

## Movement Disorders

Copy of e-mail Notification

Your article (08 014 . 1) from "Movement Disorders" is available for download

=====

Movement Disorders Published by John Wiley & Sons, Inc.

Dear Author,

Your page proofs are now available in PDF format, and are ready for your corrections. John Wiley & Sons has made this article available to you online for faster, more efficient editing. Please follow the instructions below to make your corrections as soon as possible.

Alternatively, if you would prefer to receive a paper proof by regular mail, please contact Birender/Sundeeep (e-mail: wileycs@kwglobal.com, phone: +91 (44) 42058888 ext. 310). Be sure to include your article number.

First, make sure you have a copy of Adobe Acrobat Reader software. This is free software and is available on the web (<http://www.adobe.com/products/acrobat/readstep.html>). Or, if you have the Notes annotation tool (not contained within Acrobat reader), you can make corrections electronically and return them to Wiley as an e-mail attachment (see the Notes tool instruction sheet).

Open your web browser, and enter the following web address:

<http://kwglobal.co.in/jw/retrieval.aspx>

You will be prompted to login, and asked for a password. Your login name will be your email address, and your password will be ----.

Example:

Login: your e-mail address

Password: ----

The site contains one file, containing:

- Author Instructions Checklist
- Adobe Acrobat Users - NOTES tool sheet
- Reprint Order form
- Return fax form
- A copy of your page proofs for your article

Print out this file, and fill out the forms by hand. (If you do not wish to order reprints, please mark a "0" on the reprint order form.) Read your page proofs carefully, and:

- indicate changes or corrections in the margin of the page proofs
- answer all queries (footnotes A,B,C, etc.) on the last page of the PDF proof
- proofread any tables and equations carefully
- check that any Greek, especially "mu", has translated correctly
- Check your figure legends for accuracy

You will receive hard copies of your color figure proofs by regular mail, and will be asked to check these for quality and color-matching. If the quality of the figures is unacceptable at that point, good quality hard copies (not electronic copies) of your original figures must be sent back to me.

## Movement Disorders

Copy of e-mail Notification

Within 48 hours, please fax, email or mail to the address given below:

- 1) Page proofs with corrections
- 2) Hard copy figures and/or TIFF or EPS files of figures for correction (if necessary)
- 3) Reprint Order form
- 4) Return fax form

Return to:

Steven Kyritz  
Associate Production Editor  
John Wiley & Sons  
111 River Street  
Hoboken, NJ 07030

Tel: (201) 748-6808  
Fax: (201) 748-6182  
e-mail: skyritz@wiley.com

Technical problems? If you experience problems downloading your file or any other problem with the website listed above, please contact:  
Birender/Sundeep (wileycs@kwglobal.com, phone: +91 (44) 42058888 ext. 310).

Questions regarding your article? Please don't hesitate to contact me with any questions about the article itself, or if you have trouble interpreting any of the questions listed at the end of your file. **REMEMBER TO INCLUDE YOUR ARTICLE NO. (08 014 . 1) WITH ALL CORRESPONDENCE.** This will help both of us address your query most efficiently.

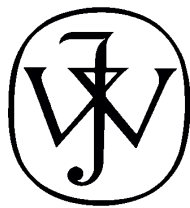
As this e-proofing system was designed to make the publishing process easier for everyone, we welcome any and all feedback. Thanks for participating in our new e-proofing system!

This e-proof is to be used only for the purpose of returning corrections to the publisher.

Sincerely,

Steven Kyritz  
Associate Production Editor  
John Wiley & Sons  
111 River Street  
Hoboken, NJ 07030

Tel: (201) 748-6808  
Fax: (201) 748-6182  
e-mail: skyritz@wiley.com



# WILEY

*Publishers Since 1807*

111 RIVER STREET, HOBOKEN, NJ 07030

## ELECTRONIC PROOF CHECKLIST, MOVEMENT DISORDERS

**\*\*\*IMMEDIATE RESPONSE REQUIRED\*\*\***

Please follow these instructions to avoid delay of publication.

**READ PROOFS CAREFULLY**

- This will be your only chance to review these proofs.
- Please note that the volume and page numbers shown on the proofs are for position only.

**ANSWER ALL QUERIES ON PROOFS** (Queries for you to answer are attached as the last page of your proof.)

- Mark all corrections directly on the proofs. Note that excessive author alterations may ultimately result in delay of publication and extra costs may be charged to you.

**CHECK FIGURES AND TABLES CAREFULLY**

- Check size, numbering, and orientation of figures.
- All images in the PDF are downsampled (reduced to lower resolution and file size) to facilitate Internet delivery. These images will appear at higher resolution and sharpness in the printed article.
- Review figure legends to ensure that they are complete.
- Check all tables. Review layout, title, and footnotes.

**COMPLETE REPRINT ORDER FORM**

- Fill out the attached reprint order form. It is important to return the form even if you are not ordering reprints. You may, if you wish, pay for the reprints with a credit card. Reprints will be mailed only after your article appears in print. This is the most opportune time to order reprints. If you wait until after your article comes off press, the reprints will be considerably more expensive.

**RETURN**

- PROOFS**  
 **REPRINT ORDER FORM**  
 **CTA (If you have not already signed one)**

**RETURN WITHIN 48 HOURS OF RECEIPT VIA FAX TO Steven Kyritz at  
201-748-6182**

**QUESTIONS?**

Steven Kyritz, Associate Production Editor

Phone: 201-748-6808

E-mail: [skyritz@wiley.com](mailto:skyritz@wiley.com)

Refer to journal acronym and article production number (i.e., MDS 20000 for *Movement Disorders* ms 20000).

## Softproofing for advanced Adobe Acrobat Users – NOTES tool

NOTE: ADOBE READER FROM THE INTERNET DOES NOT CONTAIN THE NOTES TOOL USED IN THIS PROCEDURE.

Acrobat annotation tools can be very useful for indicating changes to the PDF proof of your article. By using Acrobat annotation tools, a full digital pathway can be maintained for your page proofs.

The NOTES annotation tool can be used with either Adobe Acrobat 6.0 or Adobe Acrobat 7.0. Other annotation tools are also available in Acrobat 6.0, but this instruction sheet will concentrate on how to use the NOTES tool. Acrobat Reader, the free Internet download software from Adobe, DOES NOT contain the NOTES tool. In order to softproof using the NOTES tool you must have the full software suite Adobe Acrobat Exchange 6.0 or Adobe Acrobat 7.0 installed on your computer.

### Steps for Softproofing using Adobe Acrobat NOTES tool:

1. Open the PDF page proof of your article using either Adobe Acrobat Exchange 6.0 or Adobe Acrobat 7.0. Proof your article on-screen or print a copy for markup of changes.
2. Go to Edit/Preferences/Commenting (in Acrobat 6.0) or Edit/Preferences/Commenting (in Acrobat 7.0) check “Always use login name for author name” option. Also, set the font size at 9 or 10 point.
3. When you have decided on the corrections to your article, select the NOTES tool from the Acrobat toolbox (Acrobat 6.0) and click to display note text to be changed, or Comments/Add Note (in Acrobat 7.0).
4. Enter your corrections into the NOTES text box window. Be sure to clearly indicate where the correction is to be placed and what text it will effect. If necessary to avoid confusion, you can use your TEXT SELECTION tool to copy the text to be corrected and paste it into the NOTES text box window. At this point, you can type the corrections directly into the NOTES text box window. **DO NOT correct the text by typing directly on the PDF page.**
5. Go through your entire article using the NOTES tool as described in Step 4.
6. When you have completed the corrections to your article, go to Document/Export Comments (in Acrobat 6.0) or Comments/Export Comments (in Acrobat 7.0). Save your NOTES file to a place on your harddrive where you can easily locate it. **Name your NOTES file with the article number assigned to your article in the original softproofing e-mail message.**
7. **When closing your article PDF be sure NOT to save changes to original file.**
8. To make changes to a NOTES file you have exported, simply re-open the original PDF proof file, go to Document/Import Comments and import the NOTES file you saved. Make changes and reexport NOTES file keeping the same file name.
9. When complete, attach your NOTES file to a reply e-mail message. Be sure to include your name, the date, and the title of the journal your article will be printed in.



REPRINT BILLING DEPARTMENT • 111 RIVER STREET • HOBOKEN, NJ 07030  
 PHONE: (201) 748-8789; FAX: (201) 748-6326; E-MAIL: reprints@wiley.com

**Please complete this form even if you are not ordering reprints.**

This form MUST be returned with your corrected proofs and original manuscript. Your reprints will be shipped approximately 4 weeks after publication. Reprints ordered after printing are substantially more expensive.

JOURNAL: MOVEMENT DISORDERS Volume: \_\_\_\_\_ Issue: \_\_\_\_\_

TITLE OF MANUSCRIPT: \_\_\_\_\_

MANUSCRIPT NUMBER: \_\_\_\_\_ No. pages: \_\_\_\_\_ 1st Author: \_\_\_\_\_

**REPRINTS 8 1/4 X 11**

No. of pages	100 Reprints	200 Reprints	300 Reprints	400 Reprints	500 Reprints
	\$US	\$US	\$US	\$US	\$US
	\$US	\$US	\$US	\$US	\$US
1-4	336	501	694	890	1052
5-8	469	703	987	1251	1477
9-12	594	923	1234	1565	1850
13-16	714	1156	1527	1901	2273
17-20	794	1340	1775	2212	2648
21-24	911	1529	2031	2536	3037
25-28	1004	1707	2267	2828	3388
29-32	1108	1894	2515	3135	3755
33-36	1219	2092	2773	3456	4143
37-40	1329	2290	3033	3776	4528

REPRINTS ARE ONLY AVAILABLE IN LOTS OF 100. IF YOU WISH TO ORDER MORE THAN 500 REPRINTS, PLEASE CONTACT US AT (201) 748-8789 FOR A PRICE QUOTE.

**COVERS**

100 Covers:	\$90	200 Covers:	\$145	300 Covers:	\$200
400 Covers:	\$255	500 Covers:	\$325	Additional 100s:	\$65

- Please send me \_\_\_\_\_ reprints of the above article at \$ \_\_\_\_\_  
 Please send me \_\_\_\_\_ Generic Covers of the above journal at \$ \_\_\_\_\_

Please add appropriate State and Local Tax {Tax Exempt No. \_\_\_\_\_} .....

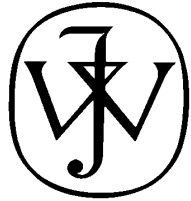
Please add 5% Postage and Handling .....

TOTAL AMOUNT OF ORDER\*\* .....

\*\*International orders must be paid in US currency and drawn on a US bank

- Please check one:  Check enclosed  Bill Me  Credit Card  
 If credit card order, charge to:  American Express  Visa  MasterCard  Discover  
 Credit Card No. \_\_\_\_\_ Signature: \_\_\_\_\_ Exp. Date: \_\_\_\_\_

**BILL TO:** Name: \_\_\_\_\_ Address/Institution: \_\_\_\_\_  
**SHIP TO:** Name: \_\_\_\_\_ Address/Institution: \_\_\_\_\_  
 Phone: \_\_\_\_\_ Fax: \_\_\_\_\_  
**Purchase order no:** \_\_\_\_\_ **E-mail:** \_\_\_\_\_



**WILEY**

*Publishers Since 1807*

***Movement Disorders***

111 RIVER STREET, 8<sup>TH</sup> FLOOR, HOBOKEN, NJ 07030

---

Telephone Number:

☎ Facsimile Number:

To: Steven Kyritz

Fax: 201-748-6182

From: \_\_\_\_\_

Date: \_\_\_\_\_

Re: \_\_\_\_\_

Pages (including  
cover sheet) \_\_\_\_\_

Message:

## Bromocriptine Use and the Risk of Valvular Heart Disease

Louis C.S. Tan, FRCP,<sup>1,2,3\*</sup> Kenneth K.C. Ng, MRCP,<sup>4</sup> Wing-Lok Au, FRCP,<sup>1,2,3</sup>  
Raymond K.K. Lee, MRCP,<sup>4</sup> Yiong-Huak Chan, PhD,<sup>5</sup> and Nigel C.K. Tan, MRCP<sup>3</sup>

<sup>1</sup>*Parkinson's Disease and Movement Disorders Centre, National Neuroscience Institute, Singapore*

<sup>2</sup>*USA National Parkinson Foundation Centre of Excellence*

<sup>3</sup>*Department of Neurology, National Neuroscience Institute, Singapore*

<sup>4</sup>*Department of Cardiology, Tan Tock Seng Hospital, Singapore*

<sup>5</sup>*Biostatistics Unit, Yong Loo Lin School of Medicine, National University of Singapore, Singapore*

AQ1

AQ2

**Abstract:** It has been reported that patients on pergolide and carbergoline have an increased risk of developing valvular heart disease. It is uncertain if bromocriptine, an ergot-derived dopamine agonist (DA) with partial 5-HT<sub>2B</sub> activity, is associated with a similar risk. We assessed the frequency of valvular heart disease in Parkinson's disease (PD) patients on bromocriptine compared to pergolide and a control group of PD patients who had not been treated on any DA. Seventy-two PD patients on bromocriptine, 21 patients on pergolide, and 47 control PD patients were recruited. Transthoracic echocardiographic studies were performed and reviewed by a blinded cardiologist. The risk for the bromocriptine group to develop any abnormal valvular regurgitation was 3.32 (adjusted OR, 95% CI: 1.11–9.92,

$P = 0.03$ ) compared to controls, whereas the risk for the pergolide group was 3.66 (adjusted OR, 95% CI: 1.22–10.97,  $P = 0.02$ ). When cumulative dose of bromocriptine was analyzed by quartiles, patients with a greater exposure to bromocriptine had significantly higher risk of developing both mild and moderate-severe regurgitations ( $P$  for trend, 0.005 and 0.019, respectively). This study demonstrated that bromocriptine use was associated with an increased risk of developing valvular heart disease, which occurred in a cumulative dose-dependent manner. © 2008 Movement Disorder Society

**Key words:** bromocriptine; valvular heart disease; 5-HT<sub>2</sub> serotonin receptors; ergotamines; pergolide; dopamine agonists

Several retrospective and prospective studies have shown that the risk of valvular heart disease in patients with Parkinson's disease (PD) is increased with the use of the dopamine agonists (DA) pergolide and cabergoline.<sup>1–3</sup> Both these drugs are ergot-derived DA and their effects on heart valves have been postulated to be mediated through their potent agonism of the 5-hydroxytryptamine 2B (5-HT<sub>2B</sub>) receptors expressed on heart valves.<sup>1–4</sup> Bromocriptine is also an ergot-derived DA that has been previously described to be a 5-HT<sub>2B</sub> antagonist<sup>5</sup> but found subsequently to be a partial agonist of 5-HT<sub>2B</sub> receptors.<sup>6–8</sup> Although there have been numerous studies on pergolide and carbergoline and

their association with valvular heart disease, the risk of valvular heart disease in patients on bromocriptine has not been properly evaluated despite a previous case report of valvular heart disease related to bromocriptine use.<sup>9</sup> To the best of our knowledge, there has only been one prospective study that included a subgroup of PD patients on bromocriptine.<sup>10</sup> As a result of bromocriptine's less potent agonism of 5-HT<sub>2B</sub> receptors and the lack of published data, many have assumed that bromocriptine is a safe drug that is not associated with valvular heart disease.<sup>3,4</sup>

Bromocriptine is the first oral DA; it has been marketed since the early 1970s. Understanding the risk of developing valvular heart disease in patients on bromocriptine is important as this drug is widely used in developing countries as first-line treatment for PD. This is because of its availability in the generic form, which significantly reduces its costs. Even in a more developed country like Singapore, bromocriptine is the only DA that is fully subsidized by the public

\*Correspondence to: Dr. Louis C.S. Tan, Department of Neurology, National Neuroscience Institute, 11 Jalan Tan Tock Seng, Singapore 308433, Singapore. E-mail: louis\_tan@nmi.com.sg

Potential conflict of interest: •••

Received 15 February 2008; Revised 8 May 2008; Accepted 20 June 2008

Published online 00 Month 2008 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22228

AQ3

healthcare system. The impact of bromocriptine's use also extends beyond PD patients as it is commonly used for the treatment of hyperprolactinaemia and restless-legs syndrome.

We conducted a prospective echocardiographic study to investigate the risk of valvular heart disease among PD patients treated on bromocriptine compared to pergolide and a control group of PD patients who had not been treated with DA before. We evaluated the severity of regurgitation for the mitral, aortic, and tricuspid valves as well as the presence of morphological abnormalities on these valves.

## METHODS

Consecutive PD patients who attended the PD and movement disorders clinic who met the study criteria were recruited. Seventy-two PD patients treated on bromocriptine and 21 patients treated on pergolide were recruited. These patients had been on these medications for 6 months or more and not been previously treated on other DA. Age-matched controls were 47 PD patients who had not been exposed to any DA. All participants had no previous history of valvular, ischemic, or other heart disease and had not been on any other ergot or anorectic agents. Patients with severe dementia precluding informed consent, and patients with Marfan's syndrome and other connective tissues disorders who were prone to develop valvular heart disease were also excluded from the study. The institutional review board of our institute approved the study, and all participants provided written consent to take part in the study.

Complete echocardiographic examinations were carried out using a commercially available ultrasonograph (Vivid 7, General Electric, Norway) with M-mode, 2-dimensional, and Doppler echocardiography (pulsed waved, continuous wave and color Doppler). Echocardiograms were obtained in the standard views and stored as 3-second clips in a DICOM format on digital video discs. The morphology of all the valves were evaluated for any valve leaflet thickening ( $>4$  mm),<sup>11</sup> the presence of calcifications, abnormal valve motion, and the presence of stenosis. Qualitative assessment of valvular regurgitation for all valves was done by visual assessment of the color Doppler envelope. The severity of regurgitation was graded as absent (0), trace (1), mild (2), moderate (3), or severe (4) according to the American Society of Echocardiography criteria and guidelines.<sup>12</sup> A rating of mild regurgitation (grade 2) and higher was considered abnormal. The assessment of significant valvular regurgitation was performed

using semiquantitative methods that included continuous wave Doppler as well as measurements of effective regurgitant orifice area and regurgitant volumes. All echocardiograms were read by a qualified cardiologist who is an experienced echocardiographer (KN). The rater was blinded to participants' prior drug history (case or controls).

A composite regurgitation score, comprising the sum of the individual regurgitation scores for the mitral, aortic, and tricuspid valves, was calculated for each participant.<sup>2</sup> We also performed a combined regurgitation analysis to assess the severity of regurgitation across all three valves. Participants were grouped into three mutually exclusive categories: "normal" (all valves with grade 0–1 regurgitation), "mild" (at least 1 valve with grade 2 regurgitation and other valves with grade 0–2 regurgitation), and "moderate-severe" (at least one valve with grade 3–4 regurgitation).

Analysis was performed using SPSS version 11. We tested differences between bromocriptine and pergolide groups versus controls using the  $\chi^2$  test for categorical variables, and the unpaired *t* test for the composite regurgitation score. We used the  $\chi^2$  test for trend to assess the linear trend for the risk of valvular regurgitation with increasing bromocriptine quartiles. Adjustments were made for age, gender, the presence of diabetes mellitus and hypertension, duration of PD diagnosis, and UPDRS motor score.

Results were considered significant if  $P < 0.05$ .

## RESULTS

The mean age of the patients and racial composition of the participants in all three groups were similar. However, the control group had more females, were older at disease onset, had shorter disease duration, and had lower Hoehn and Yahr stage and less severe UPDRS motor scores (Table 1). There was no significant difference between the three groups in relation to the presence of valvular calcification, thickening, restricted mobility, or stenosis on echocardiography.

Analyzing only single valves, the pergolide group had significantly higher frequency of mitral and aortic regurgitation (Table 2). The bromocriptine group also had a significantly higher frequency of mild aortic regurgitation. The mean composite regurgitation score was also significantly higher for the pergolide group when compared with the control group ( $P < 0.001$ ).

In the combined regurgitation analysis for the pergolide group, there was a significantly higher frequency of mild as well as moderate-severe regurgitation when compared with the control group ( $P = 0.001$ )

## BROMOCRIPTINE AND VALVULAR HEART DISEASE

3

TABLE 1. Clinical characteristics of patients

Characteristics	Bromocriptine group (n = 72)	Pergolide group (n = 21)	Control group (n = 47)
Mean age (yr)	59.4 ± 7.9	61.5 ± 10.6	61.9 ± 6.8
Male (no, %)	53 (74%)	16 (76%)	27 (57%)
Race (no, %)			
Chinese	62 (86%)	19 (90%)	40 (85%)
Indian	7 (10%)	1 (5%)	4 (9%)
Malay	3 (4%)	1 (5%)	2 (4%)
Others	0	0	1 (2%)
Mean age of diagnosis (yr)	53.6 ± 7.1	50.9 ± 9.7	59.8 ± 6.6
Mean duration since diagnosis of PD (yr)	5.8 ± 4.3	10.8 ± 6.2	2.0 ± 1.9
Mean Hoehn and Yahr stage	2.4 ± 1.0	2.5 ± 0.8	2.0 ± 0.6
Mean UPDRS motor score	24.4 ± 11.3	24.0 ± 11.6	16.7 ± 6.6
Dosage of dopamine agonist			
Mean daily dose (mg/d)	18.6 ± 9.7	1.4 ± 0.7	0
Range of daily dose (mg/d)	2.5–60	0.4–3.0	0
Mean cumulative dose (mg)	20053.7 ± 17660.9	1882.8 ± 1425.7	0
Duration of treatment (mo)			
Mean	43.6 ± 32.4	57.8 ± 27.0	0
Range	5.6–126.9	19.9–109.3	0
Hypertension (no, %)	17 (24%)	9 (43%)	21 (45%)
Diabetes Mellitus (no, %)	7 (10%)	2 (10%)	4 (9%)

All mean values are expressed as mean ± SD.

(Table 2). For the bromocriptine group, the presence of mild or moderate-severe regurgitation was of borderline significance ( $P = 0.08$ ).

The risk of developing any abnormal valvular regurgitation (mild or moderate-severe) for participants on

pergolide compared to controls was 7.29 (crude OR, 95% CI: 2.31–23.07,  $P = 0.001$ ). After adjustment, the OR was 3.66 (95% CI: 1.22–10.97,  $P = 0.02$ ).

The risk for participants on bromocriptine to develop any abnormal valvular regurgitation was 2.33 (crude

TABLE 2. Severity of regurgitation

	Bromocriptine group (n = 72)	Pergolide group (n = 21)	Control group (n = 47)
Grade of mitral regurgitation			
0–1	64 (89%)	14 (67%)	44 (94%)
2	6 (8%)	5 (24%)	2 (4%)
3–4	2 (3%)	2 (10%)	1 (2%)
P value	0.66	0.02	
Grade of aortic regurgitation			
0–1	61 (85%)	13 (62%)	43 (92%)
2	11 (15%)	3 (14%)	2 (4%)
3–4	0	5 (24%)	2 (4%)
P value	0.04	0.01	
Grade of tricuspid regurgitation			
0–1	47 (66%)	15 (71%)	38 (83%)
2	18 (25%)	4 (19%)	6 (13%)
3–4	6 (9%)	2 (10%)	2 (4%)
P value	0.15	0.54	
Mean composite regurgitation score (95% CI)	2.14 (1.72–2.56)	3.43 (2.64–4.22)	1.70 (1.23–2.17)
	$P = 0.18$	$P < 0.001$	
Combined regurgitation analysis <sup>a</sup>			
Normal	40 (56%)	6 (29%)	35 (75%)
Mild	23 (32%)	7 (33%)	7 (15%)
Moderate or severe	9 (13%)	8 (38%)	5 (11%)
P value (df = 2)	0.08	0.001	

Mild: At least one valve with grade 2 regurgitation and other valves grade 0–2.

Moderate-severe: At least one valve with grade 3–4 regurgitation.

Categories are mutually exclusive.

<sup>a</sup>Normal: All valves grade 0–1.

**TABLE 3.** Frequency of regurgitation across all 3 valves, grouped by quartiles of cumulative bromocriptine dose, compared to pergolide and control groups

Combined regurgitation analysis	Bromocriptine quartiles					Pergolide (n = 21)
	Controls (n = 47)	Q1 (n = 18)	Q2 (n = 18)	Q3 (n = 18)	Q4 (n = 18)	
Normal	35 (75%)	14 (78%)	11 (61%)	8 (44%)	7 (39%)	6 (29%)
Mild	7 (15%)	3 (17%)	5 (28%)	8 (44%)	7 (39%)	7 (33%)
Moderate or severe	5 (11%)	1 (6%)	2 (11%)	2 (11%)	4 (22%)	8 (38%)

Adjusted p(trend) for bromocriptine quartiles:  $P = 0.002$  for any abnormal regurgitation;  $P = 0.005$  for mild regurgitation;  $P = 0.019$  for moderate-severe regurgitation.

OR, 95% CI: 1.04–5.21,  $P = 0.052$ ) and 3.32 (adjusted OR, 95% CI: 1.11–9.92,  $P = 0.03$ ) compared to controls. The risk for participants to develop mild regurgitation while on bromocriptine was 2.88 (crude OR, 95% CI: 1.10–7.51) and 3.86 (adjusted OR, 95% CI: 1.09–13.69). The risk for participants to develop moderate-severe regurgitation while on bromocriptine was 1.58 (crude OR, 95% CI: 0.48–5.14) and 2.61 (adjusted OR, 95% CI: 0.51–13.35).

We examined the relationship between the cumulative dose of bromocriptine (divided into quartiles) and combined regurgitation analysis across three valves; controls and pergolide groups were used for comparison (Table 3). The frequency of abnormal regurgitation increased with increasing cumulative dose of bromocriptine (adjusted  $P$  for trend = 0.002). This dose-response relationship was present when both mild and moderate-severe valvular heart disease was analyzed separately. Among the participants who received the highest quartile of cumulative bromocriptine dose, 61% of them had valvular regurgitation. This percentage approached that of the pergolide group where 71% were found to have valvular regurgitation.

The risk of both mild regurgitation and moderate-severe regurgitation was increased with increasing cumulative dose (in quartiles) of bromocriptine (Table 4) compared to controls. The adjusted OR for developing mild valvular regurgitation doubled from 4.51 to 11.00 from the second to the third quartiles of cumulative bromocriptine dose and reached 16.47 for participants in the fourth quartile (Table 3). The risk for developing moderate to severe valvular regurgitations was 61.16 (adjusted OR) for participants in the highest quartile of cumulative bromocriptine dose.

### DISCUSSION

This study was designed to specifically assess if bromocriptine use among PD patients was associated with valvular heart disease. The participants in this study

were specially selected to ensure that they had no prior heart disease or other conditions that predisposed them to having valvular heart disease. The bromocriptine group was compared to a pergolide group that served as a positive control and a control group of participants with PD that served as a negative control.

The findings in this study suggest that bromocriptine is not as safe as previously thought<sup>3,4</sup> and is associated with valvular heart disease. The risk of participants on bromocriptine to develop valvular heart disease that was mild, moderate, or severe was more than three times that of control participants who had no prior exposure to any DA. The development of mild and moderate-severe valvular heart disease in the bromocriptine group also showed a cumulative dose-response relationship. These results suggest that the higher the exposure to bromocriptine, the higher the risk of developing both mild and moderate-severe valvular regurgitations. Higher cumulative doses have also been found previously to be associated with significantly more

**TABLE 4.** Risk of mild and moderate-severe regurgitation across all three valves in bromocriptine group, grouped by quartiles of cumulative bromocriptine dose, compared to controls

	Bromocriptine quartiles	
	Crude OR (95% CI)	Adjusted OR (95% CI)
Mild*		
Control group	1.00	1.00
Quartile 1	1.07 (0.24–4.74)	2.13 (0.42–10.94)
Quartile 2	2.27 (0.60–8.61)	4.51 (0.90–22.66)
Quartile 3	5.00 (1.40–17.85)	11.00 (1.83–66.35)
Quartile 4	5.00 (1.33–18.81)	16.47 (1.98–137.20)
$P$ for trend	0.003	0.005
Moderate-severe <sup>a</sup>		
Control group	1.00	1.00
Quartile 1	0.50 (0.05–4.67)	1.27 (0.12–14.18)
Quartile 2	1.27 (0.22–7.50)	5.26 (0.55–50.20)
Quartile 3	1.75 (0.29–10.70)	8.62 (0.66–112.53)
Quartile 4	4.00 (0.85–18.75)	61.16 (2.45–1526.88)
$P$ for trend	0.076	0.019

<sup>a</sup>Combined regurgitation analysis.

regurgitations in pergolide and carbergoline-treated patients, although this has not been demonstrated in a dose-response manner before.<sup>2,13</sup> For participants in the highest quartile of cumulative bromocriptine dose, their risk of developing valvular heart disease approached that of the pergolide group.

This study is one of only two studies to date that addresses the issue of valvulopathies associated with bromocriptine use. A previous study from Korea on PD patients on bromocriptine and pergolide did not find any increase in the frequency of valvulopathies among their patients.<sup>10</sup> The reason for their negative findings is likely to be related to their use of a lower dose and a shorter duration of treatment for both bromocriptine and pergolide. The cumulative dose, duration of treatment, and mean doses for participants in our study were all higher than that in the Korea study. For instance, the mean cumulative dose of bromocriptine in our study was almost twice that in the Korea study.

Participants in the pergolide group had significantly higher risk of developing valvular heart disease compared to the control group. These results are consistent with those reported from the Western literature.<sup>3</sup> Interestingly, this study is the first to show that pergolide is associated with valvular heart disease in an Asian cohort. In addition to the negative Korea study discussed earlier, a study from Japan also reported that pergolide was not associated with valvular heart disease.<sup>13</sup> The reason for this is more likely related to their use of different echocardiography criteria to define abnormal regurgitations rather than a difference in drug exposure as their mean doses of pergolide and duration of treatment were similar to this study.

The reason for the association of bromocriptine with valvular heart disease is likely to be related to its agonistic effects on 5-HT<sub>2B</sub> receptors on heart valves. Surgically removed heart valves from affected PD patients on pergolide and cabergoline have previously shown distinctive histopathological changes, including fibroblast proliferation and deposition of a cellular myxoid matrix on the valve surfaces.<sup>14,15</sup> These changes are similar to the changes found in patients with carcinoid syndrome and in patients who had taken ergotamine, methysergide, fenfluramine, or ecstasy, all of which are thought to be mediated through the serotonergic agonistic activity on 5-HT<sub>2B</sub> receptors.<sup>16,17</sup> As the pattern and risk of valvulopathies in our bromocriptine group was similar to that reported in pergolide and cabergoline patients with valvulopathies and in view of its 5-HT<sub>2B</sub> agonistic properties, the mechanism by which bromocriptine induces valvulopathies is likely to be the same.

There are a number of limitations in this study. The control group had a higher mean age at diagnosis, a shorter duration of illness, and had less severe motor impairment compared to the other two groups. The reason for this is inherent to the inclusion criteria, which excluded patients who had been previously treated with any DA. As such, patients who satisfied this criterion were limited to those with early stage PD patients who had not been treated on DA or elderly patients who were started directly on levodopa. Nevertheless, these differences were adjusted for our statistical analyses. The other major limitation of the study was the small numbers, particularly in the subgroup analyses of bromocriptine quartiles, which resulted in wide confidence intervals.

This is the first study to suggest that the use of bromocriptine in PD patients is associated with valvular heart disease. The results also showed a dose-response relationship with increased risk of valvulopathies associated with increased cumulative exposure to the drug. The medical community should be alerted of this association particularly in patients who are being treated on high doses of this drug over many years. Screening echocardiography may be considered for this group of patients. As the mean dose of bromocriptine (19 mg/day) in the study is considered modest when compared with the doses used in clinical trials on bromocriptine (24–52 mg/day),<sup>18–20</sup> there is a possibility that the risk of valvulopathies is even higher among non-Asians, because higher doses of DA are generally required to achieve the same therapeutic effect among non-Asians in view of their larger body mass. Further studies are therefore needed to understand the risk of bromocriptine-induced valvulopathies among other populations of PD patients.

**Acknowledgments:** We thank Ms Irene Seah Soo Hoon for assisting in this study. This project was supported by the National Medical Research Council, Singapore project no: NMRC/0995/2005.

## REFERENCES

- Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. Dopamine agonists and the risk of cardiac-valve regurgitation. *N Eng J Med* 2007;356:29–38.
- Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Eng J Med* 2007;356:39–46.
- Antonini A, Poewe W. Fibrotic heart-valve reactions to dopamine agonist treatment in Parkinson's disease. *Lancet Neurol* 2007;6:826–829.
- Roth BL. Drugs and valvular heart disease. *N Engl J Med* 2007;356:6–9.

5. Newman-Tancredi A, Cussac D, Quentric Y, et al. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptor. III. Agonist and antagonist properties at serotonin, 5HT<sub>1</sub> and 5HT<sub>2</sub> receptor subtypes. *J Pharmacol Exp Ther* 2002;303:815–822.
6. Millan MJ, Maioufiss L, Cussac D, Audinot V, Boutin J, Newman-Tancredi A. Differential actions of antiparkinson agents at multiple classes of monoaminergic receptors. I. A multivariate analysis of the binding profiles of 14 drugs at 21 native and cloned human receptor subtypes *J Pharmacol Exp Ther* 2002; 303:791–804.
7. Jahnichen S, Horowski R, Pertz HH. Agonism at 5-HT<sub>2B</sub> receptors is not a class effect of the ergolines. *Eur J Pharmacol* 2005; 513:225–228.
8. Kvernmo T, Hartter S, Burger E. A review of the receptor-binding and pharmacokinetic properties of dopamine agonists. *Clin Ther* 2006;28:1065–1078.
9. Serratrice J, Disdier P, Habib G, Viallet F, Weiller PJ. Fibrotic valvular heart disease subsequent to bromocriptine treatment. *Cardiol Rev* 2002;10:334–336.
10. Kim JY, Chung EJ, Park SW, Lee WY. Valvular heart disease in Parkinson's disease treated with ergot derivative dopamine agonists. *Mov Disord* 2006;21:1261–1264.
11. Ranganathan N, Lam JH, Wigle ED, Silver MD. Morphology of the human mitral valve. II. The valve leaflets *Circulation* 1970; 41:459–467.
12. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for the evaluation of the severity of the native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777–802.
13. Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac valvulopathy in Parkinson disease. A case-control study. *Neurology* 2006;67:1225–1229.
14. Prichett AM, Morrison JF, Edwards WD, Schaff HV, Connolly HM, Espinosa RE. Valvular heart disease in patients taking pergolide. *Mayo Clin Proc* 2002;77:1280–1286.
15. Van Camp G, Flamez A, Cosyns B, Goldstein J, Perdaens C, Schoors D. Heart valvular disease in patients with Parkinson's disease treated with high-dose pergolide. *Neurology* 2003;61: 859–861.
16. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT<sub>2B</sub> receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. *Circulation* 2000;102:2836–2841.
17. Setola V, Hufeisen SJ, Grande-Allen KJ, et al. 3,4-Methylenedioxy-methamphetamine (MDMA, "Ecstasy") induces fenfluramine-like proliferative actions on human cardiac valvular interstitial cells in vitro. *Mol Pharmacol* 2003;63:1223–1229.
18. Montastruc JL, Rascol O, Senard JM, Rascol A. A randomised controlled study comparing bromocriptine to which levodopa was later added, with levodopa alone in previously untreated patients with Parkinson's disease: a five year follow-up. *J Neurol Neurosurg Psychiatry* 1994;57:1034–1038.
19. Korczyn AD, Brunt ER, Larsen JP, et al. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. *Neurology* 1999;53:364–370.
20. Lee AJ, Katzenschlager R, Ben-Shlomo, on behalf of the Parkinson's disease research group of the United Kingdom. Ten-year follow-up of three different initial treatments in de-novo PD. A randomized trial. *Neurology* 2001;57:1687–1694.



Author Proof

AQ1: Kindly provide the department/division name for the second affiliation and also check whether the affiliations are OK as typeset.

AQ2: Kindly provide the department/division name for the fifth affiliation.

AQ3: Please indicate whether any authors may have a potential conflict of interest.



**Author Proof**