Selegiline Improves Excessive Daytime Sleepiness in Parkinson's Disease: An Open Trial

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Abstract

Excessive daytime sleepiness (EDS) is common in Parkinson's disease (PD) and may respond to dopaminergic therapies. The aim of this open-label trial was to assess the efficacy and safety of selegiline as a treatment for EDS in PD patients. In this multi-center study, 141 PD subjects were enrolled between December 2019 and October 2020, and 121 patients completed the 8-week study. Selegiline was administered at 5 mg/day in the first week and was increased to 10 mg per day during the following weeks. EDS was evaluated using the Epworth Sleepiness Scale (ESS) at baseline, week 3, and week 8. Changes in motor complications, sleep quality, and quality of life were also assessed in patients with PD. As primary outcomes, ESS scores decreased significantly in PD patients who received selegiline for 8 weeks ($P < 0.001$). As secondary outcomes, the scores of Parkinson's disease sleep scale (PDSS) and Parkinson's disease quality of life questionnaire 39 (PDQ-39) also improved after the treatment. The severity of motor fluctuation improved ($P = 0.037$), while the percentage of patients with dyskinesia and the severity of dyskinesia did not increase significantly compared with baseline. Participants treated with selegiline showed an improvement in EDS and good tolerance of the drug. This study demonstrated the efficacy of selegiline for the treatment of daytime sleepiness in PD patients.

Trial registration: clinicaltrials, NCT04870372. Registered 5 May 2021 - Retrospectively registered, <https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009J06&selectaction=Edit&uid=U00026CP&ts=2&cx=rnz8uy>.

Background

Parkinson's disease (PD) is the second most common neurodegenerative disorder, and sleep disturbance is a major disabling non-motor symptom that affects over 90% of PD patients. Sleep disturbances in PD include rapid eye movement behavior disorder (RBD), excessive daytime sleepiness (EDS), insomnia, sleep-disordered breathing, restless leg syndrome (RLS), and circadian disruption. EDS is defined as inappropriate and undesirable sleepiness during waking hours, which may occur during activities such as talking or driving.

Selegiline is a selective, irreversible monoamine oxidase type B (MAO-B) inhibitor, which improved motor symptoms and posture gait in PD compared to placebos in double-blind placebo-controlled studies^[1,2]. There are very limited data for drugs that promote wakefulness, such as modafinil for narcolepsy, with insufficient evidence of the efficacy of modafinil for the treatment of EDS in PD patients. Since other drugs have not been effective for EDS, we conducted an open-label clinical trial to determine whether selegiline would alleviate EDS in PD patients.

Methods

This open-label clinical trial was conducted at the Department of Neurology at the Second Affiliated Hospital of Soochow University, Changshu Hospital Affiliated with Nanjing University of Chinese

Medicine, Second Affiliated Hospital of Nantong University, Jiang Yuan Hospital Affiliated with Jiangsu Institute of Nuclear Medicine. **Trial registration:** clinicaltrials, NCT04870372. Registered 5 May 2021 - Retrospectively registered, <https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S0009J06&selectaction=Edit&uid=U00026CP&ts=2&cx=rnz8uy>. Detailed methods are provided in **Supplementary Methods**.

Results

The baseline characteristics of the participants are shown in **Supplemental Table 1**. One hundred and forty-one subjects were enrolled in the study, 121 completed the study, and 19 were terminated before the end of the study (see **Supplemental Fig. 1**). Of these patients, 92 were men and 49 were women with a mean age of 66.2 ± 9.1 years. The primary endpoint of this study was the efficacy of selegiline for EDS in patients with PD. However, its effect on the general quality of sleep, life, and motor complications was also evaluated.

Primary outcomes

At week 8, Epworth sleepiness scale (ESS) scores were significantly improved in PD patients compared to baseline ($P < 0.001$). The median ESS scores were 11 at baseline, 9 at week 3, and 8 at week 8. The primary outcomes for the full cohort are presented in **Supplemental Table 2**.

Secondary outcomes

The total Parkinson's disease sleep scale (PDSS) scores improved significantly after treatment with selegiline for 3 weeks and 8 weeks ($P < 0.001$) (**Supplemental Table 2**). All eight factors improved after selegiline treatment ($P < 0.01$). For factor analysis, eight sub-scales were analyzed^[3]: (1) overall quality of nighttime sleep (item 1); (2) sleep onset and sleep-maintenance insomnia (items 2 and 3); (3) nocturnal restlessness (items 4 and 5); (4) nocturnal psychosis (items 6 and 7); (5) nocturia (items 8 and 9); (6) nocturnal motor symptoms (items 10–13); (7) sleep refreshment (item 14); (8) sleep refreshment (item 15). All eight factors improved after selegiline treatment ($P < 0.01$).

The Parkinson's disease quality of life questionnaire 39 (PDQ-39) scores at baseline and after the 8 weeks of treatment were assessed (**Supplemental Table 2**). This included 39 items assessing eight aspects of quality of life in PD patients: mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. The highest scores (poorest results) for the PDQ-39 sub-domains were in mobility, activities of daily living, and cognition. Except for social support, the other seven characteristics improved after 8 weeks of treatment ($P < 0.01$). The median and interquartile ranges for bodily discomfort were the same at baseline and week 8, however, the distribution was different; the scores were 3.1 ± 2.5 at baseline and 2.7 ± 2.2 in week 8. The total scores for ESS, PDSS, and PDQ-39 improved significantly after selegiline treatment (**Fig. 1**). The percentage of patients with motor fluctuations decreased significantly after 8 weeks of treatment ($P = 0.022$). The severity of motor

fluctuation also improved ($P = 0.037$). However, there was no difference after treatment in the percentage of patients with dyskinesia or in its severity (**Supplemental Table 3**).

Discussion

Patients with EDS showed significant improvements after selegiline treatment. Inappropriate and undesirable sleepiness (EDS), quality of sleep, and quality of life improved after treatment. There are three possible causes of daytime sleepiness. First, pathophysiological alterations in the mechanisms that regulate sleep and wakefulness may result in EDS. In the brainstem, the noradrenergic locus coeruleus, the noradrenergic dorsal motor nucleus of the vagus nerve, the serotonergic dorsal raphe nucleus, the histaminergic tuberomammillary nucleus, and dopaminergic areas that are related to the arousal system controls all show degeneration in PD patients^[4]. Second, dopaminergic therapies may cause EDS. Dopamine agonists are reported to cause somnolence as a significant adverse effect^[5], and PD patients who take a dopamine agonist are more likely to have somnolence than those who do not. Third, poor nocturnal sleep is also correlated with EDS. Some sleep disorders such as RLS, periodic limb movement disorder, and RBD may lead to sleep fragmentation, which in turn results in EDS.

An evidence-based review indicated that there was insufficient data to recommend specific drugs to treat EDS^[6]. Several wakefulness-promoting agents such as modafinil^[7] or stimulants such as methylphenidate^[8] might be helpful for EDS in PD patients. More data on the efficacy and safety of these drugs are needed. Selegiline caused a subjective increase in alertness for 4–8 hours in 21 subjects with the narcoleptic syndrome for 4 weeks treatment^[9].

Selegiline is mainly metabolized into amphetamine and methylamphetamine^[9] through the liver, which may increase alertness in PD patients. Since EDS in patients with PD does not typically respond to dopaminergic therapy, selegiline may be effective in treating this condition. This study is important because it provides new information on a treatment for daytime sleepiness in PD patients.

In this study, we found a decrease in daytime sleepiness in PD patients after treatment with selegiline. Selegiline may be an effective add-on treatment for EDS syndrome in PD patients.

Abbreviations

EDS: Excessive daytime sleepiness

ESS: Epworth sleepiness scale

MAO-B: Monoamine oxidase type B

PD: Parkinson's disease

PDQ-39: Parkinson's disease quality of life questionnaire 39

PDSS: Parkinson's disease sleep scale

RBD: Rapid eye movement behavior disorder

RLS: Restless leg syndrome

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. All subjects provided informed written consent before participating in the study.

Consent for publication

All authors consent for publication.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing Interest

The authors have no conflict of interest to report.

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Authors' contributions

JRZ, CJM, CFL: Conception, organization, statistical analysis and draft the manuscript; JRZ, JPC, JL, JL, HM, XYZ, MM, XYC, YH, JC, KPX, HJ, WFL: Data collection, execution. All authors read and approved the final manuscript.

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Figures

Figure 1

Changes in ESS, PDSS, and PDQ-39 scores at baseline and after selegiline treatment. The total scores for ESS, PDSS and PDQ-39 were significantly improved after the treatment of selegiline. (A) PD patients had lower ESS scores after selegiline treatment ($P < 0.001$). (B) PD patients had higher PDSS scores after selegiline treatment ($P < 0.001$). (C) PDQ-39 scores decreased between baseline and 8 weeks after selegiline treatment ($P < 0.001$). ESS: Epworth sleepiness scale; PDSS: Parkinson's disease sleep scale; PDQ-39: Parkinson's disease quality of life questionnaire 39.

Supplementary Files

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