Rotigotine in the Treatment of Primary Restless Legs Syndrome: A Meta-analysis of Randomized Placebo-controlled Trials

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Summary: The aim of this study was to summarize the efficacy and tolerability of rotigotine in the treatment of primary restless legs syndrome (RLS). PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for English-language randomized controlled trials (RCTs) that assessed the effectiveness of rotigotine for RLS. The pooled mean change from baseline in International RLS (IRLS) Study Group Rating Scalescore and relative risk (RR) of response based on the Clinical Global Impression-Improvement (CGI-I) scale score were applied to evaluate the outcomes. The pooled proportions of adverse events (AEs) were also estimated. Six RCTs were included. The meta-analysis showed a favorable effectiveness of rotigotine *versus* placebo on RLS [mean change on IRLS score: mean difference (MD)=–4.80; 95% confidence interval (CI): –5.90 to –3.70; $P<0.00001$ and RR of response on CGI-I was 2.19; 95% CI: 1.86 to 2.58, $P<0.00001$]. The most common AEs were application site reactions, nausea, headache and fatigue. In general, rotigotine was well-tolerated in patients with primary RLS. Based on the findings from the meta-analysis, rotigotine was more significantly efficacious in the treatment of RLS than placebo. Nevertheless, long-term studies and more evidence of comparisons of rotigotine with other dopamine agonists are needed.

Key words: restless legs syndrome; rotigotine; dopamine agonist

Restless legs syndrome (RLS) is characterized by an irresistible urge to move the limbs to stop uncomfortable or odd sensations, such as burning sensation, itching, tickling or feeling of bug creeping, especially in the evening. It commonly affects the legs but also might affect the arms or torso[1]. Diagnosis of RLS is based on 4 essential clinical criteria revised by the International RLS (IRLS) Study Group[2]. RLS has been classified into primary form (without apparent causes) and secondary form (associated with pregnancy, uremia, iron deficiency, anemia, etc). The prevalence of RLS in western countries has been reported to range from 3% to 10% of the general population, while population studies in Asian countries indicate a lower prevalence[3–5]. For secondary RLS, underlying disease should be treated at first. Dopaminergic agents have been used for the treatment of RLS for a long time. Because of the side effects of levodopa, as augmentation[6], dopamine agonists (DAs) are currently considered to be an appropriate option for daily RLS treatment[7].

Rotigotine is a lipid-soluble dopamine receptor agonist, which is incorporated into a silicone-based transdermal patch that may provide a more constant drug delivery in comparison with oral administration. It is able to establish a stable plasma drug concentration during a 24-h period. It has already been proven effective in the treatment of early and advanced Parkinson's disease and has been approved for treatment of the signs and symptoms of early Parkinson's disease in the USA and Europe. But it has not been approved in China and other Asian countries. Recently, the use of rotigotine for the treatment of RLS has been assessed in numerous randomized controlled trials (RCTs)[8, 9]. We conducted a meta-analysis in order to summarize the study results in terms of efficacy and tolerability to inform the clinical management of RLS.

1 MATERIALS AND METHODS

1.1 Search Strategy

The databases EMDLINE, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for the English language articles using key words of "rotigotine" and "restless legs syndrome". The results of the search in each of the three databases were placed in a bibliography tool. The results were sifted by two reviewers (Ding and Fan) independently blinded to the authors and journals of publication. In case of disagreement between the two reviewers, a third reviewer was invited for final decision (Chen).

1.2 Inclusion Criteria

We conducted this study according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[10]. Studies were included if they met the following criteria: (1) they were double-blind, randomized, placebo-controlled trials; (2) the participants were >18 years old, fulfilled the essential

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diagnosis criteria of International Restless Legs Syndrome Study Group (IRLSSG)[9] with baseline scores at least 15 on the IRLS Study Group Rating Scale. Secondary RLS patients were ruled out; (3) the IRLS Study Group rating scale or the Clinical Global Impressions-Improvement (CGI-I) scale was used to evaluate outcomes; (4) >10 participants in each arm were recruited; (5) sufficient information was provided to evaluate treatment effect and its precision as compared with placebo.

1.3 Data Extraction

Data extraction was carried out by two reviewers (Ding and Fan) independently and accuracy was checked by another reviewer (Chen). Data collected included first author, year of publication, study design, study duration, mean age in each treatment and placebo group, sex distribution, ethnicity, disease duration, previous treatment for RLS, dosages of study drugs, proportions of patients in the treatment and placebo groups who completed the study, proportions of patients who were withdrawn, mean changes from baseline in IRLS score, proportions of responders based on CGI-I, and the prevalence of severe and serious AEs.

1.4 Assessment of Study Quality

The Cochrane Collaboration's tool for assessing risk of bias was used for quality assessment of included studies. The grade assessment consists of random sequence generation, allocation concealment, incomplete outcome data, selective outcome reporting, blinding of patients and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Each domain was graded into "low risk of bias", "high risk of bias", or "unclear risk of bias". All of the included studies were of high quality.

1.5 Assessment of Heterogeneity

Heterogeneity between studies was assessed by using Chi-squared test and I^2 statistics. Fixed-effect model was used if the heterogeneity was considered "small" or "moderate" (I^2<0.5). Random-effect model was applied if heterogeneity was considered "substantial" (I^2>0.5). Sensitivity analysis was performed to test the robustness of the results when substantial heterogeneity was detected. Publication bias was assessed by visual inspection of Begg's funnel plot.

1.6 Safety and Tolerability

The most common AEs and withdrawals due to AEs were included in this meta-analysis. The most frequently reported AEs included application site reactions, nausea, fatigue, headache, dizziness, somnolence, and pruritus. Serious AEs were defined as life-threatening hazards, death, or condition requiring medical treatment and hospitalization. Safety analysis was performed with all patients who were treated with at least one dose of study medication.

1.7 Statistical Analysis

The IRLS is a ten item questionnaire scale to measure disease severity of RLS over the previous week, developed by the International RLS Study Group. IRLS responders refer to patients whose IRLS total scores reduced at least 50% from baseline. CGI-I scale is a clinician-administrated 7 point-scale, ranging from "very much improved" to "very much worse", to assess how much the patient's illness has improved or worsened relative to baseline. CGI-I responders are defined as patients rated "much" or "very much improved" on the CGI-I scale. Treatment effect was estimated using IRLS scores and CGI-I outcomes. In each study, the mean (95% CI) change from baseline in IRLS score between the treatment group and placebo group was calculated. Treatment effect based on CGI-I outcome was estimated using the relative risk (RR) (95% CI) of treatment response relative to placebo. Efficacy analysis was performed with all intention to treat population. In this meta-analysis, treatment effects were estimated using the random-effects (RE) pooled $\Delta\mu$ (weighted mean difference between treatment and placebo)[11] and pooled RR (95% CI) was used to evaluate the inverse variance of individual effects[12]. Statistical analysis was performed using Revman 5.0 software (Cochrane, Oxford, UK, available at http://www.cochrane.org).

2 RESULTS

2.1 Search Results

Of 2795 citations (72 in MEDLINE, 2701 in EMBASE and 22 in Cochrane Central Register of Controlled Trials) found by initial search, six parallel RCTs were finally included in the meta-analysis (fig. 1). The included studies were published between 2004 and 2013. The participants in five studies were mostly Caucasians and those in the rest one were Asians. Trials lasted for 1 to 28 weeks using different doses of rotigotine (0.5 mg to 4.5 mg) (table 1).

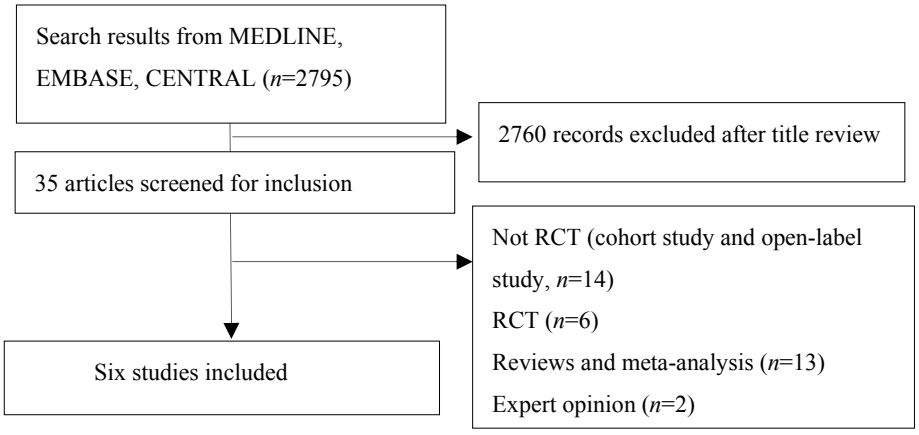

Fig. 1 Search strategy flow chart

Table 1 Baseline characteristics and overview of the included studies

Study	Medication	Safety population	ITT population	Age (*x*±*s*)	Sex (female, %)	Dose (mg)	Duration (week)	Changes of IRLS (*x*±*s*)
Stiasny *et al*[8] 2004	RTG	17	17	59.9±9.3	47.1	1.125	1	–10.5±8.2
	RTG	13	13	54.6±8.4	84.6	2.25	1	–12.3±8.3
	RTG	19	19	58.3±8.7	73.7	4.5	1	–15.7±8.3
	PBO	14	14	60.1±8.5	50.0	–	1	–8.0±8.2
Trenkwalder *et al*[13] 2008	RTG	115	112	57.3±10.1	72.0	1	24	–13.7±9.5
	RTG	112	109	57.3±12.1	75.0	2	24	–16.2±9.4
	RTG	114	112	56.5±12.0	73.0	3	24	–16.8±8.5
	PBO	117	114	59.7±10.0	70.0	–	24	–8.5±9.6
Oertel *et al*[14] 2008	RTG	52	50	58.9±9.9	74.0	0.5	6	–10.5±9.2
	RTG	64	64	57.3±10.7	68.8	1	6	–15.3±10.0
	RTG	49	49	58.4±10.6	57.1	2	6	–15.7±9.5
	RTG	65	64	57.8±10.5	73.4	3	6	–17.3±10.5
	RTG	56	53	59.9±8.6	67.9	4	6	–14.9±10.3
	PBO	55	53	58.5±11.4	60.4	–	6	–9.3±9.5
Oertel *et al*[15] 2010	RTG	46	46	60.8±9.4	76.0	1-3	8	–16.5±9.3
	PBO	21	20	56.3±9.8	70.0	–	8	–9.9±9.9
Hening *et al*[16] 2010	RTG	99	98	53.2±12.7	61.0	0.5	24	–10.9±8.9
	RTG	101	99	51.5±13.1	57.0	1	24	–11.1±9.3
	RTG	99	95	53.2±12.2	64.0	2	24	–13.4±9.2
	RTG	106	103	51.2±12.4	63.0	3	24	–14.3±9.4
	PBO	100	93	52.8±12.6	57.0	–	24	–9.0±7.7
Inoue *et al*[17] 2013	RTG	95	95	50.7±1.3	56.8	2	14	–14.3±8.9
	RTG	94	94	50.9±13.7	48.9	3	14	–14.6±9.0
	PBO	95	95	53.4±15.3	58.6	–	14	–11.6±8.2

IRLS: International Restless Leg Syndrome Study Group Rating Scale; ITT: intent-to-treat; RTG: rotigotine; PBO: placebo

2.2 Efficacy Outcomes

Compared to placebo, the overall mean change in the IRLS score of rotigotine was significantly greater [mean difference (MD)=–4.80; 95% CI: –5.90 to –3.70, I^2=5%; P<0.00001; fig. 2]. Additionally, rotigotine therapy produced statistically higher ORs of CGI-I responder rate (OR=2.19; 95% CI: 1.86 to 2.58; I^2=30%; P<0.00001; fig. 3) than placebo, further confirming its positive therapeutic effect.

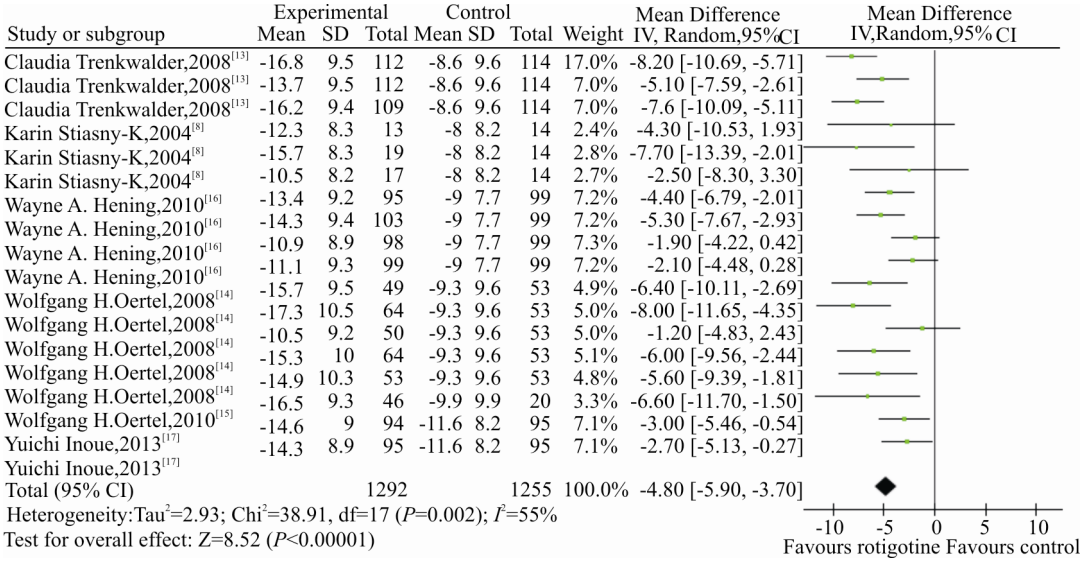

Fig. 2 Mean change of IRLS scores

IRLS: International Restless Leg Syndrome Study Group Rating Scale; ITT: intent-to-treat; SD: standard deviation; CI: confidence interval; IV: inverse variance; df: degree of freedom

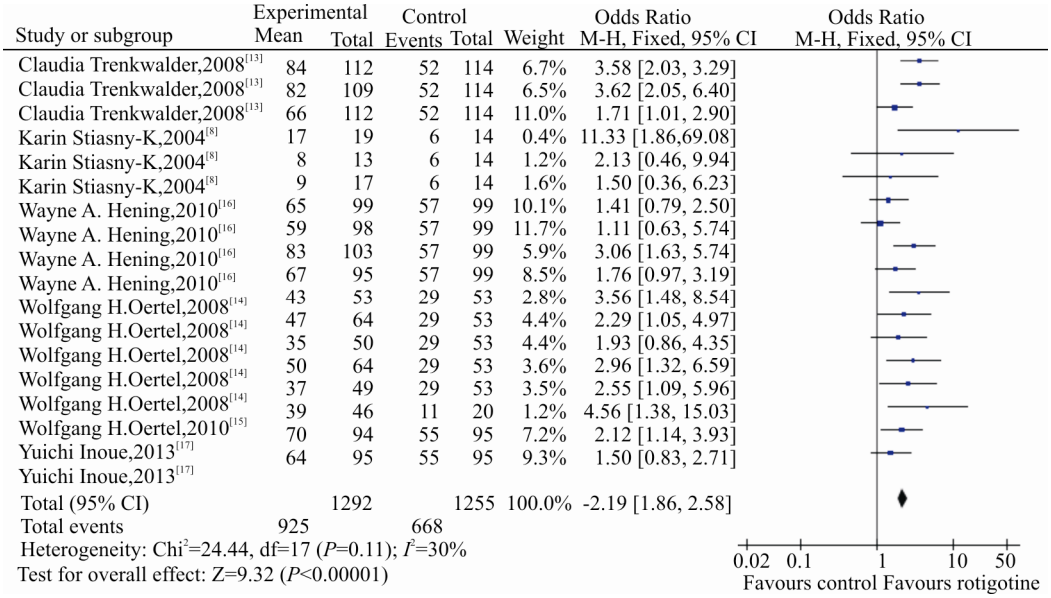

Fig. 3 Comparison of CGI-Iresponder rate

CGI-I: clinical global impressions-improvement; CI: confidence interval; M-H: Mantel-Haenszel method; df: degree of freedom

2.3 Safety Outcomes

As shown in table 2, application-site reaction, nausea, headache, fatigue and pruritus were the most frequent AEs; most were mild or moderate in intensity. In Stiasny-Kolster K's study[8], one patient (who was in the placebo group) was discontinued from the study prematurely, after 4 days of treatment due to an acute psychotic episode; no serious AEs were reported. In Trenkwalder C's trial[13], five patients receiving placebo and 25 patients receiving rotigotine had a serious AE; eight (7%) patients receiving placebo and 54 (16%) receiving rotigotine discontinued prematurely because of AEs. Oertel *et al*[14] reported that three placebo-treated patients and 12 rotigotine-treated patients discontinued prematurely from the trial because of AEs. In another study of Oertel *et al*[15], two subjects treated with rotigotine and one subject treated with placebo were withdrawn from the trial because of AEs. Hening *et al*[16] reported that four placebo subjects and 82 rotigotine subjects discontinued prematurely because of AEs. Generally, AEs were increased with increasing rotigotine dose. As shown in fig. 3, compared with rotigotine, placebo leads to much less AEs (OR=2.51; 95% CI: 1.95 to 3.22; I^2=49%; P<0.00001).

Table 2 Summary of adverse events in RCTs

Adverse events	Stiasny *et al*[8]		Trenkwalder *et al*[13]		Oertel (2008)[14]		Oertel (2010)[15]		Hening *et al*[16]		Inoue *et al*[17]	
	RTG	PBO	RTG	PBO	RTG	PBO	RTG	PBO	RTG	PBO	RTG	PBO
Application site reaction	49	14	145	2	50	1	8	1	109	5	87	7
Nausea	2	2	55	4	52	6	10	1	73	10	87	10
Headache	1	11	43	8	22	4	8	3	47	8	7	0
Fatigue	0	2	37	11	19	5	4	2	27	4	–	–
Dizziness	–	–	18	3	12	4	3	0	21	6	–	–
Pruritus	1	3	–	–	14	1	–	–	22	2	–	–
Dry mouth	–	–	17	4	12	4	–	–	14	4		
Insomnia	1	2	8	4	–	–	3	0	16	2	–	–

RTG: rotigotine; PBO: placebo

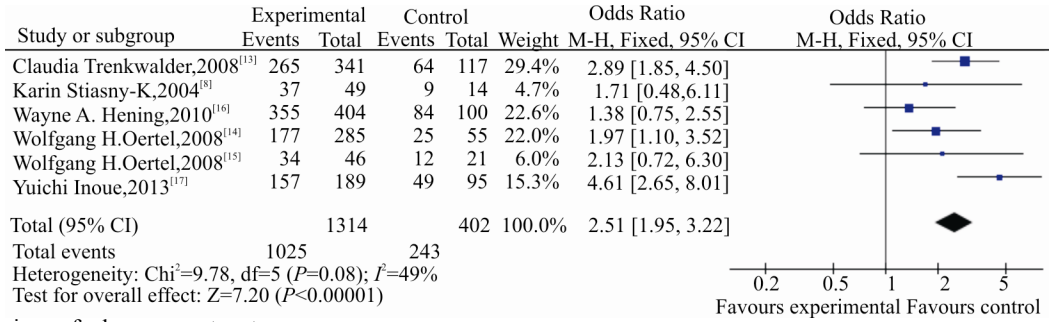

Fig. 4 Comparison of adverse events rate

CI: confidence interval; M-H: Mantel-Haenszel method; df: degree of freedom

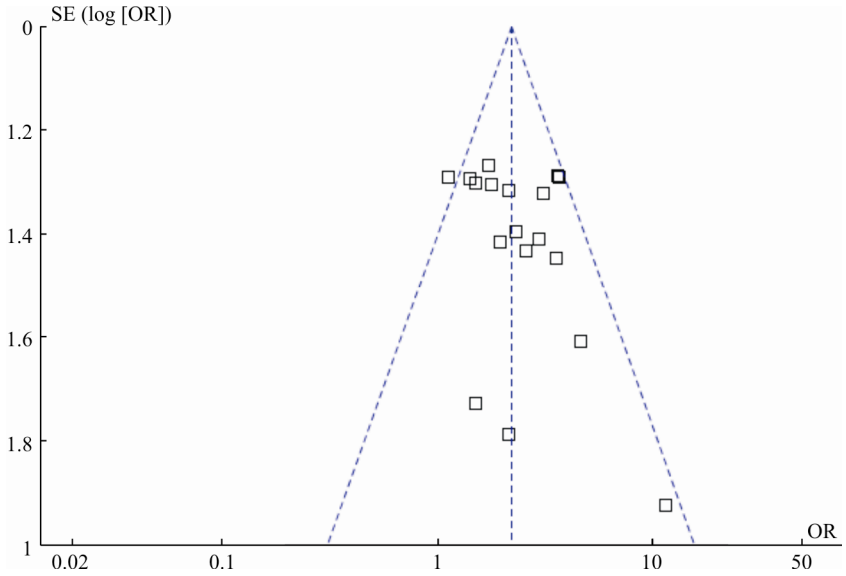

Fig. 5 Begg's funnel plot

SE: standard error; OR: odds ratio

3 DISCUSSION

Rotigotine is a non-ergot dopamine agonist activated through D1 to D5 receptors, and selects serotonergic and adrenergic receptors[18]. Rotigotine is the first dopamine agonist applied transdermally in RLS therapy. It offers a sustained drug release over a 24-h period, avoiding pulsatile release of dopamine agonists to the central nervous system. Since RLS bothers patients most in the evening and periods of rest during the day, the sustained rotigotine release seems to be preferable for RLS patients.

Augmentation is a common complication of dopaminergic treatment of RLS, characterized by the following criteria: compared with baseline, RLS symptoms occur earlier during the whole day, latency to onset of symptoms when at rest is shorter, intensity of symptoms is increased and other body parts may be involved[19]. Augmentation has been related to short plasma half-life because it is most frequently observed with levodopa treatment[20]. It is not yet investigated or theoretically elaborated on whether the continuous delivery of dopaminergics can avoid or reduce dopamine overstimulation in the spinal cord or whether such an application might exert other influences on the dopamine homeostasis. The availability of patch application of dopamine agonists (rotigotine) provides important research tools to understand the pathophysiology of augmentation and RLS itself. At the same time, patches might become an important treatment option for augmented RLS since continuous delivery of the drug reduces daytime symptoms which are characteristic of augmentation.

In advanced stages of Parkinson's disease, one trial showed 8 mg/24 h to 12 mg/24 h rotigotine was effective[21]. Another trial in advanced stages of Parkinson's disease demonstrated an effective dose range up to 16 mg/24 h rotigotine[22]. The dose required for the treatment of RLS patients is far below that required for the treatment of parkinsonian patients. The efficacy of rotigotine in treating RLS was first demonstrated by a study conducted by Stiasny-Kolster and colleagues in 2004[8]. It was a randomized, double-blind, placebo-controlled, multicentre trial that recruited 63 patients affected by moderate-to-severe idiopathic RLS. Three fixed doses of rotigotine (1.125, 2.25 and 4.5 mg) were compared with placebo over a period of 1 week. No dose titration was performed. The primary efficacy measure was the total score on the IRLS, while the RLS-6 and the CGI scales were secondary endpoints. RLS was improved by 10.5, 12.3 and 15.7 points in the IRLS by rotigotine (1.125, 2.25, and 4.5 mg, respectively), whereas the improvement with placebo was 8 points, thus demonstrating a dose-response relationship. In 2008, Oertel and colleagues[14] conducted a randomized, multicentre, double-blind, placebo controlled 6-week trial using higher doses of rotigotine. The study population consisted of severely affected patients with a long history of RLS who had been previously treated with dopaminergic drugs. Subjects received rotigotine patches with fixed doses of 0.5 mg/24 h, 1 mg/24 h, 2 mg/24 h, 3 mg/24 h or 4 mg/24 h. The primary efficacy variable was the change in IRLS total score from baseline to the end of treatment. A monotone dose-response relationship was observed in the dose range from 0.5 mg/24 h to 3 mg/24 h. The 0.5 mg/24 h dose was not statistically significantly superior to placebo. The higher dosage (4 mg/24 h) showed a minor improvement in the IRLS total score over the 3 mg/24 h dosage. Similar results were reported by Hening *et al*[16]. This randomized, double-blinded, placebo-controlled trial assessed efficacy and safety of the dopamine agonist rotigotine in the treatment of idiopathic RLS over a 6-month maintenance period. Participants were randomly assigned to five groups to receive either placebo or rotigotine (0.5, 1, 2, or 3 mg/24 h). Both 0.5 mg/24 h dose and 1 mg/24 h dose did not differ significantly from placebo. The larger proportion of *de novo* subjects in this trial, as well as the inclusion of many less severely affected subjects and the different re-

cruitment methods, might thus account for this difference in trial outcomes. While in Trenkwalder's trial[7], the therapeutic dose window for RLS was established between 1 mg/24 h and 3 mg/24 h rotigotine. In the study conducted in Asian country[17], rotigotine (2 and 3 mg/24 h) was effective without major safety concerns in Japanese patients with RLS.

Rotigotine is the first dopamine agonist applied transdermally in RLS therapy. As expected, application site reactions were reported as common AEs. Most AEs were mild or moderate in intensity. Nausea, vomiting, and somnolence are known to be associated with the pharmacological action of dopaminergic drugs. Among these frequent AEs, nausea was most common in treatment with rotigotine, incidence of AEs was lower in patients treated with rotigotine than in those treated with oral pramipexole[23] and ropinirole[24]. In all these trials, rotigotine was generally well tolerated, with a low withdrawal rate for adverse events.

It is important to note that our findings have several limitations. First, the sample size of studies was generally small. Second, duration of the studies was different. Most of the trials were short term, especially for Stiasny' study[8] which lasted for only 1 week. Third, sex or ethnicity-related differences in baseline risk might influence the summary results.

This meta-analysis gives implications for future research as well. Future studies are needed to explore (1) whether transdermal delivery of low doses of rotigotine (0.5 mg/24 h and 1 mg/24 h) can be used to treat RLS, (2) the maximum dose and the optimal dose for RLS patients.

All studies included in the meta-analysis were high-quality RCTs that might minimize selection and measurement bias. When dealing with missing data, all included trials performed intention-to-treat (ITT) analyses to avoid overoptimistic estimates of the efficacy. By far, polysomography is the only objective way to assess treatment efficacy on RLS, by which parameters such as periodical leg movements and sleep latency can be recorded[25]. However, there was only one trial conducting polysomography[15] and all efficacy outcomes in the meta-analysis were subjective. Results of these subjective rating scales are less accurate and tend to lead to bias. To some degree, this might be an explanation for the substantial heterogeneity of mean change on IRLS score and CGI responder rate.

Because unpublished studies were not included, publication bias could not be completely excluded even though no obvious evidence of such bias was detected (fig. 4).

It is noteworthy that all included studies had a dosage period ranging from 1 to 28 weeks. At present, evidence for long-term efficacy and safety of rotigotine on RLS is still absent. Augmentation, the most serious side-effect of dopaminergic medication, needs to be thoroughly evaluated in future studies. Therefore, long-term studies and observations should be carried out.

Other meta-analysis[26] has demonstrated that dopamine agonists, including cabergoline, lisuride, pergolide, pramipexole, ropinirole and sumanirole, are effective for the treatment of primary RLS as compared with placebo. But the direct dopamine agonist comparison study was rarely performed. Evidence of head-to-head comparisons of rotigotine with other dopamine agonists, anticonvulsants, and levodopa is needed.

Results of this meta-analysis showed a favorable effect of rotigotine *versus* placebo on RLS. Application site reaction, nausea, headache and fatigue were the most common adverse events in patients receiving rotigotine as compared to those receiving placebo; most were mild or moderate in intensity. Serious adverse events were barely reported both in rotigotine group and placebo group. Besides, the incidence of serious adverse events was not significantly correlated with rotigotine, thus rotigotine was well-tolerated in patients with primary RLS.

Conflict of Interest Statement

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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