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Original Article

Meta-analysis of the efficacy and tolerability of pramipexole versus ropinirole in the treatment of restless legs syndrome

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Abstract

Objective: In the absence of comparative trials a meta-analysis was performed to compare the efficacy and tolerability of the non-ergot derived dopamine agonists, pramipexole and ropinirole, in restless legs syndrome (RLS).
Methods: Frequentist fixed and random-effects models were pre-specified for the direct comparisons and a Bayesian approach for the indirect comparison. Efficacy outcomes included the mean change from baseline in the International RLS Study Group Rating Scale (IRLS) score and the percentage of responders on the clinical global impressions – improvement scale (CGI-I). Safety outcomes included the incidence of withdrawal and adverse events.
Results: The direct meta-analysis confirmed superior efficacy for both treatments versus placebo for the IRLS (pramipexole: −5.45; 95% CI: −7.70; −3.20; ropinirole: −3.16; 95% CI: −4.26; −2.05) and the CGI-I (pramipexole: OR = 2.98; 95% CI: 2.08; 4.26; ropinirole: OR = 1.99; 95% CI: 1.52; 2.60). Placebo comparisons showed a significantly higher incidence of nausea for pramipexole ($p < 0.01$), whereas nausea, vomiting, dizziness, and somnolence were significantly higher for ropinirole (all $p < 0.01$). The indirect comparison showed with a probability of ⩾95%, a superior reduction in the mean IRLS score (−2.33; 95% credibility interval [CrI]: −4.23; −0.41), higher CGI-I response rate (OR = 1.50; 95% CrI: 0.97; 2.32) and significantly lower incidence of nausea, vomiting, and dizziness for pramipexole compared to ropinirole.
Conclusion: Differences in efficacy and tolerability favouring pramipexole over ropinirole can be observed. These findings should be further confirmed in head-to-head clinical trials.

Keywords: Restless legs syndrome; Meta-analysis; Pramipexole; Non-ergot dopamine agonists; Efficacy; Safety

1. Introduction

Restless legs syndrome (RLS) is a neurological disorder characterised by unpleasant sensations in the legs and an irresistible urge to move the legs to relieve the discomfort [1,2]. RLS affects more than 2.5% of the general population, increases with age and is higher in women than in men [3]. RLS symptoms have been

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associated with impaired quality of life and increased symptoms of depression and anxiety [4]. Also sleep onset, maintenance, and quality of sleep have been found to be impaired [5]. The pathophysiology of RLS is not well understood, but research suggests that a dysregulation of dopamine function plays a role [6,7]. Medications that enhance dopamine function have been considered appropriate treatments and recommended as the first line of treatment for RLS [8]. The two non-ergot derived dopamine agonists, pramipexole and ropinirole, are the only approved dopamine agonists indicated for the treatment of moderate to severe idiopathic RLS [9,10]. Both drugs have previously been licensed for the treatment of the signs and symptoms of idiopathic Parkinson's disease [9,10].

The aim of the present study was to compare the efficacy and tolerability of pramipexole and ropinirole in the treatment of RLS using both direct and indirect meta-analysis techniques.

2. Materials and methods

2.1. Literature search and study selection

A systematic search of the literature was conducted to identify available data sources for pramipexole and ropinirole using PubMed, EMBASE, and CENTRAL databases. The search strategy was not limited by year or language of publication and included the following individual and combined search terms: "RLS," "Restless Legs," "pramipexole," "ropinirole," "placebo," "blind or double blind." Additionally, for ropinirole, the manufacturing company's trial register was searched [11]. Study reports for the four pramipexole clinical trials in RLS were made available by the manufacturer.

Studies had to meet the following criteria to be considered for inclusion in the primary meta-analyses: randomised, double blind, placebo-controlled trials idiopathic RLS and using change in the International RLS Study Group Rating Scale (IRLS) score as the primary endpoint. Criteria were relaxed for the sensitivity analysis, where change in the IRLS score was not required to be a primary study endpoint.

2.2. Selection of outcome measures

2.2.1. Efficacy

A wide range of objective and subjective (physician or patient-rated) outcome measures have been used to assess severity or improvement in RLS symptoms. The two most commonly used outcome measures in the pramipexole and ropinirole trials were the IRLS and clinical global impressions – improvement scale (CGI-I). In the trials reviewed, the CGI assessed the overall improvement of RLS symptoms as assessed by the clinical investigator. Both outcome measures were included in the meta-analysis.

The IRLS is a 10-item patient completed instrument assessing the frequency and severity of RLS symptoms over the preceding week, developed and validated by the International RLS Study Group [12]. Responses are graded from 0 to 4 (e.g. 0 = absence of problem, 4 = very severe problem), with a maximum total score of 40. The reduction in the severity of the symptoms is measured as the mean change (reduction) in IRLS total severity scores.

The CGI-I is a clinician completed, 7-point scale ranging from 1 ("very much improved") to 7 ("very much worse") [13]. The reporting interval covers seven days. A treatment response on the CGI-I scale was defined as a report of "very much improved" (score of 1) or "much improved" (score of 2), assessing a patient's overall condition.

2.2.2. Safety and tolerability

The most frequently reported reasons for discontinuation, which are lack of efficacy, adverse events (AEs) or other reasons, were included in the meta-analysis. For the AEs, the analysis was focused on the most frequently reported AEs (>5%) for the pramipexole or ropinirole groups, which included nausea, headache, fatigue, somnolence, vomiting, dizziness, insomnia, and nasopharyngitis.

2.3. Data extraction

Information on study design (treatment comparators, dosage, trial duration, and patient population), along with patient baseline characteristics (age, sex, and IRLS score) and summary statistics of efficacy (IRLS and CGI-I) and tolerability outcomes (as detailed above) were extracted from the qualifying studies.

2.4. Statistical analysis

2.4.1. Between-study heterogeneity at baseline

Between-study differences were assessed using either the analysis of variance (ANOVA) on continuous baseline measures (age, IRLS score) or the Cochran–Mantel–Haenszel test for categorical variables such as gender.

2.4.2. Efficacy and tolerability outcome measures

The only continuous outcome included in the meta-analysis, the mean change in IRLS score, was reported using the absolute mean difference.

Binary outcomes such as response on the CGI-I scale and AEs were calculated using the log-odds ratio. Log-odds ratios were back-transformed and treatment differences were reported as odds-ratios (OR).

2.4.3. Direct comparison

We performed a meta-analysis to combine the clinical efficacy endpoints (IRLS and CGI-I) for each of the selected pramipexole and ropinirole trials. Both drugs are compared to a common comparator which is placebo. The results of the direct comparison (drug versus placebo) will provide for each drug a single clinical efficacy estimate. The pooled estimate for each drug is a weighted average of the individual estimate, using the inverse-variance of each trial as a weight. The direct meta-analyses were performed to estimate effect sizes for each active drug versus placebo and were conducted using a classical frequentist and Bayesian approach [14] (see Technical Appendix (A) for model details). The Cochran *Q*-test for heterogeneity was used to assess between-study variability. However, this test is known to have low power, especially when applied to a small number of studies. The heterogeneity test was therefore completed using an alternative approach suggested by Higgins et al. (2003) [15] to quantify the effect of heterogeneity by providing a measure to estimate the degree of inconsistency in the study results, the *I*-square (I^2).

I^2 measures the proportion of inconsistency in individual studies that cannot be explained by chance. Values for I^2 range between 0% and 100%, with lower values representing less heterogeneity. An informal categorization classifies values of 25%, 50%, and 75% as representative of low, moderate, and high heterogeneity, respectively. In the random-effect models, the presence of heterogeneity was also measured by the between-study variance (τ^2) with $\tau^2 = 0$ indicating no presence of heterogeneity.

Forest plots of individual study estimates with confidence intervals were presented to provide a complementary means to detect any presence of heterogeneity by visual inspection.

Superiority tests for each outcome were performed for the direct comparisons of the two treatments compared with placebo using a two-sided $(1 - \alpha)$ level confidence interval (with $\alpha = 2.5\%$).

2.4.4. Indirect comparison

Due to the absence of comparative trials for pramipexole and ropinirole in the treatment of RLS, an indirect meta-analysis using placebo as the common comparator was performed using a Bayesian meta-analysis approach [16,17] (see Technical Appendix (B & D) for model details and WinBUGS code).

The parameters in all Bayesian meta-analysis models were estimated using Markov Chain Monte Carlo (MCMC) methods implemented in WinBUGS 1.4.1 [18].

Convergence was assessed by considering different initial starting values and by varying the lengths of both 'burn-in' and sample size [19]. Final parameter estimates are based on a 'burn-in' length of 50,000 iterations and a sample size of 100,000.

Non-inferiority of pramipexole versus ropinirole was tested first, followed by superiority (hierarchical testing). Clinical non-inferiority was specified using a predefined non-inferiority margin for pramipexole versus ropinirole. Non-inferiority means that the treatment effect of pramipexole versus ropinirole is no worse than the pre-specified non-inferiority margin denoted as Δ (see Technical Appendix (C) for more details). As suggested by the Committee for Medicinal Products for Human Use (CHMP) [20], the selection of the non-inferiority margin was based upon a combination of statistical reasoning and clinical judgment. The non-inferiority margin was defined for the mean change in IRLS score and CGI-I response. Margins were based on the report "Recommendation of the Commission" from the French transparency committee (December 2004) [21] and on the report "Rapport public d'évaluation" from the AFSSAPS (November 2004) [22], regarding the treatment of ropinirole in RLS. From these two reports, a difference of six points between the active treatment group and placebo on the IRLS and a difference from 12% to 20% for the number of CGI-I responders ("much improved" or "very much improved") between the active treatment group and placebo was determined to be clinically significant. Also, a treatment difference >3 points on the IRLS was quoted as clinically meaningful by the SMC [23,24]. In addition, the lower bound of the 95% CI for the treatment effect (change in IRLS score) from the 12-week pramipexole study and one of the 12-week ropinirole studies was found to be −2.1 points and −2.0 points, respectively [34,52]. Combining the information from these sources, a difference of 2.5 points for the IRLS score between pramipexole and ropinirole and a 10% change for the number of CGI-I responders were considered as non-significant clinical differences and used as the non-inferiority margins.

For both the direct and indirect comparisons, using a Bayesian approach, the associated posterior probabilities of non-inferiority and superiority were estimated, as well as 95% credibility intervals (CrI) which are analogous to frequentist confidence intervals (CI). Whilst 95% equal tail-area (2.5%) CrIs are presented, posterior probabilities $\geqslant 95\%$ were deemed to indicate *statistical superiority*.

2.4.5. Sensitivity analyses

Sensitivity analyses were performed to test the robustness of the results including pramipexole and ropinirole trials in RLS, which used the same outcome measures but had different study designs. Also, various non-informative prior distributions were applied to the between-study variance for the indirect comparison using random-effects models [25].

3. Results

3.1. Study data and literature search

From the literature search performed in December 2005 and updated in July 2006, a total of 14 studies in the treatment of RLS (4 for pramipexole [26–29] and 10 for ropinirole [30–39]) were identified. All were recent studies published between 1999 and 2006.

A search of the ropinirole manufacturer's trial register resulted in a total of 12 clinical trials for ropinirole in RLS [40]. Four clinical studies were conducted by the manufacturer of pramipexole to evaluate the efficacy and safety of PPX in RLS for which study reports were made available [29,41–43].

From the literature search, four investigator initiated studies were identified that used small sample sizes without evidence of power calculations (range: 7–22 patients) and different endpoint definitions [26–28,32], and three other studies differed in study designs, inclusion criteria, or primary endpoints [29,31,33].

Two of the four clinical trials conducted by the manufacturer and nine of the ropinirole trials had different designs (withdrawal studies, open-label extension studies, or polysomnographic studies) and did not use change in IRLS score as the primary endpoint. Hence, they were excluded from the primary meta-analysis. The two polysomnographic studies, each for pramipexole and ropinirole, were, however, included in the sensitivity analysis [29,33].

Therefore, the primary meta-analysis included two trials for pramipexole and three trials for ropinirole [30,34,37].

3.2. Study design and baseline characteristics

The primary objective of all eligible studies was to compare the efficacy and safety of the study drugs, pramipexole or ropinirole, with placebo in the treatment of RLS. Study inclusion criteria were similar for all pramipexole (ropinirole) trials: adult male and female patients aged between 18 and 80 years (18–79 years) with idiopathic (primary) RLS, a total score >15 ($\geqslant 15$) on the IRLS scale at baseline, and the presence of RLS symptoms of at least two to three days per week within the previous three months (a history of at least 15 nights of RLS symptoms during the previous month). The primary outcome was the mean change from baseline in the IRLS total score at the end of the trial. The change was adjusted for baseline characteristics (age and IRLS at baseline for pramipexole and only on IRLS at baseline for ropinirole). Adjusting for age in the pramipexole studies had no significant impact on the primary endpoint. The response on the CGI-I scale was a co-primary endpoint in the pramipexole studies, and a secondary endpoint in the ropinirole studies.

Table 1 illustrates the study design and baseline characteristics of the two pramipexole studies ($n = 689$) [41,42] and the three ropinirole studies ($n = 931$) [30,34,37] included in the meta-analysis.

The pramipexole studies differed in design with a treatment duration between six and twelve weeks [41,42]. Also the six-week study used a flexible dose design with doses of 0.125–0.75 mg and the twelve-week study used a fixed dose design of 0.25, 0.50, and 0.75 mg [41,42]. All ropinirole studies used a flexible dose design with doses of 0.25–4.0 mg over a treatment period of twelve weeks [30,34,37]. In testing for overall between-study heterogeneity for studies included in the main analysis, no heterogeneity was found for gender ($p = 0.558$), age ($p = 1.000$), and baseline IRLS score ($p = 0.568$).

The two polysomnographic studies included in the sensitivity analysis had additional inclusion criteria that required patients to have a PLMI of $\geqslant 5$ periodic leg movements per hour of sleep during the polysomnography visit at or prior to baseline. The primary outcome was the mean change in periodic leg movement while change in IRLS and CGI-I response were evaluated as secondary endpoints.

3.3. Direct meta-analyses

Both frequentist and Bayesian approaches provided similar results. Only the results from the random-effects frequentist approach are provided for the direct comparison.

3.3.1. Heterogeneity

Between-study heterogeneity was assessed using the Q-test and the I^2 for the fixed-effects model and the between-study variance estimate τ^2 for the random-effects models. The Q-test was not statistically significant for any outcomes considered in the analysis; however, using the I^2 criteria, moderate heterogeneity was found between the pramipexole studies for the mean change in IRLS score ($I^2 = 54.25\%$) and the number of withdrawals due to any reasons ($I^2 = 51.38\%$), withdrawal due to adverse events ($I^2 = 38.71\%$), the incidence of nasopharyngitis ($I^2 = 44.27\%$) and nausea ($I^2 = 26.77$). For all other outcomes the heterogeneity was found to be low ($<25\%$). The heterogeneity between the ropinirole trials was low with the exception of withdrawal due to adverse events ($I^2 = 54.10\%$). For the random effects model the τ^2 showed overall low between-study heterogeneity for the pramipexole and ropinirole studies (most values for τ^2 being 0 or close to 0) with the exception of change in IRLS ($\tau^2 = 1.44$) in the pramipexole studies. Between-study heterogeneity was found to be lower for the ropinirole studies than the pramipexole studies included in the meta-analysis.

Table 1
Study design and patient baseline characteristics

Study by treatment	Duration follow up (weeks)	Drug	Dose (mg)	Safety population (*N*)	FAS/ITT[a] population (*N*)	Female (%)	Age (years) mean (SD)	Baseline IRLS score mean (SD)	Adjusted mean change in IRLS score (SE)	CGI-I responder rates *n*/*N* (%)
Pramipexole										
Trials included in primary analysis										
520[41]	6	PPX	Flexible (0.125–0.75 mg)	230	224	64.3	55.4 (11.6)	24.7 (5.2)	−12.3 (0.6)	141/224 (62.9)
	6	PBO	–	115	114	68.4	55.8 (10.9)	24.9 (5.4)	−5.7 (0.9)	37/114 (32.5)
543[42]	12	PPX	0.25 mg	88	88	63.6	53.4 (12.7)	23.4 (4.9)	−12.8 (1.0)	65/87 (74.7)
	12	PPX	0.5 mg	80	79	54.4	49.6 (12.7)	22.9 (5.1)	−13.8 (1.0)	53/78 (67.9)
	12	PPX	0.75 mg	90	87	66.7	50.9 (12.4)	24.1 (5.2)	−14.0 (1.0)	62/85 (72.9)
	12	PBO	–	86	85	63.5	51.5 (14.0)	23.5 (5.2)	−9.3 (1.0)	43/84 (51.2)
Trial included in sensitivity analysis										
515[29]	3	PPX	0.125 mg	21	21	71.4	60.0 (10.1)	22.4 (4.6)	−11.7 (1.4)[c]	13/21 (61.9)
	3	PPX	0.25 mg	22	22	72.7	54.8 (10.9)	23.0 (3.4)	−15.3 (1.9)[c]	15/22 (68.2)
	3	PPX	0.5 mg	22	22	81.8	58.4 (9.5)	23.6 (3.7)	−17.6 (1.7)[c]	19/22(86.4)
	3	PPX	0.75 mg	22	21	61.9	54.5 (12.2)	21.7 (4.7)	−15.2 (1.5)[c]	18/21 (85.7)
	3	PBO	–	22	21	81.0	53.3 (11.1)	22.9 (4.2)	−6.2 (1.4)[c]	9/21 (42.9)
Ropinirole										
Trials included in primary analysis										
190[37]	12	RPR	Flexible (0.25–4 mg)	146	146	60.3%	54.0 (11.1)	24.4 (5.8)	−11.0 (0.7)	78/146 (53.4)
	12	PBO	–	138	138	65.9	56.2 (11.2)	25.2 (5.6)	−8.0 (0.7)	56/137 (40.9)
194[34]	12	RPR	Flexible (0.25–4 mg)	131	131	58.0	54.9 (10.9)	23.6 (5.9)	−11.2 (0.8)	78/131 (59.5)
	12	PBO	–	136	135	61.4	56.0 (11.3)	24.8 (5.4)	−8.7 (0.8)	53/134 (39.6)
249[30]	12	RPR	Flexible (0.25–4 mg)	187	187	58.3	52.2 (12.8)	22.0 (5.0)	−13.5 (0.6)	137/187 (73.3)
	12	PBO	–	193	193	63.7	52.4 (13.2)	21.6 (4.8)	−9.8 (0.6)	109/193 (56.5)
Trial included in sensitivity analysis										
191[33]	12	RPR	Flexible (0.25–4 mg)	36	32	65.9	54.6 (12.1)	–[b]	−10.7 (1.5)	17/32 (53.1)
	12	PBO	–	37	33	58.0	53.2 (12.9)	–[b]	−9.6 (1.4)	17/33 (51.5)

[a] Full analysis set (FAS), Intention-to-treat analysis (ITT).
[b] Not available.
[c] SE estimated from SD.

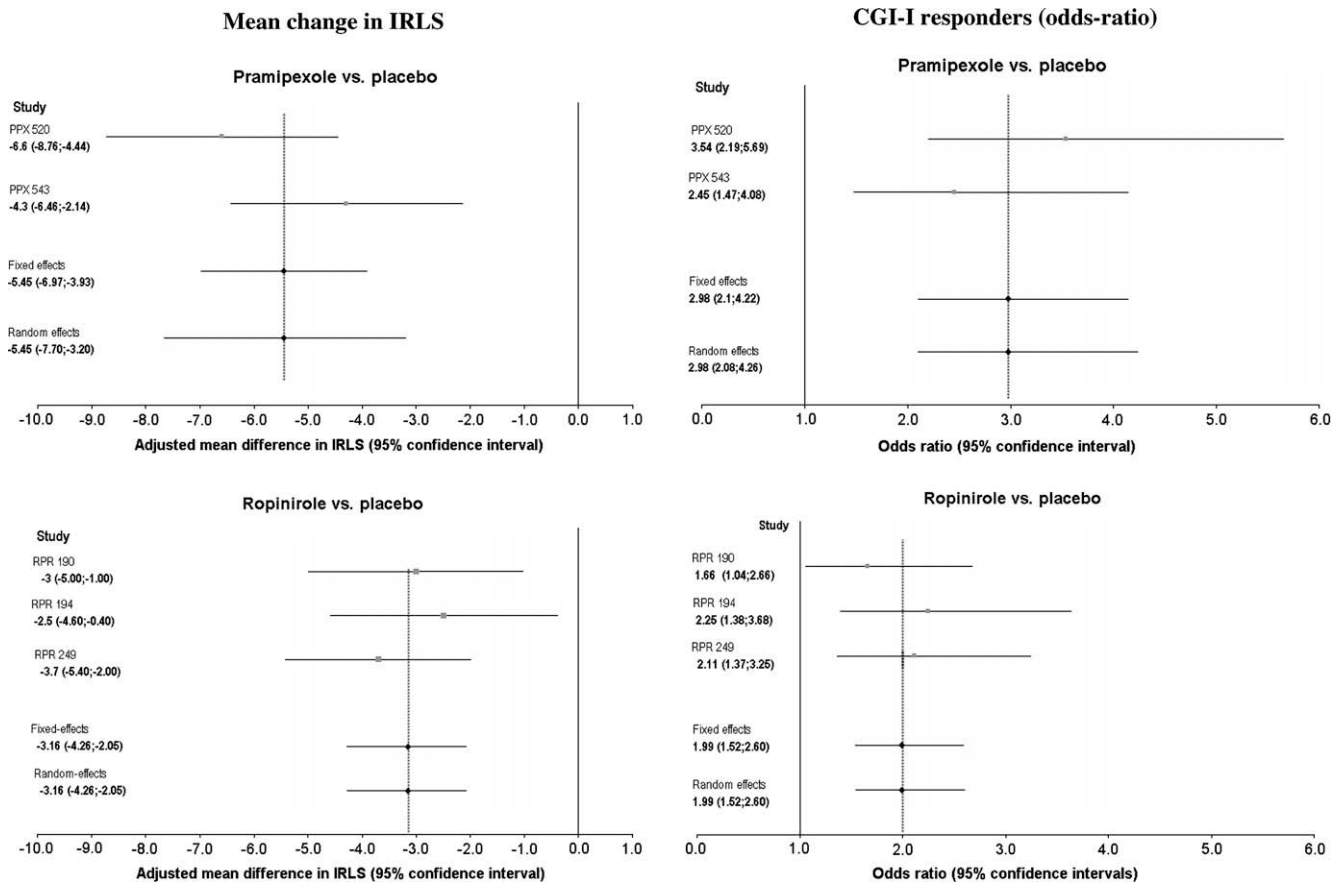


Fig. 1. Direct comparisons drug versus placebo for both efficacy outcomes.

While investigating the forest plots, it appeared that the six-week study for pramipexole showed, on average, a larger change in IRLS score and higher CGI-I responder rate than the pramipexole twelve-week study (Fig. 1). However, both frequentist fixed and random-effects estimates were very similar for pramipexole, suggesting an absence of substantial heterogeneity for these two outcomes. Therefore, only results from the random-effects models are reported here (Tables 2 and 3). Heterogeneity was found to be low between the ropinirole studies (Fig. 1).

3.3.2. Efficacy outcomes

The mean change from baseline in the IRLS score was statistically, significantly larger for both drugs compared to placebo (pramipexole: −5.45; 95% CI: −7.70; −3.20; ropinirole: −3.16; 95% CI: −4.26; −2.05; all $p < 0.0001$). Also the odds-ratios of the proportion of CGI-I responders were statistically, significantly higher (pramipexole: OR = 2.98; 95% CI: 2.08; 4.26; ropinirole: OR = 1.99; 95% CI: 1.52; 2.60; all <0.0001). CGI-I responder rates of the direct comparison for pramipexole and ropinirole, each against placebo, can alternatively be expressed using the numbers needed to treat (NNT). The NNT is defined by the number of patients who need to be treated with the new treatment rather than the control treatment for one additional patient to benefit. Results of the direct comparison provide a NNT of 4 (95% CI: 3; 5) for pramipexole and 6 (95% CI: 4; 10) for ropinirole. The NNTs calculated from the direct comparison confirm the results of the NNTs calculated from the individual studies for pramipexole (the NNT for trial 520 was: 3; 95% CI: 2; 5 and for trial 543: 5; 95% CI: 3; 11) and ropinirole (the NNT for trial 190 was: 8; 95% CI: 4; 99; for trial 194: 5; 95% CI: 3; 12 and for trial 249: 6; 95% CI: 4; 14).

3.3.3. Tolerability outcomes

Compared to placebo, nausea was found with a statistically, significantly higher incidence in patients receiving pramipexole (OR = 3.02; 95% CI: 1.38; 6.63; $p = 0.006$), whereas patients receiving ropinirole showed a significantly higher incidence of nausea (OR = 8.37; 95% CI: 5.66; 12.38; $p < 0.0001$), somnolence (OR = 2.02; 95% CI: 1.27; 3.24; $p = 0.003$), vomiting (OR = 6.94; 95% CI: 3.24; 14.84; $p < 0.0001$), and dizziness (OR = 2.19; 95% CI: 1.31; 3.66; $p = 0.003$). Incidence of withdrawal due to lack of efficacy was found to be lower in ropinirole patients compared to placebo (OR = 0.39; 95% CI: 0.18; 0.87; $p = 0.021$).

Table 2
Direct comparison (random-effects model): drug versus placebo

Outcomes	PBO n/N (%)	PPX n/N (%)	Treatment effect[a,b]	τ^2
Pramipexole (PPX) versus placebo (PBO)				
Efficacy				
Mean change in IRLS (SE)[c]	−7.25 (0.68)	−12.94 (0.43)	−5.45 (−7.70; −3.20)***	1.435
Response to the CGI-I	80/198 (40.4)	321/474 (67.7)	2.98 (2.08; 4.26)***	0.004
Tolerability				
Withdrawals due to any reasons	19/201 (9.5)	64/488 (13.1)	1.19 (0.52; 2.72)	0.185
Adverse events	8/201 (4.0)	36/488 (7.4)	1.37 (0.50; 3.80)	0.215
Lack of efficacy	9/201 (4.5)	12/488 (2.5)	0.58 (0.23; 1.46)	0
Other	2/201 (1.0)	16/488 (3.3)	2.33 (0.60; 9.00)	0
Nausea	11/201 (5.5)	77/488 (15.8)	3.02 (1.38; 6.63)**	0.088
Headache	26/201 (13.0)	76/488 (15.6)	1.18 (0.73; 1.91)	0
Fatigue	11/201 (5.5)	34/488 (7.0)	1.36 (0.67; 2.74)	0
Somnolence	7/201 (3.5)	32/488 (6.6)	1.69 (0.72; 3.97)	0
Vomiting	4/201 (2.0)	14/488 (2.9)	1.36 (0.43; 4.38)	0
Dizziness	12/201 (6.0)	33/488 (6.8)	1.02 (0.48; 2.18)	0.041
Insomnia	10/201 (5.5)	29/488 (6.0)	1.01 (0.47; 2.16)	0
Nasopharyngitis	13/201 (6.5)	27/488 (5.5)	0.84 (0.32; 2.20)	0.219
Outcomes	PBO n/N (%)	RPR n/N (%)	Treatment effect[a,b]	τ^2
Ropinirole (RPR) versus placebo (PBO)				
Efficacy				
Mean change in IRLS (SE)[a]	−8.95 (0.40)	−12.06 (0.40)	−3.16 (−4.26;-2.05)***	0
Response in CGI-I	218/464 (47.0)	293/464(63.2)	1.99 (1.52;2.60)***	0
Tolerability				
Withdrawals due to any reasons	84/467 (18.0)	86/464 (18.5)	1.03 (0.74; 1.44)	0
Adverse events	26/467 (5.6)	31/464 (6.7)	1.17 (0.51; 2.68)	0.290
Lack of efficacy	22/467 (4.7)	9/464 (1.9)	0.39 (0.18; 0.87)*	0
Other	36/467 (7.7)	46/464 (9.9)	1.32 (0.83;2.08)	0
Nausea	35/467 (7.5)	187/464 (40.3)	8.37 (5.66; 12.38)**	0
Headache	94/467 (20.1)	89/464 (19.2)	0.94 (0.68; 1.31)	0
Fatigue	17/467 (3.6)	29/464 (6.3)	1.75 (0.94; 3.27)	0
Somnolence	29/467 (6.2)	55/464 (11.9)	2.02 (1.27; 3.24)**	0
Vomiting	8/467 (1.7)	51/464 (11.0)	6.94 (3.24; 14.84)***	0
Dizziness	24/467 (5.1)	50/464 (10.8)	2.19 (1.31; 3.66)**	0.003
Insomnia	28/467 (6.0)	23/464 (5.0)	0.81 (0.45; 1.44)	0
Nasopharyngitis	23/467 (4.9)	21/464 (4.5)	0.94 (0.51; 1.73)	0

[a] Treatment difference in IRLS.
[b] Odds-ratio for response in CGI-I and all tolerability outcomes.
[c] Mean (SE) based on weighted average.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.0001$.

3.4. Indirect comparison meta-analysis

3.4.1. Efficacy outcomes

The indirect meta-analysis using a fixed-effects model tested first for non-inferiority of pramipexole against ropinirole using the pre-specified non-inferiority margins for IRLS and CGI-I and then for superiority, including both statistical significance and clinical significance as presented in Table 3 and Fig. 2. Results show a superior reduction for the primary outcome with a mean change in IRLS of −2.33 points (95% CrI: −4.23; −0.41) for pramipexole versus ropinirole. The probability that pramipexole was non-inferior to ropinirole for this outcome was 100%, while there was a 99% probability that the difference was greater than zero and a 43% probability that it was greater than the pre-specified clinically significant difference. Similar results favouring pramipexole over ropinirole were found for CGI-I responders. The odds of responding were 1.50 (95% CrI: 0.97; 2.32) for pramipexole versus ropinirole, which translated into a probability of pramipexole being non-inferior by 99%, the difference being greater than zero and greater than the pre-specified clinically significant difference with a probability of 97% and 92%, respectively.

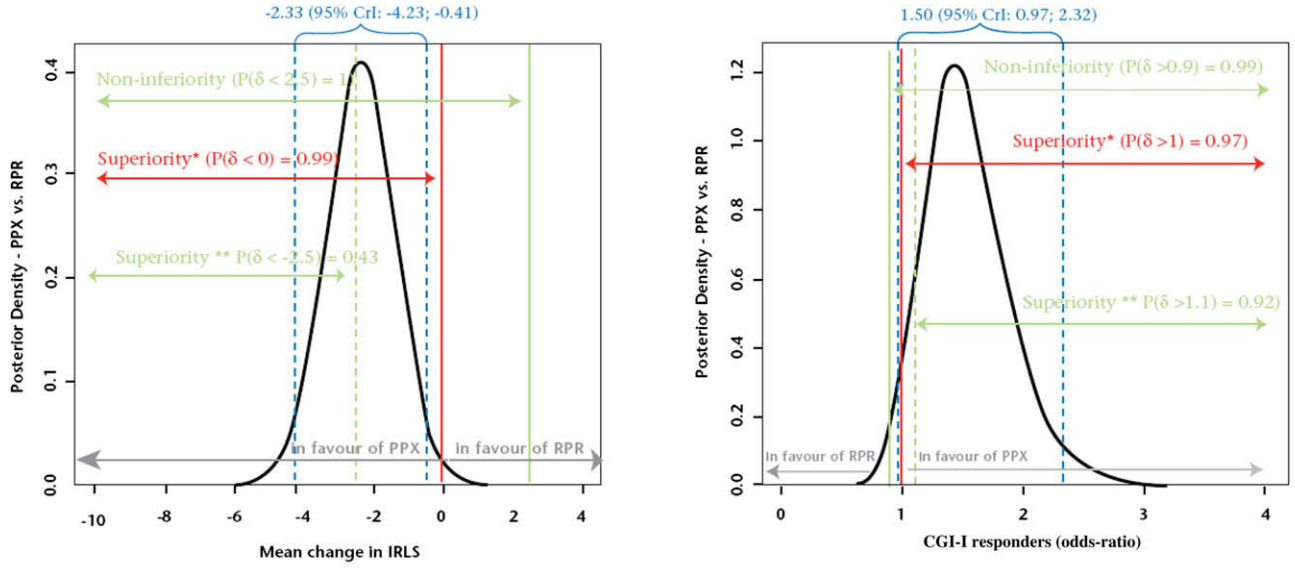
3.4.2. Tolerability outcomes

The incidence of nausea (OR = 0.37; 95% CrI: 0.18; 0.84), vomiting (OR = 0.21; 95% CrI: 0.05; 0.93), and

Table 3
Indirect comparison (fixed-effects model): pramipexole (PPX) versus ropinirole (RPR)

Outcomes	Treatment effect[a,b] [mean/ median (95% CRI)] PPX versus RPR	Probability of non-inferiority[c]	Probability of PPX > RPR is significant[d]	Probability of PPX > RPR is clinically relevant[e]
Efficacy				
Mean change in IRLS[a]	−2.33 (−4.23; −0.41)	1.00	0.99	0.43
Response in CGI-I[b]	1.50 (0.97; 2.32)	0.99	0.97	0.92
Tolerability				
Withdrawals due to any reasons	1.27 (0.68; 2.47)		0.23	
Lack of efficacy	1.54 (0.47; 5.54)		0.24	
Adverse events	1.29 (0.53; 3.44)		0.30	
Other	1.99 (0.53; 11.43)		0.17	
Nausea	0.37 (0.18; 0.84)		0.99	
Headache	1.27 (0.72; 2.29)		0.21	
Fatigue	0.76 (0.30; 2.02)		0.71	
Somnolence	0.89 (0.35; 2.48)		0.60	
Vomiting	0.21 (0.05; 0.93)		0.98	
Dizziness	0.47 (0.20; 1.13)		0.95	
Insomnia	1.26 (0.50; 3.39)		0.32	
Nasopharyngitis	0.90 (0.36; 2.33)		0.58	

[a] Treatment effect: absolute mean change in IRLS.
[b] Treatment effect: odds-ratios for response in CGI-I, and all tolerability outcomes.
[c] Non-inferiority: area under the curve from 2.5 for IRLS:]−∞ to 2.5 [and 0.9 for CGI-I:] 0.9 to +∞ [.
[d] Superiority: area under the curve from 0 for IRLS:]−∞ to 0 [; and 1 for CGI-I:] 1 to +∞ [.
[e] Clinical superiority: area under the curve from −2.5 for IRLS:]−∞ to −2.5 [; and 1.1 for CGI-I:] 1.1 to +∞ [.



Where $\delta = d_{ck} - d_{cb}$ (See Appendix B for more details)
Three important probabilities can be deduced from above Figures:

- Probability of non-inferiority of pramipexole to ropinirole, with a non-inferiority margin of 2.5 for IRLS and 10% for CGI-I => area under the curve from the vertical solid line with the X-value of 2.5 for IRLS:]- ∞to 2.5[; or 0.9 for CGI-I:] 0.9 to + ∞[
- Probability of superiority* of pramipexole to ropinirole area under the curve from the vertical solid line with the X-value of 0 for IRLS:]- ∞to 0[; and 1 for CGI-I:] 1 to + ∞[
- Probability of clinical superiority** of pramipexole to ropinirole with a non-inferiority margin of -2.5 for IRLS and 1.1 for CGI-I => area under the curve from the vertical dotted line with the X-value of −2.5 for IRLS:]- ∞to -2.5[; and 1.1 for CGI-I:]1.1 to + ∞[

The vertical dotted lines represent the border of the 95% CrI of the parameter.

Fig. 2. Indirect comparison: posterior distribution pramipexole versus ropinirole for both efficacy outcomes.

dizziness (OR = 0.47; 95% CrI: 0.20; 1.13) was found to be significantly lower under treatment with pramipexole compared to ropinirole, with a probability of 99%, 98% and 95% for each outcome, respectively.

3.4.3. Sensitivity analyses

Several sensitivity analyses were performed to test the robustness of the analysis. The results of adding the polysomnographic studies for pramipexole [29] and ropinirole [33] to the meta-analysis showed the same patterns, favouring pramipexole over ropinirole for the efficacy and safety outcomes: pramipexole was superior to ropinirole with a probability of 99% for the mean change in the IRLS score (−3.09; 95% CrI: −4.84; −1.34) and response on the CGI-I (OR = 1.63; 95% CrI: 1.07; 2.47). Pramipexole was associated with a considerably lower incidence of nausea (OR = 0.40; 95% CrI: 0.20; 0.88), vomiting (OR = 0.19; 95% CrI: 0.05; 0.83), and dizziness (OR = 0.40; 95% CrI: 0.18; 0.95) versus ropinirole, with a probability of both 99% for nausea and vomiting and 95% for dizziness.

Using different non-informative prior distributions (uniform (0,2); half-normal (0, 2), and gamma (0.0001; 0.0001)) on the between variance study estimate τ^2 for the random-effects models resulted in the same mean (for IRLS)/median (for odds-ratio) estimates but with wider credibility intervals.

4. Discussion

Several expert reviews in the treatment of RLS have been published. Most recent reviews [44–47] have suggested that dopaminergic agents including levodopa, pramipexole, ropinirole, cabergoline, pergolide, and rotigotine are the best-studied agents to be considered in first-line treatment of restless legs syndrome (RLS) [8]. Levodopa was the first dopaminergic agent used in the treatment of RLS and is mainly used for patients with mild and intermittent symptoms or for patients who have only periodic limb movements in sleep. The development of augmentation renders it less useful for daily treatment. Dopamine agonists generally have a longer half-life duration and are more useful for patients whose symptoms present for a more sustained period. Ergoline derivatives such as pergolide or cabergoline have a high sustained action (40-h half-life) and may cause less augmentation during treatment; however, they have been implicated in heart valve disorders and fibrotic syndromes. Consequently, pergolide has recently been withdrawn from the market by the FDA [48].

As a result of their potential adverse effects on cardiac function, ergoline drugs have recently ceded place to the non-ergoline agonists [46]. Two non-ergoline derivatives, ropinirole and pramipexole, are currently approved for use in Europe and the United States. They generally require some titration to reach the effective dose. Several other dopaminergics have been tested in patients with RLS [46]. Apomorphine can be given as a subcutaneous preparation and has a rapid onset of action. Rotigotine and lisuride, two patch preparations which offer the advantage of continuous release, may also reduce augmentation. These drugs are currently under development.

Consequently, we performed a meta-analysis to compare the efficacy and tolerability of the only two non-ergoline dopamine agonist treatments in RLS (pramipexole and ropinirole) that have been approved by regulatory authorities and are both indicated for the treatment of moderate to severe idiopathic RLS.

Meta-analysis is a well-established statistical technique for pooling the results of individual clinical trials, allowing for overall conclusions to be made on the evidence concerning effect sizes of interventions and differences between comparators, where comparative trials are lacking. Song et al. [49] proposed that an adjusted indirect comparison may provide useful information on the relative efficacy of the competing treatments with results usually, but not always, agreeing with those of head-to-head randomised trials.

The number of pramipexole and ropinirole studies in RLS retrieved through the literature search was small, with a total of 14 studies of which only five were eligible for inclusion in the main meta-analysis. Trial designs across the selected studies were similar with regard to outcome measures and patient characteristics. The direct meta-analyses illustrated that pramipexole and ropinirole are significantly more effective than placebo for the mean change in IRLS score from the baseline, as well as the proportion of CGI-I responders. Compared to placebo, adverse event rates were more common for treatment with ropinirole, with nausea, somnolence, vomiting, and dizziness being significantly more frequent. Pramipexole showed a significantly higher incidence only for nausea compared to placebo. NNTs were calculated from the direct comparison, confirming the patterns observed for the individual study NNTs. There are debates on whether reporting NNTs from meta-analysis is misleading, as they are highly sensitive to variation in risk differences between studies [50]. However, as the meta-analysis was performed on relatively homogeneous trials, we believe that the NNTs based on the pooled relative risk estimates determine the potential benefit of each treatment for an individual patient.

The indirect comparison between pramipexole and ropinirole using placebo as the common comparator showed that the reduction in the IRLS score and the proportion of CGI-I responders was in favour of pramipexole both for the probability of non-inferiority and the probability of these differences being statistically and clinically meaningful. The tolerability results demonstrated significantly lower incidence of nausea, vomiting, and dizziness in patients being treated with pramipexole.

Sensitivity analyses were performed in order to test the robustness of these findings. Due to the very small amount of information, the use of random-effects

models with different prior distributions resulted in an increase in the uncertainty around the treatment difference estimates, but results remained very consistent with those obtained with the fixed-effects models. The inclusion of the two polysomnographic studies in the analysis further favoured pramipexole. This is partially due to the introduction of the pramipexole polysomnographic study, which also has a shorter trial duration compared to the other trials included in the meta-analysis. The ropinirole polysomnographic study had previously been pooled with the three other twelve-week studies to estimate the treatment dose of CGI-I responders [51]. One of the restrictions of the current analysis was the impossibility of exploiting the full power of Bayesian analysis [25]. The limited number of identified or external studies did not enable the construction of informative prior distributions for the random-effects model. Therefore, the results of the sensitivity analyses based on three selected non-informative priors for the between-study variance only resulted in an increase of uncertainty around the estimates.

All ropinirole trials had a twelve-week treatment duration, and therefore inclusion of the six-week pramipexole trial (520 study) in the meta-analysis may have benefited pramipexol. We, therefore, explored the influence of each individual study on the overall results by removing each one in turn and re-running the models. The model fit was assessed by calculating the DIC and residual deviance [52], and data-model consistency was examined by comparing the actual data points with those predicted by the model using Bayesian mixed *p*-values [53,54].

In terms of study influence on response in CGI-I, no single study unduly affects the overall result, though for IRLS, removing study 520 does produce an overall pooled estimate of difference in mean change from the baseline which, whilst in the same direction as that using all studies, has much greater uncertainty associated with it and consequently produces a posterior probability of superiority of PPX over RPR of 0.79.

In terms of model fit, both fixed-effect models for CGI and IRLS appeared to fit well with residual deviances of 8.9 and 10.1, respectively, based on 10 data points. No single data point appeared to contribute unduly to the overall residual deviance, and there was no evidence of data-model inconsistency, with the lowest *p*-value being 0.25.

The occurrence of adverse events was found to be more frequent in the first weeks of treatment with dopamine agonists, as confirmed by the literature [55] and the findings from the pramipexole clinical trials included in the meta-analysis [42]. Therefore, the inclusion of the 520 study did not favour pramipexole with respect to the incidence of adverse events.

The 520 study had the second longest observation period in the pramipexole development program and had to be included in the meta-analysis apart from study 543.

The possibility of study selection bias is always a potential threat to the validity of meta-analyses. However, we aimed to limit the possibility of selection bias by including additional studies in the sensitivity analysis. Also, the potential for publication bias was reduced by having identified all published studies for both pramipexole and ropinirole through the literature search, availability of study reports for pramipexole, and studies listed in the clinical trial register for ropinirole. However, due to the limited number of studies included in the meta-analyses, formal methods for either the detection of or adjustment for publication bias could not be used [56].

Findings of this meta-analysis require further investigation into the factors contributing to differences in efficacy and tolerability of the two treatments under study. Potential factors to be investigated include treatment half-life, effective treatment dose, titration period, and treatment effect on depressive symptoms, pain, and quality of life.

In conclusion, differences in efficacy and tolerability favouring pramipexole over ropinirole can be observed. These findings should be further confirmed in head-to-head clinical trials.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.sleep.2007.11.020.

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