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Comparison of drug efficacy and safety for restless legs syndrome: A Meta-analysis

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Restless legs syndrome (RLS) is a sensory disorder characterized by sensory abnormalities (paresthesia) during the waking state, at rest, and at sleep onset. Currently, three RLS drugs—pramipexole, gabapentin enacarbil, and rotigotine—are approved for use in the national medical insurance system in Japan. In the present study, we conducted a meta-analysis to compare the efficacy and safety of these three drugs. The target patients were idiopathic RLS patients who had been diagnosed as having moderate-to-severe RLS on the International Restless Legs Syndrome Study Group Rating Scale (IRLS). The efficacy end point was the mean difference of change in IRLS score. The safety endpoint was the number of adverse effects. The efficacy endpoints were integrated using the weighted mean difference (WMD) for each treatment group compared with a placebo group. We integrated safety assessment items using the risk difference(RD). When comparing the integrated WMDs of the three RLS therapeutics indirectly, the reduction in IRLS scores was the highest for rotigotine, followed by pramipexole, and then gabapentin enacarbil, but no significant differences were found between the three drugs. With regard to safety, a significant difference in the integrated WMDs was found between pramipexole and rotigotine; however, no significant differences were observed between pramipexole compared with gabapentin enacarbil or rotigotine compared with gabapentin enacarbil. These findings provide evidence to support drug selection in the clinical setting.

Key Words: restless legs syndrome, meta-analysis , efficacy, safety

Introduction

Restless legs syndrome (RLS) is a perceptual disorder characterized by aberrant sensations during the waking state, at rest, and at sleep onset. RLS is characterized by an unpleasant sensation in the lower extremities that the legs should be moved that starts at rest, improves with exercise, and exacerbates from the daytime to the evening/nighttime.

The prevalence of RLS is reported to be 1–4% in Japan[1,2)]. RLS is divided into primary (idiopathic), whose cause is not found, and secondary, which coexists with other diseases. Secondary RLS is often accompanied by cerebrovascular disease, Parkinson's disease, polyneuritis, chronic renal failure (especially in dialysis patients), and iron deficiency anemia, often in conditions prone to iron deficiency, such as

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during pregnancy. If RLS develops, affected individuals feel discomfort in the lower extremities and feel that they must move their legs. Symptoms intensify in the evening and nighttime, and sleep disorders such as sleeplessness and awakening often occur, which reduces daytime activity and causes anxiety and depression, greatly affecting daily life[3].

In RLS, abnormal (nociceptive) perceptions generated in resting skeletal muscle pass through myelinated nerve fibers and are transmitted to the cortical sensory area via dorsal root cells, creating an unusual sensation. On the other hand, intrinsic perceptions carrying information such as the contraction/relaxation of skeletal muscle travel through unmyelinated nerve fibers to the brain, and at the same time, suppress the sensitivity of dorsal root cells. In other words, it is speculated that when the stimulation of the intrinsic sensory system is increased by exercise, nociceptive perception is suppressed and abnormal sensations are less likely to be transmitted to the sensory area of the cerebral cortex.

The severity of RLS can be assessed using the International Restless Legs Syndrome Study Group Rating Scale (IRLS), which can also determine the course of treatment. RLS severity is classified based on the IRLS total score as follows: 1–10 points indicates mild RLS, 11–20 points indicates moderate RLS, 21–30 points indicates severe RLS, 31–40 points indicates very severe RLS.

Treatment for RLS includes both drug and non-drug therapy; non-drug therapy includes discontinuation of drugs and items causing RLS, sleep hygiene instruction, appropriate exercise, etc., when drugs are not effective. Drugs that have been shown to be effective include dopamine agonists, levodopa preparations, benzodiazepines, and anticonvulsants. Currently, only three drugs are approved for RLS in Japan: pramipexole, gabapentin enacarbil, and rotigotine. In the present study, the efficacy and safety of these three agents were compared and examined with the aim of compiling evidence to aid in drug selection in the clinical setting.

Methods

1. Research paper collection

We conducted a search for research papers in the MEDLINE database and The Cochrane Library with the following conditions: "restless legs syndrome pramipexole placebo" OR "restless legs syndrome gabapentin enacarbil placebo" OR "restless legs syndrome rotigotine placebo" and limited the results to randomized controlled trials.

2. Recruitment criteria

The inclusion criteria for the literature were a randomized controlled trial with study design, and the target patients were idiopathic RLS patients diagnosed as moderate to severe RLS on the IRLS severity scale. The efficacy endpoint was the mean difference between changes in IRLS scores, and the safety endpoint was the number of adverse events.

3. Data extraction

The data extracted from the document search included the study design (randomized, with or without masking), inclusion/exclusion criteria for the study patients, age, sex, number of cases, administration period, intervention, and results of each evaluation item (mean difference of change in IRLS score, number of adverse effects).

4. Evaluation of research quality

The quality of the research in the targeted papers was evaluated using the Jadad score[4] shown below.

Jadad score:

1) Was the study described as randomized (this includes terms such as randomly, random, and randomization)? (Yes: 1, No: 0)
2) Was the method used to generate the sequence of randomization fully described and appropriate (table of random numbers, computer-generated, etc.)? (Yes: 1, No: –1)
3) Was the study described as double-blind? (Yes: 1, No: 0)
4) Was the double-blinding method fully described and appropriate (identical placebo, active placebo, dummy, etc.)? (Yes: 1, No: –1)
5) Was there a description of withdrawals and dropouts? (Yes: 1, No: 0)

The highest possible score is 5 points, with 3 or more points indicating a high-quality study, and 2 or fewer points indicating a low-quality study.

5. Quality assessment

Two authors independently performed primary screening. We selected papers that each met the selection criteria and compared the results of the two people. Also in the secondary screening, two authors independently read the full text and compared the two results. When two people's opinion was different, the opinion of the third party was taken in and the adoption paper was decided.

6. Data synthesis

The meta-analysis in the present study was performed using StatsDirect (ver. 3, http:www.statsdirect.com/, StatsDrect Limited). The efficacy evaluation was integrated using the weighted mean difference (WMD) for each treatment group compared with a placebo group, and the safety evaluation were integrated using the risk difference (RD). The I statistic (I^2) was used to test heterogeneity. The integrated WMD and RD and their 95% confidence intervals were calculated using a random-effects model, and effectiveness and safety were evaluated statistically. The efficacy and safety of each RLS treatment were compared and examined using the indirect method[5].

7. Examination of publication bias

The publication bias was examined using the Kendall rank correlation coefficient calculated using the method of Begg[6]. The level of significance was set at 0.10.

Results

1. Search results

Of the 56 research papers identified, 19 met the inclusion criteria, among which, seven were on pramipexole, six on gabapentin enacarbil, and six on rotigotine. The research paper selection process is shown in Figure 1.

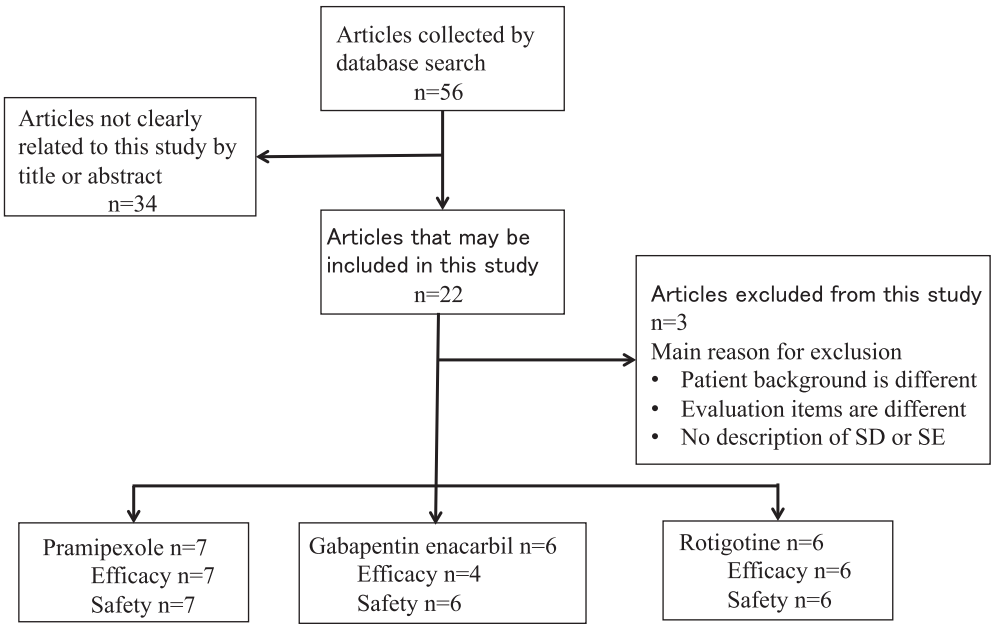

Fig.1 Study retrieval and selection

2. Content of the research papers to be analyzed

Tables 1–3 show the details of the papers on pramipexole, gabapentin enacarbil, and rotigotine, respectively, that were analyzed in the present study. All papers reported randomized controlled trials with a parallel group design and were considered high quality (Jadad score of 3 or more). No sensitivity analysis excluding low-quality studies was performed as low-quality studies were not included in the selected papers.

The inclusion criterion for the patients in all studies was a diagnosis of moderate-to-severe primary (idiopathic) RLS on the IRLS. All studies involving patients with secondary RLS, pregnant or

lactating women, patients with renal dysfunction, and patients using other RLS medications were excluded.

Table 1 Study Characteristics for Trials Comparing Pramipexole and Placebo.

Study	Title	Year	Study design	Masking	Number of treatment group	Number of placebo group	Jadad study Quality score
Ferini, 2008[7]	Effect of pramipexole on RLS symptom and sleep : A rondomized, double-blind, placebo-controlled trial.	2008	RCT	double blind	178	179	5
Högl, 2011[8]	Efficacy and augmentation during 6 months of double-blind pramipexole for restless legs syndrome.	2011	RCT	double blind	162	159	3
Zhang, 2015[9]	Pramipexole for Chinese people withy primary restless legs syndrome : a 12-week multicenter, randomized, double-blind study	2015	RCT	double blind	102	102	5
Ma, 2012[10]	Efficacy and safety of pramipexole in chinese patients with restless legs syndrome : Result from a multi-center, randomized, double-blind, placebo-controlled trial.	2012	RCT	double blind	195	92	4
Montagna, 2011[11]	Randomized trial of pramipexole for patients with restless legs syndrome (RLS) and RLS-related impairment of mood.	2011	RCT	double blind	203	199	4
Ortel, 2007[12]	Efficacy of pramipexole in restless legs syndrome : A six-week, multicenter, rondomized, double-blind study.	2007	RCT	double blind	224	114	5
Winkelman, 2006[13]	Efficacy and safety of pramipexole in restless legs syndrome.	2006	RCT	double blind	87	85	5

RCT : Randomized controlled trials

Table 2 Study Characteristics for Trials Comparing Gabapentin enacarbil and Placebo.

Study	Title	Year	Study design	Masking	Number of treatment group	Number of placebo group	Jadad study Quality score
Bogan,2015[14]	Treatment respone to sleep, pain, and mood disturbance and their correlation with sleep disturbance in adult patients with moderate-to-severe primary restless legs syndrome : Pooled analyses from 3 trials of gabapentin enacarbil.	2015	RCT	double blind	149	135	4
Lal, 2012[15]	A randomized, double-blind, placebo-controlled, dose-response study to assess the pharmacokinetics, efficacy, and safety of gabapentin enacarbil in subjects with restless legs syndrome.	2012	RCT	double blind	45	41	5
Inoue, 2013[16]	Gabapentin enacarbil in Japanese patients with restless legs syndrome : a 12-week, randomized, double-blind, placebo-controlled, parallel-group study.	2013	RCT	double blind	113	116	3
Lee, 2011[17]	A randomized, double-blind, placebo-controlled study to assess the efficacy and tlerability of gabapentin enacarbil in subjects with restless legs syndrome.	2011	RCT	double blind	113	97	5
Bogan, 2010[18]	Long-term maintenance treatment of restless legs syndrome with gabapentin enacarbil : Arondmized controlled study.	2010	RCT	double blind	96	98	5
Walters, 2009[19]	Gabapentin enacarbil in restless legs syndrome : A phase 2b, 2-week, randmized, double-blind, placebo-controlled trial.	2009	RCT	double blind	32	33	4

RCT : Randomized controlled trials

Table 3 Study Characteristics for Trials Comparing Rotigotine and Placebo.

Study	Title	Year	Study design	Masking	Number of treatment group	Number of placebo group	Jadad study Quality score
Borreguero, 2016[20]	Effect of rotigotine on daytime symptoms in patients with primary restless legs syndrome : a randomized, placebo-controlled study	2016	RCT	double blind	101	49	5
Hening, 2010[21]	Rotigotine improves restless legs syndrome : A 6-month randomized, double-blind, placebo-controlled trial in the United States.	2010	RCT	double blind	103	99	4
Inoue, 2013[22]	Efficacy and safety of rotigorine in Japanese patients with restless legs syndrome : A phase 3, multicenter, randmized, placebo-controlled, double-blind, parallel-group study.	2013	RCT	double blind	94	95	4
Oertel, 2008[23]	Efficacy of rotigotine transdermal system in severe restless legs syndrome : A rondmized, double-blind, placebo-controlled, six-week dose-finding trial in Europe.	2008	RCT	double blind	64	53	5
Stiasny-Kolster, 2004[24]	Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome : A double-blind, placebo-controlled pilot study.	2004	RCT	double blind	19	14	4
Trenkwalder, 2008[25]	Efficacy of rotigotine for treatment ofmoderate-to-severe restless legs syndrome : A randomized, double-blind, placebo-controlled trial.	2008	RCT	double blind	112	114	3

RCT : Randomized controlled trials

3. Efficacy

In total, seven, four, and six studies analyzed the efficacy of pramipexole, gabapentin enacarbil, and rotigotine, respectively. Moderate-to-strong heterogeneity was observed between each RLS treatment compared with the placebo (Table 4).

Table 4 Pooled Efficacy Endpoints (WDM) of Treatment versus Placebo

Treatment	Number of Studies	Point Estimate (95% CI)	Heterogeneity (I^2)(%)
Pramipexole	7	-4.71 (-5.70, -3.72)	36.9
Gabapentin enacarbil	4	-3.64 (-5.10, -2.18)	33.2
Rotigotine	6	-5.48 (-7.66, -3.30)	68.9

CI : confidence interval

I^2 : I statistics

Significant decreases in IRLS scores compared with placebo were seen in seven studies on pramipexole, four on gabapentin enacarbil, and six on rotigotine. WMD were -4.71（95 % CI, -5.70 to -3.72）for pramipexole vs. praceco, -3.64(95 % CI, -5.10 to -2.18) for gabapentin enacarbil vs. placebo, -5.48(95% CI,-7.66 to -3.30) for rotigotine vs. placebo. The integrated WMD showed a significant decrease compared with the placebo for all three drugs (Figs. 2–4).

Trial	Pramipexole n	Placebo n	WMD (95% CI)	
Ferini, 2008	178	179	-3.80	(-5.74, -1.86)
Hogl, 2011	162	159	-3.00	(-5.12, -0.87)
Ma, 2012	195	92	-5.10	(-7.26, -2.94)
Montagna, 2011	203	199	-6.10	(-8.03, -4.17)
Ortel, 2007	224	114	-6.60	(-8.68, -4.52)
Winkelman, 2006	87	85	-4.70	(-7.47, -1.93)
Zhang, 2015	102	102	-3.80	(-5.59, -2.01)
Total	1151	930	-4.71	(-5.70, -3.72)

WMD :weight mean difference

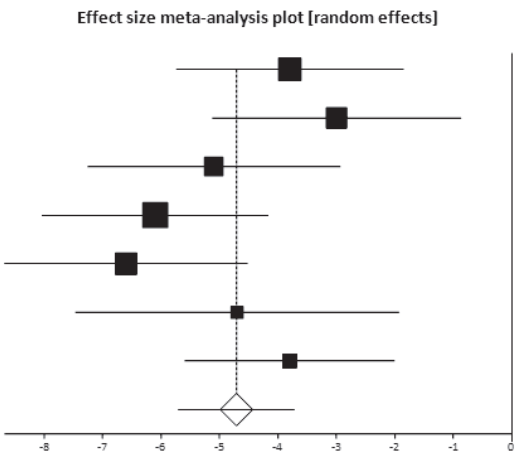

Fig.2 Meta-analysis of the IRLS for Pramipexole versus Placebo

Trial	Gabapentin enacarbil n	Placebo n	WMD (95% CI)	
Bogan,2015	149	135	-3.60	(-5.35, -1.85)
Inoue, 2013	113	118	-2.42	(-4.81, -0.03)
Lee, 2011	113	97	-3.20	(-5.50, -0.90)
Walters, 2009	32	33	-7.20	(-11.0, -3.40)
Total	407	381	-3.64	(-5.10, -2.18)

WMD :weight mean difference

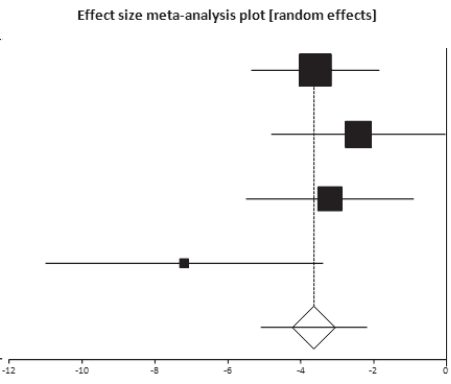

Fig.3 Meta-analysis of the IRLS for Gabapentin enacarbil versus Placebo

Trial	Rotigotine n	Placebo n	WMD (95% CI)	
Borreguero, 2016	101	49	-2.20	(-5.20, 0.80)
Hening, 2010	103	99	-5.30	(-7.67, -2.93)
Inoue, 2013	94	95	-3.00	(-5.45, -0.55)
Oertel, 2008	64	53	-8.00	(-11.68, -4.32)
Stiasny-Kolster, 2004	19	14	-7.70	(-13.37, -2.03)
Trenkwalder, 2008	112	114	-8.20	(-10.69, -5.71)
Total	493	424	-5.48	(-7.66, -3.30)

WMD :weight mean difference

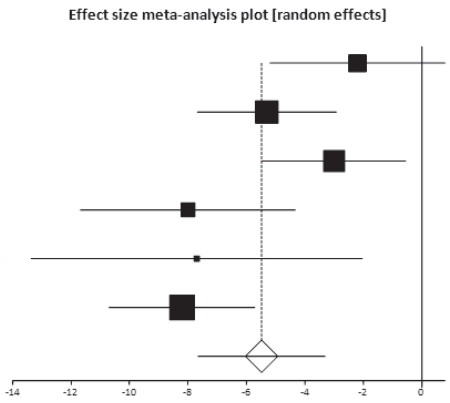

Fig.4 Meta-analysis of the IRLS for Rotigotine versus Placebo

When comparing the integrated WMDs of the three RLS therapeutics indirectly, the reduction in IRLS scores was the highest for rotigotine, followed by pramipexole and then gabapentin enacarbil. WMD were -1.07 (95% CI, 0.69 to -2.83) for pramipexole vs. gabapentin enacarbil, 1.84 (95% CI,4.46 to –0.78) for gabapentin enacarbil vs. rotigotine, 0.77 (95 % CI,3.16 to -1.62) for rotigotine vs. pramipexole. No significant differences were seen between the three drugs (Table 5).

No publication bias was observed in all integrations.

Table 5 Indirect Comparisons of Efficacy of Pramipexole vs Gaba pentin enacarbil vs Rotigotine

Indirect Comparison	Difference Favors	Difference WMD	95% CI	Significant Difference
Pramipexole vs Gabapentin enacarbil	Pramipexole	-1.07	(0.69, -2.83)	No
Gabapentin enacarbil vs Rotigotine	Rotigotine	1.84	(4.46, -0.78)	No
Rotigotine vs Pramipexole	Rotigotine	0.77	(3.16, -1.62)	No

WMD : weighted mean difference

CI : confidence interval

4. Safety

In total, seven, six, and six studies analyzed the safety of pramipexole, gabapentin enacarbil, and rotigotine, respectively. Moderate-to-strong heterogeneity was observed between each RLS treatment and the placebo (Table 6).

Table 6 Pooled Safety Endpoints (RD) of Treatment versus Placebo

Treatment	Number of Studies	Point Estimate (95% CI)	Heterogeneity (I^2)(%)
Pramipexole	7	0.11 (0.07, 0.15)	18.1
Gabapentin enacarbil	6	0.13 (0.05, 0.21)	57.4
Rotigotine	6	0.21 (0.16, 0.27)	75.6

CI : confidence interval

I^2 : I statistics

In many studies, no adverse effects (RD) were reported; however, three were reported in primary studies with pramipexole, three with gabapentin enacarbil, and four with rotigotine, all having significant differences compared with the placebo. RD were 0.11 (95 % CI,0.07 to 0.15)for pramipexole vs. praceco, 0.13 (95 % CI, 0.05 to 0.21) for gabapentin enacarbil vs. placebo, 0.20 (95 % CI,0.08 to 0.32) for rotigotine vs. placebo. The integrated RD was significantly different from placebo for all three drugs (Figs. 5–7).

Trial	Pramipexole n	Placebo n	RD (95% CI)	
Ferini, 2008	182	187	0.12	(0.02, 0.22)
Hogl, 2011	166	163	0.07	(-0.03, 0.17)
Ma, 2012	202	103	0.19	(0.07, 0.31)
Montagna, 2011	203	200	0.10	(-0.001, 0.19)
Ortel, 2007	224	114	0.18	(0.07, 0.29)
Winkelman, 2006	258	86	0.05	(-0.03, 0.12)
Zhang, 2015	102	102	0.14	(-0.0002, 0.27)
Total	1337	955	0.11	(0.07, 0.15)

RD :risk difference

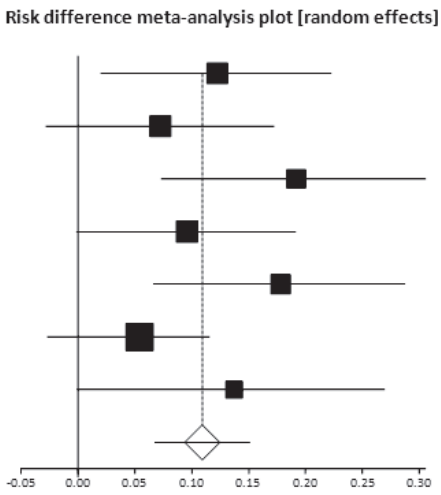

Fig.5 Meta-analysis of the Adverse events for Pramipexole versus Placebo

Trial	Gabapentin enacarbil n	Placebo n	RD (95% CI)	
Bogan, 2010	96	98	0.05	(-0.09, 0.19)
Bogan,2015	151	135	0.06	(-0.04, 0.15)
Inoue, 2013	114	116	0.14	(0.03, 0.24)
Lal, 2012	45	41	0.23	(0.06, 0.40)
Lee, 2011	111	96	0.06	(-0.05, 0.16)
Walters, 2009	33	33	0.39	(0.18, 0.59)
Total	550	519	0.13	(0.05, 0.21)

RD :risk difference

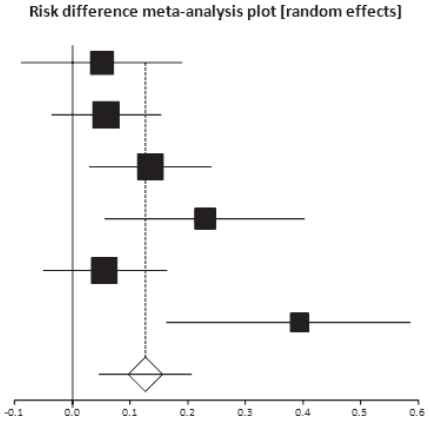

Fig.6 Meta-analysis of the Adverse events for Gabapentin enacarbil versus Placebo

Trial	Rotigotine n	Placebo n	RD (95% CI)	
Borreguero, 2016	101	49	0.19	(0.03, 0.35)
Hening, 2010	106	100	0.05	(-0.05, 0.14)
Inoue, 2013	94	95	0.35	(0.22, 0.46)
Oertel, 2008	65	55	0.30	(0.12, 0.46)
Stiasny-Kolster, 2004	19	19	0.00	(-0.28, 0.28)
Trenkwalder, 2008	114	117	0.25	(0.13, 0.36)
Total	499	435	0.20	(0.08, 0.32)

RD :risk difference

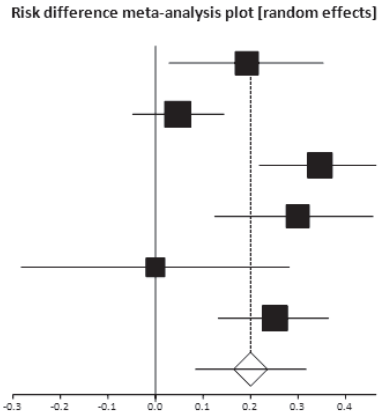

Fig.7 Meta-analysis of the Adverse events for Rotigotine versus Placebo

With regard to safety, when comparing the integrated RDs of the three RLS drugs indirectly, a significant difference was found for pramipexole compared with rotigotine (RD was -0.1 (95%CI, -0.16 to -0.02)); however, no significant differences were observed between pramipexole compared with gabapentin enacarbil (RD was -0.02 (95%CI, -0.11 to 0.07)) or rotigotine compared with gabapentin enacarbil (RD was -0.08 (95%CI, -0.17 to 0.03)) (Table 7).

A publication bias was observed in the two integration results in the safety review. In pramipexole, Begg-Mazumder: Kendall's tau = 0.714 P = 0.03, and in gabapentin enacarbil, Begg-Mazumder: Kendall's tau = 0. 733 P = 0.06.

Table 7 Indirect Comparisons of Safety of Pramipexole vs Gabapentin enacarbil vs Rotigotine

Indirect Comparison	Difference Favors	Difference RD	95% CI	Significant Difference
Pramipexole vs Gabapentin enacarbil	Pramipexole	-0.02	(-0.11, 0.07)	No
Gabapentin enacarbil vs Rotigotine	Gabapentin enacarbil	-0.08	(-0.17, 0.03)	No
Rotigotine vs Pramipexole	Pramipexole	-0.1	(-0.16, -0.02)	Yes

RD : risk difference

CI : confidence interval

Discussion

In the present study, a meta-analysis was conducted to compare indirectly the efficacy and safety of pramipexole, gabapentin enacarbil, and rotigotine for primary (idiopathic) RLS patients diagnosed with moderate-to-severe RLS according to the IRLS. Placebo-paired comparisons were integrated using a random-effects model.

In the analysis of efficacy, IRLS scores showed a significant decrease in all three drugs. When the integrated WMDs of the three RLS drugs were compared indirectly in terms of effectiveness, the reduction rate in IRLS scores tended to be highest for rotigotine, followed by pramipexole and then gabapentin enacarbil. In addition, no significant difference was found between gabapentin enacarbil and rotigotine. In patients with moderate-to-severe primary (idiopathic) RLS according to the IRLS, clinical doses of rotigotine appeared to be most effective. In this study, the reduction rate of IRLS scores was used as an evaluation index of efficacy; however, in addition to the IRLS, the Clinical Global Impression scale and subjective sleep items (e.g., evaluation of sleep disorder) are used as an evaluation index for the efficacy of RLS drugs, and the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale are used to assess daytime sleepiness. It will be necessary to analyze studies involving these indexes in future research.

In the safety analysis, all three drugs showed a significant risk of causing adverse effects compared with the placebo. When comparing the integrated RDs of the three RLS drugs indirectly, a significant difference was found for pramipexole compared with rotigotine. In patients with moderate-to-severe primary (idiopathic) RLS according to the IRLS, the safest drug, when compared at clinical doses, is considered to be pramipexole, followed by gabapentin enacarbil and then rotigotine. Adverse effects common to all patients in the analyzed studies were headache, nausea, and dizziness. Further, among the three agents, only rotigotine comes in the form of a patch, and thus, an application site reaction is a characteristic adverse effect. However, no patients dropped out because of serious skin problems, and thus, it was considered appropriate to use the adverse effect rate as a safety evaluation item. It is important to take the type of adverse effects associated with each drug into account when considering the choice of treatment.

Iftilhar.I.H et al. performed a meta-analysis of their effects on pramipexole, ropinirole, rotigotine, pregabalin, gabapentin enacarbil for RLS[26]. The result was that all treatments were superior to placebo. However, no significant difference was found in the comparison among the drugs. These results are consistent with our results. Their meta-analysis compares the major side effects common to each drug in terms of safety, but our study compares the number of side effects. This result is considered to be important information in drug selection.

Publication bias was observed in the integration of pramipexole and gabapentin enacarbil. Since all the calculation results are low power, submission of research papers in this theme is desired in the future. And this integration result should be judged carefully on the assumption that there is publication bias.

Subgroup analysis was performed for highly heterogeneous integration results, but no significant change was found in I^2. From this, it can be considered that the cause is racial differences and complications of the target patients.

This study is limited in terms of its indirect comparison of efficacy and safety. In order to obtain reliable evidence in the future, it is desirable to compare directly the differences in efficacy and safety between the drugs used in this study.

In addition, analyzing other evaluation indexes would enable the efficacy and safety of RLS drugs to be assessed in multiple ways, promoting treatment that is individualized for each patient.

Conflict of interest

The authors declare no conflicts of interest.

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