Excessive Daytime Sleepiness in Parkinson’s Disease: Clinical Implications and Management

Yun Shen, Jun-Ying Huang, Jie Li, Chun-Feng Liu

1Department of Neurology and Suzhou Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China
2Jiangsu Key Laboratory of Neuropsychiatric Diseases and Institute of Neuroscience, Soochow University, Suzhou, Jiangsu 215123, China

Abstract

Objective: Excessive daytime sleepiness (EDS) is one of the most common sleep abnormalities in patients with Parkinson’s disease (PD), yet its multifactorial etiology complicates its treatment. This review summarized recent studies on the epidemiology, etiology, clinical implications, associated features, and evaluation of EDS in PD. The efficacy of pharmacologic and non-pharmacologic treatments for EDS in PD was also reviewed.

Data Sources: English language articles indexed in PubMed and Cochrane databases and Chinese-language papers indexed in Wanfang and National Knowledge Infrastructure databases that were published between January 1987 and November 2017 were located using the following search terms: “sleepiness”, “sleep and Parkinson’s disease”, and “Parkinson’s disease and treatment”.

Study Selection: Original research articles and critical reviews related to EDS in PD were selected.

Results: EDS is a major health hazard and is associated with many motor and nonmotor symptoms of PD. Its causes are multifactorial. There are few specific guidelines for the treatment of EDS in PD. It is first necessary to identify and treat any possible factors causing EDS. Recent studies showed that some nonpharmacologic (i.e., cognitive behavioral therapy, light therapy, and repetitive transcranial magnetic stimulation) and pharmacologic (i.e., modafinil, methylphenidate, caffeine, istradefylline, sodium oxybate, and atomoxetine) treatments may be effective in treating EDS in PD.

Conclusions: EDS is common in the PD population and can have an immensely negative impact on quality of life. Its causes are multifactorial, which complicates its treatment. Further investigations are required to determine the safety and efficacy of potential therapies and to develop novel treatment approaches for EDS in PD.

Key words: Excessive Daytime Sleepiness; Parkinson’s Disease; Sleep Disorders

Introduction

Parkinson’s disease (PD) is the second-most common neurodegenerative disorder. In recent years, the nonmotor symptoms of PD have received increasing attention, one of which is excessive daytime sleepiness (EDS). This review summarized recent studies on the epidemiology, etiology, clinical implications, associated features, and evaluation of EDS in PD. In addition, the efficacy of pharmacologic and nonpharmacologic treatments for EDS in PD was also reviewed.

EDS is defined as an inability to maintain wakefulness and alertness during the major waking episodes of the day that results in periods of irresistible need for sleep or unintended lapses into drowsiness or sleep.[1] EDS is a major health hazard in PD, affecting 21–76% of PD patients with an incidence of 6% per year.[2–4] The prevalence of EDS is higher in PD patients than in the general population, with controlled studies showing subjective sleepiness in 34–54% of PD patients compared with 16–19% of controls.[5,6]

An important feature of EDS that must be taken into account is the “sudden onset of sleep”, which is when a patient suddenly falls asleep during periods of inactivity or low...
activity. Sudden onset of sleep is reported by 1–31% of PD patients and most patients are not able to completely recall the event.[9,10] Some PD patients also exhibit significant features of narcolepsy, including cataplexy and sleep-onset rapid eye movement (REM) periods (SOREMPs) in the multiple sleep latency test (MSLT).[11] Sudden onset of sleep contributes significantly to disease burden and negatively impacts quality of life, impairs daytime functioning, and is associated with motor vehicle crashes.[10] However, many PD patients may not be aware of their sleepiness.

**Clinical Implications**

EDS in PD is not persistent, and its presence may fluctuate over time. In general, the proportion of PD patients with EDS increases over time with longer follow-up. A longitudinal study revealed a progressive increase in EDS prevalence from 4% at baseline to 41% after 8 years of follow-up.[11]

EDS is associated with and influences other motor and nonmotor symptoms of PD. Longitudinal studies report that the presence of EDS is associated with clinical variables such as male gender, poorer nighttime sleep, cognitive impairment, autonomic dysfunction, hallucinations, depression, anxiety, probable behavior disorder, advanced disease, the postural instability-gait difficulty motor phenotype, less severe dyskinesias, dosage of dopamine agonists, and use of antihypertensives.[12-14] A longitudinal study showed that predictors of the incident development of EDS included autonomic dysfunction, anxiety, and cerebrospinal fluid phosphorylated tau/total tau ratio.[14]

Clinicians have also noted the impact of mood symptoms on EDS in PD. A recent review article reported a significant positive correlation between depression and EDS and a weak correlation between anxiety and EDS in PD patients. The magnitude of the correlation depended on how EDS was measured; it was medium when EDS was subjectively measured and small when EDS was objectively measured.[15]

PD patients with EDS exhibit alterations in brain structure and function (e.g., brain volume, white matter integrity as indicated by fractional anisotropy, cerebral metabolism).[15] It is impossible to determine whether EDS is a potential manifestation of more severe brainstem neurodegeneration.

Some evidence suggested that EDS predicted the conversion of PD. Sleepy adults had a more than 3-fold increased risk of PD, compared with non-sleepy adults (odds ratio: 3.3; 95% confidence interval [CI]: 1.4–7.0, \( P < 0.01 \)).[14] Another study showed that EDS (i.e., an Epworth Sleepiness Scale [ESS] score >8 at the time of REM sleep behavior disorder [RBD] diagnosis) predicted more rapid conversion to parkinsonism and dementia in patients with idiopathic RBD (iRBD).[17]

Another study showed that EDS (i.e., ESS score ≥14) was significantly associated with an increased risk of developing PD in iRBD patients (adjusted hazard ratio: 3.6; 95% CI: 1.6–7.9, \( P < 0.01 \)).[18] By contrast, a prospective follow-up study assessing a large cohort of patients with iRBD and controls found no difference in baseline ESS score between those who eventually converted and those who remained disease free.[19] This discrepancy between studies might result from differences in sample size, follow-up period, cutoff values for ESS score, and conversion time from RBD diagnosis or onset.

EDS may also be independently associated with risk of cognitive decline. Among 4894 elderly people, those who felt sleepy during the daytime had an increased risk of cognitive decline 8 years later.[20]

**Etiology**

The etiology of EDS in PD is multifactorial. First, EDS may involve alterations in pathophysiological mechanisms involved in the regulation of sleep and wakefulness. In the brainstem, neurodegeneration within ascending arousal systems controls neurotransmission across several neuronal nuclei such as the noradrenergic locus coeruleus, noradrenergic dorsal motor nucleus of the vagus nerve, serotonergic dorsal raphe nucleus, histaminergic tuberomammillary nucleus, and dopaminergic areas. In particular, adenosine is a neurotransmitter that promotes non-REM sleep and cholinergic neurons in laterodorsal tegmental and pedunculopontine tegmental nuclei promote REM sleep. Because PD progression may co-occur with the degeneration of neurons controlling wakefulness and sleep, it could lead to sleep disorders including EDS.[9,21]

Second, EDS could be an adverse outcome of dopaminergic therapy. Several studies showed that dopaminergic agents (e.g., levodopa) and agonists (e.g., pramipexole, ropinirole, and rotigotine) caused somnolence.[22-24] PD patients taking a dopamine agonist were sleepier than those treated with levodopa alone.[25-27] Combination therapy with levodopa and a dopamine agonist was associated with the highest risk of EDS.[28] Furthermore, the influence of dopaminergic therapy on EDS was dose-dependent,[29,30] and some investigators believed that PD patients who take high doses of dopaminergic therapy are prone to irresistible sleep attacks.[31]

Third, EDS may be linked to poor (i.e., nonrestorative) nocturnal sleep. Polysomnographic studies showed that PD patients have significantly shorter total sleep time, lower sleep efficiency, and sleep architectural changes.[32] Many coexistent primary sleep disorders (e.g., restless legs syndrome [RLS], periodic limb movement disorder, and RBD), motor disturbances (e.g., nocturnal akinesia, bradykinesia, rest tremor, and inability to turn over in bed), and other nonmotor symptoms (i.e., pain, depression, nocturia, and hallucinations, temperature dysregulation due to dysautonomia) could also lead to sleep fragmentation, which in turn could result in EDS.[33-35] In particular, the presence of RBD might be associated with greater sleepiness in PD, as some studies reported that PD patients with EDS had a higher rate of RBD than those without EDS and that PD patients with probable RBD experienced a higher level of sleepiness than those without RBD.[36-38] It is unclear whether RLS directly contributes to EDS. One study showed...
no difference in subjective sleepiness between PD patients with and without RLS. However, the EDS in Multiple System Atrophy (SLEEMSA) study reported that RLS predicted EDS in PD. Furthermore, although sleep-disordered breathing might play a role in EDS, its overall contribution might be limited. In addition, other factors such as genes; the sleep environment; use of antihypertensive medications, benzodiazepines, antidepressants, and certain antipsychotics (e.g., serotonin-selective reuptake inhibitors, MAO-I); hypocretin (orexin) cell loss; and circadian rhythm abnormalities may also contribute to EDS in PD. Therefore, further studies are required in this area.

**Evaluation of Excessive Daytime Sleepiness in Parkinson’s Disease**

PD patients should undergo thorough sleep evaluation consisting of solicitation of the chief complaint; detailed social, family, medical, psychiatric, and sleep history; physical examination; and, if necessary, objective sleep testing with polysomnography and the MSLT.

**Subjective assessment**

Clinicians should understand the clinical presentation of sleepiness by PD patients. Patients might complain of both daytime sleepiness and disturbed nocturnal sleep and sometimes have associated complaints such as daytime fatigue, lack of concentration, and lack of symptom relief after additional sleep. It is important to distinguish sleepiness from fatigue, as there is significant overlap between the two symptoms. Fatigue is a physical or psychological feeling that can be confounded with EDS. Fatigued patients may describe themselves as feeling tired or having a lack of energy, but they do not fall asleep when sedentary.

Interviewing other people who are familiar with the patient could help provide more information that can be obtained directly from the patient.

Subjective scales have some advantages in terms of their ease of administration and ability to incorporate patient insight into the degree of the problem. The ESS is a scale that is commonly used to determine the severity of sleepiness during a given period. Many studies use a score of 10 as a cutoff to identify sleepiness. Other useful questionnaires for assessing sleepiness include the Stanford Sleepiness Scale, Pittsburgh Sleep Quality Index, Scales for Outcomes in Parkinson’s Disease-SLEEP-Daytime Sleepiness, and PD Sleep Scale. However, clinical impression of sleepiness and results of sleep questionnaires might be insufficient evidence for medical concern.

**Objective assessment**

To reduce bias and the potential impact of confounding factors, objective measures may also be appropriate. Polysomnography can identify underlying sleep disorders such as obstructive sleep apnea, insomnia, and RBD that cause night sleep fragmentation and can provide indirect evidence of EDS. Furthermore, standardized tests for assessing EDS are the MSLT and maintenance of wakefulness test. The MSLT assesses the ability to fall asleep, whereas the maintenance of wakefulness test assesses the ability to remain awake. These two tests are not routinely used to evaluate sleepiness in PD. One study found a high frequency of self-reported EDS in PD patients despite that many patients do not exhibit short sleep latency in the MSLT. However, when PD patients exhibit narcolepsy-like behavior, the MSLT could demonstrate mean sleep latency and SOREMP for differentially diagnosing narcolepsy. Furthermore, a 24-h continuous sleep recording or an actigraphic recording of at least 1 week can also be used to diagnose EDS in PD.

We believe that the appropriate selection of a subjective or objective assessment of EDS in PD is very important. Currently, there is no commonly accepted clinically useful method for diagnosing EDS in PD. Considering subjective assessments, each scale has its own advantages and disadvantages, and different studies adopt different measures of EDS, which can result in varying conclusions. Most studies compare the results of sleep questionnaires to the extensively used ESS, as it is important to understand the sensitivity, specificity, and application ranges of different criteria. Considering objective assessments, evidence of their value is low. Routine detection methods have not found meaningful results, although perhaps changes in the duration and times of testing could reveal different findings. There is also a need for more standardized assessment of EDS in PD. Therefore, objective evaluation in conjunction with subjective assessment may be the best approach to diagnosing EDS in PD.

**Management of Excessive Daytime Sleepiness in Parkinson’s Disease**

There are few specific guidelines for treating EDS and no studies on the treatment of sudden onset of sleep in PD. The treatment of EDS is complex because of its heterogeneous causes in PD patients. Treatment must be individualized and directed at the underlying causes if known. Considering the available evidence, we discuss some implications for clinical practice. The efficacy level of “clinically useful” means that evidence available is sufficient to conclude that the intervention provides clinical benefit for a given situation. “Possibly useful” means that the available evidence is suggestive but insufficient to conclude that the intervention provides clinical benefit in a given situation. “Investigational” means that the available evidence is insufficient to support the use of the intervention in clinical practice, although further study is warranted. We found no “unlikely useful” or “not useful” management approaches.

In addition to PD-related motor disabilities, EDS and sudden onset of sleep while driving are critical factors for traffic safety. Patients should be warned not to drive if they doze in unusual circumstances, especially when their
Because light activity and avoiding vigorous physical activity 3–4 h before sleeping ESS score is ≥7. It is also necessary to identify and treat any possible sleep disorders that could disrupt nocturnal sleep and to withdraw or reduce any possible drugs causing hypersomnia, such as antidepressants, antipsychotics, or sedatives. The European Federation of Neurological Societies and Movement Disorder Society-European Section recommend that managing EDS in PD patients should involve assessing nocturnal sleep disturbances; improving nocturnal sleep by reducing akinesia, tremor, and urinary frequency; recommending the cessation of driving; reducing or discontinuing sedative drugs; and reducing the dosage of dopaminergic drugs (mainly dopamine agonists) or switching to other dopamine agonists. Dopaminergic therapies could improve overnight sleep and be useful for treating RLS in PD and thereby improving EDS. However, dopamine agonist-associated sleep abnormalities, including sleep attacks, should be considered potential dose-dependent risks of dopamine and combination therapy with levodopa and dopamine agonists. Dosage reduction, monotherapy, or discontinuation in these patients could be helpful and could be replaced by selegiline, amantadine, or entacapone, which have no effects on EDS and may even reduce or resolve EDS. Although clonazepam is the mainstay of treatment for RBD, given its associated risks, benzodiazepine use should generally be avoided in PD patients with EDS. Furthermore, EDS occurs in nearly half of the PD patients treated with clozapine. Other primary sleep disorders that might cause EDS should be carefully assessed using polysomnography and treated appropriately. For example, continuous positive airway pressure treatment improves subjective and objective EDS in PD patients with obstructive sleep apnea by reducing apnea events, improving oxygen saturation, and deepening sleep. Efficacy conclusion is clinically useful. Identifying and treating primary sleep disorders is necessary and must be completed before any treatment.

Nonpharmacologic therapies for excessive daytime sleepiness
Because drug therapies have the potential for adverse side effects, nonpharmacologic treatment approaches offer a promising alternative for preventing and managing EDS in PD.

Cognitive behavioral therapy
Cognitive behavioral therapy for insomnia (CBT-I) is extensively used to treat insomnia in non-PD populations. It consists of behavioral and psychological approaches to teaching patients how to change their dysfunctional behaviors and thinking patterns. One small study found that the Insomnia Severity Index, PD Sleep Scale, and examiner-reported clinical global impression improved in PD patients who received CBT-I combined with light therapy. Therefore, in accordance with CBT-I, clinicians could recommend that patients strictly follow sleep hygiene rules such as having regular nap times and daytime physical activity and avoiding vigorous physical activity 3–4 h before sleeping. Efficacy conclusion for CBT is under investigation. CBT-I is simple to administer, but there remains insufficient evidence for its effective management of EDS in PD patients.

Light therapy
Supplementary exposure to bright light (i.e., light therapy) has beneficial effects on sleep, depression, bradykinesia, rigidity, and dyskinesias in PD patients, as light activates the suprachiasmatic nucleus and is the most effective zeitgeber of the circadian timing system. A randomized, placebo-controlled clinical study found that bright light therapy twice daily in 1-h intervals for 14 days significantly reduced ESS in PD patients (15.8 ± 3.1 at baseline vs. 11.2 ± 3.3 after intervention). Possible reasons for this effect were that light therapy improves PD severity, daytime alertness, nighttime sleep quality, or sleep fragmentation by influencing the circadian system and promoting dopamine release. Because light therapy is noninvasive and has only mild and transient side effects, including headache, nausea, and hypomania, consideration of its use is warranted for the treatment of EDS in PD. However, there is a lack of consensus on the optimal parameters of light therapy for PD. Efficacy conclusion for light therapy is possibly useful. Light therapy may potentially be efficacious in preventing EDS, although future studies are required to determine its optimal timing, dosage, and treatment duration.

Repetitive transcranial magnetic stimulation
Transcranial magnetic stimulation (TMS) is a noninvasive tool applied in different paradigms to obtain direct measures of cortical excitability. Repetitive TMS (rTMS) induces direct, trans-synaptic neuronal activation. High-frequency rTMS (>5 Hz) increased cortical excitability, whereas low-frequency rTMS (<1 Hz) had the opposite effect. Combining rTMS with electroencephalography may be a useful approach to treating sleep disorders such as obstructive sleep apnea, RLS, narcolepsy, RBD, sleepwalking, sleep-wake disturbances after traumatic brain injury, and chronic insomnia. In PD patients, rTMS improved motor deficits (considering both UPDRS-III scores and gait parameters). One recent case report of a narcolepsy patient who received 25 sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex demonstrated that rTMS might be a safe and effective alternative strategy for treating narcolepsy-like symptoms. Efficacy conclusion for TMS is under investigation. No studies have yet focused on the efficacy of rTMS for treating EDS in PD. Future studies should seek to define optimal stimulation parameters, such as timing, duration, electrode placement, coil orientation, and physiological state of the patient.

Pharmacologic therapies for excessive daytime sleepiness
If nonpharmacologic strategies do not improve EDS, drug therapies can be considered. There are few recommendations for the pharmacological management of EDS in PD, as
few multicenter clinical trials have been conducted in this area.\textsuperscript{[66,67]} A Movement Disorder Society evidence-based medicine review concluded that there was insufficient data to recommend any specific drug for the long-term treatment of EDS in PD patients.\textsuperscript{[68]} Limited data exist for the use of wakefulness-promoting agents such as modafinil and armodafinil or stimulants such as methylphenidate or dextroamphetamines.

Modafinil

Modafinil, a medication approved by the US Food and Drug Administration to treat narcolepsy, is a wake-promoting agent and is indicated for most forms of EDS. A recent meta-analysis reported that modafinil effectively reduced ESS score, with an overall mean difference of 2.2 (95% CI: −3.9 to −0.6) and without significant heterogeneity among studies.\textsuperscript{[69]} However, modafinil did not alter objective measures of sleepiness.\textsuperscript{[70,71]} In clinical practice, modafinil is given once a day in the morning on an empty stomach. The starting dose is usually 100 mg and can be increased slowly to 400 mg as needed. Modafinil is well tolerated in the treatment of EDS and has a low prevalence of side effects such as headache, nausea, dry mouth, and anorexia.\textsuperscript{[69,72]} However, for older PD patients, especially those with severe cardiovascular disease or other underlying cardiac abnormalities, the cardiovascular effects of modafinil, including elevated blood pressure and heart rate, are a concern.\textsuperscript{[73]} However, these side effects appear to be mild and decrease with dose reduction.\textsuperscript{[68]} As alternatives to modafinil, other drugs that are generally well tolerated with a low prevalence of side effects could be considered. Although data on their efficacy are limited, it is reasonable to consider their use for treating EDS in PD in clinical practice. Efficacy conclusion for modafinil is possibly useful. There is insufficient evidence to draw conclusions about the efficacy and safety of modafinil for treating EDS in PD, although its use might be helpful in clinical practice.

Methylphenidate

Methylphenidate, the piperazine derivative of amphetamine, increases the release and inhibits the reuptake of catecholamines, including dopamine and norepinephrine. Its effects may be mediated by the restoration of balance between dopamine and norepinephrine neurotransmitters. An open-label study reported that methylphenidate dramatically reduced EDS in PD patients, with high doses of methylphenidate improving motor and gait symptoms in the presence and absence of levodopa.\textsuperscript{[74]} In clinical practice, methylphenidate is initially prescribed at 10 mg/d, with a recommended maximum dose of up to 80 mg/d. Possible adverse events related to methylphenidate therapy are reduced appetite, nausea, headache, insomnia, and psychosis.\textsuperscript{[75]} PD patients can receive methylphenidate 2 weeks after discontinuation of monoamine oxidase inhibitors. Efficacy conclusion for methylphenidate is possibly useful. There is insufficient evidence to draw conclusions about the efficacy and safety of methylphenidate for treating EDS in PD, although its use might be helpful in clinical practice.

Caffeine

Caffeine, an adenosine antagonist, reduces somnolence in the general population. A decade ago, it also attracted attention due to its potential neuroprotective effect. A meta-analysis reports that caffeine reduces the risk of PD (relative risk: 0.7; 95% CI: 0.6–0.8).\textsuperscript{[76]} In a long-term randomized controlled trial assessing the effects of caffeine on EDS in PD, patients given up to 200 mg caffeine twice a day for 6 weeks showed a non-significant reduction in ESS score (−1.7 points; 95% CI: −3.6 to 0.1), whereas clinical global impression of EDS improved per protocol analysis.\textsuperscript{[77]} In a more recent study, caffeine slightly improved EDS over the first 6 months, with the clinical effect lessening over time.\textsuperscript{[78]} There are many potential explanations for this discrepancy between studies, including different study populations and trial durations. Caffeine could affect EDS or the sensation of alertness and is an inexpensive intervention that is well tolerated in most individuals. Efficacy conclusion for caffeine is under investigation. The magnitude of the impact of caffeine on EDS in PD patients is unclear. It may be reasonable to try intermittent moderate doses of caffeine and repeat if improvement is observed.

Sodium oxybate

Sodium oxybate, the sodium salt of g-hydroxybutyrate, is used to treat cataplexy and EDS in narcolepsy and has been tested in PD patients. An open-label polysomnographic study reported that nocturnally administered sodium oxybate improved subjective sleepiness, sleep quality, and fatigue as well as slow wave sleep in PD patients.\textsuperscript{[79]} Recently, a randomized, double-blind, placebo-controlled, crossover, Phase IIA study reported that sodium oxybate was effective in treating EDS and nocturnal sleep disturbance with Class I evidence. This study used both objective and subjective assessments and showed that sodium oxybate improved mean sleep latency, ESS score, and slow-wave sleep duration.\textsuperscript{[80]} Sodium oxybate should be taken in the evening and once again during the night. Its side effects are nausea, insomnia, headache, dizziness, vomiting, weight loss, psychiatric complications, and sleep apnea.\textsuperscript{[81]} It increased apnea-hypopnea index in PD patients\textsuperscript{[78]} and induced de novo obstructive sleep apnea and parasomnias.\textsuperscript{[82]} Efficacy conclusion for sodium oxybate is possibly useful. Evidence suggested that sodium oxybate might be efficacious for treating EDS in PD. However, stringent patient monitoring and larger follow-up trials are warranted.

Istradefylline

A single-center, open-label study reported that istradefylline, a selective adenosine A2A receptor antagonist, significantly improved EDS 2 and 3 months after PD patients received 20–40 mg/d istradefylline once daily in the morning. The underlying mechanism may be that istradefylline enhances alertness while having no negative impact on sleep.\textsuperscript{[82,83]} Efficacy conclusion for istradefylline is under investigation. The use of istradefylline might be helpful in clinical practice, although further studies are warranted.
Conclusions
EDS is common in the PD population and can have an immensely negative impact on quality of life. Its causes are multifactorial, which complicates its treatment. More and larger studies are needed to demonstrate the efficacy and safety of pharmacologic and nonpharmacologic treatments for EDS in PD. Furthermore, efforts should focus on planning and executing clinical trials to develop novel treatment approaches.

Financial support and sponsorship
This work was supported by grants from the National Key R&D Program of China (No. 2017YFC0909100), National Natural Science Foundation of China (No. 91649114), Jiangsu Provincial Social Development Projects (No. BE2017653), Jiangsu Provincial Medical Key Discipline Project (No. ZDXKB2016022), Jiangsu Key Laboratory of Neuropsychiatric Diseases (No. BM2013003), and Suzhou Clinical Research Center of Neurological Disease (No. Szxx201503). This work was also partly supported by grants from the Suzhou Youth Technology Project Foundation (No. KJXW2016104) and Priority Academic Program Development of Jiangsu Higher Education Institutions.

Conflicts of interest
There are no conflicts of interest.

References
1. American Academy of Sleep Medicine. International Classification of Sleep Disorders III. Darien, IL: American Academy of Sleep Medicine; 2014.
2. Hobson DE, Lang AE, Martin WR, Razmz A, Rivest J, Fleming J, et al. Excessive daytime sleepiness and sudden-onset sleep in Parkinson disease: A survey by the Canadian Movement Disorders Group. JAMA 2002;287:455-63. doi: 10.1001/jama.287.4.455.
3. Falup-Pecurariu C, Diaconu Ş. Sleep dysfunction in Parkinson's disease. Int RevNeurobiol 2017;133:719-42. doi: 10.1016/bs.irn.2017.05.033.
4. Loddo G, Calandra-Buonaura G, Sambati L, Giannini G, Cecere A, Cortelli P, et al. The treatment of sleep disorders in Parkinson's disease: From research to clinical practice. Front Neurol 2017;8:42. doi: 10.3389/fneur.2017.00042.
5. Stavitsky KS, Saurman JL, McNamara P, Cronin-Golomb A. Sleep in Parkinson’s disease: A comparison of actigraphy and subjective measures. Parkinsonism Relat Disord 2010;16:280-3. doi: 10.1016/j.parkreldis.2010.02.001.
6. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson’s disease from 2005 to 2015. Sleep Med Rev 2017;35:33-50. doi: 10.1016/j.smrv.2016.08.001.
7. Ghorayeb I, Loundou A, Auquier P, Dauvilliers Y, Bioulac B, Tison F, et al. A nationwide survey of excessive daytime sleepiness in Parkinson’s disease in France. Mov Disord 2007;22:1567-72. doi: 10.1002/mds.21541.
8. Montastruc JL, Brefel-Courbon C, Senard JM, Bagheri H, Ferreira J, Rascol O, et al. Sleep attacks and antiparkinsonian drugs: A pilot prospective pharmacoepidemiologic study. Clin Neuropharmacol 2001;24:181-3. doi: 10.1097/00003282-200105000-00015.
9. Bliwise DL, Trotti LM, Juncos JJ, Factor SA, Freeman A, Rye DB, et al. Daytime REM sleep in Parkinson’s disease. Parkinsonism Relat Disord 2013;19:101-3. doi: 10.1016/j.parkreldis.2012.08.003.
10. Sobreira-Neto MA, Pena-Pereira MA, Sobreira ES, Chagas MH, Fernandes RM, Tumas V, et al. High frequency of sleep disorders in Parkinson’s disease and its relationship with quality of life. Eur Neurol 2017;78:330-7. doi: 10.1159/000481939.
11. Gjerstad MD, Alves G, Wentzel-Larsen T, Aarsland D, Larsen JP. Excessive daytime sleepiness in Parkinson disease: Is it the drugs or the disease? Neurology 2006;67:853-8. doi: 10.1212/01.wnl.0000233980.25978.9d.
12. Zhu K, van Hulten JJ, Marinus J. Course and risk factors for excessive daytime sleepiness in Parkinson’s disease. Parkinsonism Relat Disord 2016;24:34-40. doi: 10.1016/j.parkreldis.2016.01.020.
13. Tholfsen LK, Larsen JP, Schulz J, Tynsnes OB, Gjerstad MD. Development of excessive daytime sleepiness in early Parkinson disease. Neurology 2015;85:162-8. doi: 10.1212/ WNL.000000000001737.
14. Amara AW, Chahine LM, Caspell-Garcia C, Long JD, Coffey C, Högl B, et al. Longitudinal assessment of excessive daytime sleepiness in early Parkinson’s disease. J Neurol Neurosurg Psychiatry 2017;88:653-62. doi: 10.1136/jnnp-2016-315023.
15. Wen MC, Chan LL, Tan LC, Tan EK. Mood and neural correlates of excessive daytime sleepiness in Parkinson’s disease. Acta Neurol Scand 2017;136:84-96. doi: 10.1111/anec.12704.
16. Abbott RD, Ross GW, White LR, Tanner CM, Masaki KH, Nelson JS, et al. Excessive daytime sleepiness and subsequent development of Parkinson disease. Neurology 2005;65:1442-6. doi: 10.1212/01.wnl.0000183056.89950.0d.
17. Arnulf I, Neutel D, Herlin B, Golmard JL, Leu-Semenescu S, Cohen de Cock V, et al. Sleepiness in idiopathic REM sleep behavior disorder and Parkinson disease. Sleep 2015;38:1529-35. doi: 10.5665/sleep.5040.
18. Zhou J, Zhang J, Lam SP, Chan JW, Mok V, Chan A, et al. Excessive daytime sleepiness predicts neurodegeneration in idiopathic REM sleep behavior disorder. Sleep 2017 [Epub ahead of print]. doi: 10.1093/sleep/zxx041.
19. Postuma RB, Gagnon JF, Pelletier A, Montplaisir JY. Insomnia and somnolence in idiopathic RBD: A prospective cohort study. NPJ Parkinsons Dis 2017;3:9. doi: 10.1038/s41531-017-0011-7.
20. Jaussent I, Bouyer J, Ancelin ML, Barr C, Foubert-Samier A, Ritchie K, et al. Excessive sleepiness is predictive of cognitive decline in the elderly. Sleep 2012;35:1201-7. doi: 10.5665/sleep.25187.
21. Parkinson Study Group. Pramipexole vs. levodopa as initial treatment for Parkinson disease: A randomized controlled trial. Parkinson Study Group JAMA 2000;284:1931-8. doi: 10.1001/jama.284.15.1931.
22. Tanner CM. Dopamine agonists in early therapy for Parkinson disease: Promise and problems. JAMA 2000;284:1971-3. doi: 10.1001/jama.284.15.1971.
23. Comella CL. Daytime sleepiness, agonist therapy, and driving in Parkinson disease. JAMA 2002;287:509-11. doi: 10.1001/jama.287.4.509.
24. Ondo W, Dat Vuong K, Khan H, Atassi F, Kwac K, Jankovic J, et al. Daytime sleepiness and other sleep disorders in Parkinson’s disease. Neurology 2001;57:1392-6. doi: 10.1212/wnl.57.8.1392.
25. Avorn J, Schneeweiss S, Sudarsky LR, Benner J, Kiyota Y, Levin R, et al. Sudden uncontrollable somnolence and medication use in Parkinson disease. Arch Neurol 2005;62:1242-8. doi: 10.1001/archneur.62.8.1242.
26. O’Suilleabhain PE, Dewey RB Jr. Contributions of dopaminergic investigations to treatment of idiopathic RBD. Neurology 2007;69:2100-1. doi: 10.1212/01.wnl.0000270268.96666.4f.
27. O’Sullivan PE, Dewey RB Jr. Sleep attacks and antiparkinsonian drugs: A pilot prospective pharmacoeconomic study. Clin Neuropharmacol 2001;24:181-3. doi: 10.1097/00003282-200105000-00015.
28. Montastruc JL, Brefel-Courbon C, Senard JM, Bagheri H, Ferreira J, Rascol O, et al. Sleep attacks and antiparkinsonian drugs: A pilot prospective pharmacoeconomic study. Clin Neuropharmacol 2001;24:181-3. doi: 10.1097/00003282-200105000-00015.
29. Bliwise DL, Trotti LM, Juncos JJ, Factor SA, Freeman A, Rye DB, et al. Daytime REM sleep in Parkinson’s disease. Parkinsonism Relat Disord 2013;19:101-3. doi: 10.1016/j.parkreldis.2012.08.003.
30. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson’s disease from 2005 to 2015. Sleep Med Rev 2017;35:33-50. doi: 10.1016/j.smrv.2016.08.001.
drugs and disease severity to daytime sleepiness in Parkinson disease. Arch Neurol 2002;59:986-9. doi: 10.1001/archneur.59.6.986.

28. Paus S, Brecht HM, Köster J, Seeger G, Klockgether T, Wüllner U, et al. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson’s disease. Mov Disord 2003;18:659-67. doi: 10.1002/mds.10417.

29. Arnulf I, Konofal E, Merino-Andreu M, Houeto JL, Mesnage V, Welter ML, et al. Parkinson’s disease and sleepiness: An integral part of PD. Neurology 2002;58:1019-24. doi: 10.1212/WNL.58.7.1019.

30. Hauser RA, Gauger L, Anderson WM, Zesiewicz TA. Pramipexole-induced somnolence and episodes of daytime sleep. Mov Disord 2000;15:658-63. doi: 10.1002/1531-8257(200007)15:4%3C658::AID-MDS1009%3E3.0.CO;2-N.

31. Frucht S, Rogers JD, Greene PE, Gordon MF, Fahn S. Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999;52:1908-10. doi: 10.1212/WNL.52.9.1908.

32. Shipper I, Minio‑Vizzut A, Klein C, Goldstein R, Prokhorov T, Theitler J, et al. Excessive daytime sleepiness in patients with Parkinson’s disease: A polysomnography study. Mov Disord 2006;21:1432-8. doi: 10.1002/mds.21002.

33. Bhat S, Chokroverty S. Hypersomnia in neurodegenerative diseases. Sleep Med Clin 2017;12:443-60. doi: 10.1016/j.smc.2017.03.017.

34. Lees AJ, Blackburn NA, Campbell VL. The nighttime problems of symptoms, depression and dopaminergic treatment. Eur J Neurol 2013.6239.

35. Shpirer I, Miniovitz A, Klein C, Goldstein R, Prokhorov T, Theitler J, et al. Summary of the recommendations of the EFNS/MDS-ES review on therapeutic management of Parkinson’s disease. Eur J Neurol 2013;20:5‑15. doi: 10.1111/j.1468-1331.2012.03866.x.

36. Diederich NJ, McIntyre DJ. Sleep disorders in Parkinson’s disease: Many causes, few therapeutic options. J Neurol Sci 2012;314:12-9. doi: 10.1016/j.jns.2011.10.025.

37. Nardone R, Höller Y, Brigo F, Tezzon F, Golaszewski S, Trinka E, et al. Applications of transcranial magnetic stimulation in sleep medicine. Sleep Med Rev 2012;16:177-85. doi: 10.1016/j.sleep.2013.04.025.

38. Vedrine F, Diederich NJ, McIntyre DJ. Using non-invasive transcranial stimulation to improve motor and sleep function in Parkinson’s disease: A systematic review and meta-analysis. Sci Rep 2017;7:14840. doi: 10.1038/s41598-017-13260-z.

39. Lai JB, Han MM, Xu Y, Hu SH. Effective treatment of narcolepsy-like symptoms with high-frequency repetitive transcranial magnetic stimulation: A case report. Medicine (Baltimore) 2017;96:e8645. doi: 10.1097/MD.0000000000008645.
66. National Collaborating Centre for Chronic Conditions. Parkinson’s Disease: National Clinical Guideline for Diagnosis and Management in Primary and Secondary Care. London: Royal College of Physicians (UK); 2006.

67. Zesiewicz TA, Sullivan KL, Chaudhuri KR, Morgan JC, Gronseth GS, et al. Practice parameter: Treatment of nonmotor symptoms of Parkinson disease: Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2010;74:924-31. doi: 10.1212/WNL.0b013e3181d5524.

68. Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, et al. The movement disorder society evidence-based medicine review update: Treatments for the non-motor symptoms of Parkinson’s disease. Mov Disord 2011;26 Suppl 3:S42-80. doi: 10.1002/mds.23884.

69. Rodrigues TM, Castro Caldas A, Ferreira JJ. Pharmacological interventions for daytime sleepiness and sleep disorders in Parkinson’s disease: Systematic review and meta-analysis. Parkinsonism Relat Disord 2016;27:25-34. doi: 10.1016/j.parkreldis.2016.03.002.

70. Högl B, Saletu M, Brandauer E, Glatzl S, Frauscher B, Seppi K, et al. Modafinil for the treatment of daytime sleepiness in Parkinson’s disease: A double-blind, randomized, crossover, placebo-controlled polygraphic trial. Sleep 2002;25:905-9.

71. Ondo WG, Fayle R, Atassi F, Jankovic J. Modafinil for daytime somnolence in Parkinson’s disease: Double blind, placebo controlled parallel trial. J Neurol Neurosurg Psychiatry 2005;76:1636-9. doi: 10.1136/jnnp.2005.058580.

72. Roth T, Schwartz JR, Hirshkowitz M, Erman MK, Dayno JM, Arora S, et al. Evaluation of the safety of modafinil for treatment of excessive sleepiness. J Clin Sleep Med 2007;3:595-602.

73. Dolder CR, Davis LN, McKinsey J. Use of psychostimulants in patients with dementia. Ann Pharmacother 2010;44:1624-32. doi: 10.1345/aph.1P341.

74. Devos D, Krystkowiak P, Clement F, Djadjian K, Cottencin O, Wauquier N, et al. Improvement of gait by chronic, high doses of methylphenidate in patients with advanced Parkinson’s disease. J Neurol Neurosurg Psychiatry 2007;78:470-5. doi: 10.1136/jnnp.2006.100016.

75. Leonard BE, McCartan D, White J, King DJ. Methylphenidate: A review of its neuropharmacological, neuropsychological and adverse clinical effects. Hum Psychopharmacol 2004;19:151-80. doi: 10.1002/hup.579.

76. Noyce AJ, Bestwick JP, Silveira-Moriyama L, Hawkes CH, Giovannoni G, Lees AJ, et al. Meta-analysis of early nonmotor features and risk factors for Parkinson disease. Ann Neurol 2012;72:893-901. doi: 10.1002/ana.23687.

77. Postuma RB, Lang AE, Munhoz RP, Charland K, Pelletier A, Moscovitch M, et al. Caffeine for treatment of Parkinson disease: A randomized controlled trial. Neurology 2012;79:651-8. doi: 10.1212/WNL.0b013e318263570d.

78. Postuma RB, Anang J, Pelletier A, Joseph L, Moscovitch M, Grimes D, et al. Caffeine as symptomatic treatment for Parkinson disease (Café-PD): A randomized trial. Neurology 2017;89:1795-803. doi: 10.1212/WNL.0000000000004568.

79. Ondo WG, Perkins T, Swick T, Hull KL Jr., Jimenez JE, Garris TS, et al. Sodium oxybate for excessive daytime sleepiness in Parkinson disease: An open-label polysomnographic study. Arch Neurol 2008;65:1337-40. doi: 10.1001/archneur.65.10.1337.

80. Büchele F, Hackius M, Schreglmann SR, Omlor W, Werth E, Maric A, et al. Sodium oxybate for excessive daytime sleepiness and sleep disturbance in Parkinson disease: A randomized clinical trial. JAMA Neurol 2018;75:114-8. doi: 10.1001/jamaneurol.2017.3171.

81. Wang YG, Swick TJ, Carter LP, Thory MJ, Benowiz NL. Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): Abuse, misuse, dependence, and diversion. J Clin Sleep Med 2009;5:365-71.

82. Suzuki K, Miyamoto M, Miyamoto T, Watanabe Y, Suzuki S, et al. Istradefylline improves daytime sleepiness in patients with Parkinson’s disease: An open-label, 3-month study. J Neurol Sci 2017;380:230-3. doi: 10.1016/j.jns.2017.07.045.

83. Du JJ, Chen SD. Current nondopaminergic therapeutic options for motor symptoms of Parkinson’s disease. Chin Med J 2017;130:1856-66. doi: 10.4103/0366-6999.211555.
帕金森病的日间嗜睡：临床意义和管理

目的：帕金森病（PD）的日间嗜睡（EDS）是一种常见的睡眠障碍。因发病的多因素，而导致治疗的复杂性。在这篇综述中，我们收集了最近PD的EDS相关的文献，对其流行病学、病因、临床意义、特征、评估方法及治疗进行总结。

数据来源：我们对1987年1月到2017年11月发表在PubMed上的英文文献和万方及中国知网上的中文文献进行收集，选用的关键词为：“睡眠”、“睡眠和帕金森病”、“帕金森病和治疗”。

研究选择：关于PD的EDS的原创研究文章和综述。

结果：EDS能严重影响健康，且与PD的许多运动和非运动症状密切相关。EDS的发病存在多因素。目前，PD的EDS的治疗缺少明确的指南。PD的EDS的管理首先需要明确并治疗可能导致EDS的相关因素。最近的研究显示一些非药物（认知行为治疗、光疗、重复经颅磁刺激）和药物（莫达非尼、哌醋甲酯、咖啡因、伊曲茶碱、羟丁酸钠、阿托西汀）治疗方法可能有效。

结论：将来的研究需要进一步评估治疗的安全性和有效性，并探索关于PD的EDS的新型治疗方法。