program are that it is based on previous studies and evidence-based treatment protocols, integrates actual knowledge from patient education, empowers participants, and changes behavior. It addresses people with MS-related fatigue during a short inpatient rehabilitation period and provides 6.5 hours in which to gain knowledge, acquire new skills, and receive support through intensive peer exchange. After the first session, participants trained targeted behaviors in a clinical context, and at the last session they formulated goals related to behavior change in daily life. Further research should verify the possible role and benefit of trained peers during IEME and after discharge,⁵² and the real effect of IEME on self-efficacy, fatigue, and quality of life should be assessed after return home. Efficacy should be compared with that of other management interventions in a randomized clinical trial.

In conclusion, this study has shown the feasibility of the IEME program in an inpatient setting and the value that participants attribute to peer exchange. The group intervention with peers is a powerful element in health promotion and is considered a key aspect in the self-management of people with chronic diseases.⁵² For this reason, health professionals and rehabilitation institutions should make an effort to guarantee patients the benefit of well-designed group therapies, even if this is an organizational challenge. Based on the findings of this study and the developed materials (OT training concept, manual, and workbook), it is possible for other rehabilitation centers to implement inpatient education for people with MS-related fatigue and to support an effective knowledge transfer into practice, making sure to share the principles of IEME with multidisciplinary teams to support behavioral change. □

PRACTICE POINTS

- We developed the Inpatient Energy Management Education (IEME) program for the management of MS fatigue during inpatient rehabilitation stays.
- In a pilot study, the IEME program was feasible, participant satisfaction was high, and behavioral changes were reported.
- Currently, no information about the efficacy of IEME after patients return home is available.

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Chapter 3

Three-week inpatient energy management education for persons with multiple sclerosis-related fatigue: Feasibility of a randomized clinical trial

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Three-week inpatient energy management education (IEME) for persons with multiple sclerosis-related fatigue: Feasibility of a randomized clinical trial

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ABSTRACT

Background: Multiple sclerosis (MS)-related fatigue limits participation in everyday activities and has a considerable impact on quality of life (QoL), thereby affecting productivity and employment. Outpatient education interventions involving energy conservation strategies and cognitive behavioral therapy techniques are helpful. However, no inpatient program is currently available. The inpatient energy management education (IEME) program is a novel group-based intervention that lasts for 6.5 h and is conducted by a trained occupational therapist (OT) during a 3-week period of inpatient rehabilitation. Persons with MS (pwMS) and OTs previously evaluated the IEME positively in a pilot study test run. The aim of this study was to evaluate the feasibility of a research protocol and collect preliminary data on the IEME effect size.

Methods: To assess the feasibility of conducting a randomized clinical trial, pwMS-related fatigue were recruited during a 3-week inpatient rehabilitation. Six IEME (experimental) group sessions or progressive muscle relaxation (PMR, control) group sessions comprised part of a personalized rehabilitation program. The recruitment and assessment procedures, dropout and follow-up assessment rates and the treatment fidelity were evaluated, and six telephone interviews were conducted with IEME participants after they returned home. Outcomes were fatigue impact, occupational performance, self-efficacy regarding energy conservation strategies, and QoL at baseline, discharge, and 4 months. Paired-sample and independent-samples *t*-tests were used to assess within- and between-group effects. Effect sizes were estimated using Cohen's *d*.

Results: Between August and November 2017, 47 pwMS were included and randomized. The dropout rate (4.2%) was low and the sample was balanced. The PMR was a well-accepted control intervention. The OTs reported no problems in conducting the IEME, and treatment fidelity was high. IEME participants confirmed the adequacy of the IEME. Within-group differences in fatigue impact and some QoL dimensions at discharge were significant ($p < 0.05$) in both groups. The IEME alone resulted in significant improvements in self-efficacy regarding energy conservation strategies, with a large effect size (Cohen's *d*: 1.32; 95% CI: 0.54–2.1), and in the QoL physical functioning dimension at T2 (Cohen's *d*: 1.32; 95% CI: 2.11–0.53). IEME participants spent significantly less time in individual OT sessions. A sample size of 192 participants in a randomized controlled trial would be sufficient to detect clinically relevant between-group differences.

Conclusion: This feasibility study has provided promising preliminary data about the effect of the IEME. The research protocol was confirmed to be feasible and a future study is justified. This study was registered in the German Clinical Trials Register (no. DRKS00011634).

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1. Introduction

Fatigue is one of the most common symptoms in persons with multiple sclerosis (pwMS) (Compston and Coles, 2008). Among such individuals, 65% consider it one of their three most troubling symptoms (Weiland et al., 2015). MS-related fatigue limits participation in everyday activities (Krupp, 2006) and has a considerable impact on quality of life (QoL), thereby affecting productivity and employment (Flensner et al., 2008). The National Institute for Health and Care Excellence guidelines (NICE, 2014) recommend a multidisciplinary approach for the management of fatigue, involving concurrent exercise therapy, self-management, and education, along with medication. The use of energy conservation strategies and cognitive behavioral therapy (CBT) techniques as part of a manualized outpatient group-based intervention has been shown to be moderately helpful (Asano and Finlayson, 2014; Blikman et al., 2013).

In many European countries, multidisciplinary rehabilitation for pwMS is delivered in specialized rehabilitation centers, where pwMS benefit from short intensive inpatient rehabilitation. The evidence-based outpatient education protocols (Thomas et al., 2013; Mathiowetz et al., 2005) are not compatible with the inpatient context as, in this context, it is usually impossible to create stable education groups over several weeks. Currently, it is still difficult to provide standardized group-based fatigue management education during short intensive inpatient rehabilitation courses. For this reason, we developed an inpatient energy management education (IEME) program (Hersche et al., 2019), integrating the principles of patient education (Lorig and Holman, 2003) and empowerment (Castro et al., 2016), the trans-theoretical model of change (Norcross et al., 2011), the social cognitive theory (Bandura, 1977), and energy conservation strategies and cognitive behavioral techniques (Michie et al., 2013). The IEME is 6.5 h in duration and was conducted by a trained occupational therapist (OT) over a 3-week period.

An IEME pilot in 2017 included 12 pwMS-related fatigue (Hersche et al., 2019). The experiences of the IEME participants and OTs were recorded during focus groups to refine the program materials and to verify the program's feasibility in an inpatient setting. During the 3-week rehabilitation period, IEME participants showed behavioral change. Nevertheless, we could not draw conclusions regarding the strength of the intervention effects with respect to variables such as self-efficacy, fatigue impact, or QoL at discharge or the long-term effects of the program. To evaluate the effects of the IEME, a randomized controlled trial (RCT), in which the IEME is compared to another group-based intervention, is necessary. Conducting a feasibility study provides important preliminary data (i.e., effect size and sample size estimation) needed to increase the likelihood of success in a larger RCT and minimizes any waste of financial resources (Thabane et al., 2010).

The specific aims of the present study were to assess: (1) the recruitment and follow-up rates and reasons for exclusions; (2) protocol compliance of OTs; (3) patient satisfaction with treatment; (4) time requirements; (5) changes in outcomes of interest within and between groups; and (6) treatment effect size of the IEME.

2. Materials and methods

We performed a single-blinded randomized controlled feasibility study (Thabane et al., 2010). Ethical approval was obtained from the Local Research Ethics Committee (BASEC 2016-02142), and the study was prospectively registered in the German Clinical Trials Register (DRKS00011634).

2.1. Setting

The Rehabilitation Centre Valens (RCV) in Switzerland provides personalized and goal-oriented multidisciplinary inpatient rehabilitation. The number and types of therapeutic interventions are defined at

admission based on the goals and preferences of each person. The RCV treats approximately 400 pwMS every year over 2–4-week periods.

2.2. Participants

The pwMS who were on the waiting list for a 3-week rehabilitation period at the RCV from August to November 2017, and who fulfilled the following inclusion criteria: >18 years of age; confirmed diagnosis of MS according to the McDonald criteria (Polman et al., 2011); Fatigue Severity Scale score > 4 (Valko et al., 2008); and Expanded Disability Status Scale (EDSS) score ≤ 6.5 (Kurtzke, 1983), were informed by post about the study. A few days before admission, they were contacted by phone by a researcher (AW) who verified their literacy in German and agreement to attend the IEME or control (progressive muscle relaxation [PMR] intervention, in addition to a 3-week rehabilitation as usual (RAU) program. The exclusion criteria comprised the following: telephone-based Mini Mental State Examination score < 21 (Newkirk et al., 2004) and Beck Depression Inventory-fast screening score > 4 (Neitzer et al., 2012). Prior to their involvement in any study procedures, each participant provided informed consent to participate.

2.3. Intervention procedures

All participants took part in the RAU program. This individualized program included physiotherapy (endurance and reinforcement training), occupational therapy (ability and adaptation training), speech therapy, neuropsychological training, and counseling (involving a physician and/or social worker), if relevant. The difficulties due to fatigue were discussed in individual OT sessions but no systematic fatigue management education was provided as part of RAU. In addition to RAU, the participants received the experimental or control intervention. That means that IEME participants received fatigue management group-based education during the experimental intervention and that they attended individual OT sessions only for other issues. The control group worked on fatigue management and other OT relevant issues during individual OT sessions as part of RAU. Neither participants nor OTs could be blinded to the interventions.

Experimental intervention: The goal of the IEME is to ensure that participants learn how to manage available energy in order to achieve a satisfying and meaningful daily routine. Participants acquired knowledge and understanding about factors that influence energy and the consequences of fatigue on their habits and lifestyle. Subsequently, they identified and implemented tailored behavior modification. The IEME involved face-to-face education sessions of 6.5 h in duration over a 3-week period, which was conducted by a trained OT. The IEME started with a 1-h individual session, followed by five 1-h self-contained IEME group sessions (min. 2, max. 7 pwMS) delivered twice a week, and it concluded with a 0.5-h individual session. Between the IEME sessions, the participants received training regarding the use of energy conservation strategies and planned the implementation of behavioral changes in their daily routine using self-training tasks. Six weeks after returning home, the participants received reinforcement in the form of a letter (Table 1). The treatment manual describes every session in detail, integrating the behavioral change techniques that can be used (Michie et al., 2013). The participant workbook contains detailed information on all topics, worksheets, and self-training tasks.

Control intervention: PMR was developed in 1938 by Edmond Jacobson (Conrad and Roth 2007). The aim of PMR is to achieve enhanced mental relaxation by reducing muscle tension (Dayapoğlu and Tan, 2012). PMR involves a standardized series of relaxation exercises (involving 11 large muscle groups) combined with deep breathing. During the PMR sessions, the participants lay on the floor in a quiet room and were instructed by a trained physical therapist for 1 h. The control participants attended six 1-h face-to-face group sessions of PMR (max. 12 participants), which were held twice a week over a 3-week period. They were also encouraged to continue to perform the PMR

Table 1

Description of the experimental intervention: inpatient energy management education (IEME).

Delivery modality	Lesson topic		Applied behavior change techniques	IEME - Materials
Individual face-to-face, 1 h	Energy account	Self - training	Shaping knowledge	Workbook for participants Manual for OT
Group (2–7 pwMS) face-to-face, 1 h	Break Management		Experience exchange & social support	
	Occupational balance		Feedback & monitoring	
	Use of body & environment		Compared behavior & outcomes	
	Simplifying activities		Goals & action planning	
Individual, face-to-face, 0.5 h	Effective communication		Antecedents	
	My goals		Self-belief	
	Reinforce input			

exercises after discharge from the clinic. Research has shown that PMR has a moderate to large effect on QoL in pwMS (Ghafari et al., 2009). At 6 weeks after discharge, a reinforcement letter was sent to all control participants, to foster continuation of the PMR exercises.

2.4. Assessments and outcomes

Process quality: Two researchers (AW, RH) were involved in the recruitment, screening and follow-up data collection. Reasons for exclusion and data on the refusal, dropout, and follow-up assessment rates were gathered. At the end of the study, difficulties identified during the recruitment and data collection processes and possible improvements to the study protocol were recorded.

Treatment fidelity: The OTs used an IEME checklist that included all the steps and tasks described in the treatment manual for treatment fidelity monitoring. The number of steps and tasks varied from 14 to 17 per IEME group session.

Participant satisfaction: At week 10 after baseline, six IEME participants were contacted based on their personal characteristics (sex, age, MS type and onset, EDSS score, education level, employment status, and housing), for a semi-structured, audio-recorded, telephone interview. The aim was to maximize the sample diversity and to record participants' experiences after returning home from the RCV. The interview guidelines focused on four main topics: study procedures, the group-based nature of the IEME, the feasibility of applying the energy management strategies in the participants' daily routine, and the challenge of implementing behavioral changes. The interviews were arranged for a date and time that was convenient for each participant.

Time requirements Two types of time requirements were recorded. (1) Study management time: time spent by AW and RH on recruitment and data collection (based on daily records). (2) Intervention time: time spent by participants in OT sessions (individual and group) during their 3-week rehabilitation course (based on daily records held by the RCV central planning office).

Estimate of treatment effect size: We used five self-assessment scales at baseline, at week 3 (end of interventions and discharge, T1), and 4 months after baseline (T2) to assess the outcomes. The Modified Fatigue Impact Scale (MFIS) (Kos et al., 2007) evaluated the impact of fatigue on daily life. The Occupational Self-Assessment (OSA) (Kielhofner et al., 2010) measured self-reported changes in competence regarding 21 daily activities and is a useful tool for collaborative treatment planning. Health-related QoL (HRQoL) was assessed using the Medical Outcome Study 36-item Short Form Health Survey (SF-36) (Ware and Sherbourne 1992). Self-efficacy was assessed using the University of Washington Self-Efficacy Scale (UW-SES, MS Version) (Amtmann et al., 2012) and the Self-Efficacy for Performing Energy Conservation Strategies Assessment (SEPECSA) (Liepold and Mathiowetz, 2005). All instruments were self-reported questionnaires, relatively brief (total duration, 45 min) and easy to administer, with robust psychometric properties. A blinded assessor, who was not involved in treatment, delivered the instructions to complete the questionnaires and conducted the scoring.

2.5. Randomization

The aim was to include around 50 participants over 4 months. Block randomization (four persons per block) was based on computerized random number generation. A blinded statistician (SD) prepared consecutively numbered opaque envelopes. After patients provided informed consent, AW opened an envelope and allocated participants to IEME (experimental intervention) or PMR (control intervention).

2.6. Statistical methods

Data were analyzed using Stata 15 software (Stata Corp., College Station, TX, USA). Key baseline sociodemographic and health variables were compared between the IEME and PMR groups using independent-samples *t*-tests for continuous data, and chi square tests for categorical data. Paired *t*-tests were used to assess within-group change over time. Independent-samples *t*-tests were used on the changes in the scores (post- vs. pre-intervention) to assess between-group effects. All tests were two sided and considered significant at the $p < 0.05$ level. As a standardized measure of effect size, we estimated the treatment effects using Cohen's *d*. We also calculated the sample size (based on a power of 0.8) needed for a future effectiveness study.

3. Results

3.1. Recruitment (process quality)

Between July and November 2017, 83 pwMS on the RCV waiting list were informed about the study. Sixty-three pwMS met the inclusion and exclusion criteria, of which 47 (76%) agreed to participate (Table 2), while 16 declined to participate. Twenty-four pwMS were allocated to IEME and 23 to PMR. Most participants attended at least five out of six sessions of the interventions to which they were allocated (IEME: $n = 22$, 91%; PMR: $n = 15$, 78%). In both groups, the main reasons for discontinuation were premature discharge from the RCV, missed sessions due to absent therapists, other conflicting appointments and noncompliance. Two participants (dropout rate, 4.2%) in the PMR group wished to stop treatment after one session. During the study, 10 participants had incomplete assessments (loss rate, 21.2%). At T2, the results from 35 pwMS (18 IEME/17 PMR participants) were included in the final analysis (response rate, 74.4%; Fig. 1).

3.2. IEME protocol treatment fidelity of OTs

During the study period, the OTs performed 46 individual and 21 group sessions. On average, they carried out 89% (range, 78.8–94.6%) of the tasks described in the IEME manual.

3.3. Participant satisfaction

Six telephone interviews with IEME participants (Table 3) were conducted (duration: 17–25 min). The transcripts were analyzed using

Table 2
Socio-demographic characteristics of participants.

Variables	Intervention groups		
	IEME (n = 24)	PMR (n = 23)	p-value
Age (years): mean (SD), range	51.2 (1.7), 35–68	51.8 (2.2), 31–70	0.836 ^a
Sex (female): n (%)	16 (66.7)	15 (65.2)	0.917 ^b
Self-reported disease type: n (%)			
Relapsing-remitting	7 (29.2)	8 (34.8)	0.844 ^b
Secondary progressive	7 (29.2)	8 (34.8)	
Primary progressive	6 (25.0)	5 (21.7)	
Progressive relapsing	3 (12.5)	2 (8.7)	
Not stated	1 (4.1)	–	
Years since diagnosis			
Mean (SD), range	13.5 (10.2), 1–39	14.3 (9.8), 0–37	0.774 ^a
MS-related fatigue and disability			
Fatigue Severity Scale: mean (SD)	9.8 (22.4)	10.1 (22.8)	0.966 ^a
EDSS: mean (SD), range:	5.3 (1.14), 3–6.5	4.8 (1.47), 2.5–6.5	
OSA: five most important goals, n (%)			
Physically doing what I need to do	9 (10)	14 (17)	0.47 ^b
Getting where I need to go	6 (7)	10 (12)	
Taking care of the place where I live	6 (7)	8 (9)	
Accomplishing what I set out to do	9 (11)	5 (6)	
Working towards my goals	7 (8)	5 (6)	
Level of education (years of schooling): n (%)			
Lower-secondary education (<12)	3 (12.5)	3 (13.0)	0.204 ^b
Upper-secondary education (12–16)	14 (58.3)	11 (47.9)	
Tertiary level education (>16)	6 (25)	9 (39.1)	
Not stated	1 (4.1)	–	
Employment status: n (%)			
Full-time (>30 h per week)	4 (16.7)	2 (8.7)	
Part-time (≤30 h per week)	6 (25)	6 (26)	
Self-employed	3 (12.5)	2 (8.7)	
Non-employed (housework, in education, retired)	9 (37.5)	13 (56.5)	
Not stated	2 (8.3)	–	
Housing: n (%)			
Single	5 (20.8)	5 (21.7)	1.000 ^b
Married or cohabiting	18 (75)	18 (78.3)	
Unknown	1 (4.2)	–	
Housing with children (≤18 years)	5 (27.8)	7 (38.9)	0.480 ^b
Number of cohabiting persons: mean/range	2.4/2–3	2.7/2–4	0.153 ^a

IEME: Inpatient energy management education; PMR: Progressive muscle relaxation; MS, multiple sclerosis; OSA: Occupational Self-Assessment; EDSS: Expanded Disease Severity Scale, n: number; SD: standard deviation;

^a t-test;

^b chi-square test.

thematic analysis (Braun and Clarke, 2006) by RH. According to the respondents, the experiences were generally positive. The study information was clear and the procedures needed no changes. Completing the self-assessments required a minimum of 30 min of full attention and deep thinking. The participants reported difficulties with the UW-SES due to questions involving double negatives and difficulties with the SF-36 because it required information about daily activities performed during the ‘last 4 weeks’, while the participants spent only 3 weeks at the RCV, and they had no daily routine while there. All the interviewed participants judged the IEME approach as very interesting and enriching. They had positive memories of exchanges between group members, the discussions on the different topics and the non-judgmental, supportive atmosphere. Although most participants stated that the education provided little new knowledge, they appreciated the time spent on in-depth reflection and on the practical application of fatigue management strategies. All participants achieved some behavioral change; however, this takes time and is not finished yet. Workload reduction and ergonomic behavior were easier to implement, whereas the redesign of daily structure, roles and responsibilities appeared to be more challenging because it was easy to fall back into old patterns. The

participants thought that the behavioral changes were their own responsibility, but that a local group or OT could help to improve their self-confidence during the implementation of the changes.

3.4. Required time

Study management time: The screening procedure required 20 min per patient. The study administration and organization required 50 min per patient.

Intervention time: IEME participants spent a mean of 285 min in group sessions and 102 min (95% CI: 65–140 min) in individual OT sessions as part of RAU. PMR participants spent the same time (mean, 297 min) in group sessions but had significantly more individual OT time as part of RAU (mean, 172 min; 95% CI: 216–128 min; $p = 0.024$)

3.5. Outcomes and treatment effect sizes

Changes in outcome measures were compared within and between groups at baseline, T1 and T2 (Table 4). Regarding fatigue impact (MFIS), both groups improved significantly, with no significant difference between groups. Regarding perceived competence during daily activities (OSA), the change was larger at T1 compared to T2. IEME participants showed significant improvements in the OSA subscale ‘managing and relationships’ (OSA-MR), whereas PMR participants remained at the pre-intervention level. However, there were no significant differences between groups in the OSA-MR scores. No changes were observed in self-efficacy regarding managing MS symptoms (UW-SES, MS Version). In contrast, the SEPECSA score improved in the IEME group, which resulted in a significant difference between the two groups at T2.

Regarding HRQoL (SF-36), IEME participants had improved ‘physical functioning’ subscale scores at T1 and maintained this change at T2. These changes were significantly different from the scores in the PMR group. Regarding the ‘role limitations due to physical health’ subscale, the IEME group showed an increase at T1 whereas the control group showed no significant change. However, there was no significant difference between groups. Regarding the ‘vitality/fatigue’ and ‘emotional well-being’ subscales, both groups increased significantly, with no significant difference between the groups. Regarding the ‘role limitations due to emotional problems’ and ‘pain and general health’ subscales, no significant changes over time were observed in the IEME or PMR groups.

The within-group effect size (Cohen's d) (Cohen, 1992) on fatigue impact (MFIS) was large in both groups at T1 (IEME: 1.1; PMR: 0.86) and declined to a medium effect at T2 (IEME: 0.68; PMR: 0.64). There were also large between-group effect sizes for SEPECSA and SF-36-PF (physical functioning) (at T2); medium effect sizes for OSA-MR (at T1) and OSA-SEA (satisfaction, enjoyment, actualization) (at T2); and very small to no effects for the other SF-36 dimensions and MFIS (Fig. 2). A sample size of 192 participants (power, 0.8) would facilitate the detection of clinically relevant differences at T2 in the OSA-SEA too.

4. Discussion

The objective of this study was to evaluate the feasibility of a research protocol for comparing a novel IEME group-based intervention for pwMS-related fatigue (during a multidisciplinary RAU program) to PMR. Due to the RAU provided to both groups, we did not expect significant between-group effects on fatigue impact. However, we predicted significantly higher self-efficacy in the IEME group due to the format and content of the experimental intervention. Between-group differences in outcomes showed comparatively large effect sizes regarding SEPECSA and one HRQoL dimension (SF-36-physical functioning). As expected, because of the relatively small sample size in this study, the between-group differences in the other outcomes were not significant.

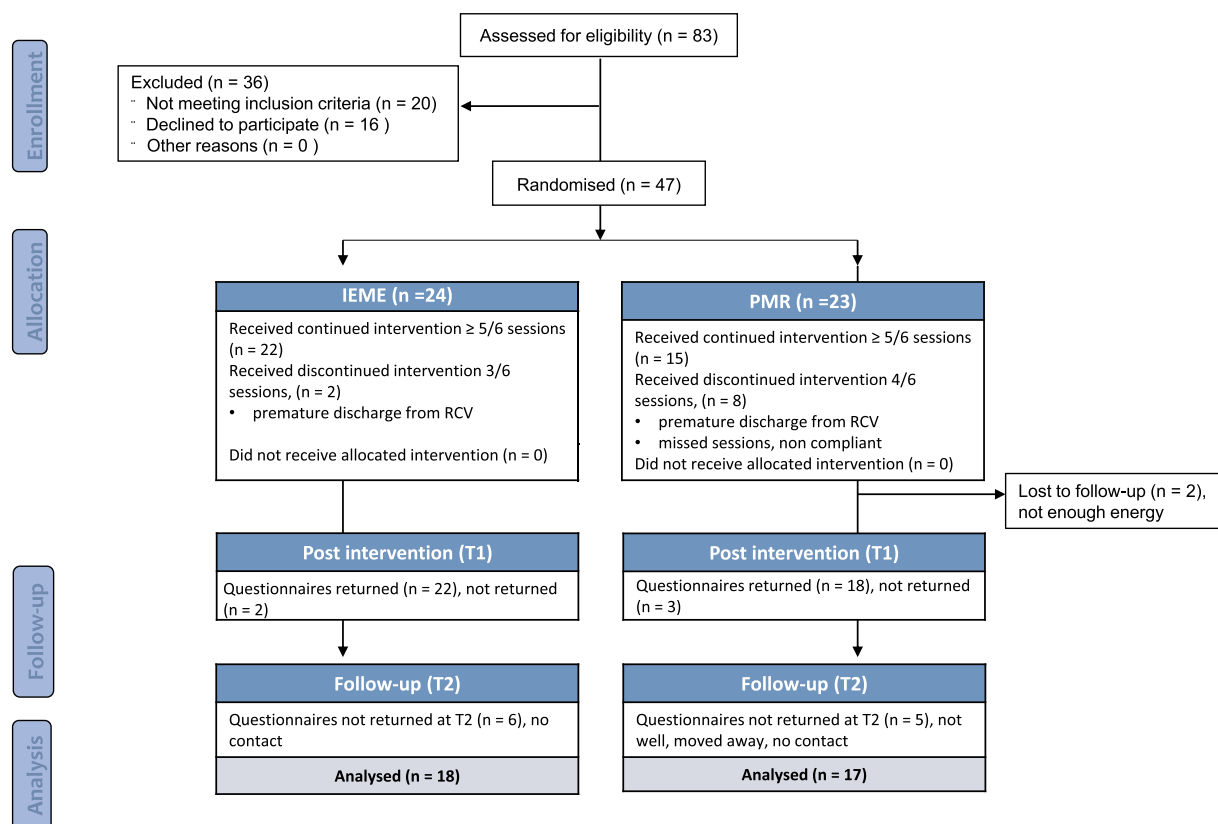


Fig. 1. Study flow diagram. RCV, Rehabilitation Centre Valens; T1, 3 weeks after baseline; T2, 4 months after baseline.

Table 3

Characteristics of interviewed IEME participants.

Gender: n (female/male)	3/3
Age: years (range)	39–57
EDSS: (median/range)	5/3–6.5
Years from onset: (range)	2–27
Education: years of schooling (<12 / 12–16 / >16)	2/3/1
Employment status: n (full-time / part-time/ family work)	2/1/3
Housing: n (single / cohabitation)	1/5

EDSS: expanded disability status scale.

Process quality: The inclusion and exclusion criteria were suitable for the characteristics of the pwMS at the RCV and permitted a high recruitment rate (56%). The sample was well balanced and the dropout rate was low. In general, PMR was a well-accepted control intervention. The study procedures and information were considered clear, but the use of the UW-SES and SF-36 (at T1) have to be reconsidered. The IEME participants expressed positive opinions about program, and the OTs had no problems in conducting the IEME, which confirms the conclusions of our previous study (Hersche et al., 2019).

Outcomes of interest and effect size: Both interventions, together with RAU, improved fatigue impact (MFIS), self-perceived performance of basic tasks of living (OSA-BT), satisfaction, enjoyment and actualization (OSA-SEA), and the HRQoL dimensions of fatigue/vitality and emotional well-being (SF-36) at T1. The improvements were maintained until T2 in the case of MFIS and SF-36-fatigue. In contrast to PMR + RAU, IEME + RAU yielded improvements in self-efficacy (SEPECSA), performance regarding managing and relationships (OSA-MR), and two HRQoL dimensions (SF-36 PF and RL due to physical health).

The Fatigue Impact Scale (FIS), and the corresponding short form, MFIS, are the most commonly used primary outcome tools in energy conservation management (ECM) studies (Asano and Finlayson, 2014). Asano and Finlayson (2014) reported a medium pooled effect size for

educational interventions, while Miller and Soundy (2017) identified improvements in 45% (10/22) of CBT intervention studies and 100% (26/26) of ECM intervention studies. These studies compared fatigue management education to waiting list controls or bland control interventions while, in our study, pwMS participated in IEME or PMR, in addition to intensive multidisciplinary rehabilitation, which explains the relatively large within-group effect sizes observed at T1, and the medium effect sizes at T2. To interpret the cumulative effect of the 3-week rehabilitation period on fatigue impact in this study, it is useful to know that Asano and Finlayson (2014) reported a medium pooled effect size for physical exercise.

Regarding the change in self-efficacy (SEPECSA) in the IEME group, our results (1.2 at T1 and 1.4 at T2) are promising because they are higher than 0.92, which is considered by Liepold and Mathiowetz (2005) to be a clinically relevant change and in line with the results of Van Heest et al. (2017) after a six-session one-to-one fatigue management course and the results of Mathiowetz et al. (2005) after an group-based outpatient course.

Regarding occupational performance (OSA), IEME improved performance in meaningful daily activities, a finding which is supported by previous studies on MS-related fatigue (Kos et al., 2015, 2016; Lexell et al., 2014).

Regarding HRQoL, the SF-36 score is a widely used secondary outcome in education intervention studies involving pwMS. Blikman et al. (2013) reported in their meta-analysis that ECM treatment yielded short-term improvements in three SF-36 dimensions (role limitation, social function and mental health). These findings are only partially consistent with our data, as we detected the largest effect size in the SF-36 dimension of physical functioning.

These data indicate that IEME + RAU does not affect the perceived impact of fatigue significantly more than PMR + RAU, but it improves competence in daily activities (OSA) and reduce perceived participation restriction (SF-36-PF). In our study, all participants benefited from a

Table 4

Outcome data for fatigue impact, occupational performance, self-efficacy and quality of life.

Group n: (T1/T2)	BL	T1	T2
Modified Fatigue Impact Scale (MFIS) total			
IEME (18/14) ^a	47.3 ± 14.3	31.7 ± 13.9	34.5 ± 16.6
PMR (15/15) ^a	44.5 ± 12.8	32.1 ± 15.8	34.5 ± 10.9
Within-group difference from baseline ^b			
IEME Δ		−15.6 [−23.3; −7.8] ^d	−10.6 [−18.6; −2.7] ^d
PMR Δ		−12.4 [−20.0; −4.8] ^d	−7.4 [−14.0; −0.8] ^d
Between-group difference from baseline ^c		−3.2 [−13.7; 7.4]	−3.2 [−13.0; 6.5]
OSA-BT (basic tasks of living)			
IEME (22/16) ^a	15.9 ± 1.45	16.9 ± 1.82	16.37 ± 2.22
PMR (17/17) ^a	15.4 ± 1.66	16.3 ± 1.76	15.82 ± 2.19
Within-group difference from baseline ^b			
IEME Δ		0.96 [0.4; 1.5] ^d	0.33 [−0.6; 1.2]
PMR Δ		0.88 [−0.01; 1.8] ^d	0.41 [−0.8; 1.6]
Between-group difference from baseline ^c		0.08 [−0.9; 1.1]	−0.08 [−1.5; 1.4]
OSA-MR (managing and relationships)			
IEME (21/15) ^a	26.7 ± 2.99	29.2 ± 2.74	28.3 ± 2.47
PMR (17/16) ^a	27.5 ± 2.32	28.6 ± 2.89	27.6 ± 3.32
Within-group difference from baseline ^b			
IEME Δ		2.5 [1.3; 3.6] ^d	1.0 [−0.2; 2.2] ^d
PMR Δ		1.1 [−0.5; 2.7]	0.45 [−0.7; 1.5]
Between-group difference from baseline ^c		1.4 [−0.5; 3.2]	0.1 [−1.7; 1.9]
OSA-SEA (satisfaction, enjoyment, actualization)			
IEME (21/15) ^a	19.9 ± 3.35	22.1 ± 2.43	21.7 ± 1.99
PMR (16/17) ^a	20.6 ± 2.10	22.0 ± 2.06	20.3 ± 2.21
Within-group difference from baseline ^b			
IEME Δ		2.26 [0.8; 3.7] ^d	1.43 [−0.2; 3.0]
PMR Δ		1.4 [0.4; 2.5] ^d	0.42 [−0.6; 1.4]
Between-group difference from baseline ^c		0.82 [−1.0; 2.6]	1.0 [−0.8; 2.8]
The University of Washington Self-Efficacy Scale for Multiple Sclerosis (UW-SES)			
IEME (13/13) ^a	42.3 ± 5.7	41.4 ± 8.0	41.7 ± 5.6
PMR (15/14) ^a	42.9 ± 4.1	40.5 ± 8.0	39.4 ± 4.2
Within-group difference from baseline ^b			
IEME Δ		−0.9 [−4.1; 2.3]	−1.6 [−3.9; 0.7]
PMR Δ		−2.4 [−6.9; 2.1]	−4.0 [−7.1; −0.8] ^d
Between-group difference from baseline ^c		1.5 [−4.0; 6.9]	2.4 [−1.4; 6.1]
Self-efficacy of performing energy conservation strategies assessments (SEPECSA)			
IEME(20/14) ^a	6.6 ± 1.7	7.8 ± 1.7	8.0 ± 1.2
PMR(16/17) ^a	7.5 ± 1.1	8.5 ± 2.2	7.3 ± 1.0
Within-group difference from baseline ^b			
IEME Δ		1.2 [0.6; 1.7] ^d	1.4 [0.6; 2.1] ^d
PMR Δ		0.9 [−0.3; 2.2]	−0.2 [−0.8; 0.4]
Between-group difference from baseline ^c		0.21 [−1.0; 1.4]	1.5 [0.7; 2.4] ^d
SF-36-PF (physical functioning)			
IEME (22/17) ^a	35.0 ± 20.8	46.8 ± 21.8	44.8 ± 24.7
PMR (17/16) ^a	32.5 ± 17.2	36.9 ± 20.9	30.0 ± 16.5
Within-group difference from baseline ^b			
IEME Δ		11.8 [7.0; 16.6] ^d	11.0 [5.5; 20.5] ^d
PMR Δ		4.4 [−1.0; 9.9]	−4.2 [−10.9; 2.5]
Between-group difference from baseline ^c		7.3 [0.3; 14.4] ^d	15.2 [3.9; 26.5] ^d
SF-36-RL (role limitations due to physical health)			
IEME (21/17) ^a	30.4 ± 38.8	64.3 ± 38.4	44.8 ± 24.7
PMR (15/14) ^a	36.7 ± 42.1	41.7 ± 34.9	30.0 ± 16.5
Within-group difference from baseline ^b			
IEME Δ		33.9 [16.2; 51.7] ^d	16.9 [−0.53; 34.3]
PMR Δ		5.0 [−23.3; 33.3]	14.3 [−17.1; 45.7]
Between-group difference from baseline ^c		28.9 [−1.5; 59.4]	2.6 [−30.0; 35.3]
SF-36-FV (fatigue/vitality)			
IEME (22/18) ^a	33.0 ± 15.9	52.9 ± 16.5	46.5 ± 16.6
PMR (17/17) ^a	35.9 ± 11.6	51.8 ± 19.7	43.5 ± 18.3
Within-group difference from baseline ^b			
IEME Δ		19.9 [11.8; 28.1] ^d	11.7 [5.6; 17.8] ^d
PMR Δ		15.9 [8.7; 23.0] ^d	8.2 [0.7; 15.7] ^d
Between-group difference from baseline ^c		4.0 [−6.8; 14.9]	3.5 [−5.8; 12.7]
SF-36-EWB (emotional well-being)			
IEME (22/18) ^a	70.2 ± 18.9	81.1 ± 11.6	76.9 ± 15.1
PMR (18/17) ^a	63.6 ± 16.5	73.9 ± 12.7	69.2 ± 13.4
Within-group difference from baseline ^b			
IEME Δ		10.9 [3.8; 18.1] ^d	2.0 [−2.6; 6.6]
PMR Δ		10.3 [3.3; 17.3] ^d	6.4 [−2.0; 14.7]
Between-group difference from baseline ^c		0.6 [−9.1; 10.4]	−4.3 [−13.3; 4.6]

Abbreviations: IEME, inpatient energy management education; PMR, progressive muscle relaxation; MFIS, Modified Fatigue Impact Scale; OSA, Occupational Self-Assessment; SF-36, health-related quality of life short form survey.

^a Values represent mean ± SD.

^b Δ = T1/2-BL [95% CI]. BL = Baseline; T1 = Time-point 1 (at discharge, 3 weeks from BL); T2 = Time-point 2 (4 months from BL).

^c Between groups Δ = IEME Δ − PMR Δ [95% CI].

^d Statistically significant differences (p-value ≤ 0.05).

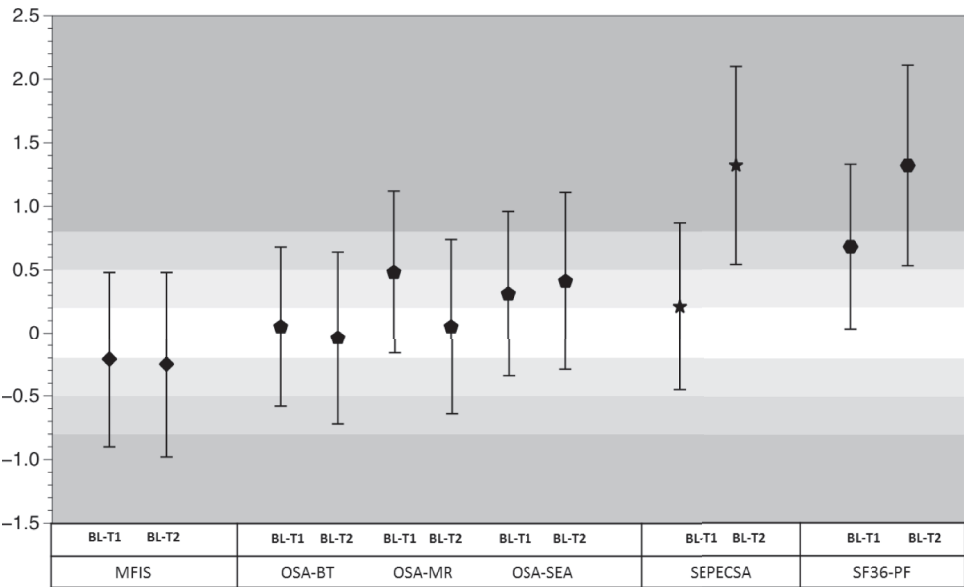


Fig. 2: Between-group effect sizes (Cohen's *d*) regarding fatigue impact, occupational performance, self-efficacy and quality of life. > 0.2, > 0.5 and > 0.8 indicate small, medium and large effect sizes, respectively. Abbreviations: MFIS, Modified Fatigue Impact Scale; OSA, Occupational Self-Assessment; BT, OSA subscale basic tasks of living; MR, OSA subscale managing and relationships; SEA, OSA subscale satisfaction, enjoyment, actualization, SEPECSA, Self-Efficacy for Performing Energy Conservation Strategies Assessments; SF-36-PF, Short Form 36 subscale physical functioning; BL = baseline; T1 = timepoint 1 (at discharge, 3 weeks after BL); T2 = timepoint 2 (4 months after BL).

Fig. 2. Between-group effect sizes (Cohen's *d*) regarding fatigue impact, occupational performance, self-efficacy and quality of life. >0.2, >0.5 and >0.8 indicate small, medium and large effect sizes, respectively. Abbreviations:MFIS, Modified Fatigue Impact Scale; OSA, Occupational Self-Assessment; BT, OSA subscale basic tasks of living; MR, OSA subscale managing and relationships; SEA, OSA subscale satisfaction, enjoyment, actualization, SEPECSA, Self-Efficacy for Performing Energy Conservation Strategies Assessments; SF-36-PF, Short Form 36 subscale physical functioning; BL = baseline; T1 = timepoint 1 (at discharge, 3 weeks after BL); T2 = timepoint 2 (4 months after BL).

higher level of endurance and force due RAU, but only the IEME group, with its focus on behavioral change, improved self-efficacy, and perceived physical functioning (SF-36-PF) after the participants' return home. These outcomes are relevant, as they are linked to the goals declared by the participants at baseline, and they may indicate more effective management of fatigue in daily life. We hypothesize that, owing to their increased self-efficacy after the IEME, the participants increasingly applied useful strategies in everyday life, their range of action increased and they felt less restricted.

4.1. Strengths and limitations

This study provides sufficient and promising data for the development of a future large-scale RCT. The outcomes of IEME showed promising effect sizes. An important limitation of the study protocol is the lack of a control arm with IEME only, due to the restrictions in inpatient rehabilitation settings. According to the stages of change model (Norcross et al., 2011), long-term follow-up could provide further important information about the maintenance of behavioral change over time. Bias between groups was reduced by ensuring comparable treatment durations.

5. Conclusion

This feasibility study has successfully provided information about all the original research questions. The SEPECSA and OSA should be used to measure primary outcomes at T1, T2 and long-term follow-up, whereas the SF36 should be used at baseline, T2 and long-term follow-up. It may be useful to include the MFIS, which captures the effects of the multidisciplinary rehabilitation of all patients, as a secondary outcome. The IEME was effective in the short term (T1), and even more in the long term (T2), in improving self-efficacy in performing ergonomic behavioral change and fatigue management strategies. At the same time, IEME reduced individual OT time during inpatient rehabilitation and it positively affected the perceived influence of MS-related fatigue

on physical functioning and vitality.

Declarations of Competing Interest

None.

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Chapter 4

Fatigue self-management education in persons with disease-related fatigue: A comprehensive review of the effectiveness on fatigue and quality of life

Hersche R¹, Roser K¹, Weise A, Michel G², Barbero M². (2021).

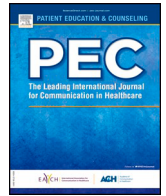
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Review article

Fatigue self-management education in persons with disease-related fatigue: A comprehensive review of the effectiveness on fatigue and quality of life

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ABSTRACT

Objectives: To systematically synthesize the effectiveness of fatigue self-management education (SME) on fatigue and quality of life (QoL) in persons with disease-related fatigue, and to describe the intervention characteristics.

Methods: We systematically reviewed the literature on SMEs in people with disease-related fatigue. We included randomized controlled trials (RCT), which aimed to improve self-management skills for fatigue in daily life. We synthesized the effectiveness and mapped the intervention characteristics.

Results: We included 26 RCTs studying samples from eight disease groups. At follow-up, 46% studies reported statistically significant improvements on fatigue and 46% on QoL. For persons with cancer 6/8 and multiple sclerosis 8/10 RCTs showed positive evidence in favor of SME. The range of effect sizes was wide (d : 0.0 – 0.8). Delivery modalities (inpatient, outpatient, home), interactions (individual, group, remote), and duration [range (h): 1–17.5] varied.

Conclusions: The overall evidence on the effectiveness of SMEs on fatigue and QoL is limited and inconsistent. For persons with cancer and multiple sclerosis, the evidence provides a positive effect. The RCTs with medium to large effect on QoL indicate the potential benefit of SMEs.

Practical implication: Duration and peer interaction should be considered when tailoring SMEs to populations and contexts.

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1. Introduction

Disease-related fatigue (referred to as fatigue) is a common, multifactorial underlying symptom in a broad range of chronic conditions [1]. Fatigue is described as the difficulty or inability to initiate activity (subjective sense of weakness); reduced capacity to maintain activity (easy fatigability); or difficulty with concentration, memory, and emotional stability (mental fatigue) [2]. It involves complex pathophysiological and psychological processes that are still not fully understood [3].

Cancer-related fatigue (CRF) has been reported to be experienced by up to 80% of patients [4] and to be the most distressing symptom during and after treatment for cancer [5]. Severe fatigue is also highly prevalent in neurological [6,7] (e.g., multiple sclerosis) and rheumatic disorders [8] and is a common experience among persons with chronic obstructive pulmonary disease, diabetes or survivors of heart failure [9–12]. Due the subjective nature of fatigue and the lack of specific therapies, it is often neglected or ignored by clinicians, although it is rated by patients as one of the key factors resulting in a decreased quality of life (QoL) [1]. Independent of the underlying mechanism, fatigue causes similar consequences across different disease populations. Work capacity and or the household, educational, avocational, social engagement; and self-care activities decrease. Everyday routines, habits and roles must be modified, which impairs QoL and increases disability [13].

Self-management education (SME) of patients is a common approach to deal with chronic conditions [14]. This complex intervention is a systematic learning experience combining different methods, such as the provision of information and behavior change techniques, to influence the way patients experience their condition or side effects of the illness [15]. The aim of SME is to teach patients how to cope with a condition and to enable the acquisition of helpful behaviors, habits, and routines [16]. In SME the agent of change is the person itself. SME targets the integration of new skills through higher self-efficacy and behavior change and thereby aims to reduce the impact of fatigue and to improve long-term social participation and QoL. Complex interventions such as SME are characterized by a variety of interacting intervention components [17,18]. There might be several mechanisms of action taken and the targeted outcome dimensions might differ. SMEs often allow a certain degree of flexibility and tailoring to individuals and situations in which they are carried out. The variety and the difficulty levels of behaviors required by those delivering and those receiving the intervention are high [17].

According to Lorig et al. [14], independently of the underlying disease, SME addresses medical, emotional and role management tasks. Five self-management skills (problem solving, decision making, resource utilization, forming of a patient/health care

provider partnership, and taking action) build thereby the core elements of the intervention [14]. The medical and behavioral management of fatigue focuses on symptom reduction or adherence to treatment programs (e.g., diet, sleep hygiene, or exercise) and is often part of nursing, physiotherapy or physician intervention. The emotional management mainly addresses thoughts, beliefs and behaviors related to fatigue; it is approached by cognitive behavior therapy (CBT) and sometimes combined with relaxation exercise and provided mainly by psychologists or other experts (e.g., specialized nurses). The coping with everyday tasks and duty is part of role management and is addressed by occupational therapists (OTs), who use energy conservation and management strategies, e.g., daily activity schedules, occupational balance or workload and environment adaptation. Emotional and role issues are often addressed contemporaneously and delivered by therapists from different disciplines with different practice models (e.g., nurse, psychologist, OT). While progress has been made evaluating CBT, OT or psychosocial interventions in different disease populations with fatigue [16,19–22], evaluations of the effectiveness of patient education which teaches self-management skills of persons with disease-related fatigue is lacking. What is missing is the knowledge on which intervention elements enable persons with fatigue to incorporate self-management skills into their daily routines to optimize performance, and to improve most effectively perceived fatigue and QoL. According to Plow et al. [22], this is mainly due to the complexity of the interventions (i.e. high heterogeneity of delivery modalities), the inconsistent use of labels and terminology by different disciplines and the lack of a standardized conceptual framework to describe the applied behavior change strategies. The interventions are often inconsistently described and their implementation is challenging and requires many resources [17,23]. Complex interventions like SME are difficult to evaluate because of many possible outcome dimensions, instruments and measurement time-points. Additionally, methodological biases of clinical trials (i.e. small and underpowered sample sizes, selection bias, low follow-up rate) may complicate the evaluation [17,23].

The aims of this systematic literature review were therefore to a) synthesize the effectiveness of SME to improve fatigue and QoL of persons with disease-related fatigue and b) systematically describe the intervention characteristics. The findings will inform on the possible benefits of SME and map procedures, formats and settings.

2. Materials and methods

2.1. Data sources

The present systematic literature review followed the PRISMA reporting guidelines [25]. The following databases were searched

from conception until February 3, 2021 (last search date): MEDLINE, CINAHL, PsycINFO and Scopus electronic database.

2.2. Search strategy

For search term selection, the research question was divided into persons with disease-related fatigue; patient education and its components; and QoL. These key terms were extended through synonyms (Table A1. and the detailed electronic search strategy for MEDLINE Table A2). To increase the consistency of our research results, we followed back the results from 25 systematic reviews and included all relevant studies in the initial pool of our search (table A3).

2.3. Inclusion and exclusion criteria

Articles were eligible if they met the following hierarchical inclusion criteria: (1) primary research article written in English, German, French or Italian and published in a peer-reviewed journal, (2) randomized clinical trial that provides data on effectiveness with a sample size $N \geq 30$, and (3) investigated the effect of a self-management education intervention on fatigue and QoL in people with fatigue.

2.3.1. Person-related criteria

Patients were aged > 18 years and diagnosed with any disease in which fatigue is a main symptom and is caused by the pathological processes of the disease and its treatment (e.g., cancer, multiple sclerosis, rheumatic disorders, heart failure). Fatigue severity or impact had to be assessed at baseline. We excluded studies in which only patients with a mental health disorder were eligible (e.g., depression, schizophrenia or dementia), diseases with unclear etiology due to their controversial causation theories (e.g. chronic fatigue syndrome, Gulf War veterans' illnesses) and patients with any kind of sleep disorder.

2.3.2. Intervention-related criteria

For the intervention to be classified as a SME, at least one of the following criteria had to be met [26]: (1) imparting health-related information that influences values, beliefs, attitudes and motivations, (2) achieving health or illness-related learning through knowledge acquisition, assimilation and dissemination, or (3) leading to the development of skills or lifestyle/behavior modification. The aim of the intervention had to be to improve self-management skills for disease-related fatigue and its consequences in everyday life. Therefore, interventions that aimed to reduce fatigue through exercise (e.g., fitness, yoga, relaxation, mindfulness) or companion education with other therapeutic interventions were excluded. The intervention had to be described sufficiently.

2.3.3. Outcome-related criteria

At least one self-reported QoL measurement (e.g., health-related QoL, well-being, or life satisfaction) and one fatigue assessment had to be included. We only included studies with at least 3 time points, (baseline, post intervention, follow-up) or two time points when the second time point was at least 1 month post intervention.

2.4. Study selection

Two reviewers (RH and KR) independently performed the title/abstract screening and the full-text assessment. Discrepancies were resolved by consensus. Remaining disagreements were resolved by GM.

2.5. Data extraction

The authors collaboratively developed an Excel data sheet to document and organize data from the eligible articles. From each study, RH extracted article characteristics (title, authors, year, journal), study characteristics (location, study aim, research design, sample size, outcome measures), sample characteristics (diagnosis, mean age, gender, partnership status and employment), intervention characteristics (aim, total duration, session length, frequency, delivery format, professionals involved), intervention focus (theoretical background, self-management tasks addressed and skills trained [14], and behavior change techniques (BCT) applied [27]). To improve the rating consistency of the intervention details, AW randomly rated 14 of the 26 (54%) included interventions independently, and consensus was achieved with RH by discussion if needed. RH also extracted data related to major findings on fatigue and QoL (means, SD, effect size, p-value) and recorded whether the difference between compared arms was statistically significant ($p < 0.05$) favoring the experimental arm, non-statistically significant, or statistically significant favoring the control arm. KR crosschecked all extracted data.

2.6. Data synthesis

The present systematic literature review was performed using best evidence synthesis method [24]. The results of the data extraction were synthesized by computing the mean, frequency and/or range for sample characteristics. The durations of the interventions were collapsed based on the median into short, medium and long-term interventions. The effect on QoL dimensions at post intervention and at the last reported follow-up was synthesized by computing Cohen's d with the Practical Meta-Analysis Effect Size Calculator [28] using the mean difference between the intervention and control groups (parallel arm RCT) or between pre- and post-intervention mean scores (crossover design) or p-values.

2.7. Assessment of methodological quality

We used the tool RoB_2.0 [29] to assess the risk of bias of the included studies. This tool is structured into five domains of bias: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported results. Through signal questions and an algorithm, the judgments (low risk, some concern, high risk) for each risk-of-bias dimension were established, and an overall risk was identified for each included study. RH conducted the risk of bias assessment. KR crosschecked the assessment, and consensus was reached by discussion if needed.

3. Results

A total of 3182 articles were identified. After the exclusion of duplicates, 2828 titles and abstracts were screened. Of the articles retrieved for further full-text assessment, 172 were excluded (Fig. 1 and Table A4). There were large differences across the studies in terms of populations studied, intervention characteristics, outcome measures used, and follow-up periods. This precluded a statistical synthesis (meta-analysis) of the available evidence.

3.1. Characteristics of studies and study samples

The 28 articles reported on 26 RCTs (2 crossover, 24 parallel arm design) and 2 follow-ups of already included RCTs. Studies were performed between 2000 and 2019 in eight different countries on eight disease groups including multiple sclerosis [MS ($n = 10$)],

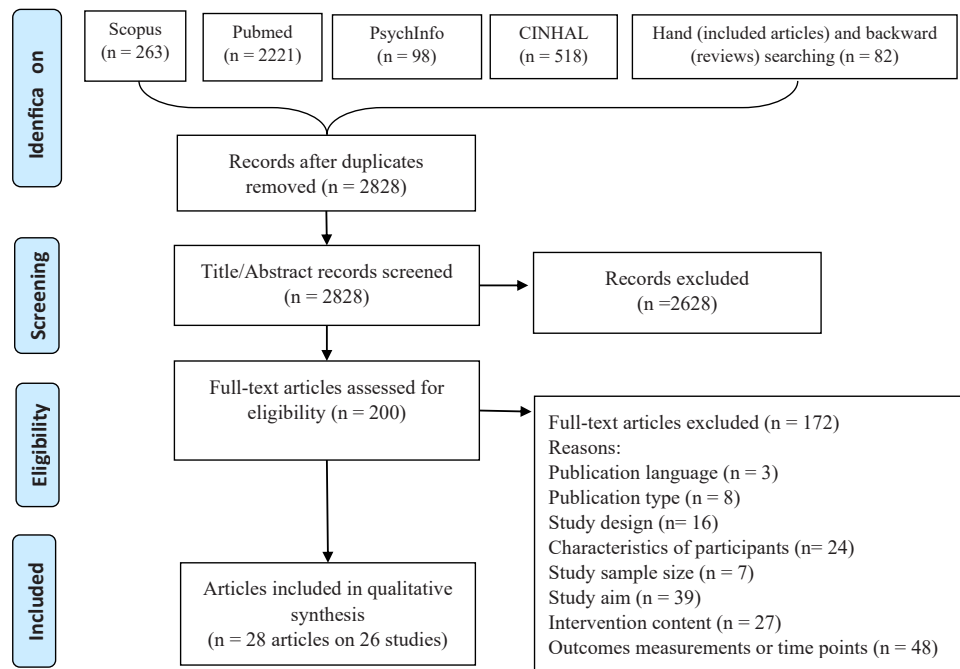


Fig. 1. Flow Diagram of literature search and article selection.

cancer (n = 8), rheumatoid arthritis [RA (n = 3)], systemic lupus erythematosus [SLE (n = 1)], heart failure [HF (n = 1)], post-polio syndrome [PPS (n = 1)], inflammatory bowel disease [IBD (n = 1)] and chronic neurological condition (n = 1), with an overall population of 3526 people. The control interventions used in these RCTs were mainly care as usual or to control for attention [30–41], alternative interventions without self-management education elements (e.g. progressive muscle relaxation) [42–44], or unspecific education through information [45–51]. Three used passive controls (waiting list) [52–55]. In two studies [43,44], the trial interventions were integrated into a multidisciplinary program. The sample size varied between 31 and 308, with a median of 113 study participants. See Table 1 for the characteristics of the pooled study population and Table 2 for the details on the study aim, sample size and experimental and control interventions for each study.

Table 1
Pooled study population characteristics for the 26 included studies.

Pooled study population: n	3526
Age (years): weighted mean (SD) / range	45.3 (7.3) / 41–65.7
Sex: female, n (range) / % (range)	2621 (25–246) / 73.3 (38–100)
Disease:	N (%)
Multiple sclerosis	1415 (51.0)
Cancer	1046 (37.7)
Rheumatoid arthritis	591 (21.3)
Systemic Lupus erythematosus	122 (4.4)
Heart failure	92 (3.3)
Chronic neurological condition	95 (3.4)
Post-polio syndrome	67 (2.4)
Inflammatory bowel disease	98 (3.5)
Partnership status:	n (%)
Living with someone	1467 (41.6)
Living alone	463 (13.1)
Not stated	1596 (45.2)
Employment:	n (%)
Employed	1060 (30.1)
Not employed	1330 (37.7)
Not stated	1137 (32.2)

Abbreviations: SD: standard deviation, n: number

3.2. Intervention characteristics

The aim of all 26 interventions was to reduce the impact of fatigue on patients' daily life through patient education and behavior changes. The intervention characteristics, the delivery modalities and the involved health professionals varied considerably between the interventions (Table 3). Seven intervention protocols [42,43,44,49,51–53] used the energy conservation and management approach based on Packer et al. [58], 7 were based on evidences and models of CBT [32,36,38,40,41,45,47]. The remaining 12 interventions were a combination of these approaches or guided by other theories. For all interventions, the active patient involvement and his/her self-management capability were core elements. The focus of the education and the issues addressed were most frequently a combination of emotional and role management tasks (12 studies, 46%) [30–32,37,38,41,45–48,50,54]. Eight studies (31%) [39,42–44,49,51–53] focused on role performance only, one (4%) [40] addressed medical and role-management tasks, while the remaining five studies (19%) [33–36,55] considered all three types of tasks. The most frequently addressed self-management skill was *taking action* (n = 25) followed by *problem solving* (n = 22) and *decision-making* (n = 21), half of the interventions taught also *using resources* (n = 9) and 11 out of 26 interventions addressed *communication with health professionals* skills too. The 26 SMEs used a different number and different combinations of the 26 BCTs [mean (SD) / median: 13 (3) / 12] described by Michie et al. [27]. *Information on the consequences of fatigue* and *encouragement of patients* were applied by 25 and *intention formation* by 24 out of 26 SMEs. Other frequently applied BCTs were *self-monitoring* (n = 23), *practice* (n = 19), *instruction* (n = 19), *goal setting* and *goal reviewing* (n = 18), while *relapse prevention* (n = 3) and *contingent rewards* (n = 2) were used rarely (Table A5).

The range of the duration [mean/IQR (h): 7.7 / 3:12] and the frequency [mean/IQR (weeks): 13.4 / 6: 18] were broad. The shortest intervention [46] had a total duration of one hour (3 sessions over 3 weeks), while the longest [51] lasted 17.5 h in total (6 × 2.5 h over 6 weeks). Out of 26 interventions, seven had a short (<4.7 h) [30,33,35,42,45,46,50], six a medium (4.7–9.4 h) [32,36,43,48,49,52]

Table 2
Study characteristics of the 26 studies reported in the 28 included articles.

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention 1 (2)
Given et al. [36] (2002) USA, ns	Cancer patients	To compare data from a supportive nursing intervention plus conventional care versus conventional care alone among patients undergoing chemotherapy	2 arms, parallel-groups RCT, (4)	71.7	58.2 (10.2)	77.0	22.1	113	Conventional care + supportive care intervention	Conventional Care
Yates et al. [46] (2005) Australia, 2000–2002	Cancer patients	To evaluate the efficacy of a brief targeted intervention that incorporates educative and supportive strategies to assist patients to develop knowledge and skills to engage in self-care behaviors.	2 arms, parallel-groups RCT, (3)	100.0	49.4 (9.4)	92.7	41.3	109	Psychoeducational intervention	General cancer education
Ream et al. [31] (2006) UK, ns	Cancer patients	To test a one-to-one, in person, intervention that aimed to educate and support patients in initiating self-care measures for managing fatigue during chemotherapy.	2 arms, parallel-groups RCT, (2)	44.7	56.5 (10.1)	66.0	30.1	103	Supportive intervention for fatigue	Standard care
Armes et al. [30] (2007) UK, 2001–2003	Cancer patients	To test if behaviorally oriented intervention is superior to usual care in reducing cancer related fatigue.	2 arms, parallel-groups RCT, (1)	60.0	59.0 (11.3)	85.5	ns	55	Brief, behaviorally oriented intervention	Standard care
Goedendorp et al. [40] (2010) Netherlands, 2005–2007	Cancer patients	To determine the efficacy of a brief nursing intervention or an extensive intervention aimed at fatigue based on CBT compared with usual care	3 arm, parallel-groups RCT, (6)	63.0	56.7 (10.8)	81.0	ns	220	intervention based on CBT	brief nursing intervention / care as usual
Purcell et al. [35] (2011) Australia, 2008–2009	Cancer patients	To test if providing pre-post radiotherapy fatigue education and support (RFES) reduced severity of fatigue experienced at the end and 6 weeks after radiotherapy.	factorial, 4 arms, parallel-groups RCT, (1)	47.2	58.8 (2.3)	ns	ns	53	CRF education intervention	Standard care
Reif et al. [54] (2013) Germany, 2008–2010	Cancer survivors	To evaluate a patient education program that aims at reducing perceived fatigue in cancer survivors.	2 arms, parallel-groups RCT, (10)	79.9	57.7 (10.1)	67.1	41.5	234	Self-management program for CFR	Waiting list
Foster et al. [45] (2016) UK, 2012–2013	Cancer survivors	To test the proof of concept of RESTORE, a web-based resource designed to increase self-efficacy to manage cancer related fatigue	2 arms parallel-groups RCT, (12)	76.7	57.8 (9.9)	ns	56.6	159	Web-based intervention to support self-management (RESTORE)	Leaflet
Mathiowetz et al. [53] (2005) USA, 2002–2003	Multiple sclerosis patients	To assess the short term efficacy and effectiveness of ECM on quality of life, fatigue and self-efficacy in patients with MS-related fatigue	2 arms cross over RCT, (1)	82.8	48.3 (8.4)	ns	42.0	169	Energy conservation course	Waiting list
Mathiowetz et al. [57] (2007) USA Finlayson [52] (2011) USA, 2007–2009	Multiple sclerosis patients	To report the 1-year follow-up of Mathiowetz (2005) To test the effectiveness and efficacy of an teleconference	2 arms cross over RCT, (1)	79.0	56.0 (9.0)	ns	27.6	181	Teleconference- fatigue management program	Waiting list (continued on next page)

Table 2 (continued)

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention
Thomas et al. [32] (2013) UK, 2008–2009	Multiple sclerosis patients	fatigue management program for people with MS. To evaluate the effectiveness and cost-effectiveness of FACETS when added to current local practice	2 arm, parallel- group RCT, (3)	72.6	49.0 (10.1)	71.3	35.4	164	Intervention applying cognitive behavioral + energy effectiveness techniques	Current local practice
Thomas et al. [56] (2014) UK		To report the 1-year follow-up of Thomas (2013)								
Ehde et al. [48] (2015) USA, 2011–2013	Multiple sclerosis patients	To evaluate the efficacy of a telephone-delivered SMI designed to help adults with MS effectively manage fatigue, chronic pain, and/or depression.	2 arms, parallel- groups RCT, (1)	87.1	52.2 (10.0)	61.3	88.3	163	Telephone self- management	Telephone MS education
Kos et al. [42] (2016) Belgium, 2011–2014	Multiple sclerosis patients	To evaluate the effectiveness of an individual self-management occupational therapy intervention program versus relaxation on the performance of and satisfaction with relevant daily activities in patients with MS-related fatigue.	2 arms parallel groups RCT, (1)	ns	41.0 (9.2)	ns	ns	31	Self-management occupational therapy	Progressive muscle relaxation
Blikman et al. [49] (2017) Netherlands, 2011–2014	Multiple sclerosis patients	To test the effectiveness of an individual ECM intervention on fatigue and participation in persons with primary MS-related fatigue.	2 arms parallel- groups RCT, (1)	74.4	47.1 (11.2)	ns	ns	86	Individual energy conservation management	Information only: 3 MS nurse consultations
Van den Akker et al. [41] (2017) Netherlands, 2011–2014	Multiple sclerosis patients	To assess the effectiveness of CBT in decreasing fatigue and improving societal participation in patients with multiple sclerosis compared to nurse consultations.	2 arm, parallel- groups RCT, (3)	76.0	48.5 (9.9)	73.6	40	91	Cognitive behavioral therapy	MS nurse consultation
Pöttgen et al. [55] (2018) Germany, 2014	Multiple sclerosis patients	To evaluate the efficacy of a self- guided online fatigue intervention in multiple sclerosis	2 arm, parallel- groups RCT, (1)	80.7	41.3 (10.2)	71.3	49	275	self-guided online fatigue intervention in MS (ELEVIDA)	Waiting list
Plow et al. [44] (2019) USA, ns	Multiple sclerosis patients	To compare the effectiveness of telephone-delivered interventions on fatigue, physical activity, and quality of life outcomes in adults with MS related fatigue	3 arms parallel- groups RCT, (1)	84.6	52.1 (8.4)	83.7	38.9	208	Fatigue self-management plus physical activity	Physical activity only / contact-control social support intervention
Hersche et al. [43] (2019) Switzerland, 2017–2018	Multiple sclerosis patients	To assess the feasibility and changes in outcomes of IEME compared to PMR in patients with MS related fatigue.	2 arms parallel groups RCT, (1)	66.0	51.2 (1.95)	76.6	48.9	47	Rehabilitation + energy management education	Rehabilitation + Progressive muscle relaxation
Ghahari et al. [51] (2010) Australia, 2007–2008	Patients with chronic neurological conditions	To test the effectiveness of the new online version of the fatigue self-management program.	3 arms, parallel- groups RCT, (1)	81.1	50.2 (12.3)	ns	34.7	95	Online fatigue Self- management program	Online information only(No treatment)
Zuidema et al. [34] (2019) Netherlands, 2014–2015	Rheumatoid arthritis patients	To evaluate the efficacy of a Web- based self-management enhancing program for patients with rheumatoid arthritis.	2 arms, parallel- groups RCT, (2)	65.6	ns	ns	42	157	Care as usual + Web- rheumatoid arthritis self- management	Care as usual
Hewlett et al. [47] (2011) UK, ns	Rheumatoid arthritis patients	To test group CBT fatigue self- management program vs. groups management program.	2 arms, parallel- groups RCT, (1)	73.8	59.2 (11.3)	ns	ns	126	CBT-group for fatigue self- management	1 h didactic group session (continued on next page)

Table 2 (continued)

First author (Publication year) Origin country, time period study conduct	Study population	General study focus/aim	Study design, center (n)	Gender [% females]	Age [mean] (SD)	Partnership status [% Living with someone]	Employment [% employed]	Sample sizes (n)	Experimental intervention	Control intervention
Hewlett et al. [37] (2019) UK, ns	Rheumatoid arthritis patients	receiving fatigue information alone in people with RA To assess impact of fatigue between a group cognitive behavior self-management course for rheumatoid arthritis fatigue compared to usual care alone	2 arms, parallel- groups RCT, (7)	79.9	ns	ns	ns	308	Reducing Arthritis Fatigue	Care as usual
Koopman et al. [38] (2016) Netherlands, 2009–2012	Patients with post- polio syndrome	To investigate the efficacy of exercise therapy and CBT in patients with post-polio syndrome on fatigue and quality of life compared to care as usual	3 arm, parallel- groups RCT, (7)	54.5	59.0 (8.1)	52.0	73.1	67	Cognitive behavioral therapy	Care as usual / Exercise therapy
Vogelaar et al. [39] (2014) Netherlands, 2010–2011	Inflammatory bowel disease patients	To assess whether solution focused therapy is more effective in improving fatigue and QoL than care as usual (CAU) in people with inflammatory bowel disease	2 arm, parallel- groups RCT, (2)	63.0	41.1 (10.3)	ns	ns	98	Solution focused therapy	Care as usual
Karlson et al. [50] (2004) USA, ns	Systemic lupus erythematosus patients	To test psycho educational intervention to improve patient self-efficacy, partner support, and problem-solving skills of the patient-partner pair to manage systemic lupus erythematosus.	2 arms, parallel- groups RCT, (2)	97.5	41.8 (11.3)	ns	ns	122	Psycho-educational Intervention in groups	Attention placebo (45 min video + monthly telephone calls)
Wang et al. [33] (2016) Taiwan, 2012	Heart failure patients	To investigate the effects of a supportive educational nursing care program on fatigue and quality of life in patients with heart failure.	2 arms, parallel- groups RCT, (1)	38.0	65.8 (0.2)	94.6	19.6	92	Supportive educational nursing	Routine nursing care

Abbreviations: CBT: cognitive behavioral therapy, MS: multiple sclerosis, RCT: randomized clinical trial, ns: not stated, CRF: cancer related fatigue, RA: rheumatoid arthritis

Table 3
Overview of intervention characteristics of the 26 studies reported in the 28 included articles.

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed			SM-skills trained			Duration and frequency: Sess- ions (n) x min., total duration [h], over (n) weeks	Delivery modalities			Lead of intervention	Home-work / self- training
			Medicale	Emotional	Role	Problem solving	Decision- making	Using resources		Communi- cation health prof.	Taking action	Place		
Given [36] cancer	to acquire knowledge, skills, behavioral reframing, how to manage experienced problems	CBT, supportive counseling, self- care management	✓	✓	✓	✓	✓	✓	✓	Out	Face to face + telephone	Individual + caregiver	Nurse	
Yates [46] cancer	to improve patients' knowledge and skills to perform self-care behaviors designed to minimize fatigue to enable fatigue management through energy management	PRECEDE model of health behavior [63]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face + telephone	Individual	Nurse	
Ream [31] cancer	to alter fatigue- related behavior	Energy conservation Psychobiologic- al entropy model [60] Fear-avoidance model of symptom management	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	cancer nurse	✓
Armes [30] cancer	to avoid deconditioning, dysfunctional cognitions about fatigue and to cope with the consequences of having cancer.	Fear-avoidance model of symptom management precipitatin- gand perpetuating factors [66]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	Nurse	✓
Goedendorp [40] cancer	to employ self-care behaviors designed to minimize fatigue to achieve behavior modifications and impact health- related self-efficacy	Health Belief Model de Vries at al. [61]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	Psy.	
Purcell [35] cancer	to increase participant's self- efficacy to manage CRF	Self-efficacy theory [59], CBT, evidence of fatigue management in cancer survivors	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	ns	
Reif [54] cancer	to teach how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	Nurse + Psy	✓
Foster [45] cancer	to teach participants how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Home	On-line	Remote	No instructor	✓
Mathiowetz [53,57] MS	to teach participants how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	OT	✓
Finlayson [52] MS	to teach participants how to manage energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	Home	Telephon- e	Group	OT	✓

(continued on next page)

Table 3 (continued)

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed		SM-skills trained			Delivery modalities			Lead of intervention	Home-work / self- training
			Medicale	Emotional	Role	Problem solving	Decision- making	Using resources	Communica- tion health prof.	Taking action		
Thomas [32,56] MS	to normalize the experience of fatigue, to use energy more effectively, to develop helpful thinking	CBT-Model, development project	✓	✓	✓	✓	✓	✓	✓	✓	HP	✓
Ehde [48] MS	to learn, apply SM- skills	Energy conservation strategies [58], CBT	✓	✓	✓	✓	✓	✓	✓	✓	SW + Psy	✓
Kos [42] MS	to achieve control over performance within the limits of energy, to increase self-efficacy in fatigue management	Energy conservation strategies [58] Self- Management [14]	✓	✓	✓	✓	✓	✓	✓	✓	OT	✓
Blikman [49] MS	to promote attitude optimum use of the available energy	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	✓	OT	✓
Van den Akker [41] MS	to influence dysfunctional cognitions, behaviors and emotions that perpetuate fatigue, to learn how control and modify the factors that influence fatigue	Cognitive behavioral model of MS- fatigue [66]	✓	✓	✓	✓	✓	✓	✓	✓	Psy	✓
Pöttingen [55] MS	to increase outcomes of fatigue impact, physical activity, and health- related quality of life.	based on evidence-based CBT principles	✓	✓	✓	✓	✓	✓	✓	✓	developer team	✓
Plow [44] MS	to increase outcomes of fatigue impact, physical activity, and health- related quality of life.	Energy conservation and management strategies [58]	✓	✓	✓	✓	✓	✓	✓	✓	OT	✓
Hersche [43] MS	to manage available energy and to achieve a satisfying and meaningful daily routine	Energy management [58], scientific evidence	✓	✓	✓	✓	✓	✓	✓	✓	OT	✓
Ghahari [51] NCD	to learn SM of fatigue	Energy conservation strategies [58]	✓	✓	✓	✓	✓	✓	✓	✓	OT	✓
			✓	✓	✓	✓	✓	✓	✓	✓	No instructor	✓ (continued on next page)

Table 3 (continued)

First author / diseases	Aim of experimental intervention	Underlying approach, model, or theory	SM-tasks addressed			SM-skills trained		Communication health prof.	Taking action	Delivery modalities			Lead of intervention	Home-work / self- training
			Medicale	Emotional	Role	Problem solving	Using resources			Place	Setting	Inter-action		
Zuidema [34] RA	to enhance patients' ability to self-manage their disease and thus improve their quality of life.	Theory of planned behavior [65]												
Hewlett [47] RA	to turn cognitive and behavioral changes into improved well-being	CBT, SM [14], experiences from clinicians and patients	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	Psy + OT	✓
Hewlett [37]RA	to modify factors which influence RA-fatigue and its impact	Framework for complex interventions [64] Integration of CB-approaches, theory of self-efficacy [59]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Group	Nurse + OT	✓
Koopman [38] PPS	to modify the perpetuating factors of fatigue	cognitive behavioral model of MS-fatigue [66]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	Psy	✓
Vogelaar [39] IBD	to focus on the existing adequate coping abilities of patients, rather than on their problems	modified to focus on fatigue management [67]		✓	✓	✓	✓	✓		Out	Face to face	Group	Psy	
Karlson [50] SLE	to improve self-efficacy, problem-solving skills to manage SLE	Self-efficacy theory [59]	✓	✓	✓	✓	✓	✓	✓	Out	+ Home	Face to face + telephone	Individual + caregiver	Nurse
Wang [33] HF	to achieving an optimal balance between restorative and restorative energy	Supportive intervention [31] Symptom model [62]	✓	✓	✓	✓	✓	✓	✓	Out	Face to face	Individual	Nurse	✓

Abbreviation: MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease, CRF: cancer-related fatigue, SM: Self-management, CBT: Cognitive Behavioral therapy, BCT: Behavior Change Techniques, S: session, OT: occupational therapist, HP: Health professional, SW: Social worker, Psy: Psychologist, ✓: declared, ns: not stated

and nine a long duration (>9.4 h) [37,38–41,47,51,53,54]. The remaining three interventions were self-tailored [34,38,55], or the duration was not clearly reported [31]. The majority of the interventions were performed in an outpatient setting (17/65%), seven at home (on-line, telephone or home visit), one used a combination [50] and one [43] was performed during an inpatient period. In this sample, 42% of the interventions used an individual interaction between patient and therapist [30,31,33,35,38,40–42,46,48,49], 27% used peer groups [32,37,39,47,52–54], 19% used both forms of interaction [36,43,44,50,51] while 12% [34,45,55] did not include any communication with an health professionals or peers (remote). The interaction was mostly face-to-face ($n = 15$), while other modalities were by phone ($n = 3$), online ($n = 4$), or a combination of different modalities ($n = 4$). In summary, 9 interventions (35%) were delivered face to face with an individual interaction in an outpatient setting [30,31,33,35,38,40–42,49], while six (23%) had a face to face group interaction in an outpatient setting [32,37,39,47,53,54]. The remaining 11 (42%) protocols had other types of combinations of intervention characteristics (online and telephone interventions, group and individual interaction). The delivering professionals were mainly OTs ($n = 9$), nurses ($n = 8$) and psychologists ($n = 7$) after a specific training or with experience in the field. In four interventions [37,47,48,54], a pair of professionals led the sessions. In 69% (18/26) of the interventions, homework and/or self-training/monitoring was a declared part.

3.3. Effects on fatigue and quality of life

In this sample of 26 complex SMEs, the time point of assessment varied according to the intervention duration and the study design (Table 4). There were six studies with one year [34,41,49,50,56,57] and one with two year follow-up data [37]. The remaining studies had a latency of 2.5–10 months with a median of 4 months from baseline to follow-up. Fatigue impact or severity were measured through self-reported questionnaires and were the primary outcome for most of the RCTs ($n = 21$). Regarding the outcome fatigue, 50% of the studies [30,31,33,36,37,39,41,44,46,52–55] showed a positive effect reporting statistically significant differences ($p < 0.05$) in favor of the experimental intervention at post intervention. Out of them, seven [31,37,41,52–55] maintained the positive effect while five [32,40,47,50,51] reported positive effects only at follow-up. In summary, 8 (30%) [34,35,38,42,43,45,48,49] of the included studies showed no effect on fatigue at any of the measured time-points.

QoL was measured with multidimensional questionnaires in most studies; half of the included studies used the Short Form Health Survey (SF36). Twelve out of 26 studies (46%) showed in at least one dimension a statistically significant positive effect and eight maintained the significant difference compared to the control intervention at follow-up. In summary, 38% of the included studies showed no effect on QoL at any of the measured time-points. Five out of 26 studies (20%) [35,38,45,48,49] showed no effect for fatigue or QoL. In the subgroup of studies with people with cancer, 6 out of 8 studies; (including 80% of the pooled cancer population, $n = 834$) [30,31,36,40,46,54] reported a significant effect on fatigue and 5 out of 8 (59%) [30,31,36,40,54] on QoL. In the subgroup of studies with persons with MS, 6 out of 10 studies (65% of the pooled MS-population, $n = 924$) [32,41,44,52,53,55] showed an effect on fatigue and 7 out of 10 (68%) [32,41–43,52,53,55] on QoL. Two out of three studies including persons with RA showed a significant decrease in fatigue (73% of the pooled RA-population, $n = 434$) and 1 out of 3 significantly improved QoL (27%).

3.4. Risk of bias

The overall risk of bias was low for 11 (42%) studies [30,32,37,41,45,48–50,54,55]. In four studies [36,38,39,42], the

randomization process was not clear, in six studies [31,33,35,36,43,46], the analysis performed to estimate the effect of assignment was inappropriate, and for eight trials [31,34,43,44,47,51–53] less than 95% of outcome data from the randomized persons were available. In three trials [31,36,43], the bias accumulation was judged as high risk (Table 4).

3.5. Statistically significant improvements and intervention characteristics

Regarding delivery modalities, 10 out of 15 SMEs (67%) with individual [30,31,33,36,40,41,44,46,50,51], 7 out of 8 (88%) with peer group [32,37,39,47,52–54], and 1 out of 3 (33%) with a remote [55] interaction found statistically significant improvements on fatigue. The pink box in the column “group” in the outcome fatigue indicates the study of Reif et al. [54] with a sample of 234 cancer patients that found a significant improvement on fatigue. For QoL, 9 out of 15 SMEs (60%) with individual [30,31,33,36,40–42,50,51], 6 out of 8 (75%) with peer group [32,39,43,52–54], and 2 out of 3 (67%) with remote [34,55] interaction reported statistically significant improvements (Fig. 2).

Regarding the duration (Fig. 3), short SMEs (<4.7 h) showed in 4 out of 7 studies (57%) [30,33,46,50] statistically significant improvement on fatigue. SMEs with a medium duration (4.7–9.3 h) showed a statically significant improvements on fatigue in 3 out of 6 studies (50%) [32,36,52], and those with a long duration (>9.3 h) in 8 out of 9 studies (89%) [37,39–41,47,51,53,54]. Four out of 7 studies (57%) with short [30,33,42,50], 4 out of 6 (67%) with medium [32,36,43,52], and 6 out of 9 (67%) [39–41,51,53,54] with long duration reported statically significant improvements on QoL.

3.6. Effect size of fatigue self-management education on quality of life

In terms of the effect size, nine studies [35,37,40,44–59] reported a change in QoL at post intervention corresponding to no practical effect ($d < 0.2$). Of the remaining studies, nine reported a small ($d \geq 0.2$) [32–34,36,38,39,50–52], six at least a medium ($d \geq 0.5$) [30,31,41–43,55] and two also large effects ($d \geq 0.8$) [53,54] in one or more measured dimensions of QoL. At the last follow-up, 80% ($n = 21$) of studies reported no or a small effect. One study [57] maintained a medium effect and four [30,42,43,54] maintained or increased towards a large in at least one subscale. The dimensions, which were most often affected positively and strongly, were related to mental health (SF36: vitality, mental health, emotional functioning, and social functioning). In contrast, those related to physical health (physical functioning, role functioning, bodily pain, general health) were less often positively affected and the effect sizes were smaller (Table 5).

4. Discussion and conclusion

4.1. Discussion

In this systematic review, we provide a comprehensive overview of the effectiveness of SME on fatigue and QoL in people living with disease-related fatigue. Moreover, we summarize the most relevant information regarding the intervention characteristics and the delivery modalities of the 26 included studies, which covered eight different disease populations with MS, cancer, and RA being the main disease groups.

The overall evidence on the effectiveness of SMEs on fatigue and QoL based on the 26 included RCTs is unclear. While the data for cancer and MS are promising, the evidence for the other diseases remain limited and inconsistent. Additionally, there is a considerable risk of bias in some of the included studies. This is in line with the findings from Farraghe et al. [69] who reported a lack of robust RCTs

Table 4
Effects on fatigue and quality of life post-intervention and at follow-up, and risk of bias for the 26 studies reported in the 28 included articles.

Disease	First author	Sample analyzed (n)	Time point of assessment weeks (n) from baseline	Fatigue outcome instrument	Quality of life outcome instrument	Effects on fatigue		Effects on quality of life		Risk of bias				
						PI	FUP	PI	FUP	R	D	MI	ME	O
Cancer	Given [36]	53/59	10 ^a / 20	Symptom Experience Scale	Short Form Health Survey (SF36; PF, SF)	+	+	+	+	—	—	✓	✓	HR
	Yates [46]	49/48	7 (PI) / 10 / 14	Fatigue experience, fatigue- management behavior ¹	EORTC QLQ-C30	+	+	+	+	✓	—	✓	✓	SR
	Ream [31]	43/43	4.5 / 9 / 13 (PI)	Fatigue VAS ¹	SF36 (reported only MH and VF)	+	+	+	+	✓	—	—	✓	HR
	Arnes [30]	28/27	12 (PI) / 16 / 39	Global fatigue (VAS-F) ¹ , Fatigue Outcome Measure (FOM), Multidimensional Fatigue Inventory (MFI)	EORTC-QLQ-C30 (PF only) + subscale Fatigue	+	+	+	+	✓	✓	✓	✓	LR
	Goedendorp [40]	82 / 77 / 81	NA / 27	Fatigue subscale of checklist Individual Strength (CIS) ¹	EORTC QLQ-C30	NA	+	NA	+	✓	✓	✓	✓	SR
	Purcell [35]	21/24	5 (PI) / 11	Multidimensional Fatigue Inventory (MFI) ¹	EuroQual-5D (EQ-5D) + VAS	+	+	+	+	✓	—	✓	✓	SR
	Reif [54]	120/114	6 (PI) / 31	Fatigue Assessment Questionnaire (FAQ) ¹	EORTC QLQ-C30 questionnaire	+	+	+	+	✓	✓	✓	✓	LR
	Foster [45]	83 / 76	6 (PI) / 12	Brief Fatigue Inventory (BFI)	Personal Wellbeing Index (PWI)	+	+	+	+	✓	✓	✓	✓	LR
	Mathiowetz [53,57]	78/91	7 (PI) / 13 / 65	Fatigue Impact scale (FIS) ¹	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	—	✓	SR
	Finlayson [52]	94 / 96	6 (PI) / 19 / 19 / 32	Fatigue impact scale (FIS) ¹ , Fatigue severity scale (FSS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	—	✓	SR
MS	Thomas [32,56]	84/80	11 (PI) / 24 / 52	Global Fatigue severity (subscale of FAI) ¹	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	LR
	Ehde [48]	75 / 88	10 (PI) / 26 / 52	Modified Fatigue Impact scale (MFIS) ¹	Short Form Health Survey (SF8)	+	+	+	+	✓	✓	✓	✓	LR
	Kos [42]	17/14	3 (PI) 16	Modified fatigue impact scale (MFIS) ¹ , Fatigue Checklist Individual Strength (CIS-20R)	Short Form Health Survey (SF36)	+	+	+	+	—	✓	✓	✓	SR
	Blikman [49]	42 / 44	8 / 16 (PI) / 26 / 52	Checklist Individual Strength (CIS20r) ¹ , Modified Fatigue Impact scale (MFIS), Fatigue severity scale (FSS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	LR
	Van den Akker [41]	44 / 47	16 (PI) / 26 / 52	Checklist Individual Strength (CIS20r) ¹ , Fatigue severity scale (FSS), Modified Fatigue Impact scale (MFIS)	Short Form Health Survey (SF36)	+	+	+	+	✓	✓	✓	✓	LR
	Pötgen [55]	139 / 136	12 (PI) / 40	Chalder Fatigue Scale ¹ , Fatigue Scale for Motor and cognitive Functions (FSMC)	Hamburg Quality of Life Questionnaire for MS (HAQUAMS)	+	+	+	+	✓	✓	✓	✓	LR
	Plow[44]	70/69/69	14 (PI) / 26	Fatigue Impact Scale (FIS) ¹	Multiple Sclerosis Impact Scale (MSIS)	+	+	+	+	✓	✓	—	✓	SR
	Hersche [43]	18/17	3 (PI) / 17	Modified Fatigue Impact Scale (MFIS)	Short Form Health Survey (SF36)	+	+	+	+	✓	—	—	✓	HR

(continued on next page)

Table 4 (continued)

Disease	First author	Sample analyzed (n) EG / CG1 / CG2	Time point of assessment weeks (n) from baseline	Fatigue outcome instrument	Quality of life outcome instrument	Effects on fatigue		Effects on quality of life		Risk of bias				
						PI	FUP	PI	FUP	R	D	MI	ME	O
NC	Ghahari [51]	34 / 28 / 33	7 (PI) / 12	Fatigue impact scale (FIS) ¹	Personal Wellbeing Index (PWI)	♦	+	+	♦	✓	✓	—	✓	SR
RA	Zuidema [34]	78/79	26 ¹ / 52	Level of fatigue (Numeric Rating Scales)	Short Form Health Survey (SF36)	♦	♦	♦	+	✓	✓	—	✓	SR
	Hewlett[47]	65/62	NA ³ / 18	Multi-Dimensional Assessment of Fatigue scale (MAF) ¹	RA Quality-of-Life scale	NA	+	NA	♦	✓	✓	—	✓	SR
PPS	Hewlett[37]	157/158	26 ^a / 52 / 78 / 104	Bristol RA Fatigue Effect (BRAFE) ¹	Global question	+	+	♦	♦	✓	✓	✓	✓	LR
	Koopman [38]	23 / 23	18 (PI) / 31 / 45	Fatigue Questionnaire (CIS20-F) ¹	Short Form Health Survey (SF36)	♦	♦	♦	♦	—	✓	✓	✓	SR
IBD	Vogelaar [39]	49 / 49	27 (PI) / 40	Checklist Individual Strength (CIS) ¹ , Fatigue severity scale (FSS), Modified Fatigue Impact scale (MFIS)	Short Form Health Survey (SF36)	+	♦	+	♦	—	✓	✓	✓	SR
SLE	Karlson [50]	64/58	26 (PI) / 52	Fatigue scale for Lupus patients	Short Form Health Survey (SF36)	♦	+	♦	+	✓	✓	✓	✓	LR
HF	Wang [33]	38/37	4 / 8 / 12 (PI)	Piper fatigue scale (PFS) ¹	Minnesota living with heart failure questionnaire (MLHFQ)	♦	NA	+	NA	✓	—	✓	✓	SR

Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease

^a: Not immediately post intervention, ¹: primary outcome, PI: post intervention, FUP: follow-up, ♦: significant positive differences, ♦: no significant differences, NA: not applicable

Risk of bias: ✓: no risk, —: some concerns; R: Bias arising from the randomization process, D: Bias due to deviations from intended interventions, MI: Bias due to missing outcome data, ME: Bias in measurement of the outcome, S: Bias in selection of the reported result, O: Overall risk of bias, LR: low risk, SR: some risk, HR: high risk

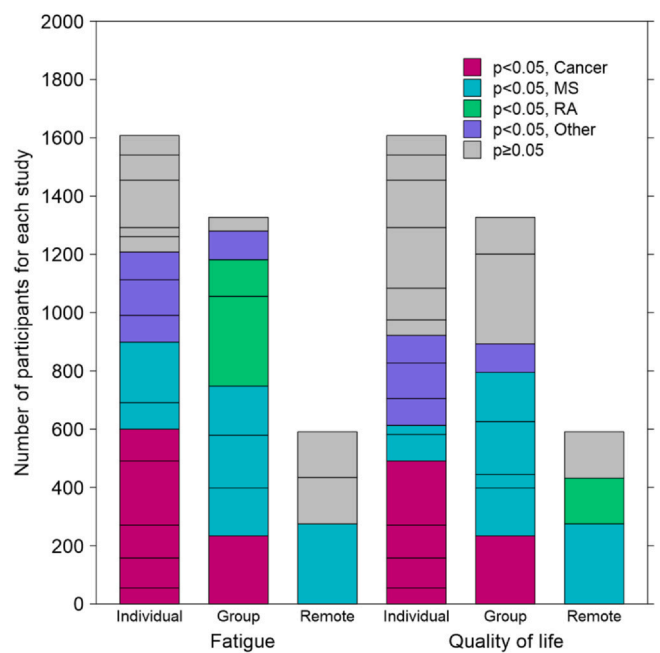


Fig. 2. Improvements in fatigue and quality of life for different delivery modalities and disease groups. Caption: Number of participants for each study with statistically significant improvement on fatigue and QoL. Studies are grouped according to delivery modalities. Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, p < 0.05: statistically significant p > =0.05: not statistically significant.

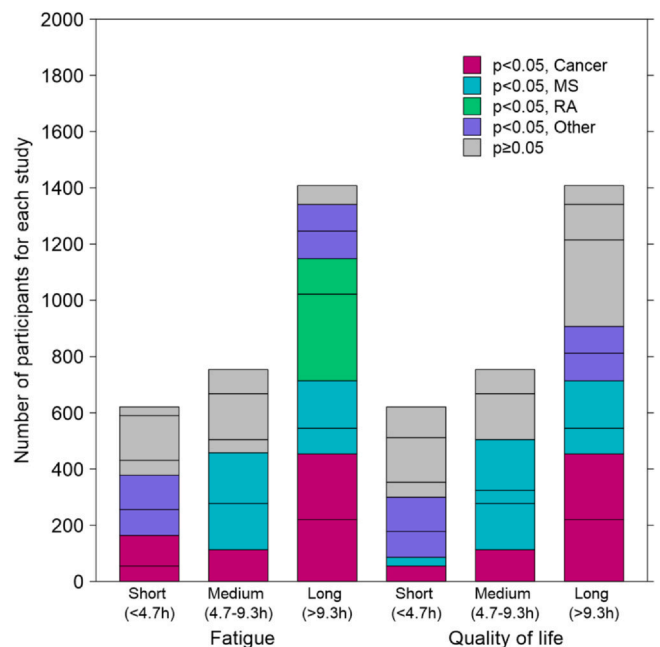


Fig. 3. Improvements in fatigue and quality of life for SMEs with different durations and disease groups. Caption: Number of participants for each study with statistically significant improvements on fatigue and QoL. Studies are grouped according to duration. Abbreviations: MS: multiple sclerosis, RA: rheumatoid arthritis, p < 0.05: statistically significant, p > 0.05: not statistically significant.

for energy management education in chronic diseases. However, only a few RCTs reported no effect at all. Considering the subgroup of 18 studies (8 with high quality) including persons with cancer (8 studies) and MS (10 studies), the evidence is moderately consistent showing positive effects in favor of SME. The proportions of studies with positive effects within these two disease populations (cancer

Table 5

Effect sizes (d) for effects on global QoL or QoL-dimensions at post intervention and follow-up for the different QoL measurements. Color key: white: no practical effect (<0.2), orange: small (>0.2), blue: medium (>0.5), green: large (>0.8) effect (according to [68]).

First author (Disease) / Quality of life measurement	Effect on quality of life dimensions or of global QoL: effect size (d)																				Analysis
	First post intervention (PI)										Last follow-up (FUP)										
	PF	RP	BP	VT	SF	RE	MH	GH	PCS	MCS	PF	RP	BP	VT	SF	RE	MH	GH	PCS	MCS	
SF36 / 8	0.25	-0.32	0.51	0.01	-0.17	-0.17	0.24	0.26	ns	ns	0.42	-0.19	1.68*	0.33	0.22	-0.17	-0.46	0.07	ns	ns	
Kos [42] (MS)	0.68	0.61	0.04	0.06	0.12	-0.28	0.59	-0.35	ns	ns	0.96*	0.69	0.52	0.17	-0.14	0.08	0.54	-0.09	ns	ns	
Hersche [43] (MS)	0.19	0.37*	0.37	0.41*	0.32*	0.26*	0.48*	0.26	ns	ns	0.27	0.39*	0.39	0.33*	0.29*	0.17	0.27*	0.19	ns	ns	
Finlayson [52] (MS)	0.17	0.63*	0.18	1.14*	0.42*	0.40	0.60*	0.08	ns	ns	0.41	0.61*	0.20	0.61*	0.61*	0.23	0.44*	0.12	ns	ns	
Mathiowetz [53,57] (MS)	-0.05	0.13	0.04	0.24	-0.07	0.09	0.15	-0.06	ns	ns	0.10	0.27	-0.06	0.35*	-0.11	0.21	0.30	-0.1	ns	ns	
Thomas [32,56] (MS)	-0.23	-0.26	-0.10	0.11	-0.04	-0.00	0.03	0.13	ns	ns	0.05	0.01	-0.30	0.10	0.04	0.19	0.06	0.10	ns	ns	
Blikman [49] (MS)	-0.1	0.41	0.22	0.52	-0.28	0.06	0.0	-0.11	ns	ns	-0.20	-0.25	0.0	0.04	-0.3	0.01	-0.18	-0.11	ns	ns	
Van den Akker [41] (MS)	0.04	NA	NA	NA	NA	NA	0.14	NA	NA	NA	-0.19	NA	NA	NA	NA	NA	0.05	NA	NA	NA	
Ehde [48] (MS)	0.24	0.15	0.29	0.39	0.20	0.00	0.27	0.24	ns	ns	0.15	0.00	-0.10	0.34*	-0.09	-0.32	-0.01	0.00	ns	ns	
Zuidema [34](RA)	NA	0.21	NA	NA	0.0	NA	NA	NA	ns	ns	NA	0.49 *	NA	NA	0.41 *	NA	NA	NA	ns	ns	
Given [36] (Cancer)	ns	ns	ns	0.6 *	ns	ns	0.7 *	ns	ns	ns	NA										PP ^a
Ream [31] (Cancer)	ns	ns	ns	ns	ns	ns	ns	ns	0.20	0.0	ns	ns	ns	ns	ns	ns	ns	0.28	0.45	ITT ^a	
Karlson [50] (SLE)	ns	ns	ns	ns	ns	ns	ns	ns	0.20	0.11	ns	ns	ns	ns	ns	ns	ns	0.20	-0.3	ITTa	
Koopman [38] (PPS)	ns	ns	ns	ns	ns	ns	ns	ns	0.29	ns	ns	ns	ns	ns	ns	ns	ns	-0.1	ns	ITTa	
Vogelaar [39] (IBD)	EORTC QLQ c30										EORTC QLQ c30										
	PF	RF	CF	SF	EF	Fatigue	PF	RF	CF	SF	EF	Fatigue	PF	RF	CF	SF	EF	Fatigue	PF	RF	Fatigue
Reif [54] (Cancer)	0.70*	0.76*	0.84*	0.78*	0.65	0.91*	1.10*	1.10*	1.34*	1.13*	1.01*	1.24	0.80*	1.10*	1.10*	1.34*	1.01*	1.24	0.54	ns	ITT ^a
Armes [30] (Cancer)	0.56*	NA	NA	NA	NA	0.0	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ITT ^a
Yates [46] (Cancer)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	PP ^a
Goedendorp [40] (Cancer)	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ns	ITTa
HAQUAMS	Fatigue	Thinking	M. upper	M. lower	Mood	Communication	Fatigue	Thinking	M. upper	M. lower	Mood	Communication	Fatigue	Thinking	M. upper	M. lower	Mood	Communication	Fatigue	Thinking	M. upper
Pöttgen [55] (MS)	0.53	0.27	0.16	0.28	0.18	0.21	0.35	0.27	0.25	0.12	0.15	0.19	ns	ns	ns	ns	ns	ns	ns	ns	ITT ^a
MLHFQ	Overall quality of life										Overall quality of life										
Wang [33] (HF)	0.46*										NA										PP ^a
Personal wellbeing Index	a - 0.19										c - 0.15										ITT ^{a,c}
Ghahari [51](NCD)	0.04										-0.06										ITT ^a
Foster [45](Cancer)	0.04										-0.06										ITT ^a
Multiple Sclerosis Impact Scale	Physical functioning										Physical functioning										ITT ^a
Plow [44] (MS)	0.06										-0.05										ITT ^a
EQ-5D	Utility										-0.31										ITT ^a
Purcell [35] (Cancer)	0.03										0.0										PP ^a
Rheumatoid arthritis-QoL	NA										NA										ITTa
Hewlett [47] (RA)	NA										0.05										ITTa
Global question	-0.02										NS										ITT ^a
Hewlett [37] (RA)	-0.02										NS										ITT ^a

Abbreviations: BL: baseline, PI: post intervention, FUP: follow-up, *: statistically significant positive effect, PP: per protocol, ITT: intention to treat, ^a: mean difference between EG vs CG1, ^b mean difference between pre - post intervention, ^c mean difference between EG vs CG2

SF-36: Short Form Health Survey: Dimensions: PF: Physical Functioning, RP: Role-Physical, BP: Bodily Pain, VT: Vitality, SF: Social Functioning, RE: Role-Emotional, MH: Mental Health, GH: General Health, PCS: Physical Component Score, MCS: Mental Component Score. EORTC-QLQc30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30: Dimensions: PF: Physical functioning, RF: Role functioning, CF: Cognitive functioning, SF: Social Functioning, EF: Emotional functioning. PWI: Personal Wellbeing Index. MSIS: Multiple Sclerosis Impact Scale, EQ-5D: EuroQual-5D, VAS: Visual Analog Scale, MLHFQ: Minnesota living with heart failure questionnaire, HAQUAMS: Hamburg Quality of Life Questionnaire for MS

MS: multiple sclerosis, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus, NCD: neurological chronic disease, HF: Heart failure, PPS: Post-polio syndrome, IBD: Inflammatory bowel disease

and MS) were in line with results from disease-specific systematic reviews on fatigue education [16,70]. The majority of the included studies reported at least small effects on one of the dimensions of QoL at post intervention. The large effects reported in some studies with persons with MS and cancer [30,43,54], and the capacity to significantly affect both outcomes, QoL and fatigue [31,48,52–55], or to even increase the positive impact on QoL at follow-up are remarkable.

The descriptive summary of these complex interventions highlights the heterogeneity of the intervention characteristics. The duration, the frequency and the delivery modalities were diverse but straight-forward to extract, while content-related elements were often described insufficiently and therefore less clear to categorize. The incomplete reporting of education interventions is a well-known problem [71]. According to Rudd et al., [72] this prevents not only a comprehensive evaluation but also the replication and the implementation of evidence-based educations in a real-world setting. We consider the TIDieR checklist [23] an indispensable tool to properly report complex interventions.

Our results show that long interventions (>9.3 h distributed over several weeks) achieved more often statistically significant differences on fatigue and QoL compared to those with a short duration. The duration and in general the dosage might therefore be one of the possible discriminative characteristics for significant and larger effects. The depth and intensity of the reflection and its pertinence are decisive points when aiming for behavioral changes [73,74]. That concerns not only the total duration, the frequency and the number

of themes addressed, but is also reflected by the concrete strategies taught during sessions and homework, the supportive materials, and the applied BCT [27]. We showed that a group of BCT was an integral part of nearly all interventions (intention formation, encouragement, information), other BCTs were less often listed. Unfortunately, the descriptions of the BCT used are often imprecise or the techniques are not discussed, which does not permit further analysis of them. Our findings concerning the set of self-management skills that were taught are supported by Plow et al. [75]. The skills *using resources* and *communicating efficiently with health professionals* received less attention and time compared to the other skills. In tendency, the self-management tasks and skills and the BCT applied did not seem to have an influence on the delivery modalities of the interventions or the outcomes. Based on learning theories, the level of participant involvement during education is a key element [73,74]. The intensity of the interactions might therefore be another key element for significant outcomes and effective interventions. Treatments which include group of peers and the exchange of their experiences is clearly different to the experiences a person might have in an individual or remote interaction [74,76,77]. It is however necessary to consider the difficulty of organizing groups, which must be compatible with the conditions of the institution and the needs of the participants. The advantage of the group setting might not compensate for the logistic and organizational challenges of the implementation and performance of a group education in a real-world setting. That might be the reason why, even though they are probably not more cost-effective, the majority (including all short

interventions) of the included SEMs in this systematic review were delivered individually. To be able to identify association between effectiveness and a set of intervention characteristics (skills, tasks, durations, interactions) a meta-regression would be the methods of choice.

Another question arising is if the person- and disease-related characteristics such as age, gender, and level of education, or the disease, the time from disease on-set, and the time point of SME have an influence on the reported effects in the different studies. For example, the data on persons with cancer and MS suggest consistently a possible efficacy when compared to others diseases. The disease-related factor remains however speculation, as long as the number of high-quality RCTs for the other diseases is limited.

The pooled study population had a mean age of 45 years and was predominantly female (73%). The included publications reported the socio-demographic information of the study participants in different ways. Detailed data on compliance were missing. It would be advisable that fatigue-focused SME is accessible from the early stage of the disease, to avoid the loss of meaningful activities and to maintain life roles and a sense of control. In this case, the content and format should be adapted to guarantee a good match between the actual needs of participants with only first and/ or mild experiences with fatigue and the self-management skills trained. To investigate these aspects, it would be necessary to perform cohort studies to observe the long-term effects of the use of self-management skills on the different life roles.

In addition to the intervention characteristics discussed above, three more methodological aspects might have an influence on the effect size and the statistical significance of the results. Although we included only studies with RCT designs, there are some important differences between them. We observed that the four studies that used waiting lists as control interventions had the highest effects. This finding could support the argument that for people living with fatigue, any kind of support or attention might have some effect due to the central importance of not being left alone with the everyday problems caused by fatigue. Another aspect to consider is the time of follow-up. The implementation of behavior changes, the mastery in performing new skills and the formation of new habits is conditioned by the personal engagement and the support from the social environment, but also by the time factor. Therefore, studies with short follow-up periods might not capture this evolution and may not sufficiently take into account the fact that it takes time to integrate behavioral changes into people's routines. The third aspect involves the outcome dimensions and instruments to assess it. The targeted outcome of patient education is the acquisition of knowledge, skills and behavior to enable the person to manage fatigue rather than to reduce symptoms. Self-efficacy is an ideal proximal indicator for estimating the effectiveness of education, while the relevant endpoint from the patient's perspective is QoL. Unfortunately, self-efficacy is often not considered at all, while QoL is usually a secondary outcome; this might be the reason why several trials did not discuss the findings for QoL, and many did not report all the tested scores. For some studies, the results for QoL measured by the SF-36 were different from those of the primary outcome fatigue, but they did not modify the overall interpretation of the randomized trials [75].

In our review, there was a predominance of studies investigating SMEs in people with MS or during / after cancer treatment, while RCTs in persons with other diseases with similar experiences of fatigue burden have been less frequently performed. During the full-text screening, we however found several pilot studies and recently published study protocols for other chronic conditions (e.g. chronic obstructive pulmonary disease, traumatic brain injury); which indicates a growing attention of researchers and clinicians of the potential benefit of patient education in fatigue management.

Limitations: The overall methodological quality of the included studies was not fully satisfactory. Education interventions are complex, and the type of RCT depends on the clinical context in which they are embedded. For four disease populations (systemic lupus erythematosus, heart failure, post-polio syndrome, inflammatory bowel disease), only one article each satisfied the inclusion criteria which limits the strength of evidence and conclusions we can draw for these populations. However, in addition to the data on statistically significant differences between the SME groups and corresponding control groups, the computation of a standardized mean effect (Cohens' d) on QoL provides the whole range of effect size of the SMEs and facilitates the comparison. We excluded persons with mental health diseases. This was because emotional and psychosocial issues might be a barrier to a successful confrontation with self-management tasks and changes in routines and behavior. The review process was carried out collaboratively between the authors to ensure consensus and maintain an over-disciplinary perspective.

4.2. Conclusions

While the overall evidence on the effectiveness of SMEs on fatigue is limited and inconsistent, for cancer and MS the data show a moderate trend towards efficacy. We described a set of complex interventions including a broad variety of study populations and were able to show that fatigue is a burden that can be approached with SME. The content of the SMEs reflect the underlining theories and the delivery modalities the needs of the people and the conditions of the clinical setting in which they are implemented. Considering the subgroup of studies including persons with cancer and MS, the evidence is moderately consistent and indicates positive effects in favor of SMEs. The studies with medium and large effect size on QoL at follow-up indicate the positive potential of SMEs, and ask for methodologically rigorous research on the common characteristics of these effective interventions.

4.3. Practical implications

The results show the potential benefit of structured SMEs on fatigue and QoL for persons with disease-related fatigue and the variety of intervention elements that can be combined for tailoring SME interventions to targeted groups and contexts.

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CRediT authorship contribution statement

Ruth Hersche: Conceptualization, Methodology, Formal analysis, Investigation, Visualization, Writing – original draft, Project administration. **Katharina Roser:** Methodology, Investigation, Validation, Visualization, Writing – review & editing. **Andrea Weise:** Investigation, Validation. **Gisela Michel:** Validation, Investigation, Writing – review & editing, Supervision. **Marco Barbero:** Writing – review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pec.2021.09.016.

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Chapter 5

General discussion

The primary goals of this thesis have been to explore the effectiveness of self-management education and to document the factors which support successful patient education in persons with diseases related-fatigue. In a long-term perspective, the results of this thesis aim to disseminate the knowledge and the implementation of evidence-based practices, and specifically ease the access to effective self-management education for people with disease-related fatigue.

The first concrete step toward this goal regarded the creation of a manualized occupational therapy-based energy management education (EME) for pwMS-related fatigue, its integration in a multidisciplinary rehabilitation setting, and the proof of its feasibility by a pilot study (Study I). However to justify a change in clinical practice it is necessary to provided data on the effectiveness of IEME preferably resulting from a randomized controlled trial (RCT). Therefore was Study II a feasibility study that aimed to generate the data, necessary to perform a large-scale randomized clinical trial in future. The aim of Study III was to map the key elements and delivery characteristics of a set of self-management educations for people with disease-related fatigue and to explore their effect size on quality of life. The systemically presented information support practitioners and institutions in the implantation of evidence-based practices, and rise at the same time new research questions and development opportunities for health professions.

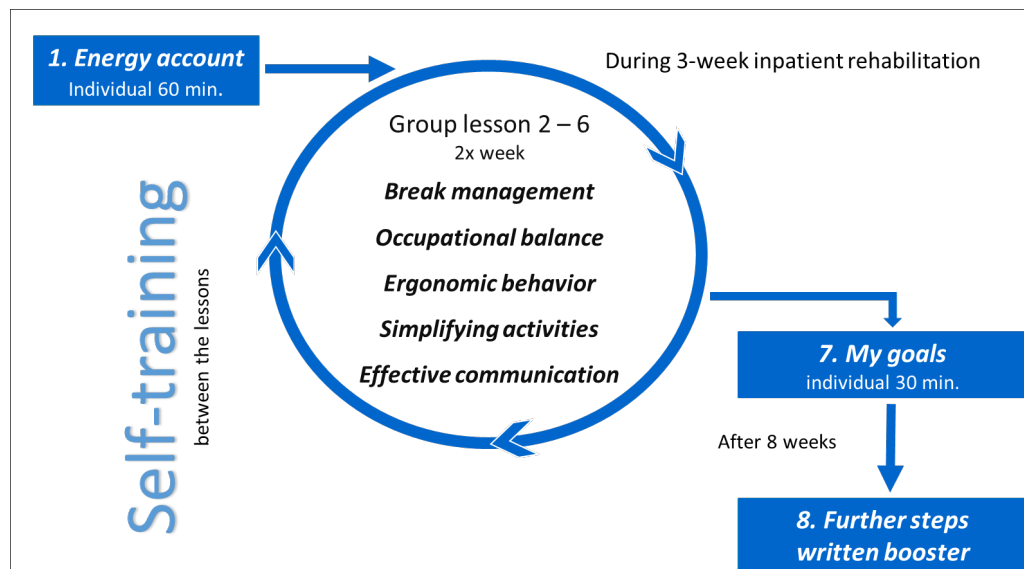
The following section first present the main findings of the three studies, interprets and discusses them in relation to the overall goal, followed by a summary on the further steps already realized and those to address in future.

Main findings

Study I, developed the IEME program, consisting in 7 sessions and integrated it without problems into the regular three-week inpatient rehabilitation program during a pilot period of 12 weeks. The workbook for the participants supported the complex intervention with understandable explanations on the main topics and specific self-training tasks. Focus group participants highly valued peer interaction, the exchange of ideas, and deep reflection. Three

OTs learned in a two-day training to use the highly manualized handbook and to achieve the goals of the different sessions. All participants were taught targeted behaviors, increasing the awareness of the potential benefits of behavior change.

Figure 1: Format and content: Inpatient Energy Management Education



Study II attested the feasibility of the RCT reporting a high recruitment (53%) and low dropout (4.2%) rates. The socio-demographic characteristics in both randomized intervention groups (IEME vs. PMR) were well balanced. The treatment fidelity was high (89% of the tasks described in the IEME manual were carried out) and confirmed the conclusions from Study I. The experimental group compared to the control had in total significant less OT minutes due to the reduced need of individual OT-sessions, and has therefore been economically convenient for the Rehabilitation Centre Valens. IEME-participants interviewed after returning home reported the implementation of some behavioral changes in their daily routines, such as workload reduction and ergonomic behavior, or the redesign of their own daily structure, roles and responsibilities.

Statistically, fatigue impact was significantly improved ($p < 0.05$) in both groups at discharge. In the dimension of perceived competence during daily activities (occupational self-assessment), IEME-participants increased in one subscale at the end of the treatment, whereas PMR participants remained at the pre-intervention level. The perceived self-efficacy in performing energy conservation strategies increased with a significant between-group difference at follow-up (four month from baseline), and a large effect size ($d: > 0.80$) of IEME. Regarding HrQoL (SF-

36) there was a large effect in one (physical functioning) and a medium effect ($d: > 0.5$) in three (mental health, bodily pain, role–physical) out of eight subscales at follow-up.

Overall, the data showed a tendency in favor of IEME in all outcome dimensions, which are however due to the relatively small sample size in this study, often not statistically significant.

Study III showed that self-management education can have a positive effect on fatigue and HrQoL in people with diseases-related fatigue. In the 26 studies included in the final analysis, eight different disease groups have been represented, showing a lack of clinical studies in many other relevant disease populations. Approximately half of the studies (13/26) reported a positive effect at post intervention with a tendency to maintain or increase at follow-up when compared to the control intervention. Among the studies with positive results, the majority reported small or medium effects in the dimensions belonging to the mental health component. The results map a set of complex interventions with a broad variety of intervention characteristics. We showed that a group of behavior change techniques (Abraham & Michie, 2008) was an integral part of every intervention, while other techniques were present only in more tailored interventions. Despite the differences, these qualitative aspects seemed not to have an influence on the effect size, except the duration and the peer-group format, which were linked more often with positive results in fatigue impact and HrQoL.

Interpretation of main findings

The following section presents the interpretation of the main findings of the thesis and discusses the topics considered especially meaningful to its overall goal.

The pilot Study I showed that IEME is well structured and accepted by participants. These are important preconditions, when a clinical trial aims to evaluate a complex intervention and to implement it afterwards into a real clinic context. According to the Medical Research Council (Craig et al., 2008) the evaluation of complex interventions is often undermined by problems of acceptability, compliance, delivery of the intervention, recruitment and retention, and smaller than expected effect sizes. It is therefore highly recommended to perform pilot and/or feasibility studies before a large-scale trial.

Complex interventions are characterized by several active interacting ingredients (Craig et al., 2008). In the case of IEME, there is the knowledge shared in the group and integrated by the OT, the guided reflection and individual analysis of main issues related to energy management,

and the acquisition of behavior skills through self-training tasks. In addition, complex interventions require trained behaviors by those delivering and a certain degree of flexibility and tailoring, without however precluding standardized procedures (Bellg et al., 2004). In fact, during the IEME-sessions, OTs apply a multitude of behavior change strategies, which have to be tailored to the specific living context of the members of the group, to their behavior change stage, and to the numbers of group sessions each member has already participated in.

For that reason, the level of treatment fidelity of the intervention protocol is an important property and a prerequisite when evaluating a complex intervention like IEME (Craig et al., 2008) or when introducing it into everyday practice (Stirman et al., 2016). The feedback from the OTs collected during the focus group in Study I and the treatment fidelity registered in Study II showed that the education program of the two-day training course addressed the education needs of the involved OTs and enabled them to perform IEME, even if they had a different amount of professional experience.

Study II showed the feasibility of the study protocol, delivered information on possible improvements and reported promising effect size of IEME. The identification of adequate outcome measures and instruments is a critical point for a clinical study aimed to evaluate a new intervention, as the dimensions in which changes are expected, how and when change is achieved may not be clear at the outset (Craig et al., 2008). The open questions in relation to IEME were not only the dosage compared to the outpatient versions, but the fact that the participants were, during the whole treatment, out of their habitual environment, which does not favor the transfer from behavior intention into action. IEME-participants were in the clinic setting and could implement in reality only a few energy conservation strategies during their stay in the Rehabilitations Centre Valens, while the most part of the strategies had to be implemented after returning home to obtain the aimed outcomes.

During literature research in the initial stage of IEME-development, and confirmed in Study III, we saw that interventions similar to IEME (e. g. Kos et al., 2007; Mathiowetz et al., 2005; S. Thomas et al., 2013), used nearly always fatigue impact as the primary outcome. In Study II, both groups showed similar changes in fatigue impact after treatment; it is therefore not caused primarily by IEME, but explained by the cumulative effect of the multidisciplinary high quality care at the Rehabilitation Centre Valens. Especially for physiotherapy, there is evidence that exercise training mitigates the perceived severity and impact of fatigue (Razazian et al., 2020; Safari et al., 2017). That opens new questions and hypotheses on a possible positive

accumulative effect of different rehabilitation interventions and underlines what the clinical guidelines for pwMS-related fatigue recommends as best practice. Indeed, IEME is a complex intervention and part of a complex rehabilitation program, making it challenging to interpret the strength of the components of the different interventions which might have interacted. This is however the reality of clinical practice in rehabilitation. The context of rehabilitation does not favor high quality clinical trials aimed to produce evidence for a single intervention or a better understanding of the determinants of the changes involved.

Based on learning theories (Bandura, 1977; Bandura & Adams, 1977), the direct and most proximal effect of IEME was expected to be an increased self-efficacy in new behaviors and acquired skills of the participants, followed by an improved perceived competence in everyday tasks, which might then positively modify the perceived fatigue impact and, in the best case, affect HrQoL. The data from study II showed clearly increased self-efficacy, small differences in occupational performance, and relevant changes in HrQoL in IEME-participants. To explore furthermore these aspects, we have focused in Study III on outcome dimensions related to fatigue and HrQoL, which we consider most relevant from a patient's point of view. The tendency to increase over time, shown in Study III, highlights the meaning of self-management education concerning HrQoL, especially in chronic disease-related fatigue and in persons with newly diagnosed conditions.

Study III described the effect on fatigue and HrQoL of self-management interventions with different characteristics, in persons living with disease-related fatigue and to highlight the skills addressed, tasks trained, and behavior change strategies applied during complex education interventions. The aim was not only to identify the most incisive factors on outcomes, and therefore interesting from the research and the development points of view, but also to provide a detailed summary of such characteristics, as it is relevant and valuable information when planning changes and their feasibility in practice (Mallonee et al., 2006).

Together with the results already discussed, Study III showed a lack of clinical trials, with exception to MS and cancer patients, and consequently of evidence-based interventions, which address the everyday management of fatigue of disease populations confronted with this kind of burden. The lack of clinical studies is caused by different levels. There is still an underestimation of the impact of fatigue, and the uptake of positive findings from trials based on patient education is slow (Glasziou et al., 2008). Also, the late academisation of health professions like OT or nurse in Europe (academic master of science in OT available since 1999,

bachelor of sciences in OT in Switzerland since 2006) and a lack of profiles able to carry out clinical research, or the difficulties in fund raising might be factors contributing to this situation (Thomann, 2019).

Another lack emerged in Study III, also recognized as a problem of complex interventions (Craig et al., 2008), is the often generic information on the behavior change strategies applied in the interventions. It is in fact, not realistic that clinicians carry out behavioral intervention based on the information provided in the published reports exactly like they should be carried out (Glasziou et al., 2008). Some of the missing details are intrinsic to the complexity of education interventions, especially the behavior and attitudes of the leading therapist are difficult to reproduce without support by experienced people. However, unified report standards like the Template for Intervention Description and Replication Checklist (Hoffmann et al., 2014), over-disciplinary terminology and taxonomies would simplify the available information and would allow a greater use of published research in clinical practice.

The primary goals of this thesis and the main findings reported can be linked to the translational sciences and their findings. This emerging discipline supports to bridge the gap between research and practice and focusing on the process of moving evidence-based programs from their development into widespread practice, and providing valuable information about factors associated with successful implementation (Stirman et al., 2016). The fact that the OTs in Switzerland were not able to perform therapy with pwMS-related fatigue in groups or to adapt the materials to their context, has depended probably on a lack of organizational and resource support by their institutions, but probably also on a lack of confidence in interpreting, synthesizing, and applying research findings. Additional factors that have prevented a major integration and evolution towards evidence-based practice were the lack of public awareness on the everyday burden of person living with fatigue and of knowledge of the role and expertise of OTs within this field.

Methodological considerations

The following section summarizes the methodological limits of the three studies and integrates them in a general consideration.

Study I used three focus groups to investigate the experience of IEME-participants and OTs. As it was a pilot, the sample size of nine participants and three OTs was small. The content analysis was oriented to improve the practical aspects of the treatment content, the materials and the self-training tasks, excluding the exploration of personal aspects of living with fatigue. The chosen method allowed gathering suggestions and exploring experiences, but did not permit to have conclusions regarding the strength of the intervention, modifying variables such as self-efficacy, or outcomes such as Modified Fatigue Impact Scale score.

Study II was a feasibility study with 47 pwMS-related fatigue, who were randomly located into two groups (IEME + RAU or PMR + RAU). Due to the restrictions of the inpatient rehabilitation setting, no group had IEME only. The only follow-up was 4 months after the baseline. No data could be gathered 6 months or one year after treatment to document behavioral changes over time and their related effects on outcome measures. These factors, together with the small sample size have limited the robustness of the data and are impeding a generalization.

Study III used a systematic literature review methodology. The 26 studies included had, due to the defined inclusion and exclusion criteria, a high variability of participants, study and intervention protocols, and the necessary homogeneity to perform a meta-analysis was not present. That prevented, together with unspecific details on the key elements (e.g. applied behavior change techniques, duration or format) the computation of an association strength between different intervention characteristics and their effect on HrQoL. The findings from this systematic review indicate that self-management education has can have positive effect on fatigue and HrQoL, but the number of high quality RCTs has to grow before more clear conclusions can be drawn.

Fatigue in chronic conditions is a widespread and burdening phenomenon. The diseases-related and psychosocial factors involved in its etiological mechanism are complex, which make it challenging to measure and treat fatigue. Due to the limited robustness of the three studies data, the still unclear mechanism and impact of fatigue in different populations, the complexity of education interventions and the care setting in which they are performed, the findings of the thesis are difficult to generalize, and request further research on different levels and in multiple directions.

Further development in practice and research

This section gives an overview of the further evolution of the OT-based energy management education (EME) as an evidence-based intervention and its accessibility for persons with fatigue in Switzerland, and the ongoing and planned research projects in this topic.

IEME was introduced at the Rehabilitation Clinic Valens during the feasibility study, and has been maintained as standard treatment in OT for all patients with disease-related fatigue. In addition, an outpatient version of EME has been created with new self-training tasks and instructions in the manual, corresponding to the needs of OTs working mainly in an outpatient or day-hospital setting. As the strategies trained during EME are not disease-specific, we have rewritten the workbook as a disease-independent version, simplifying the creation of mixed patients groups, especially relevant in the outpatient setting, and have facilitated the access to group interventions for people which otherwise wouldn't have had such opportunity. This adaptation was based on the evaluation of different treatment protocols and best practice recommendations for different populations, such as cancer (Reif et al., 2013; Sadeghi et al., 2016), rheumatoid arthritis (Hewlett et al., 2011), stroke (Eskes et al., 2015), heart failure (Kim et al., 2017), chronic pulmonary obstructive disease (Blumenthal et al., 2014), spinal cord injury (Hammell et al., 2009), traumatic brain injury (Raina et al., 2016), systemic lupus erythematosus (Karlson et al., 2004), Parkinson disease (Elbers et al., 2014) and others. This version has been evaluated during a pilot study in 2018, by a group of Swiss OT experts from different fields (Weise & Hersche, 2019).

In 2018, Andrea Weise and me held the first public two-day training course for the OTs who were interested in introducing a structured EME in their institutions or their private practices. Moreover, we have translated and culturally adapted all materials (manual and workbook) into Italian and French to reach colleagues and patients from other parts from Switzerland and Western Europe. Since then, around 100 OTs have been trained and networks of OTs have been built up from several health care practices, supporting each other through the exchange of good practice during implementation. EME courses for persons with related fatigue are now accessible in several regions in Switzerland, Germany, Austria and Italy, and are supported actively by patient organizations (e.g. Swiss MS association, Schweizerische Krebsliga, Fragile Swiss, Italian MS association). The next developments should go towards a digitized workbook that facilitates EME participants and simplifies the consultation of the diverse materials (texts,

audios, videos). Additionally, the Covid-19 pandemic has highlighted the need and accelerated our reflections on how to realize also an online format of EME in the future.

On the research side, a new study protocol for a pilot study with cancer survivors in in- and outpatient settings has been developed and gained a grant in 2020. It aims to generate data for a future RCT through a pre-post design. In addition, in July 2020 a large-scale RCT started to recruit 106 pwMS-related fatigue. It aims to investigate the effect of the combination of two different inpatient programs (high-intensity interval training + IEME versus low-intensity training + PMR) and to provide data on the effectiveness of a multidisciplinary rehabilitation during and after hospitalization. The primary endpoint of this study are changes in HrQoL from baseline to six months follow-up. Secondary endpoints include are: self-efficacy, fatigue impact, cardiorespiratory fitness and blood laboratory values. Associated to this study, an online survey will for the first time document which energy conservation strategies become part of habits and routines of EME-participants. The aim is to determine the factors, which have prevented the implementation or caused that some strategies were dropped after a brief period. These are useful information to further improve the IEME-program.

Conclusions

Fatigue is a common and disabling condition for many people with chronic diseases. The self-management education of persons enables them to implement new behavior habits and to engage successfully in daily routines and social participation through managing their available energy. The findings of this thesis highlight the meaning of self-management education concerning HrQoL in chronic disease-related fatigue and indicate that patient education performed in groups based on occupational therapy and cognitive behavior approach can affect people with diseases-related fatigue in enabling them to live a more active and satisfying life.

The motivation and the long-term goal of this work has been to bridge with relevant results between research and practices, and to empower the knowledge transfer and the implementation of evidence-based practices. As these complex interventions have to be integrated in an already highly structured health services system, the implementation is challenging and should be based on the needs of patients and practitioners, accompanied by researchers or experts with methodological knowledge, and supported by sufficient economic resources.

The different stages of the projects of this thesis, the interactions and focus, which we had overtime with all stakeholders involved, can be compared to the collaboration loop described by a translational framework and characterized by a “knowledge activation” between researcher and practitioners (Stirman et al., 2016). Creating evidence-based interventions and documenting their effectiveness are important steps towards an informed practice, but might not be enough to guarantee substantial changes. To become "best practice" according to Peters & Waterman (2004), a procedure or intervention has to enable an organization to perform notably better than in the past and to improve its organizational structure to such an extent that it creates intrinsic motivation in practitioners and the organization itself to be performed.

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Supplementary material

Study II: Template for Intervention Description and Replication Checklist

Study III: Supplementary tables and materials

The TIDieR (Template for Intervention Description and Replication) Checklist*:

Information to include when describing an intervention and the location of the information

Item number	Item	Where located **	
		Primary paper (page or appendix number)	Other † (details)
1.	<p>BRIEF NAME</p> <p>Experimental intervention: Inpatient energy management education (IEME) Control intervention: Progressive Muscle Relaxation (PMR)</p>		
2.	<p>WHY</p> <p>IEME is based on the principles of patient education (Lorig and Holman, 2003) and empowerment (Castro et al., 2016), the transtheoretical model of change (Norcross et al., 2011), the social cognitive theory, energy conservation strategies and cognitive behavioral techniques (Michie et al., 2013). The goal of IEME is to learn how to manage the own available energy in order to achieve a satisfying and meaningful daily routine. Participants acquire knowledge and understanding about factors influencing their energy level and the consequences of fatigue on their habits and lifestyle. Subsequently, they identify and implement tailored behavior modification.</p> <p>PMR was developed in 1938 by Edmond Jacobson (Conrad and Roth 2007). The aim of PMR is to achieve enhanced mental relaxation by reducing muscle tension (Dayapoğlu and Tan, 2012), and to use this kind of relaxation regularly after return home. Studies have shown a moderate to a significant effect of PMR on the quality of life in pwMS (Ghafari et al., 2009).</p>	<p>p. 4, p. 5, table 1</p> <p>p.7</p>	<p>Lorig, Kate R., and Halsted R. Holman. 2003. "Self-Management Education: History, Definition, Outcomes, and Mechanisms." <i>Annals of Behavioral Medicine</i> 26 (1): 1–7.</p> <p>Castro, Eva Marie, Tine Van Regenmortel, Kris Vanhaecht, Walter Sermeus, and Ann Van Hecke. 2016. "Patient Empowerment, Patient Participation and Patient-Centeredness in Hospital Care: A Concept Analysis Based on a Literature Review." <i>Patient Education and Counseling</i> 99 (12): 1923–39. https://doi.org/10.1016/j.pec.2016.07.026.</p> <p>Norcross, John C., Paul M. Krebs, and James O. Prochaska. 2011. "Stages of Change." <i>Journal of Clinical Psychology</i> 67 (2): 143–54. https://doi.org/10.1002/jclp.20758.</p> <p>Michie, Susan, Michelle Richardson, Marie Johnston, Charles Abraham, Jill Francis, Wendy Hardeman, Martin P. Eccles, James Cane, and Caroline E. Wood. 2013. "The Behavior Change Technique Taxonomy (v1) of 93 Hierarchically Clustered Techniques: Building an International Consensus for the Reporting of Behavior Change Interventions." <i>Annals of Behavioral Medicine</i> 46 (1): 81–95. https://doi.org/10.1007/s12160-013-9486-6.</p> <p>Conrad, Ansgar, and Walton T. Roth. 2007. "Muscle Relaxation Therapy for Anxiety Disorders: It Works but How?" <i>Journal of Anxiety Disorders</i> 21 (3): 243–64. https://doi.org/10.1016/j.janxdis.2006.08.001.</p> <p>Dayapoğlu, Nuray, and Mehtap Tan. 2012. "Evaluation of the Effect of Progressive Relaxation Exercises on Fatigue and Sleep Quality in Patients with Multiple Sclerosis." <i>The Journal of Alternative and Complementary Medicine</i> 18 (10): 983–87. https://doi.org/10.1089/acm.2011.0390.</p> <p>Ghafari, Somayeh, Fazlolah Ahmadi, Masoud Nabavi, Kazemnejad Anoshirvan, Robabe Memarian, and Mohamad Rafatbakhsh. 2009. "Effectiveness of Applying Progressive Muscle Relaxation Technique on Quality of Life of Patients with Multiple Sclerosis." <i>Journal of Clinical Nursing</i> 18 (15): 2171–79. https://doi.org/10.1111/j.1365-2702.2009.02787.x.</p>

WHAT			Hersche et al., 2019. "Development and Preliminary Evaluation of a Three-Week Inpatient Energy Management Education (IEME) Program for People with Multiple Sclerosis-Related Fatigue." <i>International Journal of MS Care</i> , https://ijmsc.org/doi/pdf/10.7224/1537-2073.2018-058 ,
3.	<p>IEME: The treatment manual describes in a detailed way every session integrating the techniques of behavior change that can be used. Every IEME-participant received the IEME-workbook that contains detailed information on all topics, worksheets and self-training tasks. Until now the IEME-manual and workbook is not published yet, but we organize IEME-introduction courses for OTs, in which participants receive the IEME-materials (Herschel et al., 2019). The IEME-manual and workbook is not yet published but we organize IEME-introduction courses for OTs, which include the IEME-materials (Hersche et al., 2019)</p> <p>PMR: PMR involves a standardized series of relaxation exercises (involving 11 large muscle groups) combined with deep breathing. Participants received only verbal instructions, no written instructions were offered. Three weeks after discharge, a reinforcement letter was sent to all participants, to foster motivation for behavioural change and continuation of the exercises.</p>	<p>p. 6, table 1</p> <p>p. 7</p>	
4.	<p>IEME started with a 1-h individual session, followed by five 1-h self-contained IEME group sessions (min. 2, max. 7 pwMS) delivered twice a week, and it concluded with a 0.5-h individual session. Between the IEME sessions, the participants received training regarding the use of energy conservation strategies and planned the implementation of behavioral changes in their daily routine using self-training tasks.</p> <p>During PMR sessions, participants are lying on the floor and follow during 1 h PMR-exercises guided by a trained physical therapist.</p>	<p>p. 6, p. 7, tab. 1</p>	
WHO PROVIDED			
5.	<p>IEME was delivered by three trained OTs.</p> <p>PMR was delivered by trained physiotherapists.</p>	<p>p.6</p> <p>p 7</p>	
HOW			
6.	<p>IEME was delivered face-to face twice a week. The first and the last session are individual sessions, session 2-6 are group-based sessions (min. 2, max. 7).</p> <p>PMR was delivered face-to-face in groups (max. 12 participants).</p>	<p>p. 6</p> <p>p. 7</p>	

WHERE		
7.	The IEME sessions were delivered in a quiet room at the Rehabilitation Centre Valens. Apart a table and the IEME materials no especially infrastructure was necessary.	p. 6
	The PMR sessions were delivered in a quiet room at the Rehabilitation Centre Valens. No especially infrastructure was necessary.	p. 7
WHEN and HOW MUCH		
8.	IEME -participants followed during a 3 weeks period seven sessions (6x1h and 1x 0.5 h; total 6.5 h).	p. 6
	PMR -participants followed during a 3 weeks period 6 sessions (6 x1h)	p.7
TAILORING		
9.	The interventions were not planned to be personalized. IEME -participated and PMR -participants were requested to follow the whole program and all sessions.	
MODIFICATIONS		
10.*	No modification of the IEME or PMR intervention was necessary during the study	
HOW WELL		
11.	Before the study started the three involved, OTs completed a training day in IEME conduction. During the study period, the OTs in charge used a checklist after every IEME sessions to report all steps and tasks completed. During the study, one researcher was available during the whole study period for questions regarding IEME sessions. No fidelity check has been made for PMR	p. 8, p. 13

12. [‡]	Based on the checklist for fidelity checking on average, they carried out 89% (range, 78.8–94.6%) of the tasks described in the IEME manual.	p.13
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**** Authors** - use N/A if an item is not applicable for the intervention being described. **Reviewers** – use ‘?’ if information about the element is not reported/not sufficiently reported.

† If the information is not provided in the primary paper, give details of where this information is available. This may include locations such as a published protocol or other published papers (provide citation details) or a website (provide the URL).

‡ If completing the TIDieR checklist for a protocol, these items are not relevant to the protocol and cannot be described until the study is complete.

* We strongly recommend using this checklist in conjunction with the TIDieR guide (see *BMJ* 2014;348:g1687) which contains an explanation and elaboration for each item.

* The focus of TIDieR is on reporting details of the intervention elements (and where relevant, comparison elements) of a study. Other elements and methodological features of studies are covered by other reporting statements and checklists and have not been duplicated as part of the TIDieR checklist. When a **randomised trial** is being reported, the TIDieR checklist should be used in conjunction with the CONSORT statement (see www.consort-statement.org) as an extension of **Item 5 of the CONSORT 2010 Statement**. When a **clinical trial protocol** is being reported, the TIDieR checklist should be used in conjunction with the SPIRIT statement as an extension of **Item 11 of the SPIRIT 2013 Statement** (see www.spirit-statement.org). For alternate study designs, TIDieR can be used in conjunction with the appropriate checklist for that study design (see www.equator-network.org).

Appendices A

Table A1. Search terms divided into the three blocks: population (P), intervention (I), and outcome (O).

(P) Patients with fatigue Fatigue	AND	(I) Patient education	AND	(O) Quality of life
		OR		OR
		self – management fatigue management nonpharmacological interventions cognitive behavioral therapy psychoeducational occupational therapy energy conservation health behavior health promotion problem solving decision making lifestyle counselling self-care empowerment work simplification behavior change modification supportive nursing		health related quality of life self-efficacy activities of daily living participation wellbeing engagement

Table A2. Search query used in MEDLINE

Last search date: February 3, 2021
((Fatigue[Title/Abstract] AND (((("quality of life"[MeSH Terms] OR ("quality"[All Fields] AND "life"[All Fields]) OR "quality of life"[All Fields]) OR ("self-efficacy"[MeSH Terms] OR ("self"[All Fields] AND "efficacy"[All Fields]) OR "self-efficacy"[All Fields])) OR ("activities of daily living"[MeSH Terms] OR ("activities"[All Fields] AND "daily"[All Fields] AND "living"[All Fields]) OR "activities of daily living"[All Fields])) OR participation[All Fields]) OR ("health"[MeSH Terms] OR "health"[All Fields] OR "well"[All Fields] OR "wellbeing"[All Fields]))) AND (((((((((((((((Nonpharmacologic[All Fields] AND interventions[All Fields]) OR ("cognitive behavioral therapy"[MeSH Terms] OR ("cognitive"[All Fields] AND "behavioral"[All Fields] AND "therapy"[All Fields]) OR "cognitive behavioral therapy"[All Fields])) OR ("self-management"[MeSH Terms] OR "self-management"[All Fields] OR ("self"[All Fields] AND "management"[All Fields]) OR "self-management"[All Fields])) OR Strategies[All Fields]) OR ("occupational therapy"[MeSH Terms] OR ("occupational"[All Fields] AND "therapy"[All Fields]) OR "occupational therapy"[All Fields])) OR ("health behavior"[All Fields] OR "health behavior"[MeSH Terms] OR ("health"[All Fields] AND "behavior"[All Fields]) OR "health behavior"[All Fields])) OR ("problem solving"[MeSH Terms] OR ("problem"[All Fields] AND "solving"[All Fields]) OR "problem solving"[All Fields])) OR ("decision making"[MeSH Terms] OR ("decision"[All Fields] AND "making"[All

Fields)) OR "decision making"[All Fields])) OR ("self-care"[MeSH Terms] OR ("self"[All Fields] AND "care"[All Fields]) OR "self-care"[All Fields])) OR ("life style"[MeSH Terms] OR ("life"[All Fields] AND "style"[All Fields]) OR "life style"[All Fields] OR "lifestyle"[All Fields])) OR ("counselling"[All Fields] OR "counselling"[MeSH Terms] OR "counselling"[All Fields])) OR ("health promotion"[MeSH Terms] OR ("health"[All Fields] AND "promotion"[All Fields]) OR "health promotion"[All Fields])) OR Energy conservation[Text Word]) OR fatigue management[Text Word]) OR Psychoeducational groups[Text Word]) OR Empowerment[Text Word]) OR behavior change[Text Word]) OR energy effectiveness[Text Word]) OR work simplification[Text Word]) OR supportive nursing care[Text Word]) AND Clinical Trial[ptyp] AND "humans"[MeSH Terms]) AND (Clinical Trial[ptyp] AND "humans"[MeSH Terms]))

Table A3. Backward searching strategy

Search terms for the scoping search in Medline (24.12.2018), which produced 215 hits. Out of them, we identified 25 systematic reviews. We followed back relevant trials and included them in the initial pool of this systematic review (n = 82).

("Patient Education as Topic"[Mesh] OR "Education"[Mesh] OR "education"[Subheading]) AND ("Fatigue"[Mesh] OR "Muscle Fatigue"[Mesh] OR "Fatigue Syndrome, Chronic"[Mesh] OR "Mental Fatigue"[Mesh]) AND Review[ptyp]

Systematic reviews consulted during backward searching

Diagnosis (number of identified reviews)	References
Multiple Sclerosis (5)	[1–5]
Rheumatoid Arthritis (2)	[6,7]
Cancer (10)	[8–17]
Stroke (1)	[18]
Chronic obstructive pulmonary disease (1)	[19]
Diabetes (1)	[20]
Chronic fatigue syndrome (2)	[21]
Kidney diseases (1)	[22]
Neuropathy (1)	[23]
Fatigue in general (1)	[24]

- [1] M.J. Wendebourg, C. Heesen, M. Finlayson, B. Meyer, J. Pöttgen, S. Köpke, Patient education for people with multiple sclerosis-associated fatigue: A systematic review, PLOS ONE. 12 (2017) e0173025.
- [2] F. Khan, B. Amatya, Rehabilitation in Multiple Sclerosis: A Systematic Review of Systematic Reviews, Archives of Physical Medicine and Rehabilitation. 98 (2017) 353–7.
- [3] P. Miller, A. Soundy, The pharmacological and non-pharmacological interventions for the management of fatigue related multiple sclerosis, Journal of the Neurological Sciences. 381 (2017) 41–54.
- [4] M. Asano, M.L. Finlayson, Meta-Analysis of Three Different Types of Fatigue Management Interventions for People with Multiple Sclerosis: Exercise, Education, and Medication, Multiple Sclerosis International. 2014 (2014) 1–12
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- [7] K. Carandang, E.A. Pyatak, C.L.P. Vigen, Systematic Review of Educational Interventions for Rheumatoid Arthritis, *American Journal of Occupational Therapy*. 70 (2016) 7006290020p1.
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Table A4: Diagnoses in the full text study sample.

Diagnoses in full text study sample: screened with full text (n) / included in review (n)

Cancer	83 / 8
Multiple Sclerosis	39 / 12
Chronic fatigue syndrome	9 / 0
Rheumatoid arthritis	17 / 3
Fibromyalgia	9 / 0
Chronic disease	6 / 1
Chronic obstructive pulmonary disease	5 / 0
Heart failure	6 / 1
Lupus	4 / 1
Diabetes	2 / 0
Inflammatory bowel disease	2 / 0
Primary care	2 / 0
Traumatic brain injury	3 / 0
QFever	2 / 0
Asthma	1 / 0
HIV	1 / 0
Post-polio syndrome	1 / 1
Postpartum	1 / 0
Stroke	1 / 0
Hypertensive patients	2 / 0
Gulf War Veterans' Illnesses	1 / 0
Hemodialysis patients	1 / 0
Renal Disease	1 / 0
Epilepsy	1 / 0
Myotonic dystrophy	1 / 0
Total disease groups	25 / 8
Total publications	200 / 28

Table A5. Frequency of applied behavior change techniques

Techniques of behavior change	Number of studies which applied technique	Percentage of studies which applied technique
Intention formation	25	< 75%
Encouragement	25	
Information consequences	24	
Information behavior-health	23	
Self-monitoring	23	
Practice	19	
Instruction	19	
Goal setting	18	
Review of behavior goals	18	
Barrier identification	16	>25 - 75%
Follow-up prompts	13	
Feedback on performance	12	
Social support	12	
Time-management	12	
Graded tasks	11	
Self-talk	10	
Social comparison	9	
Stress management	9	
Environmental cues	4	<25%
Role model	4	
Motivational interviewing	4	
Demonstration	3	
Relapse prevention	3	
Information others approval	2	
Contingent rewards	2	
Contract	0	