

Non Pharmacological Treatment of Insomnia in Multiple Sclerosis Patients: A Brief Review

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Introduction

Multiple Sclerosis (MS) is a chronic inflammatory and neurodegenerative disease with unpredictable evolution. Lesions of the central nervous system can be extensive and lead to severe disorders on a physical and cognitive standpoint [1,2].

Many studies have pointed out the problematic existence of comorbidities and especially of mental and mood disorders in MS patients [3-5]. The quality of life is often compromised [6] due to the uncertainty of the disease outcome [7], as well as by resulting depression [4]. Sleep disorders are also often reported in MS, even though it remains unclear whether they result from MS *per se* or from associated mood disorders.

Prevalence of Mood and Sleep Disorders in MS Patients

Indeed, in this population, there is a prevalence of anxiety and depression at 16.5% and 46% respectively [8]. One third of the MS patients exhibit anxiety disorders, 10% have panic disorders and 8.6% obsessive-compulsive disorders [9,10]. The prevalence of major depressive syndrome over life in MS patients ranges between 22.8% to more than 50% [11]. In addition to neurological and psychiatric morbidity, MS is associated with a disproportionately high prevalence of sleep

disorders. Obstructive sleep apnea syndrome (OSAS), restless legs syndrome (RLS) and chronic insomnia in particular, are frequent problems encountered in the MS population, and play a key role in the development of debilitating fatigue and other poor functional outcomes which, in turn, strengthen mood disorders such as anxiety and depression [12]. Some studies showed that the prevalence of sleep disorders (including insomnia) in MS patients ranged between 30 to 56% instead of 10 to 30% in the general population [13]. More recently, this prevalence was reassessed to 56% on a sample of 7700 individuals [14]. But many of these patients are probably under diagnosed since only 25% of this cohort was treated. Currently, 40% of MS patients may be at risk for insomnia [15,16]. Indeed, fatigue affects 90% of MS patients and recent studies suggest that insomnia is an independent predictor of fatigue in MS [15-18]. Yet, we know that effective treatment of these disorders may prevent fatigue [19,20].

New outcomes should therefore be explored to reduce sleep disorders, especially insomnia, in MS patients, in order to improve the mood of these patients and therefore their quality of life especially by reducing the daytime fatigue.

Psychiatric and Mood Disorders in MS Patients

Mood disorders associated with MS are often under-diagnosed or neglected [21]. They reduce compliance to treatment, exacerbate the somatic symptoms and contribute to the deterioration of functional skills and social status [22]. But above all, depression and anxiety can induce sleep disorders which in turn increase the already existing diurnal fatigue. The patients more predisposed to anxiety disorders are women, people with a history of depression or with alcohol abuse. There are also people with higher levels of social stress, or more likely to consider suicide [23,24]. The psychological stress may contribute to potentiate the disease, and more and more studies now explore this hypothesis [25,26]. We also know that there are frequent bidirectional relationships between sleep disorders and depression [27,28].

Sleep Disorders in MS

Most frequently encountered sleep disorders include Obstructive Sleep Apnea Syndrome (OSAS) and Restless Legs Syndrome (RLS). But the major sleep disorder observed in the MS population is insomnia. The International Classification of Sleep Disorders Diagnostic Manual Third Edition (ICSD-3) defines insomnia as 'a persistent difficulty with sleep initiation, duration, consolidation or quality of sleep that occurs despite the opportunity and circumstances for sleep, and results in some form of daytime impairment' [29]. As a consequence, MS patients suffer important fatigue, impaired concentration or memory, mood disturbances, excessive daytime sleepiness, behavioural problems, reduced motivation or energy, impaired social, family, academic, or occupational performance, proneness to errors, and concerns or dissatisfaction with sleep. Insomnia can result from impairments of the brain areas involved in sleep. In this case, it can be considered as a genuine disease. But it can also result from other symptoms such as nocturia, spasticity, pain, mood disorders, anxiety, and the side effects of drugs or medication. In that case, insomnia is a symptom and persists because of perpetuating factors. This is probably what happens in MS. Indeed, the most common symptoms in MS patients include chronic pain, symptoms of neurogenic bladder, spasticity, comorbid anxiety and depression. All of these symptoms have the potential to interfere with sleep onset, sleep maintenance, or the perception of poor sleep, and should therefore be considered as potential exacerbating factors for insomnia [15,30]. Similarly, the medications used to treat MS-related symptoms can interfere with sleep, especially those related to spasticity [31]. Recent data show that the complaints of insomnia are higher in MS patients who also have depression, suggesting that the treatment of insomnia should start well before the comorbid mood disorders [32]. A number of studies showed a close relationship between insomnia, depression and fatigue in MS patients [13,30,33,34]. This reflects a vicious circle between these three variables. For Strober and Arnett [35], depression and sleep disorders are better predictors of fatigue than the severity of the disease. Moreover, MS patients are at higher risk for depression than the general population. In addition, depression is worsened by sleep disorders, which in turn are exacerbated by depression. Fatigue is both a prevalent symptom in MS, and likely to enhance depression and sleep disorders [30,35]. Consequently, fatigue reported by MS patients could at least partly rely on undiagnosed sleep disorders such as insomnia. Attarian et al. [36] compared fifteen MS patients who had a fatigue complaint and fifteen MS patients without associated fatigue. In the first group, twelve patients presented sleep troubles vs only three in the second group.

It is therefore important that special attention be focused on the management of sleep disorders in MS.

Non-Pharmacological Treatment of Sleep Disorders in Multiple Sclerosis

Hypnotic use is highly prevalent among MS patients. However, it has been reported recently that carry-over effects

from hypnotic agents could contribute to daytime fatigue [37]. Similarly, among the main treatments for depression, selective serotonin reuptake inhibitors, while helpful for depressive symptoms, may sometimes worsen insomnia [38].

Therefore, it could be of interest to focus on a non-pharmacological approach to treat insomnia in MS patients. At this point, it should be stressed that the management of insomnia must be adapted to its primary diagnosis: symptom or disease. Our hypothesis is that insomnia in MS rather meets the definition of an associated symptom more than that of an intrinsic disease. Therefore, we will not consider therapeutic approaches of primary insomnia which must be rare in MS patients.

Cognitive behavioural therapy

It has been highlighted that Cognitive Behavioural Therapy for Insomnia (CBT-I) is an effective approach when treating MS patients with comorbid fatigue and depression [32]. However, for people with MS, it is important to consider physical or motor limitations. As a matter of fact, given the specific instructions that CBT-I involves, it might render this therapeutic approach, if not prohibitive, at least in some cases difficult to apply [39]. For example, these patients may need assistance in completing sleep logs. Cognitive impairments with MS may also serve as a barrier and warrant support and involvement from a partner or caregiver. Owing to high levels of fatigue, longer naps may be necessary for individuals with MS. Waiting until a person feels sleepy to get into bed may not be realistic for individuals who rely on others for assistance with getting into bed, because some individuals may need to accommodate the schedule of a caregiver or aide. Getting in and out of bed if having difficulty falling or staying asleep may not be feasible due to physical limitations. Therefore, working with individuals to make adjustments such as changing a position in bed or the environment of their bedroom (e.g. turning on lights) in these instances may be a proposed modification in the original framework of CBT-I. For individuals who are not able to restrict their time in bed to when they are sleeping as recommended in CBT-I, a sleep compression plan that will allow for more time in bed may be preferable to sleep restriction in some cases [39].

A part CBT-I, many other non-pharmacological therapies have been proposed to reduce stress and anxiety in MS patients.

Exercise

Many studies confirm the benefits of physical activity in persons with MS. Especially it allows increased confidence in performing activities without falling [40]. Physical activity could be however limited to persons with minimal and mild MS, and be less feasible in the moderate to severe forms.

Hydrotherapy

Aquatic treatments offer the benefits of the physical properties of water based on hydrostatic pressure exerting a massage effect. Hence, hydrotherapy reduces pain, fatigue and

disability and improves mood. However, it is of high cost for the necessary facilities and it can be difficult to transfer patients to it [41].

Nutritional therapy

Dietary intervention as a possible mode to help MS patients seems very appealing; however, scientific data supporting this notion remains sparse and controversial. The literature demonstrates the adverse effects of high intake of saturated fatty acids and salt on the development and course of MS. But some authors also report a correlation between favorable adequate supply of omega-3, vitamin D, B12 and folic acid and the risk of exacerbation of some MS symptoms [42].

Medicinal plants

Considering the growing interest towards introducing naturally emerged medicines, more and more consideration is given to prevention and treatment of MS lesions through natural components. There are many good candidates [43]. But more prospective investigations have to be conducted on them, and their efficiency in severe forms of MS is still questionable.

Occupational therapy

MS patients face difficulties in performing daily occupations. Social factors like unemployment contribute to dissatisfaction with the poor performance. Intervention studies are needed to investigate the role of occupational therapy in improving the performance of daily occupations at least in patients who are still able to perform on their own [44].

Acupuncture

Although many studies have suggested that acupuncture was successful in improving MS related symptoms, lack of statistical rigor and poor study design make it difficult to draw any conclusions about the true effectiveness of this intervention in the MS population [45].

Acupressure

Acupressure is a noninvasive procedure that can be used to control symptoms including fatigue. The principles of acupressure are similar to acupuncture except that no needle is used, and the acu-points are stimulated using fingers or special tools. The technique is easy to use and learn, and therefore it can be applied by the patients themselves, but there are no data on the long term effects of acupressure, or on eventual gender differences in symptom management [46].

Relaxation therapy

Relaxation has been reported to be effective on pain in MS patients. This natural intervention allows a reduction of the narcotic addiction often shown in the management of chronic pain [47]. It could, however, be insufficient by itself to significantly reduce pain symptoms in MS.

All these non-pharmacological interventions are among the methods used to reduce physical and psychological symptoms

of MS [48-50]. But currently, one of the most promising non-pharmacological treatments seems to be mindfulness based stress reduction.

Mindfulness-Based Stress Reduction (MBSR) to Treat Sleep Disorders in MS

One of the new treatments in the field of psychotherapy is MBSR. This approach was introduced in the 1970s by Kabat-Zinn et al. [51] and since then, it was applied in many problems such as coping with stress, illness and pain in patients with heart disease, cancer, AIDS, chronic pain, stress-related gastrointestinal problems, headaches, high blood pressure, depression, and anxiety as well as sleep disorders [52-55]. On a neurophysiological level, mindfulness leads to the activation of brain areas associated with positive emotions, and affects immunization functions [56-59]. Dentico et al. [60] report that the meditative practice induced changes in long-term neuronal plasticity which results in increased EEG gamma power in the central and posterior brain areas. This group showed in experienced meditators, that the increase in the parieto-occipital gamma activity also occurred during slow wave sleep [61]. This effect was correlated with the duration of practice suggesting that meditation training can permanently change the sleep EEG.

Few studies have been devoted to the effects of mindfulness in MS patients [62-64]. These studies have all demonstrated that mindfulness improved psychological symptoms of MS patients, and that these positive effects on quality of life lasted at least 6 months after the procedure. As it is often the case in chronic diseases, the feeling of self-efficacy is important in MS patients. A sense of control and acceptance of the disease can decrease the psychological and emotional impact due to the chronic nature of the disease, and therefore contribute to improve the clinical status, including the degree of fatigue [65,66]. Indeed, these are precisely the targets improved by mindfulness.

First, one of the important causes of psychological states is anxiety and depression due to pain that patients experience. In meditation, patients are trained to focus on feeling pain in the body without emotional reactions to the pain, just observing it without judgement. The observing can reduce emotional responses (such as anxiety and depression) that evoke pain in MS. In addition, meditation allows the thoughts to go and come easily, without any attempt to alter, diminish or expand them [67]. Through mindfulness training, participants learn to see their mental events as transient and not as realities, so that they may be confronted with positive or negative thoughts without being faced with anxious or depressive feelings. Mindfulness can create in these patients, the ability of acceptance of their internal experience regardless of its tone [68]. Berkovich-Ohana et al. [69] suggest that these changes reflect the increase in attentional concentration and the awareness of sensory phenomena.

In addition, its effectiveness on sleep disorders was demonstrated in a growing number of studies. MBSR shares some therapeutic purposes with CBT-I. For instance, it is a formalized psychoeducational intervention that helps individuals to self-manage and reframe worrisome and intrusive thoughts, cognitive processes which can contribute to sleep complaints [70]. Several recent studies have demonstrated the effectiveness of MBSR on chronic insomnia [71,72]. It is also of importance to mention that MBSR seems as effective as pharmacotherapy in chronic insomnia [73], but one can speculate that it is certainly less harmful than chronic medication intake. There is however an important difference between both approaches. CBT-I provides efficient techniques to manage the sleep-wake cycle and to minimize deleterious cognitive processes involved in insomnia. But this technique refers to *ad hoc* mechanisms focused on sleep only. It hardly influences the global way of thinking of the individual. By contrast, MBSR has for a goal to deeply modify the patient's perspective, not only on his sleep, but on all aspects of his life. It is a comprehensive approach that aims to fundamentally change the patient's understanding of his external and internal reality, and to enhance his ability to channel his energy and sustainably manage his emotions.

However mindfulness, as a viable approach to the treatment of insomnia, even supported by a growing number of research data, still lacks a better technical validation. As in the case of CBT-I, it remains dependent upon several variables like: patient compliance, professional skills of the team involved, high prices and non-reimbursement by social security policies in many countries.

Conclusion

Sleep problems in individuals with MS are underdiagnosed and undertreated. Moreover, there are often misunderstood components of sleep troubles like fatigue, which is one of the most common and disabling symptom of MS. Given the numerous pharmacological treatments these patients have to undergo, it seems reasonable to explore non-pharmacological issues to treat sleep troubles, in particular insomnia, in order to avoid complex and deleterious pharmacological interactions. Cognitive Behavioral Therapy for Insomnia may be an effective clinical intervention for MS patients who report symptoms of insomnia, especially since it is also effective to reduce symptoms of fatigue and depression. However, due to physical limitations of MS patients, CBT-I in its original frame may be difficult to practice. Hence, clinicians have to consider some appropriate modifications to CBT-I based on the patient's level of disability and other comorbid disorders [39]. Moreover, the effects of CBT-I might be limited to the sleep area neglecting the comorbid mood disorders in their causal dimension. So far, it seems that MBSR would be one of the best non-pharmacological therapeutic options since it could hold benefit for most people with MS, specifically in terms of quality of life, mental health and quality of sleep [63]. It is of course unclear

by now, what benefit mindfulness may hold for people with more advanced MS. Further studies are needed to clarify the feasibility, practicality, acceptability, health and psychosocial benefits of MBSR for patients with MS.

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