



Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: [www.elsevier.com/locate/jocn](http://www.elsevier.com/locate/jocn)

Review article

## Cognitive behavioral therapies and multiple sclerosis fatigue: A review of literature

Moussa A. Chalah<sup>a,b</sup>, Samar S. Ayache<sup>a,b,c,\*</sup>

<sup>a</sup> EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, France

<sup>b</sup> Service de Physiologie – Explorations Fonctionnelles, Hôpital Henri Mondor, Assistance Publique – Hôpitaux de Paris, France

<sup>c</sup> Lebanese American University Medical Center, Rizk hospital (LAUMC-RH), Beirut, Lebanon

### ARTICLE INFO

#### Article history:

Received 5 February 2018

Accepted 11 March 2018

Available online xxxxx

#### Keywords:

Multiple sclerosis

Fatigue

Cognitive behavioral therapies

CBT

Cognitive therapy

Behavioral therapy

### ABSTRACT

**Background:** Patients with multiple sclerosis (MS) commonly suffer from fatigue, a multidimensional symptom with physical, cognitive and psychosocial components that can drastically alter the quality of life. Despite its debilitating nature, the current treatment options are limited by their modest efficacy and numerous side effects. Cognitive behavioral therapies (CBT) have been applied in MS patients and might be of help in relieving fatigue. This constitutes the main objective of the current review.

**Methods:** Computerized databases (Medline/PubMed, Scopus) were consulted till January 2018, and a research was conducted according to PRISMA guidelines in order to identify original research articles published at any time in English and French languages on cognitive behavioral therapies and MS fatigue as a primary outcome. The following key terms were used: ('multiple sclerosis' OR 'MS') AND ('fatigue') AND ('cognitive behavioral therapy' OR 'CBT' OR 'cognitive therapy' OR 'CT' OR 'behavioral therapy' OR 'BT' OR 'psychotherapy').

**Results:** Fourteen papers matched the above criteria (11 trials, 2 methods and 1 study addressing CBT mechanisms of action). CBT seems to have positive effects on MS fatigue. However, the onset and duration of effects varied across the studies.

**Conclusion:** These data highlight the promising effects of CBT in MS fatigue. Admitting the limited number of studies, more protocols are needed before drawing any conclusion. Future works might benefit from combining CBT with emerging therapies such as non-invasive brain stimulation techniques which also yielded promising results in the setting of MS. This may help in long-term maintenance of fatigue relief.

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### 1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system (CNS) that usually appears between 20 and 40 years of age. From a pathophysiological perspective, the disease is characterized by processes of demyelination and axonal loss. Depending on the location and extent of lesions, patients would experience various symptoms such as motor weakness, sensory deficit, impaired balance, and urinary disturbance, to cite a few. Recent years have seen a growing interest in studying the emotional and cognitive deficits in MS population. In fact, psychiatric comorbidities can affect up to 95% of MS patients at some point during their lifetime [1]. As for cognitive decline, it would occur in up to 65% of patients and may involve

any cognitive domain such as working memory, information processing speed, attention, learning and executive function, but also social cognition which has recently gained more interest in MS [2,3]. Another important debilitating symptom of this disease is fatigue which could affect up to 75–90% of MS patients [4–6]. No clear definition exists in the literature regarding this complaint which is usually perceived as a 'lack of energy', 'lack of motivation', 'tiredness', 'exhaustion' or 'subjective lack of mental or cognitive energy' [6]. Most importantly, fatigue can drastically impact patients' quality of life (QoL) and may result in serious socio-economic difficulties, namely loss of employment [6]. Despite its debilitating nature, the available pharmacological interventions are limited by their modest efficacy and numerous side effects [4,6]; and this constitutes a real challenge for health care providers in charge of this population. Facing this reality, there was a growing interest in the application of non-pharmacological interventions for the treatment of this symptom. Among these approaches, psychotherapies seem to be of great interest in this

\* Corresponding author at: EA 4391, Excitabilité Nerveuse et Thérapeutique, Université Paris-Est-Créteil, France.

E-mail address: [samarayache@gmail.com](mailto:samarayache@gmail.com) (S.S. Ayache).

context. In particular, cognitive behavioral therapies (CBT), have been tried and could play a role in the management of MS fatigue.

The aim of the current work is to review the available literature on CBT in MS. First, an overview of the pathophysiology of MS fatigue will be provided. This will be followed by a brief definition of CBT along with the relevant studies performed in the context of MS fatigue. Finally, some recommendations will be given for future studies aiming to enhance their outcome in the management of this difficult-to-treat symptom. Pharmacological and other alternative interventions are discussed elsewhere and are beyond the scope of the present work [4–8].

## 2. Pathophysiology of fatigue in multiple sclerosis

Before dealing with the therapeutic options of MS fatigue, it is essential to understand the pathophysiology of this symptom. In recent works, fatigue has been suggested to arise from the underlying pathophysiological mechanisms of the disease itself. In other words, the immune dysregulation, which stands at the origin of MS, would result in demyelination, neurodegeneration and synaptopathy in several brain areas that take part in what was described as the 'cortico-striato-thalamo-cortical loop' of MS fatigue. This loop includes the frontoparietal cortices, thalami, and basal ganglia, among others (For reviews see [4,6]). Neuroendocrine (i.e. hypothalamo-pituitary-adrenal axis) and immune factors (i.e. pro-inflammatory cytokines) also participate in the development of this symptomatology. Other causes such as, anemia, vitamins deficiency, endocrine diseases, psychiatric comorbidities, could trigger or exacerbate fatigue perception. Interestingly, a cognitive behavioral model was suggested in the setting of MS fatigue [9]. In line with the above-cited works, this one attributes the appearance of the symptom to the primary disease factors. However, this model adds that emotional, cognitive, behavioral and physiological factors could determine the extent to which fatigue might impact daily living activity. To start, some behaviors such as overexertion (i.e. all-or-nothing behavior) may be adopted by MS patients in an attempt to meet the perceived demands and may by doing so exacerbate the symptom and increase the need to rest in order to recover [10]. Another behavior would be avoiding fatigue, by resting and day-time sleeping. This could disturb the circadian rhythm and subsequently worsen fatigue [11]. Second, in the context of MS fatigue, some cognitions (or beliefs) could arise, such as to catastrophize about experiencing fatigue or to think it is better to avoid activities that could trigger or enhance this symptom. Third, regarding emotional influence, a bidirectional relationship seems to exist between fatigue and each of anxiety and depression, both of which are frequently encountered in MS patients. On the one hand, the above-mentioned cognitions (or beliefs) might generate or worsen both complaints. On the other hand, anxiety and depression could intensify MS fatigue. Finally, in the cognitive behavioral model of MS fatigue, the previously described factors could interact with abnormal physiological changes encountered in MS such as autonomic hyperarousal, disrupted sleep-wake cycle, physical deconditioning, and inflammatory responses. Therefore, a vicious cycle would take place and result in the maintenance or exacerbation of MS fatigue [9].

These data altogether justify the rationale behind the development of CBT in the treatment of this symptom. CBT try to identify the described dysfunctional cognitions, emotions and behaviors and work on their improvement [12]. Three generations of CBT could be distinguished. The first one is behavioral therapy which highlights the importance of behavioral changes when considering a symptom. This therapy consists of learning to change specific behaviors by experiencing their consequences [13]. The second one focuses on the modulation of false beliefs or cognitions and

includes rational emotive therapies and cognitive therapies [13]. The third one is a combination of several strategies (e.g. mindfulness exercises, cognitive defusion, acceptance of undesirable beliefs or thoughts) aiming to minimize the effects of the symptom by modifying the thinking process [13].

## 3. Cognitive behavioral therapy and fatigue in multiple sclerosis

### 3.1. Study selection

A research was conducted independently by both coauthors according to PRISMA guidelines [14] in order to identify original research articles published till January 2018 in English and French languages about CBT in MS fatigue. Only studies that considered fatigue as the primary outcome were considered for this review. The following key terms were used: ('multiple sclerosis' OR 'MS') AND ('fatigue') AND ('cognitive behavioral therapy' OR 'CBT' OR 'cognitive therapy' OR 'CT' OR 'behavioral therapy' OR 'BT' OR 'rational emotive therapy' OR 'RET' OR 'psychotherapy'). The authors also manually scanned the references of the retrieved papers to look for additional sources. Initially, 19 research articles were found. Five papers were excluded because their primary outcomes were disability [15], insomnia [16], distress [17], balance and coordination [18] or unspecified [19]. Fourteen papers in English language matched the above criteria. Eleven were treatment trials, 2 presented a CBT study design and 1 assessed the mechanisms of action of CBT.

### 3.2. Multiple sclerosis studies

The current knowledge on CBT in the context of MS fatigue derives from reports that were published in the last 10 years. The pioneering study on this topic was performed by van Kessel and colleagues soon after they introduced the cognitive behavioral model of the symptom [12]. In this controlled trial, patients were randomly allocated to receive 8 weekly 50-min-sessions of CBT or relaxation training (RT). The applied CBT consisted of (1) introducing the cognitive behavioral model of MS fatigue since understanding the symptom may enhance patients' self-efficacy, (2) learning to schedule activities which would enable the patients to change their behaviors (all-or-nothing and avoidance) that might have worsened their fatigue, (3) focusing on unhelpful cognitions regarding fatigue and the disease itself, (4) restoring circadian rhythm and emphasizing on sleep hygiene, (5) managing negative emotions, and (6) addressing the role of social support. As for the control arm, RT is a broad non-specific behavioral approach. Although both techniques resulted in fatigue improvement up to 6 months following interventions, the effects were more pronounced following CBT. It is worth noting that in this study, a contamination between both groups could have arisen from the fact that they were both provided by the same psychologist. This fact limits the possibility to generalize the results to other therapists or in other clinical situations. In the light of this work, the authors were interested in understanding the mechanisms of action by which CBT exerts its positive anti-fatigue effects. For this purpose, they performed a mediation analysis [20] aiming to identify the factors that mediate the link between treatment and outcomes [21]. This analysis revealed that some behaviors (i.e. avoidance) and beliefs (negative representation of fatigue, symptom focusing, believing that symptoms reflect damage) were modified following CBT, highlighting the crucial contribution of these factors in a successful CBT.

Implementing CBT in fatigue treatment strategy might constitute a heavy and time-consuming task for psychotherapists and psychiatrists. For this reason, the same authors developed an

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