Selegiline improves excessive daytime sleepiness in Parkinson's disease: an open-label observational study

Jinru Zhang[1], Juping Chen[2], Jia Li[3], Jian Li[4], Hong Miao[2], Xiangyang Zhu[3], Meng Meng[4], Yang Han[2], Jing Chen[1], Xiaoyu Cheng[1], Kangping Xiong[1], Hong Jin[1], Weifeng Luo[1], Chengjie Mao[1], Chunfeng Liu[5]

[1]Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, Suzhou, Jiangsu 215004, China;
[2]Department of Neurology, Changshu Hospital Affiliated to Nanjing University of Chinese Medicine, Changshu, Jiangsu 215516, China;
[3]Department of Neurology, The Second Affiliated Hospital of Nantong University, Nantong, Jiangsu 226001, China;
[4]Department of Neurology, JiangYuan Hospital Affiliated to Jiangsu Institute of Nuclear Medicine, Wuxi, Jiangsu 214063, China;
[5]Jiangsu Key Laboratory of Neuropsychiatric Diseases and Institute of Neuroscience, Soochow University, Suzhou, Jiangsu 215123, China.

To the Editor: Parkinson's disease (PD) is the second most common neurodegenerative disorder, and sleep disturbance is a major disabling non-motor symptom.[1] Excessive daytime sleepiness (EDS) is defined as inappropriate and undesirable sleepiness during waking hours, which may occur during activities such as talking or driving. In PD patients, EDS increased the risk of accidents and resulted in a poor quality of life.[2]

Selegiline is a selective, irreversible monoamine oxidase type B (MAO-B) inhibitor, which improves motor symptoms and posture and gait in PD compared to placebos in double-blind placebo-controlled studies.[3,4] In patients with sleepiness, selegiline alleviates the symptoms of narcolepsy by increasing alertness.[5] Since Levodopa and dopamine agonists have little effects on EDS, we conducted an open-label clinical trial to determine whether selegiline would alleviate EDS in PD patients. We evaluated the effects of selegiline on daytime sleepiness, nighttime sleep quality, and quality of life. Referring to the adverse effects of selegiline, we studied the incidence of motor fluctuation and dyskinesia in our study.

This open-label observational study was conducted at the Department of Neurology of the Second Affiliated Hospital of Soochow University, Changshu Hospital Affiliated to Nanjing University of Chinese Medicine, Second Affiliated Hospital of Nantong University, and JiangYuan Hospital Affiliated to Jiangsu Institute of Nuclear Medicine. This clinical trial was registered at http://register.clinicaltrials.gov (NCT04870372). We focused on the observation of the efficacy of selegiline in PD patients with EDS in the real world.

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This study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University (JD-LK-2019-103-02). All subjects provided informed written consent before participating in the study. For every patient included, the written informed consent previously signed to allow the use of clinical data for research purposes was retrieved. Data were saved in a pseudonymized way and were processed according to local legal conditions.

This was a multicenter, 8-week, open-label observational study of PD patients with daytime sleepiness (Epworth Sleepiness Scale [ESS] score >7). The study consisted of two clinic visits at baseline and Week 8, and one telephone checkup at Week 3. From the day after the baseline visit, selegiline was initiated with 5 mg once daily for the first week, and the dosage of selegiline was increased to 10 mg per day for the third to the eighth weeks. Other antiparkinsonian drugs continued unchanged during the eight weeks. Changes from baseline to Week 3 and Week 8 in ESS, Parkinson's Disease Sleep Scale (PDSS), and Parkinson's Disease Quality of Life Questionnaire 39 (PDQ-39) assessments were analyzed using mixed-effect models (repeated quantitative data, and abnormal distribution). In our mixed-effect model, the scores of ESS, PDSS, and PDQ-39 were dependent variables; follow-up duration was fixed effect factor. Paired chi-squared tests were used to assess the change in the percentage of patients with motor fluctuation and dyskinesia.

One hundred and forty-one subjects were enrolled in the study, among which, 121 completed the study, and

Jinru Zhang and Juping Chen contributed equally to this work.

Correspondence to: Chengjie Mao, Department of Neurology and Clinical Research Center of Neurological Disease, The Second Affiliated Hospital of Soochow University, 1055 Sanxiang Road, Suzhou, Jiangsu 215004, China
E-Mail: drchengjiemao@163.com
Dr. Chunfeng Liu, Jiangsu Key Laboratory of Neuropsychiatric Diseases, Institute of Neuroscience, Soochow University, Suzhou, Jiangsu 215123, China
E-Mail: liuchunfeng@suda.edu.cn

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Table 1: General information and changes in ESS, PDSS, and PDQ-39 scores of Parkinson's disease patients with excessive daytime sleepiness at baseline and after 3 and 8 weeks of treatment ($n = 121$).

Items	Baseline	Week 3	Week 8	*P* values
LEDD (mg)	375 (300–450)	425 (350–500)	475 (400–550)	–
Motor fluctuation, *n* (%)	50 (41.3)	–	42 (34.7)	0.022*
Dyskinesia, *n* (%)	8 (6.6)	–	8 (6.6)	1.000
ESS score	11 (8–13)	9 (7–11)	8 (6–10)	<0.001*
PDSS total score	112 (94–120)	119 (106–129)	123 (110–131)	<0.001*
Overall quality of nighttime sleep	7 (6–8)	7 (6–9)	8 (6–9)	<0.001*
Sleep onset and maintenance insomnia	16 (12–18)	17 (14–19)	17 (15–19)	<0.001*
Nocturnal restlessness	16 (13–17)	16 (13–18)	16 (13–19)	<0.001*
Nocturnal psychosis	16 (13–19)	17 (14–19)	17 (14–19)	0.001*
Nocturia	15 (13–18)	17 (14–19)	17 (15–19)	<0.001*
Nocturnal motor symptoms	33 (29–35)	33 (30–36)	34 (31–37)	<0.001*
Sleep refreshment	8 (6–9)	9 (7–10)	9 (8–10)	0.007*
Daytime dozing	4 (3–6)	6 (4–8)	7 (4–8)	<0.001*
PDQ-39 scores	45 (19–54)	–	23 (10–45)	<0.001*
Mobility	10 (3–19)	–	7 (2–15)	0.006*
Activities of daily living	7 (2–11)	–	5 (2–9)	<0.001*
Emotional well being	5 (2–10)	–	4 (2–8)	<0.001*
Stigma	1 (0–6)	–	1 (0–4)	<0.001*
Social support	0 (0–1)	–	0 (0–1)	0.130
Cognition	7 (3–8)	–	5 (2–7)	<0.001*
Communication	2 (0–3)	–	1 (0–3)	<0.001*
Bodily discomfort	3 (1–4)	–	3 (1–4)	<0.001*

Data are presented as median (interquantile range) or numbers (%). * $P < 0.05$. ESS: Epworth Sleepiness Scale; LEDD: Levodopa-equivalent daily dose; PD: Parkinson's disease; PDQ-39: Parkinson's Disease Quality of Life Questionnaire 39; PDSS: Parkinson's Disease Sleep Scale; –: Not available.

20 were terminated before the end of the study. Of these patients, 92 were men and 49 were women with a mean age of 66.2 ± 9.1 years and a PD duration of 4 (3–7) years. The Levodopa-equivalent daily dose (LEDD) at baseline was 375 (300–450) mg. The primary endpoint of this study was the efficacy of selegiline on EDS of patients with PD. In addition, its effects on general quality of sleep and life, and motor complications were also evaluated.

Primary outcomes: At Week 8, ESS scores were significantly improved in PD patients compared with those at baseline ($P < 0.001$). The median ESS scores were 11 at baseline, 9 at Week 3, and 8 at Week 8 [Table 1].

Secondary outcomes: The total PDSS scores improved significantly after treatment with selegiline for 3 and 8 weeks ($P < 0.001$) [Table 1]. Eight sub-scales (overall quality of nighttime sleep, sleep onset and maintenance insomnia, nocturnal restlessness, nocturnal psychosis, nocturia, nocturnal motor symptoms, sleep refreshment, and daytime dozing) were analyzed.[6] All eight factors improved after selegiline treatment ($P < 0.05$).

The PDQ-39 scores at baseline and after 8 weeks of treatment were assessed [Table 1]. This included 39 items assessing eight aspects of quality of life in PD patients: mobility, activities of daily living, emotional well being, stigma, social support, cognition, communication, and bodily discomfort.[7,8] The total scores for ESS, PDSS, and PDQ-39 improved significantly after selegiline treatment [Supplementary Figure 1, http://links.lww.com/CM9/B153]. 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 in the percentage of patients with dyskinesia or its severity improvement before and after treatment [Supplementary Table 1, http://links.lww.com/CM9/B153].

Patients with EDS showed significant improvements after selegiline 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 the dopaminergic areas related to the arousal system controls all showed degeneration in PD patients.[9] Second, dopaminergic therapies may cause EDS. Dopamine agonists were reported to cause somnolence as a significant adverse effect,[10] and PD patients who took a dopamine agonist were more likely to have somnolence than those who did not.[11] Third, poor nocturnal sleep is also correlated with EDS. Some sleep disorders such as restless legs syndrome (RLS), periodic limb movement disorder, and rapid eye movement sleep behavior disorder (RBS) may lead to sleep fragmentation, which in turn results in EDS.[12]

MAO-B is a commonly used inhibitor in the treatment of PD; however, there have been no studies on the use of selegiline to treat EDS in PD patients. Selegiline caused a subjective increase in alertness for 4 to 8 h in 21 subjects

with narcoleptic syndrome after 4 weeks of treatment.[5,13] Selegiline is mainly metabolized into amphetamine and methylamphetamine through the liver,[13] which may increase alertness in PD patients. Selegiline has been shown to improve motor symptoms, but other effects were not investigated. 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 the treatment of daytime sleepiness in PD patients.

This study has some limitations: first, the control group is not included in this study; thus, the possibility of placebo effects cannot be excluded. The main reason is that it is difficult to collect the control group and lack of consideration in the design status. Further replications with the control group are needed to verify the efficacy and safety of selegiline for daytime sleepiness in PD patients. Second, we assessed EDS and sleep quality by ESS and PDSS, not by polysomnography. ESS correlates with the results of multiple sleep latency tests and overnight polysomnography.[14] Hence, we believe that ESS is an objective, easily administered measure of EDS. Finally, since selegiline has achieved good results in improving motor symptoms for PD patients,[3,4] we did not assess the motor symptoms, including Unified Parkinson Disease Rating Scale Part III; therefore, the sleep benefits may have resulted from improved motor symptoms.

In this study, we found that selegiline might be an effective add-on treatment for EDS syndrome in PD patients. Further research is needed to determine the safety and efficacy of selegiline for EDS in PD.

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Conflicts of interest

None.

References

1. Cao XY, Zhang JR, Shen Y, Mao CJ, Shen YB, Cao YL, *et al*. Fatigue correlates with sleep disturbances in Parkinson disease. Chin Med J 2020;134:668–674. doi: 10.1097/CM9.0000000000001303.
2. Fabbrini G, Barbanti P, Aurilia C, Pauletti C, Vanacore N, Meco G. Excessive daytime somnolence in Parkinson's disease. Follow-up after 1 year of treatment. Neurol Sci 2003;24:178–179. doi: 10.1007/s10072-003-0118-y.
3. Heinonen EH, Rinne UK, Tuominen J. Selegiline in the treatment of daily fluctuations in disability of parkinsonian patients with long-term levodopa treatment. Acta Neurol Scand Suppl 1989;126:113–118. doi: 10.1111/j.1600-0404.1989.tb01790.x.
4. Mizuno Y, Hattori N, Kondo T, Nomoto M, Origasa H, Takahashi R, *et al*. A randomized double-blind placebo-controlled phase III trial of selegiline monotherapy for early Parkinson disease. Clin Neuropharmacol 2017;40:201–207. doi: 10.1097/WNF.0000000000000239.
5. Hublin C, Partinen M, Heinonen EH, Puukka P, Salmi T. Selegiline in the treatment of narcolepsy. Neurology 1994;44:2095–2101. doi: 10.1212/wnl.44.11.2095.
6. Chaudhuri KR, Pal S, DiMarco A, Whately-Smith C, Bridgman K, Mathew R, *et al*. The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease. J Neurol Neurosurg Psychiatry 2002;73:629–635. doi: 10.1136/jnnp.73.6.629.
7. Dereli EE, Yaliman A, Kuru Çolaka T, Çakmak A, Razak Özdinçler A, Badilli Demirbaş Ş. Turkish version study of "Parkinson's Disease Quality of Life Questionnaire" (PDQL). Noro Psikiyatr Ars 2015;52:128–132. doi: 10.5152/npa.2015.7359.
8. Ongun N. Does nutritional status affect Parkinson's disease features and quality of life? PLoS One 2018;13:e0205100. doi: 10.1371/journal.pone.0205100.
9. Bliwise DL, Trotti LM, Juncos JJ, Factor SA, Freeman A, Rye DB. Daytime REM sleep in Parkinson's disease. Parkinsonism Relat Disord 2013;19:101–103. doi: 10.1016/j.parkreldis.2012.08.003.
10. Olanow CW, Schapira AH, Roth T. Waking up to sleep episodes in Parkinson's disease. Mov Disord 2000;15:212–215. doi: 10.1002/1531-8257(200003)15:2<212:aid-mds1002>3.0.co;2-6.
11. Ondo WG, Dat Vuong K, Khan H, Atassi F, Kwak C, Jankovic J. Daytime sleepiness and other sleep disorders in Parkinson's disease. Neurology 2001;57:1392–1396. doi: 10.1212/wnl.57.8.1392.
12. Ferreira JJ, Desboeuf K, Galitzky M, Thalamas C, Brefel-Courbon C, Fabre N, *et al*. Sleep disruption, daytime somnolence and 'sleep attacks' in Parkinson's disease: a clinical survey in PD patients and age-matched healthy volunteers. Eur J Neurol 2006;13:209–214. doi: 10.1111/j.1468-1331.2006.01262.x.
13. Roselaar SE, Langdon N, Lock CB, Jenner P, Parkes JD. Selegiline in narcolepsy. Sleep 1987;10:491–495. doi: 10.1093/sleep/10.5.491.
14. Bargiotas P, Lachenmayer ML, Schreier DR, Mathis J, Bassetti CL. Sleepiness and sleepiness perception in patients with Parkinson's disease: a clinical and electrophysiological study. Sleep 2019;42:zsz004. doi: 10.1093/sleep/zsz004.

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