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CLINICAL REVIEW

# 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 a stepwise evaluation of sleepiness as compared to fatigue in patients with MS.



## 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, primary-progressive and secondary-progressive, and progressive-relapsing (http://www.nationalmssociety.org) [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

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**List of abbreviations**

| | |
|---|---|
| CBT | cognitive behavioral therapy |
| CPAP | continuous positive airway pressure |
| ESS | Epworth sleepiness scale |
| FIS | fatigue impact scale |
| FSMC | fatigue scale for motor and cognitive functions |
| FSS | fatigue severity scale |
| ICSD-3 | International classification of sleep disorders (third edition) |
| IFN | interferon |
| 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 |

impairment (e.g., bedridden patients reported the most severe fatigue) [16].

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.

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

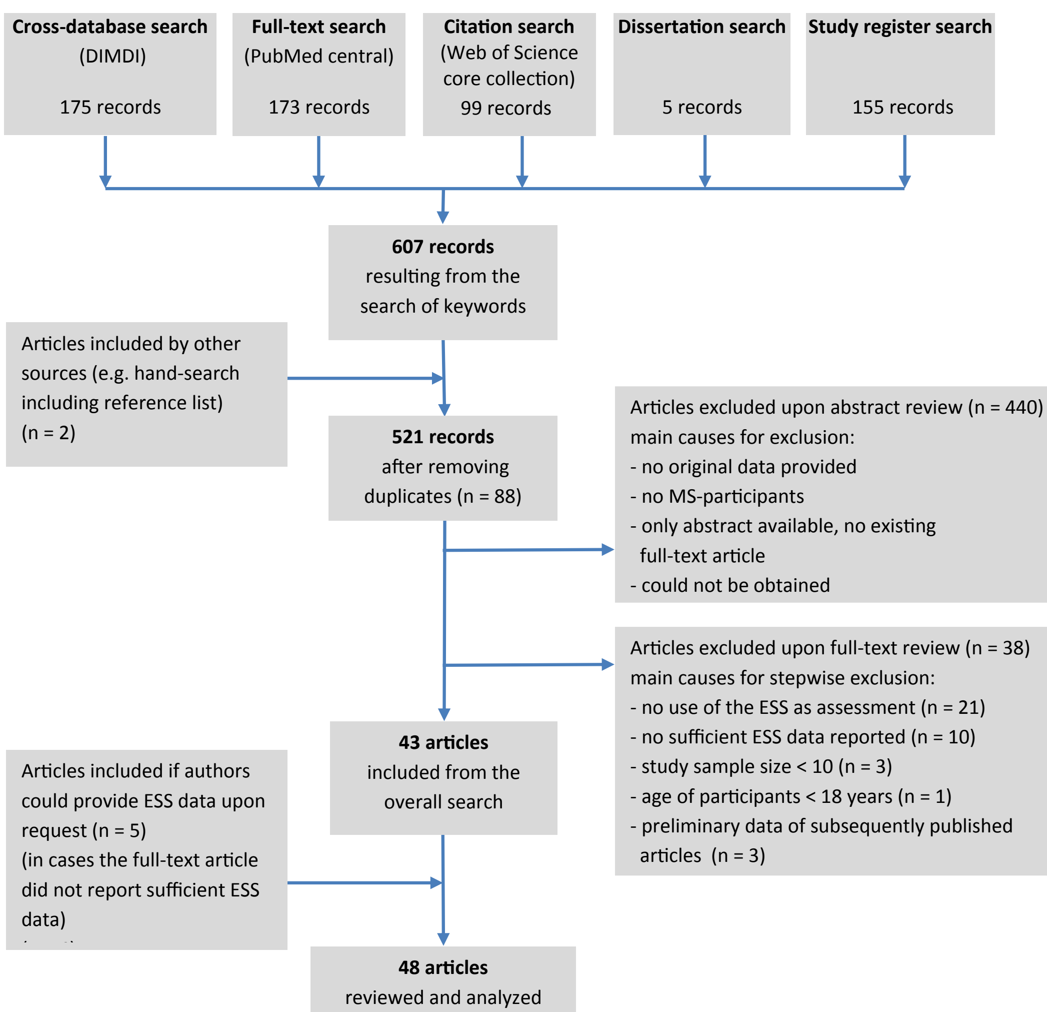


**Fig. 1.** Flow diagram of the study selection process. Legend: DIMDI: Deutsches Institut für Medizinische Dokumentation und Information (German institute of medical documentation and information); MS: multiple sclerosis; ESS: Epworth sleepiness scale.

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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.<br>• Not necessarily associated with sleep pressure.<br>• No definite sleep drive when resting (e.g., lying down to relax). | • Decreased level of alertness or wakefulness.<br>• Increased tendency to fall asleep or doze off unintentionally.<br>• 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.<br>• Strong negative impact on social and occupational functioning. | • Not commonly associated with MS.<br>• Often associated with sleep disorders. |
| Assessment by common rating scales | Fatigue severity scale (FSS)<br>- Most widely used validated scale.<br>- Evaluates the impact on motivation, physical abilities and social functioning.<br>- Self-administered, nine items.<br>- 7-point Likert scale from 1 (strongly disagree) to 7 (strongly agree).<br>- Critical cut-off: mean FSS score >4 (min: 1; max: 7) or total FSS score ≥36 (min: 9; max: 63). | Epworth sleepiness scale (ESS).<br>- Most commonly used scale in sleep research and clinical settings.<br>- Assessment of sleep propensity<br>- Self-administered, 8-item questionnaire.<br>- 4-point Likert scale (from 0 to 3) to rate the likelihood of dozing off in eight everyday situations.<br>- 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.<br>• Psychomotor vigilance task; sustained attention and vigilance tasks; driving simulator. |
| Counter-measures | • Alleviated by periods of rest, unlike weakness (asthenia).<br>• Limited efficacy of stimulants. | • Most effective: sleep or short naps, but not rest.<br>• Stimulants temporarily effective. |

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

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].

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 0–24) 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)).

## 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 (Deutsches Institut für Medizinische Dokumentation und Information [German institute of medical documentation and information]), 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.

A detailed documentation of the searches allowing for replication, can be seen in Appendix 1, which is available as an electronic

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**Table 2**
Summarized studies using the Epworth sleepiness scale (ESS) as an assessment tool in patients with multiple sclerosis (MS).

| Authors, year [reference] | N MS-patients (n controls) | N MS-patients in subgroups | Age (y) mean (SD) median* [range] | Sex female % | ESS mean (SD) median* [range] | ESS >10 (%) | Fatigue score mean (SD) median* [range] | Significant correlation ESS × fatigue score | Study design | Main outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Cross-sectional studies*** | | | | | | | | | | |
| Attarian | 30 (15) | 15 fatigue | 46.4 (–) | 73% | **12*** [2–24] | 60% | **7*** [5–11] | r not reported | CS | Significant correlation between |
| et al., 2004 [26] | | 15 non-fatigue | 33.5 (–) | total | 5* [0–19] | 13% | 3* [1–4] | p = .02 | CC | fatigue and disrupted sleep/ |
| | | | | | | | | | | abnormal sleep cycles in MS |
| | | | | | | | | | | assessed by actigraphy. |
| Beran | 12 (14) | 6 sleepiness | 47.8 (–) | 83% | **15.0** (4.4) | – | **5.1** (1.7) | – | CS^PSG | Significant relationship |
| et al., 2008 [27] | | 6 non-sleepiness | total | total | 4.8 (3.1) | – | 3.4 (1.4) | | CC | between PLMS with arousals |
| | | | | | | | | | | and increased sleepiness |
| Braley | 30 (30) | Total | 46.7 (11.3) | 70% | **11.3** (4.9) | – | – | n.s. | CS^PSG | Fatigue, tiredness, and lack of |
| et al.+ 2012 [28] | | | | | | | | | CC | energy, but not sleepiness, are |
| | | | | | | | | | | more frequent in MS compared |
| | | | | | | | | | | to controls. |
| Braley | 195 | Total | 47.1 (12.1) | 66% | 8.1 (5.1) | – | **4.6** (1.8) | FSS | CS | Sleep disturbances, especially |
| et al., 2014 [29] | | 110 elevated OSA risk | 50.3 (11.8) | 53% | 9.1 (5.0) | – | **5.1** (1.6) | r = 0.44; | CC | OSA, are frequent in MS and |
| | | 85 no elevated OSA risk | 43.0 (11.1) | 82% | 6.9 (5.1) | – | 4.0 (1.8) | p < .0001 | | may contribute to fatigue.. |
| | | 154 OSA not confirmed | 45.8 (12.2) | 68% | 7.9 (5.0) | – | **4.5** (1.8) | | | |
| | | 41 diagnosed OSA | 52.1 (10.4) | 59% | 9.0 (5.6) | – | **5.0** (1.6) | | | |
| Braley | 190 | Total | 47.0 (12.2) | 67% | 8.2 (5.1) | – | **4.6** (1.8) | – | CS | 47% of MS patients use |
| et al., 2015 [30] | | 121 fatigue | 47.6 (11.5) | 65% | 9.4 (5.3) | – | **5.7** (0.9) | | | hypnotics; carry-over effects |
| | | 69 non-fatigue | 46.4 (13.3) | 71% | 5.8 (4.0) | – | 2.5 (0.8) | | | may be involved in fatigue |
| Brass | 2375 | Total | 54.7 (12.4) | 81% | 8* [0–24] | 30% | **45*** [6–63] | – | CS | The majority of MS patients are |
| et al., 2014 [31] | | | | | | | | | | affected by one or more sleep |
| | | | | | | | | | | disorders, often undiagnosed. |
| Bøe Lunde | 90 (108) | Total (73 with valid ESS) | 45.0 (10.4) | 54% | 8.6 (4.6) | 34% | – | – | CS | Poor sleep is common in MS. |
| et al.+ 2012 [32] | | 24 good sleepers | 43.2 (12.0) | 38% | – | 22% | – | | CC | Treatment may improve sleep |
| | | 49 poor sleepers | 46.2 (10.4) | 65% | – | 42% | – | | | and quality of life. |
| Chen | 21 (11) | 11 fatigue | 30.9 (11.0) | 73% | **15.7** (7.2) | 38%- | **50.8** (6.1) | FSS | CS^PSG | Sleep disorders and excessive |
| et al., 2014 [33] | | 10 non-fatigue | 26.8 (4.1) | 70% | 9.0 (2.8) | | 26.1 (6.4) | r = 0.74; p < .001 | CC | daytime sleepiness are more |
| | | | | | | | | | | common in MS. |
| Constantinescu | 34 | 24 valid ESS data | 41.5** | 58% | 10** | – | **5.4**** | FSS | CS | No evidence of orexin A |
| et al., 2011 [34] | | | [36–49] | | [5.3–14.5] | | [4.4–6.1] | r = 0.47; p = .019 | CC | deficiency in MS but in other |
| | | | | | | | | | | CNS inflammatory diseases |
| Dias | 103 | Total | 45.8 (11.0) | 72% | 7.3 (4.8) | 23% | **4.6** (1.6) | FSS | CS | Over 40% of MS patients show |
| et al., 2012 [35] | | | | | | | | r = 0.31; p < .01 | | elevated OSA risk. |
| Elkattan | 20 (10) | 10 fatigue | 27.7 (6.5) | – | 7.2 (4.0) | – | 27.7 (6.5)[1] | – | CS^PSG | Sleep parameters do not |
| et al., 2009 [36] | | 10 non-fatigue | 28.8 (6.7) | – | 5.3 (4.2) | – | 28.8 (6.7)[1] | | CC | distinguish between fatigued |
| | | | | | | | | | | and non-fatigued MS patients |
| Frauscher | 61 (42) | Total | 34.5 (8.3) | 53% | 7.4 (3.5) | 26% | – | – | CS | No increased daytime |
| et al., 2005 [37] | | | | | | | | | CC | sleepiness in MS compared to |
| | | | | | | | | | | controls |
| Ghajarzadeh | 100 | 64 fatigue | 34.0 (8.4) | 73% | 3.8 (3.1) | 6% | *35.3 (17.6)* [05] | MFIS | CS | Significant correlations |
| et al., 2012 [38] | | 36 non-fatigue | 28.4 (8.3) | 78% | 3.6 (3.1) | 6% | *19.1 (16.5)* [05] | r = 0.33; p = .001 | | between fatigue scores and |
| | | | | | | | | | | depression, sleep quality, and |
| | | | | | | | | | | ESS |
| Heesen | 30 | 15 fatigue | 46.6 (11.7) | 60% | **10.5** (4.7) | – | **6.1** (0.7) | – | CS | Fatigue in MS may be |
| et al., 2006 [39] | | 15 non-fatigue | 42.9 (10.2) | 60% | 3.3 (2.4) | – | 1.5 (0.7) | | | influenced by increased levels |
| | | | | | | | | | | of inflammatory cytokines. |
| Kaminska | 62 (32) | Total | 47.3 (10.4) | 73% | 8.4 (4.4) | 34% | **5.1** (1.6) | FSS | CS^PSG | OSA is common in MS and |
| et al., 2012 [40] | | | | | | | | r = 0.31; p = .002 | CC | related to fatigue, but not to |
| | | | | | | | | | | sleepiness. |
| Kaynak | 37 (13) | 27 fatigue | 37.4 (8.7) | 59% | 4.4 (2.8) | 7% | **5.5** (0.9) | n.s. | CS^PSG | |
| et al., 2006 [41] | | 10 non-fatigue | 36.5 (8.4) | 50% | 3.3 (3.0) | 0% | <4 | | | |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | Sleep fragmentation observed in MS patients can be involved in MS fatigue. |
| Kister et al., 2010 [42] | 167 | 94 migraineurs | 43 (11.0) | 90% | 8.1 (–) | – | **5.0** (–) | – | CS | Migraine in MS is more frequent than in the general population. |
| | | 73 no headache | 47 (13.0) | 57% | 5.6 (–) | – | 3.6 (–) | | | |
| 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 |
| Kotterba et al., 2003 [44] | 31 | Total | 35.6 (8.3) | 58% | 6.1 (2.9) | 10% | **4.3** (1.6) | FSS r = 0.42; 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 = 0.18; 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 < .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)* [03] | 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)* [03] | r = 0.68 | | |
| | | 17 fatigue, non-sleepiness | 39.7 (9.3) | 59% | 4.6 (2.1) | – | *65.6 (33.1)* [03] | subgroups 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)* [04] | – | 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)* [04] | | | |
| 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 = .039 in fatigued | CC | |
| | | 9 non-fatigue | 41.8 (13.1) | 56% | 3.0 (3.7) | – | – | patients | | |
| Papuc et al., 2010 [52] | 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 controls, but are correlated with fatigue levels. |
| | | 10 fatigue | 34* [21–69] | 54% | 6* [2–11] | – | **5.7*** [4.8–6.6] | | CC | |
| | | 28 non-fatigue | 38* [22–55] | 60% | 6* [4–8] | – | 2.6* [1.7–4.1] | | | |
| Pokryszko-Dragan et al., 2013 [53] | 100 | Total | 42 [20–67] | 69% | 6.3 [0–19] | 19% | 3.8 [1.1–7.0] | n.s. | CS | Sleep disturbances may increase fatigue and are related to MS symptoms and therapies. |
| | | 49 fatigue | – | – | 6.4 (3.9) | – | – | | | |
| | | 51 non-fatigue | – | – | 6.2 (4.7) | – | – | | | |
| Sauter 2004 [54] | 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, sleep quality, and quality of life. |
| | | | | | | | | | CC | |
| Stanton et al., 2006 [55] | 60 | Total | 41* [19–69] | 72% | 7* [0–19] | 32% | 11* [2.5–15.8] | FSS r = 0.30; p = .022 | CS | Sleep disturbances are frequent in MS and may contribute to fatigue. |
| Veauthier et al., 2011 [56] (2013) [73] | 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 fatigue in MS |
| | | 26 fatigue | 45.3 (9.5) | 73% | **11.3** (4.2) | – | **6.0** (1.0) | | | |
| | | 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., 1997 [57] | 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 nocturnal apneas or oxygen desaturations. |

(*continued on next page*)







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**Table 2** (*continued* )

| Authors, year [reference] | N MS-patients (n controls) | N MS-patients in subgroups | Age (y) mean (SD) median* [range] | Sex female % | ESS mean (SD) median* [range] | ESS >10 (%) | Fatigue score mean (SD) median* [range] | Significant correlation ESS × fatigue score | Study design | Main outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| ***Longitudinal studies*** | | | | | | | | | | |
| Attarian et al., 2011 [58] | 29 | 15 placebo | 46.5 [31–58] | 80% | **12.5** (4.3) | – | ***11.1*** *(2.2)* $^{02}$ | – | 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)* $^{02}$ | | CC, PC | |
| Brioschi et al., 2009 [59] | 12 | Total | 43.3 (9.3) | 92% | 9.3 (3.9) | – | ***5.6*** *(0.9)* $^{01}$ | – | 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)* $^{05}$ | – | 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)* $^{05}$ | | 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 | IFNβ1a 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 IFNβ1a/b s.c. | 38.5 (9.9) | – | 4.8 (2.7) | – | **4.1** (1.9) | | | |
| | | 10 IFNβ1a/b i.m.. | 38.2 (5.4) | – | 4.9 (3.6) | – | 2.7 (1.6) | | | |
| Möller et al., 2011 [66] | 121 | 59 placebo | 40.8 (11.2) | 78% | **11.8** (5.0) | – | **5.8** (0.8) | – | LS | No effect of modafinil on fatigue in MS |
| | | 62 modafinil | 41.4 (9.5) | 63% | **11.8** (4.9) | – | **6.0** (0.8) | | PC | |
| 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 | 44.0 (9.0) | – | 9.7 (5.5) | 53% total | ***63.1*** *(9.3)* $^{05}$ | – | LS | No differences between effects of modafinil and placebo treatment on fatigue in MS |
| | | 56 modafinil | 43.8 (8.0) | – | **10.6** (4.8) | | ***63.3*** *(10.0)* $^{05}$ | | PC | |
| Svenningsson et al., 2013 [69] | 195 | Total | 39.7 (9.2) | 71% | 8.8 (–) | – | ***71.2*** *(–)* $^{04}$ | – | 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 | 42.9 (9.3) | 80% | 6* [-] | – | 20.9$^{1}$ (4.3) | – | LS | Both CBT and relaxation training are effective treatments for fatigue in MS; CBT is more effective. |
| | | 37 relaxation training | 47.0 (9.5) | 70% | 5* [-] | – | 20.3$^{1}$ (4.3) | | CC | |
| 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:** $^{01}$ FAI: fatigue assessment inventory (cut off ≥4); $^{02}$ FDS: fatigue descriptive scale (cut off >5); $^{03}$ FIS: fatigue impact scale; $^{04}$ FSMC: fatigue scale for motor and cognitive functions (mild fatigue ≥43; moderate fatigue ≥53; severe fatigue ≥63); $^{05}$ MFIS: modified fatigue impact scale (cut off >34).
**Abbreviations:** 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; IFNβ1a/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; SLD: sleep disorders; SRBD: sleep-related breathing disorder.
Boldfaced numerals denote scores above critical cut offs (e.g., ESS >10; FSS >4); Italic printed numerals mark fatigue scores other than FSS score.

**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<br>14 eszopiclone | **12.5** (4.3)<br>9.9 (3.6) | **10.5** (3.9)<br>8.2 (4.0) | ***11.1*** *[02] (2.2)*<br>***7.9*** *[02] (2.8)* | ***5.4*** *[02] (3.1)*<br>*4.6 [02] (3.6)* | 7 wk | Eszopiclone or placebo | n.s. ESS and FSS changes |
| Brioschi et al., 2009 [59] | 12 | 9.3 (–) | T1: 9.1 (3.0)<br>T2: **10.4** (4.7) | *5.6 [01] (0.9)* | T1: *4.5 [01] (1.1)*<br>T2: *5.1 [01] (1.1)* | T1: 3 mo with modafinil<br>T2: 1 mo without modafinil | Modafinil | n.s. ESS changes; significant FAI improvements T0 to T1 (Δ1.1) |
| Bruce et al., 2012 [60] | 16 placebo first<br>14 armodafinil first | 9.3 (4.3)<br>9.7 (5.0) | 9.2 (5.0)<br>**10.5** (4.3) | *18.6 [05] (10.2)*<br>*17.8 [05] (8.4)* | *18.2 [05] (10.6)*<br>*18.6 [05] (10.5)* | 1 wk change (cross-over design) | Armodafinil | n.s. ESS and FSS changes |
| Côté et al., 2013 [61] | 21 SLD, treated<br>18 SLD, untreated<br>17 no SLD | 9.6 (3.8)<br>7.6 (4.9)<br>7.9 (4.8) | 6.1 (3.8)<br>7.1 (5.5)<br>7.2 (4.2) | **5.1** (1.6)<br>**5.4** (1.5)<br>**4.8** (1.8) | **4.5** (1.7)<br>**5.1** (1.5)<br>**5.2** (1.2) | ≥3 mo | Treatment of OSA and RLS | Significant FSS (Δ0.9), MFI [06], ESS and PSQI improvements |
| García Jalón et al., 2013 [62] | 10 MS control | **12.4** (4.5) | T1: **10.2** (4.3)<br>T2: **14.0** (10.7)<br>T3: **10.6** (4.2) | **5.9** (0.9) | T1: **4.9** (1.0)<br>T2: **5.5** (0.9)<br>T3: **4.9** (1.3) | T1: intervention<br>T2: 6 wk<br>T3: 3 mo | Energy conservation program | n.s. ESS, FSS and FIS changes; significant FIS Cognitive improvements (Δ5.8) |
| | 13 MS intervention | 6.9 (4.1) | T1: 6.6 (4.2)<br>T2: 6.5 (4.9)<br>T3: 6.9 (4.1) | **5.9** (0.6) | T1: **5.0** (1.4)<br>T2: **4.7** (1.7)<br>T3: **5.2** (1.3) | | | |
| Gerhard 2009 [63] | 30 | 8.4 (3.7) | **10.2** (4.4) | 35.2[1] (16.9) | 38.8[1] (16.8) | ≥6 mo | Interferon | Significant ESS (Δ1.6) and FSS (Δ3.6) decline |
| Kallweit et al., 2013 [64] | 28 SRBD<br>41 non-SRBD | 9.7 (3.8)<br>9.4 (4.7) | 9.5 (3.0)<br>- | **5.5** (0.9) **5.7** (0.7) | 4.8 (0.6)<br>- | ≥6 mo | OSA treatment | n.s. ESS changes; significant FSS improvements (Δ1.0) |
| Mendozzi et al., 2010 [65] | 42 total<br>12 no-IMA<br>10 GA<br>10 IFNβ1a/b s.c.<br>10 IFNβ1a/b i.m. | 5.7 (3.2)<br>6.3 (3.6)<br>6.8 (2.5)<br>4.8 (2.7)<br>4.9 (3.6) | 5.6 (3.9)<br>6.4 (3.9)<br>7.6 (3.6)<br>4.8 (4.4)<br>3.5 (2.5) | 3.6 (1.8)<br>3.4 (1.6)<br>**4.4** (1.7)<br>**4.1** (1.9)<br>2.7 (1.6) | 3.7 (1.7)<br>3.5 (1.3)<br>**4.5** (1.9)<br>4.0 (1.6)<br>2.8 (1.6) | ≥seven nights | No-IMA, GA, IFNβ1a/b s.c., IFNβ1a/b i.m. | n.s. ESS and FSS changes |
| Möller et al., 2011 [66] | 62 modafinil<br>59 placebo | **11.8** (4.9)<br>**11.8** (5.0) | 9.7 (4.4)<br>9.5 (4.9) | **6.0** (0.8)<br>**5.8** (0.8) | **5.3** (1.2)<br>**5.4** (1.0) | 8 wk | Modafinil | n.s. ESS, FSS and MFIS changes |
| Rammohan et al., 2002 [67] | 72 | 9.5 [1–20] | T1: 7.2 (–)<br>T2: 7.0 (–)<br>T3: - | **5.9** [4–7] | T1: 4.7 (–)<br>T2: 5.3 (–)<br>T3: 5.3 (–) | T1: 2 wk 200 mg modafinil<br>T2: 4 wk (2 wk 400 mg)<br>T3: 7 wk (3 wk placebo washout) | Modafinil | T1: significant ESS (Δ2.3) and FSS (Δ0.8) improvements;<br>T2: significant ESS improvements (Δ2.5); n.s. FSS changes |
| Stankoff et al., 2005 [68] | 56 modafinil<br>59 placebo | **10.6** (4.8)<br>9.7 (5.5) | – | *63.3 [03] (10.0)*<br>*63.1 [03] (9.3)* | *52.3 [05] (18.5)*<br>***49. 2*** *[05] (16.6)* | 35 d | 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 [04] (–)* | *62.2 [04] (–)* | 12 mo | 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.<br>5.5 (4.6) oral | **37.4[1]** (15.8) after placebo phase | 33.6[1] (16.8) s.l.<br>34.1[1] (17.0) oral | 7 d placebo phase and 7 d of each condition (cross-over design) | Tizanidine | Significant ESS improvements (Δ1.6 only for s.l. application vs. placebo) |

(*continued on next page*)

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**Table 3** (*continued*)

| 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* [–]<br>T2: 3* [–]<br>T3: 3* [–] | 20.9[1] (4.3) | T1: 7.9[1] (4.3)<br>T2: 9.0[1] (5.3)<br>T3: 10.4[1] (6.4) | T1: 2 mo (post treatment)<br>T2: 5 mo<br>T3: 8 mo | CBT vs. relaxation training | Significantly greater fatigue reductions in the CBT group across the 8 mo compared to the relaxation training group |
| | 37 relaxation training | 5* [-] | T1: 6* [–]<br>T2: 4* [–]<br>T3: 4* [–] | 20.3[1] (4.3) | T1: 11.6[1] (5.3)<br>T2:11.1[1] (4.6)<br>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 mo (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 mo | 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:** *[01]* FAI: fatigue assessment inventory (cut off ≥ 4); *[02]* FDS: fatigue descriptive scale (cut off >5); *[03]* FIS: fatigue impact scale; *[04]* FSMC: fatigue scale for motor and cognitive functions (mild fatigue ≥43; moderate fatigue ≥53; severe fatigue ≥63); *[05]* MFIS: modified fatigue impact scale (cut off >34/45); [06] MFI: multidimensional fatigue inventory.
**Abbreviations:** CBT: cognitive behavioral therapy; GA: glatiramer acetate; IFNβ1a/b s.c.: interferon-beta 1a or interferon-beta 1b for subcutaneous injection; IFNβ1a/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 denote scores above critical cut offs (e.g., ESS >10; FSS >4); Italic printed numerals mark fatigue scores measured with fatigue scales other than FSS.

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 (TW) was designated to make the final decision. Studies were included only if they 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 y) patients with MS d) sufficient sample sizes, (n ≥ 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, they 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.

## 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 were published, disorders other than MS were investigated (e.g., sleep disorders, Parkinson's disease), or there were 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 y of age. Ten of the full text articles were excluded because no sufficient statistical ESS data were 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].

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

*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 studies applying actigraphy [26,65] were used.

*Cross-sectional data*

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, comprising 2375 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 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

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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 [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 mo 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.

## 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, 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 = 2375), 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).

### *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 when asked for symptoms of fatigue. However,

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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, 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 2375 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 under-recognized, clinical conditions in MS contributing to increased fatigue [29].

*Methodological constraints*

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.

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 associated with 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 anxiety, also need 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 under-recognized and undertreated clinical conditions in MS that are in need of specific diagnoses and appropriate treatments.

**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.

**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).

## Conflicts of interest

The authors have no conflict of interest to disclose.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2016.03.004.

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