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Tolerability and Safety of Ropinirole versus Other Dopamine Agonists and Levodopa in the Treatment of Parkinson's Disease

Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Dopamine agonists have a well established role in the treatment of Parkinson's disease. The choice of a particular dopamine agonist requires assessing the benefit-risk balance of each available medication.

Objective: The present study evaluated the tolerability and safety of ropinirole against those of other dopamine agonists (bromocriptine, cabergoline, pramipexole, rotigotine, pergolide) and placebo in monotherapy and adjuvant therapy with levodopa in the treatment of Parkinson's disease, as reported in the peer reviewed medical literature.

Methods: A systematic review of the medical literature was carried out for relevant English language articles in the MEDLINE database and Cochrane Library from January 1975 to November 2008. The searches were limited to either double-blind clinical trials or randomized clinical trials that included both patients with early Parkinson's disease receiving dopamine agonist monotherapy, and patients at a later stage on combined treatment with levodopa. The Cochrane Collaboration guidelines were followed and the following data were extracted from each study: identifier (title and bibliographical reference), classification of the quality of the evidence (Jadad criteria), type and design of the study, number of patients, patient demographics (average age, sex), Parkinson's disease stage (Hoehn and Yahr Scale), treatment (monotherapy or adjuvant to levodopa), drugs used (including dosage and duration), study objective (safety or tolerability), method of evaluation of results, randomization and blinding, and description of all the adverse events in all treatment groups. A meta-analysis was performed, calculating relative risks (RRs) and confidence intervals for the 12 most relevant adverse events. On the basis of incidence and clinical importance

criteria, the final selection of 12 adverse events was made by consensus between the investigators.

Results: Forty randomized clinical trials were included. Direct comparison of ropinirole with bromocriptine showed a lower RR of constipation for ropinirole (0.55 [95% CI 0.35, 0.89]), while the direct comparison with levodopa showed a lower RR of dyskinesia for ropinirole (0.25 [95% CI 0.09, 0.71]); no significant differences for either dyskinesia or constipation were found when a direct comparison of ropinirole and rotigotine was made. For nausea, ropinirole, pergolide and rotigotine versus placebo all demonstrated similar RRs (2.25 [95% CI 1.85, 2.74]; 2.28 [95% CI 1.54, 3.37]; and 2.08 [95% CI 1.30, 3.34], respectively). On indirect comparison of ropinirole with pramipexole, ropinirole showed a higher RR for nausea (2.25 [95% CI 1.85, 2.74] vs 1.48 [95% CI 1.24, 1.76]), dizziness (1.87 [95% CI 1.48, 2.37] vs 1.20 [95% CI 1.01, 1.43]), somnolence (2.45 [95% CI 1.30, 4.61] vs 1.68 [95% CI 1.25, 2.25]), and dyskinesia (2.71 [95% CI 1.74, 4.21] vs 2.27 [95% CI 1.58, 3.27]). Pramipexole (3.36 [95% CI 2.41, 4.68], pergolide (4.80 [95% CI 2.24, 10.29]), ropinirole (2.84 [95% CI 1.34, 5.99]), and rotigotine (4.02 [95% CI 1.23, 13.11]) all had a higher RR of hallucinations compared with placebo. Pramipexole also showed a higher RR of confusion (2.64 [95% CI 1.18, 5.91]) and constipation (2.23 [95% CI 1.53, 3.25]) compared with placebo.

Conclusions: In all the included studies, dopamine agonists, including ropinirole, exhibited a higher incidence of adverse events than placebo. Ropinirole showed an adverse event profile similar to other dopamine agonists. Consideration of the clinical characteristics of each patient and the differences in the incidence of adverse events related to each dopamine agonist, may help to optimize the dopamine agonist therapy.

Background

Dopamine agonists, although not as potent as levodopa, have contributed to the improved management of patients with Parkinson's disease both in monotherapy or combined with levodopa. Dopamine agonists have consistently shown their ability to delay the initiation of levodopa therapy and to allow the use of smaller doses of levodopa when this becomes necessary. Dopamine agonists have also shown that they can modify the course of certain motor complications associated with the use of levodopa, such as dyskinesia.[1] While levodopa, a precursor of dopamine, requires intermediate metabolic steps to achieve its pharmacological effect, dopamine agonists directly stimulate the postsynaptic dopamine D_2 receptors. Dopamine agonists can be classified in ergot and non-ergot derivates (see table, Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A22). Ropinirole, pramipexole and rotigotine belong to the group of non-ergot dopamine agonists, and pergolide, cabergoline, bromocriptine and lisuride belong to the group of ergot derivatives.[2,3] Because of the identified risk of cardiac valvulopathy requiring serial echocardiography patient follow-up, the use of pergolide and cabergoline is now reserved for selected cases.

Now the efficacy of these dopamine agonists in the treatment of Parkinson's disease has been demonstrated, it is appropriate to consider the most suitable choice of a given dopamine agonist for an individual patient according to their particular tolerability and safety profiles, in order

to decide on the most favourable benefit-risk profile.

Given that the data on the tolerability and safety for each dopamine agonist are separately reported in different effectiveness studies, it was considered useful to carry out a systematic review of all the information available to date for ropinirole, one of the most widely used dopamine agonists. The rationale of meta-analysis is to combine the results of different studies, thus obtaining indicators that allow comparison of grouped data.[4,5]

In the literature, the adverse events most frequently associated with dopamine agonists are nausea, vomiting, orthostatic hypotension, psychiatric disorders (confusion, hallucinations), headache, somnolence and dyskinesia,[1,6] although it should also be stated that dopamine agonists have also shown a positive effect on the dyskinesia associated with levodopa.

In 2003, Etminan et al.[7] published a meta-analysis that indirectly compared pramipexole and ropinirole with levodopa and placebo with regard to five adverse events. In their study, no significant differences were found in the risk of dizziness, nausea and hypotension, individually or in combination, compared with levodopa. However, when comparing with placebo, a higher risk of hypotension was seen with ropinirole (relative risk [RR] 6.46 [95% CI 1.47, 28.28]) than with pramipexole (RR 1.65 [95% CI 0.88, 3.08]). In addition, pramipexole exhibited a significantly higher risk of hallucinations compared with placebo (RR 5.20 [95% CI 1.97, 13.72]). Finally, in relation to somnolence, the study by Etminan et al.[7] found significant differences in the RR for both drugs versus placebo (RR 2.01 [95% CI 2.17, 3.16] for pramipexole and RR 5.73 [95% CI 2.34, 14.01] for ropinirole).

Considering this data, one could speculate whether the differences found are due to chance, with a similar within-class profile, or whether they represent true differences in the adverse event profile of the various dopamine agonists. Each dopamine agonist may have a specific adverse event spectrum that should be understood in order to optimize the treatment of individual patients with Parkinson's disease.

The objective of this study was to evaluate the tolerability and safety of different dopamine agonists through a systematic review and meta-analysis, taking ropinirole as a reference, analysing the 12 most relevant adverse events according to their frequency and clinical importance. In the absence of direct comparisons, indirect comparisons were made versus placebo and between drugs. Additionally, ropinirole was compared with levodopa in order to provide a more complete safety profile for this drug.

Methods

A systematic search was carried out for relevant English language papers in the MEDLINE database from January 1975 to November 2008. The keywords selected for the search strategy were 'ropinirole OR Requip', in combination with 'parkinson's disease OR parkinsonism', 'dopamine agonists', 'bromocriptine', 'pergolide', 'pramipexole', 'rotigotine', 'non ergoline dopamine agonists', 'rotigotine', 'cabergoline', 'levodopa OR L-dopa'. These key words were, in turn, combined with 'adverse events', 'adverse effects', 'CNS adverse events', 'safety', 'sleep-attack', 'drowsiness', 'sleepiness', 'valvular fibrosis', 'postural hypotension (symptomatic or asymptomatic) OR disease progression'. Finally, these searches were limited to double-blind clinical trials OR randomized clinical trials, in humans.

Although it would be interesting to include all the dopamine agonists approved worldwide, the currently limited use of dihydroergocryptine, lisuride and piribedil in clinical practice, as well as the lack of studies in the literature accomplishing the quality standards, prompted us not to include studies with data restricted to these drugs in this meta-analysis. No studies with drugs in clinical development were included. All randomized controlled clinical trials assessing the safety and tolerability of different dopamine agonists were included. Clinical trials with dopamine agonists for indications other than Parkinson's disease were not considered. There was no restriction with respect to duration of treatment, or any demographic variable.[8,9] The clinical trials selected included both patients with early Parkinson's

disease in dopamine agonist monotherapy, and patients at a later disease stage on adjunctive treatment with levodopa.

The guidelines laid down by the Cochrane Collaboration were adhered to.[10] Thus, a specific form was designed, including the following variables to be extracted from each study: identifier of the study (title and bibliographical reference), classification of the quality of the evidence according to the Jadad criteria,[11] type and design of the study, number of patients analysed, demographic characteristics of the patients (average age, sex), Parkinson's disease stage (Hoehn and Yahr Scale), treatment as monotherapy or adjuvant to levodopa, drugs used (dosage and duration of treatment), objective of the study (safety or tolerability), method of evaluation of results, randomization and blinding, and description of all the adverse events in all treatment groups. The effectiveness of the treatment was recorded, although this was not comparatively analysed since this was not the objective of this study. The extraction of data was performed by two independent assessors. A pilot exercise was carried out with two referees and a representative sample of studies to evaluate the level of concordance and to establish decision rules.

Following the described methodology, 40 studies were selected, for which an exhaustive description of all adverse events was carried out. The reasons for the selection or exclusion of studies are shown in figure 1. For the comparative studies analysed, only those that specifically stated the number of subjects in both groups for the same adverse events were included in the calculation of the tolerability parameter. Comparative studies that only reported frequencies of a specific adverse event for one group were therefore excluded. For the calculation of RR, studies were accepted only if they directly compared ropinirole with levodopa or any dopamine agonist with placebo. No studies were found that made direct comparisons between ropinirole and other dopamine agonists, except for ropinirole versus bromocriptine and ropinirole versus rotigotine. The chosen methodology permitted the following comparisons to be carried out for each adverse event: ropinirole versus placebo, ropinirole versus bromocriptine, ropinirole versus rotigotine, ropinirole versus levodopa, pramipexole versus placebo, bromocriptine versus placebo, pergolide versus placebo, cabergoline versus placebo and rotigotine versus placebo. Thus, nine pairs of comparisons were established.

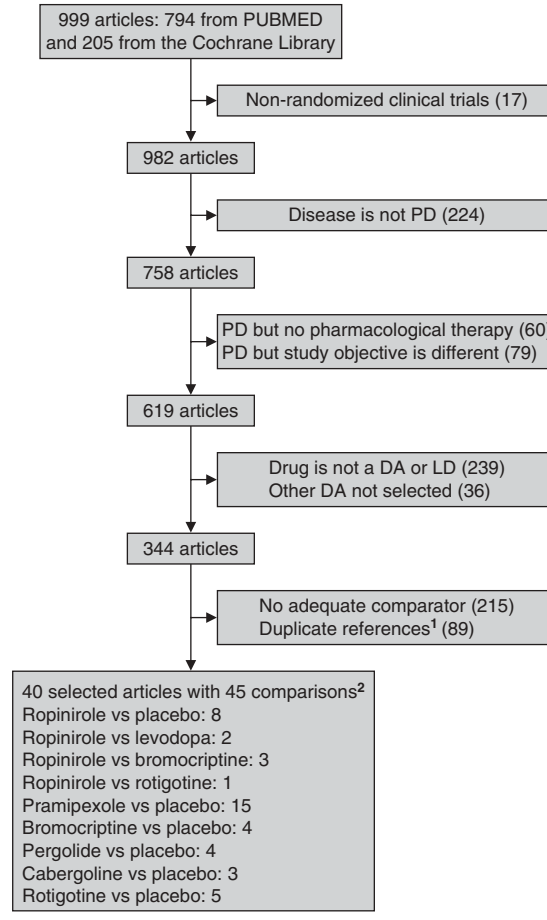

Fig. 1. Literature search flow chart. **1** Some references were duplicates and were therefore eliminated during the review process. **2** Some of the selected studies (Navan et al.,[12] Guttman[13] and Mizuno et al.[14,15]) have two different treatment groups. **DA** = dopamine agonist; **LD** = levodopa; **PD** = Parkinson's disease.

All adverse events were recorded and classified by frequency. On the basis of incidence and clinical importance criteria, a final selection of 12 adverse events was made by consensus between the investigators.

The meta-analysis techniques allowed the RR and 95% CI of each adverse event to be estimated,

following a fixed-effects model, which is considered the most appropriate method of analysis given the method for collection of adverse events and the type of samples selected.[16] The heterogeneity due to the differences in design and in patient characteristics was assessed using the I^2 statistic.[17] For each meta-analysis, the fixed-effects analysis was performed; however, when I^2 was >50%, high heterogeneity was assumed and a random effects analysis was performed.

Finally, a sensitivity analysis was carried out for each of the meta-analyses, by consecutively excluding studies in the various comparisons. A second sensitivity analysis was performed by grouping the studies with and without levodopa. The comparisons between dopamine agonists were made indirectly using placebo as a common comparator.

The Jadad score was also calculated for each of the articles included in the meta-analysis, in order to estimate the validity and quality of the articles included. The average score was 3.5.

Thus, a total of 108 possible meta-analyses were considered; however, in 35 of the cases, the meta-analysis of the data was not possible, either because it included a single clinical trial (on 27 occasions) or because no trial was found (on 8 occasions). In total, 73 meta-analyses were performed. If only one clinical trial was available, this is indicated in the results section.

Results

Following the established criteria for inclusion and exclusion, 794 studies were found and reviewed in the MEDLINE database, and 205 studies in the Cochrane database (clinical trials and reviews). Forty reports (45 comparisons in total considering that several studies contain different treatment groups) were included in the meta-analysis (figure 1).[12-15,18-55]

All selected studies are described in table I. The duration of the study, the type of Parkinson's disease and the number of patients per group are included. In table II, the absolute and relative frequencies are presented for all the adverse events associated with both the active treatment and the placebo groups. Of the 5252 adverse events detected in the 45 comparisons meta-analysed, and on the basis of incidence criteria and clinical importance, the following adverse events were selected for comparative analysis of tolerability and safety: nausea (1883 cases, 21.1%), dyskinesia (930 cases, 17.7%), dizziness (1287 cases, 15.1%), orthostatic hypotension (665 cases, 14.9%), somnolence (1139 cases, 14.1%), insomnia (679 cases, 9.7%), headaches (596 cases, 9.5%), constipation (430 cases, 7.1%), hallucinations (432 cases, 6.7%), abdominal pain (174 cases, 5.8%), vomiting (301 cases, 5.7%), and confusion (101 cases, 4.7%).

RR with their corresponding 95% CIs are presented in table III, as well as the heterogeneity analyses carried out for each of the 12 adverse events selected. The most significant results of the data meta-analysed are discussed below:

1. *Nausea:* Ropinirole, pramipexole, pergolide, rotigotine and bromocriptine all showed statistically significantly higher RR compared with placebo (table III).
2. *Dizziness:* Ropinirole, pergolide, pramipexole and rotigotine all showed significantly higher RR versus placebo (fixed analyses).
3. *Somnolence:* With the exception of cabergoline and rotigotine, all other comparisons with placebo showed statistically significantly higher RR. There were no differences on comparison between ropinirole and bromocriptine, ropinirole and levodopa or ropinirole and rotigotine.
4. *Dyskinesia:* Ropinirole, pramipexole, pergolide and rotigotine showed a higher RR for dyskinesia than placebo, while bromocriptine compared with placebo was bordering on statistical significance. The RR for ropinirole versus levodopa indicates a protective effect of ropinirole compared with levodopa for this adverse event.
5. *Insomnia:* Pramipexole, pergolide and rotigotine showed a significantly higher risk of insomnia compared with placebo.
6. *Headache:* Pramipexole showed a higher RR compared with placebo. In the remaining comparisons with placebo, a higher risk of headache was not observed for any of the treatments.
7. *Orthostatic hypotension:* With only two studies available and a total of 64 patients for this

Table I. Description of the studies

Study (y)	Study duration (wk)	Characteristics of PD	No. of patients/group
Adler et al.[56] (1997)	24	Early PD	Ropinirole 116; placebo 125
Barone et al.[24] (2007)	40	Advanced PD	Ropinirole 310; placebo 316
Brunt et al.[25] (2002)	24	PD uncontrolled by levodopa	A 131/75; B 88/51; C 148/62[a]
Giladi et al.[26] (2007)	24–33	Early PD	Ropinirole 228; rotigotine 215; placebo 118
Im et al.[27] (2003)	16	PD in patients over 40 y	Ropinirole 37; bromocriptine 39
Korczyn et al.[28] (1999)	24 intermediate results	PD in persons over 30 y	Ropinirole 168; bromocriptine 167
Lieberman et al.[29] (1998)	24	PD with motor fluctuations	Ropinirole 95; placebo 54
Mizuno et al.[14] (2007)	16	PD	Ropinirole 121; placebo 122
Rascol et al.[30] (1998)	24 intermediate results	Early PD	Ropinirole 179; levodopa 89
Whone et al.[31] (2003)	96	Early PD	Ropinirole 87; levodopa 75
Singer et al.[32] (2007)	40	PD	Ropinirole 205; placebo 205
Hoehn and Elton[33] (1985)	40	Advanced PD	Bromocriptine 27; placebo 9
Möller et al.[34] (2005)	32	Advanced PD	Pramipexole 174; placebo 180
Navan et al.[12] (2003)	12	PD	Pergolide 10; pramipexole 10; placebo 10
Jankovic et al.[35] (2007)	31	Early PD	Rotigotine 181; placebo 96
LeWitt et al.[36] (2007)	24	Advanced PD	Rotigotine 231; placebo 120
Parkinson Study Group[37] (2003)	11	Early PD	Rotigotine 166; placebo 47
Poewe et al.[38] (2007)	24	Advanced PD	Rotigotine 204; pramipexole 201; placebo 101
Watts et al.[39] (2007)	24	PD	Rotigotine 181; placebo 96
Guttman[13] (1997)	36	Advanced PD with motor fluctuations	Bromocriptine 84; pramipexole 79; placebo 83
Shannon et al.[40] (1997)	31	Early PD	Pramipexole 164; placebo 171
Parkinson Study Group[41] (1997)	10	Early PD	Pramipexole 213; placebo 51
Parkinson Study Group[42] (2007)	10	PD	Pramipexole 109; placebo 35
Pinter et al.[43] (1999)	11	Advanced PD	Pramipexole 34; placebo 44
Pogarell et al.[57] (2002)	12	Early or advanced PD	Pramipexole 44; placebo 39
Molho et al.[58] (1995)	11	Advanced PD	Pramipexole 12; placebo 12
Lieberman et al.[44] (1997)	32	Advanced PD	Pramipexole 181; placebo 179
Wermuth[45] (1998)	11	Advanced PD	Pramipexole 36; placebo 33
Wong et al.[59] (2003)	15	Early or advanced PD	Pramipexole 73; placebo 77
Mizuno et al.[15] (2003)	12	Advanced PD	Bromocriptine 105; pramipexole 102; placebo 108
Toyokura et al.[46] (1985)	8	Advanced PD	Bromocriptine 114; Placebo 108
Ahlskog et al.[47] (1996)	24	Early PD	Cabergoline 17; placebo 10
Hutton et al.[48] (1996)	24	Advanced PD	Cabergoline 83; placebo 65
Steiger et al.[49] (1996)	24	Advanced PD	Cabergoline 19; placebo 18
Brooks et al.[50] (1998)	12	Untreated PD or <6 mo treatment	Ropinirole 41; placebo 22
Rascol et al.[51] (1996)	12	PD uncontrolled by levodopa	Ropinirole 23; placebo 23
Hubble et al.[52] (1995)	9	Early PD	Pramipexole 28; placebo 27
Ahlskog and Muenter[53] (1988)	24	Advanced PD	Pergolide 25; placebo 24
Barone et al.[54] (1999)	12	Early PD	Pergolide 53; placebo 52
Olanow et al.[55] (1994)	24	Advanced PD	Pergolide 189; placebo 187

a A = low dose of levodopa + additional therapy (ropinirole or bromocriptine); B = high dose of levodopa + additional therapy (ropinirole or bromocriptine); C = levodopa or dopamine agonist + additional therapy.

PD = Parkinson's disease.

adverse event, cabergoline was the only dopamine agonist that showed a risk higher than placebo.

8. *Vomiting:* Ropinirole and rotigotine showed a higher risk versus placebo (fixed analyses).
9. *Hallucinations:* ropinirole, pramipexole, pergolide and rotigotine showed higher RRs for this adverse event versus placebo (all fixed analyses). In the remaining comparisons, no significantly different RR was observed.
10. *Confusion:* Pramipexole showed a higher risk compared with placebo (fixed analysis).
11. *Constipation:* Pramipexole showed a higher risk of constipation compared with placebo. Ropinirole showed a lower risk of constipation compared with bromocriptine.
12. *Abdominal pain:* None of the drugs studied showed a higher RR compared with placebo.

The following additional analyses were carried out. First, a sensitivity analysis to assess the weight of each study in each one of the meta-analysis performed. The results of these analyses were consistent with and pointed to the same direction as the global results of each one of the meta-analyses performed. In other words, no single study changed the significance of the reported RR for each of the meta-analyses performed.

A sub-analysis of ropinirole with or without levodopa versus placebo was likewise performed. Six meta-analyses were possible in the ropinirole only group, all of them with considerable heterogeneity (as there were only three studies) even when the random effect model was used. As for the ropinirole + levodopa group analysis, an increased RR was found for nausea (2.07; 95% CI 1.62, 2.65), dizziness (1.82 [95% CI 1.36, 2.43]), dyskinesia (2.71 [95% CI 1.74, 4.21]) and hallucinations (2.93 [95% CI 1.36, 6.33]).

Table II. Adverse events: relative frequencies and percentages

Adverse event	Ropinirole n (N [%])	Bromocriptine n (N [%])	Levodopa n (N [%])	Rotigotine n (N [%])	Pramipexole n (N [%])	Pergolide n (N [%])	Cabergoline n (N [%])	Placebo n (N [%])	Total n (N [%])
Nausea	584 (2202 [26.5])	153 (724 [21.1])	45 (164 [27.4])	300 (987 [30.4])	294 (1459 [20.2])	70 (277 [25.3])	8 (36 [22.2])	429 (3095 [13.9])	1883 (8944 [21.1])
Dizziness	315 (2202 [14.3])	130 (724 [18.0])	20 (164 [12.2])	186 (1216 [15.3])	256 (1286 [19.9])	13 (88 [14.8])	4 (19 [21.1])	363 (2838 [12.8])	1287 (8537 [15.1])
Somnolence	334 (2165 [15.4])	47 (460 [10.2])	19 (164 [11.6])	282 (1216 [23.2])	162 (1115 [14.5])	37 (277 [13.4])	2 (17 [11.8])	256 (2657 [9.6])	1139 (8071 [14.1])
Dyskinesia	167 (1132 [14.8])	53 (446 [11.9])	10 (89 [11.2])	35 (229 [15.3])	298 (1011 [29.5])	137 (224 [61.2])	0 (123 [0])	230 (1997 [11.5])	930 (5251 [17.7])
Insomnia	136 (1707 [8.0])	51 (619 [8.2])	17 (164 [10.4])	109 (1216 [9.0])	164 (899 [18.2])	22 (267 [8.2])	2 (19 [10.5])	178 (2130 [8.4])	679 (7021 [9.7])
Headache	131 (1554 [8.4])	62 (697 [8.9])	19 (164 [11.6])	133 (1216 [10.9])	101 (868 [11.6])	4 (35 [11.4])	NA	146 (1740 [8.4])	596 (6274 [9.5])
Orthostatic hypotension	67 (910 [7.4])	76 (619 [12.3])	5 (89 [5.6])	8 (410 [2.0])	225 (952 [23.6])	5 (25 [20.0])	16 (36 [44.4])	263 (1435 [18.3])	665 (4476 [14.9])
Vomiting	94 (1594 [5.9])	43 (697 [6.2])	5 (89 [5.6])	88 (987 [8.9])	17 (344 [4.9])	5 (53 [9.4])	NA	49 (1556 [3.1])	301 (5320 [5.7])
Hallucinations	66 (1258 [5.2])	46 (557 [8.3])	1 (164 [0.6])	23 (229 [10.0])	167 (1423 [11.7])	36 (224 [16.1])	8 (159 [5.0])	85 (2441 [3.5])	432 (6455 [6.7])
Confusion	24 (630 [3.8])	11 (338 [3.3])	1 (75 [1.3])	0	31 (413 [7.5])	5 (25 [20.0])	4 (142 [2.8])	25 (528 [4.7])	101 (2151 [4.7])
Constipation	91 (1743 [5.2])	60 (613 [9.8])	11 (75 [14.7])	52 (1021 [5.1])	101 (670 [15.1])	7 (35 [20.0])	2 (17 [11.8])	106 (1900 [5.6])	430 (6074 [7.1])
Abdominal pain	80 (1438 [5.6])	38 (508 [7.5])	16 (164 [9.8])	4 (215 [1.9])	6 (80 [7.5])	7 (25 [28.0])	NA	23 (585 [3.9])	174 (3015 [5.8])

N = total observed population; **n** = number of cases; **NA** = not applicable.

Discussion

By using indirect comparisons versus placebo, in monotherapy or adjuvant therapy, of the adverse event profile of ropinirole versus five well known dopamine agonists, we aimed to hypothesize that each dopamine agonist may have a specific adverse event profile. If this assumption

Table III. Relative risks (RR) of adverse events[a]

Drug	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)
	nausea				dizziness				somnolence			
ROP vs PL	8 (2117)	48.45	Fixed	**2.25 (1.85, 2.74)**	8 (2117)	44.9	Fixed	**1.87 (1.48, 2.37)**	8 (2117)	80.49	Random	**2.45 (1.30, 4.61)**
ROP vs BCP	3 (966)	57.18	Random	1.57 (0.96, 2.57)	3 (966)	0	Fixed	0.95 (0.70, 1.30)	2 (890)	0	Fixed	0.91 (0.52, 1.60)
ROP vs LVD	2 (430)	66.55	Random	1.52 (0.90, 2.56)	2 (430)	0	Fixed	1.14 (0.69, 1.90)	2 (430)	88.56	Random	1.90 (0.43, 8.34)
ROP vs ROT	1 (443)		Fixed	1.17 (0.74, 1.84)	1 (443)		Fixed	1.15 (0.58, 2.27)	1 (443)		Fixed	1.15 (0.68, 1.93)
PPX vs PL	15 (2608)	0	Fixed	**1.48 (1.24, 1.76)**	13 (2255)	14.55	Fixed	**1.20 (1.01, 1.43)**	10 (1924)	0	Fixed	**1.68 (1.25, 2.25)**
BCP vs PL	4 (638)	0	Fixed	**1.48 (1.11, 1.98)**	4 (638)	57.8	Random	1.37 (0.78, 2.41)	1 (213)		Fixed	**1.91 (1.06, 3.45)**
PGL vs PL	4 (550)	27.69	Fixed	**2.28 (1.54, 3.37)**	3 (174)	0	Fixed	**3.75 (1.21, 11.64)**	4 (550)	0	Fixed	**2.80 (1.54, 5.10)**
CBG vs PL	2 (64)	0	Fixed	1.58 (0.51, 4.86)	1 (37)		Fixed	1.89 (0.39, 9.11)	1 (27)		Fixed	3.06 (0.16, 57.93)
ROT vs PL	4 (1128)	66.46	Random	**2.08 (1.30, 3.34)**	5 (1477)	0	Fixed	**1.35 (1.02, 1.79)**	5 (1477)	69.36	Random	1.35 (0.89, 2.06)
	dyskinesia				insomnia				headache			
ROP vs PL	4 (1062)	0	Fixed	**2.71 (1.74, 4.21)**	4 (1141)	47.19	Fixed	1.03 (0.66, 1.58)	4 (876)	20.28	Fixed	1.14 (0.75, 1.73)
ROP vs BCP	2 (631)	0	Fixed	1.28 (0.91, 1.82)	3 (966)	0	Fixed	1.48 (0.93, 2.35)	3 (966)	71.78	Random	1.18 (0.44, 3.17)
ROP vs LVD	1 (268)		Fixed	**0.25 (0.09, 0.71)**	2 (430)	0	Fixed	1.20 (0.69, 2.10)	2 (430)	0	Fixed	0.89 (0.51, 1.54)
ROP vs ROT	0 (0)		NE	NE	1 (443)		Random	0.94 (0.31, 2.88)	1 (443)		Random	0.85 (0.35, 2.05)
PPX vs PL	11 (1873)	55.12	Random	**2.27 (1.58, 3.27)**	10 (1572)	0	Fixed	**1.63 (1.28, 2.08)**	11 (1411)	0	Fixed	**1.38 (1.00, 1.92)**
BCP vs PL	2 (435)	37.89	Fixed	2.30 (0.96, 5.48)	3 (425)	0	Fixed	0.94 (0.57, 1.56)	3 (602)	0	Fixed	1.51 (0.88, 2.57)
PGL vs PL	3 (445)	0	Fixed	**2.40 (1.88, 3.06)**	3 (530)	0	Fixed	**2.40 (1.13, 5.12)**	2 (69)	0	Fixed	1.76 (0.40, 7.70)
CBG vs PL	1 (188)		Fixed	0.18 (0.01, 4.29)	1 (37)		Fixed	0.95 (0.15, 6.03)	0 (0)		NE	NE
ROT vs PL	1 (349)		Fixed	**2.29 (1.10, 4.78)**	5 (1477)	6.81	Fixed	**1.90 (1.22, 2.95)**	5 (1477)	0	Fixed	1.32 (0.94, 1.84)

Continued next page

Table III. Contd

Drug	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)	No. of studies (n)	I^2 (%)[b]	Analysis	RR (95% CI)
	orthostatic hypotension				vomiting				hallucinations			
ROP vs PL	3 (258)	5.71	Fixed	1.21 (0.63, 2.30)	5 (1103)	0	Fixed	**2.84 (1.45, 5.54)**	4 (1171)	0	Fixed	**2.84 (1.34, 5.99)**
ROP vs BCP	3 (966)	0	Fixed	1.04 (0.62, 1.73)	3 (966)	51.3	Random	1.02 (0.44, 2.35)	2 (631)	0	Fixed	1.42 (0.76, 2.65)
ROP vs LVD	1 (268)		Fixed	0.80 (0.27, 2.36)	1 (268)		Fixed	1.69 (0.64, 4.43)	2 (430)	0	Fixed	4.15 (0.76, 22.72)
ROP vs ROT	0 (0)		NE	NE	1 (443)		Fixed	0.86 (0.39, 1.92)	0 (0)		NE	NE
PPX vs PL	10 (1820)	0	Fixed	1.13 (0.96, 1.33)	3 (705)	77.64	Random	0.82 (0.17, 3.87)	14 (2539)	6.7	Fixed	**3.36 (2.41, 4.68)**
BCP vs PL	3 (425)	0	Fixed	1.26 (0.89, 1.78)	3 (602)	48.41	Fixed	1.55 (0.81, 2.97)	4 (638)	71.42	Random	1.10 (0.37, 3.26)
PGL vs PL	1 (49)		Fixed	2.40 (0.51, 11.21)	1 (105)		Fixed	10.80 (0.61, 190.44)	3 (445)	0	Fixed	**4.80 (2.24, 10.29)**
CBG vs PL	2 (64)	9.17	Fixed	**2.55 (1.09, 5.94)**	0 (0)		NE	NE	3 (252)	0	Fixed	1.56 (0.47, 5.21)
ROT vs PL	2 (626)	0	Fixed	0.35 (0.15, 0.85)	4 (1128)	0	Fixed	**5.31 (2.30, 12.27)**	1 (349)		Fixed	**4.02 (1.23, 13.11)**
	confusion				constipation				abdominal pain			
ROP vs PL	2 (287)	0	Fixed	2.82 (0.77, 10.39)	4 (1616)	0	Fixed	1.27 (0.81, 1.98)	3 (635)	37.79	Fixed	1.30 (0.60, 2.81)
ROP vs BCP	2 (631)	0	Fixed	1.44 (0.50, 4.18)	3 (966)	0	Fixed	**0.55 (0.35, 0.89)**	3 (966)	15.24	Fixed	0.76 (0.47, 1.23)
ROP vs LVD	1 (162)		Fixed	4.31 (0.51, 36.08)	1 (1620)		Fixed	0.63 (0.27, 1.48)	2 (430)	0	Fixed	0.86 (0.46, 1.62)
ROP vs ROT	0 (0)		NE	NE	1 (443)		Fixed	1.21 (0.46, 3.20)	1 (443)		Fixed	1.65 (0.49, 5.56)
PPX vs PL	4 (594)	0	Fixed	**2.64 (1.18, 5.91)**	6 (1121)	9.37	Fixed	**2.23 (1.53, 3.25)**	2 (152)	75.81	Random	0.97 (0.03, 36.69)
BCP vs PL	2 (203)	81.46	Random	0.29 (0.02, 4.13)	2 (435)	0	Fixed	1.62 (0.89, 2.97)	1 (222)		Fixed	6.63 (0.83, 53.01)
PGL vs PL	1 (49)		Fixed	1.20 (0.37, 3.94)	2 (69)	24.64	Fixed	1.37 (0.48, 3.91)	1 (49)		Fixed	1.68 (0.56, 5.01)
CBG vs PL	2 (225)	0	Fixed	3.82 (0.50, 29.35)	1 (27)		Fixed	3.06 (0.16, 57.93)	0 (0)		NE	NE
ROT vs PL	0 (0)		NE	NE	4 (1235)	0	Fixed	1.26 (0.74, 2.12)	1 (333)		Fixed	0.44 (0.12, 1.60)

a 'Bold' denotes statistically significant results

b Heterogeneity due to the differences in design and in patient characteristics was assessed using the I^2 statistic.

BCP = bromocriptine; **CBG** = cabergoline; **LVD** = levodopa; **n** = no. of subjects; **NE** = not estimable; **PGL** = pergolide; **PL** = placebo; **PPX** = pramipexole; **ROP** = ropinirole; **ROT** = rotigotine.

is correct, this could be important at the time of selecting the most appropriate treatment.

A number of limitations and caveats should be mentioned to appropriately interpret the results of this study. Of the 108 possible comparisons, only 73 could be meta-analysed (they had more than one clinical trial available). In addition, 22 of the 73 meta-analyses had only two studies available (some with a relatively small number of patients), which means that results in these cases cannot be generalized. For this reason, these particular comparisons are not further discussed.

Except for bromocriptine and rotigotine, no publications were found that included direct comparisons between ropinirole and other dopamine agents. Despite this, the indirect comparison with placebo can provide us with some indication of the benefit-risk ratio of these drugs; however, since the distribution of clinical and epidemiological variables is not homogeneous over the studies, one must be cautious when drawing conclusions since spurious results could be randomly produced.

Another limitation of our review is that the principal objective for most of the studies included was efficacy, while the safety and tolerability variables were considered only as a secondary objective. In addition, most studies did not record adverse events with incidences lower than 5–10%. Therefore, conclusions can only be drawn for the most commonly reported adverse events.

It is well known that there are substantial differences between the incidence and seriousness of adverse events associated with dopamine agonists in the treatment of early Parkinson's disease, and in the treatment of Parkinson's disease in advanced phases. As a rule, adverse events are less frequent and less serious in patients in the early phases of the disease. In our study, patients with Parkinson's disease in both early and advanced phases were included, thus providing an adequate picture of the overall Parkinson's disease patient population.

A classic bias in the analysis of adverse events in clinical trials is the inclusion of studies with a short period of observation. In our review, only 10 of the 40 studies had duration longer than 6 months. Consequently, the incidence of adverse events might have been underestimated, especially in the case of very infrequent adverse events or of those only appearing over a long period of treatment, as is the case of fibrosis.[60-63] Another shortcoming is that many studies describe a titration period, but do not report the number or frequency of adverse events at each stage of the titration period, instead reporting a total of adverse events in the study period.

Estimating the RR of the comparisons for which there was only one clinical trial for a specific adverse event help in giving consistency to the results obtained, especially if they include many patients, but they have little value on their own and cannot be meta-analysed.

When analysing each individual adverse event, the following comments seem pertinent:

1. *Nausea:* This is the most common adverse event for all dopamine agonists and, in all cases, it is associated with a frequency higher than that seen with placebo. It can therefore be stated that nausea is a class effect. However, this does not apply to cabergoline, probably due to the broad CI distribution and inclusion of only two studies. Ropinirole has also shown a higher incidence of nausea than bromocriptine and levodopa; however, this finding is not confirmed by the random effects study, recommended in the case of heterogeneity. This situation poses the hypothesis that there may be differences in the incidence of nausea between dopamine agonists, which would require carrying out direct comparisons.
2. *Dizziness:* It was possible to meta-analyse five dopamine agonist comparisons (ropinirole, pergolide, bromocriptine, pramipexole and rotigotine) with placebo. The results indicate that ropinirole, pergolide, pramipexole and rotigotine exhibit higher incidences of dizziness than placebo, although this finding was not confirmed in the random effects study for bromocriptine.
3. *Somnolence:* The comparisons with placebo of the various dopamine agonists show that this adverse event is common (except for cabergoline and rotigotine). Also, no differences were found between ropinirole and bromocriptine, levodopa or rotigotine. In our review, we have not detected any episode of sleep attack, a finding that would support results from recent studies that question

its existence as a phenomenon different from daytime hypersomnolence.[64,65]

4. *Dyskinesia:* It was possible to meta-analyse four comparisons of dopamine agonists (ropinirole, pergolide, bromocriptine and pramipexole) with placebo. The results indicate that ropinirole, pergolide and pramipexole show a significantly higher RR of dyskinesia versus placebo. For bromocriptine, however, borderline statistical significance was found. The fact that ropinirole has a protective effect compared with levodopa complicates the interpretation of the data, since this increase in dyskinesia could be due to the association of levodopa with dopamine agonists. For this reason, it cannot be concluded that this is a class effect.

5. *Insomnia:* Pramipexole, pergolide and rotigotine showed a higher incidence of this adverse event versus placebo, with no heterogeneity of the data being observed. The sensitivity analysis carried out confirmed the statistical significance of this finding.

6. *Orthostatic hypotension:* Cabergoline was found to be the only dopamine agonist that has a higher risk than placebo.

7. *Vomiting:* Ropinirole and rotigotine demonstrated a higher risk than placebo. The three meta-analysed studies comparing pramipexole with placebo indicated that the risk was not higher than placebo, indicating that this might be a good treatment option in patients with this symptom.

8. *Hallucinations:* Ropinirole showed a higher incidence of hallucinations than placebo but the same incidence when compared with levodopa and bromocriptine at 6 months follow-up. Nevertheless, one published study[66] did detect a higher incidence versus levodopa on comparing the results after 5 years. Pramipexole, pergolide and rotigotine are clearly associated with a higher incidence of this adverse event. In the other comparisons, no increased risk of hallucinations was observed.

9. *Confusion:* According to the data currently available, pramipexole is not an appropriate option for patients who present with confusion.

10. *Headache:* According to the data currently available, pramipexole is not an appropriate option for patients who present with headache.

11. *Constipation:* According to the results of our study, patients experiencing constipation should avoid the use of pramipexole. In patients with constipation, ropinirole appears to be a better therapeutic option than bromocriptine since it appears to have a protective effect in comparison with this drug.

12. *Abdominal pain:* This has been detected with the same frequency in patients treated with any dopamine agonist compared with the placebo group.

In 2003, Etminan et al.[7] published a meta-analysis that showed an incidence of adverse events for ropinirole and pramipexole versus placebo similar to that found in this study. The adverse events analysed by Etminan et al.[7] were nausea, dizziness, somnolence, hypotension and hallucinations. In our study, the most frequent adverse events were, in order of frequency, nausea, dyskinesia, dizziness, orthostatic hypotension and somnolence; hallucinations were the ninth most frequently occurring event. The fact that the adverse events in our study are similar to those described by Etminan et al.[7] suggests that publication bias may be ruled out. In our study, because of their clinical relevance, abdominal pain (174 cases) was selected over dyspepsia (137 cases) and confusion (101 cases) was selected over aggravated Parkinsonism (201 cases), fatigue (168 cases), tremor (125 cases) and pain (116 cases), since some of the latter adverse events could be linked to the cause of the illness itself or represent non-specific symptoms.

In the study by Etminan et al.,[7] indirect comparisons were also carried out between drugs (pramipexole and ropinirole) because of the lack of direct comparative studies. Etminan et al.[7] found no significant differences in the risk of dizziness, nausea and hypotension, individually or for pramipexole and ropinirole combined, in comparison with levodopa. Also, Etminan et al.,[7] reported a significantly higher risk of hallucinations for pramipexole, in comparison with placebo (RR 5.20 [95% CI 1.97, 13.72]), a finding that coincides with our results (RR 3.36 [95% CI 2.41, 4.68]).

In our study, hypotension was differentiated from clinical orthostatic hypotension, since the

latter has a greater clinical relevance, and is more comparable between studies since it is an adverse event appearing in a large number of publications. This could also explain the differences we found between the results of our study and that of Etminan et al.[7]. In that study, the risk of hypotension was higher with ropinirole versus placebo (RR 6.46 [95% CI 1.47, 28.28]) than with pramipexole versus placebo (RR 1.65 [95% CI 0.88, 3.08]), although the fact that Etminan et al.[7] included the publications of Adler et al.[56] and Sethi et al.[67] as two different pieces of work must be taken into account, as Sethi et al.[67] is an extension of the earlier study. For this reason, our study did not include the study by Sethi et al.[67] In our study, the incidence of orthostatic hypotension for ropinirole was not higher than that of placebo. This finding was consistent when comparing ropinirole with levodopa or bromocriptine.

The publications used in our review coincide with those of Etminan et al.,[7] with the exception of three: the first study (Parkinson Study Group[68]) was excluded because it used a different comparator than those selected for our study (pramipexole vs levodopa); the second study (Sethi et al.[67]) was excluded because it is an extension of a study already included (Adler et al.[56]), and would introduce a bias in the selection of patients and repetition of results; and the third study (Hauser et al.[65]) was excluded because it is a retrospective study of three randomized clinical trials of somnolence.

On the other hand, we included four publications on pramipexole versus placebo dating from 2002 to 2007.[34,42,57,59] Our review also included a paper by Molho et al.,[58] which was excluded by Etminan et al.,[7] probably because it had a Jadad score of 1. The sensitivity analysis on withdrawing this article showed no changes in the results obtained, except for confusion.

In the case of ropinirole, the direct comparisons of this drug with bromocriptine showed a lower incidence of constipation (RR 0.55 [95% CI 0.35, 0.89]), while the direct comparison with levodopa showed a lower frequency of dyskinesia (RR 0.25 [95% CI 0.09, 0.71]). When the direct comparison with rotigotine was performed, no differences between both dopamine agonists were observed, probably due to the lack of a higher number of comparative clinical trials.

The sensitivity analysis confirmed the results previously discussed. In the subgroup analysis of ropinirole and levodopa, the same pattern of significance of adverse events as found in the global analysis of ropinirole versus placebo was obtained. Ropinirole, but not levodopa, was also found to exhibit a similar significance for increased RR, but did present high heterogeneity,

Table IV. Summary. Presence of each adverse event in comparison with placebo

Adverse event	Ropinirole	Bromocriptine	Cabergoline	Rotigotine	Pramipexole	Pergolide
Nausea	↑↑	↑	↔	↑↑	↑	↑↑
Dizziness	↑	↔	NA	↑	↑	↑↑↑
Somnolence	↑↑	↑	NA	↔	↑	↑↑
Dyskinesia	↑↑	↔	NA	↑↑	↑↑	↑↑
Insomnia	↔	↔	NA	↑	↑	↑↑
Headache	↔	↔	NA	↔	↑	↔
Orthostatic hypotension	↔	↔	↑↑	↔	↔	↔
Vomiting	↑↑	↔	NA	↑↑↑↑↑	↔	↔
Hallucinations	↑↑	↔	↔	↑↑↑↑	↑↑↑	↑↑↑↑
Confusion	↔	↔	↔	NA	↑↑	↔
Constipation	↔	↔	↔	↔	↑↑	NA
Abdominal pain	↔	NA	NA	NA	↔	NA

NA = one or no studies available not meta-analysed; ↔ denotes no significant difference in rate of adverse events compared with placebo; ↑ denotes increase in the rate of adverse events compared with placebo (greater number of arrows indicates greater magnitude of increase).

most likely due to the differences between the studies.

Adverse events associated with each particular dopamine agonist are summarized in table IV.

Conclusions

Our study demonstrates that dopamine agonists, including ropinirole, in the treatment of Parkinson's disease, whether in monotherapy or as adjuvant treatment, have a favourable safety profile. However, in the event of a particular adverse event that may necessitate the switching of treatments (in particular in elderly patients with polypharmacy), or in a patient with a particular medical history, the results obtained in this meta-analysis may aid the clinicians' choice of dopamine agonist. This may particularly apply in the case of patients with dizziness (pergolide carries a higher RR), orthostatic hypotension (cabergoline carries a higher RR), vomiting (rotigotine carries a higher RR), hallucinations (pergolide, rotigotine and pramipexole carry a higher RR) and confusion (pramipexole carries a higher RR). On the other hand, a decrease in the risk of constipation in patients receiving ropinirole when compared directly with bromocriptine was detected.

The description of adverse events that are more likely to be present with certain dopamine agonists, and the fact that no clear comparisons of efficacy between the different types of dopamine agonists have been undertaken, may help the clinician to individualize the treatment of Parkinson's disease motor symptoms.

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