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Topical Review

The impact of drugs for multiple sclerosis on sleep

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Abstract: Although there is a growing literature on the presence of sleep disorders in multiple sclerosis (MS), few studies have specifically addressed the impact of drugs on sleep of these patients. Moreover, even when sleep is considered, quantitative assessment by standardized questionnaires or polysomnography is lacking. The studies that have been done highlight that interferon-beta and some symptomatic medications may affect sleep, thus contributing to fatigue, depression, and poor quality of life; conversely, natalizumab and cannabinoids may improve sleep. Common limitations of the literature reviewed here are small sample size, selection bias, and often a lack of objective outcome measures. Clinicians need to remember to ask about sleep in all MS patients and intervene when appropriate. A systematic approach that takes sleep into account is recommended to enhance recognition and appropriate management of sleep disruption, including disorders related to medication. Consideration of the impact on sleep should also be part of the design of trials of new therapies.

Keywords: Multiple sclerosis, sleep disorders, disease-modifying drugs, neuroinflammation, quality of life

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Introduction

In addition to the many recognized sources of disability seen in people with multiple sclerosis (MS), sleep disorders in patients with MS are observed with higher frequencies than in the general population, with estimates ranging from 25% to 54%.[1] Insomnia, sleep breathing disorders, circadian rhythm disorders, restless legs syndrome (RLS), narcolepsy, and rapid eye movement (REM) sleep behavior disorder have all been reported. In particular, RLS is frequent in these patients, and when moderate or severe, it can disrupt sleep, causing fatigue, mood changes, and cognitive problems.[2] However, despite their impact, sleep disorders in MS remain critically under-recognized in most clinical settings.[3] Sleep dysfunction can potentially exacerbate or contribute to other MS symptoms, such as fatigue, pain, depression, and cognitive impairment, through mechanisms which may include a pro-inflammatory cytokine-mediated worsening of the autoimmune process underlying the disease.[2] In particular, poor sleep and fatigue, either independently or collectively, are often disabling and influence the quality of life in MS patients.[2] Even at the polysomnographic level, measures of disturbed sleep are associated with reduced quality of life in this population.[4]

A better understanding of the factors that contribute to sleep disturbances in MS is needed to improve treatment. Up to now, research has primarily focused on the prevalence of sleep disorders in MS, and the relationship between sleep and MS-associated fatigue.[1,5] However, other factors in addition to co-morbid sleep disorders, such as the use of the disease-modifying drugs and symptomatic therapies commonly used in MS, may play a significant role.

The goal of this review is to summarize the current knowledge on the drug-induced factors that may contribute to sleep disruption and raise awareness on the importance of considering sleep in the pharmacological management of these patients and in the design of novel treatments.

MS drugs and sleep

Data source and selection

A PubMed-based literature review was conducted. With an initial search using the keywords “multiple sclerosis” and “sleep,” 581 articles were screened in total. Adding another keyword (“disorders”), we sorted

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Table 1. Studies in patients with MS on disease-modifying medications with reported effects on sleep.

Medication	Indication in MS	Effects	Polysomnographic data	Mechanism of action
Interferon-beta[9–14]	First-line disease-modifying therapy	Fatigue, hypersomnolence, and insomnia (reduced flu-like syndrome by switching from evening to morning injections)	Reduction of sleep efficiency (improved sleep efficacy by switching from evening to morning injections)	Reduces antigen presentation and T-cell proliferation and alters cytokine expression
Glatiramer acetate[11–13,15–17]	First-line disease-modifying therapy	More frequent awakenings and daytime somnolence; increased anxiety and irritability	Not available	Partly due to an increase in anti-inflammatory cytokines (IL-4 and IL-10) through activation of the Th-2 cell pathway of immunity
Natalizumab[18,19]	Second-line disease-modifying therapy	Improvement in fatigue, daytime sleepiness, and depression	Not available	Monoclonal antibody against the α-4 subunit of α-4 β-1 integrin that inhibits the ability of activated T cells to migrate across the blood–brain barrier into the CNS

Source: Adapted from Brass et al.[2]
MS: multiple sclerosis; IL: interleukin; CNS: central nervous system.

out 402 articles. Adding the keyword "treatment," 214 articles were found. We then excluded articles about sleep in drug-naïve MS patients and studies conducted in animals or in other demyelinating disorders because their content did not fit the aim of this paper. Moreover, we did not include studies that did not sufficiently report the statistical values required and articles different from research studies and non-English written papers. We have reviewed the articles listed in the references in order to locate further data. After this process, we identified three studies about high-dose steroid treatment,[6–8] nine on first-line immunomodulatory agents (interferon-beta (IFN-β), glatiramer acetate (GA)),[9–17] 2 on natalizumab,[18,19] and 13 on cannabis-based extracts.[20–32] As summarized in Tables 1 and 2, both disease-modifying drugs and common symptomatic medications for MS may interfere with sleep.[33]

Methylprednisolone

As known, insomnia and other sleep changes, such as decreased REM sleep, are common side effects of steroid treatment, even after only a few days of administration.[34] A randomized, placebo-controlled trial of oral methylprednisolone given in pulses every 4 weeks as an add-on therapy to IFN-β-1a for the treatment of relapsing–remitting MS was carried out.[6] The authors found that steroid intake led to a significant reduction in relapse rate; however, insomnia was one of the most frequent adverse event recorded (~25% of patients).[6] As in the general population, the clinician must consider this co-morbid cause of insomnia and encourage lifestyle changes (such as proper sleep hygiene), cognitive behavioral therapy (CBT), and pharmacological intervention if needed.[35]

A very recent prospective multicenter observational study evaluated through self-report questionnaires the frequency, severity, and impact on activities of daily living of adverse effects of high-dose intravenous methylprednisolone in relapsing–remitting MS patients with a relapse. The authors observed that sleep disturbance (not better specified) was among the most common adverse events experienced by the patients (44% of 59), especially in those with high disease impact or high disability.[8]

Nevertheless, although most clinicians warn patients about the steroid-related effects on sleep, an actigraphy study evaluating the short-term tolerance of 5-day regimen of intravenous methylprednisolone demonstrated high sleep efficiency, which is discrepant with the complaints reported by the patients. The authors conclude that sleep efficiency was not disturbed by methylprednisolone in patients, whether used for a clinically isolated syndrome (CIS), MS relapse, or sub-acute disease progression.[7]

IFN-β

Since its introduction as an established therapy for relapsing–remitting MS, IFN-β has been known to affect sleep continuity, at least in the early phase of therapy,[9] although objective evidence of sleep disruption with chronic use is still lacking. Moreover, it has recently been suggested that fatigue may be linked to

Table 2. Symptomatic medications with potential effects on sleep.

Medication	Indication in MS	Effects	Polysomnographic data	Mechanism of action
Methylprednisolone[6–8]	Acute relapse	Insomnia	Decreased REM sleep	Decreased cytokine cascade, activation of T cells, and ability of immune cells to penetrate the CNS
Modafinil	Fatigue	Insomnia	Reduced sleep latency	Unknown
Methylphenidate	Fatigue	Insomnia	REM suppression	Increased catecholamine release and reuptake inhibition
Amantadine	Fatigue	Insomnia	Not available	Presynaptic dopamine releasing agent
Pemoline	Fatigue	None	Not available	CNS stimulant
4-Aminopyridine	Fatigue	Insomnia	Not available	Block of potassium channels in neurons
Baclofen	Spasticity	Sedation	Total sleep time increased and reduced wake after sleep onset	GABA-B receptor agonist
Clonazepam	Spasticity anxiety	Somnolence	Increased total sleep time, reduced sleep latency and wake after sleep onset, increased spindle activity, and reduced REM sleep	GABA-A receptor agonist
Tizanidine	Spasticity	Daytime drowsiness	Improvement in sleep induction and maintenance	Central α-2 adrenoreceptor agonist
SSRI	Depression anxiety	Insomnia or sedation	Decrease total sleep time, increase stage 1 sleep, decrease REM, increase sleep latency, "Prozac eyes," and periodic limb movements	Inhibition of serotonin reuptake
Gabapentin	Pain seizures	Sleepiness	Decreased sleep stage 1, increased sleep stage 3, reduced periodic limb movements, and increased REM sleep	May promote formation of GABA in the CNS
Oxybutynin	Urinary frequency	Sedation	Decreased REM sleep and increased REM sleep latency	Anticholinergic agent
Cannabis-based medicinal extracts[20–32]	Spasticity bladder dysfunction central neuropathic pain	Improved sleeping difficulty and sleep quality, diminished awakenings, and sleepiness	Not available	Inhibition of smooth muscle contraction, interaction with the cholinergic receptor system and/or synergism with anticholinergic medication, and analgesic properties

Source: Adapted from Brass et al.[2]
MS: multiple sclerosis; SSRI: selective serotonin reuptake inhibitors; REM: rapid eye movement; CNS: central nervous system; GABA: gamma-amino-butyric acid.

direct or indirect effects of IFN-β on the central nervous system (CNS), particularly via activation of corticotropin-releasing hormone synthesis and adrenocorticotropic axis function, and its effects on interleukin (IL)-1 and IL-6 production.[36] This may result in changes in the immune balance between pro- and anti-inflammatory cytokines within the CNS, particularly at the level of hypothalamus and limbic system.[36] In this context, although the literature is careful not to equate daytime fatigue with somnolence, increased nocturnal concentrations of serum IL-6 have also been found in non-MS patients with impaired sleep.[37] These findings further support the need to objectively investigate the chronic effects of these agents on sleep.

In a previous study aiming to evaluate the prevalence of poor sleep and the influence of sociodemographic and clinical factors on sleep quality in 90 MS (subtype not specified), Bøe Lunde et al.[13] reported that the immunotherapy in 35 patients (IFN-β $n=24$, GA $n=7$, natalizumab $n=2$, other drugs $n=2$) was independently associated with poor quality of sleep.

An actigraphy investigation by Mendozzi et al.[11] showed a reduced sleep efficiency in relapsing–remitting MS patients during the nights following the injection of IFN-β compared to no-drug nights. The effect was significant and irrespective of the pharmacological preparation of the drug and of the different timing of administration, that is, 3 days a week or once a week. Similarly, relapsing–remitting patients not receiving drug showed a better sleep efficiency especially compared to those on IFN-β once a week, possibly suggesting that adaptation to the side effects of these agents is probably never complete.[11] In the same study, the effect of IFN-β on sleep was perceived by the patients as an increase in restlessness during the night and a more difficult awakening, both at drug initiation and after chronic use. The presence of a significant correlation between total daily sleep quality ratings and objective measures of sleep continuity, such as sleep efficiency in the drug nights, suggests that the adaptation to some effects of the IFN-β on sleep may not be complete even after years of continuous therapy.[11]

Clinicians usually recommend to inject IFN-β in the evening, so that the patient can sleep through the side effects.[38] However, one recent study in a cohort of 105 relapsing–remitting MS patients has reported reduced flu-like symptoms and improved sleep efficiency by switching from evening to morning injections.[14] In detail, 1 month after changing the injection time, 29 of 50 patients (58%) who switched to morning injections reported that their flu-like syndrome was decreased, and 11 (24%) thought that it was unchanged. In addition, 23 patients (48%) reported improved sleep, and 33 patients (68%) chose to continue morning injections. Quantitative measures, however, indicated that there was no change in the severity of flu-like syndrome or the number of antipyretic doses taken for its management.[14] To the best of our knowledge, no other study has been carried out, and therefore, further replication is needed.

It is worth mentioning that other authors have shown a lower prevalence of sleep disturbances in MS patients on IFN-β, without differences in daytime sleepiness,[12] although they do not specify whether this effect was directly attributable to IFN-β or whether a potential negative effect of IFN-β on sleep was canceled out by concomitant symptomatic therapies (such as muscle relaxants, anticholinergics, carbamazepine, gabapentin, and antidepressants). Proposed mechanisms whereby IFN-β may improve sleep quality include modulation of cytokines levels or restoration of the circadian secretion of melatonin and its suppressed metabolism.[39,40]

Finally, in a study in patients with MS comparing subjective measures of daytime alertness with nocturnal polysomnography, neither periodic limb movement index nor subjective sleepiness scales were found to be associated with the use of IFN-β.[17]

The data reviewed here also provide insights as to why some of the above-mentioned studies conflict. Indeed, conflicting findings may be explained by differences in (1) the populations studied, who were essentially based on relatively small series of MS patients,[11,17] or patients with different course of the disease (i.e. relapsing–remitting vs secondary progressive);[17] (2) the assessment of quality of sleep, such as questionnaires,[12,13] actigraphy,[11] or polysomnography;[17] and (3) the exposure to IFN-β, such as the proportion of treated patients (rather small in some studies),[12,13,17] the different schedules of administration (i.e. the precise form and route),[11] or timing of injection (evening or morning injection).[14]

To summarize, there is no clear direction where the evidence on the impact of IFN-β on sleep actually points at, and therefore, a firm conclusion cannot be drawn based on the available literature. Nevertheless, IFN-β is able to affect sleep efficiency on the day of administration, even after prolonged use. The effect seems to be quantitatively modest, although patients can perceive and rate it on sleep quality logs. The possibility of mitigating the adverse effect on sleep by changing injection time might be considered.

GA

GA is generally considered to be lacking significant effects on sleep as it does not cause a flu-like syndrome.[15] Moreover, treatment was associated with a significant improvement in fatigue and a marked reduction in absence from work;[16] however, it has also been reported to cause more frequent awakenings and daytime somnolence.[11] Indirect support for a possible adverse effect of GA on sleep continuity and negative daytime consequence comes from a recent report of increased anxiety and irritability after 1 month of GA in a group of young relapsing–remitting MS patients with mild neurological disability.[36] In this study, the adverse effects on sleep were interpreted as partly due to an increase in anti-inflammatory cytokines (IL-4 and IL-10) through activation of the Th-2 pathway of immunity.[36] Nevertheless, these authors did not directly demonstrate an effect of GA on sleep, but they inferred it from the increase in anxiety and irritability. Therefore, it is not possible to provide any firm evidence for an effect of GA on sleep parameters. The above-mentioned actigraphic study

by Mendozzi et al.[11] did not assess the patients sleep during a GA off-drug period.

Other researchers did not report significant difference between the score at subjective sleep questionnaires and the use of GA.[17] Finally, no association was found between chronic insomnia and treatment with GA; transient symptoms were described as side effects.[11] No study has specifically evaluated chronic insomnia.

In conclusion, GA exposure has been associated with both altered sleep continuity and psychoemotional status, although they are often not clinically significant. The lack of objective sleep studies makes any further speculation difficult.

Monoclonal antibodies

Two studies have focused on the association between clinically reported relevant changes in MS fatigue under natalizumab treatment and strongly associated factors, such as sleep and daytime sleepiness.[18,19] The results clearly demonstrated that natalizumab-treated patients exhibit improvements not only in fatigue but also in daytime sleepiness, cognitive function, depression, and general quality of life from baseline to 1 year later. No study concerning sleep has been presented so far in MS patients on other monoclonal antibodies, such as alemtuzumab, rituximab, daclizumab, or ocrelizumab.

Cannabis-based extracts

The well-recognized positive effects on urinary symptoms, spasticity, pain, and difficulty in sleeping suggest that cannabis medicinal extracts act at numerous sites within the CNS.[20] Improved subjective scores for pain, spasticity, and ability to sleep have been reported after treatment with pure delta-9-tetrahydrocannabinol (THC).[20] Treatment with THC (2.5 mg/spray) and cannabidiol (CBD; 2.5 mg/spray) significantly alleviated pain, although the improvement in spasticity and sleeping did not reach statistical significance, probably as a result of the small number of patients enrolled in the study.[20] In contrast, a randomized double-blind, placebo-controlled crossover study did not show significant differences for the sleep-related clinical measures considered, although patients tended to fall asleep more easily while on cannabis-extract oral capsules standardized to THC (2.5 mg) and CBD (0.9 mg),[24] highlighting that cannabis medications are not the same in their side effect profile.

Sativex® oromucosal spray (nabiximols) is a cannabinoid-based medicine comprising 2.7 mg of THC and 2.5 mg of CBD at a nearly 1:1 fixed ratio. It is widely available as add-on therapy for adult MS patients with moderate-to-severe spasticity who do not respond adequately to first-line medications.[41] The efficacy of Sativex was reported to be significantly superior to placebo also for sleep disruption.[21] In another study, the efficacy of Sativex spray on central neuropathic pain and sleep-related quality in MS has been assessed after 14 weeks of treatment.[22] A significant difference in the sleep quality score in favor of the treated group was observed, although this was balanced by the observation that daytime sleepiness was the most commonly reported sleep-related adverse event.[22,23] Interestingly, in another study, this treatment was found to be effective and mostly well tolerated in reducing pain and sleep disturbance in patients with MS-related central neuropathic pain.[25] Given that this improvement occurred without a corresponding significant change in mood, the authors suggest that patients have felt a benefit from intrinsic reduction in pain, sleep improvement, or both.[25]

A recent review, including four randomized controlled trials,[21,29,42,43] two extension studies,[27,44] and a prospective noninterventional study in clinical practice with a long-term extension phase,[45,46] has shown that approximately 40% of patients with moderate-to-severe spasticity resistant to the current available oral antispasticity agents reached relevant symptomatic relief with Sativex oromucosal spray that was accompanied by improvement of spasticity-associated symptoms or functional impairment, including sleep quality.[41] In particular, in one study,[44] the proportion of patients who rated their sleep quality as "bad" or "very bad" decreased from 13% to 11%, whereas those who rated it as "good" or "very good" increased from 50% to 59%; in another investigation,[21] 61% of Sativex responders also achieved a $\geqslant$30% improvement on the sleep quality Numerical Rating Scale (NRS); in the prospective observational MOVE 2 study,[45] the add-on therapy with Sativex produced a significant 24.3% decrease from baseline to week 4 in the mean sleep disturbances NRS score, and among patients who progressed to the 12-month extension study,[46] there was a highly significant 37.2% reduction from baseline in the mean sleep disruption NRS score. Although results on a study-by-study basis were variable generally because of methodological issues, the benefits were consistently more pronounced in Sativex responders and were maintained during long-term treatment up to 1 year without need to increase the dosage.[41] Moreover, according to the same review paper,[41] patients who achieve a significant response in terms of symptomatic relief of spasticity might be expected to also gain similar improvement in the domains of sleep quality and

other related symptoms. However, whether the benefits of Sativex as demonstrated in these studies were a direct effect or secondary to the relief of spasticity is uncertain and cannot be concluded from the available data.[41] Finally, it is noteworthy to mention that planned, sudden interruption of Sativex for 2 weeks caused interrupted sleep in 16% of patients during the withdrawal period.[27]

In conclusion, sleep disturbances in MS generally improved with cannabinoid treatment; beneficial effects are also demonstrated on spasticity and pain-related sleep disturbance, as well as on the quality of sleep.

Other drugs

To date, no study aiming at an objective evaluation of other disease-modifying therapies, such as mitoxantrone, fingolimod, laquinimod, teriflunomide, and dimethyl fumarate on sleep function in MS has been carried out. Similarly, it is known that the use of immunosuppressive drugs (i.e. azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil) is significantly associated with poor sleep quality in rheumatic diseases (i.e. systemic lupus erythematosus),[47] although this still needs to be verified in MS population.

Finally, drugs used to alleviate other MS-related symptoms, including over-the-counter medications, also have the potential to interfere with sleep and worsen daytime sleepiness and fatigue. Given the high frequency of utilization in this population, careful efforts should be directed at screening for these medications and assessing possible effects on sleep.

Discussion

This is the first review looking at the impact on sleep of disease-modifying drugs or symptomatic therapies in the MS population. The main finding is that IFN-β therapy and some symptomatic medications in patients with MS may affect sleep and contribute to fatigue, depression, and poor quality of life; conversely, treatment with natalizumab or cannabinoid generally improves sleep. Data on other therapeutic options, such as GA, immunosuppressive, and more recent drugs, are lacking or limited. Nevertheless, since several immunologic factors have been implicated in the development of sleep disorders, and MS is proven to be characterized by immune abnormalities, the notion that MS and sleep disorders share a similar background seems to be reasonable.[48] The increasing knowledge on the effects of inflammatory mediators on the expression of genes that are involved in cellular circadian clock networks might provide an explanation for both sleep disorders and daytime sleepiness in MS.[49]

A systematic, practical approach that takes sleep into account is recommended to enhance recognition and facilitate appropriate management. Clinicians need to ask about sleep in all MS patients and refer on when appropriate, bearing in mind that some of the sleep disturbances might be drug related. Referral to the sleep specialist should be considered for the management of conditions that require polysomnographic diagnosis. Moreover, MS treatment might also have an impact on some sleep disorders that are highly prevalent in MS; for instance, according to a recent review by Marrie et al.,[50] RLS has a prevalence ranging from 14.4% to 57.5% in MS population. However, up to now, the relationship between drugs and co-morbid sleep disorders in MS still needs to be explored. Finally, as sleep has been shown to impact the general health status, improving sleep may contribute significantly to improve quality of life.

The main limitations of the studies we reviewed are often the small numbers of subjects, the selection bias, and a lack of standardized sleep questionnaire or polysomnographic data. Given that both MS and sleep disruption generate pro-inflammatory cytokine profiles, it would be intriguing to assess how co-morbid sleep disturbances affect the cytokine profile, and whether treatment for sleep disorders would be able to modulate the levels of systemic and cellular pro-inflammatory mediators and the leukocyte expression of pro-inflammatory genes. Interestingly, a recent randomized controlled trial found that CBT and tai chi reversed cellular and genomic markers of inflammation in older adults with insomnia,[51] thus providing an evidence-based molecular framework to understand the potential effects of insomnia treatment on inflammation. Moreover, CBT for insomnia had the additional effect of increasing activity of IFN-responsive transcription factors,[51] consistent with prior findings that CBT increases ex vivo production of IFN.[52] These findings have potential crucial implications for inflammatory diseases and immuno-mediated CNS disorders, such as MS. Large, prospective, multicenter, cohort studies, using both subjective questionnaire and objective polysomnographic data, are mandatory to address these points. Meanwhile, ongoing randomized controlled trials of novel MS drugs should also consider measures of change in self-reported sleep and sleep disorders.

In conclusion, along with already existing moves to increase awareness and treatment of sleep disorders in

people with MS, clinicians should consider the possibility that both disease-modifying therapies and drugs used for symptom control may be contributing. Recognizing and addressing the underlying cause of sleep disturbance may facilitate its management with the ultimate goal of improving patients' quality of life.

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