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Original Article

# The efficacy and safety of rotigotine transdermal patch for the treatment of sleep disorders in Parkinson's disease: a meta-analysis

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ABSTRACT

*Objectives:* Sleep disturbances are one of the most common non-motor symptoms in Parkinson's disease (PD), and more frequently in advancing stage, almost 67–78.6% of PD patients experience some form of sleep disturbance [1–3]. Our objective is to conduct a meta-analysis of randomized controlled trials to demonstrate the efficacy and safety of rotigotine (RTG) transdermal patch for the treatment of sleep disorder in PD.

*Methods:* RevMan5.3 from the Cochrane Library was used to conduct a meta-analysis, primary outcome measure was score of sleep scale in Parkinson's Disease, the mean change in scores of each subscale was treated as a continuous variable and the weighted mean difference (WMD) was calculated as the difference between the mean scale of sleep score in the treatment and control groups.

*Results:* A total of five studies were included, and primary outcome measured by "PDSS" or "PDSS-2" score revealed a significant improvement in RTG treated patients compared to control [WMD: −6.66, 95% CI: (−8.54, −4.79), $p < 0.0001$], after the removal of two articles with high heterogeneity, the meta-analysis conclusion remained robust to methodological changes [WMD −3.90, 95%CI (−6.11, −1.69), $p = 0.0005$] and distinctly decreased heterogeneity was shown in the final result ($I^2 = 7\%$).

*Conclusions:* As for the safety of RTG, it is well tolerated and safe [WMD: 1.68, 95%CI: (1.33, 2.13), $p < 0.0001$], application site reaction and nausea are among the most frequent side effects.

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## 1. Introduction

Sleep disturbances are one of the most common non-motor symptoms in Parkinson's disease (PD), and more frequently in advancing stage, almost 67–78.6% of PD patients experience some form of sleep disturbance [1–3]. Sleep disorders that plague PD patients may be classified into two categories: nocturnal sleep disorders and daytime manifestation. Not only sleep fragmentation, rapid eye movement sleep behavior disorder (RBD), restless legs syndrome (RLS) during night, but also excessive sleepiness during daytime, have possible severe impact on quality of life (QoL) [4] in PD patients.

Rotigotine (RTG) transdermal patch [5] is a non-ergot dopamine receptor agonist delivered via a silicone-based transdermal patch. RTG shows high affinity binding with D3, D2 and D1 receptors, about 20-fold higher selectivity for D3 than D2 receptor, greater than 100-fold selectivity for D3 over D1 receptor (rank order: D3>D2L > D1 = D5). Besides its dopaminergic stimulation, RTG has agonistic activity at 5-TH1A receptors [6]. With once-daily application, the patch matrix not only provides continuous plasma drug levels at steady state over 24 h, but also maintains non-fluctuating striatal dopamine-receptor stimulation. As far as we know, though there has been an increased medication frequency, routine oral medication can hardly provide steady drug levels. Over time, PD patients develop complications of motor fluctuations and dyskinesia that are related partly due to pulsatile stimulation and erratic gastric emptying. Currently, clinicians have increasingly focused on exploration of new dosage form in PD. It has reported levodopa-carbidopa intestinal gel (LC-IG) [7] may reduce troublesome dyskinesia in advanced Parkinson's disease, however, LC-IG administered to the upper intestine via a percutaneous endoscopic gastrojejunostomy (PEG-J) tube and portable infusion pump, is invasive and too expensive to bear the cost. In contrast, RTG transdermal patch is non-invasive and affordable.

The efficacy and safety of RTG transdermal system for the treatment of early [8,9] to advanced [10–12] PD patients have been proved in both experiment on animals and Randomized Controlled

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**Abbreviation**

| | |
|---|---|
| RTG | Rotigotine transdermal patch |
| WMD | Weighted mean difference |
| CI | Confidential interval |
| PD | Parkinson's disease |
| RBD | Rapid eye movement sleep behavior disorder |
| RLS | Restless legs syndrome |
| QoL | Quality of life |
| LC-IG | Levodopa-carbidopa intestinal gel |
| PEG-J | Percutaneous endoscopic gastrojejunostomy |
| MeSH | The Medical Subject Headings |
| PDSS | Parkinson's Diseases Sleep Scale |
| PDSS-2 | Score or the modified Parkinson's Diseases Sleep Scale |
| ESS | Epworth Sleepiness Scale |
| PSQI | Pittsburgh Sleep Quality Index |
| RCTs | Randomized Controlled Trials |
| DAs | Dopaminergic Agonists |
| NMSS | Non-motor symptoms score |
| H&Y | Hoehn & Yahr |
| SD | Standard deviation |

Trials on PD patients. A continuous dopaminergic stimulation improves both diurnal and nocturnal motor disability, and exert a positive effect on nocturnal sleep quality.

## 2. Methods

### 2.1. Data source

A systematic literature search of from Pubmed, MEDLINE, EMBASE, Cochrane Library, Web of Science was conducted through April 2018. A search strategy was conducted through using the Medical Subject Headings (MeSH) and their related uncontrolled terms from entry terms in PubMed and other literature: “RTG”, “sleep”, “sleep disorders”, in combination with “Parkinson's disease”, “randomized controlled trials”. In addition, a manual search of references from reports of clinical trials or review articles was performed to identify additional relevant trials.

### 2.2. Study selection

Trials were included in the analysis if they were randomized, controlled trials of RTG on the treatment of sleep disorders in PD that:

(1) reported Randomized Controlled Trials of RTG on the treatment of sleep disorders in early or advanced PD since 2000;
(2) reported efficacy data in the form of the Parkinson's Diseases Sleep Scale (PDSS) score or the modified Parkinson's Diseases Sleep Scale (PDSS-2);
(3) all the objects of study up to the UK Brain Bank Criteria of idiopathic Parkinson's disease with Hoehn & Yahr Stage of 1–4;
(4) reported with stable treatment with levodopa and stable doses of any concomitant antiparkinsonian medication for at least four weeks before enrollment;
(5) reported withdrawal due to adverse events, protocol violation, unsatisfactory therapeutic effect, or broken consent, loss of follow-up and other unexpected reasons;

We excluded trials that:

(1) reported the sleep status in other form of Epworth Sleepiness Scale (ESS), Pittsburgh Sleep Quality Index (PSQI), the “sleep/fatigue” item of NMSS score;
(2) reported observational studies, single-arm, open-label, post hoc analysis of RCTs. the most recent publication was selected for analysis although the previous results were reviewed for the missing data where applicable. Safety and tolerability were assessed by evaluating the incidence of commonly reported adverse events including somnolence, dizziness, hallucinations, nausea, vomiting and hypotension.

### 2.3. Validity assessment

Cochrane Collaboration's tool for assessing risk of bias [13] was used to assess the methodological quality of the included quality of the included trials. The items on the list were divided into seven areas:

(1) generation of the allocation sequence;
(2) concealment of the allocation sequence;
(3) blinding;
(4) attrition and exclusions;
(5) other generic sources of bias;
(6) biases specific to the trial design (eg, crossover or cluster randomized trial);
(7) biases that might be specific to a clinical specialty.

We follow the protocol above to evaluate the RCTs included, two investigators independently evaluated all trials with disagreement settled by consensus or by discussion with a third investigator.

### 2.4. Data abstraction

By means of a standardized data abstraction Excel form, one investigator did the first review and collected the data, the secondary researcher repeated validity. The following information was acquired in the each trial: author identification, year of publication, and methodological quality (based on the Cochrane collaboration's tool criteria), study population (including study inclusion criteria, and severity of disease at baseline), sample size, duration of patient follow-up, agent and dose utilized, treatment of early- or late-stage disease, baseline of PDSS, PDSS-2, incidence of adverse drug events (such as application reaction, somnolence, dizziness, hallucinations, nausea, vomiting, and hypotension).

### 2.5. Statistical analysis

We combined the results of each trial by using standard meta-analytic methods to estimate the overall treatment effect. We classified trials with regards to the randomized treatment comparison: RTG versus placebo; RTG versus pramipexole, RTG versus ropinirole.

RevMan5.3 from the Cochrane Library was used to conduct a meta-analysis, primary outcome measure was score of sleep scale in Parkinson's Disease, and scores of two main subscales: Parkinson's Disease Sleep Scale (PDSS), modified Parkinson's Disease Sleep Scale (PDSS-2), the mean change in scores of each subscale was treated as a continuous variable and the weighted mean difference (WMD) was calculated as the difference between the mean scale of sleep score in the treatment and control groups. If there only existed low heterogeneity ($I^2$ <0.5, p>0.10) among all included trials, fixed effect model was used; If there existed high heterogeneity ($I^2$ > 0.5, p < 0.10), random effect model was used to calculate

the WMD and its 95% confidence interval (CI), and it is necessary for us to find the source of heterogeneity. For trials in which mean difference or standard deviation (SD) change between groups were not reported separately for each group, we calculated a pooled estimate for difference in means was calculated by DerSimonian–Laird random-effects model. A two-sided p-value <0.05 was considered statistically significant.

## 3. Result

### 3.1. Study identification and selection

Through the nationwide and worldwide Database, 100 potential literature citations were included in our research. In sum, 21 studies were left for full-text reviewing after exclusion of irrelevant articles. Of these, 11 did not belong to Randomized Controlled Trials (RCTs): four post hoc analysis of RECOVER, four single-arm studies, three observational studies; two RCTs belonged to conference paper without full text; two reviews, and one mainly focused on the Restless Legs Syndrome (RLS). Thus, we identified five eligible articles, the flow chart describing selection procedure of the trials is showed in Fig. 1.

Evaluation of risk biases were listed in Fig. 2, Fig. 3.

### 3.2. Basic characteristics of the selected studies

In total, 1187 patients were included in five studies [11,14–17]. Of those, 546 were in the RTG group, 274 in the placebo, 201 in the pramipexole group, and 166 in the ropinirole group. The basic characteristics and methodology of the selected studies are summarized in Table 1. Patients' age ranged from 50.1 to 78.2 years old. Duration of disease since PD diagnosis ranged from less than one year to 15.5 years, duration of treatment consisted of the screening, titration and maintenance, ranging from five weeks to 29 weeks.

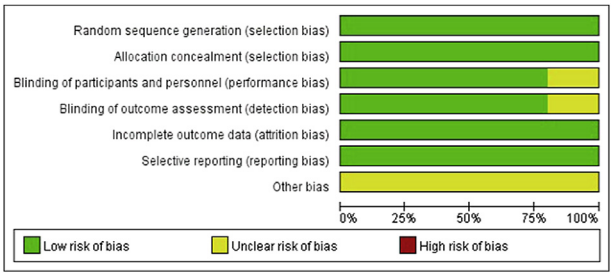


**Fig. 2.** Risk of bias graph. (Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies).

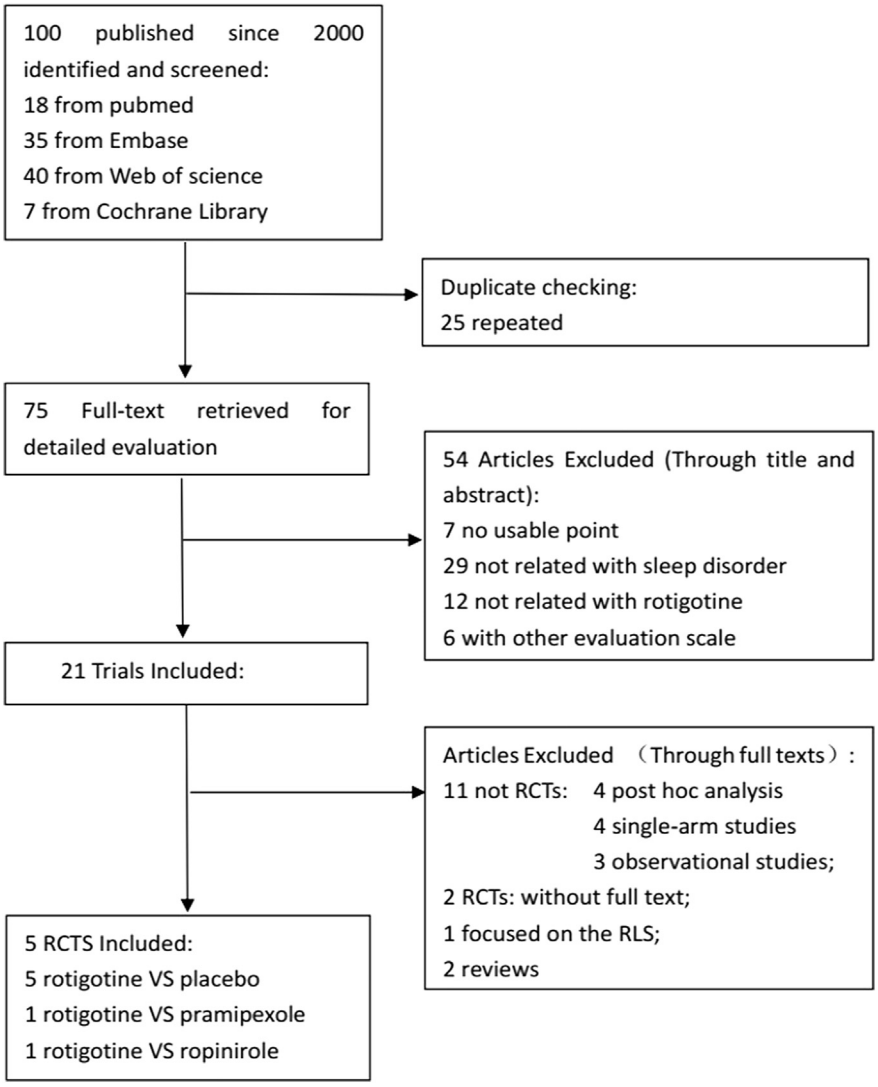


**Fig. 1.** Flow diagram of trial identification, inclusion and exclusion. (RCTs: Randomized Controlled Trials; RLS: Restless Legs Syndrome).

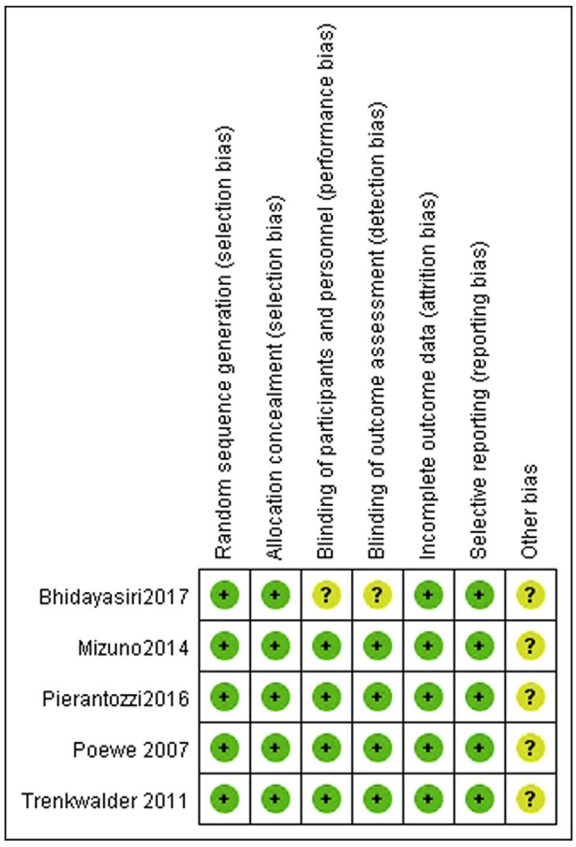


**Fig. 3.** Risk of bias summary graph. (Risk of bias summary: review authors' judgements about each risk of bias item for each included study).

### 3.3. Quantitative data synthesis

#### 3.3.1. Treatment effect of RTG in sleep scale score

*3.3.1.1. RTG transdermal patch vs placebo.* A total of five trials (n = 820) evaluated RTG versus placebo [11,14–17]. In all five RCTs, patients had a greater response to RTG than patients who received placebo as evidenced by a significantly greater reduction in their PDSS, PDSS-2. [WMD: −6.66, 95% CI: (−8.54, −4.79), p < 0.0001]. However, heterogeneity was very high among included studies ($I^2$ = 87%), furthermore, we conducted a heterogeneity assessment to find the source of heterogeneity.

*3.3.1.2. RTG transdermal patch vs other dopaminergic agonists (DAs).* Not many RCTs could be found to compare RTG with other DAs, only two RCTs [11,17] were investigated, and two oral dopamine agonists: pramipexole, ropinirole were respectively compared with RTG. RTG and pramipexole were similarly efficacious and both treatments were better than placebo, mean improvement (SD) on the PDSS score were 4.9 [19.3] for pramipexole, and 4.3[21.1] for RTG, −2.8[21.6] for placebo. Compared with other DAs, RTG was not inferior to ropinirole, mean improvement on the PDSS-2 score [3.0 (19.3) for ropinirole, and 3.7(21.1) for RTG].

#### 3.3.2. Assessment of heterogeneity

Three main factors: clinical heterogeneity, methodological heterogeneity, and statistical heterogeneity contributed to the source of heterogeneity. Different evaluation method, race, region, statistical analysis, and quality of literature may lead to great heterogeneity. At the very beginning, different evaluation methods were discussed, and divided into three subgroups to evaluate. However,

**Table 1**
Basic characteristic of selected studies.

| Author (Year) | patients n | Mean age (SD), Y | | Mean Dosage/Duration | Duration of Disease, y | | Baseline mean (SD) sleep score | | Randomized comparison |
|---|---|---|---|---|---|---|---|---|---|
| | | Rotigotine | placebo | | Rotigotine | placebo | Rotigotine | placebo | |
| Bhidayasiri [14] (2017) | 34 | 60.6 (9.5) | 63.5 (12.5) | 10.46 ± 4.63 mg/24 h 9–16 w | 9.5 (6.0) | 8.3 (5.1) | PDSS-2: 23.7 (11.4) | 20.2 (8.1) | Rotigotine vs placebo |
| Pierantozzi [15] (2016) | 42 | 63.28 (2.98) | 64.04 (2.90) | 9.14 ± 1.85 mg/24 h 12–20 w | 4.13 (0.3) | 4.28 (0.26) | PDSS: 85.19 (10.28) | 84.43 (7.49) | Rotigotine vs placebo |
| Trenkwalder [11] (2011) | 265 | 64.8 (9.3) | 64.4 (10.6) | 16 mg/24 h($Dose_{max}$) 5–12 w | 4.6 (4.2) | 4.9 (4.6) | PDSS-2: 19.3 (9.3) | 20.5 (10.4) | Rotigotine vs placebo |
| Poewe [17] (2007) | 305 | 64.3 (9.0) | 65.0 (10.0) | 12.95 ± 3.54 mg/24 h 20–28 w | 8.4 (4.7) | 8.5 (5.0) | PDSS: | NA | Rotigotine vs placebo |
| Poewe(2) [17] (2007) | 405 | 64.3 (9.0) | 63.2 (9.7) | 12.95 ± 3.54 mg/24 h 20–28 w | 8.4 (4.7) | 8.5 (5.0) | PDSS: | NA | Rotigotine vs pramipexole |
| Mizuno [18] (2014) | 248 | 64.8 (8.8) | 65.3 (7.9) | 12.9 mg/24 h 20 w | 7.0 (4.9) | 7.0 (4.2) | PDSS-2: 12.3 (8.9) | 15.0 (9.2) | Rotigotine vs placebo |
| Mizuno(2) [18] (2014) | 330 | 64.8 (8.8) | 67.0 (7.9) | 12.9 mg/24 h 20 w | 7.0 (4.9) | 6.8 (4.2) | PDSS-2: 12.3 (8.9) | 14.3 (9.2) | Rotigotine vs ropinirole |

PDSS: Parkinson's Disease Sleep Scale; PDSS-2: modified Parkinson's Disease Sleep Scale; NMSS: Non-Motor Symptom Scale.
NA: not available,"Poewe (2)" refers to "rotigotine vs pramipexole", which is used to differentiate from "Poewe"; "Mizuno (2)" refers to "rotigotine vs ropinirole", which is used to differentiate from "Mizuno".

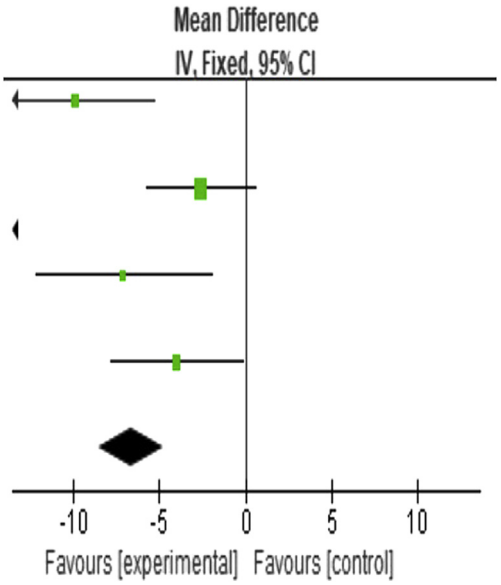


**Fig. 4.** Forest plot with five trials.

each group still with not low heterogeneity shown in the following forest plots (Fig. 4), which revealed that different evaluation methods was not to blame for the high heterogeneity.

Sensitivity analysis was performed using the leave one-out approach. Two studies [14,15] had impact on the pooled results of total sleep scores comparison in the RTG versus control, after the removal of them, the meta-analysis conclusion remained robust to methodological changes [WMD −3.90, 95%CI (−6.11, −1.69), p = 0.0005] and distinctly decreased heterogeneity was shown in the final result ($I^2$ = 7%), which was shown in Fig. 5.

Both of two removed studies were evaluated for a second time according to.

Cochrane collaboration's tool for risk of bias. The trial [14] from Thailand published in 2017 can hardly meet the good quality RCT without blinding and had different inclusion criteria and aim of study to evaluate nocturnal mobility.

Patients with nocturnal hypokinesia (defined as a score of one on item nine of the PDSS-2) were recruited to this study, but other included trials without this limitation. Another trial [15] from Italy published in 2016 was a good-quality RCT, but utilized an unconventional protocol that either patch was maintained from 18:00 h to awakening, not maintained for 24 h, which was different from other included trials.

### 3.3.3. Adverse events

Upon meta-analysis of tolerability endpoints, the use of RTG was associated with higher odds of experiencing adverse events [WMD 1.68, 95%CI: (1.33, 2.13), p < 0.0001] as compared with placebo shown in Fig. 6. Application site reaction, nausea, somnolence, headache were listed in Table 2 to evaluate the incidence of these four adverse events, higher incidence of application site reaction and nausea happened in the RTG compared to placebo, p value proved the statistical significance. Adverse events, such as somnolence, dizziness, and headache showed no significant correlation with use of RTG and still need more sample size to verify.

## 4. Discussion

This is the first meta-analysis provides substantiation for the use of RTG to improve sleep disorder in Parkinson's disease. Five randomized clinical trials with seven comparisons were included in accordance with the guideline of Cochrane Handbook for systematic reviews of interventions. Through subgroup and sensitivity analysis, one RCT with different inclusion standard and one RCT with unconventional treatment of RTG were removed, the final meta-analysis made up of the remaining three RCTs and five comparisons demonstrates that patients receiving RTG transdermal patch exhibit significant improvement in their sleep symptoms RTG is the only one dopamine receptor agonist that has been approved by FDA as transdermal patch. With once-daily application, the patch matrix provides continuous, non-fluctuating plasma drug levels at steady state. RTG is considered to improve sleep disorders in Parkinson disease by improving fluctuation of motor symptom and non-motor symptoms.

The efficacy of RTG for the treatment of the motor symptoms of PD has been established in several published clinical trials [14,16]. RECOVER trial [16], as the first large-scale, double blind trial to evaluate early morning motor symptom and sleep in PD, showed

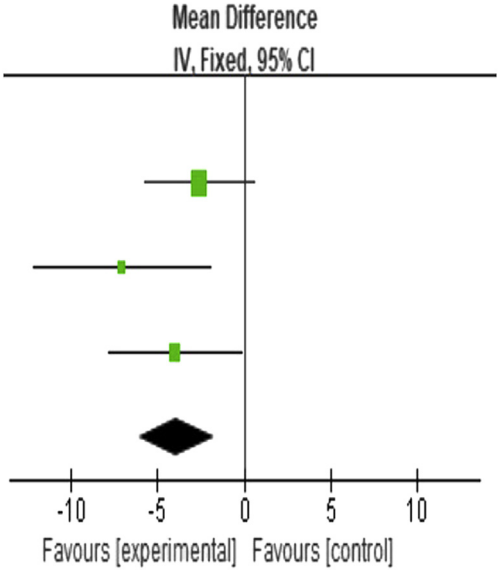


**Fig. 5.** Modified forest plot with three trials.

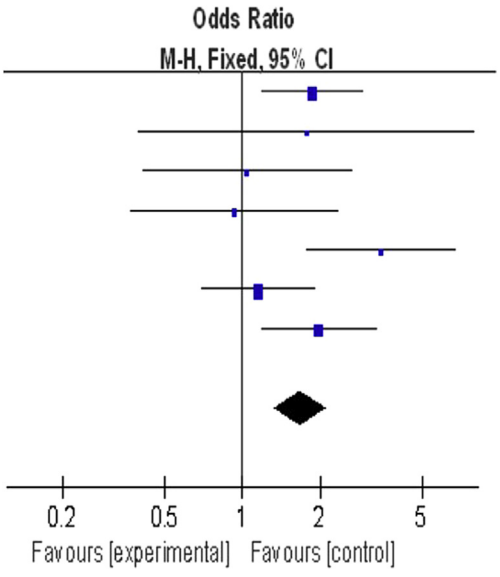


**Fig. 6.** Forest plot of adverse events Table Legend.

**Table 2**
Basic characteristic of adverse events.

| Adverse events | RTG vs placebo | | P value No. of studies |
|---|---|---|---|
| | No. of studies | Odd Ratio (95% Confidence Interval) | |
| Application site reaction | 7 | 3.54 [2.44, 5.15] | $p < 0.00001$ |
| Nausea | 7 | 1.76 [1.21, 2.55] | $p = 0.003$ |
| Somnolence | 5 | 1.48 [0.89, 2.46] | $p = 0.13$ |
| Dizziness | 3 | 1.32 [0.76, 2.28] | $p = 0.33$ |
| Headache | 5 | 0.95 [0.55, 1.64] | $p = 0.86$ |

great improvement in the RTG group on 10 items, particularly "difficulty falling asleep," "urge to move arms or legs," and "uncomfortable and immobile". One post hoc analysis of RECOVER trial [18] demonstrated low to moderate correlation between the early motor symptoms and nocturnal sleep disorders through r value (Pearson Correlation Coefficient) and t-test in the UPDRS Part III score and PDSS-2 score. Another RCT [14] from Thailand confirmed the results of RECOVER study and showed distinct improvement in nocturnal hypokinesia than placebo group by increasing the number ($p < 0.001$) and the degree of turning in bed, which, to some extent, revealed the reduction of nocturnal motor disability may benefit sleep quality. Positive change also can be seen in the non-motor symptoms score (NMSS), especially in the domains of "sleep/fatigue" [19] and "mood/apathy" [20]. The double-blind trial [20] (NCT01300819), included 211 rotigotine and 122 placebo in the full analysis set, "mood/apathy" domain was detected significantly improvement in the RTG group ($p < 0.05$). One multicenter, double-blind, placebo-controlled study [19] provided meaningful improvement in "sleep/fatigue" item either in the low-dose or high-dose RTG group [mean reduction (SD) (0.9)(7.3) for placebo, (−3.0)(7.3) for low dose RTG, (−3.5)(6.5) for high dose RTG], though it didn't improve PD-related apathy in the patient-rated Apathy score ($p = 0.859$).

It is still unclear what mechanism these improvements are based on, either a indirect improvement of daytime and nocturnal motor symptoms (akinesia or dystonia), or a direct effect of RTG on certain sleep mechanism [18].

## 5. Conclusion

With once-daily application, the patch matrix of rotigotine provides continuous, non-fluctuating plasma drug levels at steady state. It has proved in our meta that RTG exerts a positive effect on sleep disorders in Parkinson's disease, with good safety and tolerability.

## Data availability

The data that support the findings of this study are available from pubmed, MEDLINE, EMBASE, Cochrane Library, Web of Science.

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This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Author contribution

Zheng-Tong Ding and Lu Fei conceived and designed the study, Lu Fei, Dao Zhou searched the database and reviewed all the included articles, then discussed and decided which articles to be left. The final decision was made by the corresponding author, Zheng-Tong Ding.

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## Conflict of interest

The authors declare that there are no competing interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.002.

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