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Increased Risk of Somnolence with the New Dopamine Agonists in Patients with Parkinson's Disease

A Meta-Analysis of Randomised Controlled Trials

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Abstract

Background: Recent case reports and letters have alerted practitioners to the risk of sleep attacks, usually preceded by somnolence, in patients with Parkinson's disease treated with pramipexole and ropinirole.

Objective: To quantify the risk of somnolence with the new dopamine agonists pramipexole and ropinirole in patients with Parkinson's disease.

Methods: We searched MEDLINE, EMBASE, International Pharmaceutical Abstracts and Cochrane Library, contacted experts and pharmaceutical manufacturers, and manually reviewed all references retrieved to identify possible articles to include. Information on randomisation, blinding, type of treatment and reporting of somnolence were abstracted by 2 independent reviewers. Disagreements were resolved by a third author.

Analysis: We made 2 separate analyses. The first analysis compared the risk of somnolence in patients taking either pramipexole or ropinirole to that in patients taking placebo. The second analysis compared the risk of somnolence with these drugs (plus levodopa) versus that with levodopa alone. We calculated pooled relative risk estimates using the random effects model and when no heterogeneity was detected we used the fixed effects model.

Results: Four trials were included in the analysis of patients taking pramipexole or ropinirole compared with those taking placebo. The pooled relative risk of somnolence in this analysis was 4.98 [95% confidence interval (CI) 1.79 to 13.89]. Seven trials were included in the analysis of patients taking levodopa and

pramipexole or ropinirole compared with those taking levodopa alone. The pooled relative risk was 2.06 (95% CI 1.47 to 2.88).

Conclusion: Patients with Parkinson's disease using pramipexole or ropinirole are at higher risk of experiencing somnolence relative to patients taking placebo. Patients taking levodopa plus either one of these dopamine agonists are at higher risk than those taking levodopa alone. Clinicians should carefully weigh this risk against the benefit of these agents when prescribing these drugs.

Pramipexole and ropinirole are dopamine agonists with dopamine D_2 and D_3 receptor activity that have been recently introduced as adjunctive therapy in the treatment of Parkinson's disease. These agents have pharmacological profiles that differ from that of the older agents bromocriptine and pergolide.[1-3] The use of dopamine agonists is advocated both in early and advanced stages of the disease, as it may reduce the need for levodopa and thus delay the complications induced by this drug.

Recent case reports have suggested the possibility of increased risk of sleep attacks associated with the use of pramipexole and ropinirole.[4,5] Patients reported that they suddenly fell asleep (i.e. had a sleep attack) during daily activities, including reading, driving or eating. There have also been 8 cases of motor vehicle accidents potentially linked to these agents.[4] These sleep attacks are usually preceded by a period of somnolence or drowsiness.[6] Since the case reports of sleep attacks have only appeared recently, only 1 of the clinical trials that evaluated ropinirole and pramipexole measured the occurrence of this adverse effect.[7]

It has not been shown yet that sleep attacks are a consequence of somnolence. However, the hypothesis that both adverse effects are related is plausible. In order to estimate the risk of somnolence with the new dopamine agonists pramipexole and ropinirole, as an indirect estimate of the risk of sleep attacks, we performed a meta-analysis of randomised controlled trials.

Methods

We used 4 databases to identify all randomised controlled trials conducted in patients with Parkinson's disease that compared either ropinirole or pramipexole with placebo or levodopa. We searched MEDLINE, EMBASE, the Cochrane Library and International Pharmaceutical Abstracts (IPA). In addition, we contacted the pharmaceutical manufacturers for any published data that we could have missed in our search. We also systematically searched the reference lists of the retrieved articles.

We entered terms including 'pramipexole' and 'ropinirole' both as subject heading and text words. We then searched for all trials that had measured somnolence by using terms including 'somnolence' and 'drowsiness' both as subject heading and text words. We combined the 2 searches.

Inclusion Criteria

Studies of patients with Parkinson's disease were included if they met the following criteria: (i) randomised controlled trials; (ii) patients received pramipexole or ropinirole; and (iii) somnolence or drowsiness were measured either as primary outcome or adverse event. All potential trials were independently reviewed by 2 authors, and discrepancies were resolved in a consensus meeting with a third.

Analysis

We conducted 2 separate analyses. In the first analysis we selected studies that measured the risk of somnolence in trials evaluating patients taking pramipexole or ropinirole compared with those taking placebo. In the second analysis, we measured the risk of somnolence with pramipexole or ropinirole in trials that involved patients taking levodopa. We calculated the pooled relative risk (RR) with its corresponding 95% confidence intervals (CI) using the random effect model when heterogeneity of ef-

Table I. Characteristics of the studies of pramipexole or ropinirole in levodopa-naive patients

Study	No. of patients	Patient characteristics	Intervention	RR of somnolence (95% CI)	Duration (wks)	Mean daily dosage of drug (mg)
Adler et al.[1]	241	Patients with early PD not receiving any PD drugs except selegiline	R *vs* placebo	7.5 (3.3 to 17.1)	6	8.3
Parkinson Study Group[13]	264	Patients with early stage PD not receiving levodopa for the last 3 months	P *vs* placebo	2.0 (1.0 to 4.1)	10	1.5, 3.0, 4.5, 6.0
Shannon et al.[14]	335	Patients with early stage PD not receiving levodopa or dopamine agonists for the last 2 months	P *vs* placebo	2.1 (1.2 to 3.7)	24	3.5
Brooks et al.[15]	63	Patients with early stage PD not receiving levodopa or dopamine agonists for the last 2 weeks	R *vs* placebo	13.4 (1.9 to 97.0)	12	6.54

CI = confidence interval; **P** = pramipexole; **PD** = Parkinson's disease; **R** = ropinirole; **RR** = relative risk.

fects between studies was present, or the fixed effect model when no heterogeneity was detected.[8] Because the number of studies included was relatively small, we used a bootstrap version of the DerSimonian and Laird's test statistic to estimate heterogeneity.[9] The bootstrap version of this statistic overcomes the difficulty of testing for heterogeneity when studies are scarce, and is thus a more germane approach in this case.

Results

Our search identified 15 potential studies. Four studies were excluded for the following reasons: 1 study had combined data from both published and unpublished studies,[2] 1 study was duplicated in another journal,[10] and 2 studies were excluded since they were an extension of larger studies that included the same patients.[11,12] Eleven studies evaluating 2066 patients met our inclusion criteria. Four of these studies, those with patients receiving monotherapy, were included in the first analysis (pramipexole or ropinirole versus placebo),[1,13-15] and 7 in the second analysis which included patients receiving combination therapy (pramipexole or ropinirole versus levodopa).[3,7,16-20]

The characteristics of the studies included in the first analysis are presented in table I and figure 1. There were 2 studies comparing ropinirole with placebo[1,15] and 2 studies comparing pramipexole with placebo.[13,14] The total number of patients included in these studies was 903. In 1 of the studies, levodopa therapy was given to some patients of both groups towards the end of the study.[1]

In our analysis of studies that used pramipexole or ropinirole and placebo, we detected some heterogeneity of effects between studies (p value of Q* = 0.006). This heterogeneity is attributable to the small study by Brooks et al.,[15] which contains a zero cell (no adverse event in the placebo group). We therefore used the random effects model to calculate the pooled RR of somnolence, the value of which was 4.98 (95% CI 1.79 to 13.89). The attributable proportion of somnolence (pooled RR minus 1/pooled RR) is 0.80. This suggests that 8 of 10 occurrences of somnolence in patients who are taking new dopamine agonists are caused by these drugs.

In the second analysis, we analysed 7 studies including 1163 patients, the characteristics of which are summarised in table II and figure 1. Four studies were in patients taking ropinirole[3,16,18,19] and 3 in those taking pramipexole.[7,17,20] The patients in these studies had advanced Parkinson's disease and were stabilised on constant dosages of levodopa. The pooled RR of somnolence in patients taking pramipexole or ropinirole (plus levodopa) compared with those taking levodopa alone was 2.06 (95% CI 1.47 to 2.88). In this second analysis, no heterogeneity was detected (p value of Q* = 0.65), and thus the fixed effects model was used to

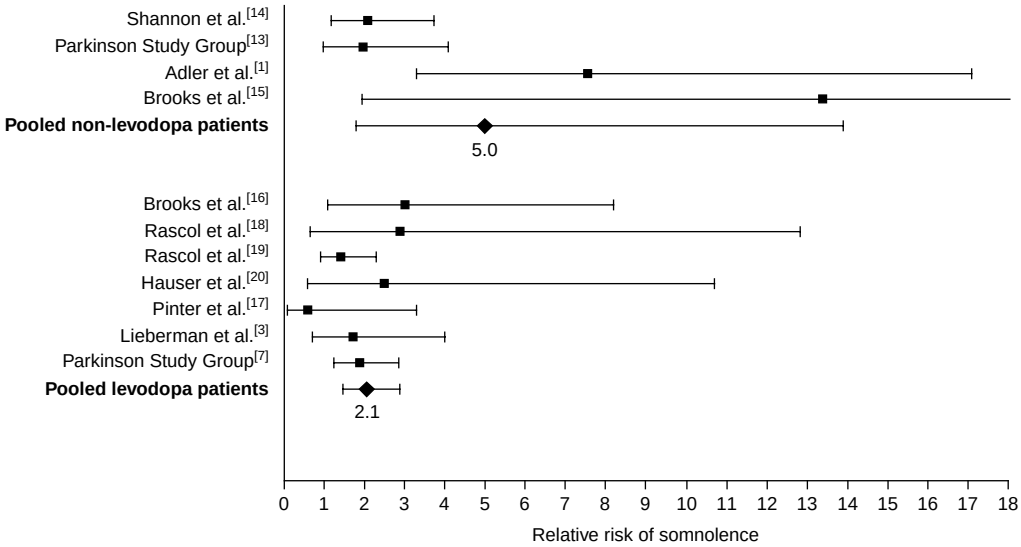

Fig. 1. Relative risks and 95% confidence intervals of randomised clinical trials of pramipexole and ropinirole.

produce the summary measure. In 2 studies[7,19] of this group, only a proportion of the patients had a supplemental dose of levodopa. To take into account the possibility that these studies might change the results of the meta-analysis, we performed a sensitivity analysis and checked the results when these 2 studies were deleted. The results were very similar when these 2 studies were not included. The pooled RR increased very slightly from 2.1 with all studies included to 2.3 when the 2 studies were excluded.

Additionally, we carried out a separate analysis for each drug. The pooled RR for ropinirole across those 6 studies that used it was 3.04 (95% CI 2.03 to 4.54), and that of pramipexole across 5 studies was 2.22 (95% CI 1.55 to 3.18).

Discussion

Despite differences in their design, the results of the individual studies are consistent. Our results show that patients taking pramipexole or ropinirole are at an approximately 5 times higher risk of experiencing somnolence than those taking placebo. Among patients taking levodopa, the risk of somnolence in patients also taking pramipexole and ropinirole compared with those taking levodopa alone is doubled.

Only the most recent of the clinical trials included in the meta-analysis measured the occurrence of sleep attacks (2 patients with pramipexole and 1 with levodopa).[7] This study was the only one that was published after the first case reports of sleep attacks.

Patients describe their experience of sleep attacks as suddenly falling asleep during daily activities including driving. During this time patients are unaware of their surrounding and potentially cognitively impaired. One patient described his experience as follows: 'I was driving home when all of a sudden I was heading into a large tree'.[21]

Sleep attacks occur on average 7 months after the first dose of the drug,[4] and may thus be difficult to monitor in the context of a clinical trial since the average duration of the trials here was only about 12 weeks. Therefore, it would have been unlikely that they would have been observed during this time frame.

Three main sources of drug information in Britain,[22] Canada[23] and the US[24] do not consistently warn clinicians about this adverse event associated

with these new agents. The British National Formulary (BNF) clearly states that 'drowsiness including sudden onset of sleep may affect performance of skilled tasks; patients should not drive or undertake potentially dangerous activities'.[22] On the other hand, the Canadian Compendium for Pharmaceutical Specialties (CPS) only states 'patients should be cautioned not to drive a motor vehicle or operate hazardous machinery until they are reasonably certain ropinirole therapy does not affect their ability to engage in such activities'.[23] The Physicians' Desk Reference states 'patients should be advised that Requip® [ropinirole] may cause somnolence. Accordingly, they should be advised neither to drive a car nor to operate other complex machinery until they have gained sufficient experience on Requip® to gauge whether or not it affects their mental and or performance adversely'.[24]

Somnolence may be particularly important to younger patients with Parkinson's disease. In a recent study with pramipexole in younger patients (average age 42 years), patients on pramipexole had significantly higher incidence of somnolence compared with placebo (36 versus 5.9%, respectively).[25] These younger patients may be more likely to drive than older patients and therefore may be at a higher risk of motor vehicle accidents. Clinicians must be aware of this potentially life-threatening adverse event.

Our meta-analysis has some limitations. First, as in every meta-analysis, the quality of the individual studies may largely influence the results of the review. Secondly, it is possible that our findings are not limited to pramipexole and ropinirole but may be shared by other dopamine agonists including bromocriptine, pergolide, cabergoline and lisuride. Clinicians have argued that all dopamine agonists as well as levodopa may cause somnolence.[26] However, the evidence on risk of somnolence from dopamine agonists other than pramipexole or ropinirole is limited. We are unaware of any randomised controlled trial evaluating the risk of somnolence with bromocriptine. Only 2 studies have evaluated the risk of somnolence with pergolide relative to placebo.[27,28] These studies showed an increased risk of somnolence in patients taking pergolide compared with those taking placebo (15.1 versus 5.8% and 10 versus 3%, respectively). However, this increase in risk is smaller than that seen among patients with pramipexole or ropinirole. As for the risk of somnolence related to levodopa, our analysis shows that it is far below that related to pramipexole and ropinirole.

Because of the relatively small number of studies, we could not explore the presence of a dose-response relationship with pramipexole and ropinirole. Some authors have argued that reducing the dosage of these drugs may reduce the risk of sleepiness. However, even dosages of pramipexole as low as 3 mg/day produce a considerable burden of somnolence.[7] Finally, this meta-analysis did not directly measure the risk of sleep attacks. However, we believe that the increase in risk of somnolence would potentially increase the risk of sleep attacks.

Conclusion

Patients taking pramipexole or ropinirole are at a considerably higher risk of experiencing somnolence

Table II. Characteristics of studies of pramipexole or ropinirole in patients receiving levodopa

Study	No. of patients	Intervention	Duration	P or R mean dosage (mg/day)	L mean dosage (mg/day)	RR of somnolence (95% CI)
Parkinson Study Group[7]	301	P *vs* L	23.5mo	2.78	235 in P group, 509 in L group	1.9 (1.2 to 2.8)
Lieberman et al.[3]	149	R *vs* L	6mo	NS	759 in R group, 843 in L group	1.7 (0.7 to 4.0)
Brooks et al. [16]	282	R *vs* L	12 wks	NS	NS	3.0 (1.1 to 8.2)
Pinter et al.[17]	77	P *vs* L	4 wks	3.59	511 in P group, 583 in L group	0.6 (0.1 to 3.3)
Rascol et al.[18]	46	R *vs* L	12 wks	6.6	663 in R group, 715 in L group	3.0 (0.7 to 13.3)
Rascol et al.[19]	268	R *vs* L	5y	16.5	427 in R group, 753 in L group	1.4 (0.9 to 2.3)
Hauser et al.[20]	40	P *vs* L	10 wks	4.3	NS	2.5 (0.6 to 10.7)

CI = confidence interval; **L** = levodopa; **NS** = not stated; **P** = pramipexole; **R** = ropinirole; **RR** = relative risk.

relative to those taking placebo. Patients taking either of these drugs in addition to levodopa are at increased risk versus patients taking levodopa alone. Physicians should carefully weigh the benefits of these drugs versus their potential risks.

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