Efficacy and safety of light therapy for Parkinson disease

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To the Editor: Parkinson disease (PD) is the second most common neurodegenerative disorder associated with significant disability and negative impact on quality of life (QoL), affecting 2% to 3% of the population ≥65 years of age.[1] Although the disorder is defined by motor features including asymmetric tremor, bradykinesia, and rigidity, various non-motor features are typically seen, including cognitive impairment, depression, sensory symptoms, autonomic dysfunction, and sleep disturbances. Due to the complexity, PD is challenging to treat. There are currently no effective treatments to prevent or halt the progression of PD.

In recent years, light therapy (LT), consisting of exposure to different kinds of artificial light, has been applied to a variety of disorders including circadian misalignment, seasonal and non-seasonal depression, sleep disorders, mood disorders, and cognitive dysfunction. Previous studies have found that LT might have a substantial therapeutic potential for motor and non-motor symptoms of PD. LT is usually administered with bright, fluorescent light delivered via a light box or other devices. The parameters of LT include wavelength, total daily exposure time, intensity, and timing of exposure during the day.

Considering the therapeutic potential of LT for PD, it is important to gain insight into the effects of LT on PD patients. Given that several randomized controlled trials (RCTs) have been published, we sought to critically examine the efficacy and acceptability of LT in PD. We performed a systematic review of RCTs of LT for PD and quantitatively summarized the results using meta-analysis to determine the efficacy of LT for improvement in PD symptoms.

This systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered at the International Prospective Register of Systematic Reviews (No. CRD42020170794). The extant literature through to May 22, 2021, was searched through the following databases: Embase, PubMed, Cochrane, Web of Knowledge, ClinicalTrials.gov, Chinese national knowledge infrastructure, and Wanfang databases. In addition to the electronic search strategies, a manual cross-reference search of the bibliographies of relevant articles was conducted. Studies were selected for the review if they included (1) participants meeting a diagnosis of idiopathic PD, as defined by the UK Parkinson Disease Society Brain Bank Criteria or the Movement Disorders Society (MDS) diagnostic criteria; (2) a specific light intervention, (3) a randomized trial design with a control condition; and (4) outcome measures of PD symptoms. We excluded studies if (1) active intervention included a combination of LT with another treatment and (2) participants had other comorbidities as a primary diagnosis of interest. Cochrane Collaboration Risk of Bias tool was used to assess the risk of bias in the individual studies.

Outcome data for meta-analysis using identified RCTs were systematically extracted. The pooled effect size for each outcome variable of motor and non-motor symptoms was calculated. For dichotomous outcomes (e.g., adverse effects), the number of events and the total number of patients were extracted and analyzed using odds ratios (OR). For individual trials with no events in any group, a continuity correction of 0.5 was added to each cell for each effect measure. For continuous outcomes (e.g., depression rating scales), data extracted included the mean and standard deviation (SD) of the pre-test and post-test values, mean and SD of change scores, and sample size in each group and analyzed using mean difference (MD) or standard mean difference (SMD). When these data were not available, data in the form of standard error,

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confidence intervals (CIs), median, the minimum and maximum values, or the first and third quartiles were converted into mean and SD using previously suggested statistical formulas. Heterogeneity was assessed using Q statistics and I^2; a low P value for Q statistics and/or $I^2 > 40\%$ indicated significant heterogeneity. The data synthesis and analysis were conducted using The Cochrane Collaboration Review Manager 5.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Supplementary Figure 1, http://links.lww.com/CM9/A798 shows the flow diagram for the search and selection of studies following PRISMA guidelines. After screening and removal of duplicates, a total of 12 full-text articles met the eligibility criteria. Four articles were excluded because of lack of randomized design, one article because the intervention combined LT with other treatments and one article because it is the protocol of another study. Six studies were eligible for analysis.[2-7] Supplementary Figure 2, http://links.lww.com/CM9/A798 shows the summary of the risk of bias assessment. Supplementary Tables 1 and 2, http://links.lww.com/CM9/A798 show the main characteristics of the included studies.

Motor symptoms of PD were assessed with the Unified Parkinson Disease Rating Scale (UPDRS) III in three studies,[2,5,6] with the MDS UPDRS III in two studies.[3,7] Meta-analysis of the five studies employing a fixed effect model indicated that compared with control conditions, LT did not significantly improve clinician-rated motor function (SMD = −0.12; 95% CI, −0.41 to 0.16, $P = 0.390$) [Supplementary Figure 3, http://links.lww.com/CM9/A798]. Depression was assessed in five studies.[2-6] A fixed effect model indicated that LT did not significantly reduce depression scores compared to control groups (SMD = −0.11; 95% CI, −0.40 to 0.17, $P = 0.440$) [Supplementary Figure 4A, http://links.lww.com/CM9/A798]. Subjective quality of sleep was assessed in two studies.[5,6] Improvement of sleep quality was greater for LT than the control, with an overall medium effect size (SMD = 0.46; 95% CI, 0.06 to 0.85, $P = 0.020$) [Supplementary Figure 4B, http://links.lww.com/CM9/A798]. Daytime sleepiness was evaluated in five studies, mainly using Epworth Sleepiness Scale (ESS). Pooled analysis of five studies indicated no significant improvement in daytime sleepiness (SMD = -0.19; 95% CI, -0.47 to 0.10, $P = 0.200$) [Supplementary Figure 4C, http://links.lww.com/CM9/A798]. Three of the five studies reported the data of ESS > 10, which means more severe symptoms. Of note, the pooled results of the three trials indicated that LT had a greater improvement in daytime sleepiness than controls for patients with more severe symptoms, with a small to moderate effect size (MD = –1.81; 95% CI, −3.37 to −0.25, $P = 0.020$) [Supplementary Figure 4D, http://links.lww.com/CM9/A798]. Two trials evaluated the effect of LT on the fatigue symptom.[4,5] Results of a fixed effect model of the two studies indicate that LT did not significantly improve fatigue compared with control groups (SMD = −0.15; 95% CI, −0.64 to 0.35, $P = 0.560$) [Supplementary Figure 4E, http://links.lww.com/CM9/A798]. QoL was evaluated in three studies. The pooled SMD was 0.07 (95% CI, −0.29 to 0.42; $P = 0.710$) for QoL indicating no significant difference between LT and control conditions [Supplementary Figure 4F, http://links.lww.com/CM9/A798]. Data for the adverse effect of LT were available for all trials. The pooled OR was 2.27 (95% CI, 1.02 to 5.06; $P = 0.044$) for adverse effect, indicating that the incidence of adverse events was higher in the LT groups than in the control groups [Supplementary Figure 5, http://links.lww.com/CM9/A798]. The adverse events reported in these studies included eyestrain, itchy eyes, headache, gastrointestinal complaints, and feeling of general malaise.

LT as a novel alternative treatment for PD has a potential application prospect. However, only a few RCTs assessed the efficacy of LT on PD. To our knowledge, this is the first systematic review and meta-analysis to address the effect of LT in the management of PD. For the analysis, we did not find any significant difference in motor function, depression, daytime sleepiness, fatigue, and QoL between LT and controls. However, when we only pooled the participants with ESS scores > 10 for analysis, we found a significant improvement of ESS by 1.81 points. It has been previously reported that the minimal clinically relevant difference (MCRD) of the ESS lies between −2 and −3.[8] Our effect size is approaching the MCRD. Thus, we considered it of potential clinical importance, which means that the evidence of LT to improve daytime sleepiness in patients with ESS scores > 10 (severe daytime sleepiness symptom) might be put in a real clinical situation. Although our meta-analysis indicated a significant improvement in self-rated sleep quality with a medium effect size, the result was based on only two studies and needs more validation.

There are several main limitations to this review. First, the trials included had a small sample size and were conducted in a single center. Second, only a few symptoms of PD have been studied and there are still a lot of symptoms that have not been assessed by the RCTs included. These symptoms include autonomic dysfunction (e.g., orthostatic hypotension, constipation, sweating dysfunction, and erectile dysfunction), sensory abnormalities (e.g., olfactory dysfunction, pain, paresthesia, and akathisia), and cognitive and neurobehavioral abnormalities (cognitive decline, apathy, anxiety, and hallucinations). Third, long-term impact of LT on PD was not investigated based on the current evidence.

In conclusion, our findings suggest that LT might be of value specifically to treat PD patients with severe daytime sleepiness symptom (ESS > 10) or be used to improve the sleep quality of PD. LT might be of value specifically to treat PD patients with more severe daytime sleepiness associated with poor sleep quality. In addition, although we found that LT had a higher incidence of adverse effects than the controls, the adverse effect was mild and transitory. We consider LT as a safe treatment for PD patients. There is a need for a multi-center study to confirm the suggested potential benefits here of LT in PD.

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Conflicts of interest

None.

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