Scientific Research Publishing

Journal of Biosciences and Medicines, 2020, 8, 1-16
https://www.scirp.org/journal/jbm
ISSN Online: 2327-509X
ISSN Print: 2327-5081

Insomnia and Excessive Daytime Sleepiness in Parkinson's Disease Patient—A Review Article

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How to cite this paper: Schreiner, T.G. (2020) Insomnia and Excessive Daytime Sleepiness in Parkinson's Disease Patient—A Review Article. *Journal of Biosciences and Medicines*, **8**, 1-16.
https://doi.org/10.4236/jbm.2020.87001

Received: May 12, 2020
Accepted: June 30, 2020
Published: July 3, 2020

Abstract

Sleep-wake disorders play an important role among non-motor symptoms in Parkinson's Disease, being a constant subject of research in recent years. There are a multitude of sleep-wake disturbances that worsen the patient's quality of life, insomnia and excessive daytime sleepiness being two of the most frequent complaints. The aim of this review is to highlight the most relevant clinical trials conducted during the last 5 years, focusing on the problematic of insomnia and daytime sleepiness correlated with Parkinson's Disease and its treatment. Three electronic databases (Pubmed, Science Direct and Google Scholar) were searched during March and April 2020 for articles on this topic, finally selecting 21 most relevant articles that we have included in this review. Interesting aspects regarding correlation between sleep-wake disorders and Parkinson's disease were found, showing that non-motor symptoms may be independent of the disease itself. We discussed the most recent advances in treatment opportunities and the adverse effects, with insomnia and daytime sleepiness among the most common complaints. Besides newly developed pharmacological therapy, consisting in mostly dopaminergic agonists or levodopa adjuvant drugs. Other possibly effective therapies on sleep-wake disorders such as deep brain stimulation, dietary changes, bright light therapy and alternative medicine protocols are also reviewed. Insomnia and excessive daytime sleepiness are common complaints in Parkinson's disease patients, being either self-standing non-motor symptoms or adverse effects of the antiparkinsonian medication, diminishing patient's quality of life. The efferves-cence of research on this topic shows promising results, with new clinical trials still to come in the near future.

Keywords

Parkinson's Disease, Insomnia, Excessive Daytime Sleepiness, Sleep-Wake Disorders Treatment

1. Introduction

Non-motor symptoms (NMS) in Parkinson's disease are a broadly discussed topic nowadays, besides ameliorating the motor symptoms (tremor, dyskinesia, postural rigidity), researchers and neurologists focusing on the management of NMS [1] [2] [3]. Among NMS, sleep-wake disturbances are frequently encountered symptoms by the patient, having negative impact also on the motor symptoms management and on patient's quality of life (QoL) [4]. There are many sleep-wake disorders (**Table 1**) that may occur during daytime such as excessive daytime sleepiness (EDS), fatigue, restless legs syndrome and circadian sleep-wake disorders. However, most disorders are related to sleep: insomnia, rapid eye movement (REM) sleep behavior disorder, non-REM parasomnias, and sleep apnea syndromes [5] [6].

As the spectrum of sleep-wake disorders is too broad to be thoroughly reviewed in one single article, two of the most common patient's complains, *i.e.* insomnia and EDS will be presented here.

Insomnia, one of the most common complaints in PD patients, can be broadly defined as a quantitative and qualitative discomfort of sleep. Usually, the insomniac has the following symptoms: difficulty to fall asleep, difficulty to maintain a relaxing sleep, waking up many times during the night, and early awakening in the morning with the inability to return to sleep [7]. There are multiple causes for insomnia in parkinsonians, motor impairment as the main condition of the disease and antiparkinsonian medication playing important roles. Firstly, impairment of mobility during night due to elimination of dopamine intake during the night and the addition of neuropsychiatric symptoms (anxiety, depression) have a certainly negative impact on sleep quality, generating insomnia. Moreover, the majority of parkinsonian drugs have important side effects, being potential causes for insomnia, as the studies reviewed here will also demonstrate.

Two different diagnostic modalities for insomnia are used by neurologists nowadays. A detailed anamnesis of the patient and their relatives or caregivers is a good first step to begin with, as long as the clinician asks question-related to duration of sleep, habits of sleep initiating and morning awakenings, and numbers of

Table 1. Sleep-wake disorders in Parkinson's Disease patient.

Sleep-wake disorders in Parkinson's Disease patient
Insomnia
Excessive daytime sleepiness (EDS)
Rapid eye movement (REM) sleep behavior disorder
Non-REM parasomnias
Sleep apnea syndrome
Fatigue
Restless legs syndrome and periodic limb movement disorder
Circadian sleep-wake disorders

sleep interruptions during the night [8]. They have been established a couple of international scales with good sensitivity that can help the neurologist in assessing insomnia. Although having some limitations, Epworth sleeping scale, Parkinson's disease sleep scale and Stanford Sleepiness Scale are just a few examples of the scales used successfully worldwide and also in the studies reviewed in this work [9] [10].

Another important, more sensitive and specific tool for evaluating sleep is polysomnography. Used extensively in studies but also in everyday practice, this method offers the possibility to diagnose several sleep disturbances, being preferred in monitoring REM sleep disorders or sleep apnea.

Lastly, actigraphy is more and more used by sleep specialists in diagnosing different sleep-wake disturbances. This method implies recording of the occurrence and degree of limb movement activity. For sleep measurements, actigraphic devices, usually worn over wrists and ankles are helpful to quantify insomnia also in PD patients.

Regarding the treatment, aspects related further in this article, during the last years numerous studies were conducted, researchers probing various pharmacological and non-pharmacological therapies in order to improve the patients QoL.

EDS, the increased tendency to fall asleep during daytime, is a common symptom in PD patients, affecting more than 55% of patients [11], contributing to poor QoL and increased risk of harm. This condition must be differentiated from fatigue, a vaguer symptom that reflects lack of energy, physical and mental exhaustion, and apathy, but no sleeping risk [12] [13].

The causes of EDS are multiple, different directions being studied in the literature. Firstly, according to some trials, the disease itself may contribute to sleepiness, as PD duration and severity are related to EDS [14]. However, more recent results show that EDS is not correlated to deterioration of motor symptoms in PD or substantia nigra degeneration [15]. Medication plays also an essential role in EDS, as in insomnia and other sleep-wake disturbances. Dopamine agonists, as shown also in trails reviewed in this work, have a significant contribution to EDS in PD patients, regardless the duration of disease.

The diagnosis of EDS follows the same pathway as in the case of insomnia, validated questionnaires translated in multiple languages such as the Epworth sleepiness scale are used by neurologists in order to diagnose EDS. The treatment remains a challenge for the clinician, numerous trials being conducting as researchers are trying to find effective remedies for this complaint.

In this context, this study aims to be a narrative review of the literature regarding the problematic of insomnia and EDS in Parkinson's disease patients, focusing on the most relevant studies conducted during the last 5 years and presenting some introspects on possible efficient treatments for this two sleep-wake disturbances.

2. Material and Methods

In order to achieve the aim of this article, three electronic databases (Pubmed,

Science Direct and Google Scholar) were searched for articles published in the English language from January 1, 2015 to present, pertaining to adult humans with PD and insomnia and/or EDS.

The following combination of terms was used to search for Parkinson's disease associated with insomnia or EDS: ("Parkinson disease" OR "primary parkinsonism") AND ("sleeplessness" OR "insomnia") AND ("somnolence" OR "sleepiness" OR "excessive daytime sleepiness"). The following exclusion criteria were used: non-English language, abstract only articles, animal researches, review articles, opinion-based letters-to-the-editors, and non-PD trials. The identification and selection process is presented in Figure 1.

After the search, application of exclusion criteria, and selection of the most relevant trials, a total of 21 articles were included in this review.

3. Results and Discussion

Improvement of treatment for PD is a constant concern for neurologist nowadays, proof being the multitude of clinical trial conducted in order to find the right medication in right doses and administration forms for specific parkinsonian patient's groups. Although the classical motor symptoms such as dyskinesia or freezing were major concerns for researchers, focus on sleep-wake disturbances is growing. As a result, our search revealed 6 studies that discussed the correlation between PD and insomnia (Table 2), while another 15 recent studies reported on the problematic of EDS in PD patients (Table 3).

Insomnia and PD

Development and arrival of new drugs on the market impose studies to assess safety, benefit and possible adverse reaction in the general population, the same being valid for emergent therapeutics used in PD. Catechol-O-methyltransferase (COMT) inhibitors are a well-known class of medication broadly used in com-

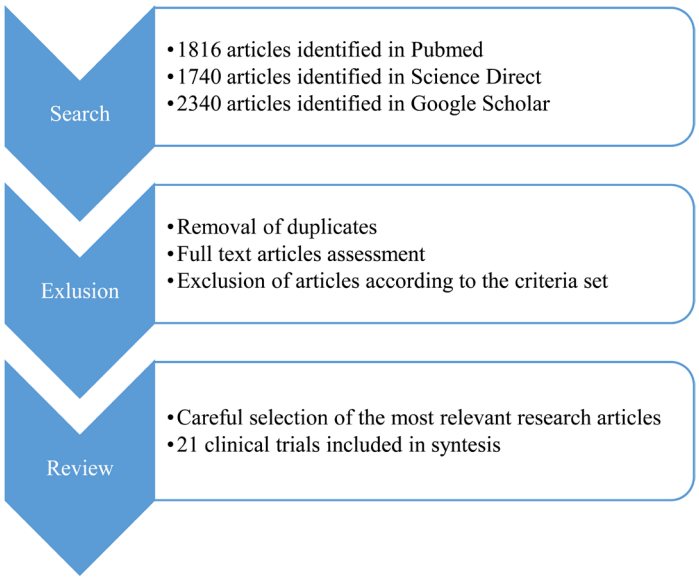

Figure 1. Search process.

Table 2. Clinical trials on insomnia and Parkinson's disease.

Clinical trials on insomnia and Parkinson's Disease		
Name of paper	**Author(s)**	**Journal/Issue**
Efficacy and safety of SQJZ herbal mixtures on nonmotor symptoms in Parkinson disease patients: Protocol for a randomized, double-blind, placebo-controlled trial	Shi J, Tian J, Li T, Qin B, Fan D, Ni J, Wei M *et al.*	Medicine (Baltimore) 2017, 96(50): e8824
Efficacy of Yokukansankachimpihange on sleep disturbance in Parkinson's disease: A study protocol of a randomized, double blind, placebo-controlled pilot trial	Jang JH, Lee J, Jung I, Yoo H	Medicine (Baltimore) 2018, 97(26): e11298
Opicapone as an adjunct to levodopa in patients with Parkinson's disease and end-of-dose motor fluctuations: a randomized, double-blind, controlled trial	Ferreira JJ, Lees A, Rocha JF, Poewe W, Rascol O, Soares-da-Silva P	Lancet Neurology 2016, 15(2): 154-165
Randomized, placebo-controlled trial of ADS-5102 (amantadine) extended-release capsules for levodopa-induced dyskinesia in Parkinson's disease (EASE LID 3)	Oertel W, Eggert K, Pahwa R, Tanner CM, Hauser RA, Trenkwalder C, Ehret R *et al.*	Movement Disorders 2017, 32(12): 1701-1709
Real-world pharmacological treatment patterns of patients with young-onset Parkinson's disease in Japan: a medical claims database analysis	Kasamo S, Takeuchi M, Ikuno M, Kawasaki Y, Tanaka S, Takahashi R, Kawakami K	Journal of Neurology 2019, 266: 1944-1952
Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study	Postuma RB, Iranzo A, Hu M, Högl B, Boeve BF, Manni R, Oertel WH *et al.*	Brain. 2019, 142(3): 744-759

bination with Levodopa in order to decrease peak-trough variations of levodopa and increase its plasma elimination half-life [16]. By now, tolcapone and entacapone are the only two COMT inhibitors available for clinical use, both having limitations. While tolcapone is known for liver toxicity, requiring liver function monitoring and special care in patients with associated liver dysfunctions, the efficacy of entacapone is limited, requiring frequent dosing. The need for a more safer and efficacious COMT inhibitor led to the apparition of a novel, once-daily, potent third-generation medicament, Opicapone. Ferreira *et al.*, in their study, evaluated the safety and efficacy of opicapone as an adjunct to levodopa in the treatment of PD patients with dyskinesia [17]. The results were promising, as the addition of opicapone 50 mg enabled the physician to adjust the levodopa daily regimen, by reducing total daily dose and number of intakes, improving the motor fluctuations. For us, this study is important because it reveals an important adverse effect of this otherwise efficient medication. Compared to placebo, opticapone 50 mg caused insomnia in 7 patients of the test-group (6%), however same result being obtained in case of entacapone. This conclusion is in line with other data in literature, demonstrating that insomnia in PD patients may be an iatrogenic symptom provoked by antiparkinsonian medication.

Amantadine, a well and long-known medication for PD, is still a subject of intense research nowadays. One example could be the study conducted by Oertel *et al.*, showing that amantadine may be administered also as extended-release capsules, hoping to control troublesome levodopa-induced dyskinesia. Regarding

Table 3. Clinical trials on EDS and Parkinson's disease.

Clinical trials on EDS and Parkinson's Disease		
Name of paper	**Author(s)**	**Journal/Issue**
A randomized trial of a low-dose Rasagiline and Pramipexole combination (P2B001) in early Parkinson's disease	Olanow CW, Kieburtz K, Leinonen M, Elmer L, Giladi N, Hauser RA, Klepiskaya OS, *et al.*	Movement Disorders 2016, 32: 783-789
Acupuncture in the treatment of fatigue in Parkinson's disease: A pilot, randomized, controlled, study	Kong KH, Ng HL, Li W, Ng DW, Tan SI, Tay Ky, Au WL *et al.*	Brain Behavior 2017, 8(1): e00897
Bright light therapy with a head-mounted device for anxiety, depression, sleepiness and fatigue in patients with Parkinson's disease	Raymackers J, Andrade M, Baey E, Vanneste M, Evrard F	Acta Neurologica Belgica 2019, 119: 607-613
Caffeine as symptomatic treatment for Parkinson disease (Café-PD): A randomized trial.	Postuma RB, Anang J, Pelletier A, Joseph L, Moscovich M, Grimes D, Furtado S, *et al.*	Neurology. 2017, 89(17): 1795-1803
Daytime sleepiness may be an independent symptom unrelated to sleep quality in Parkinson's disease	Liguori C, Mercuri NB, Albanese M, Olivola E, Stefani A, Pierantozzi M	Journal of Neurology 2019 Mar, 266(3): 636-641
Effects of rotigotine transdermal patch in patients with Parkinson's disease presenting with non-motor symptoms—results of a double-blind, randomized, placebo-controlled trial	Antonini A, Bauer L, Dohin E, Oertel WH, Rascol O, Reichmann H, Schmid M *et al.*	European Journal of Neurology 2015, 22(10): 1400-1407
Effects of transcranial direct current stimulation on executive function in Parkinson's disease	Doruk D, Gray Z, Bravo GL, Pascual-Leone A, Fregni F.	Neuroscience Letters 2014, 582: 27-31
Homotaurine in Parkinson's disease	Ricciardi L, De Nigris F, Specchia A, Fasano A	Neurological Sciences 2015, 36: 1581-1587
Impact of inability to turn in bed assessed by a wearable three-axis accelerometer on patients with Parkinson's disease	Uchino K, Shiraishi M, Tanaka K, Akamatsu M, Hasegawa Y	PLoS One. 2017, 12(11): e0187616
Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial	Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP	Movement Disorders 2018, 33(8): 1306-1314
Low-frequency versus high-frequency stimulation of the pedunculopontine nucleus area in Parkinson's disease: a randomised controlled trial	Nosko D, Ferraye MU, Fraix V, Goetz L, Chabardès S, Pollak P, Debû B	Journal of Neurology Neurosurgery and Psychiatry 2015, 86: 674-679
Rasagiline improves polysomnographic sleep parameters in patients with Parkinson's disease: a double-blind, baseline-controlled trial	Schrempf W, Fauser M, Wienecke M, Brown S, Maaß A, Ossig C, Otto K, *et al.*	European Journal of Neurology 2018, 25: 672-679
Repeated sessions of transcranial direct current stimulation evaluation on fatigue and daytime sleepiness in Parkinson's disease	Forogh B, Rafiei M, Arbabi A, Motamed MR, Madani SP, Sajadi S	Neurological Sciences 2017, 38: 249-254
Sodium Oxybate for Excessive Daytime Sleepiness and Sleep Disturbance in Parkinson Disease: A Randomized Clinical Trial	Büchele F, Hackius M, Schreglmann SR, Omlor W, Werth E, Maric A, Imbach LL *et al.*	JAMA Neurology 2018, 75(1): 114-118
Sublingual apomorphine (APL-130277) for the acute conversion of OFF to ON in Parkinson's disease	Hauser RA, Olanow CW, Dzyngel B, Bilbault T, Shill H, Isaacson S, Dubow J, *et al.*	Movement Disorders 2016, 31: 1366-1372
Timed Light Therapy for Sleep and Daytime Sleepiness Associated with Parkinson Disease: A Randomized Clinical Trial	Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC	JAMA Neurology 2017, 74(4): 411-418
Zonisamide improves wearing-off in Parkinson's disease: A randomized, double-blind study	Murata M, Hasegawa K, Kanazawa I, Fukasaka J, Kochi K, Shimazu R; Japan Zonisamide on PD Study Group	Movement Disorders 2015, 30(10): 1343-1350

to our interests in sleep-wake disturbances, the authors showed that insomnia is an adverse effect of this medication, with 4 out of 37 patients (10.8%) suffering from insomnia versus 0% in case of the placebo [18].

Another important class of therapeutics in PD with encouraging results is dopamine agonists (DA). Opposite to levodopa, having a less potent efficacy on motor symptoms but concomitantly also less motor adverse reactions, DA is used as first-line therapy in younger patients. The study conducted by Kasamo *et al.* comes to complete the actual knowledge on DA use in young-onset Parkinson's disease. As the authors mentioned, among the most frequent comorbidities, insomnia was the second most frequent, 30 out of 131 patients (22.9%) complaining about this particular sleep disorder. The nature of NMS remains an elusive problematic also in this study on the Japanese cohort, as the exact cause for insomnia could not be determined. The young age and short disease duration suggests that insomnia is also a comorbidity found in early PD stage, possibly preceding the appearance of motor symptoms, thus being considered a potential clinical marker for PD. Moreover, the study did not differentiate insomnia by categories of DA, being hard to draw a conclusion among effects of different dopamine agonists on sleep-wake rhythm [19].

In search to determine if there is a correlation between sleep disorders as NMS and a future risk of PD, Postuma and colleagues wanted to assess if idiopathic REM sleep behavior disorder could facilitate the development of PD or dementia. Besides REM sleep disorders, insomnia and daytime somnolence were also studied, but no significant predictive value was found [20]. According to the studies mentioned above [17] [18] [19] [20], it seems that insomnia found in PD patients is correlated with the antiparkinsonian medication, being a significant accuse regardless the drug therapy.

As neurologists are trying to find ways to counteract insomnia, non-conventional methods are gaining popularity. As a result, two recent protocols regarding use of alternative medicines were also reviewed. In one article, Shi and colleagues are planning a multicenter trial to test the effects of SQJZ herbal mixtures (used in traditional Chinese medicine) on non-motor symptoms, hoping to ameliorate them, including insomnia [21]. Another trial in preparation and conducted by Jang *et al.* will be focusing on another herbal medicine utilized in traditional Chinese medicine, Yokukansan [22]. As this traditional herb is thought to improve sleep disturbances, this randomized, double blind, placebo-controlled pilot trial will bring measurable evidence of the mechanism of action of the substance and the real impact, if any, on NMS in PD patients.

Daytime sleepiness and PD

The research conducted to assess EDS outnumbers the studies on insomnia highlighted above.

The exact correlation between EDS and PD is yet to be fully understood, the research of Liguori *et al.* may offer some insights to this issue. According to them, EDS may be present in the premotor stages of disease or in de novo PD patients, invalidating previous knowledge according to which EDS more promi-

nent as the disease progresses. Moreover, EDS seems not to be related to other symptoms of the complex non-motor spectrum of PD, thus it should be treated differently from other sleep-wake disturbances. In particular, since the improvement of nocturnal sleep seems to not allow the amelioration of EDS, both non-pharmacological protocols and pharmacological treatments targeting the control of vigilance and alertness merit further investigations to minimize the damaging impact of daytime sleepiness on quality of life of PD patients. However, as the authors mention, the limited population of patients included in this study, a limitation of the analysis, requires further research on this topic [23].

While conventional antiparkinsonian medication (rotigotine, apomorphine, rasagiline) is still extensively studied with regards of effects on EDS or other NMS, new forms of more or less invasive therapeutic methods are brought to the public eye.

Rotigotine, one of the most widely used dopamine antagonists, is available as transdermal patch with prolonged release, being among the first-line therapies for young PD patients without additional comorbidities. In his clinical trial, Antonini *et al.* have studied the effect of rotigotine on NMS, being the first trial to use change in NMS Scale total score as the primary outcome measure. Compared to placebo, the medication showed significant improvements in only two domains of the NMS Scale: "mood/apathy" ($P = 0.047$) and "miscellaneous" ($P = 0.043$), improvement in the individual item "excessive sweating" being the main response driver for the amelioration of the "miscellaneous" domain. However, improvement in the total score of NMS Scale was not superior to placebo, rotigotine showing no significant effect on EDS [24].

Another dopamine antagonist, rasagiline, was studied in a double blind, baseline-controlled trial conducted by Schrempf *et al.* The researchers showed that, although rasagiline improved sleep parameters as measured by polysomnography in PD patients with sleep disturbances, no overall sleep quality improvement was noticed by the patient [25]. This result is in line with Antonini's study on rotigotine, where EDS was not significantly modified.

Olanow *et al.* went a step further, testing the combination of a low-dose rasagiline and pramipexole as a new treatment option for patients with early PD. The good clinical efficacy was doubled by a low risk of adverse events, this combination showing no clinically significant problems with respect to daytime sleepiness or sudden onset sleep episodes, only mild and transient somnolence episodes were encountered [26].

Another adjuvant for the standard levodopa therapy is zonisamide, first used as an antiepileptic, then showing important benefits on motor complication, such as wearing-off and dyskinesia. The novelty of Murata *et al.* study is the demonstration of efficacy and safety of 50 mg/d dose of zonisamide in a Japanese patients cohort, the neurologists exploring also the effect adverses of this medication. Although showing significant reduction of the "off" periods and improved "off" level of activity of daily life (UPDRS II) in PD patients, insomnia

and somnolence were registered as medication side-effects, in line with other antiparkinsonian treatments. Somnolence was found in 8 out of 128 patients (6.3%) compared to 2.3% in the placebo group, while insomnia was as frequently found in the placebo group as in the testing groups [27].

While standard pharmacologic therapy reaches its limits regarding efficacy of symptom management in PD, motor fluctuations being unsatisfactorily controlled, new forms of medication are continually emerging. This is the case of Hauser *et al.* work, the first study of a new sublingual apomorphine formulation in PD patients. It was shown that apomorphine administered sublingually appeared to provide a convenient, rapid and reliable method for treating OFF episodes. However, this came at a certain cost, patient complaining of significant adverse effects: dizziness (7 of 19 patients, 36.8%) and somnolence (6 of 19 patients, 31.6%) were the two most common complaints [28].

Along antiparkinsonian therapy, clinical trials on other pharmacological principles were conducted in the recent years. For example, Büchele *et al.* studied the impact of Sodium Oxybate on EDS and sleep disturbances in PD. It was demonstrated that Sodium oxybate-related improvements of sleep and EDS correlated significantly, while sleep disturbances induced by the compound predicted inefficient therapy. This study is also important because it reveals the reciprocal association between nighttime sleep and EDS [29].

Offering a different approach, another study to be mentioned is the trail conducted by Uchino and his Japanese team. In that study, patient's turnover movements, a frequent symptom encountered in PD, were recorded during sleep, however, showing no direct correlation to EDS or sleep disturbances. On the other hand, use of anti-psychotic drugs and higher UPDRS score were significantly associated with daytime sleepiness [30].

Besides pharmacological therapies, more invasive therapeutic measures are tested in order to alleviate NMS. One of the methods used as complementary therapy in order to reduce the burden of NMS is transcranial direct current stimulation, a technique that uses a weak direct electrical current to stimulate different areas of the brain. Use mainly to stimulate the prefrontal cortex in order to ameliorate executive function and working memory [31], Forogh *et al.* studied for the first time the implications of this method on sleep-wake disturbances in PD patients. While it was effective on fatigue reduction in PD, no significant effect was found on daytime sleepiness in any time point. These results may be explained by the positive effects of this technique on mood and depressive symptoms, resulting also in fatigue improvement [32].

Another similar study, conducted on only 9 patients and coordinated by Nosko, aimed to compare low-frequency and high-frequency stimulation of the pedunculopontine nucleus area in PD patients. Regardless the stimulation frequency, stimulation of the pedunculopontine nucleus alters the states of alertness and sleep, provoking sleep when patient receives stimulation with 80 Hz frequencies and above (high-frequency). In 8 out of 9 patients, daytime sleepiness was

greater under high than under low-frequency stimulation, the difference being significant ($p < 0.01$) for this group, low-frequency increasing patient's alertness [33].

Non-pharmacological therapies were also tried in order to reduce the burden of NMS, especially sleep-wake disorders. We found 3 studies related to dietary changes that may be considered efficient in better controlling of NMS and 2 studies about the implications of light therapy. Phillips *et al.* compared the impact of low-fat versus ketogenic diet in PD, showing that it can be plausible and safe for PD patients to maintain these diets for 8 weeks. Both diet groups showed significantly improvements in motor and non-motor symptoms, with greater improvements of non-motor symptoms in the ketogenic group. The ameliorating of the EDS and other NMS can at the cost of possible adverse reactions: excessive hunger in the low-fat group and intermittent exacerbation of the tremor and/or rigidity in the ketogenic group were the most frequently encountered complains [34].

Another study conducted by Postuma and his team wanted to demonstrate whether motor and non-motor PD symptoms may be changed under chronical caffeine consumption. Caffeine showed temporary benefit on daytime alertness, but no long-term sustained benefit. There was noted some improvements on the MDS-UPDRS daytime sleepiness question at 6 months, with equivocal lowering of SCOPA-sleep. These effects may be however chance findings, as the main goal of the study was to assess implications of caffeine on motor symptoms, with no significant improvement in motor manifestation (Class I evidence) or symptomatic effect [35].

Another compound showing interesting impact on PD symptoms was homotaurine. Ricciardi and colleagues conducted the first trial on the use of homotaurine in PD patients with cognitive impairment, administering the subjects, in addition to the existing therapy, for 6 months 2 tablets of 50 mg homotaurine, daily. Final data confirmed the safety of homotaurine and its beneficial effect on excessive sleepiness and possibly on memory [36].

Bright light therapy has gained popularity during the last years, as it has been successfully used to treat a variety of conditions, including seasonal and non-seasonal depression, sleep and mood disorders. Thus, Raymackers *et al.* wanted to proof the clinical impact of light therapy on NMS in PD patients. Results weren't so promising, as their head-mounted device (Luminette®) did not show significant beneficial effect of bright light on depression, anxiety, daytime sleepiness and fatigue, compared to placebo light therapy [37]. Only small not statistically significant ameliorations in EDS were mentioned, especially in patients with higher Epworth Sleep Scale scores. Contradictory results are found in the study of Videnovic *et al.* Here, 31 patients were enrolled (13 males and 18 females; mean [SD] disease duration, 5.9 [3.6] years), bright light therapy resulting in significant improvements in EDS, as assessed by the Epworth Sleepiness Scale score (mean [SD], 15.81 [3.10] at baseline vs 11.19 [3.31] after the intervention).

Moreover, both bright and dim-red light therapy were associated with improvements in sleep quality [38].

Alternative medicine will always be a valid option in treating unpleasant symptoms, EDS making no exception. Kong and his colleagues searched on the implications of acupuncture on fatigue, demonstrating the safety of the methods [39]. Because there is no satisfactory therapy for daytime sleepiness, acupuncture may play an adjuvant role in alleviating sleep-wake symptoms in PD patients, the exact physiological mechanism remaining to be elucidated.

4. Conclusions

Along with motor symptoms, PD researchers are focusing more intensively on the non-motor symptoms. There are still questions regarding the pathophysiology of the NMS, recent studies showing that sleep-wake disturbances may not be related to the advanced stages of PD, being also found in early disease patients and premotor stages [15] [23], however more studies should be done to reveal the etiology of NMS.

As new therapeutic modalities, both pharmacologic and non-pharmacologic, appear, their impact on NMS is now regarded as important as their influence on the motor fluctuations. In all the above-mentioned studies [17] [18] [19] [20] [24]-[29], scientists were concerned about the side effects of the medication, with respect to sleep-wake symptoms. As demonstrated, most of the antiparkinsonian medication utilized nowadays provokes insomnia and EDS to patients, these side effects being among the most frequently encountered by PD patients. In the attempt to ameliorate sleep-wake status, alternative methods are implemented, from dietary changes such as ketogenic diet, low-fat diet, and homotaurine intake to invasive pedunculopontine nucleus stimulation, bright light therapy and traditional Chinese medicine remedies (acupuncture, traditional herbs).

There is a continuous need to improve PD patient's quality of life by ameliorating the treatment, finding new therapeutic methods and diminishing the adverse effects. By gathering the most important clinical trials of the last 5 years on PD with respect to insomnia and EDS, this review is a valuable starting point for future research.

5. Limitations of This Study

As stated already in the methodology, only English-language articles (human clinical trial type) published during the last 5 years were included in this review. Thus, non-English articles, other review-type articles, research articles conducted on animals, and opinion-based letters-to-the-editors were omitted. Moreover, as sleep-wake disorders found in PD patients include a wide range of symptoms, because of space and time limitations, only insomnia and EDS were mentioned here. Sleep apnea syndromes, fatigue and rapid eye movement (REM) disorders are topics that will be addressed in future articles.

Financial Disclosure

All costs regarding research, writing, review, and approval of the publication were borne by the author.

Ethics Approval

No human or animal experiments were conducted in this study. No participation consent was needed. All sources used for documentation were adequately mentioned with respect to copyright laws.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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Abbreviation Meaning

COMT	Catechol-O-methyltransferase
DA	Dopamine agonist
EDS	Excessive daytime sleepiness
MDS-UPDRS	Movement Disorder Society-Unified Parkinson's Disease Rating Scale
NMS	Non-motor symptoms
PD	Parkinson's Disease
QoL	Quality of life
REM	Rapid eye movement
SCOPA-sleep	Scales for Outcomes in Parkinson's Disease-Sleep
SQJZ	Mixture of Chinese herbs formula