EXPERT OPINION

Risk of heart failure following treatment with dopamine agonists in Parkinson's disease patients

Santiago Perez-Lloret, María Verónica Rey, James Crispo, Daniel Krewski, Marise Lapeyre-Mestre, Jean-Louis Montastruc & Olivier Rascol[†]
[†]*Faculty of Medicine, Department of Clinical Pharmacology, Toulouse, France*

Introduction: Dopamine agonists (DAs) are frequently used to treat early or advanced Parkinson's disease (PD) patients. They have been shown to be efficacious for the treatment of motor symptoms and for delaying levodopa-induced dyskinesias. However, their utilization is limited by the risk of adverse drug reactions, some of which affect the cardiovascular system. Recently, the US FDA identified a possible association between exposure to pramipexole and the risk of heart failure.
Areas covered: This article begins by reviewing the pharmacodynamic and cardiovascular effects of DAs on PD patients. Pharmacoepidemiological studies about the association between DAs and heart failure are then evaluated.
Expert opinion: Four nested case-control studies were reviewed. In general, results showed higher heart failure risk following use of pramipexole or cabergoline. Although the effects of cabergoline may be explained by the induction of cardiac valve fibrosis, the basis for the significantly increased risk associated with pramipexole is unclear. It remains to be determined if these are dose-related effects, at what point they occur during the course of treatment, and if the risk is the same for all patients irrespective of other potential modifying factors, such as age and sex.

Keywords: adverse drug reactions, cardiovascular events, dopamine agonists, heart failure, Parkinson's disease, pharmacovigilance, pramipexole

Expert Opin. Drug Saf. (2014) ***13****(3):351-360*

1. Introduction

Levodopa remains the 'gold standard' for treating Parkinson's disease (PD) [1]. Nevertheless, its initial impressive therapeutic efficacy is frequently limited within a few years by the emergence of motor complications (such as fluctuations or abnormal movements) and other neurological problems [2,3]. As a consequence, the treatment of patients with PD has expanded to incorporate additional pharmacologic approaches, including the use of dopamine receptor agonists and inhibitors of the monoamine oxidase-B and/or catechol-*O*-metyltransferase enzymes.

Bromocriptine was the first dopamine agonist (DA) to be used as an adjunct to levodopa therapy for PD patients experiencing motor fluctuations [4]. Presently, nine different DAs are available worldwide for the treatment of PD, three of which are ergot derivates (bromocriptine, cabergoline, pergolide, lisuride), while the remaining five are not (apomorphine, piribedil, pramipexole, ropinirole, and rotigotine). Pergolide was withdrawn from the US and Canadian markets in 2007 because of concerns about adverse cardiovascular events [5,6], although it is still available in Europe [7]. Piribedil and lisuride are not available in North America.

informa
healthcare

Article highlights.

- Dopamine agonists are frequently used in the symptomatic treatment of early or advanced Parkinson's disease patients and delay levodopa-induced dyskinesias.
- Recently, the US FDA identified a possible association between exposure to pramipexole and the risk of heart failure.
- Four nested case-control studies were reviewed. In general, results showed higher heart failure risk following use of pramipexole or cabergoline.
- The effects of cabergoline may be explained by the induction of cardiac valve fibrosis. The basis for the significantly increased risk associated with pramipexole remains unknown.
- It remains to be determined if these are dose-related effects, at what point they occur during the course of treatment, and if the risk is the same for all patients, irrespective of other potential modifying factors such as age and sex.

This box summarizes key points contained in the article.

Multiple randomized controlled trials and a large body of clinical experience support the efficacy of DAs with respect to symptomatic control of motor symptoms in both early and advanced PD [8]. DAs also delay the occurrence of levodopa-induced motor complications, reduce off-time in patients with wearing off, [8] and can be used to ameliorate some nonmotor symptoms such as depression [9].

Adverse drug reactions (ADRs) of dopaminergic and non-dopaminergic origin often complicate the treatment of PD with DAs. The former can be classified as peripheral (including gastrointestinal reactions such as nausea and vomiting or cardiovascular reactions such as orthostatic hypotension and leg edema) or central (psychotic or behavioral syndromes and sedative reactions) [8]. The most frequent nondopaminergic ADRs include fibrotic reactions with ergot derivatives, application site reactions with subcutaneous apomorphine or rotigotine transdermal patches, skin reactions with bromocriptine, and ocular disturbances with cabergoline [8].

Recently, the US FDA evaluated the risk of heart failure by a pooled analysis of randomized clinical trials [10]. All randomized, placebo-controlled, Phase II and III clinical trials of pramipexole submitted by the manufacturer (Mirapex®, Boehringer Ingelheim) were analyzed. Results showed that the frequency of newly diagnosed heart failure was nonsignificantly higher with pramipexole (0.29%) as compared to placebo (0.14%) [10].

The objectives of this paper are to review the general pharmacodynamic characteristics and cardiovascular effects of DAs and to evaluate the evidence linking exposure to DAs with heart failure.

With this in mind, literature searches were conducted in Pubmed to identify publications about the relationship between heart failure and exposure to DAs. Only four articles on this topic were found, which will be reviewed in Section 4. Therefore, we took the opportunity to review their cardiovascular effects and pharmacodynamic bases for such effects, aiming to identify clues about the possible mechanisms of heart failure with DAs.

2. Pharmacodynamic characteristics of DAs

We begin by reviewing the localization and actions of dopamine receptors, which are the main targets of DAs. A summary of their localization and effects in the human body is given in **Table 1**. We will focus on cardiovascular effects resulting from the activation of these receptors. Full discussion of the pharmacodynamic properties of DAs can be found elsewhere [11,12].

The central dopaminergic neuron system comprises three main pathways: the nigrostriatal, the mesolimbic/mesocortical, and the tubular-infundibular pathways [11]. The nigrostriatal pathway originates in the substantia nigra pars compacta, projects to the striatum, and is involved in regulating basal ganglia function. The mesolimbic and mesocortical pathways originate in the ventral tegmental area (A10), project to cortical structures, affect cognitive function and motivation, and are also part of the reward system [13]. The tubular-infundibular pathway originates in the hypothalamus, projects to the hypophysis and other targets, and is involved in neuroendocrine regulation and wake–sleep cycle generation. Activation of dopamine receptors in some of these pathways can produce cardiovascular effects. For example, some studies suggest that the basal ganglia are involved in autonomic regulation of blood pressure and heart rate [14]. In a group of 34 healthy subjects, striatal dopamine D2/D3 receptor binding correlated negatively with supine resting systolic blood pressure and heart rate, and positively with supine resting heart rate variability [15].

Dopamine also inhibits prolactin secretion [16]. Prolactin increases heart rate and vascular tone, [17,18] and induces endothelial dysfunction leading to inflammation and altered function [19]. In the heart, D_1-, D_3- and D_4 agonists show no major effects, whereas D_2 agonists decrease heart rate and left ventricular contractility [20].

Dopamine also exerts pronounced cardiovascular and renal effects by activating both D1-like and D2-like dopamine receptors located at various sites within the cardiac, vascular, and renal regions [11,21,22]. For example, stimulation of D1-like receptors induces vasodilatation and natriuresis, whereas stimulation of D2-like receptors results in inhibition of norepinephrine release and inhibition of aldosterone secretion, contributing to vasodilatation and sodium excretion. Effects on vessel walls are mediated by postjunctional D1-like and prejunctional D2-like receptors. Interestingly, intravenous administration of apomorphine to dogs resulted in blood pressure fall due to vasodilation, which in turn, led to increased heart rate, stroke volume, and cardiac output [23].

The kidney, a target of dopamine, expresses both D1-like and D2-like receptors [11,21]. Renal D1-like receptors exhibit vascular and tubular localization. Acting on these receptors,

Table 1. Dopamine receptors.

	D1 family		D2 family		
	D_1	D_5	D_2	D_3	D_4
Function					
Adenylate cyclase	+	+	-	?	?
PIP turnover	+	+	-	?	?
Distribution					
Brain	Striatum Nucleus accumbens	Hypothalamus Hippocampus	Striatum Substantia nigra	Olfactory tubercle Hypothalamus Mesolimbic pathway	Frontal cortex Midbrain
Periphery	Heart Kidney	Vascular Kidney	Vascular Heart Sympathetic ganglia	Vascular Kidney	Heart Kidney
Effects on blood pressure regulation					
Heart rate/contractility	0	?	-	-	-
Natriuresis and diuresis	+	+	+	+	?
Vasodilation	+	+	+	+	?
Other	-	Inhibition of AT1 receptor expression Inhibitory effect on vascular proliferation	Antagonize AngII	Inhibition of AT1 receptor expression and rennin excretion	Antagonize vasopressin- and aldosterone-dependent water and sodium reabsorption

AngII: Angiotensin II; AT1: Angiotensin receptor 1; PIP: Phosphoinositolphosphate.

dopamine inhibits renal sodium–potassium pump activity and the Na^+/H^+ exchanger, which produces a salt-losing effect. On the other hand, D2-like receptors have been shown to inhibit renin release. Dysfunction of the renal dopaminergic system has been proposed as a pathogenetic factor in some forms of hypertension [24].

Dopamine receptors are also expressed in sympathetic ganglia [25]. For example, in anesthetized dogs and *in vitro* studies on arterial preparations, D_2-receptor agonists inhibited norepinephrine release. Furthermore, D_2 receptors have also been found in the adrenal medulla and in isolated chromaffin cell preparations. In a recent study, quinpirole-induced inhibition of the sympathetic vasopressor outflow is primarily mediated by activation of dopamine D2-like receptors [26]. A similar effect has been observed with D_5 receptors [21].

Dopamine has been hypothesized to affect insulin secretion, based on findings of hyperinsulinemia following administration of neuroleptics to normal subjects and reduced insulin secretion in PD patients treated with levodopa [27,28]. *In vitro* studies performed in isolated pancreatic islets further suggest the participation of D_2 receptors in insulin secretion. Interestingly, D2R knockout mice demonstrate impairment of insulin response to glucose, high fasting glucose levels, and glucose intolerance [27,28]. Bromocriptine has also recently been shown to be effective for the treatment of type 2 diabetes mellitus, probably by reducing insulin resistance when administered at appropriate circadian moments [29,30]. Finally, it has been shown that dopamine inhibits histamine-induced endothelial exocytosis by activating D2-like receptors, thus reducing Von Willebrand factor secretion [31].

DAs differ in their affinities for dopamine receptors. As demonstrated in **Table 2**, bromocriptine is a D2-like receptor agonist and a weak D1-like receptor antagonist, while apomorphine and pergolide are mixed D1- and D2-like receptor agonists. Ropinirole and pramipexole bind selectively to D2-like receptors [12,32,33], with pramipexole being most selective. Within the D2-like receptor family, these agonists have higher affinity for the D_3 receptor compared with D_2 receptor, with pramipexole again showing higher selectivity.

DAs also bind to nondopaminergic receptors (**Table 2**). For example, ergolinic derivatives demonstrate high to moderate affinity for a variety of nondopaminergic receptors such as α-adrenergic (α 1 and α 2) and serotonergic (5HT1 and 5HT2) receptors [12,32,34-36]. Nonergolinic receptors are devoid of appreciable effects on 5HT or α1-adrenergic receptors but retain considerable activity on α2-adrenergic receptors.

α2-adrenoceptors belong to the superfamily of G-protein-coupled receptors [37,38]. On one hand, they bind to the inhibitory G proteins Gi and Go and decrease adenylcyclase activity; however, they are also coupled to Gs-proteins, thus increasing adenylcyclase activity. Activation of these receptors could decrease cellular cAMP levels at low agonist concentrations, while at higher concentrations cAMP may be increased. There are three main receptor subtypes, referred to as receptors A – C, respectively. A fourth originally described subtype, the adrenoceptor (receptor D), is now accepted as an A-subtype receptor.

The A-subtype receptor is the major autoreceptor in sympathetic neurons, where it inhibits the release of norepinephrine. The C-subtype also functions as an autoreceptor, but it is expressed in sympathetic nerve endings more than in central adrenergic neurons. It has been suggested that

Table 2. Binding affinity of dopamine agonists for dopaminergic and nondopaminergic receptors.

Agonists	D1-like	D2-like	5HT1	5HT2	α-1	α-2
Ergolinic derivates						
Bromocriptine	0	++	++	+++	++	++
Cabergoline	0/+	+++	++	++	++	++
Pergolide	+	+++	+	+++	++	++
Nonergolinic compounds						
Apomorphine	++	++	0/+	0/+	0/+	++
Piribedil	0/+	+++	0	0/+	0/+	++
Pramipexole	0/+	+++	0/+	0/+	0/+	++
Ropinirole	0	+++	0	0/+	0/+	+
Rotigotine	0	+++	+	?	+	+

+++: Strong; ++: Moderate; +: Mild; 0: No effect.

C-subtype receptors may control norepinephrine release at low-action potential frequencies. In contrast, the A-subtype seems to operate primarily at high-stimulation frequencies in sympathetic nerves, and may thus be responsible for controlling noradrenaline release during maximal sympathetic activation. In contrast, α2-B adrenoreceptors are found mainly postsynaptically throughout the body.

In summary, based on their pharmacodynamic profile, DAs may be expected to i) reduce sympathetic tone and sodium retention, thus leading to reduced blood pressure; ii) reduce heart rate and contractility, thus leading to reduced cardiac oxygen consumption; iii) reduce insulin resistance, leading to improved metabolic functioning; and iv) to reduce Von Willebrand Factor secretion, thus leading to reduced coagulability potential. Interestingly, all these effects should theoretically lead to cardioprotection. In the following section, the cardiovascular effects of DAs observed experimentally will be reviewed.

3. Cardiovascular effects of DAs

Short-term cardiovascular responses to bromocriptine administration were previously explored in healthy subjects [39]. Ten healthy subjects, 31 ± 2 years of age, were evaluated following administration of bromocriptine (2.5 mg) alone and after blocking peripheral D2-like receptors by domperidone. An electrocardiogram was performed in the supine and sitting positions, and the low-frequency (LF) component, the high-frequency (HF) component, and the LF/HF ratio were calculated. The latter is used as an index of sympatovagal balance, whereas the HF component, is thought to represent the vagal cardiac influence. Change from the supine and sitting positions induced an increase in the LF/HF ratio, a reduction in the HF component, and increased norepinephrine release. Administration of bromocriptine led to a reduction of blood pressure, a reduction in norepinephrine release, and an increase in the LF/HF ratio. These effects were not completely blocked by pre-administration of domperidone, a peripheral blocker of dopamine receptors. Indeed, a decrease in diastolic blood pressure was still observed. Norepinephrine release was not altered and the LF/HF ratio (a marker of sympathetic tone) decreased. These results suggest that blood pressure reduction after treatment with bromocriptine occurs by peripheral and central mechanisms. The peripheral mechanisms involve inhibition of norepinephrine release, which induces a reflex increase in the sympathetic cardiac influence. Peripheral blockade of dopamine receptors did not mitigate bromocriptine's hypotensive effects, although a reduction of sympathetic tone was seen in this case.

The effects of bromocriptine on blood pressure and pulse rate were also studied in 20 untreated PD patients in whom bromocriptine monotherapy was initiated [40]. Results showed a dose-dependent reduction in supine systolic and diastolic blood pressure, offset by a small increase in heart rate. In a group of untreated PD patients, administration of a D1 agonist significantly decreased blood pressure and peripheral norepinephrine release in the supine position and caused orthostatic hypotension [41].

Cardiovascular effects of extended treatment with pergolide were studied in 40 patients, in whom treatment was initiated after inclusion in the study [42]. During the course of treatment with pergolide, seven patients experienced arrhythmias, two experienced syncope, and eight of them experienced orthostatic hypotension. Critical atrial fibrillation has also been observed with ropinirole [43].

Recently, cardiovascular effects of rotigotine were explored in 34 *de novo* PD patients [44]. Rotigotine is a nonergolinic agent with low affinity for the α2-adrenergic receptors (**Table 1**). Results showed that drug administration did not modify cardiovascular parameters, including orthostatic blood response or cardiac responses to the valsalva maneuver, or to deep breathing.

Treatment with ergot and nonergot DAs induces leg edema more frequently than levodopa [8]. In different clinical trials, frequency of edemas with pramipexole was 42% versus 15% with levodopa and 16% with ropinirole or cabergoline versus 3% in control groups treated with levodopa [8]. Risk factors for peripheral edema include female sex and cardiovascular comorbidities. A recent study reported that edemas were more frequent with DAs as compared to levodopa, with no statistically significant differences among the different DAs [45].

Table 3. Studies exploring the association between exposure to DAs and the occurrence of heart failure.

Author, year	Arbouw *et al.* 2012 [50]	Mokhles *et al.* 2012 [51]	Renoux *et al.* 2012 [53]	Hsieh and Hsiao 2013 [52]
Study design	Nested case-control	Nested case-control	Nested case-control	Nested case-control
Source	PHARMO database	Health Improvement Network (UK), Health Search Database (Italy); Integrated Primary Care Information & PHARMO (Holland)	UK General Practice Research Database	Taiwan's National Health Insurance research database
Study base	At least one prescription for a dopaminergic agent after the age of 55 (1994 – 2007)	1 year of medical history; new users of either DAs or levodopa for PD	Users of antiparkinsonian; 40 – 89 years of age between 1997 and 2009	Users of antiparkinsonian drugs between 2001 and 2010
Definition of exposure	At least one prescription within 1 year before the index date	Any prescription for DA or levodopa	Actual or past use of DAs	Actual or past use of DAs
Event definition	Hospitalization for a coronary, peripheral or cerebral vascular event	Incident HF confirmed by review of electronic recordings	Incident HF confirmed by review of electronic recordings	Incident HF
Controls	Matched to case patients on gender, duration of prescription and age (5 years)	Matched to each case on database, age (±2 years) and sex	Drug indication, age, sex, new user status and year of entry	Age, gender and cohort entry year
Sample size	Study base = 8094. Cases = 542, controls = 2155	Study base = 25,459. Cases = 527, controls = 38,641	Study base = 26,814. Cases = 783, controls = 7454	Study base = 27,135. Cases = 1707, controls = 3414
Confounding factors assessed	Prior hospitalization due to ischemic events or other events, co-medication	Concomitant cardiovascular, autoimmune, Gastrointestinal or metabolic disorders, co-medication	Alcohol, smoking, Body mass index, comorbidities, co-medications	Reason for prescription, comorbidities, co-medications

DA: Dopamine agonist; HF: Heart failure; PD: Parkinson's disease.

Ergot-derived DAs can induce pleuropulmonary, pericardiac, and/or retroperitoneal fibrosis [8]. Indeed, the risk of valvular fibrosis is significantly higher for these agents compared to nonergolinic DAs [45]. It has been suggested that this effect is mediated by the activation of the 5HT2B receptor [46]. Interestingly, there are no reports on heart valve fibrosis with lisuride, which is a 5HT2B receptor antagonist [47].

Apart from these alterations, ergot-derived compounds do not appear to alter cardiac morphology [48,49].

4. Association between exposure to DAs and heart failure

To the best of our knowledge, four studies to date have explored the relationship between exposure to DAs and the occurrence of heart failure [50-53]. They provided mixed results. Study protocols - nested case-control studies within cohorts obtained from healthcare databases - are summarized in **Table 3**. Study databases comprised patients of defined ages with prescriptions for dopaminergic drugs used in PD, parkinsonian syndromes, restless leg syndrome, hyperprolactinemia, or acromegaly. Although only one study population was limited to PD patients, patients older than 50 years treated with antiparkinsonian drugs generally represent PD cases. Exposure was defined as one or more prescriptions of a DA, and patients were classified as current or past users of this class of drug. Nonexposure was defined as patients without such a prescription. In one study, however, only subjects on levodopa were included in this group. The outcome was diagnosis of heart failure in the majority of studies based on a review of electronic health records. In one study, the outcome was defined as hospitalization for a coronary, peripheral or cerebral vascular event.

Such studies are restricted by many of the same limitations, which may explain a number of inconsistencies regarding results, some of which were initially identified by The US FDA [10]. First, the inclusion of non-PD patients, reflecting the use of antiparkinsonian for other indications, may have introduced some heterogeneity in the populations under study. Second, cardiovascular comorbidities were different in exposed and nonexposed groups, being generally more frequent in cases than in controls. Some degree of information bias might have been introduced by the fact that DAs induce peripheral edemas, which might have prompted the search for other

Table 4. Risk of heart failure with dopamine agonists.

	Mokhles *et al.* 2012 [51]	Renoux *et al.* 2012 [53]	Hsieh and Hsiao 2013 [52]
Any dopamine agonist	-	1.58 (1.26 – 1.96)	1.22 (0.89 – 1.67)
Ergolinic compounds	1.03 (0.69 – 1.55)	-	1.46 (1.00 – 2.12)
Cabergoline	1.30 (0.76 – 2.22)	2.07 (1.39 – 3.07)*	2.39 (0.41 – 14.12)
Bromocriptine	0.79 (0.19 – 3.25)	-	1.54 (0.93 – 2.55)
Pergolide	0.78 (0.41 – 1.46)	1.42 (0.95 – 2.12)	1.39 (0.77 – 2.48)
Nonergolinic compounds	1.18 (0.85 – 1.62)	-	1.24 (0.84 – 1.82)
Pramipexole	1.61 (1.09 – 2.38)*	1.86 (1.21 – 2.85)*	1.40 (0.75 – 2.61)
Ropinirole	0.82 (0.50 – 1.34)	1.23 (0.85 – 1.77)	1.22 (0.76 – 1.95)

Odds ratio as obtained from logistic regression are shown.
*$p < 0.05$.

cardiovascular diseases, including heart failure. Finally, heart failure diagnosis was not confirmed by an independent review of medical charts. It must also be mentioned that the effect of some DAs, such as rotigotine, piribedil or apomorphine, could not be properly analyzed due to insufficient power.

Results from the three studies that used heart failure as the study outcome will be reviewed. The study from Renoux and colleagues included 26,814 users of antiparkinsonian drugs in whom 787 cases of heart failure (possible or probable) were diagnosed during the follow-up (annual rate = 8.7 per 1000) [53]. Such cases were matched to 7454 controls (up to 10 per case). Body mass index (BMI), smoking, alcohol abuse, frequency of cardiovascular and metabolic comorbidities, and frequency of treatment by diuretics were higher in cases compared to controls. Thirty-two heart failure cases (4.1%) were on pramipexole versus 211 (2.8%) controls (adjusted odds ratio (OR), 95% CI = 1.86, 1.21 – 2.85). Ropinirole was used by 40 (5.1%) cases and 385 (2.5%) controls (1.23, 0.85 – 1.77), cabergoline was used by 36 (4.6%) cases and 217 (2.9%) controls (2.07, 1.39 – 3.07) and pergolide was used by 32 (4.1%) cases and 261 (3.5%) controls (1.42, 0.95 – 2.12). Increased risk of HF with pramipexole was not modified by dose and therapy duration. Similarly, previous cardiovascular or peripheral edema history and prior levodopa or DA use did not modify the risk of heart failure with pramipexole.

In the study by Mokhles and colleagues, 527 possible or probable HF cases were detected in 25,459 levodopa or DAs new users [51]. Finally, 518 HF cases were matched to 38,641 cases. Cases had higher frequency of cardiovascular, metabolic, and respiratory comorbidities. Cabergoline was used by 15 (2.9%) HF cases and 1159 (3.0%) controls (1.30, 0.76 – 2.22), pergolide was used by 11 (2.1%) cases and 663 (1.7%) controls (0.78, 0.41 – 1.46), bromocriptine was used by 2 (0.4%) cases and 155 (0.4%) controls (0.79, 0.19 – 3.25), pramipexole was used by 31 (6.0%) cases and 1806 (4.7%) controls (1.61, 1.09 – 2.38), and ropinirole was used by 18 (3.5%) cases and 1720 (4.5%) controls (0.82, 0.50 – 1.34). There was no dose effect but risk was greater during the first 3 months of pramipexole use and in patients > 80 years of age.

Hsieh and Hsiao identified 1707 HF cases among 27,135 users of antiparkinsonian drugs, who were matched to 3414 controls [52]. As observed in previous studies, cardiovascular and metabolic comorbidities and treatments were more frequent among cases. Pramipexole was used by 28 (1.6%) of HF cases and 42 (1.2%) controls (1.40, 0.75 – 2.61), ropinirole was used by 46 (2.7%) cases and 69 (2.0%) controls (1.22, 0.76 – 1.95), cabergoline was used by 2 (0.1%) cases and 5 (0.2%) controls (2.39, 0.41 – 14.12), pergolide was used by 33 (1.9%) cases and 47 (1.4%) controls (1.39, 0.77, 2.48), and bromocriptine was used by 45 (2.6%) cases and 60 (1.8%) controls (1.54, 0.93 – 2.55).

Risk of HF with the different DAs as observed by Mokhles and colleagues, Renoux and colleagues, and Hsieh and Hsiao are summarized in **Table 4**.

Arbouw *et al.* [50] assessed the relationship between exposure to DAs and the frequency of hospitalizations due to ischemic events in PD patients by analyzing the PHARMO database. Patients with at least one prescription for a medication containing levodopa and aged of 55 years between 1994 and 2006 were included. Cases were subjects with hospitalizations due to coronary, peripheral, or cerebrovascular events after 1997. Four controls per case were selected, matched for gender, duration of prescription, history available, and age. Risk of hospitalization was nonsignificantly increased with DAs (OR [95% CI], 1.19 [0.95 – 1.49]). These results had to be interpreted cautiously, as they did not exclusively assess heart failure, but ischemic effects leading to hospitalization. On one hand, ischemic heart disease is the leading cause of heart failure but not the only one [54]. Furthermore, peripheral or cerebrovascular events were included, which are not related to heart failure.

5. Conclusions

DAs have a central role in the treatment of PD. Nonetheless, their use can be complicated by an increased risk of some serious ADRs, some of which are of cardiovascular origin. Among cardiovascular ADRs, one of the most frequent is orthostatic hypotension and the most severe is cardiac valve fibrosis leading to regurgitation, which is only observed with

ergolinic compounds. Results from nested case-control studies herein reviewed suggest that pramipexole and cabergoline might increase the risk of heart failure in PD patients. Initial results suggest that this reaction may be more frequent in aged subjects and during the first few months after beginning treatment in those treated with pramipexole.

6. Expert opinion

DAs exert a range of cardiovascular effects related to the activation of dopaminergic and nondopaminergic receptors. They reduce peripheral resistance, increase salt and water excretion, reduce endothelial activation, and reduce insulin resistance by central and peripheral mechanisms. It is, therefore, not surprising that DAs have been used experimentally for the treatment of hypertension [55] and have been shown to be efficacious for the treatment of type 2 diabetes [56].

Results suggest that cabergoline and pramipexole appear to increase the risk of heart failure. It was suggested that for cabergoline, cardiac valve fibrosis might lead to heart failure. However, this happens infrequently [57] and might not fully account for the proposed relationship. Mokhles and colleagues performed an exploratory analysis restricted to heart failure cases preceded by new onset cardiac valve regurgitation occurring after the start of drug use [51]. results showed that cabergoline but not pramipexole was related to heart failure occurrence. These results, however, do not rule out the possibility that cabergoline increase the risk of both events, which are otherwise not associated to one another.

The link between pramipexole and heart failure, while intriguing, is difficult to explain. One possibility is that pramipexole increases the risk of peripheral edema, which can lead to a false diagnosis of heart failure. Nonetheless, results reported by Renoux and colleagues suggest that the risk of heart failure associated with pramipexole was independent of the presence of peripheral edemas [53].

Pramipexole's effects were more pronounced during the initial months after beginning treatment [51]. As heart failure is a chronic condition, this may argue in favor of an unmasking effect of pramipexole. In the present context, subjects starting on pramipexole may be more closely monitored because of known cardiovascular ADRs, leading to enhanced diagnosis of a subclinical chronic heart failure. Nonetheless, it is clear that this result needs to be confirmed, before any firm conclusion is drawn.

It is also possible that pramipexole impacts adversely on the cardiovascular profile, leading to heart failure only in subjects with risk factors, such as male gender, less education, physical inactivity, cigarette smoking, overweight, diabetes, or hypertension [54]. This coincides with the observation that heart failure risk was higher in aged subjects and that cases had more cardiovascular antecedents, comorbidities, and co-medications in all studies reported to date [51-53].

Intriguingly, based on its pharmacodynamic properties, a cardioprotective effect of pramipexole may be postulated. Indeed, as discussed in Section 2, it may reduce blood pressure load, heart oxygen consumption, insulin resistance, and hypercoagulability. However, previous experience cautions against such simplified reasoning. For example, based on its pharmacodynamic properties, milrinone was initially thought to have therapeutic potential for treating heart failure, but was later shown to increase mortality [58]. Ibopamine, a DA, has also been shown to reduce survival in patients with heart failure [59]. Similarly, pramipexole appears to alter cardiovascular function in an adverse way, leading to heart failure. The fact that its pharmacodynamic characteristics might theoretically suggest a cardioprotective effect may indicate that this drug acts on that this drug acts on pathways that are not fully elucidated. Therefore, more research on the mechanism of DAs action of action is warranted.

Interestingly, ropinirole does not appear to lead to an increased risk of heart failure, suggesting a specific effect of pramipexole. The major difference between these drugs is affinity to D_3 receptors, which is higher for pramipexole. At this point, how activation of such receptors might alter cardiac function remains unclear.

Many unanswered questions regarding the risk of heart failure associated with exposure to pramipexole warrant further investigation. First, the cardiovascular effects of pramipexole in PD patients should be investigated, ideally in a comparative study with other DAs. Second, more information is needed to fully characterize the relationship between DAs and heart failure, including the effects of dose, treatment duration, clinical relevance, and if they are modified by co-administration of other antiparkinsonian drugs. Finally, a risk-benefit analysis should be conducted, focusing on patient groups with higher risk of heart failure. For example, if the risk of heart failure is only increased in pramipexole users over 80 years of age, then its impact in the general population may be less obvious, as these subjects are not frequently treated with DAs due to a higher risk of neuropsychiatric complications [60]. It is also recommended that in future studies, diagnosis of heart failure be based on echocardiography and most importantly on the measure of natriuretic peptides circulating levels [61].

Declaration of interest

S Perez Lloret, MV Rey, M Lapeyre-Mestre, J Crispo, and J-L Montastruc have no conflict of interests to disclose. D Krewski serves as Chief Risk Scientist and CEO at Risk Sciences International (www.risksciences.com), which has conducted work on other pharmaceutical products for federal government clients. O Rascol has acted as an advisor for most drug companies developing antiparkinsonian medications including DAs such as Boehringer-Ingelheim, GSK, Britannia, UCB, Servier and has received unrestricted scientific grants from GSK, Novartis, Boehringer-Ingelheim, Faust Pharmaceuticlas, Eisai, Lundbeck, TEVA and Euthérapie, Solvay.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Birkmayer W, Hornykiewicz O. The effect of l-3,4-dihydroxyphenylalanine (=DOPA) on akinesia in parkinsonism. Parkinsonism Relat Disord 1998;4:59-60
2. Nutt JG. Levodopa-induced dyskinesia: review, observations, and speculations. Neurology 1990;40:340-5
3. Rascol O, Payoux P, Ory F, et al. Limitations of current Parkinson's disease therapy. Ann Neurol 2003;53(Suppl 3):S3-12
4. Calne DB, Teychenne PF, Leigh PN, et al. Treatment of parkinsonism with bromocriptine. Lancet 1974;2:1355-6
5. U.S. Drug and Food Administration. FDA Announces Voluntary Withdrawal of Pergolide Products. 2007. Available from: http://www.fda.gov/newsevents/newsroom/pressannouncements/2007/ucm108877.htm [Last accessed 17 September 2013]
6. Health Canada. Cease Sale of Permax (pergolide mesylate) in Canada as of August 30, 2007 - For Health Professionals. 2007. Available from: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2007/14469a-eng.php [Last accessed 17 September 2013]
7. European Medicines Agency. Questions and Answers on the review of ergot-derived dopamine agonists. 2008. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Ergot_derived_dopamine_agonists_31/WC500011445.pdf [Last accessed 17 September 2013]
8. Perez-Lloret S, Rascol O. Dopamine receptor agonists for the treatment of early or advanced Parkinson's disease. CNS Drugs 2010;24:941-68

• **Complete review on the efficacy and safety of DAs for the treatment of PD.**

9. Barone P, Poewe W, Albrecht S, et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 2010;9:573-80
10. Administration US FAD. FDA Drug Safety Communication: Ongoing safety review of Parkinson's drug Mirapex (pramipexole) and possible risk of heart failure. 2012. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm319779.htm [Last accessed 10 September 2013]

•• **One of the first communication about the possibility of increased frequency of heart failure with pramipexole.**

11. Emilien G, Maloteaux JM, Geurts M, et al. Dopamine receptors–physiological understanding to therapeutic intervention potential. Pharmacol Ther 1999;84:133-56
12. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. Clin Ther 2006;28:1065-78
13. Taber KH, Black DN, Porrino LJ, et al. Neuroanatomy of dopamine: reward and addiction. J Neuropsychiatry Clin Neurosci 2012;24:1-4
14. Pazo JH, Belforte JE. Basal ganglia and functions of the autonomic nervous system. Cell Mol Neurobiol 2002;22:645-54
15. Yeh TL, Yang YK, Chiu NT, et al. Correlation between striatal dopamine D2/D3 receptor binding and cardiovascular activity in healthy subjects. Am J Hypertens 2006;19:964-9
16. Gonzalez-Iglesias AE, Murano T, Li S, et al. Dopamine inhibits basal prolactin release in pituitary lactotrophs through pertussis toxin-sensitive and -insensitive signaling pathways. Endocrinology 2008;149:1470-9
17. Manku MS, Horrobin DF, Zinner H, et al. Dopamine enhances the action of prolactin on rat blood vessels. Implications for dopamine effects on plasma prolactin. Endocrinology 1977;101:1343-5
18. Molinari C, Grossini E, Mary DA, et al. Prolactin induces regional vasoconstriction through the beta2-adrenergic and nitric oxide mechanisms. Endocrinology 2007;148:4080-90
19. Stamatelopoulos KS, Georgiopoulos GA, Sfikakis PP, et al. Pilot study of circulating prolactin levels and endothelial function in men with hypertension. Am J Hypertens 2011;24:569-73
20. Polakowski JS, Segreti JA, Cox BF, et al. Effects of selective dopamine receptor subtype agonists on cardiac contractility and regional haemodynamics in rats. Clin Exp Pharmacol Physiol 2004;31:837-41
21. Zeng C, Zhang M, Asico LD, et al. The dopaminergic system in hypertension. Clin Sci (Lond) 2007;112:583-97
22. Gomez Mde J, Rousseau G, Nadeau R, et al. Functional and autoradiographic characterization of dopamine D2-like receptors in the guinea pig heart. Can J Physiol Pharmacol 2002;80:578-87
23. Nakayama H, Nakayama T, Carnes CA, et al. Electrophysiologic and hemodynamic effects of apomorphine in dogs. Toxicol Appl Pharmacol 2001;177:157-61
24. Hussain T, Lokhandwala MF. Renal dopamine receptor function in hypertension. Hypertension 1998;32:187-97
25. Missale C, Nash SR, Robinson SW, et al. Dopamine receptors: from structure to function. Physiol Rev 1998;78:189-225
26. Manrique-Maldonado G, Gonzalez-Hernandez A, Marichal-Cancino BA, et al. The dopamine receptors mediating inhibition of the sympathetic vasopressor outflow in pithed rats: pharmacological correlation with the D(2) -like type. Basic Clin Pharmacol Toxicol 2011;109:506-12
27. Garcia-Tornadu I, Ornstein AM, Chamson-Reig A, et al. Disruption of the dopamine d2 receptor impairs insulin secretion and causes glucose intolerance. Endocrinology 2010;151:1441-50
28. Garcia-Tornadu I, Perez-Millan MI, Recouvreux V, et al. New insights into the endocrine and metabolic roles of dopamine D2 receptors gained from the Drd2 mouse. Neuroendocrinology 2010;92:207-14
29. Gaziano JM, Cincotta AH, O'Connor CM, et al. Randomized clinical trial of quick-release bromocriptine among patients with type 2 diabetes on overall safety and cardiovascular outcomes. Diabetes Care 2010;33:1503-8
30. Gaziano JM, Cincotta AH, Vinik A, et al. Effect of bromocriptine-QR (a quick-release formulation of bromocriptine mesylate) on major adverse cardiovascular events in

type 2 diabetes subjects. J Am Heart Assoc 2012;1:e002279

31. Zarei S, Frieden M, Rubi B, et al. Dopamine modulates von Willebrand factor secretion in endothelial cells via D2-D4 receptors. J Thromb Haemost 2006;4:1588-95
32. Piercey MF. Pharmacology of pramipexole, a dopamine D3-preferring agonist useful in treating Parkinson's disease. Clin Neuropharmacol 1998;21:141-51
33. Tulloch IF. Pharmacologic profile of ropinirole: a nonergoline dopamine agonist. Neurology 1997;49:S58-62
34. Fariello RG. Pharmacodynamic and pharmacokinetic features of cabergoline. Rationale for use in Parkinson's disease. Drugs 1998;55(Suppl 1):10-16
35. Montastruc JL, Rascol O, Senard JM. Current status of dopamine agonists in Parkinson's disease management. Drugs 1993;46:384-93
36. Piercey MF, Hoffmann WE, Smith MW, et al. Inhibition of dopamine neuron firing by pramipexole, a dopamine D3 receptor-preferring agonist: comparison to other dopamine receptor agonists. Eur J Pharmacol 1996;312:35-44
37. Gyires K, Zadori ZS, Torok T, et al. alpha(2)-Adrenoceptor subtypes-mediated physiological, pharmacological actions. Neurochem Int 2009;55:447-53
38. Philipp M, Brede M, Hein L. Physiological significance of alpha(2)-adrenergic receptor subtype diversity: one receptor is not enough. Am J Physiol Regul Integr Comp Physiol 2002;283:R287-95
39. Franchi F, Lazzeri C, Barletta G, et al. Centrally mediated effects of bromocriptine on cardiac sympathovagal balance. Hypertension 2001;38:123-9
40. Quinn N, Illas A, Lhermitte F, et al. Bromocriptine in Parkinson's disease: a study of cardiovascular effects. J Neurol Neurosurg Psychiatry 1981;44:426-9
41. Durrieu G, Senard JM, Rascol O, et al. Blood pressure and plasma catecholamines in never-treated parkinsonian patients: effect of a selective D1 agonist (CY 208-243). Neurology 1990;40:707-9
42. Leibowitz M, Lieberman AN, Neophytides A, et al. The effects of pergolide on the cardiovascular system of 40 patients with Parkinson's disease. Adv Neurol 1983;37:121-30
43. Di Giacopo R, Fasano A, Fenici R, et al. Rare and serious cardiac side effects during ropinirole titration. Mov Disord 2010;25:1509-10
44. Rocchi C, Pierantozzi M, Pisani V, et al. The impact of rotigotine on cardiovascular autonomic function in early Parkinson's disease. Eur Neurol 2012;68:187-92
45. Perez-Lloret S, Bondon-Guitton E, Rascol O, et al. Adverse drug reactions to dopamine agonists: a comparative study in the French Pharmacovigilance Database. Mov Disord 2010;25:1876-80
46. Antonini A, Tolosa E, Mizuno Y, et al. A reassessment of risks and benefits of dopamine agonists in Parkinson's disease. Lancet Neurol 2009;8:929-37
47. Hofmann C, Penner U, Dorow R, et al. Lisuride, a dopamine receptor agonist with 5-HT2B receptor antagonist properties: absence of cardiac valvulopathy adverse drug reaction reports supports the concept of a crucial role for 5-HT2B receptor agonism in cardiac valvular fibrosis. Clin Neuropharmacol 2006;29:80-6
48. Tan LC, Ng KK, Au WL, et al. Bromocriptine use and myocardial function. Mov Disord 2011;26:923-4
49. Rasmussen VG, Poulsen SH, Dupont E, et al. Ergotamine-derived dopamine agonists and left ventricular function in Parkinson patients: systolic and diastolic function studied by conventional echocardiography, tissue Doppler imaging, and two-dimensional speckle tracking. Eur J Echocardiogr 2008;9:803-8
50. Arbouw ME, Movig KL, Guchelaar HJ, et al. Dopamine agonists and ischemic complications in Parkinson's disease: a nested case-control study. Eur J Clin Pharmacol 2012;68:83-8

•• **A nested case-control study on the frequency of Ischemic complications with DAs.**

51. Mokhles MM, Trifiro G, Dieleman JP, et al. The risk of new onset heart failure associated with dopamine agonist use in Parkinson's disease. Pharmacol Res 2012;65:358-64

•• **Nested case-control study on the risk of heart failure with DAs.**

52. Hsieh PH, Hsiao FY. Risk of heart failure associated with dopamine agonists: a nested case-control study. Drugs Aging 2013;30(9):739-45

•• **Nested case-control study on the risk of heart failure with DAs.**

53. Renoux C, Dell'Aniello S, Brophy JM, et al. Dopamine agonist use and the risk of heart failure. Pharmacoepidemiol Drug Saf 2012;21:34-41

•• **Nested case-control study on the risk of heart failure with DAs.**

54. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up study. Arch Intern Med 2001;161:996-1002
55. Tayebati SK, Lokhandwala MF, Amenta F. Dopamine and vascular dynamics control: present status and future perspectives. Curr Neurovasc Res 2011;8:246-57
56. Holt RI, Barnett AH, Bailey CJ. Bromocriptine: old drug, new formulation and new indication. Diabetes Obes Metab 2010;12:1048-57
57. Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. N Engl J Med 2007;356:39-46
58. Packer M, Carver JR, Rodeheffer RJ, et al. Effect of oral milrinone on mortality in severe chronic heart failure. The PROMISE Study Research Group. N Engl J Med 1991;325:1468-75
59. Hampton JR, van Veldhuisen DJ, Kleber FX, et al. Randomised study of effect of ibopamine on survival in patients with advanced severe heart failure. Second Prospective Randomised Study of Ibopamine on Mortality and Efficacy (PRIME II) Investigators. Lancet 1997;349:971-7
60. Perez-Lloret S, Rey MV, Ratti L, et al. Pramipexole for the treatment of early Parkinson's disease. Expert Rev Neurother 2011;11:925-35
61. Palazzuoli A, Beltrami M, Ruocco G, et al. The role of natriuretic peptides for the diagnosis of left ventricular dysfunction. ScientificWorldJournal 2013;2013:784670

Affiliation

Santiago Perez-Lloret[1] MD PhD,
María Verónica Rey[1] PharmD,
James Crispo[2] MSc PhD,
Daniel Krewski[2] PhD MHA,
Marise Lapeyre-Mestre[1] MD PhD,
Jean-Louis Montastruc[1] MD PhD &
Olivier Rascol[†1,3] MD PhD
[†]Author for correspondence
[1]Professor,
Hospital and University Paul Sabatier of Toulouse, France and INSERM CIC9023 and UMR 825, Department of Clinical Pharmacology and Neurosciences, Toulouse, France
[2]University of Ottawa, McLaughlin Centre for Population Health Risk Assessment, 1 Stewart Street, Ottawa, Ontario, K1N 6N5, Canada
[3]Faculty of Medicine, Department of Clinical Pharmacology, 37 Allées Jules Guesde, 31000, Toulouse, France
Tel: +33 5 61 14 59 62;
Fax: +33 5 61 14 56 42;
E-mail: olivier.rascol@univ-tlse.fr