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Adverse Drug Reactions to Dopamine Agonists: A Comparative Study in the French Pharmacovigilance Database

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Abstract: Pharmacodynamical differences between dopamine agonists (DAs) suggest differences in their adverse drug reactions (ADRs) profile. In this study, frequencies of ADR to DAs or levodopa reports in the French Pharmacovigilance Database were explored. Reports occurring between January 1, 1984 and December 31, 2008 were selected (2,189 for DAs and 1,315 for levodopa). The numbers of ADRs by system organ class were compared using ropinirole as a reference. Diurnal somnolence was less frequently reported with all DAs when compared with ropinirole ($P < 0.001$). Impulse control disorders (ICDs) were more frequently reported with pramipexole ($P < 0.001$). Significant difference was found among DAs in the frequency of confusion or disorientation ($P < 0.001$), nausea and vomiting ($P < 0.05$), or edemas ($P < 0.001$). No difference among DAs was observed in the frequency of hallucination or arterial hypotension ADR reports ($P = 0.3$ and $P = 0.1$). Pleural effusions were more frequently reported with pergolide or bromocriptine ($P < 0.001$). Somnolence or ICD reports were less frequent with levodopa, whereas confusion was more frequently reported. In summary, our data show significant differences in the kind of ADRs reported for each DA. © 2010 Movement Disorder Society

Key words: dopamine agonists; adverse drug reactions; pharmacovigilance; ropinirole; pramipexole; bromocriptine; pergolide; apomorphine

Dopamine agonists (DAs) are indicated in Parkinson's disease (PD), restless leg syndrome (RLS), or hyperprolactinemia.[1] DAs exhibit important differences in pharmacodynamic properties.[2] Ergot DAs (i.e., bromocriptine, cabergoline, lisuride, and pergolide) have higher affinities for the 5-HT1 and 5-HT2 receptors than nonergot DAs (i.e., apomorphine, quinagolide, pramipexole, piribedil, and ropinirole). Pramipexole has a higher selectivity for the D2-like family, followed by ropinirole, and then by ergot DAs. D3/D2 receptor selectivity is pramipexole > ropinirole > ergot DAs. Ergot DAs are also alpha-adrenoceptor antagonists.[3]

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Significant differences in the frequency of adverse events to DAs were found during randomized clinical trials (RCTs) in PD or RLS.[4,5] Although frequencies of somnolence, hallucination, or anxiety cases were higher with nonergot DAs, incidence of vomiting, arterial hypotension, or depression was higher with ergots. Pramipexole in RLS induced less nausea, vomiting, or dizziness than ropinirole. Other observational studies showed that frequency of valvular heart disease in PD was higher with ergot when compared with nonergot DAs.[6]

All this findings suggest possible differences in the safety profile of the DAs. To further explore these differences, we compared the frequency of adverse drug reaction (ADR) reports to the French pharmacovigilance system between the DAs currently available in France.

METHODS

Source of Data

The French pharmacovigilance system was first established in 1973 and consists of a network of 31 re-

gional centers. The French Pharmacovigilance Database (FPD) was established in 1985 to record spontaneous reporting of ADRs,[7] while reporting "serious" or "unlabeled" ADRs has been mandatory since 1995.[8] A "serious" ADR is defined as any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability/incapacity, or is life threatening.[9] Spontaneous reports submitted to the FPD, in which the products containing any DA were "suspected" as defined by WHO,[9] independently from the level of imputability, were extracted from January 1, 1984 (date of first report of an ADR to DAs) to December 31, 2008. ADRs to levodopa (L-dopa) were also analyzed. Total number of ADRs, number of "serious" ADRs, and number of ADRs by system organ class (according to the Medical Dictionary for Drug Regulatory Activities®) were compared between the DAs currently marketed in France. Information about DAs dose was not systematically collected in this work.

In France, apomorphine, bromocriptine, lisuride, pergolide, piribedil, pramipexole, or ropinirole are marketed as antiparkinsonian drugs and bromocriptine, cabergoline, lisuride, or quinagolide for hyperprolactinemia. Pramipexole and ropinirole are the two sole DAs marketed for RLS.[1] Ropinirole was used as the referential DA as it is nowadays the most commonly used DA for the treatment of PD and RLS in France.

Notoriety biases[10] could be suspected for some ADRs to DAs: (1) cardiac valvulopathies could have been reported more frequently with pergolide when compared with the other DAs after the Lilly France "Dear Doctor Letter" in September 2003;[11] (2) excessive diurnal somnolence reactions reported to nonergolinic DAs could have been prompted by Frucht et al. initial reports in 1999[12]; and (3) Giovannoni et al. findings in 2000[13] could have boosted the exploration of impulse control disorders (ICDs). The effect of these potential biases was explored by dividing the studied 24-year time span in shorter periods according to the different dates of these safety alerts.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher exact test when appropriate. To avoid alpha error inflation when comparing ADRs frequencies between DAs, test-wise alpha error was set at 0.006. Thus, experiment-wise alpha error remained below the desired 0.05 level. Odds ratio and 99.3% confidence interval were calculated for each DA using ropinirole as a reference. Statistical analyses were performed using Epi Info Version 6.

RESULTS

Between 1984 and 2008, 2,189 ADRs in which at least one AD or 1,315 in which L-dopa was suspected were reported to the French pharmacovigilance system (Table 1). Gender distribution of cases was ~50/50 for drugs not used in hyperprolactinemia. On the contrary, for cabergoline, quinagolide, lisuride, or bromocriptine, female cases prevailed when compared with other DAs (65 vs. 50%, $P < 0.03$).

Total and by-drug ADRs frequencies according to "seriousness" or organ class are shown in Table 1. Comparisons of ADR frequency most commonly associated with DAs (according to the system organ class) are shown in Table 2. Diurnal somnolence was less frequently reported with all DAs or L-dopa when compared with ropinirole. Results remained unchanged when the study period was split in two subperiods: January 1984 to December 1999 and January 2000 to December 2008.

ICDs (i.e., hypersexuality, compulsive shopping, eating, or gambling) were more frequently reported with pramipexole and less with bromocriptine or L-dopa. Results remained unchanged when the study period was split in two subperiods: January 1984 to December 2000 and January 2001 to December 2008.

Edemas were less frequently reported with L-dopa when compared with ropinirole. Although a significant difference could be noticed among DAs in the frequency of confusion and disorientation ($P < 0.001$), nausea and vomiting ($P < 0.05$), no single comparison yielded significant differences with ropinirole. Cardiac valvulopathy was significantly more frequently reported with pergolide when compared with ropinirole. All cases of cardiac valvulopathies were reported after September 2003. Pleural effusion was more frequently reported with bromocriptine or pergolide, without differences between the periods January 1984 to September 2003 and October 2003 to December 2008.

DISCUSSION

In this study, significant differences in the type of ADRs reported to the French pharmacovigilance system according to the different DAs were found, providing further evidence about possible differences in the safety profile of the DAs.

Our study suffers from some mandatory limitations. First, underreporting of ADRs to pharmacovigilance system is usual and may reach 90% of cases.[14] Nonetheless, underreporting rate was shown to be similar for several drugs from the same therapeutic class,[15] and this methodology was further validated by our

TABLE 1. *Frequency of ADRs (according to the system organ class) reported with DAs to the French pharmacovigilance system between 1984 and 2008*

Dopamine agonist	"Serious" ADRs, N = 1,163 n (%)	Neuropsychiatric, N = 861 n (%)	General, N = 423 n (%)	Cutaneous, N = 357 n (%)	Gastrointestinal, N = 382 n (%)	Vascular, N = 350 n (%)	Cardiac, N = 219 n (%)	Respiratory/Mediastinic, N = 182 n (%)	Metabolic, N = 122 n (%)	Ocular, N = 65 n (%)
Ropinirole (N = 277)	112 (40)	73 (26)	43 (16)	20 (7)	33 (12)	18 (6)	13 (5)	4 (1)	3 (1)	6 (2)
Apomorphine (N = 60)	13 (22)*	8 (13)	11 (18)	12 (20)*	12 (20)	4 (7)	2 (3)	3 (5)	0 (0)	2 (3)
Piribedil (N = 616)	202 (33)	156 (25)	69 (11)	64 (10)	60 (10)	55 (9)	17 (3)	8 (1)	34 (6)	9 (1)
Pramipexole (N = 48)	16 (33)	27 (56)*	3 (6)	0 (0)	1 (2)	1 (2)	2 (4)	4 (8)	6 (13)	3 (6)
Quinagolide (N = 24)	10 (42)	4 (17)	7 (29)	0 (0)	3 (13)	3 (13)	1 (4)	1 (4)	1 (4)	2 (8)
Bromocriptine (N = 846)	200 (24)*	192 (23)	133 (16)	123 (15)*	89 (11)	98 (12)	35 (4)	74 (9)*	18 (2)	17 (2)
Cabergoline (N = 50)	21 (42)	4 (8)	3 (6)	4 (8)	5 (10)	9 (18)	1 (2)	3 (6)	0 (0)	6 (12)*
Lisuride (N = 94)	22 (23)*	26 (28)	17 (18)	8 (9)	17 (18)	10 (11)	4 (4)	5 (5)	6 (6)	1 (1)
Pergolide (N = 174)	83 (48)	26 (15)*	18 (10)	9 (5)	12 (7)	13 (7)	79 (45)*	26 (15)*	1 (1)	2 (1)
Levodopa (N = 1,315)	484 (36)	345 (26)	119 (9)	117 (9)	150 (11)	139 (11)	65 (5)	54 (4)	53 (4)	17 (1)
Global Comparison	$P < 0.001$	$P < 0.001$	$P < 0.0016$	$P < 0.001$	$P = 0.07$	$P < 0.05$	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$

*$P < 0.006$ vs. ropinirole.

group with step 2 analgesic drugs[16] or for drugs causing dilated cardiomyopathy.[17] Second, a number of important factors, such as patients' diagnosis, age, related comorbidities or comedications, age at onset of PD, DAs doses, or changes in reporting patterns during the 24-year studied time span, could have introduced some bias in the results. Regrettably, as these data are not available in the FPD, biases could not be conveniently ruled out, leading to intrinsic limitations of this study. On the other hand, "notoriety biases" were excluded for diurnal somnolence or ICD but not for cardiac valvulopathies.

Diurnal somnolence was initially described with nonergot DAs,[12] but later with other DAs as well.[18,19] Our results suggest that the risk of somnolence is higher with nonergot DAs, which is in line with some recent experimental studies in the human.[20]

The frequency of ICD reports was higher with pramipexole and lower with bromocriptine when compared with ropinirole, in line with the fact that pramipexole and bromocriptine show the higher and the lower affinity for D3-receptor, respectively.[2]

The frequency of cardiac valvulopathy was higher with pergolide when compared with ropinirole. In this case, a notoriety bias is a likely explanation for these results, as no ADRs were reported before that date. Nonetheless, pleural effusions, which is an early sign of pleural fibrosis, another possible effect of 5HT2a,b receptor activation was more frequently reported with pergolide or bromocriptine even before September 2003, which cannot be explained by the same notoriety bias.

Cutaneous ADRs were more frequently reported with bromocriptine or apomorphine. Subcutaneous nodules are frequent complication of subcutaneous apomorphine application.[21] On the other hand, alopecia and skin eruptions have been reported with bromocriptine,[22] but rarely. Bromocriptine can induce skin changes in the mouse, probably by affecting alpha-MSH secretion,[23] providing some rationale for the present findings in humans.

No difference was found in the frequency of arterial orthostatic hypotension between DAs, which is consistent with previous results,[5] suggesting that orthostatic hypotension may be more closely related to the dopaminergic receptor stimulation than effects on other receptors.[3]

Although some differences were observed globally in the frequency of confusion and disorientation, nausea and vomiting, vascular or metabolic ADRs were found, no single difference with ropinirole was found. No difference was found in the frequency of hallucinations. Somnolence or ICD reports were less frequent with L-dopa, while surprisingly the frequency of confusion was greater when compared with ropinirole. This might be due to notoriety biases to the fact that

TABLE 2. *Frequency of specific ADRs (according to the system organ class) most commonly reported with DAs to the French pharmacovigilance system between 1984 and 2008*

	Neuropsychiatric				General	Gastrointestinal	Vascular	Cardiac	Respiratory
	Diurnal somnolence	Impulse control disorders	Confusion/ Disorientation	Hallucination	Edemas	Nausea/ Vomits	Hypotension	Valvulopathy	Pleural effusion
Dopamine Agonist	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Ropinirole (N = 277)	63 (23)	10 (4)	14 (5)	27 (10)	15 (5)	20 (7)	9 (3)	1 (0)	1 (0)
Apomorphine (N = 60)	0 (0)	4 (7)	1 (2)	1 (2)	1 (2)	3 (5)	1 (2)	1 (2)	0 (0)
Piribedil (N = 616)	62 (10)	4 (1)	76 (12)	66 (11)	13 (2)	35 (6)	31 (5)	3 (0)	1 (0)
Pramipexole (N = 48)	1 (2)	9 (19)	3 (6)	7 (15)	3 (6)	1 (2)	0 (0)	0 (0)	0 (0)
Quinagolide (N = 24)	0 (0)	0 (0)	1 (4)	1 (4)	0 (0)	2 (8)	0 (0)	0 (0)	0 (0)
Bromocriptine (N = 846)	29 (3)	4 (0)	62 (7)	90 (11)	71 (8)	54 (6)	33 (4)	2 (0)	20 (2)
Cabergoline (N = 50)	2 (4)	0 (0)	0 (0)	3 (6)	1 (2)	3 (6)	1 (2)	0 (0)	1 (2)
Lisuride (N = 94)	7 (7)	0 (0)	12 (13)	16 (17)	8 (9)	14 (15)	3 (3)	0 (0)	2 (2)
Pergolide (N = 174)	12 (7)	2 (1)	7 (4)	15 (9)	9 (5)	4 (2)	3 (2)	40 (23)	4 (2)
Levodopa (N = 1,315)	88 (7)	10 (1)	173 (13)	129 (10)	17 (1)	50 (4)	84 (6)	14 (1)	6 (1)
Global Comparison	$P < 0.001$ OR (CI)	$P < 0.001$ OR (CI)	$P < 0.001$ OR (CI)	$P = 0.1$ OR (CI)	$P < 0.001$ OR (CI)	$P < 0.05$ OR (CI)	$P = 0.3$ OR (CI)	$P < 0.001$ OR (CI)	$P < 0.006$ OR (CI)
Ropinirole	1	1	1	1	1	1	1	1	1
Apomorphine	–	1.90 (0.4–10.14)	0.32 (0.02–5.65)	0.16 (0.01–2.70)	0.30 (0.02–5.27)	0.68 (0.12–3.91)	0.54 (0.03–9.17)	4.68 (0.09–232.00)	–
Piribedil	0.38 (0.20–0.65)*	0.20 (0.04–1.03)	2.64 (0.95–6.03)	1.11 (0.57–2.15)	0.38 (0.13–1.10)	0.77 (0.35–1.71)	1.40 (0.50–3.88)	1.35 (0.10–32.43)	0.45 (0.02–8.55)
Pramipexole	0.07 (0.01–1.16)	6.2 (1.60–23.90)*	1.25 (0.21–7.59)	1.58 (0.45–5.54)	1.16 (0.19–6.97)	0.27 (0.02–4.66)	–	–	–
Quinagolide	–	–	0.82 (0.04–15.00)	0.40 (0.02–7.00)	–	1.17 (0.14–9.82)	–	–	–
Bromocriptine	0.12 (0.06–0.20)*	0.10 (0.02–0.50)*	1.49 (0.65–3.44)	1.10 (0.58–2.08)	1.60 (0.72–3.58)	0.88 (0.42–1.86)	1.10 (0.40–3.02)	0.65 (0.10–18.91)	6.68 (1.97–22.67)*
Cabergoline	0.14 (0.02–1.06)	–	–	0.59 (0.10–3.32)	0.36 (0.02–6.35)	0.82 (0.14–4.75)	0.50 (0.03–9.21)	–	5.63 (0.29–109.56)
Lisuride	0.27 (0.09–0.80)*	–	2.75 (0.88–8.56)	1.90 (0.74–4.85)	1.62 (0.46–5.66)	2.25 (0.81–6.24)	0.91 (0.14–5.66)	–	6.00 (0.65–55.69)
Pergolide	0.25 (0.10–0.62)*	0.30 (0.04–2.56)	0.79 (0.22–2.90)	0.87 (0.34–2.20)	0.95 (0.29–3.12)	0.30 (0.07–1.38)	0.50 (0.08–3.11)	82.39 (5.00–1,350)*	6.49 (1.14–37.09)*
Levodopa	0.24 (0.15–0.39)*	0.20 (0.06–0.69)*	2.85 (1.30–6.26)*	1.01 (0.55–1.86)	0.23 (0.09–0.62)*	0.51 (0.24–1.08)	1.80 (0.67–4.80)	2.97 (0.17–51.35)	1.27 (0.06–24.84)

OR (CI) = Odds ratio and 99.3% confidence interval.
*$P < 0.006$ vs. ropinirole.

L-dopa is more commonly used in aged and cognitively impaired patients. Finally, cabergoline was associated with a higher risk of ocular ADRs (i.e., visual perturbations, reduced visual accuracy, visual hallucinations, pupillary spasm, or other). The reason for this finding remains unclear, although this drug is known to affect ocular physiology in animals.[24]

Although RCTs are the first source of efficacy information about drugs, they suffer from important limitations regarding safety evaluation.[8] Studies based on pharmacovigilance databases, such as the present one, have the potential to offer a picture more in line with usual medical practice. Therefore, even though this study suffers from a number of intrinsic limitations, it offers important pieces of evidence that should be taken into account when evaluating the risk-benefit ratio of DAs. Nonetheless, the aforementioned limitations as well as the exploratory nature of this study advise caution in the interpretation of these results.

In summary, we found significant differences in the type of DAs-related ADRs reported to the French pharmacovigilance system. Diurnal somnolence frequency was highest with ropinirole, whereas ICD frequency was highest with pramipexole and lowest with bromocriptine. Cutaneous ADRs were more frequently reported with apomorphine or bromocriptine. Pleural effusion prevailed with pergolide or bromocriptine. These data further emphasize the differences in the safety profile of the different DAs, thus contributing with DAs' risk-benefit ratio comparison.

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