Risks of Cardiac Valve Regurgitation and Heart Failure Associated with Ergot – and Non-ergot Derived Dopamine Agonist Use in Patients with Parkinson's Disease: A Systematic Review of observational studies

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Short title: Dopamine agonists and the risk of cardiac events

Abstract

Background

Dopamine agonists (DAs) are commonly used in the therapy of Parkinson's disease (PD). However, several observational studies have suggested a putative association between DAs and specific cardiac adverse events.

Objectives

To systematically review and summarize the available epidemiologic evidence on the association between use of ergot- and non-ergot derived DAs and the risk of valvular heart disease, specifically cardiac valve regurgitation (CVR), and heart failure (HF) in patients with PD.

Methods

The databases MEDLINE/PubMed and EMBASE were searched for all relevant articles published before February 2015. Studies were eligible if they met the following inclusion criteria: exposure to any approved non-ergot- or ergot-derived DA, presentation of original data, inclusion of an unexposed reference group, and valvular heart disease or heart failure as the primary outcome of interest.

Results

13 publications for CVR were identified (2 nested case-control, 1 cohort and 10 cross-sectional studies). Compared with non-ergot DAs or other anti-parkinsonian drugs, exposure to ergot-derived DAs pergolide and cabergoline was associated with an increased risk of CVR among PD patients. Incidence rate ratios (IRR) in the nested case-control and cohort studies ranged from 2.00 to 7.10 and 4.58 to 4.90, respectively. Longer treatment duration and higher dose of those

DAs was also associated with a higher risk of CVR. Risk of HF was estimated in 3 nested case-control and 1 cohort study. Use of cabergoline (IRR range: 1.30 to 2.39) and the non-ergot-derived DA pramipexole (IRR range: 1.40 to 1.81) was associated with a higher HF risk among patients with PD. Pergolide may also be associated with a higher risk of HF.

Conclusion

Despite the heterogeneous methodological approaches of the included studies, there is strong evidence that treatment with pergolide and cabergoline is associated with a higher risk of cardiac valve regurgitation, and moderate evidence that treatment with pramipexole and cabergoline is associated with a higher risk of heart failure in patients with Parkinson's disease.

Key Messages

- Long-term use of pergolide and cabergoline is associated with dose-dependent increased risk of cardiac valve regurgitation (strong evidence).
- Pramipexole and cabergoline are associated with in an increased risk of heart failure (moderate evidence).

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease that generally affects the elderly. Dopamine agonists (DAs) are used either alone as the first-line treatment or in combination with levodopa for the symptoms of PD [1, 2], and are also prescribed for other conditions such as restless leg syndrome or hyperprolactinemia. DAs alone are effective in the early treatment of motor symptoms in PD and, in combination with levodopa, in the delay of levodopa-induced dyskinesias [3]. DAs may be ergot-derived or non-ergot-derived and are used in various dosages depending on indication and the patient's response to treatment. Ergot-derived DAs include pergolide, cabergoline, bromocriptine, and lisuride. Approved indications for ergot-derived DAs include PD, restless legs syndrome, hyperprolactinemia, lactation suppression and acromegaly. For example, cabergoline is used as treatment of hyperprolactinemia, but at 10 times lower dosages than in PD. Non-ergot-derived DAs include ropinirole and pramipexole, and less potent agonists which are used for the treatment of PD and restless legs syndrome [4]. These drugs have been associated with several adverse effects. In particular, cardiac valve regurgitation has been reported in patients treated with pergolide and cabergoline [5-7]. In 2007, the U.S. Food and Drug Administration (FDA) announced that pergolide had been withdrawn from the US market by its manufacturers due to the risk of valvular disease [8]. While cabergoline is not approved for PD treatment in the US [9], it is still approved for the treatment of hyperprolactinemia and for lactation suppression in Canada. In Europe, pergolide and cabergoline are still approved in PD but restricted to second-line use, and treatment requires close monitoring [10, 11]. In addition to the assumption that these drug-induced severe valve disorders can lead to heart failure (HF) if undetected, DAs may also increase the risk of HF. Indeed, HF has been observed in association

with the non-ergot-derived DA pramipexole in randomized trials, although the number of events was too small to draw any firm conclusion [12].

No review summarized the most recent existing evidence on the cardiac risk associated with the use of dopamine agonists in PD, especially concerning the association between pramipexole and HF. Moreover, previous systematic reviews were mainly based on cross-sectional studies which do not allow for a reliable quantification of risk. Therefore, we conducted a systematic literature review on the association between DA treatment in PD and the risk of valvular heart disease, specifically cardiac valve regurgitation (CVR), and HF.

2. Methods

2.1. Systematic Search

Potentially eligible studies were identified through a systematic search on the electronic publication databases MEDLINE/PubMed and EMBASE from the earliest available online year of indexing up to and including February 11, 2015. The search strategy was based on a combination of concepts that addressed the study population, the exposure of interest, and the outcome of interest: Parkinson's disease AND Dopamine Agonists AND cardiac events as complications/unintended effects.

The following search algorithm was applied to Medical Subject Headings and free-text words in MEDLINE/PubMed: (Parkinsonian Disorders OR Parkinson*) AND (Dopamine Agonists OR dopamine* agonist* OR antiparkinson* OR bromocriptine OR cabergoline OR dihydroergocryptine OR lisuride OR pergolide OR apomorphine OR piribedil OR pramipexole OR ropinirole OR rotigotine OR talipexole) AND (Heart Valve Diseases OR valvular heart disease* OR valvulopath* OR ((valve* OR valvular*) AND heart* AND disease*) OR Heart

Failure OR heart failure* OR Cardiomyopathies OR cardiomyopath*). A similar search strategy was applied to EMBASE. We also examined the references of relevant articles retrieved by the computerized search and those in previous reviews on PD and either CVR or HF. Duplicate publications from the same study were removed using EndNote X7. All publications written in English, German, French, and Spanish were eligible for screening.

2.2. Eligibility Criteria and Data Collection

The two outcomes of interest were valvular heart disease, specifically CVR, and HF.

Studies eligible for the systematic review were observational studies presenting original data with a study population defined as patients with PD or patients treated with anti-parkinsonian drugs which included both patients with PD and patients with other conditions. However, studies assessing the risk associated with DAs only in patients with conditions other than PD, such as restless legs syndrome or hyperprolactinemia, were not eligible. Each study had to include an active ergot-derived or non-ergot-derived DA treatment group, as the exposure of interest, and a comparison group. Depending on study design, the comparison group could be either an unexposed reference group of untreated PD patients or of patients treated with other anti-parkinsonian agents, such as other DAs or levodopa. Studies that only included healthy controls as the comparison group, or that did not provide a sufficiently defined comparison group, e.g. articles without any information on exposure or underlying disease were excluded. Studies were excluded if they did not provide any description of characteristics of the study population, or if frequencies of cardiac events given exposure status could not be calculated.

We developed a structured data extraction form (Supplement S1) to record the following data from each individual study if available: year of publication, country, years of study conduct,

study design, source population, sample size, inclusion and exclusion criteria, duration and severity of PD, percentage of male sex and mean age, type of comparison group (e.g., treated with non-DA anti-parkinsonian drugs, other DAs, untreated PD patients), number of participants per treatment group, exposure of interest (e.g., new users, prevalent users), definition of exposure, definition of the outcome, number of events per treatment group, matching variables or covariates adjusted for in the analysis, and adjusted estimates of measure of association between DA treatment and outcome (CVR or HF).

Furthermore, we developed a questionnaire based on the Newcastle-Ottawa Scale [13] to assess the quality of the eligible studies by evaluating information such as appropriate selection of the comparison/control group, appropriate exposure and outcome ascertainment, and appropriate adjustment for confounders.

Eligibility screening for inclusion and the extraction of information for the selected studies was performed independently by two investigators (TT and CR) in accordance with the PRISMA checklist [14]. Differences were resolved by consensus.

3. Results

3.1. Included Studies

The initial search identified 651 publications, of which 612 were excluded based on review of the title and abstract (Figure 1). The main reasons for exclusion were irrelevance for the systematic review as the publications did not address the study question, no adequate comparison group, review articles, comments, letters, and case reports. The remaining 39 articles were reviewed in detail independently by two reviewers and 23 articles were further excluded.

Therefore, 16 studies were included in this systematic review. All were observational studies, consisting of 10 cross-sectional, 5 nested case-control, and 1 cohort study. Twelve publications addressed the primary outcome CVR, three publications studied the secondary outcome HF, and one (the cohort study) evaluated risk of both CVR and HF.

3.2. Cardiac valve regurgitation

Among the 13 studies that addressed the primary outcome CVR, two were nested case-control studies [15, 16], one was a cohort study [17], and 10 were cross-sectional studies [18-27]. Their characteristics are presented in Table 1. The studies were conducted in North America (n=1), Europe (n=7), and Asia (n=5), and included a total of 21,995 individuals (2,554 ergot DA users, 2,046 non-ergot DA users, 17,278 PD patients unexposed to DAs, 117 patients without PD/healthy controls) in whom 532 CVR events were identified (Table 2).

Ten studies compared treatment with DAs, ergot and/or non-ergot-derived, to treatment with no DAs or to untreated PD patients. The 3 remaining studies only compared ergot-derived DAs to non-ergot-derived DAs [19, 22, 24]. Three studies additionally compared the exposed groups to healthy controls [19, 22, 27].

3.2.1. Cohort and nested case-control studies assessing the risk of CVR

Table 1 describes the characteristics and the main results of the included studies. Schade et al. investigated the risk of CVR in patients treated with pergolide or cabergoline [15]. They reported an adjusted incidence rate ratio (IRR) of CVR of 7.1 (95% CI 2.3-22.3) among patients who were currently exposed to pergolide and of 4.9 (95% CI 1.5-15.6) among current cabergoline users compared to no current or recent use of DAs. The rate of CVR was not increased with current use of other DAs. Adjusted IRRs were increased with daily doses greater than 3 mg of

pergolide compared to daily doses of 3 mg or less, and duration of use greater than 6 months. Trifiro et al. evaluated the effect of ergot and non-ergot DAs on CVR [16]. They observed an increased risk of CVR with ergot-derived DAs, particularly cabergoline, but not with non-ergot-derived DAs. Adjusted odds ratios (ORs) were 4.58 (95% CI 2.40-8.75) among current cabergoline users and 2.00 (95% CI 0.61-6.56) among current pergolide users compared to current/past levodopa users. An increased risk was observed for daily doses of 3 mg or more for pergolide, as well as for patients treated with cabergoline for more than 6 months. There was a trend towards an increased risk with longer duration of pergolide but this analysis was based on two exposed cases only. Discontinuation of cabergoline was associated with a lower risk compared to current users of cabergoline (OR 0.15, 95% CI 0.03-0.69) [16].

The study cohort by Zadikoff et al. included new users of pergolide or levodopa who were event free during the 5 years following their initial prescription, and cohort entry was set 5 years after this first prescription [17]. Exposure of interest was defined as different durations of pergolide use in the 5 years prior to cohort entry. The rate of a hospital admission for CVR was higher among pergolide users compared to those exposed to levodopa when treated 1-4 years (hazard ratio (HR) 2.4, 95% CI 1.0-5.4).

Overall, these studies showed evidence of an increased risk of CVR among patients with PD treated with the ergot-derived DAs pergolide and cabergoline, but neither with other ergot-derived DAs nor with any non-ergot-derived DAs. Incidence rate ratios (IRR) in the nested case-control and cohort studies ranged from 2.00 to 7.10 for pergolide and 4.58 to 4.90 for cabergoline. Daily doses of more than 3 mg, as well as treatment duration of more than 6 months with pergolide and cabergoline, were associated with an increased risk of CVR.

3.2.2. Cross-sectional studies

Ten studies that assessed the risk of CVR associated with DA treatment in PD were cross-sectional studies. Nine of these studies were conducted at single centers [19-27]. PD severity was assessed by the Hoehn and Yahr score [28] in eight studies [19-24, 26, 27]. Ergot-derived DA users had higher scores, indicating increased severity of disease, than individuals in the comparison groups. Pergolide users had the highest Hoehn and Yahr scores among ergot-derived DA users (Table 1). CVR was confirmed by echocardiography in all studies using grading by valve scores [29].

Pergolide use was an exposure of interest in all studies. Eight studies additionally investigated the association between the use of other DAs, such as cabergoline [19, 20, 22-25, 27], bromocriptine [21, 25, 26], or pramipexole [19, 20, 22, 25], and the prevalence of CVR.

All studies observed a significantly higher prevalence of CVR among ergot-derived DA users, especially in PD patients treated with pergolide and cabergoline, compared to users of non-ergot-derived DAs, or other anti-parkinsonian drugs (Table 1). Five studies observed a higher prevalence of CVR among patients treated with a higher daily or cumulative dose of either pergolide or cabergoline [18, 20, 21, 25, 26], whereas four studies did not observe any differences, probably due to small sample size or overall low daily dose in the exposed group [19, 22-24]. Moreover, in two studies a higher prevalence of CVR was found with longer treatment duration with cabergoline [20, 25]. The other three studies did not find any association, likely due to small sample size [19, 21, 22].

Three studies investigated the prevalence of CVR in bromocriptine users and found discrepant results, thus precluding any firm conclusion about the association between bromocriptine use and

the risk of CVR [21, 25, 26]. Discrepancies in findings are possibly due to different duration and dose of treatment, and small sample size.

Overall, prevalence of CVR was higher in Parkinson patients treated with pergolide or cabergoline. Higher daily or cumulative dose in ergot-derived DAs was associated with a higher prevalence of CVR. Non-ergot-derived DAs were not associated with a higher prevalence of CVR.

3.3. Heart failure

Four studies were identified that evaluated the risk of HF in patients treated with anti-parkinsonian drugs (Table 3), 3 nested case-control studies and one cohort study [17, 30, 12, 31]. The studies were conducted in Europe (UK, Italy, Netherlands), Canada, and Asia (Taiwan), and included 64,343 individuals in whom 3,821 HF events were identified (Table 4).

Mokhles et al. [30] observed an increased incidence rate of newly diagnosed HF (adjusted OR 1.61, 95% CI 1.09–2.38) among PD patients who currently used the non-ergot-derived DA pramipexole, but not among patients who currently used the other non-ergot-derived DA ropinirole or any ergot-derived DA, compared to current/past use of levodopa. The risk of HF was increased in the first three months of treatment in current users of pramipexole (OR 3.06, 95% CI 1.74–5.39), while the risk disappeared with longer duration of use. Duration of other DA use was not associated with risk of HF and there was no dose-effect.

The study conducted by Renoux et al. [12] showed that current use of any dopamine agonist compared with non-use, was associated with an increase in the adjusted incidence rate of heart failure (IRR 1.58, 95% CI 1.26–1.96). In particular, pramipexole and cabergoline were associated with an increase in the incidence rate of HF (adjusted IRR 1.86, 95% CI 1.21–2.85,

IRR 2.07, 95% CI 1.39–3.07, respectively). The rate of HF was increased for other DAs, including pergolide (IRR 1.42, 95% CI 0.95–2.12), but was not statistically significant. Dose-response and duration-response analyses were based on current use of pramipexole compared to non-current use. There was no evidence of an increased risk with dose or duration.

Hsieh et al. [31] observed an increased risk of HF among patients currently treated with ergot-derived DAs (adjusted OR 1.46, 95% CI 1.00–2.12) but not among patients currently treated with non-ergot-derived DAs (OR 1.24, 95% CI 0.84–1.82) in their Taiwanese study sample. Perhaps due to a lack of statistical power, there was not a clear pattern of increased risk with current use of pramipexole (OR 1.40, 95% CI 0.75-2.61). Longer cumulative duration of any pramipexole use was not associated with an increase in risk of HF compared to non-use.

The cohort study by Zadikoff et al. investigated the risk of hospital admissions for congestive HF among pergolide compared to levodopa users according to duration of use [17]. The group treated with pergolide for 1-4 years showed an increased risk of congestive HF compared to the group only treated with levodopa (HR 2.35, 95% CI 1.02-5.41). Pergolide use for <1 year and >4 years was not associated with an increased risk of HF.

These studies indicate that use of cabergoline (IRR range: 1.30 to 2.39) and the non-ergot-derived DA pramipexole (IRR range: 1.40 to 1.81) is associated with a higher risk of HF. There is some indication that pergolide use might be associated with a higher risk of HF as well.

4. Discussion

Our results indicate that the ergot-derived DAs pergolide and cabergoline are associated with an increased risk of CVR in PD patients, compared with those treated with non-ergot-derived DAs, non-DAs, or untreated patients. It is unclear whether bromocriptine could be associated with an

elevated risk of CVR in PD patients. This association was investigated in only three studies, all cross-sectional, with discrepant findings, most likely due to variation in treatment dose and duration, and lack of statistical power. However, several case reports have suggested an association between bromocriptine and valvular heart disease in PD patients [32, 33]. As bromocriptine could potentially act as a partial agonist at the 5-HT_{2B} receptors on heart valves [34], further research is needed. There is no evidence that other DAs are associated with an increased risk of CVR.

The risk of CVR increases with longer treatment duration and higher dose of the ergot-derived DAs pergolide and cabergoline. Two studies also showed that discontinuation of cabergoline for PD treatment was associated with regression of CVR [16, 35]. The evidence was based on few studies with a robust methodology. Findings that did not support the positive dose-response or duration-response relationship were likely due to small sample size. The majority of the identified studies were cross-sectional and thus they estimated the prevalence rather than the incidence of CVR among exposed and unexposed subjects with uncertainty regarding the timing of exposure. The selection of the study population of these cross-sectional studies was mostly based on convenience samples and therefore, there was not sufficient information available to identify possible selection bias in those studies. However, the results were consistent across studies despite varying study designs and methodological differences. Dose and duration of DA treatment varied across studies, which likely explain the different magnitudes of the association estimates. These results are in accordance with previous reviews that also found an association between pergolide and cabergoline treatment in PD and CVR, but not with other DAs [5-7]. The mechanism behind the increased rate of CVR in PD patients treated with ergot-derived DAs, such as pergolide and cabergoline, is likely due to their additional function as potent agonists at

the 5-HT_{2B} serotonin receptors of cardiac myocytes. Stimulation of 5-HT_{2B} receptors induces proliferation of fibroblasts within valve tissue, which leads to valvular damage [34, 36].

This systematic review also indicates that the non-ergot-derived DA pramipexole increases the risk of HF compared to other anti-parkinsonian drugs although the evidence is only based on few studies with a total of 2150 patients exposed to pramipexole of whom 91 patients had heart failure. Notably, the FDA has been carrying out a safety review on the association between pramipexole and possible risk of heart failure and has notified healthcare professionals about the potential risk [37]. A recent small cross-sectional study examined left ventricular function in 55 PD patients treated with pramipexole or ropinirole in association with levodopa, or levodopa alone and did not find any evidence of myocardial dysfunction in patients taking pramipexole and ropinirole [38]. Thus, the association between pramipexole and the risk of HF warrants further investigation [39], in particular with regards to the effect of various doses and treatment duration. Moreover, the underlying biological mechanism of pramipexole adverse effect on the heart is still unclear.

Even though results were mostly not statistically significant, there is some indication that cabergoline and pergolide are associated with an increased risk of HF as well. There is only little evidence of an effect of dose or duration of treatment. As advanced CVR can cause HF [40, 41], an association between pergolide and cabergoline use and an increased risk of HF would be expected. Indeed, valvular regurgitation can lead to ventricular volume overload which increases myocardial strain that can ultimately result in overt heart failure. However, the number of exposed cases and thus the statistical power of the included studies was small resulting in wide confidence intervals and thus, precluding any firm conclusion.

There were several strengths in our study. We performed a systematic literature review with a well-defined search strategy and we developed search algorithms for the individual publication databases. Thus, it is likely that we identified all major relevant publications. The review of eligible studies and data extraction were performed independently by two investigators in order to increase the validity of the study results. The identified studies were conducted in different settings, e.g. hospital-based or population-based, and different countries which increase the generalizability of the results.

Regarding limitations of our systematic review, we did not contact the authors to obtain information on missing data. However, the most relevant information was available in the selected publications. Two studies were not restricted to PD patients only. Still, the majority of patients were treated for PD (55-70%), whereas other indications including rest legs syndrome and hyperprolactinemia accounted for about 6% and unidentified reasons for about 20% of the study population [12, 31], and results were comparable to studies only including PD patients. We did not conduct a meta-analysis as the included studies were too heterogeneous with regards to their methods, and only a few, i.e., the cohort and nested case-control studies, had a robust methodology to assess the risk of cardiac events. Moreover, estimates of some of the cross-sectional studies could have been biased as it was partly unclear how the study population, particularly the comparison group, was selected; or how the exposure and outcome of interest were assessed. Still, our summary based on the current available evidence reports findings in accordance with previous reviews and public health decisions.

5. Conclusion

Pergolide and cabergoline are associated with an increased risk of CVR. This risk increases with dose and duration of treatment. There is some indication that pramipexole, cabergoline, and pergolide are associated with an increased risk of HF. However, the evidence for the association with HF is weaker than reported for CVR, particularly for pergolide. These results are consistent across studies using various designs and in different geographical settings. Thus, from a public health point of view close cardiac monitoring is advised when treating patients with PD with these DAs.

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Compliance with Ethical Standards

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Conflict of Interest

SS has received research grants and participated in advisory board meetings and/or as a speaker at conferences for Bayer, Boehringer-Ingelheim and Bristol- Myers-Squibb. TT, JB, and CR declare no conflict of interest.

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Figure 1: Study selection for the systematic review