Safety and Efficacy of Rotigotine for Treating Parkinson's Disease: A Meta-Analysis of Randomised Controlled Trials

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Received, May 16, 2017; Revised, June 14, 2017; Accepted, July 14, 2017; Publishes July 15, 2017.

ABSTRACT - We aimed to comprehensively analyse the safety and efficiency of rotigotine for treating Parkinson's disease (PD). We conducted systematic literature searches of Cochrane library, PubMed and Embase databases up to April 2016, with 'Rotigotine', 'Parkinson Disease ' and 'Parkinson's disease' as key searching terms. Outcomes, including Unified Parkinson's Disease Rating Scale (UPDRS) Part III and Part II scores, 'off' time, adverse events (AEs), serious AEs and discontinuation because of AEs, were compared between rotigotine and placebo groups under a fixed or random effect model. For dichotomous and continuous data, risk ratio (RR) and weighted mean difference with their corresponding 95% confidence intervals (95% CIs) were taken as the effect sizes to calculate merged results. Twelve eligible studies were included. For patients with early or advanced PD, rotigotine could significantly improve UPDRS Part III and Part II scores ($p < 0.001$) and it had significantly higher incidence of AEs than the placebo ($p < 0.001$). Regarding discontinuation because of AEs, rotigotine showed a significant advantage over placebo in patients with early PD, whereas the overall result demonstrated no statistically significant difference between the groups. Rotigotine can improve daily living and motor ability of patients with PD, although it has higher incidence of AEs. Rotigotine might be more appropriate for patients with advanced PD than for those with early PD.

INTRODUCTION

Parkinson's disease (PD), which can be classified into primary or idiopathic, secondary or acquired, hereditary, Parkinson with other syndromes or multiple system degeneration according to its origin, has a great influence on the motor system [1]. Early PD symptoms include rigidity, shaking, difficulty in walking and slowness of movement, with its later symptoms being dementia and depression [2]. The neurodegenerative disorder ranks second only to Alzheimer's disease. In 2013, PD occurs in 5.3 million people and accounted for approximately 103,000 deaths worldwide [3,4]. In addition, the disease is more common in the elderly, with its incidence increasing from 1% in the population over 60 years to 4% in those over 80 years [5].

Although PD cannot be cured, medications, surgery and other treatments can relieve its symptoms [6]. Drugs used for treating associated dyskinesia mainly included opamine agonists (e.g. rotigotine), levodopa and MAO-B inhibitors [7]. Rotigotine, which is delivered by a transdermal patch, is administered once daily; is safe and can improve symptoms, such as motor difficulties, in patients with early PD [8-11]. At the same time, the rotigotine transdermal system may also relieve non-motor symptoms including fatigue, anhedonia, apathy and depression in patients with PD [12]. Jankovic *et al.* demonstrated that the rotigotine transdermal system had clinically relevant and statistically significant efficacy over placebo in patients with early PD and was well-tolerated [13]. Scheller *et al.* found that rotigotine-treated animals exhibited significantly improved symptoms compared with the vehicle-treated ones, suggesting that rotigotine conferred partial protection to the dopamine terminals [14].

In 2013, Zhou *et al.* [15] performed a meta-analysis to explore the safety and efficacy of rotigotine for PD, although they only analysed six studies, with the included reports containing significant heterogeneity. Various outcome indicators, including Unified Parkinson's Disease Rating Scale (UPDRS) Part III and Part II scores,

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'off' time, adverse events (AEs), serious AEs, discontinuation because of AEs, have been used to evaluate the controlling and adverse effects of drugs on PD in clinical studies [16-18]. To comprehensively analyse safety and efficiency of rotigotine for treating PD, we performed a meta-analysis to elucidate the controlling and adverse effects of this drug.

MATERIAL AND METHODS

Search strategy

Studies were performed by comprehensively searching the literature from Cochrane library, PubMed and Embase databases up to April 2016. The key searching terms included 'Rotigotine', 'Parkinson Disease' and 'Parkinson's disease'.

Inclusion and exclusion criteria

Literature searches and screening of titles, abstracts and full texts were performed by two reviewers. Disagreements during literature screening were settled by discussions with a third reviewer. The inclusion criteria for literature selection were as follows: (1) the study was a randomised controlled trial (RCT); (2) patients diagnosed with PD were included in this study; (3) drugs for the experimental and control groups were rotigotine and placebo, respectively; (4) the study included at least one of the following outcome indicators: UPDRS Part III and Part II scores, 'off' time, AEs, serious AEs or discontinuation because of AEs. Studies were excluded if they fulfilled the following criteria: (1) studies were reviews, letters, meeting summaries, etc.; (2) studies had no eligible outcomes and (3) studies had no extractable data.

Data extraction and quality assessment

The following information was extracted and assessed by two independent reviewers: first author's name, publication time, geographic area, medication time, case characteristics, case numbers, patients' ages, drugs for experimental and control groups and outcome indicators. Subsequently, quality assessment was performed for the included RCTs using the Cochrane evaluation system [19]. Data extraction and quality assessment disagreements were also solved by discussions with a third reviewer.

STATISTICAL ANALYSIS

For dichotomous and continuous data, the risk ratio (RR) and weighted mean difference (WMD) with their corresponding 95% confidence intervals (95% CIs) were taken as the effect sizes for calculating merged results. Mean change differences (terminal-baseline) between experimental and control groups were compared. Cochran-based I^2 test and Q test [20] were utilised to detect the heterogeneity among studies. The random effects model was selected when significant heterogeneity was determined ($p < 0.05$, $I^2 > 50\%$), whereas the fixed effects model was applied when homogeneous outcomes were discovered ($p > 0.05$, $I^2 < 50\%$). Further, subgroup analysis was performed according to the types of PD.

Publication bias

Using Egger's test [21], we examined the publication bias in the eligible studies. All statistical analyses were conducted using the STATA 11.0 software (STATA, College Station, TX, USA).

RESULTS

Eligible studies

According to the search strategy, 1305 related studies were selected. After excluding 186 repeated articles, 1119 studies remained. After screening for the title and abstract, another 1095 ineligible studies were excluded and 24 reports remained for further full-text inspection. Seven studies involving RCT-based post-hoc analysis, three studies involving no control groups and two studies with no eligible results were further eliminated. Finally, a total of 12 eligible studies were included in the current meta-analysis [8-10, 13, 22-29]. A detailed flow chart of study selection procedure is shown in Figure 1.

Study characteristics and quality assessments

All of the included studies were double-blind RCTs and were performed in several countries, such as Japan, USA, India and Mexico. Rotigotine was delivered through a transdermal patch in all of the studies. There were no significant differences in baseline indicators, such as age, sex ratio and the disease progression between experimental and control groups (Table 1). As all eligible studies were double-blind RCTs, there was a low risk of bias for implementing blinding. Because some of the included studies did not provide detailed methods for concealing allocation or implementing blinding, the risks of reporting and lost-to-follow-up biases were low. Overall, all the included studies were of moderate to high qualities (Figure 2).

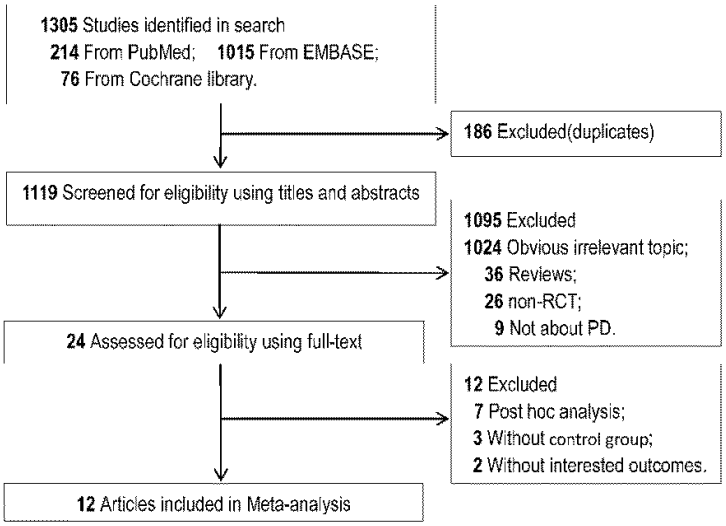
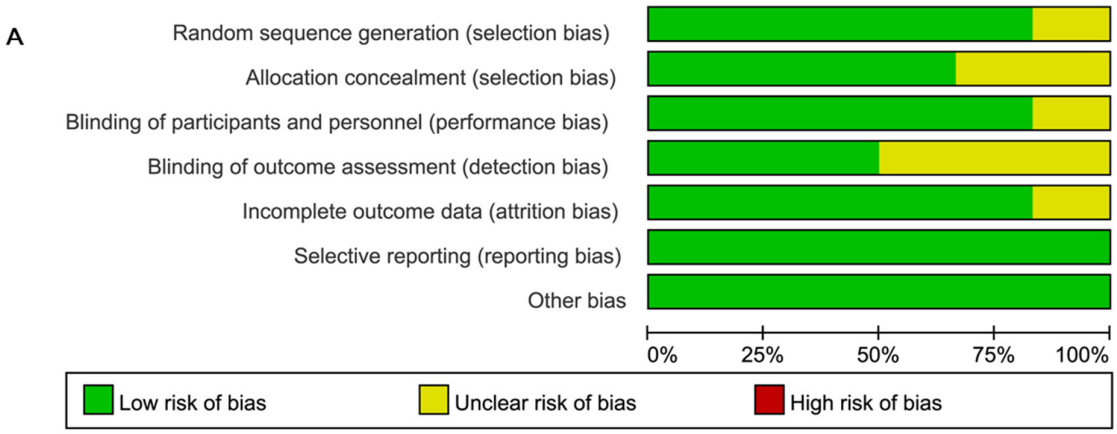


Figure 1. Literature screening flow chart



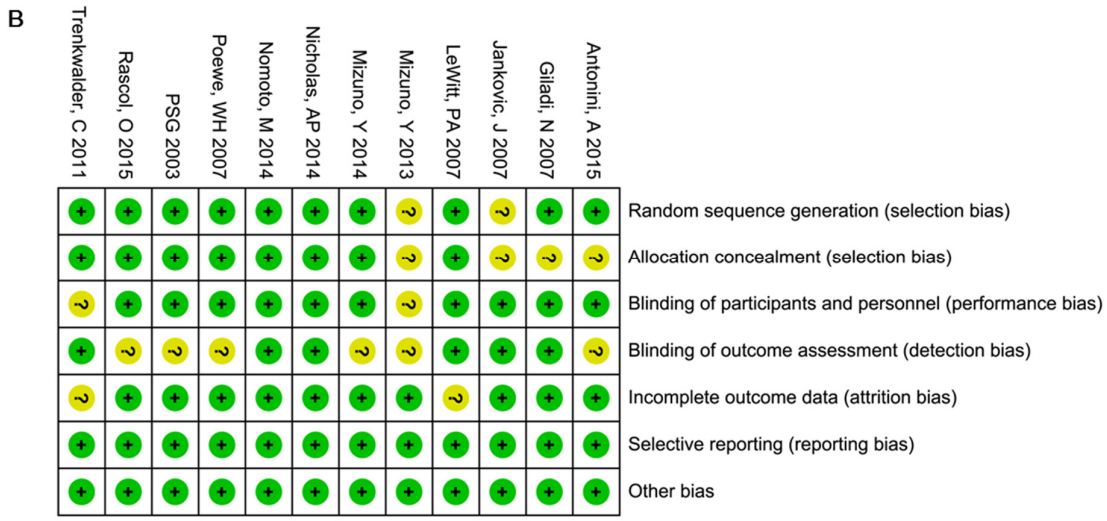


Figure 2. Quality assessments of the included studies - A. Bias risk of the included studies. B. Sensitivity and specificity of the included studies. '+': low risk of bias and '?': unclear risk of bias.

Table 1. Characteristics of the included studies.

Author	year	Country	Stage of PD	duration (weeks)	comparison, n	Participants, M/F, age(ys), duration of PD (ys)	Outcomes
Antonini, A	2015	12 European countries	Mixed PD	12	Rotigotine TP, 224	129/95, 68.0(9.4), 2.8(0, 20.6)	UPDRS Part III, AEs, serious AEs, D-AES
					placebo TP, 125	67/58, 66.6(9.8), 2.2(0, 14.1)	
Rascol, O	2015	Germany, Poland, Slovakia, US	Advanced PD	12	Rotigotine TP, 35	19/16, 66.5(11.9), 5.9(3.5)	AEs, serious AEs, D-AES
					placebo TP, 33	17/16, 65.3(13.8), 5.6(4.7)	
Mizuno, Y	2014	Japan	Advanced PD	16	Rotigotine TP, 168	61/103, 64.8(8.8), 7.0(4.9)	UPDRS Part III, UPDRS Part II, off-time, AEs, serious AEs, D-AES
					placebo TP, 85	42/42, 65.3(7.9), 7.0(4.2)	
Nicholas, AP	2014	US, India, Mexico, Peru, and Chile	Advanced PD	16	Rotigotine TP, 101 a	77/24, 65.4(10.5), 7.51(3.87)	
					Rotigotine TP, 107	79/28, 64.6(9.0), 7.27(3.94)	UPDRS Part III, UPDRS Part II, off-time, AEs, serious AEs, D-AES
					Rotigotine TP, 104	73/31, 64.6(10.4), 7.79(3.92)	
					Rotigotine TP, 94	56/38, 63.2(11.6), 7.49(4.75)	
					placebo TP, 108	74/34, 64.8(10.2), 7.23(3.76)	
Nomoto, M	2014	Japan	Advanced PD	19	Rotigotine TP, 86	34/52, 67.0(6.8), 7.5(6.0)	UPDRS Part III, UPDRS Part II, off-time, AEs, serious AEs, D-AES
					placebo TP, 86	44/42, 66.8(8.3), 5.4(3.0)	
Mizuno, Y	2013	Japan	Early PD	19	Rotigotine TP, 88	33/55, 30-79, 2.0(1.8)	UPDRS Part III, UPDRS Part II, AEs, serious AEs
					placebo TP, 88	37/51, 30-79, 1.8(1.9)	
Trenkwalder, C	2011	12 countries	Mixed PD	12-22	Rotigotine TP, 191	123/68, 64.8(9.3), 4.6(4.2)	UPDRS Part III, UPDRS Part II, AEs, serious AEs, D-AES
					placebo TP, 96	61/35, 64.4(10.6), 4.9(4.6)	
Giladi, N	2007	NA	Early PD	37	Rotigotine TP, 215	118/97, 61.1, 1.4	serious AEs, D-AES
					placebo TP, 118	68/50, 60.4, 1.2	
Jankovic, J	2007	US and Canada	Early PD	24	Rotigotine TP, 181	123/58, 62.0(10.3), 1.3(1.3)	UPDRS Part III, UPDRS Part II, D-AES
					placebo TP, 96	58/38, 64.5(10.7), 1.4(1.3)	

Table 1. Continued…

LeWitt, PA	2007	US and Canada	Advanced PD	12	Rotigotine TP, 120	78/40, 66.5(10.0), 7.7(4.3)	UPDRS Part III, UPDRS Part II, off-time, D-AES
					Rotigotine TP, 111	71/40, 64.5(10.4), 7.8(4.6)	
					placebo TP, 120	74/46, 66.3(9.6), 7.7(4.0)	
					placebo TP, 118	68/50, 60.4, 1.2	
Poewe, WH	2007	77 centres in Europe, South Africa, Australia, and New Zealand	Advanced PD	16	Rotigotine TP, 204	132/69, 64.3(9.0), 8.9(4.4)	UPDRS Part III, UPDRS Part II, off-time, AEs, serious AEs, D-AES
					placebo TP, 101	71/29, 65.0(10.0), 8.5(5.0)	
PSG	2003	NA	Early PD	11	Rotigotine TP, 49	30/19, 61.8(9.8), 1.2(1.4)	UPDRS Part III, UPDRS Part II, serious AEs, D-AES
					Rotigotine TP, 47	36/11, 60.9(8.3), 1.5(2.0)	
					Rotigotine TP, 48	31/17, 61.3(10.9), 1.2(1.0)	
					Rotigotine TP, 51	30/21, 60.5(10.7), 1.1(1.2)	
					placebo TP, 47	23/24, 62.3(10.5), 1.3(1.4)	

US, United States; NA, not available; PD, Parkinson disease; TP, transdermal patch; ys, years; D-AES, discontinuation due to AEs.

Meta-analysis

Curative effect

Comparison of UPDRS Part III scores between rotigotine and placebo groups are shown in Figure 3A. According to the types of PD, patients were classified into advanced, early and mixed PD (both early and advanced PD) subgroups. Results pooled from all subgroups showed statistically significant differences [WMD = −3.63; 95% CI: (−4.49 - −2.76); $p < 0.001$]. Statistically significant differences were also detected in advanced PD [WMD = −4.45; 95% CI: (−6.14 - −2.76); $p < 0.001$], early PD [WMD = −3.13; 95% CI: (−4.00 - −2.26); $p < 0.001$] and mixed PD [WMD = −2.61; 95% CI: (−3.90 - −1.31); $p < 0.001$] subgroups. However, the advanced PD subgroup had significant heterogeneity ($I^2 = 66.4\%$; $p = 0.018$), which was absent in early and mixed PD subgroups ($p > 0.05$, $I^2 < 50\%$).

Similarly, the UPDRS Part II scores between rotigotine and placebo groups were compared and the pooled result was statistically significant [WMD = −1.54; 95% CI: (−2.01 - −1.08); $p < 0.001$]. Differences in advance PD [WMD = −2.04; 95% CI: (−2.60 - −1.48); $p < 0.001$], early PD [WMD = −0.91; 95% CI: (−1.31 - −0.52); $p < 0.001$] and mixed PD [WMD = −1.30; 95% CI: (−2.18 - −0.42); $p = 0.004$] subgroups were also statistically significant. Significant heterogeneity was observed in general and not in the individual subgroups (Figure 3B).

Only patients with advanced PD had the outcome indicator of 'off' time, exhibiting statistically significant differences [WMD = −0.95; 95% CI: (−1.23 - −0.67); $p < 0.001$]. No significant heterogeneity was observed in the advanced PD subgroup ($I^2 = 12.6\%$, $p = 0.333$) (Figure 3C).

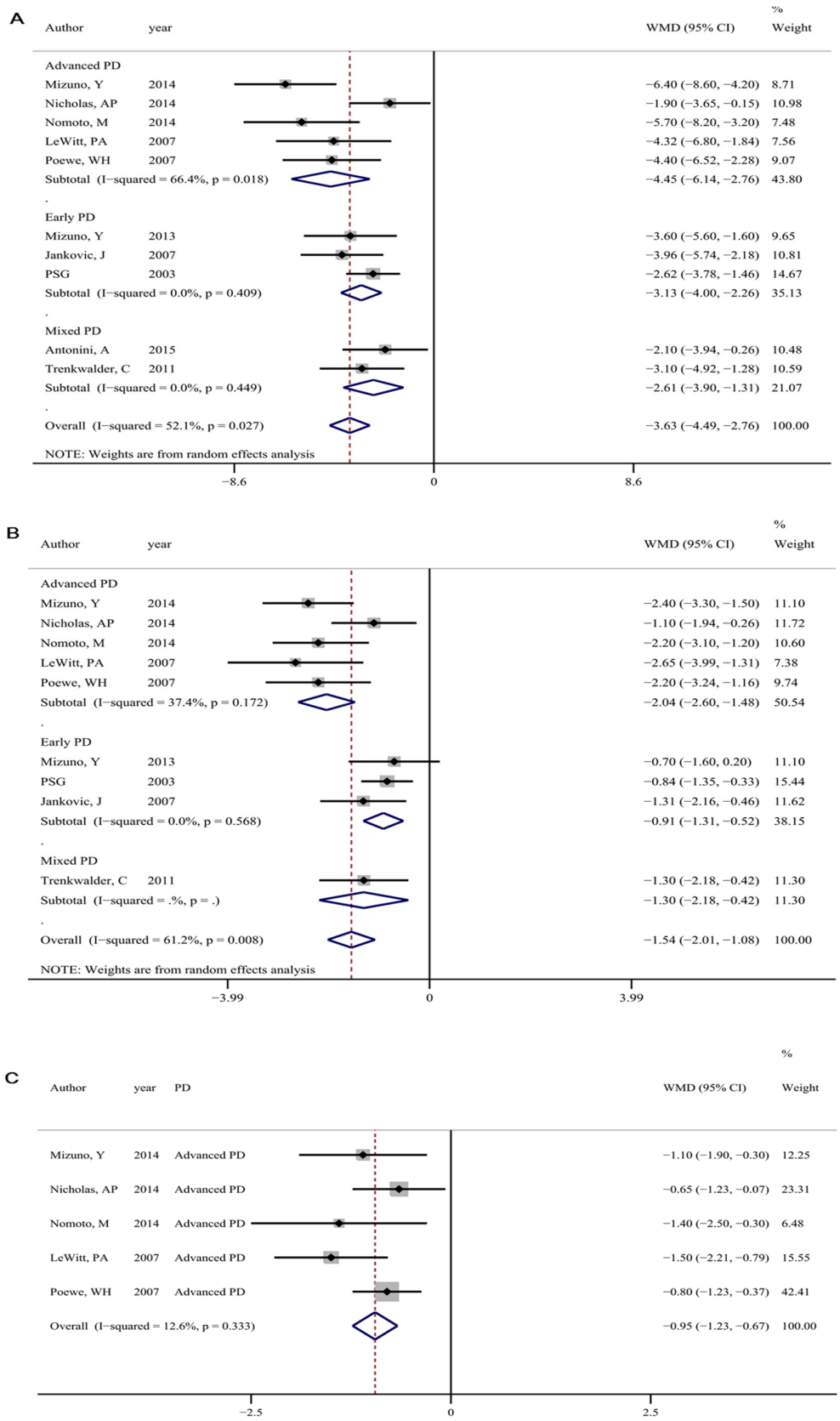


Figure 3. Comparison of curative effects between rotigotine and placebo groups. A. Comparison of Unified Parkinson's Disease Rating Scale (UPDRS) Part III scores between rotigotine and placebo groups. B. Comparison of UPDRS Part II scores between rotigotine and placebo groups. C. Comparison of 'off' time between rotigotine and placebo groups.

Adverse effect

Comparison of incidences of AEs between rotigotine and placebo groups is shown in Figure 4A. The overall result was statistically significant [RR = 1.15; 95% CI: (1.09 - 1.22); $p < 0.001$]. There were statistically significant differences in advanced PD [RR = 1.09; 95% CI: (1.02 - 1.17); $p < 0.001$], early PD [RR = 1.20; 95% CI: (1.03 - 1.40); $p < 0.001$] and mixed PD [RR = 1.29; 95% CI: (1.12 - 1.49); $p < 0.001$] subgroups. No significant heterogeneity was observed in general or in the subgroups ($p > 0.05$, $I^2 < 50\%$).

Comparative results of serious AEs are shown in Figure 4B. The overall result was not statistically significant [RR = 1.06; 95% CI: (0.75 - 1.50); $p = 0.757$]. Differences in advance PD [RR = 0.85; 95% CI: (0.52 - 1.37); $p = 0.497$], early PD [RR = 1.54; 95% CI: (0.79 - 3.03); $p = 0.207$] and mixed PD [RR = 1.05; 95% CI: (0.48 - 2.30); $p = 0.896$] subgroups were not statistically significant. In addition, no significant heterogeneity was observed in general or in the subgroups ($p > 0.05$, $I^2 < 50\%$).

Comparison of incidences of the discontinuation because of AEs between rotigotine and placebo groups is shown in Figure 4C. The overall result was not statistically significant [RR = 1.40; 95% CI: (1.10 - 1.77); $p = 0.006$]. Differences in the early PD subgroup [RR = 2.73; 95% CI: (1.58 - 4.72); $p < 0.001$] were statistically significant, while those in advanced PD [RR = 1.05; 95% CI: (0.77 - 1.42); $p = 0.769$] and mixed PD [RR = 1.37; 95% CI: (0.77 - 2.42); $p = 0.285$] subgroups were not statistically significant. No significant heterogeneity was observed in general or in the subgroups ($p > 0.05$, $I^2 < 50\%$).

Publication bias

Egger's test was used to assess the publication biases in the analyses of AEs, serious AEs and discontinuation because of AEs. Our results showed no significant publication bias among the eligible studies with respect to AEs ($p = 0.295$), serious AEs ($p = 0.229$) and discontinuation because of AEs ($p = 0.277$).

DISCUSSION

This meta-analysis was performed to analyse the safety and efficiency of rotigotine for treating PD. Twelve eligible studies were chosen for the current meta-analysis by literature screening. Rotigotine was found to significantly improve UPDRS Part III and Part II scores compared with the placebo in patients with early and advanced PD. AEs and not serious AEs were reported at significantly higher incidence in the rotigotine group relative to the placebo group. A significant difference for the effect of rotigotine on discontinuation because of AEs was observed in patients with early PD compared with the placebo group, while the overall result was not statistically significant.

Trenkwalder *et al.* performed a placebo-controlled, double-blind, multinational trial and found that rotigotine could significantly improve the modified Parkinson's Disease Sleep Scale (PDSS-2) and UPDRS Part III scores in comparison with the placebo [10]. Patients, who received the maximum dose of rotigotine, exhibited a significantly improved UPDRS Part I, II and III scores, indicating that rotigotine is effective, safe and well-tolerated for the treating patients with early-stage PD [25, 30]. Both the mean UPDRS Part III and PDSS-2 scores improve at end of maintenance, which means that the rotigotine transdermal system can improve sleep disturbances and motor function for up to 1 year [31]. UPDRS Part III score changes were significantly different between rotigotine and placebo groups. Additionally, rotigotine at maximal doses of 16 mg/24 h is safe and efficacious in Japanese patients with advanced PD [27]. UPDRS is utilised to assess the severity of PD and is composed of part I (behaviour, mentation and mood), part II (activities of daily living) and part III (motor sections) [32]. Thus, rotigotine can improve daily living and motor ability of patients with PD.

Pham *et al.* deemed that rotigotine transdermal system was effective in decreasing morbidity in patients with PD, but was associated with AEs, including nausea, somnolence and application-site reaction, in patients with PD [22, 23, 33]. Nicholas *et al.* also reported higher incidence of AEs, including dry mouth, application-site reactions, dyskinesia and nausea, in the rotigotine group (8 mg/24 h) than in the placebo group [26]. Furthermore, Trenkwalder *et al.* found that the most common AEs were nausea (rotigotine, 21% and placebo, 9%), dizziness (rotigotine 10% and placebo, 6%) and application-site reactions (rotigotine, 15% and placebo, 4%) [10]. These results indicate that rotigotine has higher incidence of AEs.

Meta-analysis involving the safety and efficacy of rotigotine in PD has been conducted previously. This previous study obtained results that were similar to the present meta-analysis. Both studies supported that rotigotine could improve symptoms of patients with PD and had higher incidence of AEs.

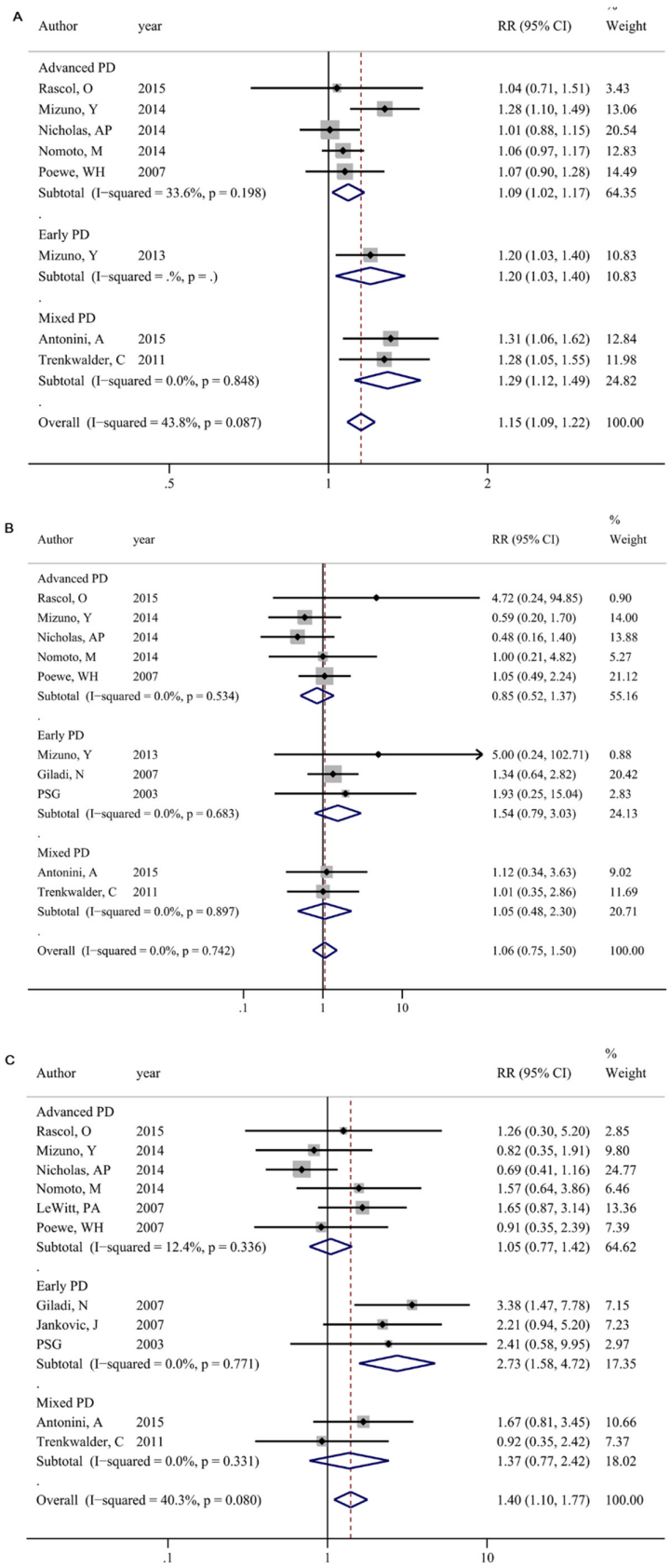


Figure 4. Comparison of adverse effects between rotigotine and placebo groups. A. Comparison of AEs between rotigotine and placebo groups. B. Comparison of serious AEs between rotigotine and placebo groups. C. Comparison of discontinuation because of AEs between rotigotine and placebo groups.

However, the present meta-analysis is superior to the previous one. In this study, multiple outcome indicators have been analysed to evaluate the curative and adverse effects of PD. Besides, more studies of moderate or high quality have been included in our meta-analysis. The heterogeneity was small and no significant publication bias was detected in the eligible studies. Despite the above advantages, the total number of cases was small, which should be considered as a limitation of this study. Thus, further research is needed to support our results.

In conclusion, our findings indicated that rotigotine could improve daily living and motor ability of patients with PD, albeit having higher incidence of AEs. Rotigotine might be more appropriate for patients with advanced PD than for patients with early PD. However, these results still need to be confirmed by more RCTs with larger samples.

REFERENCES

1. Toulouse A, Sullivan AM (2008) Progress in Parkinson's disease—where do we stand? Progress in neurobiology 85: 376-392.
2. Jankovic J (2008) Parkinson's disease: clinical features and diagnosis. Journal of Neurology, Neurosurgery & Psychiatry 79: 368-376.
3. Naghavi M, Wang H, Lozano R, Davis A, Liang X, et al. (2015) Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 385: 117-171.
4. Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, et al. (2015) Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 386: 743-800.
5. de Lau LM, Breteler MM (2006) Epidemiology of Parkinson's disease. The Lancet Neurology 5: 525-535.
6. Donovan S (2003) Parkinson's disease treatment. Google Patents.
7. Conditions NCCfC (2006) Symptomatic pharmacological therapy in Parkinson's disease.
8. Group PS (2003) A controlled trial of rotigotine monotherapy in early Parkinson's disease. Archives of neurology 60: 1721.
9. Giladi N, Boroojerdi B, Korczyn AD, Burn DJ, Clarke CE, et al. (2007) Rotigotine transdermal patch in early Parkinson's disease: A randomized, double-blind, controlled study versus placebo and ropinirole. Movement disorders 22: 2398-2404.
10. Trenkwalder C, Kies B, Rudzinska M, Fine J, Nikl J, et al. (2011) Rotigotine effects on early morning motor function and sleep in Parkinson's disease: A double-blind, randomized, placebo-controlled study (RECOVER). Movement disorders 26: 90-99.
11. Giladi N, Fichtner A, Poewe W, Boroojerdi B (2010) Rotigotine transdermal system for control of early morning motor impairment and sleep disturbances in patients with Parkinson's disease. Journal of neural transmission 117: 1395-1399.
12. Chaudhuri KR, Martinez-Martin *P*, Antonini A, Brown RG, Friedman JH, et al. (2013) Rotigotine and specific non-motor symptoms of Parkinson's disease: post hoc analysis of RECOVER. Parkinsonism & related disorders 19: 660-665.
13. Jankovic J, Watts RL, Martin W, Boroojerdi B (2007) Transdermal rotigotine: double-blind, placebo-controlled trial in Parkinson disease. Archives of neurology 64: 676-682.
14. Scheller D, Chan *P*, Li Q, Wu T, Zhang R, et al. (2007) Rotigotine treatment partially protects from MPTP toxicity in a progressive macaque model of Parkinson's disease. Experimental neurology 203: 415-422.
15. Zhou C-Q, Li S-S, Chen Z-M, Li F-Q, Lei *P*, et al. (2013) Rotigotine transdermal patch in Parkinson's disease: a systematic review and meta-analysis. PLoS One 8: e69738.
16. Simuni T, Borushko E, Avram MJ, Miskevics S, Martel A, et al. (2010) Tolerability of isradipine in early Parkinson's disease: a pilot dose escalation study. Movement disorders 25: 2863-2866.
17. Pfeiffer RF, Gutmann L, Hull KL, Bottini PB, Sherry JH, et al. (2007) Continued efficacy and safety of subcutaneous apomorphine in patients with advanced Parkinson's disease. Parkinsonism & related disorders 13: 93-100.
18. Fernandez HH, Vanagunas A, Odin *P*, Espay AJ, Hauser RA, et al. (2013) Levodopa–carbidopa intestinal gel in advanced Parkinson's disease open-label study: Interim results. Parkinsonism & related disorders 19: 339-345.
19. Higgins JP, Green S (2008) Cochrane handbook for systematic reviews of interventions: Wiley Online Library.
20. Higgins J, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. Bmj 327: 557-560.
21. Hollis MA, Ehrlich DJ, Murphy RA, Kosicki BB, Rathman DD, et al. (1997) Monolithic array of test sites. Google Patents.
22. Antonini A, Bauer L, Dohin E, Oertel W, Rascol O, et al. (2015) Effects of rotigotine transdermal patch in patients with Parkinson's disease presenting with non-motor symptoms–results of a double-blind, randomized, placebo-controlled trial. European Journal of Neurology 22: 1400-1407.
23. LeWitt PA, Lyons KE, Pahwa R, Group SS (2007) Advanced Parkinson disease treated with rotigotine

transdermal system PREFER Study. Neurology 68: 1262-1267.
24. Mizuno Y, Nomoto M, Hasegawa K, Hattori N, Kondo T, et al. (2014) Rotigotine vs ropinirole in advanced stage Parkinson's disease: A double-blind study. Parkinsonism & related disorders 20: 1388-1393.
25. Mizuno Y, Nomoto M, Kondo T, Hasegawa K, Murata M, et al. (2013) Transdermal rotigotine in early stage Parkinson's disease: A randomized, double-blind, placebo-controlled trial. Movement disorders 28: 1447-1450.
26. Nicholas AP, Borgohain R, Chaná *P*, Surmann E, Thompson EL, et al. (2014) A Randomized Study of Rotigotine Dose Response on 'Off' Time in Advanced Parkinson's Disease. Journal of Parkinson's disease 4: 361-373.
27. Nomoto M, Mizuno Y, Kondo T, Hasegawa K, Murata M, et al. (2014) Transdermal rotigotine in advanced Parkinson's disease: a randomized, double-blind, placebo-controlled trial. Journal of neurology 261: 1887-1893.
28. Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, et al. (2007) Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson's disease: a double-blind, double-dummy, randomised controlled trial. The Lancet Neurology 6: 513-520.
29. Rascol O, Zesiewicz T, Chaudhuri K, Asgharnejad M, Surmann E, et al. (2015) A Randomized Controlled Exploratory Pilot Study to Evaluate the Effect of Rotigotine Transdermal Patch on Parkinson's Disease–Associated Chronic Pain. The Journal of Clinical Pharmacology.
30. Güldenpfennig WM, Poole KH, Sommerville KW, Boroojerdi B (2005) Safety, tolerability, and efficacy of continuous transdermal dopaminergic stimulation with rotigotine patch in early-stage idiopathic Parkinson disease. Clinical neuropharmacology 28: 106-110.
31. Trenkwalder C, Kies B, Dioszeghy *P*, Hill D, Surmann E, et al. (2012) Rotigotine transdermal system for the management of motor function and sleep disturbances in Parkinson's disease: results from a 1-year, open-label extension of the RECOVER study. Basal ganglia 2: 79-85.
32. Baatile J, Langbein W, Weaver F, Maloney C, Jost M (2000) Effect of exercise on perceived quality of life of individuals with Parkinson's disease. Journal of rehabilitation research and development 37: 529.
33. Pham DQ, Nogid A (2008) Rotigotine transdermal system for the treatment of Parkinson's disease. Clinical therapeutics 30: 813-824.