Review Article

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

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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 irrepressible 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

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activity. Sudden onset of sleep is reported by 1–31% of PD patients and most patients are not able to completely recall the event.[7,8] 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).[9] 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 predated 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, $P < 0.01$).[16] 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.[6,39] Furthermore, although sleep-disordered breathing might play a role in EDS, its overall contribution might be limited.[40,41]

In addition, other factors such as genes; the sleep environment; use of antihypertensive medications, benzodiazepines, antipsychotics, and certain antidepressants (e.g., serotonin-selective reuptake inhibitors, MAO-I);[42] hypocretin (orexin) cell loss;[43] and circadian rhythm abnormalities may also contribute to EDS in PD. Therefore, further studies are required in this area.[44]

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.[45] 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.[46] 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.[47]

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.[48] 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.[49] 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.[50]

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,[2] especially when their

ESS score is ≥7.[2] 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.[51]

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[45,52] and may even reduce or resolve EDS.[4,28,52-54] 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.[55]

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.[56] 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.[57] 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.[4,58] 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.[59,60] 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.[61] 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.[62,63] In PD patients, rTMS improved motor deficits (considering both UPDRS-III scores and gait parameters).[64] 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.[65] 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.[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.[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.[69] However, modafinil did not alter objective measures of sleepiness.[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.[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.[73] However, these side effects appear to be mild and decrease with dose reduction.[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.[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.[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).[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 in per protocol analysis.[77] In a more recent study, caffeine slightly improved EDS over the first 6 months, with the clinical effect lessening over time.[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.[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.[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.[81] It increased apnea-hypopnea index in PD patients[78] and induced *de novo* obstructive sleep apnea and parasomnia.[80] 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.[82,83] Efficacy conclusion for istradefylline is under investigation. The use of istradefylline might be helpful in clinical practice, although further studies are warranted.

Atomoxetine

Atomoxetine, a selective norepinephrine reuptake inhibitor, has been shown to be beneficial for EDS in PD patients, possibly through alerting effects on norepinephrine neurons in the locus coeruleus. Constipation and insomnia are the most common adverse events. Efficacy conclusion for atomoxetine is under investigation. The use of atomoxetine 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.

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Conflicts of interest

There are no conflicts of interest.

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帕金森病的日间嗜睡：临床意义和管理

摘要

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，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01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。