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REVIEW

# Excessive Daytime Sleepiness in Parkinson's Disease

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**Abstract:** Excessive daytime sleepiness (EDS) is one of the most common sleep disorders in Parkinson's disease (PD). It has attracted much attention due to high morbidity, poor quality of life, increased risk for accidents, obscure mechanisms, comorbidity with PD and limited therapeutic approaches. In this review, we summarize the current literature on epidemiology of EDS in PD to address the discrepancy between subjective and objective measures and clarify the reason for the inconsistent prevalence in previous studies. Besides, we focus on the effects of commonly used antiparkinsonian drugs on EDS and related pharmacological mechanisms to provide evidence for rational clinical medication in sleepy PD patients. More importantly, degeneration of wake-promoting nuclei owing to primary neurodegenerative process of PD is the underlying pathogenesis of EDS. Accordingly, altered wake-promoting nerve nuclei and neurotransmitter systems in PD patients are highlighted to providing clues for identifying EDS-causing targets in the sleep and wake cycles. Future mechanistic studies toward this direction will hopefully advance the development of novel and specific interventions for EDS in PD patients.

**Keywords:** excessive daytime sleepiness, Parkinson's disease, epidemiology, wakefulness, dopaminergic neurons, dopaminergic agents

## Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder, with the second highest neurologic incidence, characterized pathologically by abnormal α-synuclein aggregation and significant dopaminergic neuron death in substantia nigra pars compacta (SNc).[1,2] The disease manifests with various motor and non-motor symptoms. Some non-motor symptoms, including sleep disorders, depression, olfactory dysfunction, constipation and autonomic dysfunction, may precede motor deficits for decades followed by some severe negative impacts on patients' daily life, which has attracted much attention in recent years.[3,4]

As one of the most common non-motor manifestations, sleep disorders affect about 90% of PD population.[5] In addition, sleep disorders encompass a broad range of sleep problems, such as insomnia, rapid eye movement (REM) sleep behavior disorders (RBD) and excessive daytime sleepiness (EDS).[6,7] It is of great urgency to keep a watchful eye on EDS due to its high morbidity, poor quality of life, increased risk for accidents, obscure mechanisms, comorbidity with PD and limited treatment options.

EDS refers to an irrepressible need for sleep or unintended lapses into drowsiness or sleep as a result of the inability to stay awake and alert during waking episodes of the day.[8] EDS presents in 20–60% of PD patients, with an incidence increasing over time.[9] Besides the differences in demographic characteristics, such a wide range of prevalence is also attributed to sample size and inconsistent assessment tools used to evaluate EDS in different studies (Table 1). A meta-analysis including 12,439 PD patients has shown that the pooled prevalence of subjective EDS in PD is 35.1%.[10] Notably, all 59 studies included in this meta-analysis used a score of 10 as the cut-off value for the Epworth Sleepiness Scale (ESS) to identify EDS (positive if score > or ≥10). EDS was noted as one of the prodromal symptoms of PD.[11] Previous longitudinal studies established that old adults with EDS had great likelihood to develop PD.[12,13] Furthermore,

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**Table 1** The Prevalence of EDS in PD Patients

| Study (Country) | Study Type | Sample Size | Measures for EDS | Mean Age (Years Old) | Male Proportion | Disease Duration (Years) | Hoehn-Yahr Stage | Nighttime Sleep | Anti-PD Medications | Cognitive Function | Prevalence |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Weerkamp NJ et al 2013 (the Netherlands)[179] | Cross-sectional study | 73 | PDSS | 78.7 | 45% | 10.1 | 4 | Poor sleep quality (mean PDSS score: 3.13/4) | Mean LEDD: 673 mg | 56.9% of patients had dementia on MMSE | 60.6% |
| Videnovic A et al 2014 (USA)[38] | Cross-sectional study | 20 | ESS≥10 | 64.1 | 45% | 6.7 | 2–4 | Poor sleep quality (mean PSQI score: 6.1) | Mean LEDD: 436.6mg | Exclude the patients with MMSE <26 | 60% |
| Yong MH et al 2011 (Singapore)[46] | Case-control study | 56 | ESS ≥10 MSLT<5min | 65.4 | 61% | 6.4 | 2.5 | RLS, OSA | Mean LEDD: 409.4mg | Not mentioned | 44.1% (ESS) 12.7% (MSLT) |
| Goulart FO et al 2009 (Brazil)[47] | Cohort study | 50 | ESS ≥10 | 70.5 | 44% | 6.3 | 2.5 | Not mentioned | Excluded patients who received dopaminergic treatment during the past 24 weeks | Mean MMSE scores: 25.8 | 44% |
| Monaca C et al 2006 (France)[67] | Prospective study | 222 | ESS>10 | 65.5 | 43% | 9.5 | Not mentioned | 55% of patients had OSA | Mean LEDD: 697 mg | Excluded PD patients with dementia | 43.2% |
| Dagmar Verbaan et al 2008 (the Netherlands)[60] | Cohort study | 420 | SCOPA-SLEEP >4 | 61.1 | 64% | 10.5 | 2–3 | 27% of patients had nighttime sleep problems | Mean LEDD: 608 mg | Cognitive impairment | 43% |
| Bjornara KA et al 2014 (Norway)[30] | Cross-sectional | 107 | ESS >10 | 68.2 | 61% | 4 | 2 | Mean PDSS score: 5.7 | Mean LEDD: 599 mg | Not mentioned | 29% |
| Ghorayeb I et al 2014 (France)[180] | Prospective study | 1625 | ESS≥10 | 69.5 | 57% | 6.1 | 2 | Not mentioned | Mean LEDD: 585 mg | Exclude the patients with MMSE ≤24 | 29% |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Prudon B et al 2014 (UK)[39] | Cohort study | 156 | ESS≥10 | 66.5 | 63% | 0.4 | 1–3 | 46.2% reported impaired sleep quality with PSQI>5 | Mean LEDD: 540 mg | Exclude the patients with MMSE <24 | 26.4% |
| Havlikova E et al 2011 (Slovakia)[181] | Cross-sectional | 93 | ESS>10 | 68 | 50% | 6.1 | 2 | 73.1% had nighttime sleep problems | 10.7% on levodopa alone; 22.6% on DA agonists alone; 8.6% on both | Exclude the patients with MMSE <24 | 23.7% |
| Suzuki K et al 2008 (Japan)[33] | Multi-center study | 188 | ESS≥10 | 66.4 | 45% | 6.9 | 2.5 | Poor nighttime sleep (mean PSQI score: 6.7) | Mean LEDD: 456.3mg | Exclude the patients with MMSE <24 | 21.3% |

**Abbreviations**: PDSS, The Parkinson's Disease Sleep Scale; ESS, Epworth sleepiness scale; PSQI, the Pittsburgh Sleep Quality Index; MSLT, Multiple Sleep Latency Test; MMSE, Mini Mental State Examination; DA, Dopamine; RLS, Restless Leg Syndrome; OSA, Obstructive Sleep Apnea; LEDD, levodopa equivalent dose daily.


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researchers found that higher rate of RBD patients with EDS developed PD than those without EDS.[14,15] However, other longitudinal studies reached negative conclusion that ESS >14 failed to predict conversion to neurodegenerative diseases in a RBD cohort, arguing against EDS be a reliable predictor of the development of neurodegeneration in patients with idiopathic RBD.[16]

It was estimated that 27% of PD patients reported sleep attacks at least once a day, and 19% of patients experienced sleep episodes during activities of daily living.[17] Even 8% of PD patients suffered from sleep attacks while driving, which could lead to motor vehicle accidents.[18] In addition to threatening the safety, EDS reduces the efficiency of daytime work and learning, affects the daily life of PD patients, and increases the burden of caregivers (someone who cares for PD patients).[19]

Although public understanding of EDS has gradually progressed over the past few decades, much remains unknown. Treatment options are limited due to associated adverse effects. Regarding the treatment of EDS in PD patients, some pharmacologic therapies such as modafinil and caffeine and nonpharmacologic therapies such as supplementary exposure to bright light are probably promising. However, the safety and efficacy of most therapeutic options need to be verified in a larger population.[20] Therefore, the mechanisms of EDS in PD need to be elucidated in order to develop effective treatments. In this article, we summarized current literature on epidemiology of EDS in PD and compared the presence of EDS in PD patients and other populations. Moreover, the etiology, relevant risk factors and pathophysiological mechanisms of EDS in PD are also reviewed.

# Epidemiology

## The Measures and Related Prevalence of EDS in PD

Given the adverse effects of EDS on PD patients, it is necessary to identify EDS accurately. Currently, a number of subjective and objective measures are used to screen PD patients for their propensity for increased daytime sleepiness, the most widely used of which are ESS and multiple sleep latency test (MSLT).

ESS, a self-administered subjective scale for EDS, has been validated to be reliable in PD populations.[21,22] The ESS has been shown to have a sensitivity of 93.5% and a specificity of 100% for a score of greater than 10 and have high internal consistency and test-retest reliability in healthy subjects over a period of 5 months.[23,24] In addition, the ESS scores have been recommended to assess the severity of daytime sleepiness and a score of more than 16 indicates a high level of subjective sleepiness.[21,25] MSLT has been extensively used to measure the severity of objective EDS by examining the ability to fall asleep.[26] According to the International Classification of Sleep Societies (3rd edition) criteria, a mean sleep latency (MSL) of less than 8 minutes can be measured in patients with narcolepsy or idiopathic hypersomnia, which represents pathological sleepiness.[8] As reported, the test-retest reliability of the MSLT was 0.97 in healthy volunteers over a period of 4–14 months while the sensitivity and specificity of the MSLT with MSL less than 8 minutes were 94.5% and 73.3%, respectively.[23,27] The maintenance of wakefulness test (MWT) as another objective measure of EDS can examine the ability to keep awake. For individuals who are suspected of being unable to stay awake, the MWT is commonly used to assess their alertness to prevent safety issues. In addition, the MWT can also evaluate the response of patients with excessive sleepiness to treatment.[28]

Extensive studies showed that subjective EDS was common in PD patients in different countries. A case-control analysis in the United States found that 25% of PD patients reported daytime sleepiness with the ESS scores >10.[29] A cross-sectional study in Norway revealed subjective EDS in 29% of PD patients while another cross-sectional study in the Netherlands showed that the prevalence of subjective EDS in PD patients was 29.7%.[30,31] A cross-sectional study in France reported subjective sleepiness measured by ESS scores ≥10 in 33.5% of PD patients compared to 16.1% of age-matched controls.[17] A cross-sectional study in China found that 22.5% of PD patients suffered from subjective EDS and a multi-center study in Japan revealed that 21.3% of PD patients had EDS.[32,33]

Notably, ascertaining EDS properly remains challenging due to the common comorbidity of cognitive impairment in PD patients.[34] Several studies obtained clinical information from close family members or daily caregivers of PD patients who were unable to complete sleep questionnaires independently.[35–37] Other studies excluded PD patients with cognitive impairment, which could lead to the underestimated prevalence of EDS.[33,38,39] Fatigue is a symptom that may confound

the diagnosis of EDS in PD patients due to their similar clinical manifestations.[40] Besides, Valko et al found that 72.9% of PD patients with EDS simultaneously suffered from fatigue.[41] Accordingly, clinicians should be careful to distinguish EDS from fatigue in PD patients. Currently, it could be an unbiased way to diagnose EDS in PD to combine subjective with objective assessments of sleepiness.[42]

However, some studies revealed a discrepancy between subjective and objective measures of sleepiness in PD.[43,44] A study in France showed that objective sleepiness was present in 13.4% of 134 PD patients compared to 46.3% of subjective sleepiness and ESS scores had a weak negative correlation with MSLT latency.[45] A case-control study in an Asian population reported no difference in objective daytime sleepiness measured by MSLT between PD patients and healthy controls (16.7% vs 12.7%, $p = 0.54$) but significant difference in subjective sleepiness measured by ESS of two groups (41.1% vs 19.1%, $p = 0.01$).[46] Moreover, a recent study in Switzerland found no significant correlation between the objective sleepiness measured by MSLT and subjective sleepiness measured by ESS.[42] Therefore, future investigations need to clarify a reason for the discrepancy and optimize evaluation approaches for EDS in PD population.

## Comparison of EDS in PD Population and Other Populations

EDS not only occurs in PD patients, but also in patients with other neurological disorders, as well as the general population. A follow-up study showed that in PD, Alzheimer's disease (AD) and age-matched controls, the prevalence of subjective EDS at baseline were 41%, 18% and 10%, respectively.[37] Several controlled studies found that 33.5–44% of PD patients suffered from subjective sleepiness compared to 16% of general population (ie, age-matched healthy volunteers or geriatric patients without PD).[17,47] In addition, higher mean ESS scores were reported in PD patients compared to healthy controls and AD patients.[37,46] Similarly, a meta-analysis revealed that the prevalence and mean ESS scores of patients with essential tremor were significantly lower than those of PD patients, highlighting daytime sleepiness in PD subjects.[48]

There are comparisons on the presence of EDS in PD and other α-synucleinopathies including multiple system atrophy (MSA) and dementia with Lewy Bodies (DLB). A study revealed that subjective EDS was in 29% of PD patients and 28% of MSA patients compared to 2% of controls. Likewise, mean ESS scores in PD and multiple system atrophy were equally higher than those in controls.[49] Another comparative study showed that 43.8% of PD patients and 61.5% of MSA patients had subjective EDS.[50] Boddy et al found that subjective daytime sleepiness was also prevalent in DLB patients and PD patients with dementia with the prevalence rate of 50% and 57%, respectively, which was higher than that of PD patients without dementia.[37]

These epidemiological data revealed that EDS was severer and more common in α-synucleinopathies than in the age-matched general population and other neurodegenerative diseases such as AD and essential tremor, suggesting neurodegeneration due to α-synucleinopathies might play a more important role in the development of EDS than age-related neurodegeneration.

## Risk Factors of EDS in PD

To date, longitudinal studies on PD have identified several risk factors of EDS, including age, gender, disease duration and severity, some nonmotor and motor symptoms, antiparkinsonian medications and nighttime sleep problems.[51,52]

### Gender and Age

In PD patients, men appeared to experience more and severer EDS than women, and the proportion of men with EDS was significantly higher than that of men without EDS, pointing to the gender male as a risk factor for EDS in PD.[53,54] In addition, extensive research revealed that patients with EDS were older than those without EDS, suggesting that aging might play another important role in the EDS development.[53,55]

However, it remains unclear whether obstructive sleep apnea (OSA) plays a role in the relationship of higher risk of EDS with male sex and older age in PD. As reported, OSA was common in PD patients with a prevalence of 28% and elderly men had the greater likelihood of suffering from OSA.[56] Besides, OSA has been associated with severe EDS in PD patients. Similarly, another study found that PD patients with high risk of OSA had significantly higher ESS scores,

compared to those with low risk of OSA.[57] Therefore, the independent association of higher risk of EDS with male sex and older age in PD needs to be further clarified considering the confounding effect of OSA.

### Disease Severity

Several studies demonstrated that PD patients with EDS had higher Unified PD Rating Scale scores and Hoehn and Yahr stages relative to those non-EDS PD patients, supporting the positive correlation between EDS and advancing PD.[10,52] The disease severity could be also reflected by evident non-motor and motor symptoms. Previous studies assessed risk factors for EDS in PD and found several symptoms, including cognitive impairment or dementia, deteriorated autonomic function, disability, hallucination and depression, were independently associated with the development of EDS.[58,59]

These findings suggested the development of EDS was associated with advancing PD, consistent with the view that EDS can be a result of spreading neurodegenerative process in PD.

### Disease Duration

The presence of EDS has been reported to be associated with longer disease duration of PD.[60] A longitudinal study revealed that 46% of PD patients without EDS at baseline developed this symptom during 5-year follow-up.[51] Likewise, another community-based cohort study assessed the development of EDS in PD patients over 8 years and found that the occurrence of EDS increased from 5.6% at baseline to 22.5% within a 4-year follow-up and 40.8% after 8 years.[35] Notably, researchers found that EDS in early PD was reversible in the first few years but the symptom of daytime sleepiness became more persistent over time.[35,52]

Conceivably, the development of EDS can be attributed to different causes. In other words, several modifiable etiologies, such as antiparkinsonian medications and poor nighttime sleep, contribute to the emergence of reversible EDS in PD while persistent EDS can be due to impaired wake-promoting nuclei by spreading neurodegeneration of PD.[52]

## Etiology and Pathophysiological Mechanisms of EDS in PD

Based on the high prevalence, it is crucial to find out why EDS is so common in PD patients. In fact, the etiology of EDS in PD is multifactorial. As mentioned above, antiparkinsonian medications, primary sleep disorders and impaired wake-promoting nuclei due to primary neurodegenerative lesions of PD are the extensively accepted causes of EDS.[61] Moreover, genetic susceptibility is associated with an increased risk of EDS in PD. A recent cross-sectional study revealed that DQB1*06:02 (an HLA risk allele for narcolepsy)-positive PD patients were three times more likely to develop EDS than DQB1*06:02-negative PD patients and no significant differences were found in nighttime sleep between the two groups, suggesting that narcolepsy phenotype in PD patients is a cause of EDS independent of nocturnal sleep disturbances.[62]

### Antiparkinsonian Medications

Drug therapy is necessary for PD patients to relieve motor and non-motor symptoms, of which dopaminergic drugs are the most widely used. However, extensive research revealed that almost all antiparkinsonian medications affect EDS in PD patients (Table 2).[63–65]

Dopaminergic therapies, including levodopa and DA agonists, can cause or aggravate daytime sleepiness, which might be attributed to their sedative effects.[66] A prospective study showed that 28.4% of PD patients reported EDS after receiving dopaminergic treatment and most of these patients had an ESS score of more than 10.[67] In a previous study, the mean sleep latency by the MSLT was significantly diminished (8.1±4.7min vs 11.6 ± 4min, $P < 0.005$) in PD patients after receiving dopaminergic treatment, suggesting that EDS could be a class effect of dopaminergic drugs.[68]

Similar influences on EDS in PD have been reported of DA agonists. Several studies indicated that daytime sleepiness occurred more frequently in patients on pramipexole than those on placebo or other anti-PD drugs, suggesting pramipexole could contribute to EDS.[69–71] A long-term clinical trial revealed PD patients initially treated with pramipexole showed higher prevalence (57.4% vs 35.2%, $P = 0.002$) of daytime sleepiness together with higher ESS scores (11.3 vs 8.6, $P < 0.001$) than those initially treated with levodopa. Based on this finding, pramipexole might have

**Table 2** Effects of Antiparkinsonian Medications on EDS in PD Patients

| Drug | Pharmacological Action | Study | Study Type | Sample Size | Dosage (mg/d) | Medication Duration (Weeks) | Results | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Levodopa | The former of dopamine, increase the concentration of dopamine in brain | Arnulf et al 2002[131] | Systematic study | 54 | 654 | >4 | Mean MSL:6.3±0.6min; mean ESS scores:14.3±4.1 (after treatment) | Negative effect |
| | | Parkinson Study Group, 2000[72] | RCT | 151 | 300, 450, 600 | 96 | 17.3% of PD patients on levodopa reported EDS. | |
| Pramipexole | Selective D2/D3 dopamine agonist | Etminan et al 2001[70] | Meta-Analysis | 264 | 1.5–6.0 | 10 | Patients on pramipexole or ropinirole had a 4.98-fold risk of EDS compared to controls. | Negative effect |
| | | | | 335 | 3.5 | 24 | | |
| | | Avorn et al 2005[69] | Case-control study | 929 | 7.2 | 24 | Patients on pramipexole were 2.2-fold more likely to develop EDS than those on levodopa. | |
| | | Hauser et al 2014[71] | Open-label extension study | 408 patients with early PD | 0.375–4.5 | 80 | EDS was present in 13.6% of patients on pramipexole. | |
| | | | | 329 patients with advanced PD | | | | |
| Rotigotine | D1-D5 dopamine agonist | Watts et al 2007[77] | RCT | 277 | 6 | 24 | Somnolence was reported in 33% of patients on rotigotine compared to 20% patients on placebo. | Negative effect |
| | | Elmer et al 2012[74] | Open-label extension study | 217 | 16 | 288 | 54% patients on rotigotine reported EDS. | |
| | | LeWitt et al 2013[76] | | 359 | 4–16 | 192 | EDS incidence: 18–25%/patients-year; ESS scores increased from 7.1 to 8.4. | |
| | | | | 258 | | 288 | | |
| | | Giladi et al 2013[75] | | 381 | 8 | 288 | EDS incidence: 23%/patients-year | |

(*Continued*)


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**Table 2** (Continued).

| Drug | Pharmacological Action | Study | Study Type | Sample Size | Dosage (mg/d) | Medication Duration (Weeks) | Results | Outcomes |
|---|---|---|---|---|---|---|---|---|
| Apomorphine | D1/D2/D3 dopamine agonist | Pahwa et al 2007[79] | RCT | 107 | 2–10 | 24 | 10% of patients on apomorphine reported somnolence compared to nobody on placebo. 19.1% of patients on apomorphine reported EDS. | Negative effect |
| | | Hattori et al 2014[81] | | 31 | 4.49 | 12 | | |
| Entacapone | COMT inhibitor | Bares et al 2003[84] | Case reports | 3 | 600,800 | 3, 8 | All of 3 patients reported EDS | Negative effect |
| | | Koller et al 2005[83] | Open-label study | 169 | Not reported | 4 | 6.5% of patients on entacapone reported somnolence. | |
| Ropinirole | Selective D2/D3 dopamine agonist | Avorn et al 2005[69] | Case-control study | 173 | 13.4 | 24 | Patients on ropinirole were 1.8-fold as likely to develop EDS than those on levodopa. | Negative effect |
| | | Pahwa et al 2007[96] | RCT | 202 on ropinirole vs 191 on placebo | 18.8 | | EDS incidence: 7% vs 4%; ESS scores: 7.8 vs 7.7 | No relationship |
| | | Rektorova et al 2008[98] | Prospective multicenter Study | 44 | 9–15 | | No significant changes in ESS scores between baseline and post-treatment. | |
| | | Chaudhuria et al 2012[97] | RCT | 387 | 2–24 | | No difference in the changes of ESS scores between patients on ropinirole and those on placebo. (0.2, P=0.70; 0.3, P=0.38) | |
| | | Kang et al 2017[95] | Observational study | 413 | 8.4±5.5 | | No difference in ropinirole doses between patients with EDS and those without EDS (8.9 vs.8.2, P=0.22). | |
| | | Dusek et al 2010[99] | Open-label study | 33 | 17.2 | 13 | ESS scores were significantly decreased in patients after switching to ropinirole prolonged-release from ropinirole immediate-release (12.0 vs 14.1, P<0.05) | Improvement |
| Piribedil | Selective D2/D3 dopamine agonist; alpha-2 receptors antagonist | Eggert et al 2014[100] | RCT | 80 | 100–300 | 11 | Higher reduction in ESS scores in piribedil group than placebo group (3.8 vs 2.1, P=0.01). | Improvement |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Amantadine | Enhance dopamine transmission | Mehta et al 2021[107] | RCT | 196 | 274 | 12 | 34.1% of patients on amantadine improved EDS compared to 23.0% of those on placebo(P<0.05) | Improvement |
| Selegiline | MAO-B inhibitor; metabolize to L-amphetamine | Lyons et al 2010[88] | Open-label study | 60 | 2.5 | 12 | Orally disintegrating selegiline with decreasing dosages of dopamine agonist reduced 94% of EDS | Improvement |
| | | Gallazzi et al 2021[108] | Cohort study | 45 | 10 | | ESS scores significantly reduced from 12.96 to 7.91 | |
| Rasagiline | MAO-B inhibitor | Schrempf et al 2018[109] | RCT | 30 | 1 | 8 | No difference in the frequency between rasagiline group and placebo group (6.8% vs 6.7%) | Improvement |
| | | Hauser et al 2014[110] | | 316 | | 18 | ESS scores significantly decreased after rasagiline treatment (9.0 vs 8.1, P=0.011) | No relationship |
| Safinamide | MAO-B inhibitor; inhibit glutamate release | Liguori et al 2018[111] | Observational study | 61 | Not reported | 16 | ESS scores significantly decreased after safinamide treatment (9.8 vs.8.02, P<0.05) | Improvement |
| | | Santos et al 2021[112] | | 50 | 100 | 24 | ESS scores significantly decreased after safinamide treatment (9.2 vs.6.93, P=0.012) | |

**Abbreviations**: RCT, Randomized comparison trial; COMT, Catechol-O-methyltransferase; MAO-B, Monoamine oxidase-B; EDS, Excessive daytime sleepiness; ESS, Epworth sleepiness scale.


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a stronger effect on EDS relative to levodopa.[72] However, compared with levodopa or DA agonist monotherapy, combination therapy with the two drugs increased the ESS scores.[73]

Several randomized, double-blind trials evaluated the long-term safety and tolerability of transdermal rotigotine in PD patients in the United States and Canada and noted daytime somnolence as a common adverse event, affecting 18–33% of patients on rotigotine.[74–77] Nevertheless, a recent study on rotigotine in PD patients in the United States found that neither subjective nor objective sleepiness changed before and after rotigotine treatment.[78] A randomized, placebo-controlled study reported that EDS occurred in 8.9–14.3% of patients on apomorphine, but not in patients on placebo, a finding supported by two other studies on apomorphine in PD.[79–81] Notably, a case study reported that a PD patient suffered from somnolence episodes following increasing doses of pergolide whereas somnolence disappeared after decreasing doses of pergolide. Moreover, lower latency of sleep onset was found in PD patients taking on pergolide compared with those on placebo, suggesting that EDS is not a specific effect related to the non-ergoline class DA agonists.[82]

In addition to dopaminergic therapies, entacapone, a catechol-O-methyltransferase inhibitor, was shown to induce EDS in PD patients. In an open-label study, 6.5% of PD patients changing from immediate release carbidopa/levodopa to carbidopa/levodopa/entacapone reported increased sleepiness, which supported the findings in previous case reports.[83–85]

Notably, the risk of daytime sleepiness is related to the dose of dopaminergic medications. EDS is more common in PD patients taking higher dosages of DA agonists and levodopa, typically in the dose-increasing phase or after a period of time on a stable dosage.[65,86] Two studies found that levodopa equivalent dose predicted EDS in PD patients, suggesting that EDS in PD was associated with the amount of dopaminergic drugs.[49,87] In addition, decreasing dosages of dopaminergic drugs was shown to relieve subjective daytime sleepiness in PD patients in an open-label study.[88] In some animals and healthy population studies, dopaminomimetic agents, including DA, levodopa and DA agonists, have been shown to induce biphasic effects on sleep and wakefulness depending on varying concentrations.[89–91] Low doses enhance sleep via D2-like inhibitory autoreceptors, while high doses promote alertness and reduce slow-wave sleep and REM sleep possibly through the activation of D1-like and D2-like postsynaptic receptors. Several studies showed that dopamine D1 receptor agonist promoted wakefulness while D2 receptor agonist increased sleep.[92,93] Based on relevant literature, divergent dose-dependent effects of DA agonists in healthy subjects vs PD patients may be related to the imbalance of D1 receptor and D2 receptor activity. That is to say, relatively hyperactivated D2 receptor due to the loss of D1 receptor or increased D2 receptor expression in PD could lead to sleepiness when using dopaminergic agents.[94] Besides, the loss of PD-specific DA neurons responsible for promoting and maintaining wakefulness may be the contributor of EDS in PD patients. This hypothesis can also explain why EDS frequently occurs in PD patients.

It appears that some DA agonists have different effects on EDS. A cross-sectional observational study found no significant correlation between ropinirole and EDS in PD patients.[95] The finding was in accordance with previous studies, suggesting that ropinirole did not contribute to sleepiness in PD.[96–98] Interestingly, another study reported that patients changing from ropinirole immediate release to prolonged release showed an improvement from daytime sleepiness.[99] Compared with the vague effect of ropinirole on EDS, piribedil seemed to attenuate daytime sleepiness in PD patients. One randomized controlled trial (RCT) showed a reduction in ESS scores in patients switching from pramipexole or ropinirole to equivalent dose of piribedil relative to those continuing on pramipexole or ropinirole, suggesting piribedil was potentially beneficial against EDS in PD patients.[100] Such positive effects might be due to the unique antagonistic activities of piribedil at alpha-2 receptors, resulting in promoting cholinergic transmission and norepinephrine activity, which was proved to enhance awakening.[101–104] Interestingly, selective D1 receptor agonist has been shown to efficiently relieve sleepiness while D2 receptor agonist had no significant effect on EDS in MPTP-induced PD macaque model.[92] In addition, a recent study revealed that mevidalen, the dopamine D1 receptor positive allosteric modulator, can contribute to prolonged MSL measured by MSLT and enhance wakefulness in healthy sleep-deprived healthy volunteers.[93] As previously discussed, however, most D2 receptor agonists, including pramipexole and ropinirole, could induce EDS in PD patients. Accordingly, divergent affinity for D1 and D2 receptors could result in different effects on EDS of dopaminergic drugs, which is associated with the activities of striatal neurons. Indeed, striatonigral neurons expressing D1 receptor have been demonstrated to promote wakefulness whereas striatopallidal neurons expressing D2 and A2A receptors induce sleep.[105,106]

Regarding amantadine and monoamine oxidase-B inhibitors, several studies revealed their advantageous effects on EDS. A recent study demonstrated a significant improvement in daytime sleepiness in patients on extended-release amantadine compared to those on placebo, suggesting amantadine had potential benefits against EDS in PD patients.[107] In a 12-week open-label study, 94% of patients with EDS showed significant improvement in subjective sleepiness after adding orally disintegrating selegiline and decreasing DA agonist dosages.[88] Likewise, a recent study reported that daytime somnolence was significantly improved in 45 PD patients treated with 10 mg of selegiline for 3 months, which was explained by the central excitatory effect of the selegiline metabolite amphetamine.[108]

A double-blind, baseline-controlled trial revealed a reduction in ESS scores in patients treated with 1 mg of rasagiline.[109] However, another RCT demonstrated that 1 mg of rasagiline as an add-on to dopaminergic therapy did not change daytime sleepiness in PD patients.[110] This was supported by an observational study, which showed that daytime sleepiness was significantly improved in PD patients on safinamide, the third-generation monoamine oxidase-B inhibitors, but not in patients on rasagiline.[111] An open-label prospective study also reported an improvement of safinamide on daytime sleepiness, which might be related to the glutamatergic system involved in sleep-wake rhythm since safinamide could regulate the release of glutamate in some brain areas.[112–114]

Taking together, most anti-PD medications seemingly have dose-dependent negative effects on EDS, but some other drugs such as piribedil and selegiline may ameliorate EDS in PD patients. Therefore, it is recommended to carefully evaluate the symptom of daytime sleepiness and then select reasonable anti-PD drugs for patients.[20]

## Other Sleep Disorders

As reported, other sleep disorders, including insomnia, RBD, OSA and restless legs syndrome (RLS), are common in PD patients and frequently coexist with EDS. A longitudinal cohort study revealed that nighttime sleep problems were present in 34% of PD patients who suffered from subjective EDS.[60] Another polysomnographic study found that 69% of PD patients with objective EDS experienced OSA and RLS on overnight polysomnography.[46]

In fact, sleep architectures have been shown to change in PD patients and mainly manifest with nighttime sleep problems such as sleep fragmentation, difficulty in falling asleep and early awakening, which could cause EDS.[51,53,115] A prospective study found that insomnia was more prevalent in PD patients with EDS than those without EDS.[41] Suzuki et al found a significant difference in frequency of EDS between PD patients with and without RLS.[116] Furthermore, several studies reported a positive correlation between RLS severity and EDS in PD.[50,117] Notably, the relationship between EDS and RLS in PD remains an issue of debate since inconsistent results were reported.[118,119] The association between poor nighttime sleep and EDS might be partially explained by the regulation of sleep homeostasis. Due to prolonged duration of wakefulness at night, somnogenic factors accumulate gradually, which leads to increased sleep pressure during the day and daytime sleepiness.[120]

In addition to sleep homeostasis regulation, however, it seems that a shared pathogenesis underlies the relationship between EDS and RBD in PD. Rolinski et al demonstrated that PD patients with RBD had increased frequency of EDS and higher ESS scores compared to those without RBD, implying RBD correlated to worse daytime sleepiness in PD patients.[121] The association was still statistically significant after adjusted for other variables such as age and gender; similar findings were reported in other studies.[122,123] As the prodromal symptoms of PD, the relationship between EDS and RBD in PD might be related to the disruption of cholinergic system within brainstem. On the one hand, the widespread degeneration within brainstem could impair the subcoeruleus complex and the pedunculopontine nucleus, which are in charge of REM atonia and awakening, respectively.[124,125] On the other hand, RBD in PD could be affected by cholinergic denervation in related neocortex, limbic cortex, and thalamus those receive cholinergic input from pedunculopontine nucleus.[126]

Although EDS emerges as a common symptom in OSA patients, the role of OSA in EDS in PD patients remains controversial. Several studies revealed no difference in the incidence of OSA between PD patients with EDS and those without EDS.[127,128] Moreover, a recent large sample study among European population showed no significant causal association between OSA and PD, implying that OSA might not be a risk factor for PD.[129] However, a study in Chinese PD patients found that ESS scores were higher in PD patients with OSA than those without OSA, suggesting that OSA worsened EDS.[56] This finding was consistent with another study on risk factors of OSA in PD.[57] Two studies found that

objective sleepiness by the MSLT was related to higher apnea hypopnea index in PD patients, while one study found no correlation between objective sleepiness and apnea hypopnea index in sleepy PD patients.[45,130,131] OSA is characterized by intermittent hypoxia and sleep fragmentation, which could be responsible for EDS in PD.[132] That is, OSA can trigger neuroinflammation via intermittent hypoxia and sleep fragmentation, and lead to neuronal damage in multiple wake-promoting brain regions, such as dopaminergic ventral periaqueductal gray and noradrenergic locus coeruleus, resulting in the development of EDS in PD patients.[133]

Collectively, sleep homeostasis regulation, as well as damaged wake-promoting brain regions may explain the relationship between primary sleep disorders and EDS in PD patients. Poor nighttime sleep can lead to compensatory EDS through the regulation of sleep homeostasis. The impairment of wake-promoting brain regions can be a shared pathogenesis of EDS and other sleep disorders in PD patients and neuroinflammation triggered by OSA can worsen such a pathological process.

## Impaired Wake-Promoting Nerve Nuclei Due to PD Neurodegeneration

Sleep and wakefulness are regulated by multiple brain regions and neurotransmitter systems.[134] Sleep or awakening condition are disturbed with neural nuclei of sleep-wake system destroyed.[135] Although the pathogenesis of EDS in PD remains unknown, growing evidence suggests that degenerative changes in the structure of some brain regions involved in arousal correlated with EDS in PD (Figure 1).

### Neuronal Pathology of PD

It has been well recognized that the core of pathology in PD is DA neuron death in SNc and the presence of Lewy body.[136] Pathogenic mechanisms have been proposed to converge in alpha-synuclein misfolding and abnormal aggregation, impaired protein clearance, mitochondrial dysfunction, oxidative stress and neuroinflammation.[2,137] The PD-specific loss of nerve cells has been reported to occur in SNc along with other brain regions, such as locus coeruleus, the dorsal motor nucleus of the vagus, pedunculopontine nucleus, the medullary reticular formation, nucleus basalis of Meynert, ventral tegmental area (VTA), dorsal raphe nucleus and thalamus.[138,139] Extensive research has also shown that in addition to dopaminergic system, cholinergic, noradrenergic, serotonergic, orexinergic, glutamatergic, and adenosine pathways are also involved in the pathogenesis with PD progression.[139] Several postmortem studies in PD patients revealed that histamine levels and innervation in SN increased and the expression of histamine receptors changed in SN, caudate nucleus, and putamen. Moreover, the histamine methyltransferase-mRNA in SN was found to be negatively correlated with PD disease duration, implying that altered histaminergic system might partly contribute to PD pathology.[140,141] Notably, growing evidence indicates that the dopaminergic system plays a pivotal role in maintaining wakefulness. In fact, Eban-Rothschild et al demonstrated that the awake state would be suppressed to promote sleep when inhibiting the activities of VTA dopaminergic neurons, suggesting that VTA dopaminergic neurons are necessary for arousal.[142] Except for VTA neurons, early experimental studies proposed that ventral periaqueductal gray matter (vPAG) dopaminergic neurons could be one neuronal population to mediate arousal.[143,144] Indeed, vPAG dopaminergic neurons were found to show c-Fos immunoreactivity during wakefulness but not during sleep, and lesions of these neurons resulted in reduced wakefulness and increased sleep.[145] Although vPAG dopaminergic neurons are involved in the maintenance of wakefulness, postmortem studies have not yet reported loss of wake-active ventral periaqueductal gray matter dopaminergic neurons in PD patients.[139] Collectively, in the pathologic course of PD, the fiber connections among wake-promoting nerve nuclei get damaged and the wake-promoting neurotransmitters decrease.[104] Accordingly, the function of wakefulness maintenance grows weakened and then leads to sleepiness.

### Radiology Images on Altered Brain Areas in PD Patients with EDS

Imaging revealed changes in brain structures and function in PD patients with EDS. Matsui et al found greatly diminished fractional anisotropy values of the fornix fiber in PD patients with EDS and demonstrated the fornix fiber degeneration was related to EDS in PD patients.[146] An independent magnetic resonance imaging study showed distinct gray matter atrophy in the frontal, temporal, occipital lobes, and nucleus basalis of Meynert in PD patients with EDS,

compared with those without EDS and controls.[147] However, a multimodal imaging study revealed an increase in grey matter volume of the bilateral hippocampus and parahippocampal gyrus, as well as amplified axial diffusivity values in the left anterior thalamic radiation and corticospinal tract. These alterations might be related to uninhibited signaling pathways or compensatory alteration due to anatomical or functional deficits in other brain regions.[148] Likewise, PD patients with EDS in a resting state functional magnetic resonance imaging study displayed an increase of spontaneous neural activity in the left paracentral lobule. By contrast, reduced activity was observed in the left cerebellum and inferior frontal gyrus where functional connectivity was also decreased, suggesting neural downregulation and associated compensatory mechanisms in patients presenting EDS.[149]

### Related Wake-Promoting Neurotransmitter Systems

Specifically, two [$^{123}$I] FP-CIT single-photon emission computed tomography studies demonstrated a correlation between ESS scores and DA transporter loss in striatum, caudate nucleus and putamen in early PD. This finding suggested that the severity of EDS may relate to dopaminergic nigrostriatal degeneration at this stage.[59,150] Yoo et al revealed ESS scores negatively correlated with thalamic monoamine availability (including DA, serotonin, and norepinephrine). Besides, they found decreased thalamic monoamine availability appeared to be an independent predictor of EDS in early and drug-naive PD. These findings implied that disruption of these monoaminergic systems could be a cause of EDS in PD.[151] In line with this study, another human postmortem study found α-synuclein distributed across the thalamus in PD.[152] In addition, the paraventricular nucleus of the thalamic was reported to play a critical role in maintaining wakefulness through projections with nucleus accumbens and with the orexinergic systems.[153] Nevertheless, Wilson et al demonstrated that serotonergic dysfunction in PD was related to nocturnal sleep problems, but not to EDS.[154] Similarly, another study found a substantial decline in availability of raphe serotonin transporter four years after diagnosis of PD, lacking a correlation with EDS.[155]

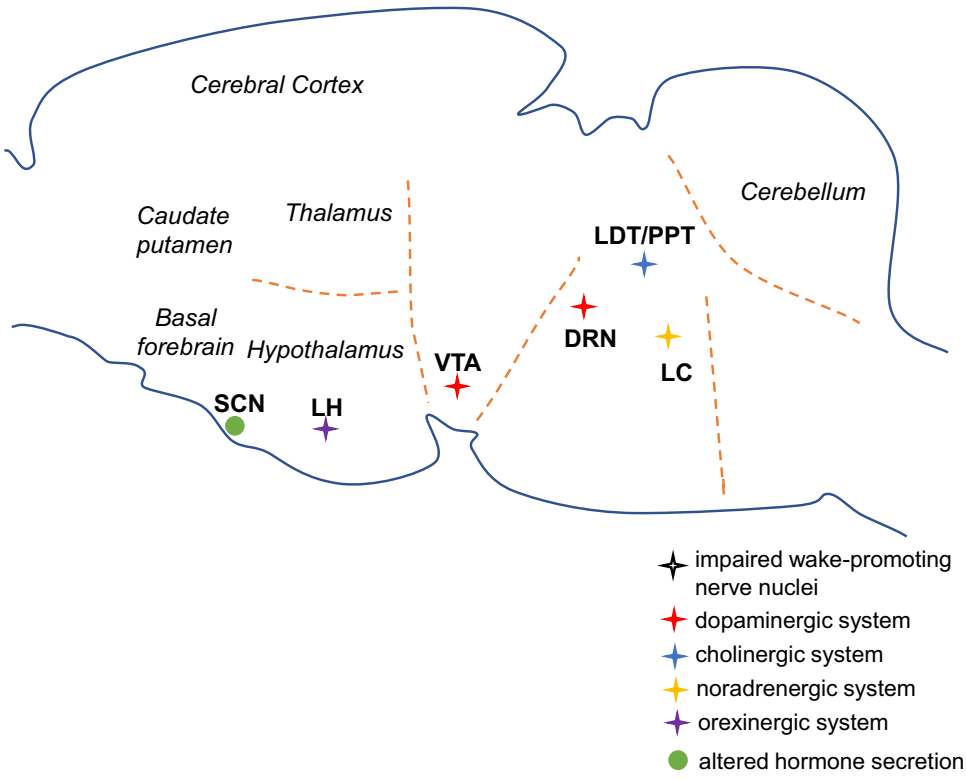


**Figure 1** Possible underlying brain-pathophysiological mechanisms in PD patients with EDS.
**Notes**: Brain areas labeled in italics have been reported to change in PD patients with EDS while the nerve nuclei in bold might be targets of the pathogenesis in PD patients with EDS. (This figure is based on a schema of a mouse brain but not the human brain).
**Abbreviations**: DRN, dorsal raphe nucleus; LC, locus coeruleus; LDT, laterodorsal tegmental nucleus; LH, Lateral hypothalamus; PPT, pedunculopontine tegmental nucleus; SCN, suprachiasmatic nucleus; VTA, ventral tegmental area.

Orexin neurons in the lateral hypothalamus densely project to monoaminergic and cholinergic neurons in forebrain and brainstem and involve sleep-wake regulation and maintain arousal.[156] Previous studies reported a decline both in the orexin concentration levels in ventricular CSF and in the density of orexin cells in hypothalamus.[157–159] They also found orexin system degenerated with the severity of the disease in the PD patients. However, two other studies measured orexin levels in ventricular CSF of PD patients with and without objective daytime sleepiness and demonstrated lack of correlation between objective daytime sleepiness and lumbar orexin levels.[160,161] Such evidence suggests that orexin be not the major pathophysiological mechanism of EDS in PD.

Collectively, impaired dopaminergic pathway appears to represent the promising pathogenesis of EDS in PD, excluding the orexinergic and serotonergic systems.[59,90,154] In addition, damaged cholinergic system is also the potential pathogenesis of EDS due to its close relationship with various symptoms related to EDS.[162,163]

## Peripheral Connections of Impaired Wake-Promoting Nuclei

Specific wake-promoting nuclei and neurotransmitter systems responsible for EDS in PD remain obscure, but EDS-related symptoms can provide clues to find out peripheral connections of impaired wake-promoting nuclei and tie EDS to specific neuroanatomical areas of PD degeneration.

Jester et al reported that PD patients with EDS experienced extra cognitive deficits in processing speed and executive control in comparison with those without EDS.[164] Additionally, EDS was previously demonstrated to be a predictive factor for the future impairment of cognitive function.[165] The postural instability gait difficulty (PIGD) dominant motor phenotype may give us insight into the relationship between disability and EDS, since a high PIGD score could predict the development of disability as well as EDS.[51,55] Several studies revealed a positive correlation between EDS and mood measures in PD patients.[52,55,166] Depression appeared significantly related to EDS while anxiety was weakly correlated with EDS, but the degree of correlation varied with subjective or objective sleepiness.

Indeed, EDS was closely related to cognitive impairment and depression in PD. These non-motor symptoms shared several common risk factors including severity of motor impairment and longer disease duration, and thus were identified as a symptom complex associated with advancing PD.[167,168] Such a close relationship reinforces the notion that progressing neurodegeneration is more likely to underlie the development of EDS and related non-motor and motor manifestations in PD.[58]

It has been established that depression in PD was associated with the loss of serotonergic neurons projecting to the limbic regions and the disturbances of dopaminergic and noradrenergic systems in the locus coeruleus in control of alertness.[169] The PIGD features in PD patients seemed to be attributed to the cholinergic dysfunction in pedunculopontine nucleus and basal forebrain, which can also lead to failure to maintain wakefulness.[162,170,171] Cognitive impairment in PD has been linked to damage of thalamus and the nucleus basalis of Meynert in the substantia innominata of the basal forebrain, based on reduced gray matter volume and increased mean diffusivity in a diffusion tensor imaging study.[163] Interestingly, similar damage was also reported in the two brain regions of PD patients with EDS.[147,151] Since the nucleus basalis of Meynert is the primary source of cholinergic input from basal forebrain to the cortex, the relation may be explained by the disruption of cholinergic system which controls cognitive function and promote awakening.[163,170,172]

Circadian rhythm dysfunction has been postulated as a promising research topic due to its close correlation with nearly all non-motor manifestations, including damaged sleep and alertness in PD patients.[64] As one of the sleep-wake regulations, circadian rhythm dysfunction circadian rhythmicity is dominated by the endogenic biological clock of suprachiasmatic nucleus in the anterior hypothalamus and regulated by external zeitgebers and endogenous signals. Light is the strongest external zeitgebers. In addition, physical activity, temperature and mealtime are also environmental zeitgebers. The endogenous factors of circadian rhythmicity include melatonin and age.[173–175]

The amplitude and amount of melatonin secretion in those with EDS decreased significantly, compared to the PD patients without EDS.[38] Likewise, Breen et al found cortisol and melatonin levels in blood increased and decreased, respectively.[176] Videnovic et al showed an inverse correlation between age and the amplitude/amount of melatonin secretion in PD patients, but not in healthy controls.[38] These findings revealed that altered hormone might be associated with abnormal sleep in PD patients. In addition to changes in endogenous factors, many studies have observed that therapies to restore circadian rhythm, such as strong light therapy and exercise therapy, can improve EDS in PD patients.[177,178]

## Conclusions

In summary, EDS is one of the most prevalent sleep disorders in PD population and has a negative impact on the safety and quality of these patients' lives. Multiple factors contribute to EDS in PD patients, including the use of antiparkinsonian medications, coexistent nighttime sleep problems and primary neurodegenerative lesions of PD. Most dopaminergic drugs induce or aggravate reversible EDS in PD patients in a dose-dependent manner, while some other anti-PD drugs improve EDS, which can be attributed to different pharmacological mechanisms. Thorough summary on the effects of commonly used anti-PD drugs on EDS in this review can support the rational clinical medication in sleepy PD patients. The presence of persistent EDS was much associated with primary neurodegenerative lesions of PD. As pointed out in the review, damaged wake-promoting nerve nuclei and neurotransmitter systems including dopaminergic, cholinergic and noradrenergic systems can be the pathogenesis of EDS in PD patients. These efforts provide clues for subsequent imaging studies or mechanism research to effectively ascertain specific wake-promoting nerve nuclei responsible for EDS in PD. Future exploration toward this direction may hopefully shed light on developing effective, mechanisms-driven treatment options.

## Abbreviations

AD, Alzheimer's disease; CSF, Cerebrospinal fluid; DA, Dopamine; DLB, Dementia with Lewy Bodies; EDS, Excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, Obstructive sleep apnea; MSA, Multiple system atrophy; MSLT, Multiple sleep latency test; PD, Parkinson's disease; PIGD, Postural instability gait difficulty; RBD, Rapid eye movement sleep behavior disorders; RCT, Randomized controlled trial; REM, Rapid eye movement; RLS, Restless legs syndrome; SNc, Substantia nigra pars compacta; VTA, ventral tegmental area; vPAG, ventral periaqueductal gray matter.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article. HL and JL contributed equally to this paper. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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