

# Cognitive Behavioral Therapy for invisible symptoms in Multiple Sclerosis

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## Abstract

*Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by visual impairment, physical pain, cognitive and physical impairments, alterations in balance as well as “invisible” symptoms, such as fatigue and depression. After a presentation of the disease and the biopsychosocial model of health, the aim of the review was to explore different studies focused on the efficacy of psychotherapy in patients with Multiple Sclerosis, in particular the application of Cognitive Behavioral Therapy (CBT) for the treatment of fatigue by applying a specific cognitive-behavioral model. Research on CBT treatment for depression as well as the correlation between depression and fatigue in MS are discussed. Finally, the limitations and efficacy of CBT interventions as part of a multidisciplinary treatment for non-psychological diseases, such as Multiple Sclerosis, are reported in order to provide a support for the CBT intervention of this pathological condition.*

**Keywords:** Multiple Sclerosis; Fatigue; CBT.

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## 1. Introduction

Multiple Sclerosis (MS) is a chronic autoimmune disease of the central nervous system characterized by visual impairment, physical pain, cognitive and physical disabilities and alterations in balance (Compston & Coles, 2008). Some scholars identified a series of “invisible” symptoms, such as fatigue, pain, depression, and anxiety (White, White, & Russell, 2008).

Currently, the dominant model of clinical approach is the biopsychosocial model (Engel, 1977; George & Engel, 1980), which offers a broader perspective of the disease including the interaction between biological, psychological, and social factors. The contrast between biological and psychological is overcome. There are, in fact, many organic diseases, such as hypertension, chronic pain, gastrointestinal disorders and autoimmune diseases (Palomba, 2004) – such as MS - which worsen due to an abnormal psychophysiological responsiveness.

It is important to consider Cognitive Behavioral Therapy (CBT) to modify the cognitive, emotional and behavioral responses that exacerbate the present symptoms. Other authors have shown neurobiological changes after CBT treatment (Goldapple, Segal, Garson, Lau, Bieling, Kennedy *et al.*, 2004) that appear to influence the clinical recovery by modulating the functioning of specific sites in the limbic and cortical regions.

Psychophysiological factors become co-factors of the disease (Palomba, 2004) if not treated, so it is important to treat them to improve the person's quality of life and symptoms.

Some results have shown that changes in depression and fatigue significantly predicted changes in subjective cognitive impairments but not in objective neuropsychological performance (Kinsinger, Lattie, & Mohr, 2010).

The knowledge of the reciprocity between biological and psychological events has led to the application of psychological therapy also in medical diseases. Thanks to behavioral medicine and health psychology, based on a biopsychosocial model, the primary purpose becomes the promotion and maintenance of an individual's physical and mental health (Castellano, Platania, Varrasi, Pirrone, & Di Nuovo, 2020).

More than 500 studies have been carried out concerning the efficacy of CBT in psychiatric diseases, psychological problems and medical problems with psychological components (Beck, 2020); behavioral treatment has also been applied to improve motor skills, to reduce Parkinson's tremors (Mohr, Müller, Mattes, Rosin, Federmann, Strehl *et al.*, 1996) and to rehabilitate

brain-damaged patients (Jacobs, 1998). Regarding the scope of the review, the care of patients with MS requires a multidisciplinary treatment to offer a greater awareness and recognition of symptoms within a comprehensive view of this disease (Grobberio & Falautano, 2013).

In recent years, some studies have analyzed the efficacy of CBT treatment for chronic pain (Ehde, Alschuler, Day, Ciol, Kaylor, Altman *et al.*, 2019), anxiety (Carrigan, Dysch, & Salkovskis, 2018), depression (Bakshi, Shaikh, Miletich, Czarnecki, Dmochowski, Henschel *et al.*, 2000; Mohr, Hart, & Goldberg, 2003), and fatigue beliefs (Van Kessel, Moss-Morris, Willoughby, Chalder, Johnson, & Robinson, 2008; Knoop, Van Kessel, & Moss-Morris, 2012; Van den Akker, Beckerman, Collette, Eijssen, Dekker, & de Groot, 2016; Van den Akker, Beckerman, Collette, Twisk, Bleijenbergh, Dekker *et al.*, 2017).

The aim of this review was to explore the important benefits of psychotherapy, especially CBT, in MS disease, especially in the treatment of fatigue and depressive symptoms, in order to offer input to the application of CBT and to a multidisciplinary view of the disease.

## 2. A multidisciplinary treatment for the fatigue beliefs

Most patients with MS declare that the symptom of fatigue is one of the most troublesome in the illness (Compston & Coles, 2008; Vucic, Burke, & Kiernan, 2010). In fact, in patients with MS the prevalence rate of this symptom is between 75% and 95% (Braley & Chervin, 2010). According to the recommendations of the Multiple Sclerosis Council for Clinical Practice Guidelines (Multiple Sclerosis Council for Clinical Practice Guidelines, 1998), fatigue is the lack of physical and/or mental energy perceived by the patients or by the caregivers, that interferes with the individual's normal and desired activities. Fatigue includes: fatigability and less resistance to effort; fatigue of the short-circuit, related to damaged nerves; MS fatigue, with sudden occurrence and without effort; mental fatigue, as the difficulties to perform also simple cognitive tasks and in the maintenance of attention and concentration; and finally, fatigue related to mood. Fatigue is considered an "invisible symptom" of MS (White *et al.*, 2008), it is multidimensional and difficult to assess because it is subjective. It negatively influences the quality of life, the daily activities and working life of the individuals and can cause unemployment (Strober, Christodoulou, Benedict, Westervelt, Melville, Scherl *et al.*, 2012) and social withdrawal (Smith & Arnett, 2005). For the treatment of fatigue in MS guidelines, a multidisciplinary approach that

includes pharmacological treatment, rehabilitation, physiotherapy, occupational therapy and learning strategies of energy saving is recommended. However, the guidelines do not mention psychotherapy, although in the last years it has had promising outcomes for the treatment of fatigue and other psychological symptoms like depression.

Interest in this aspect of the disease has increased; indeed, there are some studies that have been conducted on non-pharmacological treatment for neurological symptoms, such as fatigue in MS (Blikman, Huisstede, Kooijmans, Stam, Bussmann, & van Meeteren, 2013; Hourihan, 2015).

In this review the results show that in the short-term, energy conservation management (ECM) treatment may be more effective than no treatment in reducing the impact of fatigue and in improving the Quality of Life scales (physical role, social function, and mental health) in patients with MS.

A study has revealed that the implementation intention, in combination with the physical activity program, reduces fatigue and improves mobility, while physical activity accompanied by the mindfulness intervention appears to be effective in improving mobility and in reducing the impact of the disease in patients' lives (Torkhani, Dematte, Slawinski, Csillik, Gay, Bensmail *et al.*, 2021). Mindfulness-based therapy appears to be an effective approach for motor and non-motor functions of MS patients (Lopes & Keppers, 2021), even when administered online (Sesel, Sharpe, Beadnall, Barnett, Szabo, & Naismith, 2019). In fact, there is no proven pharmacological treatment for fatigue in MS (Solari, Uitdehaag, Giuliani, Pucci, & Taus, 2002; Möller, Poettgen, Broemel, Neuhaus, Daumer, & Heesen, 2011) and Veauthier and colleagues suggest to introduce the Berlin Treatment Algorithm for MS fatigue in which CBT or mindfulness-based intervention is included (Veauthier, Hasselmann, Gold, & Paul, 2016).

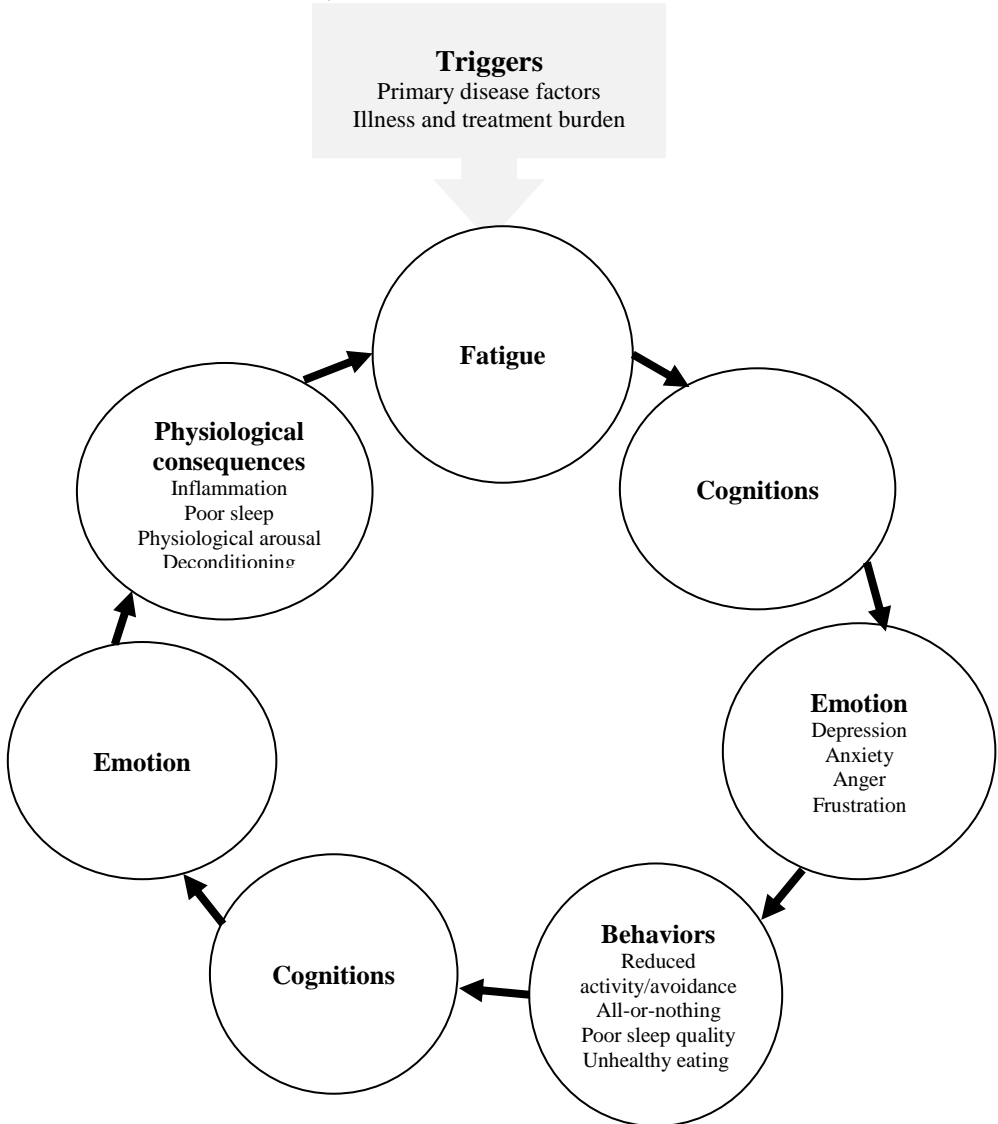
### *2.1. A cognitive behavioral model of fatigue in MS*

Researchers have identified two mechanisms that lead to fatigue: primary factors, such as neuronal and immunological dysfunctions, and secondary factors, such as insomnia, depression, stress, reduced physical activity and adverse effects of medications (Bol, Duits, Hupperts, Vlaeyen, & Verhey, 2009). Secondary factors include beliefs and convictions that maintain the symptom of fatigue (Knoop *et al.*, 2012). Psychologists and psychotherapists could be of help in curing this particular aspect of the disease.

The first model of fatigue in MS is the model of Van Kessel and Moss-

Morris (2006), who hypothesized a disease-related trigger and, subsequently, other factors that maintain and worsen fatigue, which are cognitive, emotional, physiological and behavioral responses to this symptom (Fig. 1).

Figure 1 – *Cognitive behavioral model of fatigue in MS, from Picariello and collaborators (Picariello, Norton, Moss-Morris, Macdougall, & Chilcot, 2020)*



Fatigue initially develops as a result of a neurological dysfunction. The subsequent cognitive interpretation of this symptom - as permanent and uncontrollable – and others factors (catastrophic distortion of the illness, orientation on the symptoms and beliefs concerning the harm of the body) increase the patient's anxiety and negative mood. As a result, the patient exhibits inactivity and excessive rest to regain strength. Ultimately, these dysfunctional behaviors produce physiological consequences, such as insomnia and anxiety-related activation of arousal, maintaining the cycle of fatigue (Van der Werf, Evers, Jongen, & Bleijenberg, 2003; Van Kessel & Moss-Morris, 2006). This vicious cycle also increases the inflammatory process, the sleep-wake dysfunction and the nervous and endocrine system response to stress (Picariello *et al.*, 2020). Recent research by Van Kessel and colleagues has explored the efficacy of the cognitive behavioral model of fatigue in MS patients with a 14-month individual training and also with telephone sessions (Van Kessel *et al.*, 2008). Each session was structured as a classic cognitive behavioral therapy session (plans, weekly review, homework, discussion, session summary, feedback) and, in addition, the authors wrote a handbook on the cognitive behavioral treatment of fatigue.

The treatment involved the following phases:

1. Introduction to the cognitive behavioral model of fatigue and to the biopsychosocial model to increase self-efficacy;
2. Introduction to the cognitive behavioral therapy and model;
3. Activity planning that reduces avoidance and changes of 'all or nothing' behaviors;
4. Restoration of the sleep-wake rhythm;
5. Alternative explanation of MS symptoms;
6. Modification of dysfunctional beliefs about MS and fatigue;
7. Management of negative emotions;
8. Increase of social support.

The outcomes of Van Kessel and collaborators revealed that CBT is more effective than relaxation training in the treatment of fatigue in MS (Van Kessel *et al.*, 2008). Moreover, patients reported secondary improvement with depression, anxiety and stress.

## *2.2. Beliefs that mediate the positive effect of CBT on fatigue*

Knoop and colleagues analyzed beliefs and behaviors that worsened and maintained the symptom of fatigue and underlined factors that mediated a positive effect on fatigue thanks to the cognitive behavioral therapy (Knoop

*et al.*, 2012). According to the authors, specific beliefs about fatigue were uncontrollability and persistence, but beliefs about the illness were also important, such as the catastrophic distortion of the illness or the idea that inactivity was better to avoid the embarrassing symptoms associated to the illness. Regarding dysfunctional behaviors that worsened the symptom of fatigue, the authors found that patients made an excessive effort to satisfy the requests but obtained an adverse effect, such as more fatigue and the need to rest. This behavior is referred to as “all or nothing”. Other behaviors derived and maintained the symptom of fatigue, such as the need for rest and avoidance as well as the excessive rest and daytime sleep, which changed the sleep-wake rhythm and generated more fatigue (Strober & Arnett, 2005). Finally, emotions like depression and anxiety, were found to be generated by beliefs about fatigue and the MS disease, which increased fatigue (Strober & Arnett, 2005).

Knoop and collaborators (Knoop *et al.*, 2012) showed that an 8-week individual session of cognitive behavioral treatment reduced the levels of fatigue as well as the symptoms of depression and anxiety in a group of MS patients, compared to a group exposed to a relaxation training. Following the treatment, Van Kessel and colleagues analyzed three specific beliefs about MS: catastrophic symptoms; shame about the symptoms and the belief that symptoms were signals of harm to the body (Van Kessel *et al.*, 2008). In addition, they considered the negative representation of fatigue as an uncontrollable symptom, hard to understand, continuous and with serious consequences. Target behaviors of the study were rest, avoidance, “all or nothing” behaviors and problems with sleep.

The aim of this study was to verify the efficacy of CBT to reduce the cognitive and behavioral changes that maintained fatigue and to identify the variable that mediated the positive effect of CBT in fatigue. Finally, another purpose was to verify whether cognitive and behavioral changes were independent from changes in the variables connected to depression and anxiety. The results show that a more positive representation of the symptom of fatigue (i.e., more controllable and understandable, time-limited and without serious consequences) following a CBT treatment, reduced the severity of fatigue. Moreover, we found that cognitive changes were more likely the variables mediating the positive effect of CBT on fatigue. Behaviors and beliefs about the illness did not mediate the effect of CBT on fatigue; the same was true for the reduction of the depressive symptom. Our results suggest working with specific beliefs about fatigue during CBT treatment to reduce fatigue, even if the association between fatigue and

depression was shown to be ambivalent.

Positive effects on the severity of fatigue in the short term were confirmed by a recent study by Van den Akker and collaborators following a CBT treatment with 12 sessions (8 in the first two months and 4 in the last two months) during a total period of 4 months, compared to a control group who received only information about fatigue in tree consultancies during a period of 4 months (Van den Akker *et al.*, 2017). The treatment included different phases: formulating the goals; sleep-wake regulation; modification of beliefs about MS and fatigue; regulation of physical, social and mental activity; introduction to the importance of environment and pain manipulation. Evidence supported the Van Kessel and Moss-Morris (2006) model also in this case.

In a recent meta-analysis, the first to verify the efficacy of CBT in the symptom of fatigue, Van den Akker and colleagues argued that CBT should be used as an evidence-based treatment of fatigue in MS patients (Van den Akker *et al.*, 2016). The authors reported positive effects of short-term cognitive-behavioral treatments, more specifically of 8 individual or group sessions, which were conducted face-to-face or by telephone, or both face-to-face and via telephone. Another recent review of fatigue education programs in MS patients confirmed these findings Bakshi *et al.*, 2000; Mohr *et al.*, 2003; Van Kessel *et al.*, 2008; Chruzander, Gottberg, Ytterberg, Backenroth, Fredrikson, Widén Holmqvist *et al.*, 2016). Among various education programs (online, face-to-face or telephone contact, individual or group sessions), CBT programs were reported to be more effective than other non-cognitive behavioral education programs (Wendebourg, Heesen, Finlayson, Meyer, Pöttgen, & Köpke, 2017).

These results suggest the efficacy of CBT in the treatment of fatigue, but further studies are needed to investigate the long-term effects and identify more successful strategies.

### 3. CBT for depression in MS patients

It has been reported that, among MS patients, 50% develop depression (Feinstein, Magalhaes, Richard, Audet, & Moore, 2014; Marrie, Cohen, Stuve, Trojano, Sørensen, Reingold *et al.*, 2015). Depression may occur as an independent affective disorder, as a response in time within 3 months from the diagnosis or because of the inflammatory process degeneration within the central nervous system (Capone, 2019).

Capone (2019) reported that MS patients presented Major Depressive



Disorder with a higher percentage than other neurological illnesses and above 71% compared to people without MS. Depression in this case was characterized by anxiety, dysphoria, irritability, anger, and somatic complaints. Less frequent manifestations were anhedonia, apathy and sense of guilt. As a result of their subjective nature, depressive symptoms can also be classified as “invisible symptoms” (White *et al.*, 2008) and include fatigue, anxiety, and pain. “Invisible symptoms” should be treated because depression has a decisive impact on the quality of life of individuals and increases the risk of suicide – 7,5 times higher than the general population (Marrie *et al.*, 2015) – and it causes additional alterations of the cognitive functions (Capone, 2019).

According to a meta-analysis (Hind, Cotter, Thake, Bradburn, Cooper, Isaac *et al.*, 2014), an 8-week CBT treatment for depression in MS, in individual or group sessions with face-to-face or telephone contact, was effective and increased the patients’ quality of life. As results from the literature, treatment consisted of behavioral activation, increased social interaction, and the identification and modification of thinking and distortions. CBT with MS patients was shown to allow learning strategies for depression, anxiety and negative thoughts, although some patients viewed treatment as a long process that continued after therapy sessions and into everyday life (Gottberg, Chruzander, Backenroth, Johansson, Ahlström, & Ytterberg, 2016). CBT treatment of the symptoms and of the thoughts, emotions and behaviors connected to the illness in MS patients could offer a more understandable view of Multiple Sclerosis and increase awareness and acceptance of this condition in everyday life.

### *3.1. The relationship between fatigue and depression in MS patients*

Fatigue is a characteristic symptom of depression and it is possible to hypothesize that a CBT treatment for depression can also reduce fatigue.

Mohr and colleagues (Mohr *et al.*, 2003) compared a 16-week individual CBT treatment for depression with a sertraline therapy and a group therapy. The authors found that the severity of fatigue was reduced in all three therapies. More specifically, change in depression-related fatigue was influenced by mood changes rather than physical (sleep, diet, energy) or cognitive (guilt, worthlessness) changes.

Neurobiology explains the importance of the relationship between fatigue and depression: the exacerbation of Multiple Sclerosis, caused by immune activation, increases the symptoms of depression (Fassbender, Schmidt,

Mößner, Kischka, Kühnen, Schwartz *et al.*, 1998). At the same time, a treatment for depression reduces proinflammatory cytokines responsible for multiple sclerosis symptoms, including fatigue (Mohr, Goodkin, Islar, Hauser, & Genain, 2001).

However, according to other authors, CBT for depression did not influence fatigue assessment (Chruzander *et al.*, 2016). Likewise, Van Kessel and collaborators (Van Kessel *et al.*, 2008) discovered that only cognitive factors mediated the positive effect of CBT on fatigue and were independent of depression.

Furthermore, the relationship between fatigue and depression was shown to be ambiguous (Bol *et al.*, 2009). On the one hand, depression may be responsible for increased fatigue and for this reason a CBT treatment for depression may reduce fatigue in MS patients (Bakshi *et al.*, 2000). On the other hand, according to Rodgers and colleagues (Rodgers, Manjaly, Calabrese, Steinemann, Kaufmann, Salmen *et al.* 2021), fatigue mediates the association between non-somatic depressive symptoms and the quality of life in MS patients.

Notwithstanding, a few studies considered the relationship between fatigue and depression during a CBT treatment (Wendebourg *et al.*, 2017).

Finally, it remains unclear whether CBT for depression could influence fatigue symptoms in MS patients, although there are favorable outcomes for depression symptoms with biological consequences.

CBT for depression could be an alternative treatment to pharmacological therapies for MS patients with both symptoms of fatigue and depression, but more studies are needed to understand the efficacy of CBT in fatigue.

## 4. Discussion

Cognitive Behavioral Therapy finds application in different areas: Judith Beck (2020) cites numerous studies on the efficacy of CBT in psychiatric disorders (Major Depressive Disorder, Generalized Anxiety Disorder, Panic Disorder, Schizophrenia), in psychological problems (couple or family problems, pathological grief, anger) and medical problems with psychological components. Medical problems with psychological components are, for example, chronic back pain, migraine, tinnitus, cancer pain, somatoform disorders, irritable bowel syndrome, chronic fatigue syndrome and others. In the late Sixties, psychologists and physicians suggested techniques and principles of therapy and behavior modification for the resolution of medical problems. This is how Behavioral Medicine

was born (Martin & Pear, 2019). At the same time, Health Psychology was born thanks to the contribution of experimental, social and applied psychology with the aim to promote and maintain the psycho-physical health of the individual, based on a biopsychosocial model. In recent years, benefits of psychological interventions, such as Group psychotherapy treatment (Langenmayr & Schöttes, 2000), or Psychosocial interventions (Sesel, Sharpe, & Naismith, 2018), have been found in patients with Multiple Sclerosis.

Psychotherapy, in particular cognitive behavioral therapy, collaborates with medicine for individual wellbeing: some scholars revealed neurobiological modifications after a CBT treatment in various pathologies (Goldapple *et al.*, 2004) as well as the reduction of proinflammatory cytokines, responsible for multiple sclerosis symptoms (Mohr *et al.*, 2001).

Studies on CBT treatment in MS patients focused on different aspects, different treatment modalities (individual or group sessions, face-to-face or telephone contacts), different durations and different research methodologies. For this reason, there are some limitations to comparing these studies.

However, the results of several studies (Bakshi *et al.*, 2000; Mohr *et al.*, 2003; Van Kessel *et al.*, 2008; Knoop *et al.*, 2012; Blikman *et al.*, 2013; Hourihan, 2015; Van den Akker *et al.*, 2016; 2017) found the efficacy of CBT in the symptom of fatigue.

Indeed, a recent review has shown that most psychological interventions were successful in improving the quality of life of patients (Gil-González, Martín-Rodríguez, Conrad, & Pérez-San-Gregorio, 2020), while another review investigated the role of non-pharmacological interventions, such as psychotherapy, for the treatment of other symptoms, such as chronic pain, in Multiple Sclerosis (Amatya, Young, & Khan, 2018).

## 5. Conclusions

CBT could be integrated with other therapies or could be used as an alternative therapy to pharmacological therapies, especially for patients with drug-resistant MS.

More studies are needed to understand the relationship between depression and fatigue and to explore the efficacy of CBT on both depression and fatigue in MS patients.

According to a multidisciplinary approach to illness and to a biopsychosocial model of health, these findings have important clinical

implications. CBT, with further experimental studies, can be integrated into the treatment of Multiple Sclerosis and other non-psychological diseases in order to understand how thoughts, emotions and behaviors can influence the biology of the illness and reduce the “invisible symptoms”.

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