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Daytime sleepiness versus fatigue in patients with multiple sclerosis: A systematic review on the Epworth sleepiness scale as an assessment tool

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Summary

Fatigue is a frequent and distressing symptom in patients with multiple sclerosis (MS). In contrast, sleepiness, characterized by difficulties to stay awake and alert during the day, seems to be less prevalent in MS; however exact studies are lacking. In addition, there is a semantic confusion of the concepts of "fatigue" and "sleepiness", which are often used interchangeably. We conducted a systematic review of studies using the Epworth sleepiness scale (ESS) for the assessment of daytime sleepiness in patients with MS. The summarized results of 48 studies demonstrate that sleepiness, as indicated by elevated ESS scores, is less prevalent and less severe than fatigue but is present in a significant proportion of patients with MS. In most cross-sectional and longitudinal studies, there was a moderate association between ESS scores and various fatigue rating scales. Longitudinal studies on the effect of wakefulness-promoting agents failed to show a consistent improvement of sleepiness or fatigue as compared to placebo. It has also been shown that daytime sleepiness is frequently associated with comorbid sleep disorders that are often underrecognized and undertreated in MS. Sleepiness and potential sleep disorders may also precipitate and perpetuate fatigue in patients with MS and should be part of the differential diagnostic assessment. To support an appropriate decision-making process, we propose an algorithm for the evaluation of sleepiness as compared to fatigue in patients with MS.

Keywords: Multiple sclerosis; fatigue; daytime sleepiness; Epworth sleepiness scale; systematic review

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List of abbreviations

CPAP	continuous positive airway pressure
ESS	Epworth sleepiness scale
FIS	fatigue impact scale
FSS	fatigue severity scale
ICSD-3	International classification of sleep disorders (third edition)
MFIS	modified fatigue impact scale
MS	multiple sclerosis
NFI-MS	neurological fatigue index
PLMD	periodic limb movement disorder
PSG	polysomnography
PSQI	Pittsburgh sleep quality index
RLS	restless legs syndrome
SRBD	sleep-related breathing disorder

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Introduction

Multiple sclerosis (MS) is an inflammatory, demyelinating and neurodegenerative autoimmune disease of the central nervous system (CNS) [1]. It is the leading cause of non-traumatic neurologic disability in young adults [2]. MS is a chronic disease, whose clinical course can be defined as relapsing-remitting (RRMS), primary-progressive (PPMS) and secondary-progressive (SPMS), and progressive-relapsing (PRMS) (http://www.nationalmssociety.org) ~~active or inactive and progressive or non-progressive~~ [3]. It involves a spectrum of neurologic symptoms, such as sensory disturbances, impaired vision, paresis, gait difficulties and bladder dysfunction. In addition, fatigue, as well as cognitive decline, reflects the presence and distribution of damage in the CNS and may vary considerably among individuals. MS-related fatigue is ascribed to multifactorial etiologies including inflammatory cytokines, nocturia, pain, infection, anxiety and depression [4]. In addition, poor sleep and sleep disorders, such as restless legs syndrome (RLS), have been identified as contributing factors for MS-related fatigue and are more common in MS patients compared to healthy controls [5,6].

It is reported that 53-92% of patients with MS are affected by fatigue and as many as 46-66% suffer on a daily basis [7–12]. Fatigue is a disabling symptom that can be described as a feeling of tiredness, exhaustion, weariness or lassitude. It is commonly measured by self-rating scales such as the fatigue severity scale (FSS) [13]. In about one third of the patients, fatigue may present as the initial symptom of MS [14]. Overall, 28-60% of patients report that fatigue is their most distressing symptom [12, 14, 15], being a major cause of unemployment and early retirement in MS [16, 17]. Severe fatigue is also related to increased instances of physical disability, neurological impairment and mobility impairment (e.g., bedridden patients reported the most severe fatigue) [16].

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Fatigue is distinct from sleepiness, which is defined by the International Classification of Sleep Disorders (ICSD-3) as the inability to stay awake and alert during the day, leading to episodes of an irrepressible need for sleep or unintended lapses into drowsiness or sleep [18] (Table 1). Sleepiness predisposes people to develop serious performance impairments in daily functioning and is a risk factor for potentially life-threatening domestic, occupational, and vehicular accidents [18]. The complaint of excessive sleepiness during the normal wake period is also a pivotal symptom for sleep disorders of hypersomnolence, as classified by the ICSD-3.

--- *Insert Table 1 about here* ---

Recently, sleep disorders in MS, as well as the causes and consequences of daytime sleepiness in patients with MS, have gained more attention in research, suggesting that sleepiness is an underrecognized and overlooked symptom in MS. In contrast to the huge body of literature on the presence of fatigue in MS, to our knowledge, there is no systematic epidemiological study on the frequency of sleepiness in MS.

The wide spectrum of fatigue prevalence rates in MS patients may be due to the use of different assessment methods based on various definitions and interpretations of the term “fatigue”. In clinical practice as well as in the scientific literature, “fatigue” and “sleepiness” are frequently used interchangeably [19]. Individuals may even subsume both terms under the complaint of “being tired”. Nevertheless, “fatigue”, “sleepiness” or “tiredness” refer to distinct concepts and provide different semantic connotations [20]. The need to distinguish between fatigue and sleepiness is supported by other studies showing that both conditions substantially differ in implications for diagnosis and treatment, subjective experience, and their underlying neurobiological mechanisms [19, 21, 22].

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A widely used approach to evaluate daytime sleepiness on a subjective level, is the employment of the Epworth sleepiness scale (ESS), a self-administered 8-item questionnaire assessing sleep propensity [23]. A total ESS score greater than 10 (range 0 to 24) is indicative for increased sleepiness. In the instructions, the ESS asks for the likelihood of dozing off or falling asleep in different everyday situations, "in contrast to feeling just tired"[23]. Thus, the ESS quantifies daytime sleepiness using behavioral correlates and circumvents subjective evaluations of states of tiredness, sleepiness or fatigue. Assessing sleepiness by this approach avoids semantic confusion, which is a problem when using fatigue questionnaires that are based on self-reports.

The aim of this systematic review is to summarize the results of published studies using the ESS for the assessment of daytime sleepiness in patients with MS. We focused on the frequency and extent of daytime sleepiness compared to fatigue as assessed by self-administered rating scales such as the FSS or other related scales (e.g. neurological fatigue index, NFI-MS, modified fatigue impact scale, MFIS).

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Methods

Literature search and identification of studies

Studies were identified by searching electronic databases and scanning reference lists of articles. The present review only includes studies that used the ESS, which was published in 1991, as an assessment-tool. Therefore, articles that were published before 1991 were not considered. No other limits (e.g. language restrictions) were applied. The search strategy was developed by a subject specialist (RP) in collaboration with an information specialist and librarian who is trained and experienced in conducting comprehensive literature searches (HK). Database searches were conducted by HK on May 14, 2014, with an update on April 22, 2015. In addition, registers for clinical trials were searched on August 04, 2015. While our search strategy was not peer-reviewed, we strived to design, carry out and report the literature search according to current checklists and recommendations [24, 25].

The research question was translated into two search concepts, “multiple sclerosis” and “Epworth sleepiness scale” that were combined using the Boolean operator AND. The search strategy was adapted to the various databases and search interfaces. This included selecting feasible search terms, syntax, and relevant subject headings. The searches were designed to be sensitive and potentially over-inclusive to avoid missing any relevant articles. We searched 28 medical and psychological reference databases hosted by DIMDI, including MEDLINE, Embase, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials. In addition, a full text search was conducted in PubMed Central. In Web of Science Core Collection, we searched for studies on MS that cite the original article about the “Epworth sleepiness scale” by Johns, [23]. Several dissertation databases and four registers for clinical trials were also consulted.

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A detailed documentation of the searches allowing for replication, can be seen in Appendix 1, which is available as an electronic supplement. The reference lists of articles that were regarded eligible were scanned by AF, NK, and RP.

Eligibility assessment

Eligibility assessment was performed independently in a standardized manner by three reviewers (RP, AF, and NK). Disagreements were solved by consensus. If no agreement could be reached, another author (TCW) was designated to make the final decision. Studies were included only if the contained the following: (a) original investigations - articles in which no original data was published were excluded (e.g. mostly reviews, letters to the editor etc.). (b) published ESS data - the article had to provide statistical data of the ESS score (e.g. mean, median). (c) adult (≥ 18 years) patients with MS. (d) sufficient sample sizes, ($n \geq 10$) that allowed for inferential statistics, i.e. no case reports or studies providing only descriptive data. Finally, no restrictions concerning duration of illness, subtype of MS or other specifications were applied. We also did not limit this review to studies with special interventions.

Data extraction

A data-extraction sheet was developed and pilot-tested on 10 pseudo-randomly selected articles. After applying some adaptive changes, it was used for extracting information from all included studies (see Table S1 - Appendix 3). The data extraction was performed by one of the authors (AF) and examined by another (NK). If there were any ambiguities concerning the data it was discussed by a committee of three additional authors (RP, RW, and TCW). From each study we extracted the information presented in Tables 2 and 3.

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Results

Study selection

Disagreements regarding eligibility assessment between the reviewers (AF, RP, and NK) were minor and could be resolved by consensus. Our cross-database search yielded 607 records. After removing duplicates, 521 records remained and were screened for relevance. 440 records were excluded because no original data was published, disorders other than MS were investigated (e.g. sleep disorders, Parkinson`s disease), or there was no ESS data specified in the abstract and no full text articles were available. If the record was categorized as potentially relevant, the full text article was assessed for eligibility. 21 studies were not included because the ESS was not used as an assessment tool. In three studies, the number of participants was too small (< 10) to be included. One of the full text articles was excluded because the patients were younger than 18 years of age. Ten of the full text articles were excluded because no sufficient statistical ESS data was published. However, if the corresponding author of these studies could provide ESS data on request, the articles were included in the study selection (n = 5; see supplementary material - Appendix 2). Finally, our systematic review comprised 48 studies (Table 2) [26-73].

--- Insert Table 2 about here ---

The flow diagram of the selection process is presented in Figure 1. Detailed information of articles excluded by full-text review is given in Appendix 4 of the supplementary material.

--- Insert Figure 1 about here ---

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Review findings

No systematic epidemiological studies on the prevalence of daytime sleepiness in MS patients using the ESS as a main outcome parameter have been published so far. Out of 48 original articles, about one-third (30%) of the studies comprised a larger MS sample size, i.e. at least 100 patients were included. The majority of articles (67%) had a cross-sectional study design, while the others, in most cases, used a long-term longitudinal study design to assess different treatment effects of medication and other interventions such as treatment of sleep disorders [58–72]. In particular, two studies investigated the effect of continuous positive airway pressure (CPAP) treatment on respiratory disturbances occurring during sleep, which are defined as sleep-related breathing disorder (SRBD) [61, 64]. As the ESS and FSS are trait-specific questionnaires, potential improvements of both scores depend on lasting interventions (i.e., from one week to several months). Thus, we did not consider temporary pharmacological effects lasting only a few hours as longitudinal data [51]. We also used baseline results of longitudinal studies to gain cross-sectional data on ESS- and fatigue scores. Out of all investigations, 19 studies provided data on the correlation between the ESS and the FSS (89%) or other fatigue scales (e.g. NFI-MS, MFIS). Finally, for objective measures of sleep disorders in MS patients, nine studies using polysomnography (PSG) [27, 30, 33, 36, 40, 41, 49, 56, 61] and two study applying actigraphy [26, 65] were used.

<u>Cross-sectional data</u>

Among the studies reporting on fatigue levels (n = 40), increased fatigue scores (e.g. FSS > 4 or MFIS > 34) were found in the vast majority (78%) and were mostly well above their critical cut-offs. Increased daytime sleepiness, as defined by a mean ESS score above 10, was detected in 11 studies (23%) reporting ESS values in either total samples or subgroups of patients. The largest non-systematic survey of sleep disorders in the MS population to date,

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comprising 2,375 patients, suggests increased daytime sleepiness in 30% of the respondents based on an ESS score above 10 [31] (see Table 2). Within the patient groups, elevated mean ESS scores mostly ranged from 10.5 to 12.5 and were close to their critical cut-off value. Only a single study, with 21 fatigued MS patients, showed a higher mean ESS score for the whole group (15.7) [33]. On an individual level, the proportion of MS patients with elevated ESS scores was up to 61% in those studies that provided frequency data (23 studies in total). Six studies with population sizes of at least 100 MS-patients reported frequencies of increased ESS scores between 19% and 53%.

Among the 19 studies that investigated the correlation between ESS and fatigue scores, six found no significant correlation between the two [28, 41, 47, 48, 53, 54]. The other studies reported low [45] to high correlations [33] (from r = 0.18 to 0.74) with most correlations being in the moderate range (r = 0.30 to 0.47) [30, 34, 35, 38, 40, 44, 46, 51, 55]. Several studies using PSG or actigraphy found an association between an increased level of sleepiness or fatigue and objectively measured sleep disorders such as disrupted sleep/abnormal sleep cycles [26], impaired sleep quality [33, 41, 49, 56], periodic limb movement disorder (PLMD) [27] or SRBD [40, 61]. Only one polysomnographic study did not find a difference in the sleep parameters between the fatigued versus non-fatigued MS-patients [36].

Longitudinal data

Our search yielded 16 studies reporting ESS data at baseline and at follow-up (see Table 3). Six studies specifically evaluated the efficacy of wakefulness-promoting agents (e.g. modafinil or armodafinil) on fatigue or sleepiness. In two placebo-controlled studies, modafinil [66] or armodafinil [60] did not significantly improve fatigue or sleepiness at all. Among two further studies using placebo, one demonstrated a substantial placebo effect on fatigue with no additional benefit from modafinil [68], whereas the other study only reported

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significant improvements in fatigue compared to the placebo run-in phase [67]. Two non-placebo-controlled studies with modafinil showed significant improvement on either both fatigue and sleepiness [72] or fatigue alone [59]. The impact of other medications focusing on various clinical effects (e.g. on sleep quality or as disease-modifying immunotherapies) was assessed by five other studies. In two placebo-controlled studies, the hypnotic agent eszopiclone had no significant effect on ESS or FSS [58], while the nightly sublingual administration of the antispasmodic drug tizanidine significantly reduced next-day spasticity and was associated with a reduction of the ESS-score. This effect was unexpected, since day-dose tizanidine typically increases daytime hypersomnolence ~~reduced sleepiness~~ [70]. In three observational studies involving immune modulatory drugs, natalizumab improved both sleepiness and fatigue [69], whereas interferon-beta, which may provoke sleep disturbances, did not change [65] or even negatively affected both conditions in the long term [63]. The injection of interferon-beta impaired sleep efficiency during the following night and led to short-term effects of sleepiness and fatigue during the next day [65].

Three of the 16 longitudinal studies investigated the effects of sleep disorder treatment. One study showed a significant improvement of both fatigue and sleepiness, particularly for the treatment of SRBD [61]. Two other studies found that either CPAP-therapy [64] or treatment of different sleep disorders (e.g. RLS, PLMD, insomnia, SRBD) [73] were associated with a significant but moderate decrease of FSS scores, whereas ESS scores did not change. Participants of a cognitive behavioral therapy group improved significantly more over time (6 month follow-up) than participants of relaxation training, in terms of fatigue as assessed by the FSS. Such an improvement was not found for the ESS [71]. In a single study, an energy conservation program to manage fatigue was tested [62]. Significant improvement of cognitive scores on the fatigue impact scale (FIS) could be observed, but no significant changes in all other outcome variables, including FSS and ESS, were found.

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--- Insert Table 3 about here----

Discussion

In our comprehensive literature search we strived to find all available evidence on the use of the ESS as an assessment tool in adult patients with MS. Finally, we identified 48 studies that fulfilled our inclusion criteria.

The majority of studies showed clinically significant fatigue in MS, whereas sleepiness was reported to be less frequent and less severe. Nevertheless, a substantial number of fatigued patients showed increased ESS scores as well. Some studies investigating the association between sleepiness and fatigue revealed weak to moderate correlations between both conditions, mainly depending on the presence of comorbid sleep disorders. In general, sleep disorders such as SRBD [61, 74] or PLMD [27] and impaired sleep quality are often associated with fatigue or sleepiness [33, 56]. Importantly, the small number of available placebo-controlled, interventional studies showed that wakefulness-promoting agents, such as modafinil or armodafinil, were not consistently effective to reduce either sleepiness or fatigue in the long-term [60, 66, 68]. These findings are in line with a 2015 Cochrane database review reporting weak and inconclusive evidence for the efficacy of stimulants, such as modafinil, pemoline or amantadine, as pharmacological treatments for fatigue in MS [75].

The extent of sleepiness and fatigue in MS

In almost all (85%) selected studies using the ESS as an assessment tool, fatigue scores (typically measured with the FSS) were also presented. Increased fatigue in patients with MS,

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as indicated by elevated fatigue rating scores, was present in the majority (78%) of the reviewed studies that provided fatigue data. This finding is in accordance with previous epidemiological studies that showed high prevalence of fatigue in patients with MS [7–10].

In contrast, increased daytime sleepiness (mean ESS score > 10) was observed less frequently (26% of the studies), comprising a limited number of patients with MS (see Table 2). Two studies reporting mean ESS scores of 15.0 and 15.7 referred to two subgroups that were *a priori* defined as sleepy or fatigued comprising only 6 (total n = 12) or 11 (total n = 21) MS patients, respectively. [27, 33]. Of note, the study by Beran and colleagues [27] used the ESS as a specific selection criterion (ESS score ≥ 9) for patients with and without daytime sleepiness. In few other studies indicating pathological sleepiness on a group level, patients were selected regarding fatigue (fatigue descriptive scale ≥ 5) in combination with complaints of sleep disturbances [58]. This was particularly the case for interventional studies investigating the efficacy of wake-promoting substances [66, 68]. In some other studies showing increased ESS scores in patient subgroups, the patients had specifically been selected for increased fatigue levels [26, 33, 39, 56].

In all studies with more than 150 MS patients, the mean ESS score did not indicate increased sleepiness. In the two largest samples of MS patients by Mills and Young [47] (n = 559 with valid ESS data) and Brass and colleagues [31] (n = 2,375), the average ESS scores were 7.9 (mean) and 8 (median), respectively - well below the critical cut-off score. Despite the low mean ESS scores of the study sample published by Brass and colleagues [31], 30% of the patients scored above 10, indicating increased sleepiness. In general, daytime sleepiness does not seem to be a prominent and frequent symptom in MS patients on a group level, but may be present in a substantial number of patients (ranging up to 61%) on an individual level (Table 2).

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The association of sleepiness and fatigue

The majority of studies typically showed increased fatigue scores without overlapping sleepiness. Only one single study, comprising no more than 14 MS patients found increased ESS scores without corresponding elevated fatigue levels [60]. Our results indicate that fatigue without sleepiness is frequent, while sleepiness without fatigue is rare. Thus, if pathological fatigue is present, ESS scores can be either high or low. These findings are in accordance with a pilot study by Merkelbach and Schulz [22], indicating that sleepiness may vary to a noticeable extent independently from fatigue. The authors also suggest sleep disorders as a critical intervening factor that amplifies sleepiness in a subgroup of fatigued MS patients [46]. By extending their preliminary results in a larger study, the authors demonstrated in a single-item analysis of the ESS that only a subset of ESS items referring to self-paced activation for functioning was closely associated with fatigue as assessed by the FSS [46].

Few studies specifically distinguished between the concepts of sleepiness versus fatigue on a semantic level [27, 46], while 19 studies investigated the relationship between both clinical conditions in more detail. These studies, which explored the relationship between the ESS as a main outcome parameter and fatigue scales found mainly moderate correlations between both conditions.

Semantic confusion of concepts

Sleepiness and fatigue are two interrelated but distinct phenomena [19], that can be easily confused [76]. The terms are often used as synonyms, both colloquially and in the scientific literature [77]. In clinical interviews, patients with hypersomnolence often use the term fatigue to describe their symptoms of excessive daytime sleepiness [78]. One particular study showed that patients with narcolepsy and patients with insomnia both scored high on the FSS

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when asked for symptoms of fatigue. However, only narcoleptic patients reported sleepiness as an increased propensity to fall asleep during the day assessed by the ESS [79]. In insomnia research, it is well established to differentiate between both concepts as clinical criteria, as patients with primary insomnia complain about excessive fatigue during the day, but not about sleepiness as defined above [80]. Because the meaning of both terms differs between languages, the assessment of fatigue and sleepiness is even more difficult. This is especially true for the FSS, which uses the term “fatigue” without any further specifications.

There is converging evidence that fatigue and sleepiness are two different concepts with a limited overlap of symptoms. Because fatigue is mostly poorly defined, applied assessment tools are often not precise enough to distinguish between both conditions [81]. Few original studies on MS (e.g. [27, 46]) have explicitly distinguished between the concepts of sleepiness and fatigue and have explored the relationship between both clinical conditions in more detail. In many other studies, the terms fatigue and sleepiness are used inconsistently, sometimes even synonymously [76]. In general, the terms fatigue, tiredness and sleepiness are rarely explored differentially, and their lack of distinction is a major issue in clinical research and practice [21].

The impact of sleep disorders

Fatigue in MS appears to be multifactorial, with a component of fatigue directly attributable to the MS disease process (primary fatigue), as well as to secondary chronic illness factors, such as pain, medication, depression or other comorbidities, including poor sleep [4, 82, 83]. It has been reported that at least 50 % of patients with MS complain about sleep disturbances or poor sleep [5, 84]) Recent studies suggest that primary sleep disorders may intensify MS-related fatigue [31, 85]. In addition, patients with MS are at an increased risk of secondary or comorbid forms of insomnia because common symptoms of MS (e.g. nocturia, pain,

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spasticity, paraesthesias, depression, and anxiety) often interfere with restorative sleep. Specific sleep disorders such as RLS, PLMD, and SRBD have also been reported to be present at higher frequencies in MS patients than in the general population [4, 6, 33, 86]. Comorbid sleep disorders and poor sleep are often unrecognized clinical conditions in MS and may additionally contribute to fatigue [29, 87]. This notion is supported by the findings that treatment of different sleep disorders, particularly SRBD, is effective to reduce fatigue in MS [61, 64, 73].

The largest study included in our review comprised 2,375 MS patients and focused on the frequency of sleep disorders and their association with fatigue and sleepiness [31]. As assessed by the ESS, the prevalence of daytime sleepiness was reported to be 30%, while that for abnormal fatigue measures was 60%. Increased sleepiness and fatigue scores were associated with positive screenings for insomnia, SRBD, and RLS that showed prevalence rates of 32%, 38%, and 37%, respectively. Thus, more than 70% of this large MS cohort screened positive for at least one or more sleep disorders [31]. Studies using sleep questionnaires, actigraphy or PSG found a positive correlation between subjectively or objectively measured disrupted sleep and fatigue in MS patients [26, 27, 40, 48, 56, 61]. Kaynak and colleagues [41] found that the total arousal index was higher in a subgroup of fatigued patients compared to a non-fatigued group. However, another polysomnographic study investigating sleep-related correlates of fatigue in MS, reported conflicting results [36]. In the case of increased daytime sleepiness, sleep disorders associated with hypersomnolence may be highly prevalent, yet underrecognized, clinical conditions in MS contributing to increased fatigue [29].

Methodological constraints

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Our systematic review provides a qualitative and descriptive survey of the summarized studies that include original data. We may have failed to identify all relevant studies as the ESS might not be mentioned in the fields available via the databases' search interfaces. There was noticeable heterogeneity between studies with respect to study design, experimental procedures, and the quality of data sets on ESS or FSS. Therefore, no meta-analysis of effect sizes regarding sleepiness or fatigue scores was feasible for this review. As an operational definition of daytime sleepiness, we used sleep propensity as assessed by the ESS. However, the ESS is a subjective rating of sleep propensity in daily life and covers only one specific aspect of the multi-dimensional concept of sleepiness [88]. In addition, even though the ESS is widely used as an assessment tool in clinical practice and research, this instrument has only modest psychometric properties. The reliability and validity of the ESS as a unidimensional scale for sleepiness has been questioned by a number of studies [89]. However, due to the huge body of findings on the ESS and the knowledge of its strengths and limitations, utilizing the ESS as an assessment tool for evaluating sleepiness in MS seems to be an appropriate approach. Studies on MS comparing subjective and objective measures of sleepiness (e.g. multiple sleep latency test, maintenance of wakefulness test, or pupillography sleepiness test) are rare [27, 40, 41, 49, 90] and beyond the scope of our review but warrant further research.

Implications for clinical practice

Sleepiness may confound measures developed to assess fatigue (see also Table 1). In general, individuals seem to subsume sleepiness under the broader notion of being tired or feeling fatigued. Thus, if patients with MS present fatigue as chief complaints or score high on fatigue scales, clinicians should be aware of the heterogeneity of the various symptoms. To evaluate sleepiness and fatigue in MS as two distinct clinical conditions, we suggest the following approach. ~~presented in a basic flow chart (Figure 2).~~

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~~*--- Insert Figure 2 about here ---*~~

Firstly, MS patients with complaints of fatigue should be evaluated with regard to the severity and clinical significance of the symptoms (e.g. by using the FSS, the MFIS or other rating scales on the impact of fatigue). Secondly, sleepiness should be evaluated by the assessment of clinical signs of daytime sleepiness and supplemented by the use of the ESS. Increased daytime sleepiness may be indicative of sleep disorders associated with hypersomnolence and call for specific diagnostic procedures (ICSD-3). However, hypersomnolence can also be due to insufficient sleep caused by a lack of sleep hygiene or habitual short sleep times. Even if there are no signs of elevated sleep propensity during the day (i.e. ESS $\leq$ 10), MS patients may complain about fatigue due to poor sleep or sleep disturbances, which are highly prevalent in MS [5, 84]. Thus, overall fatigue or tiredness, but not sleepiness, is a core daytime symptom of insomnia that can perpetuate MS-related fatigue similarly to depression [38, 55, 56]. As mentioned above, sleep disturbances and poor sleep are common in MS and may contribute significantly to daytime fatigue.

Veauthier & Paul suggested that MS patients with fatigue (e.g. MFIS > 34) and impaired sleep quality (e.g. Pittsburgh sleep quality index (PSQI) > 5) should undergo further sleep evaluation and, if appropriate, sleep assessment in a sleep laboratory using PSG (e.g. to distinguish between pain, spasticity, and RLS) [6]. In cases of increased fatigue or sleepiness ~~or tiredness~~ associated with ~~poor sleep~~ non-restorative sleep, sleep disturbances observed by others (e.g. heavy snoring, apneas, leg movements) or impaired daytime functioning, MS patients should also be evaluated regarding sufficient sleep quantity and symptoms of specific sleep disorders such as RLS, PLMD, SRBD, or insomnia. Diagnosed sleep disorders have to be treated by sleep experts accordingly. The use of medications causing sedation or hypersomnia, as well as comorbid somatic or psychiatric disorders such as depression and

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anxiety, also needs to be taken into account. Patients with symptomatic sleepiness may particularly benefit from wakefulness-promoting agents, activity, or daytime naps but not from rest [21]. If clinically significant fatigue is primary and intrinsic to the MS pathology, therapy should focus on fatigue-specific treatment such as energy conservation programs, cooling therapy or cognitive-behavioral therapy [71, 91, 92].

Conclusions

Given the high but often underestimated prevalence of disturbed sleep in MS, patients with MS who suffer from fatigue that affects daily functioning should undergo a sleep evaluation if there are any signs of poor or non-restorative sleep. Within the prominent complaint of fatigue, sleepiness as a distinctive symptom can be easily overlooked. If patients with MS report fatigue or tiredness, specific aspects of unintentional sleep or the propensity to fall asleep should be assessed. In this context, the ESS, as a short and easy-to-administer questionnaire, may be used as an additional assessment tool. The presence of daytime sleepiness can guide diagnostic evaluations with respect to comorbid sleep disorders associated with hypersomnolence, allowing potential treatment by effective countermeasures of sleepiness (e.g. wakefulness-promoting agents; avoidance of monotony, utilizing power naps, no rest).

Although sleepiness seems to be less prevalent and less severe than fatigue, it is present in a substantial number of patients with MS. Yet, sleepiness and tiredness-related fatigue due to sleep disturbances are both underrecognized and undertreated clinical conditions in MS that are in need of specific diagnoses and appropriate treatments.

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Practice points

- Sleepiness and fatigue are two interrelated, albeit distinct concepts with limited overlap.
- In patients with MS, fatigue is more prevalent and severe than daytime sleepiness.
- Fatigue without sleepiness is frequent in MS, whereas sleepiness without fatigue is rare.
- High scores on fatigue scales are often accompanied by increased daytime sleepiness. Therefore, the ESS should also be applied in MS patients with increased fatigue scores. Both clinical conditions may be associated with sleep disorders.
- Increased sleepiness, as well as significant complaints of fatigue and poor sleep, warrants further assessment of potential comorbid sleep disorders or negative effects of hypnotic use. Elevated ESS scores may be indicative of sleep disorders associated with hypersomnolence and demand specific treatment of daytime sleepiness.
- The clinical significance of daytime sleepiness in MS patients remains unknown; nevertheless it may be presumed that it diminishes the quality of life of the patients.

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Research agenda

- The assessment of the prevalence of daytime sleepiness in MS is needed. This requires a systematic epidemiological study using the ESS or other questionnaires in a large population of patients with MS focusing on the assessment of daytime sleepiness as the inability to stay awake and alert.
- Cross-sectional studies on distinct subtypes of MS should take into account both concepts of fatigue and sleepiness, using adequate and established assessment tools for each condition.
- Longitudinal studies are necessary to clarify whether the course of MS is related to the development of fatigue, sleepiness or sleep disorders.
- Prospective studies following MS patients with different subtypes should be performed to allow for the analysis of the association between fatigue, sleepiness or potential sleep disorders and the clinical MS status of the patients including the severity of disability as well as MRI findings.
- Studies comparing objective assessments of daytime sleepiness (e.g. maintenance of wakefulness test, pupillography, vigilance or sustained attention tasks) with subjective measures of sleepiness and fatigue are needed in patients with MS
- In MS, systematic studies using the ESS or other screening tools for hypersomnolence are needed. Abnormal findings should be validated using more specific assessments (e.g. polysomnography).

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References

1. Weissert R. The Immune Pathogenesis of Multiple Sclerosis. *J Neuroimmune Pharmacol* 2013;**8**:857–866.
2. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014;**83**:1022–1024.
3. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 2014;**83**:278–286.

*4. Krupp LB, Serafin DJ, Christodoulou C. Multiple sclerosis-associated fatigue. *Expert Rev Neurothera* 2010;**10**:1437–1447.

5. Merlino G, Fratticci L, Lenchig C, Valente M, Cargnelutti D, Picello M et al. Prevalence of 'poor sleep' among patients with multiple sclerosis: an independent predictor of mental and physical status. *Sleep Med* 2009;**10**(1):26–34.
6. Veauthier C, Paul F. Sleep disorders in multiple sclerosis and their relationship to fatigue. S*leep Med* 2014;**15**(1):5–14.
7. Asenbaum S, Zeitlhofer J, Kollegger H, Klösch, G & Vass, K. Sleep quality and fatigue in multiple sclerosis- preliminary results. *Sleep Research Online* 1999;**2**(Suppl. 1):475.
8. Colosimo C, Millefiorini E, Grasso MG, Vinci F, Fiorelli M, Koudriavtseva T et al. Fatigue in MS is associated with specific clinical features. *Acta Neurol Scand* 1995;**92**(5):353–5.
9. Iriarte J, Subirá ML, Castro P. Modalities of fatigue in multiple sclerosis: correlation with clinical and biological factors. *Mult Scler* 2000;**6**(2):124–30.
10. Krupp LB, Pollina DA. Mechanisms and management of fatigue in progressive neurological disorders. *Curr Opin Neurol* 1996;**9**(6):456–60.

ACCEPTED MANUSCRIPT

11. Vercoulen JH, Hommes OR, Swanink CM, Jongen PJ, Fennis JF, Galama JM et al. The measurement of fatigue in patients with multiple sclerosis. A multidimensional comparison with patients with chronic fatigue syndrome and healthy subjects. *Arch Neurol* 1996;**53**(7):642–9.
12. Freal JE, Kraft GH, Coryell JK. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil* 1984;**65**(3):135–8.
13. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;**46**(10):1121–3.
14. Krupp LB, La Alvarez, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. *Arch Neurol* 1988;**45**(4):435–7.
15. Kinkel RP. Fatigue in multiple sclerosis: Reducing the impact through comprehensive management. *Int J MS Care* 2000;**2**(3):3–10.
16. Hadjimichael O, Vollmer T, Oleen-Burkey M. Fatigue characteristics in multiple sclerosis: the North American Research Committee on Multiple Sclerosis (NARCOMS) survey. *Health Qual Life Out* 2008:**6**:100.
17. Smith MM, Arnett PA. Factors related to employment status changes in individuals with multiple sclerosis. *Mult Scler* 2005;**11**(5):602–609.
18. American Academy of Sleep Medicine. *International classification of sleep disorders*. 3rd ed. IL, USA: Darien;2014.
19. Shen J, Barbera J, Shapiro CM. Distinguishing sleepiness and fatigue: focus on definition and measurement. *Sleep Med Rev* 2006;**10**(1):63–76.
20. Sukovic. A. *Measuring the meaning of "sleepy", "fatigued" and "tired": a semantic differential study*.[Thesis]:Flinders University;2007.

ACCEPTED MANUSCRIPT

21. Neu D, Linkowski P, le Bon O. Clinical complaints of daytime sleepiness and fatigue: how to distinguish and treat them, especially when they become 'excessive' or 'chronic'? *Acta Neurol Belg* 2010;**110**(1):15–25.

22. Merkelbach S, Schulz H. What have fatigue and sleepiness in common? *J Sleep Res* 2006;**15**(1):105–6.

*23. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;**14**(6):540–5.

24. McGowan J, Sampson M, Lefebvre C. An Evidence Based Checklist for the Peer Review of Electronic Search Strategies (PRESS EBC). *Evidence Based Library and Information Practice* 2010;**5**(1):149–54.

25. Atkinson KM, Koenka AC, Sanchez CE, Moshontz H, Cooper H. Reporting standards for literature searches and report inclusion criteria: making research syntheses more transparent and easy to replicate. *Res Syn Meth* 2015;**6**(1):87–95.

*26. Attarian HP, Brown KM, Duntley SP, Carter JD, Cross AH. The relationship of sleep disturbances and fatigue in multiple sclerosis. *Arch Neurol* 2004;**61**(4):525–8.

27. Beran RG, Ainley LA, Holland G. Sleepiness in multiple sclerosis: A pilot study. *Sleep Biol Rhythms* 2008;**6**(4):194–200.

*28. Braley TJ, Chervin RD, Segal BM. Fatigue, Tiredness, Lack of Energy, and Sleepiness in Multiple Sclerosis Patients Referred for Clinical Polysomnography. *Mult Scler Int* 2012;**2012**:673936.

29. Braley T, Segal B, Chervin RD. Obstructive Sleep Apnea and Fatigue in Patients with Multiple Sclerosis. *J Clin Sleep Med* 2014;**10**(2):155–62.

30. Braley TJ, Segal BM, Chervin RD. Hypnotic use and fatigue in multiple sclerosis. *Sleep Med* 2015;**16**(1):131–7.

*31. Brass SD, Li CS, Auerbach S. The Underdiagnosis of Sleep Disorders in Patients with Multiple Sclerosis. *J Clin Sleep Med* 2014;**10**(9):1025–31.

ACCEPTED MANUSCRIPT

*32. Bøe Lunde HM, Aae TF, Indrevåg W, Aarseth J, Bjorvatn B, Myhr KM et al. Poor Sleep in Patients with Multiple Sclerosis. *PLoS ONE* 2012;**7**(11):e49996.

33. Chen JH, Liu XQ, Sun HY, Huang Y. Sleep Disorders in Multiple Sclerosis in China: Clinical, Polysomnography Study, and Review of the Literature. *J Clin Neurophysiol* 2014;**31**(4):375–81.

34. Constantinescu CS, Niepel G, Patterson M, Judd A, Braitch M. Orexin A (hypocretin-1) levels are not reduced while cocaine/amphetamine regulated transcript levels are increased in the cerebrospinal fluid of patients with multiple sclerosis: No correlation with fatigue and sleepiness. *J Neurol Sci* 2011;**307**(1):127–31.

35. Dias RA, Hardin KA, Rose H, Agius MA, Apperson ML, Brass SD. Sleepiness, fatigue, and risk of obstructive sleep apnea using the STOP-BANG questionnaire in multiple sclerosis: a pilot study. *Sleep Breath* 2012;**16**(4):1255–65.

36. Elkattan MM, El-Serafy OA, Helmy SM, Kishk NA. Exploring the Relationship Between Fatigue and Sleep Disturbances in Multiple Sclerosis. *Egypt J Neurol Psychiat Neurosurg* 2009;**46**(1):193–202.

37. Frauscher B, Egg R, Brandauer E, Ulmer H, Berger T, Poewe W et al. Daytime sleepiness is not increased in mild to moderate multiple sclerosis: a pupillographic study. *Sleep Med* 2005;**6**(6):543–7.

38. Ghajarzadeh M, Sahraian MA, Fateh R, Daneshmand A. Fatigue, depression and sleep disturbances in Iranian patients with multiple sclerosis. *Acta Med Iran* 2012;**50**(4):244–9.

39. Heesen C, Nawrath L, Reich C, Bauer N, Schulz K, Gold SM. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* 2006;**77**(1):34–9.

40. Kaminska M, Kimoff RJ, Benedetti A, Robinson A, Bar-Or A, Lapierre Y et al. Obstructive sleep apnea is associated with fatigue in multiple sclerosis. *Mult Scler* 2012;**18**(8):1159–69.

ACCEPTED MANUSCRIPT

41. Kaynak H, Altintaş A, Kaynak D, Uyanik O, Saip S, Ağaoğlu J et al. Fatigue and sleep disturbance in multiple sclerosis. *Eur J Neurol* 2006;**13**(12):1333–9.

42. Kister I, Caminero AB, Monteith TS, Soliman A, Bacon TE, Bacon JH et al. Migraine is comorbid with multiple sclerosis and associated with a more symptomatic MS course. *J Headache Pain* 2010;**11**(5):417–25.

43. Knudsen S, Jennum PJ, Korsholm K, Sheikh SP, Gammeltoft S, Frederiksen JL. Normal levels of cerebrospinal fluid hypocretin-1 and daytime sleepiness during attacks of relapsing-remitting multiple sclerosis and monosymptomatic optic neuritis. *Mult Scler* 2008;**14**(6):734–8.

44. Kotterba S, Eren E, Fangerau T, Malin J, Sindern E. Sleepiness and fatigue in multiple sclerosis - comparison of different measuring instruments. *Fortschr Neurol Psychiatr* 2003;**71**(11):590–4.

45. Labuz-Roszak B, Kubicka-Baczyk K, Pierzchala K, Machowska-Majchrzak A, Skrzypek M. Fatigue and its association with sleep disorders, depressive symptoms and anxiety in patients with multiple sclerosis. *Neurol Neurochir Pol* 2012;**46**(4):309–17.

*46. Merkelbach S, Schulz H, Kölmel HW, Gora G, Klingelhöfer J, Dachsel R et al. Fatigue, sleepiness, and physical activity in patients with multiple sclerosis. *J Neurol* 2011;**258**(1):74–9.

47. Mills RJ, Young CA. The relationship between fatigue and other clinical features of multiple sclerosis. *Mult Scler* 2011;**17**(5):604–12.

48. Moreira, N C V, Damasceno RS, Medeiros, C A M, Bruin, P F C de, Teixeira, C A C, Horta WG et al. Restless leg syndrome, sleep quality and fatigue in multiple sclerosis patients. *Braz J Med Biol Res* 2008;**41**(10):932–7.

*49. Neau J, Paquereau J, Auche V, Mathis S, Godeneche G, Ciron J et al. Sleep disorders and multiple sclerosis: a clinical and polysomnography study. *Eur Neurol* 2012;**68**(1):8–15.

ACCEPTED MANUSCRIPT

50. Neumann M, Sterr A, Claros-Salinas D, Gütler R, Ulrich R, Dettmers C. Modulation of alertness by sustained cognitive demand in MS as surrogate measure of fatigue and fatigability. *J Neurol Sci* 2014;**340**(1-2):178–82.

51. Niepel G, Bibani RH, Vilisaar J, Langley RW, Bradshawb CM, et al. Association of a deficit of arousal with fatigue in multiple sclerosis: Effect of modafinil. *Neuropharmacology* 2013;**64**:380–8.

52. Papuć E, Stelmasiak Z, Grieb P, Rejdak K. CSF hypocretin-1 concentrations correlate with the level of fatigue in multiple sclerosis patients. *Neurosci Lett* 2010;**474**(1):9–12.

53. Pokryszko-Dragan A, Bilińska M, Gruszka E, Biel Ł, Kamińska K, Konieczna K. Sleep disturbances in patients with multiple sclerosis. *Neurol Sci* 2013;**34**(8):1291-1296.

54. Sauter MC. *Abnorme Tagesmüdigkeit bei Multipler Sklerose: Zusammenhänge mit Fatigue, Tagesschläfrigkeit, Vigilanz, Depression, Angst und Lebensqualität* [Dissertation]. Wien: Universität Wien;2004.

55. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler* 2006;**12**(4):481–6.

*56. Veauthier C, Radbruch H, Gaede G, Pfueller CF, Dörr J, Bellmann-Strobl J et al. Fatigue in multiple sclerosis is closely related to sleep disorders: a polysomnographic cross-sectional study. *Mult Scler* 2011;**17**(5):613–22.

57. Wunderlin BW, Kesselring J, Ginzler H, Walser B, Kuhn M, Reinhart WH. Fatigue in multiple sclerosis is not due to sleep apnoea. *Eur J Neurol* 1997;**4**(1):72–8.

58. Attarian H, Applebee G, Applebee A, Wang B, Clark M, McCormick et al. Effect of eszopiclone on sleep disturbances and daytime fatigue in multiple sclerosis patients. *Int J MS Care* 2011;**13**(2):84–90.

59. Brioschi A, Graminga S, Werth E, Staub F, Ruffieux C, Bassetti C et al. Effect of Modafinil on Subjective Fatigue in Multiple Sclerosis and Stroke Patients. *Eur Neurol* 2009;**62**(4):243–9.

ACCEPTED MANUSCRIPT

60. Bruce J, Hancock L, Roberg B, Brown A, Henkelman E, Lynch S. Impact of Armodafinil on Cognition in Multiple Sclerosis: A Randomized, Double-blind Crossover Pilot Study. *Cogn Behav Neurol* 2012;**25**(3):107–14.

61. Côté I, Trojan DA, Kaminska M, Cardoso M, Benedetti A, Weiss D et al. Impact of sleep disorder treatment on fatigue in multiple sclerosis. *Mult Scler* 2013;**19**(4):480–9.

62. García Jalón EG, Lennon S, Peoples L, Murphy S, Lowe-Strong A. Energy conservation for fatigue management in multiple sclerosis: a pilot randomized controlled trial. *Clin Rehabil* 2013;**27**(1):63–74.

63. Gerhard R. *Fatigue und Tagesschläfrigkeit bei Patienten mit schubförmig remittierender Multipler Sklerose (RR-MS) unter Therapie mit Interferon beta-1a (Avonex)* [Dissertation]. Bochum: Ruhr-Universität Bochum;2009.

64. Kallweit U, Baumann CR, Harzheim M, Hidalgo H, Pöhlau D, Bassetti CL et al. Fatigue and Sleep-Disordered Breathing in Multiple Sclerosis: A Clinically Relevant Association. *Mult Scler Int* 2013;**2013**:1-7.

65. Mendozzi L, Tronci F, Garegnani M, Pugnetti L. Sleep disturbance and fatigue in mild relapsing remitting multiple sclerosis patients on chronic immunomodulant therapy;an actigraphic study. *Mult Scler* 2010;**16**(2):238–47.

66. Möller F, Poettgen J, Broemel F, Neuhaus A, Daumer M, Heesen C. HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. *Mult Scler* 2011;**17**(8):1002–9.

67. Rammohan KW, Rosenberg JH, Lynn DJ, Am Blumenfeld, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two centre phase 2 study. *J Neurol Neurosurg Psychiatry* 2002;**72**(2):179–83.

68. Stankoff B, Waubant E, Confavreux E, Edan G, Debouverie M. Modafinil for fatigue in MS: A randomized placebo-controlled double-blind study. *Neurology* 2005;**64**(7):1139–43.

ACCEPTED MANUSCRIPT

69. Svenningsson A, Falk E, Celius EG, Fuchs F, Schreiber K, Berkö S et al. Netalizumab Treatment Reduces Fatigue in Multiple Sclerosis. Results from the TYNERGY Trial;A Study in the Real Life Setting. *PLoS ONE* 2013;**8**(3):e58643.

70. Vakhapova V, Auriel E, Karni A. Nightly sublingual tizanidine HCl in multiple sclerosis: clinical efficacy and safety. *Clin Neuropharmacol* 2010;**33**(3):151–4.

71. van Kessel K, Moss-Morris R, Willoughby E, Chalder T, Johnson MH, Robinson E. A Randomized Controlled Trial of Cognitive Behavior Therapy for Multiple Sclerosis Fatigue. *Psychosom Med* 2008;**70**(2):205–13.

72. Zifko UA, Rupp M, Schwarz S, Zipko HT, Maida EM. Modafinil in treatment of fatigue in multiple sclerosis. *J Neurol* 2002;**249**(8):983-987.

73. Veauthier C, Gaede G, Radbruch H, Gottschalk S, Wernecke K, Paul F. Treatment of sleep disorders may improve fatigue in multiple sclerosis. *Clin Neurol Neurosurg* 2013;**115**(9):1826–30.

74. Kaminska M. *Sleep-disordered breathing and fatigue in multiple sclerosis* [Thesis]:McGill University Library;2010.

75. Mücke M, Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P et al. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev* 2015:**5.**

76. Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro CM. Subjective fatigue and subjective sleepiness: two independent consequences of sleep disorders? *J Sleep Resarch* 2005;**14**(3):245–53.

77. Sukovic A, Lack LC, Wright HR. Quantifying the differences in meaning between „sleepy“, „tired“, and „fatigued“. *J Sleep Resarch* 2008;**17**(Suppl. 1):176.

78. Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *Chest* 2000;**118**(2):372–9.

ACCEPTED MANUSCRIPT

79. Valko PO, Bassetti CL, Bloch KE, Held U, Baumann CR. Validation of the fatigue severity scale in a Swiss cohort. *Sleep* 2008;**31**(11):1601–7.

80. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. *Sleep* 2006;**29**(9):1155–73.

81. Pigeon WR, Sateia MJ, Ferguson RJ. Distinguishing between excessive daytime sleepiness and fatigue: toward improved detection and treatment. *J Psychosom Res* 2003;**54**(1):61–9.

82. Multiple Sclerosis Council for Clinical Practice Guidelines. Fatigue and Multiple Sclerosis: *Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis*. Washington, DC: Paralyzed Veterans of America;1998.

83. Kos D, Kerckhofs E, Nagels G, D'hooghe MB, Ilsbroukx S. Origin of fatigue in multiple sclerosis: review of the literature. *Neurorehabil Neural Repair* 2008;**22**(1):91–100.

84. Tachibana N, Howard RS, Hirsch NP, Miller DH, Moseley IF, Fish D. Sleep problems in multiple sclerosis. *Eur Neurol* 1994;**34**(6):320–3.

85. Kaminska M, Kimoff RJ, Schwartzman K, Trojan DA. Sleep disorders and fatigue in multiple sclerosis: evidence for association and interaction. *J Neurol Sci* 2011;**302**(1-2):7–13.

86. Sieminski M, Losy J, Partinen M. Restless legs syndrome in multiple sclerosis. *Sleep Med Rev* 2015;**22**:15–22.

87. Brass S, Duquette P, Proulx-Therrien J, Auerbach S. Sleep disorders in patients with multiple sclerosis. *Sleep Med Rev* 2010;**14**(2):121–9.

88. Cluydts R, Valck E, Verstraeten E, Theys P. Daytime sleepiness and its evaluation. *Sleep Med Rev* 2002;**6**(2):83–96.

*89. Kendzerska TB, Smith PM, Brignardello-Petersen R, Leung RS, Tomlinson GA. Evaluation of the measurement properties of the Epworth sleepiness scale: a systematic review. *Sleep Med Rev* 2014;**18**(4):321–31.

ACCEPTED MANUSCRIPT

90. Egg R, Högl B, Glatzl S, Beer R, Berger T. Autonomic instability, as measured by pupillary unrest, is not associated with multiple sclerosis fatigue severity. *Mult Scler* 2002;**8**(3):256–60.

91. Sauter C, Zebenholzer K, Hisakawa J, Zeitlhofer J, Vass K. A longitudinal study on effects of a six-week course for energy conservation for multiple sclerosis patients. *Mult Scler* 2008;**14**(4):500–5.

92. Schwid SR, Petrie MD, Murray R, Leitch J, Bowen J, Alquist A et al. A randomized controlled study of the acute and chronic effects of cooling therapy for MS. *Neurology* 2003;**60**:1955–1960.

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Figure legends

Figure 1 Flow diagram of the study selection process

Legend below figure:

MS: multiple sclerosis; ESS: Epworth sleepiness scale

~~**Figure 2** Flow diagram of the diagnostic assessment of sleepiness and fatigue in multiple sclerosis (MS)~~

~~*Legend below figure:*~~

~~ESS: Epworth sleepiness scale; FSS: fatigue severity scale; MFIS: modified fatigue impact scale; PSG: polysomnography; PSQI: Pittsburgh sleep quality index~~

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Table 1 Comparison of fatigue and sleepiness as two different domains

	Fatigue	**Sleepiness**
Definition	*"Fatigue is a subjective lack of physical and/or mental energy that is perceived by the individual or the caregiver to interfere with usual and desired activities."* (p. 2) [82]	*"Sleepiness is the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep."* (p. 143) [18]
Symptoms	• Feelings of tiredness, exhaustion, weariness or lassitude • not necessarily associated with sleep pressure • no definite sleep drive when resting (e.g. lying down to relax)	• Decreased level of alertness or wakefulness • increased tendency to fall asleep or doze off unintentionally • sleep drive when resting (e.g. lying down to nap)
Semantics	• Tiredness is commonly used as synonym (e.g. by insomniacs)	• Tiredness is commonly used as synonym (e.g. by narcoleptics)
Characteristics in MS	• Common and most troublesome symptom • strong negative impact on social and occupational functioning	• Not commonly associated with MS • often associated with sleep disorders

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Table 1 continued

Assessment by common rating scales	**Fatigue severity scale** (FSS) - most widely used validated scale - evaluates the impact on motivation, physical abilities and social functioning - self-administered, 9 items - 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree) - critical cut-off: mean FSS score >4 (min: 1; max: 7) or total FSS score ≥36 (min: 9; max: 63)	**Epworth sleepiness scale** (ESS) - most commonly used scale in sleep research and clinical settings - assessment of sleep propensity - self-administered, 8-item questionnaire - 4-point Likert scale (from 0 to 3) to rate the likelihood of dozing off in eight everyday situations - critical cut-off: total ESS score >10 (min: 0; max: 24)
Objective assessments	• No validated measures available	• Maintenance of wakefulness test; multiple sleep latency test; EEG; pupillography • psychomotor vigilance task; sustained attention and vigilance tasks; driving simulator
Counter-measures	• Alleviated by periods of rest, unlike weakness (asthenia) • limited efficacy of stimulants	• Most effective: sleep or short naps, but not rest • stimulants temporarily effective

EEG: electroencephalography; ESS: Epworth sleepiness scale; FSS: fatigue severity scale; MS: multiple sclerosis

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Table 2 Summarized studies using the Epworth sleepiness scale (ESS) as an assessment tool in patients with multiple sclerosis (MS) – cross-sectional studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Attarian et al. 2004 [26]	30 (15)	15 fatigue 15 non-fatigue	46.4 (-) 33.5 (-)	73% total	**12*** [2-24] 5* [0-19]	60% 13%	**7*** [5-11] 3* [1-4]	r not reported p=.02	CS CC	Significant correlation between fatigue and disrupted sleep/abnormal sleep cycles in MS assessed by actigraphy.
Beran et al. 2008 [27]	12 (14)	6 sleepiness 6 non-sleepiness	47.8 (-) total	83% total	**15.0** (4.4) 4.8 (3.1)	- -	**5.1** (1.7) 3.4 (1.4)	-	CS[PSG] CC	Significant relationship between PLMS with arousals and increased sleepiness
Braley et al.[+] 2012 [28]	30 (30)	Total	46.7 (11.3)	70%	**11.3** (4.9)	-	-	n.s.	CS[PSG] CC	Fatigue, tiredness, and lack of energy, but not sleepiness, are more frequent in MS compared to controls.
Braley et al. 2014 [29]	195	Total 110 elevated OSA risk 85 no elevated OSA risk 154 OSA not confirmed 41 diagnosed OSA	47.1 (12.1) 50.3 (11.8) 43.0 (11.1) 45.8 (12.2) 52.1 (10.4)	66% 53% 82% 68% 59%	8.1 (5.1) 9.1 (5.0) 6.9 (5.1) 7.9 (5.0) 9.0 (5.6)	- - - - -	**4.6** (1.8) **5.1** (1.6) 4.0 (1.8) **4.5** (1.8) **5.0** (1.6)	FSS r=.44; p<.0001	CS CC	Sleep disturbances, especially OSA, are frequent in MS and may contribute to fatigue..
Braley et al. 2015 [30]	190	Total 121 fatigue 69 non-fatigue	47.0 (12.2) 47.6 (11.5) 46.4 (13.3)	67% 65% 71%	8.2 (5.1) 9.4 (5.3) 5.8 (4.0)	- - -	**4.6** (1.8) **5.7** (0.9) 2.5 (0.8)	-	CS	47% of MS patients use hypnotics; carry-over effects may be involved in fatigue
Brass et al. 2014 [31]	2375	Total	54.7 (12.4)	81%	8* [0-24]	30%	**45*** [6-63]	-	CS	The majority of MS patients are affected by one or more sleep disorders, often undiagnosed.
Bøe Lunde et al.[+] 2012 [32]	90 (108)	Total (73 with valid ESS) 24 good sleepers 49 poor sleepers	45.0 (10.4) 43.2 (12.0) 46.2 (10.4)	54% 38% 65%	8.6 (4.6) - -	34% 22% 42%	- - -	-	CS CC	Poor sleep is common in MS. Treatment may improve sleep and quality of life.

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Table 2 continued (2) – cross-sectional studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Chen et al. 2014 [33]	21 (11)	11 fatigue 10 non-fatigue	30.9 (11.0) 26.8 (4.1)	73% 70%	**15.7** (7.2) 9.0 (2.8)	38% -	**50.8** (6.1) 26.1 (6.4)	FSS r=.74; p<.001	CS[PSG] CC	Sleep disorders and excessive daytime sleepiness are more common in MS.
Constantinescu et al. 2011 [34]	34	24 valid ESS data	41.5** [36-49]	58%	10** [5.3-14.5]	-	**5.4** ** [4.4-6.1]	FSS r=.47; p=.019	CS CC	No evidence of orexin A deficiency in MS but in other CNS inflammatory diseases
Dias et al. 2012 [35]	103	Total	45.8 (11.0)	72%	7.3 (4.8)	23%	**4.6** (1.6)	FSS r=.31; p<.01	CS	Over 40% of MS patients show elevated OSA risk.
Elkattan et al. 2009 [36]	20 (10)	10 fatigue 10 non-fatigue	27.7 (6.5) 28.8 (6.7)	- -	7.2 (4.0) 5.3 (4.2)	- -	27.7 (6.5)[1] 28.8 (6.7)[1]	-	CS[PSG] CC	Sleep parameters do not distinguish between fatigued and non-fatigued MS patient.s
Frauscher et al. 2005 [37]	61(42)	Total	34.5 (8.3)	53%	7.4 (3.5)	26%	-	-	CS CC	No increased daytime sleepiness in MS compared to controls
Ghajarzadeh et al. 2012 [38]	100	64 fatigue 36 non-fatigue	34.0 (8.4) 28.4 (8.3)	73% 78%	3.8 (3.1) 3.6 (3.1)	6% 6%	*35.3 (17.6)*°[5] *19.1 (16.5)*°[5]	MFIS r=.33; p=.001	CS	Significant correlations between fatigue scores and depression, sleep quality, and ESS
Heesen et al. 2006 [39]	30	15 fatigue 15 non-fatigue	46.6 (11.7) 42.9 (10.2)	60% 60%	**10.5** (4.7) 3.3 (2.4)	- -	**6.1** (0.7) 1.5 (0.7)	-	CS	Fatigue in MS may be influenced by increased levels of inflammatory cytokines.
Kaminska et al. 2012 [40]	62 (32)	Total	47.3 (10.4)	73%	8.4 (4.4)	34%	**5.1** (1.6)	FSS r=.31; p=.002	CS[PSG] CC	OSA is common in MS and related to fatigue, but not to sleepiness.
Kaynak et al. 2006 [41]	37 (13)	27 fatigue 10 non-fatigue	37.4 (8.7) 36.5 (8.4)	59% 50%	4.4 (2.8) 3.3 (3.0)	7% 0%	**5.5** (0.9) < 4	n.s.	CS[PSG]	Sleep fragmentation observed in MS patients can be involved in MS fatigue.
Kister et al. 2010 [42]	167	94 migraineurs 73 no headache	43 (11.0) 47 (13.0)	90% 57%	8.1 (-) 5.6 (-)	- -	**5.0 (-)** 3.6 (-)	-	CS	Migraine in MS is more frequent than in the general population.
Knudsen et al. 2008 [43]	48 MS and MON	Total	- [21-57]	71%	5.6 (2.9)	10%	-	-	CS	Intact hypocretin system in both subgroups, no increased sleepiness

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Table 2 continued (3) – cross-sectional studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Kotterba et al. 2003 [44]	31	Total	35.6 (8.3)	58%	6.1 (2.9)	10%	**4.3** (1.6)	FSS r=.42; p<.05	CS	Terms ”sleepiness” and “fatigue” are often confused, but different scales allow for differentiation
Labuz-Roszak et al. 2012 [45]	122	Total	37.7 (10.8)	71%	6.3 (3.9)	21%	**40.6** (14.8)[1]	FSS r=.18; p=.03	CS	Fatigue is frequent in MS and moderately correlated with depression and anxiety.
Merkelbach et al. 2011 [46]	80	Total	43.2 (9.8)	71%	8.1 (3.7)	-	**4.4** (1.6)	FSS r=0.42; p<0.001	CS	Physical activity correlates with disease severity, but not with fatigue or sleepiness.
Mills and Young[+] 2011 [47]	635	559 valid ESS data	46.6 (10.9)	71%	7.9 (4.5)	-	-	n.s.	CS	Fatigue is correlated with disability, disease type and sleep duration (u-shaped correlation).
Moreira et al. 2008 [48]	44	32 RLS	40.7 (14.8)	67%	5.7 (4.0)	7%	-	n.s.	CS	MS patients with RLS show greater disability, poorer sleep and increased levels of fatigue.
		12 non-RLS	44.1 (13.4)	75%	5.7 (3.0)	total	-			
Neau et al. 2012 [49]	205	Total questionnaire	43.7 (11.1)	76%	7.3 (4.8)	31%	*81.6 (34.2)*°[3]	FIS	CS[PSG]	Sleep disturbances and excessive daytime sleepiness are frequent in MS.
	25 with PSG	8 fatigue + sleepiness	40.1 (11.2)	63%	**14.7** (0.5)	-	*118.2 (23.8)*°[3]	r=.68 subgroups		
		17 fatigue, non-sleepiness	39.7 (9.3)	59%	4.6 (2.1)	-	*65.6 (33.1)*°[3]	p<.0001		
Neumann et al. 2014 [50]	35 (15)	30 fatigue	44.7 (7.1)	73%	8.2 (2.1)	0%[x]	***75.6*** *(13.5)*°[4]	-	CS	Reaction time is an objective marker for fatigability.
		5 non-fatigue	45.3 (6.1)	40%	5.4 (3.0)	-	***49.4*** *(10.6)*°[4]			
Niepel et al.[+] 2013 [51]	26 (9)	Total	-	65%	5.6 (4.1)	15%	-	r=0.41	CS	Fatigued MS patients have reduced levels of alertness and sympathetic activity. Modafinil shows alerting and sympathomimetic short-term effects.
		17 fatigue	49.4 (9.2)	71%	7.0 (3.8)	-	-	p=0.039 in	CC	
		9 non-fatigue	41.8 (13.1)	56%	3.0 (3.7)	-	-	fatigued patients		

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Table 2 continued (4) – cross-sectional studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Papuc et al.	38 (15)	Total	36* [21-68]	53%	6* [2-11]	-	**5.5*** [1.7-6.6]	-	CS	CSF hypocretin-1 levels do not differ between MS and
2010 [52]		10 fatigue	34* [21-69]	54%	6* [2-11]	-	**5.7*** [4.8-6.6]		CC	controls, but are correlated with fatigue levels.
		28 non-fatigue	38* [22-55]	60%	6* [4-8]	-	2.6* [1.7-4.1]			
Pokryszko-Dragan et al.	100	Total	42 [20-67]	69%	6.3 [0-19]	19%	3.8 [1.1-7.0]	n.s.	CS	Sleep disturbances may increases fatigue and are related
2013 [53]		49 fatigue	-	-	6.4 (3.9)	-	-			to MS symptoms and therapies.
		51 non-fatigue	-	-	6.2 (4.7)	-	-			
Sauter	30	Total	40.4 (9.2)	67%	9.7 (4.2)	13%	**5.2** (1.1)	n.s.	CS	MS patients differ from controls in sleep efficiency,
2004 [54]									CC	sleep quality, and quality of life.
Stanton et al.	60	Total	41* [19-69]	72%	7 * [0-19]	32%	11* [2.5-15.8]	FSS	CS	Sleep disturbances are frequent in MS and may
2006 [55]								r=.30; p=.022		contribute to fatigue.
Veauthier et al.	141	66 PSG total	43.2 (10.0)	68%	8.9 (4.7)	-	**4.5** (1.8)	-	CS[PSG]	Significant relationship between sleep disorders and
2011 [56]		26 fatigue	45.3 (9.5)	73%	**11.3** (4.2)	-	**6.0** (1.0)			fatigue in MS
(2013) [73]		40 non-fatigue	42.0 (10.2)	65%	7.5 (4.5)	-	3.6 (1.6)			
		75 no PSG total	45.4 (10.8)	67%	8.2 (4.6)	-	**4.8** (1.7)			
		21 fatigue	44.5 (10.6)	55%	9.8 (4.4)	-	**5.9** (1.0)			
		54 non-fatigue	45.9 (10.9)	72%	7.6 (4.5)	-	**4.4** (1.7)			
Wunderlin et al.	10	Total	45.0 (8.0)	80%	9.2 (5.3)	40%	**4.5** (1.7)	-	CS	Fatigue and daytime sleepiness cannot be explained by
1997 [57]										nocturnal apneas or oxygen desaturations.

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Table 2 continued (5) – cross-sectional data of longitudinal studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Attarian et al. 2011 [58]	29	15 placebo	46.5 [31-58]	80%	**12.5** (4.3)	-	***11.1*** *(2.2)*°[2]	-	LS	Eszopiclone increases total sleep time, but does not improve fatigue in MS.
		14 eszopiclone	45.0 [25-64]	87%	9.9 (3.6)	-	***7.9*** *(2.8)*°[2]		CC, PC	
Brioschi et al. 2009 [59]	12	Total	43.3 (9.3)	92%	9.3 (3.9)	-	***5.6*** *(0.9)*°[1]	-	LS	Modafinil improves fatigue in MS, no changes in physical activity
Bruce et al. 2012 [60]	30	16 after placebo (phase I)	49.9 (7.2)	88%	9.3 (4.3)	-	*18.6 (10.2)*°[5]	-	LS	Armodafinil improves delayed verbal recall, no other changes in other outcome parameters.
		14 after placebo (phase II)	47.7 (6.0)	79%	9.7 (5.0)	-	*17.8 (8.4)*°[5]		PC	
Côté et al. 2013 [61]	62	21 SLD treated	51.3 (8.3)	62%	9.6 (3.8)	-	**5.1** (1.6)	-	LS[PSG]	Treatment of OSA and RLS improves fatigue in MS.
		18 SLD untreated	49.8 (8.8)	78%	7.6 (4.9)	-	**5.4** (1.5)			
		17 no SLD	41.9 (10.7)	77%	7.9 (4.8)	-	**4.8** (1.8)			
García Jalón et al. 2013 [62]	23	10 MS control	52.0 (7.0)	60%	**12.4** (4.5)	-	**5.9** (0.9)	-	LS	High acceptance of an energy conservation program by MS patients
		13 MS intervention	45.9 (9.9)	77%	6.9 (4.1)	-	**5.6** (0.6)			
Gerhard 2009 [63]	30	Total	36.0 (10.4)	67%	8.4 (3.7)	37%	35.2 (16.9)[1]	-	LS	IFN1β1a treatment increases fatigue, and improves cognitive functions.
Kallweit et al. 2013 [64]	69	Total	49.8 (9.2)	70%	-	-	-	-	LS	High prevalence of SRBD in MS patients; continuous positive airway pressure therapy decreases fatigue but not sleepiness.
		28 SRBD	53.3 (9.5)	57%	9.7 (3.8)	61%	**5.5** (0.9)			
		41 non-SRBD	47.4 (8.3)	78%	9.4 (4.7)	44%	**5.7** (0.7)			
Mendozzi et al. 2010 [65]	42	Total	39.4 (7.4)	-	5.7 (3.2)	14%	3.6 (1.8)	-	LS	IFNβ and glatiramer acetate treatment decrease sleep efficiency in MS assessed by actigraphy
		12 no-IMA	41.8 (5.7)	-	6.3 (3.6)	-	3.4 (1.6)			
		10 glatiramer acetate	38.6 (8.4)	-	6.8 (2.5)	-	**4.4** (1.7)			
		10 IFN1β1a/b s.c.	38.5 (9.9)	-	4.8 (2.7)	-	**4.1** (1.9)			
		10 IFN1β1a/b i.m..	38.2 (5.4)	-	4.9 (3.6)	-	2.7 (1.6)			

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Table 2 continued (6) – cross-sectional data of longitudinal studies

Authors, year [reference]	N MS-patients (n controls)	N MS-patients in subgroups	Age mean (SD) median* [range]	Sex female %	ESS mean (SD) median* [range]	ESS >10 (%)	Fatigue score mean (SD) median* [range]	Significant correlation ESS x fatigue score	Study design	Main outcome
Möller et al. 2011 [66]	121	59 placebo 62 modafinil	40.8 (11.2) 41.4 (9.5)	78% 63%	**11.8** (5.0) **11.8** (4.9)	- -	**5.8** (0.8) **6.0** (0.8)	-	LS PC	No effect of modafinil on fatigue in MS
Rammohan et al. 2002 [67]	72	Total	44.0 [23 -61]	75%	9.5 [1-20]	-	**5.9** [4-7]	-	LS PC	Modafinil significantly improves fatigue.
Stankoff et al. 2005 [68]	115	59 placebo 56 modafinil	44.0 (9.0) 43.8 (8.0)	- -	9.7 (5.5) **10.6** (4.8)	53% total	***63.1*** *(9.3)*°[5] ***63.3*** *(10.0)*°[5]	-	LS PC	No differences between effects of modafinil and placebo treatment on fatigue in MS
Svenningsson et al. 2013 [69]	195	Total	39.7 (9.2)	71%	8.8 (-)	-	**71.2** (-)°[4]	-	LS	Natalizumab improves fatigue, sleepiness, quality of life, depression, and cognition.
Vakhapova et al. 2010 [70]	16	Total	45.4 [26-60]	-	6.4 (5.6) after placebo	-	**37.4** (15.8)[1] after placebo	-	LS PC	Sublingual tizanidine improves daytime sleepiness and spasticity in MS
Van Kessel et al.+ 2008 [71]	72	35 CBT 37 relaxation training	42.9 (9.3) 47.0 (9.5)	80% 70%	6* [-] 5* [-]	- -	20.9[1] (4.3) 20.3[1] (4.3)	-	LS CC	Both CBT and relaxation training are effective treatments for fatigue in MS; CBT is more effective.
Zifko et al. 2002 [72]	50	Total	40.4 (10.3)	60%	9.7 (3.9)	-	30.3 (8.5)[1]	-	LS	Modafinil treatment improves fatigue and sleepiness in MS.

Symbols: *median; ** median [interquartile range]; ~ longitudinal study; [+] data provided on request; [PSG] use of PSG; [x] ESS score >10 exclusion criterion; - data not reported

Statistics: F/non-F: subdivision in fatigued and non-fatigued subgroups; n: number of participants; n.s.: not significant; p: p-value; r: correlation coefficient; SD: standard deviation

Fatigue Scales: FSS: fatigue severity scale (cut off >4); [1] FSS total score (cut off >36)

Other Fatigue Scales: °[1] FAI: fatigue assessment inventory (cut off ≥4); °[2] FDS: fatigue descriptive scale (cut off >5); °[3] FIS: fatigue impact scale; °[4] FSMC: fatigue scale for motor and cognitive functions (mild fatigue ≥43; moderate fatigue ≥53; severe fatigue ≥63); °[5] MFIS: modified fatigue impact scale (cut off >34)

CBT: cognitive behavioral therapy; CC: case-controlled; CS: cross-sectional study; IFN1β1a/b s.c.: interferon-beta 1a or interferon-beta 1b for subcutaneous injection; IFN1β1a/b i.m.: interferon-beta 1a or interferon-beta 1b injected intramuscularly; LS: longitudinal study; MON: monosymptomatic optic neuritis; no-IMA: no treatment with immunomodulant agents; OSA: obstructive sleep apnea; PC: placebo-controlled; PLMS: periodic limb movements in sleep; PSG: polysomnography; RLS: restless legs syndrome; SRBD: sleep-related breathing disorder; SLD: sleep disorders

Boldfaced numerals ~~numerics~~ denote scores above critical cut offs (e.g. ESS >10; FSS >4); Italic printed numerals ~~numerics~~ mark fatigue scores other than FSS score

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Table 3 Additional information on longitudinal studies using the Epworth sleepiness scale (ESS) as an assessment tool in patients with multiple sclerosis (MS)

Authors, year [reference]	N MS-patients	ESS baseline mean (SD) median* [range]	ESS follow-up / intervention mean (SD) / median* [range]	Fatigue baseline mean (SD)	Fatigue follow-up/ intervention mean (SD)	Follow-up period to baseline	Intervention	Intervention efficacy
Attarian et al. **2011** [58]	15 placebo 14 eszopiclone	**12.5** (4.3) 9.9 (3.6)	**10.5** (3.9) 8.2 (4.0)	***11.1***°[2] *(2.2)* ***7.9***°[2] *(2.8)*	***5.4***°[2] *(3.1)* *4.6*°[2] *(3.6)*	7 weeks	Eszopiclone or placebo	n.s. ESS and FSS changes
Brioschi et al. 2009 [59]	12	9.3 (-)	T1: 9.1 (3.0) T2: **10.4** (4.7)	*5.6*°[1] *(0.9)*	T1: *4.5*°[1] *(1.1)* T2: *5.1*°[1] *(1.1)*	T1: 3 months with modafinil T2: 1 month without modafinil	Modafinil	n.s. ESS changes; significant FAI improvements T0 to T1 (Δ1.1)
Bruce et al. 2012 [60]	16 placebo first 14 armodafinil first	9.3 (4.3) 9.7 (5.0)	9.2 (5.0) **10.5** (4.3)	*18.6*°[5] *(10.2)* *17.8*°[5] *(8.4)*	*18.2*°[5] *(10.6)* *18.6*°[5] *(10.5)*	1 week change, (cross-over design)	Armodafinil	n.s. ESS and FSS changes
Côté et al. 2013 [61]	21 SLD, treated 18 SLD, untreated 17 no SLD	9.6 (3.8) 7.6 (4.9) 7.9 (4.8)	6.1 (3.8) 7.1 (5.5) 7.2 (4.2)	**5.1** (1.6) **5.4** (1.5) **4.8** (1.8)	**4.5** (1.7) **5.1** (1.5) **5.2** (1.2)	≥3 months	Treatment of OSA and RLS	Significant FSS (Δ0.9), MFI°[6], ESS and PSQI improvements
García Jalón et al. 2013 [62]	10 MS control 13 MS intervention	**12.4** (4.5) 6.9 (4.1)	T1: **10.2** (4.3) T2: **14.0** (10.7) T3: **10.6** (4.2) T1: 6.6 (4.2) T2: 6.5 (4.9) T3: 6.9 (4.1)	**5.9** (0.9) **5.9** (0.6)	T1: **4.9** (1.0) T2: **5.5** (0.9) T3: **4.9** (1.3) T1: **5.0** (1.4) T2: **4.7** (1.7) T3: **5.2** (1.3)	T1: intervention T2: 6 weeks T3: 3 months	Energy conservation program	n.s. ESS, FSS and FIS changes; significant FIS Cognitive improvements (Δ5.8)
Gerhard 2009 [63]	30	8.4 (3.7)	**10.2** (4.4)	35.2[1] (16.9)	38.8[1] (16.8)	≥6 months	Interferon	Significant ESS (Δ1.6) and FSS (Δ3.6) decline

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Table 3 continued (2)

Authors, year [reference]	N MS-patients	ESS baseline mean (SD) median* [range]	ESS follow-up / intervention mean (SD) / median* [range]	Fatigue baseline mean (SD)	Fatigue follow-up/ intervention mean (SD)	Follow-up period to baseline	Intervention	Intervention efficacy
Kallweit et al. 2013 [64]	28 SRBD 41 non-SRBD	9.7 (3.8) 9.4 (4.7)	9.5 (3.0) -	**5.5** (0.9) **5.7** (0.7)	4.8 (0.6) -	≥6 months	OSA treatment	n.s. ESS changes; significant FSS improvements (Δ1.0)
Mendozzi et al. 2010 [65]	42 total 12 no-IMA 10 GA 10 IFN1β1a/b s.c. 10 IFN1β1a/b i.m.	5.7 (3.2) 6.3 (3.6) 6.8 (2.5) 4.8 (2.7) 4.9 (3.6)	5.6 (3.9) 6.4 (3.9) 7.6 (3.6) 4.8 (4.4) 3.5 (2.5)	3.6 (1.8) 3.4 (1.6) **4.4** (1.7) **4.1** (1.9) 2.7 (1.6)	3.7 (1.7) 3.5 (1.3) **4.5** (1.9) 4.0 (1.6) 2.8 (1.6)	≥ 7 nights	No-IMA, GA, IFN1β1a/b s.c., IFN1β1a/b i.m.	n.s. ESS and FSS changes
Möller et al. 2011 [66]	62 modafinil 59 placebo	**11.8** (4.9) **11.8** (5.0)	9.7 (4.4) 9.5 (4.9)	**6.0** (0.8) **5.8** (0.8)	**5.3** (1.2) **5.4** (1.0)	8 weeks	Modafinil	n.s. ESS, FSS and MFIS changes
Rammohan et al. 2002 [67]	72	9.5 [1-20]	T1: 7.2 (-) T2: 7.0 (-) T3: -	**5.9** [4-7]	T1: 4.7 (-) T2: 5.3 (-) T3: 5.3 (-)	T1: 2 weeks 200 mg modafinil T2: 4 weeks (2 weeks 400 mg) T3: 7 weeks (3 weeks placebo washout)	Modafinil	T1: significant ESS (Δ2.3) and FSS (Δ0.8) improvements; T2: significant ESS improvements (Δ2.5); n.s. FSS changes
Stankoff et al. 2005 [68]	56 modafinil 59 placebo	**10.6** (4.8) 9.7 (5.5)	- -	*63.3°[3] (10.0)* *63.1°[3] (9.3)*	***52.3***°[5] *(18.5)* ***49. 2***°[5] *(16.6)*	35 days	Modafinil	Significant MFIS improvements for both groups (modafinil: Δ11.0 vs. placebo: Δ13.9), but no benefit of modafinil compared to placebo
Svenningsson et al. 2013 [69]	143	8.8 (-)	7.5 (-)	*71.2°[4] (-)*	*62.2°[4] (-)*	12 months	Natalizumab	Significant ESS (Δ1.33) and FSMC (Δ9.0) improvements
Vakhapova et al. 2010 [70]	16	6.4 (5.6) after placebo phase	4.8 (4.6) s.l. 5.5 (4.6) oral	**37.4**[1] (15.8) after placebo phase	33.6[1] (16.8) s.l. 34.1[1] (17.0) oral	7 days placebo phase and 7 days of each condition (cross-over design)	Tizanidine	Significant ESS improvements (Δ1.6 only for s.l. application vs. placebo)

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Table 3 continued (3)

Authors, year [reference]	N MS-patients	ESS baseline mean (SD) median* [range]	ESS follow-up / intervention mean (SD) / median* [range]	Fatigue baseline mean (SD)	Fatigue follow-up/ intervention mean (SD)	Follow-up period to baseline	Intervention	Intervention efficacy
Van Kessel et al.[+] 2008 [71]	35 CBT	6* [-]	T1: 3* [-] T2: 3* [-] T3: 3* [-]	20.9[1] (4.3)	T1: 7.9[1] (4.3) T2: 9.0[1] (5.3) T3: 10.4[1] (6.4)	T1: 2 months (post treatment) T2: 5 months T3: 8 months	CBT vs. relaxation training	Significantly greater fatigue reductions in the CBT group across the 8 months compared to the relaxation training group
	37 relaxation training	5* [-]	T1: 6* [-] T2: 4* [-] T3: 4* [-]	20.3[1] (4.3)	T1: 11.6[1] (5.3) T2:11.1[1] (4.6) T3:12.5[1] (5.2)			
Veauthier et al. 2013 [73]	58 total	9.1 (4.6)	8.5 (4.6)	**4.7** (2.3)	**4.0** (1.8)	16 months (median)	Treatment of sleep disorders	n.s. ESS changes; significant FSS improvements on in the entire cohort (Δ0.7), but n.s. changes in subgroups; significant MFIS improvements in good compliance subgroup (Δ15)
	13 good compliance	9.5 (5.9)	9.4 (5.9)	**4.8** (1.1)	**4.3** (1.5)			
	12 moderate compliance	9.8 (4.8)	9.3 (5.9)	**5.5** (3.9)	3.9 (2.2)			
	17 no compliance	**10.8** (3.7)	**10.2** (2.9)	**4.8** (1.7)	**4.4** (1.7)			
	4 no feedback	6.0 (4.5)	6.8 (3.3)	**4.9** (1.5)	3.2 (1.9)			
	12 no sleep disorder	6.4 (2.9)	5.7 (2.5)	3.3 (1.5)	3.4 (1.6)			
Zifko et al. 2002 [72]	50	9.7 (3.9)	4.9 (2.9)	30.3[1] (8.5)	25.4[1] (3.7)	3 months	Modafinil	Significant ESS (Δ4.8) and FSS (Δ4.9) improvement

Statistics: n: number of participants; n.s.: not significant; SD: standard deviation; T1-3: times of assessment; Δ: changes; - data not reported

Fatigue Scales: FSS: fatigue severity scale (cut off >4); [1] FSS total score (cut off >36)

Other Fatigue Scales: °[1] FAI: fatigue assessment inventory (cut off ≥ 4); °[2] FDS: fatigue descriptive scale (cut off >5); °[3] FIS: fatigue impact scale; °[4] FSMC: fatigue scale for motor and cognitive functions (mild fatigue ≥43; moderate fatigue ≥53; severe fatigue ≥63); °[5] MFIS: modified fatigue impact scale (cut off >34/45); °[6] MFI: multidimensional fatigue inventory

CBT: cognitive behavioral therapy; GA: glatiramer acetate; IFN1β1a/b s.c.: interferon-beta 1a or interferon-beta 1b for subcutaneous injection; IFN1β1a/b i.n. interferon-beta 1a or interferon-beta 1b injected intramuscularly; no-IMA: no treatment with immunomodulant agents; OSA: obstructive sleep apnea; PSQI: Pittsburgh sleep quality index; RLS: restless legs syndrome; SRBD: sleep-related breathing disorder; SLD: sleep disorders; s.l.: sublingual

Boldfaced numerals ~~numerics~~ denote scores above critical cut offs (e.g. ESS >10; FSS >4); Italic printed numerals ~~numerics~~ mark fatigue scores measured with fatigue scales other than FSS

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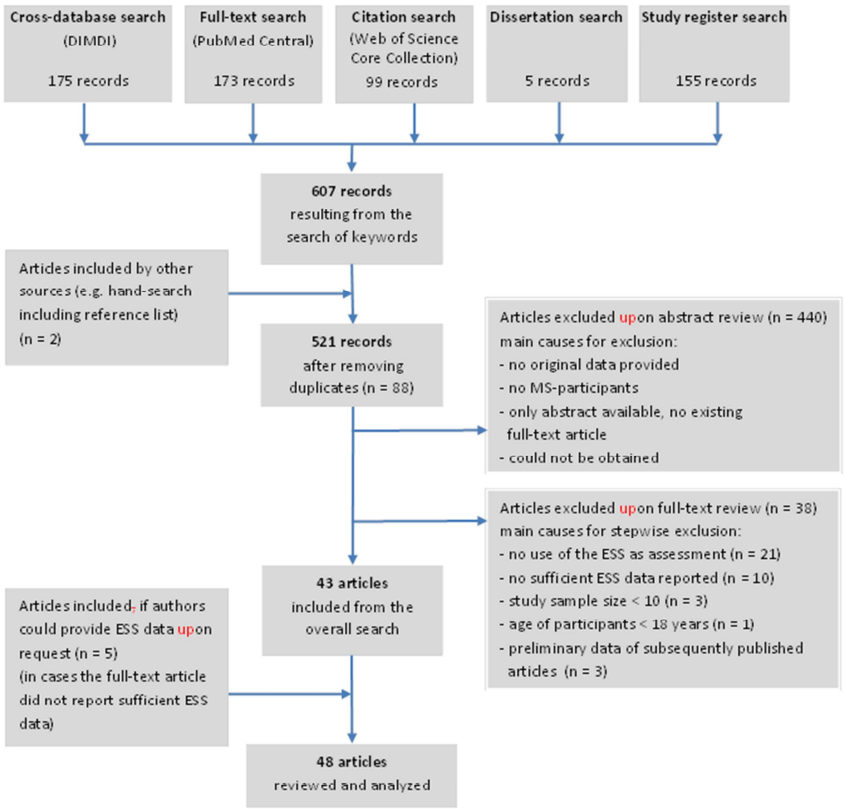

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